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VIEWPOINT

JIACM 2014; 15(3-4): 170-1

Science meets spirituality?

*BM Hegde**

"I want to know how God created this world.

I am not interested in this or that phenomenon, in the spectrum of this or that element.

I want to know His thoughts;

the rest are details."

– Albert Einstein.

What is this new awakening in the midst of so much advances in the Western science? "How could such silly and retrograde questions be asked in the first place", will be the reader's first reaction? I understand! I have no quarrel with such people although at times I worry as to why we developed this lethargy to find the truth about the working of this universe (multiverse)? "Every child", said Alexis Carrel, "is a genius at birth, ONLY to be converted into an idiot in school." I did not agree with him when I first read it but am convinced now. Every child can and does think. Anyone who can think becomes a scientist – one who tries to get answers to insurmountable questions in life. Our present schools do not let you think as that is not the essence of education which demands one to learn and work only in the known sphere of our experience.

Schools also teach the Western science as the 'be all' and 'end all' of all there is to be known. Today's education does not aim at creating healthy minds but are lost in producing wealthy careers only. If a child asks the teacher in school as to what was there before the Big Bang, her pet answer would be: "space and matter came only after the Big Bang, there being nothing before the Big Bang; she might even laugh at the child by asking what is on the north of the North Pole? By the time that child comes to college or medical school it will have numbed its brain that the child is not able to think rationally at all.

Nobel laureates like Peter Medawar tell us that science is designed to answer only certain (mundane) questions and not answer such esoteric questions like what after death? Or why does the heart contract, etc. He compares science to a railway engine designed to run on a track but not fly like an aeroplane. In his classic, *Limits of Science*, a clever man tries to wriggle out of a difficult situation as the reductionist Western science is incapable of answering the "why" question although it tries to answer "how" or "how much". Unfortunately the answers needed are for the "why" questions only. As a doctor for more than five decades I get disillusioned by modern Western science. Why does a young man, apparently healthy, die suddenly of a massive heart attack despite his having done everything scientifically correctly while an elderly gentleman with advanced coronary artery disease still chugs on beyond eighty?

When one goes deep, science is simply making models, which are mathematical constructs, and with verbal jargon they are supposed to work. It doesn't work that way though. Newton's Laws of deterministic predictability have been upturned by Einstein's relativity while the latter does not fit into quantum mechanics. When you see liquid helium climb up the sides of its container to overflow, one wonders as to what happened to all our laws of thermodynamics. Liquid helium, kept in a silicon bowl, leaks out through its intact base! When we claim that the heart, a small muscular structure weighing just 300 gms, pumps blood into a capillary system of totally 500,000 kilometres, which are thinner than our hair, not letting even a red blood cell to pass through easily, we are not being truthful. But neither did we ask such questions nor do we let our students do that. Quantum mechanics – the most advanced physics – has achieved a lot, but is found wanting when it comes to actuality in our lives. There still exist questions needing answers. When I read science books which are more than one hundred years old, the authors did have sentences like "My God, only God can answer this question!" Today's science wants to be all knowing and the God concept does not seem to exist there. Some of the fanatics among them even detest the word God! We seem to have lost our humility – the cornerstone of wisdom – to our Western thinking in science, which a couple of physicists, Harry Steven and Trevor Pinch, call science as a Golem to frighten people in their colonies to be kept under subjugation.

A recent science study in biology of experiments with rats

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showed that the sex and sweat smell of the researcher affect the results to the extent of forty per cent – male researchers being more effective. The observer's consciousness does affect the results. This brings us to the ultimate actuality. Cogito ergo sum – I think, therefore, I am – did destroy science of the West. That was the concept where Rene Descartes cut-off the human body into the thinking part – res Cogitans and the other part – res Extensa, thereby sowing the seed of reductionism which is at the root of the present rotting science. However, in the new context of actuality it explains the opposite of what Descartes meant! That statement makes a great truth come out and that is that the centre of our universe is our consciousness ('mind' for the lay man). Quantum physics is absolutely right when it says everything exists as energy vibrations but collapses into matter on observation. That final awareness, observation of the observer, his/her consciousness is what makes this world to come alive. How very true indeed!

Robert Lanza, a genius of a physician and his co-author, Bob Bermer, a maverick astronomer, have written that wonderful book of insight into science where they claim that the world lives around life and for life-bio centrism – as they call that all-encompassing consciousness which is at the root of all science. The reductionist view that a few particles inside our brain cells create consciousness does not make sense even to the elementary school kids. The world is far from a giant clock that somehow got fully wound at the time of the Big Bang to be unwinding on its own mysterious ways to run the world! Evidence for the Big Bang itself is untenable. In fact, most scientific theories have been proven wrong according to another great science thinker, John OM Bockris, in his book, *The New Paradigm*. After all, science theories are made by human consciousness and will have to have drawbacks.

All the above-mentioned advances in our thinking will lead to better days for our suffering humanity as medicine would become bio-centric, and not drugs- and surgery-centric reductionism. Matter being energy, mind becomes the body in the uncertainty principle. Candace Pert, a daring young researcher at the 'Palace', that is NIH (National Institutes of Health), did show to the world for the first time that opiate receptors also exist outside the brain. She lost her job. Now we know that the human mind resides in every single cell at the cell membrane called MemBrain. Providentially, I had written in my book in 1993 that there is a possibility of a mind in every cell. The editor of the publication had questioned me about my serendipitous thinking! He did not believe it though then. Alas, he is no more, a God's good man that he was!

Recent research at Oxford led by Professor Bingel elegantly showed that all healing occurs, NOT because of our medicines but because of the patient's belief in the doctor and the medicines he gives, true placebo effect, another brainchild of consciousness. Only one thinking scientists in the western world, Max Planck, has written that "consciousness is fundamental and all matter is derived from the consciousness and not vice versa. I don't think that the best surgeon will be able to heal a surgical wound in a dead body without consciousness! Consciousness, therefore, runs this world as suggested by Robert Lanza. (W) holistic science will change the healing world as energy can heal all ills. Unfortunately, science today understands just about 5% of the world' energy store. Rest is in the realm of occult energy used by our spiritualists for times out of the mind.

Caring and sharing is spirituality in essence. Occult healing methods were used in healing in many civilisations and with success. We will have to reinvent them again for the good of mankind. Let us get out of our arrogant mind-set that only science can solve all our problems. This in part is due to the success of reductionist science-based technologies like the semi-conductors, etc., whichhave made life apparently more comfortable at the cost of our good health. Let wisdom prevail and God help mankind. We still need that kind of God to help us but not the religions which make money in the name of God. A true healer is God incarnate.

"The scientists' religious feeling takes the form of a rapturous amazement at the harmony of natural law, which reveals an intelligence of such superiority that, compared with it, all the systematic thinking and acting of human beings is an utterly insignificant reflection."

– Albert Einstein.

"Universities are the cathedrals of the modern age.
They shouldn't have to justify their existence by utilitarian criteria."

– David Lodge:
Nice Work, IV.

ORIGINAL ARTICLE

JIACM 2014; 15(3-4): 172-6

Vitamin D status and serum osteocalcin levels in post-menopausal osteoporosis: Effect of bisphosphonate therapy

M Beg, N Akhtar**, MF Alam***, I Rizvi****, J Ahmad*****, A Gupta*******

Abstract

***Context:** Osteocalcin or Bone Gla Protein (BGP) is a bone specific protein. It is the major and most thoroughly characterised non-collagenous protein in mature human bone. Osteocalcin is now considered as an important marker for bone turnover. Vitamin D status plays an important role in mineralisation of the skeleton at all ages.*

***Aims:** The present study was designed to evaluate: the prevalence of hypovitaminosis D in post-menopausal females, significance of serum osteocalcin in evaluation of osteoporosis, and to determine the effect of risedronate therapy on serum osteocalcin in post-menopausal females with osteoporosis.*

***Materials and methods:** One hundred and forty-eight post-menopausal women between 40 to 80 years attending the hospital OPD were studied. To be eligible for the study they had to have been post-menopausal for at least one year and had decreased bone mineral density (lumbar spine or right or left femoral neck or both T-score -1.0 or less). The diagnosis of osteoporosis was made based on T-scores (BMD) at the lumbar spine (L1 to L4) and femoral neck by DEXA (GE Lunar Densitometer). Patients with chronic conditions affecting skeletal health and patients on drugs affecting the skeleton were excluded from the study. Serum 25 (OH) vitamin D was estimated using LIAISON 25 OH Vitamin-D chemiluminescent immunoassay. Osteocalcin level in the serum was estimated by LIAISON Osteocalcin assay. Patients with osteoporosis were treated with risedronate 35 mg/week and were reassessed after 1 year.*

***Results:** Out of 148 post-menopausal females, 101 subjects had vitamin D deficiency (≤20 ng/ml) and 30 subjects had vitamin D insufficiency (21 - 29 ng/ml). Thus, prevalence of hypovitaminosis D in post-menopausal females was 88.51%. Serum osteocalcin was found to be significantly higher in post-menopausal women with osteoporosis as compared to post-menopausal women without osteoporosis ($p < 0.05$). On correlation analysis, inverse relationship was found between BMD and serum osteocalcin levels ($r2 = -0.770$, $p < 0.05$). There was a significant reduction in serum osteocalcin after 1-year treatment with risedronate ($p < 0.05$).*

***Conclusion:** Serum osteocalcin is a promising marker of bone turnover in post-menopausal women with osteoporosis, as it was found to be elevated in osteoporosis; also, its level reduced after treatment with risedronate. Therefore, osteocalcin provides a dynamic measure of bone remodelling and it can be potentially useful in diagnosis and monitoring of response to therapy in patients of osteoporosis. We also concluded that hypovitaminosis D is very common in our clinical setup, thus underlining the importance of adequate calcium and vitamin D supplementation before starting bisphosphonates or any other specific treatment for osteoporosis.*

***Key words:** Osteocalcin, vitamin D, osteoporosis, risedronate.*

Introduction

Osteoporosis is defined as a "progressive systemic skeletal disorder characterised by consequent increase in bone fragility and susceptibility to fracture"[1]. Osteoporosis has a tremendous impact on the lives of many post-menopausal women. Fractures are potentially devastating complications of osteoporosis. Also, the number of osteoporotic fractures are increasing as the population ages, and assessment of skeletal health is becoming an important component of a woman's routine care[2]. World-wide the life-time risk for women to have osteoporotic fracture is 30 - 40%[3]. Occurrence of osteoporosis is 10 years earlier in Indian people than in the West. It currently affects approximately one in three women and one in five men over age 50[2]. Nutrition is a critical component in the pathogenesis, prevention, and treatment of osteoporosis[4]. Among nutrients, calcium and vitamin D play an important role in the mineralisation of the skeleton at all ages, an alteration in vitamin D status and/or a reduced synthesis of 1, 25-dihydroxy vitamin D predispose to secondary hyperparathyroidism, which enhances bone remodelling and causes cortical bone loss[5]. Osteocalcin or Bone Gla Protein (BGP) is a bone specific protein. It is the major and most thoroughly characterised non-collagenous protein in mature human bone, where it constitutes 1 - 2% of the total protein[6]. It is a small protein of 49 amino

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acids including 3 residues of gamma-carboxyglutamic acid, with a molecular weight of 5,800 Da[7]. Its synthesis is dependent upon the presence of active metabolites of vitamin D, especially 1, 25-dihydroxyvitamin D and it requires vitamin K for the conversion by carboxylation of three glutamate residues to gamma-carboxyglutamate[6]. The present study was designed to evaluate: the prevalence of hypovitaminosis D in post-menopausal females, significance of serum osteocalcin in evaluation of osteoporosis, and to determine the effect of risedronate therapy on serum osteocalcin in post-menopausal females with osteoporosis.

Materials and methods

The present study was conducted at the Department of Medicine, Centre for Diabetes and Endocrinology and Department of Obstetrics and Gynaecology, J. N. Medical College and Hospital, AMU, Aligarh, UP. One hundred and forty-eight post-menopausal women between 40 to 80 years attending the hospital OPD were studied. To be eligible for the study they had to have been post-menopausal for at least one year and had decreased bone mineral density (lumbar spine or right or left femoral neck or both T-score -1.0 or less).

The diagnosis of osteoporosis was made based on T-scores (BMD) at the lumbar spine (L1 to L4) and femoral neck by DEXA (GE Lunar Densitometer) as follows:

Category	Definition
Normal	A value of BMD or BMC ± 1 S.D of the young adult reference mean
Low bone mass (osteopenia)	A value of BMD or BMC > 1 S.D and < 2.5 S.D lower than the young adult reference mean
Osteoporosis	A value of BMD or BMC > 2.5 S.D lower than the young adult reference mean
Severe osteoporosis (established osteoporosis)	A value of BMD or BMC > 2.5 S.D lower than the young adult reference mean in the presence of one or more fragility fractures.

Out of 148 post-menopausal women, 73 had osteoporosis (according to the above mentioned definition). These 73 females also included 16 patients presenting to the emergency/orthopaedic department with fragility fracture. A fragility fracture was defined as one that occurred as a result of minimal trauma, such as a fall from a standing height or less, or occurred without identifiable trauma. Rest of 75 post-menopausal women without osteoporosis served as control.

Exclusion criteria for the study were oestrogen replacement therapy within 1 year, deranged renal function (serum creatinine >1.5 mg%) or renal calculi, abnormal thyroid function, significant liver disease, history of cancer, peptic ulcer, or oesophageal disease requiring prescription. Regular therapy with phosphate binding antacid, therapy with any other drug that affects the skeleton, e.g., steroids, anti-resorptive therapy, anticonvulsant, anticoagulants, etc. Informed consent was obtained from all the subjects participating in the study; and the study was approved by the local ethical committee. A detailed history and physical examination was carried out for every subject who entered in the study as per a pre-designed proforma. Examination comprised of a thorough physical examination, assessment of vital parameters, anthropometry and systemic examination. Bone mineral density (BMD) was measured using DEXA at baseline and after one year by GE Lunar Densitometer. Serum 25 (OH) vitamin D was estimated using LIAISON 25 OH vitamin D chemiluminescent immunoassay. vitamin D sufficiency was defined as serum 25 (OH) vitamin D in the range of 30 to 100 ng/ml, vitamin D insufficiency as values between 21 - 29 ng/ml, and values $\leq$ 20 ng/ml were defined as vitamin D deficiency. Osteocalcin level in the serum was estimated by LIAISON Osteocalcin assay. Seventy-three post-menopausal females with osteoporosis included in the study protocol received risedronate 35 mg weekly. These patients were also given elemental calcium of 100 mg/day and vitamin D of 1,000 IU/day. All patients with osteoporotic vertebral fractures were also treated conservatively with bed rest, analgesics, anti-osteoporotic medication (risedronate) and brace application besides elemental calcium and vitamin D. All patients were reassessed after one year of taking the treatment by noticing change over baseline in BMD and level of serum osteocalcin. Statistical analysis was performed using SPSS version 16 statistical package for windows (SPSS, Chicago, IL).

Observations

The baseline characteristics of 148 post-menopausal women are shown in Table I.

The mean age of post-menopausal females without osteoporosis was 51 ± 3.88 years and post-menopausal with osteoporosis was 56.57 ± 8.15 yrs. Similarly, mean duration of menopause in post-menopausal females without osteoporosis group was 3.85 ± 1.82 and in post-menopausal females with osteoporosis group was 9.56 ± 5.80 suggesting significant difference in the two groups. There was a significant difference in the BMD lumbar spine in the two groups ($p < 0.05$). BMD lumbar spine was 1.20 ± 0.18 in the post-menopausal women without osteoporosis group as compared to 0.81 ± 0.13 in the osteoporosis group. Similarly there was significant difference in the BMD hip in the two groups ($p < 0.05$).

Table I: Showing baseline characteristics of study subjects.

S. No.	Parameter	Post-menopausal without osteoporosis N = 75		Post-menopausal with osteoporosis N = 73		P value
		Mean	S.D	Mean	S.D	
1	Age (years)	51	3.88	56.57	8.15	< 0.05
2	Time since menopause (years)	3.85	1.82	9.56	5.80	< 0.05
3	BMI (kg/m^2)	26.61	4.12	25.73	5.72	NS
4	BMD - lumbar spine (g/cm^2)	1.20	0.18	0.81	0.13	< 0.05
5	T. score - lumbar spine	1.41	0.29	-3.14	1.10	< 0.05
6	BMD - hip (g/cm^2)	1.22	0.15	0.81	0.15	< 0.05
7	T. score – Hip	1.34	0.26	-1.87	1.03	< 0.05
8	Whole blood ionised calcium (mmol/l)	1.16	0.10	1.07	0.09	< 0.05
9	Serum 25 (OH) vit D (ng/ml)	15.22	6.23	19.51	8.58	< 0.05
	Deficiency (≤ 20 ng/ml)	12.49	3.19	13.64	3.87	NS
	Insufficiency (21 - 29 ng/ml)	21.78	1.71	23.56	2.77	< 0.08
	Normal (30 - 100 ng/ml)	31.34	1.66	34.49	2.63	< 0.05
10	S.TSH (mIU/l)	2.90	1.23	2.65	2.05	NS
11	S. creatinine (mg/dl)	1.14	0.19	0.95	0.16	< 0.05
12	Serum osteocalcin (ng/ml)	9.87	1.04	22.62	2.25	< 0.05

Mean T- score at lumbar spine was 1.41 ± 0.29 and -3.14 ± 1.0 in post-menopausal women without osteoporosis and with osteoporosis respectively, suggesting a significant difference in the two groups ($p < 0.05$). Similarly, there was significant difference in the mean T-score at hip ($p < 0.05$).

Out of 148 post-menopausal females, 101 subjects had vitamin D deficiency (≤ 20 ng/ml) and 30 subjects had vitamin D insufficiency (21 - 29 ng/ml). Thus, prevalence of hypovitaminosis D in post-menopausal females was (88.51%). Out of seventy-five post-menopausal female without osteoporosis, fifty-eight (77.33%) had vitamin D deficiency (≤ 20 ng/ml), twelve (16.0%) had vitamin D insufficiency (21 - 30 ng/ml), and only five females (6.66%) had vitamin D in the normal range (30 - 100 ng/ml). Out of seventy-three post-menopausal females with osteoporosis group, forty-three (58.90%) had vitamin D deficiency (≤ 20 ng/ml), eighteen (24.65%) had vitamin D insufficiency (21 - 30 ng/ml) and twelve females (16.43%) had vitamin D in the normal range (30 - 100 ng/ml). So, prevalence of vitamin D deficiency and insufficiency was 68.24% and 20.27% respectively in post-menopausal females.

Serum osteocalcin was found to be significantly higher in post-menopausal women with osteoporosis as compared to post-menopausal women without osteoporosis ($p < 0.05$), mean serum osteocalcin was 22.62 ± 2.25 ng/ml in osteoporosis group as compared to 9.87 ±1.04 ng/ml in the other group. Whole blood ionised calcium was 1.16 ± 0.10 mmol/l and 1.07 ± 0.09 mmol/l in post-menopausal women without osteoporosis and with osteoporosis respectively, suggesting a significant difference between the two groups. On correlation analysis an inverse relationship was found between BMD and serum osteocalcin levels ($r2 = -0.770$, $p < 0.05$). A positive correlation was also noted between BMD and vitamin D, however it was not statistically significant ($r 2 = 0.201$, $p < 0.089$).

On comparing impact of duration of menopause on BMD and serum osteocalcin levels, patients with < 10 years of menopause had mean BMD at spine 0.86 ± 0.13 g/cm^2, mean BMD at hip 0.86 ± 0.15 g/cm^2 and mean serum osteocalcin 22.35 ± 2.10 ng/ml, while patients with > 10 yrs of menopause had mean BMD at spine 0.75 ± 0.11 g/cm^2, mean BMD at hip 0.75 ± 0.13 g/cm^2 and mean serum osteocalcin 22.92 ± 2.41 ng/ml. On applying paired t-test there was significant difference in the two groups in terms of mean BMD, but there was not much difference in the two groups in terms of mean serum osteocalcin (Table II).

Seventy-three post-menopausal females with osteoporosis were treated with risedronate 35 mg weekly, baseline mean BMD at lumbar spine was 0.81 ± 0.13 g/cm^2, and after one year of treatment with risedronate, the mean BMD at lumbar spine was 0.92 ± 0.10 g/cm^2; this increase in BMD was statistically significant ($p < 0.05$). Similarly, there was a significant increase in BMD-hip after 1 year treatment with risedronate ($p < 0.05$). Mean serum osteocalcin levels

Table II: Impact of duration of menopause on BMD and serum osteocalcin.

S. No.	Parameter	Patients with < 10 years of menopause N = 38		Patients with ≥ 10 years of menopause N = 35		P value
		Mean	S.D	Mean	S.D	
1	BMD (spine) (g/cm²)	0.86	0.13	0.75	0.11	< 0.05
2	T. score (spine)	-2.73	1.08	-3.59	0.96	< 0.05
3	BMD (hip) (g/cm²)	0.86	0.15	0.75	0.13	< 0.05
4	T. score hip	-1.52	0.85	-2.25	1.09	< 0.05
5	Serum osteocalcin (ng/ml)	22.35	2.10	22.92	2.41	< 0.27

Table III: Pre- and post-treatment comparison of BMD and serum osteocalcin.

S. No.	Parameter	Pre-treatment (N = 73)		Post-treatment (N = 73)		P value
		Mean	S.D	Mean	S.D	
1	BMD - lumbar spine (g/cm²)	0.81	0.13	0.92	0.10	< 0.05
2	T - score (spine)	-3.14	1.10	-2.46	0.77	< 0.05
3	BMD - hip (g/cm²)	0.81	0.15	0.90	0.11	< 0.05
4	T - score (hip)	-1.87	1.03	-1.52	0.73	< 0.015
5	Serum osteocalcin (ng/ml)	22.62	2.25	18.22	1.23	< 0.05

in pre-treatment and post-treatment groups were 22.62 ± 2.26 ng/ml and 18.22 ± 1.23 ng/ml respectively; on applying paired t-test there was a significant change in the two groups ($p < 0.05$). The comparison of pre-treatment and post-treatment parameters is shown in Table III.

Mild side-effects like upper gastrointestinal disturbance and headache, etc., were reported in a small number of patients taking risedronate, but none of the patients reported any serious adverse effect.

Discussion

The present study was carried out with the aims to determine the prevalence of hypovitaminosis D in post-menopausal women, significance of serum osteocalcin in evaluation of osteoporosis, and to determine the effect of risedronate therapy on serum osteocalcin in post-menopausal females with osteoporosis.

Normal bone metabolism depends on the presence of appropriate repletion of vitamin D. Although only few patients with osteoporosis exhibit obvious biochemical signs of hypovitaminosis D, vitamin D insufficiency has been shown to have adverse effects on calcium metabolism, osteoblastic activity, matrix ossification, bone mineral density (BMD), and bone remodelling[8]. Low serum 25 (OH) vitamin D concentration is associated with secondary hyperparathyroidism, increased bone turnover, reduced BMD, and increased risk of osteoporotic fractures[9]. In our study, we found that majority of the subjects had hypovitaminosis D. Out of seventy-five post-menopausal females without osteoporosis, fifty-eight (77.33%) had vitamin D deficiency (≤20 ng/ml), twelve (16.0%) had vitamin D insufficiency (21 - 30 ng/ml), and only five females (6.66%) had vitamin D in the normal range (30 - 100 ng/ml). Out of seventy-three post-menopausal females with osteoporosis group, forty-three (58.90%) had vitamin D deficiency (≤20 ng/ml), eighteen (24.65%) had vitamin D insufficiency (21 - 30 ng/ml) and twelve females (16.43%) had vitamin D in the normal range (30 - 100 ng/ml). So, prevalence of vitamin D deficiency and insufficiency was 68.24% and 20.27% respectively in post-menopausal females. The overall prevalence of hypovitaminosis D was 88.51%. Prevalence of hypovitaminosis D in post-menopausal women was found to be 47% in Thailand, 49% in Malaysia, 90% in Japan, and 92% in South Korea[10]. Harinarayan *et al* reported vitamin D deficiency in 70% females and insufficiency in 23% females in their study from South India in 2011[11]. Goswami *et al* found hypovitaminosis D was present in up to 90 per cent of apparently healthy subjects in Delhi[12]. Skin complexion, poor sun exposure, vegetarian food habits, low milk intake, high phytates in food, and lack of vitamin D food fortification programme explain the high prevalence of vitamin D deficiency in India despite its sunny climate.

In the present study, serum osteocalcin level in post-menopausal female without osteoporosis was 9.87 ± 1.04 (ng/ml), while post-menopausal female with osteoporosis had level of 22.62 ± 2.25 (ng/ml) suggesting

significant increase in bone marker level in females with osteoporosis as compared to females without osteoporosis ($p < 0.05$). Correlation analysis between BMD and osteocalcin showed strong negative correlation ($r2 = - 0.77$, $p < 0.05$). A case control study of 90 post-menopausal women showed results that were consistent with the results of the present study, in that there was a significant inverse correlation of proximal femur BMD with osteocalcin[13]. Verit *et al* reported that serum osteocalcin levels in post-menopausal osteoporotic women were significantly higher than in pre-menopausal non-osteoporotic women[14]. Hari Kumar *et al* also reported a significant negative correlation between osteocalcin and BMD[15]. In osteoporotic women, deficiency of calcium leads to lowering of formation of hydroxyapatite crystals. Thus, rate of bone mineralisation is decreased. Osteocalcin has a high affinity for calcium, so increased free osteocalcin is available in the circulation. This explains the increased concentration of osteocalcin in the serum of osteoporotic post-menopausal women. Our study also showed a positive correlation between vitamin D and BMD, although the relation was not statistically significant ($r2 = 0.201$, $p < 0.089$). Thus, in osteoporosis, low level of vitamin D and increased osteocalcin level are seen. Kuchuk *et al* studied on 7,441 post-menopausal women from 29 countries and found a strong positive correlation between Vitamin D and BMD, while significant negative correlation with osteocalcin[16]. As stated above, in our study also, a significant negative correlation was found between BMD and osteocalcin, although correlation between vitamin D and BMD was not found to be statistically significant which can be due to the small sample size.

We also observed that serum osteocalcin in post-menopausal females with osteoporosis after one year of treatment with risedronate (35 mg/week) was 18.22 ± 1.23 ng/ml. Thus change in osteocalcin after treatment was 4.4 ng/ml (19.45%) suggesting a significant reduction in osteocalcin level in post-treatment group as compared to pre-treatment group ($p < 0.05$). Ones *et al* also found a significant reduction in osteocalcin levels after treatment with alendronate[17]. Jagtap *et al* also reported reduction in osteocalcin after anti-resorptive therapy[2].

Thus we can conclude that serum osteocalcin is a promising marker of bone turnover in post-menopausal women with osteoporosis, as it was found to be elevated in osteoporosis; also, its level reduced after treatment with risedronate. Therefore, osteocalcin provides a dynamic measure of bone remodelling and it can be potentially useful in the diagnosis and monitoring of response to therapy in patients of osteoporosis. We also concluded that hypovitaminosis D is very common in our clinical setup, thus underlining the importance of adequate calcium and vitamin D supplementation before starting bisphosphonates or any other specific treatment for osteoporosis.

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ORIGINAL ARTICLE

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A study on the clinical profile of stroke in relation to glycaemic status of patients

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Abstract

Objectives: The objectives of this study are to evaluate: (i) the type of stroke, (ii) the size of the stroke, and (iii) severity of stroke in relation to the glycaemic status of the patients and to establish a correlation between them, and to give a guideline for preventive and on-going therapy. This study showed that haemorrhagic lesions with bigger sizes are more common among those with higher glucose levels. These patients had a higher mortality rate. The increased incidence of stroke with increasing age is also related to the deteriorating glucose tolerance with age. The increased mortality rate of stroke patients in the newly diagnosed diabetics indicated the importance of early detection of diabetics and of the effect of treatment upon stroke outcomes in the diabetic patients and stress hyperglycaemia.

Key words: Euglycaemia, glycosylated haemoglobin (HbA_{1c}), haemorrhagic stroke, hyperglycaemia, infarction, stress hyperglycaemia.

Introduction

A stroke or cerebrovascular accident is defined as the abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus the definition of stroke is clinical and laboratory studies including brain imaging are used to support the diagnosis[1]. As reported by Frederic[2], 11.3% of cases of stroke gave history of diabetes when compared with 2% in the general population. The incidence of diabetes was found to be twice as high in patients admitted to hospital with any type of stroke than in patients with other neurologic diseases. The increased risk of stroke in diabetes and the increased prevalence rate of stroke in diabetes as compared to the general population was confirmed by a study done by Wolf *et al*[3]. Diabetics as well as patients with stress hyperglycaemia have severe stroke and these patients are associated with poor prognosis. The mortality rate from stroke in diabetics was twice that of the general population[4]. Glucose tolerance also deteriorates with age[5].

Multivariant studies also show that blood glucose is a significant predictor of death[6].

Diabetic macrovascular diseases including coronary heart diseases, stroke, and peripheral vascular diseases were common causes of morbidity and mortality among people with diabetes mellitus[7]. As reported by several studies, it was found that hyperglycaemia in non-diabetic patients after acute stroke is a stress response reflecting more severe neurological damage. However, it is also suggested that hyperglycaemia influences the outcome of stroke severity independently[8]. Hence, the present study has been designed to objectively assess the clinical profile of stroke in relation to the glycaemic status of the patients.

Increased blood glucose concentration at or around the time of a cerebral ischaemic event may worsen outcome; even mild hyperglycaemia (6.6 mmol/l) may result in increased brain damage and delayed recovery. Studies in rats showed that insulin improved the functional recovery from brain ischaemia, probably through its effects on glucose and lactate levels[8].

Materials and methods

The study was an institutional study at two centres. A total of 50 cases of stroke in the age of 30 - 75 years during the period from January 2011 up to December 2011 (eleven months) were included in the study at Jawaharlal Nehru Institute of Medical Sciences and Regional Institute of Medical Sciences, Imphal. CT scan was performed in all the cases within 3 days of onset of symptoms to confirm the diagnosis and to ascertain the type of stroke (ischaemic/haemorrhagic) and size of stroke (small, medium, or large). Small-sized stroke was defined as 5 mm in diameter and not visible in more than two adjacent slices; large-sized stroke as 10 mm in diameter or involving one complete vascular territory, medium-size stroke was in-between small and large.

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Inclusion criteria

All patients admitted within 72 hours after onset of stroke.

Exclusion criteria

1. The other causes that present with clinical features similar to stroke, i.e., subdural haematoma, epilepsy, sub-arachnoid haemorrhage.
2. Any prior neurological disability from previous stroke or other diseases.

Criteria for diagnosis of diabetes mellitus was done following the criteria of American Diabetes Association (ADA, 2011); symptoms of diabetes plus random blood concentration³ 200 ml/dl or fasting plasma glucose 126 ml/dl or HbA1c > 6.5% or two-hour plasma glucose³ 200 ml/dl during an oral glucose tolerance test.

The plasma venous glucose level was taken within 24 hours after admission for every patient. Glycosylated haemoglobin (HbA_{IC}) was done to ascertain whether it was stress diabetes or newly diagnosed diabetes.

The patient with a raised blood glucose on admission and normal HbA_{IC} level was considered as having stress hyperglycaemia.The patients were divided into 4 groups: euglycaemic patients with no history of diabetes having normal blood glucose and normal HbA_{IC} concentration; patients with stress hyperglycaemia (no history of diabetes with normal HbA_{IC} but raised blood sugar at admission); newly diagnosed diabetics (no history of diabetes, HbA_{IC} greater than normal); and lastly, known diabetic patients. Degree of glucose control as assessed by HbA_{1C} is stated in Table VI.

Results

Out of the 50 patients, 15 cases (30%) of stroke occurred in the age group of 51 - 60 years; another 13 cases (26%) occurred in the age group of 61 - 70 years (Table I). This shows that the commonest age group is in the age group 50 - 60 years as detected by our study.

Table I: Age-wise distribution of patients.

Age groups in years	No. of patients
Up to 40	2 (4%)
41 – 50	10 (20%)
51 – 60	23 (46%)
61 – 70	10 (2%)
Above 70	5 (10%)
Total cases	**50 (100%)**

There are 20 cases of stroke with euglycaemia, 30 cases of stroke with hyperglycaemia including stress hyperglycaemia, newly detected diabetes, and known diabetes. Out of these patients with hyperglycaemia, 14 cases (28%) occurred in known diabetes patients, 11 (22%) occurred in new diabetes patients, and 5 (10%) occurred in stress hyperglycaemia. This shows that stroke occurs mostly in known diabetics (Table II).

Table II: Classification of patients according to glycaemic status.

Glycaemic status	No. of cases	Percentage
Euglycaemic	20	40%
Stress hyperglycaemic	5	10%
New diabetic	11	22%
Known diabetic	14	28%
Total	**50**	**100%**

Seventy-five per cent of cases of strokes in the euglycemic goup presented as ischaemia (15 out of 20) and five cases in the same group occurred as haemorrhage (5 out of 15). All stress hyperglycaemic strokes were haemorrhagic (100%), and also all the strokes occurred in the new diabetic group were haemorrhagic strokes (100%). 85.71% of stroke in the known diabetic group were haemorrhagic strokes (12 out of 14). This shows that haemorrhagic strokes occurred in the hyperglycaemic patients, maximum being in the stress hyperglycaemia and new diabetics (Table III).

Table III: Types of stroke in different glycaemic states.

Glycaemic status	Ischaemia no. (%)	Haemorrhage no. (%)
Euglycaemic	15 (75%)	5 (25%)
Stress hyperglycaemic	0 (0%)	5 (100%)
New diabetic	0 (0%)	11 (100%)
Known diabetic	2 (14.28%)	12 (85.71%)
Total	**17**	**33**

Table IV shows the relation of the sizes of strokes and glycaemic status of the patients. Large-sized strokes (> 10 mm) occurred only in known diabetics (85.71%), new diabetics (100%), and stress hyperglycaemia (100%). Small-sized strokes (0 to 5 mm) occured only in euglycaemic patients (50%), medium-sized strokes (> 5 to 10 mm) occursed in euglycaemics (50%) and known diabetics (14.28%). This table shows that large-sized strokes (> 10 mm) are common only in hyperglycaemic patients, maximum (100%) being in hyperglcaemia and known diabetics.

Table III shows all the stress hyperglycaemic patients, newly detected diabetics, had large-sized haemorrhagic lesions > 10 mm diameter and 83.3% of the known diabetics had large-sized haemorrhagic lesions (> 10 mm diameter).The small-sized lesions (up to 5 mm diameter)

occurred in only euglycaemic patients (40%).

Medium-sized lesions (> 5 mm up to 10 mm) were present only in euglycaemics (40%) and 16.7% of known diabetics (Table IV).

The clinical outcome of the patients is shown in Table V. A poor clinical outcome was more in stress hyperglycaemics, newly detected diabetics, and known diabetics. All the stroke patients in the newly detected diabetic group expired (100% mortality rate) and 66.7% of all the known diabetics left hospital as their condition deteriorated. Thus, a positive correlation is ultimately established between type, size of stroke, and diabetic status.

Table IV: Size of lesions (by CT) at different glycaemic states.

Size of lesions (CT) at different glycaemic states						
Glycaemic states	**Small 0 - 5 mm**		**Medium > 5 - 10 mm**		**Large > 10 mm**	
Euglycaemic	10	50%	10	50%	Nil	Nil
Stress hyperglycaemic	0	0%	0	0%	5	100%
New diabetic	0	0%	0	0%	11	100%
Known diabetic	0	0%	2	14.28%	12	85.71%

Table V: Clinical outcome of patients.

Clinical outcome	Euglycaemic		Stress hyperglycaemic		Newly detected		Known diabetic	
Improvement	20	10%	3	60%	10	90.91%	10	42.85%
Death	0	0%	2	40%	1	9.09%	3	21.42%
Left hospital	6	30%	0	0%	0	0%	1	7.14%

Table VI: Glycosylated Hb (HbA_{IC}).

Interpretation of HbA_{IC} level	Degree of glucose control
> 10	Poor
9 - 10%	Fair
8 - 9%	Good
7 - 8%	Excellent
6 - 7%	Near-normal glycaemia
< 6%	Non-diabetic

Discussion

According to our study, there is a higher prevalence of diabetes in patients with acute stroke in the age group of 51 - 60 years, which is in agreement with some findings[9]. However, other studies found a maximum prevalence among the 41 - 50 years age group[6]. The majority of the strokes were ischaemic and were mainly in the euglycaemic patients.

The present study shows a high prevalence of known diabetics presenting with acute stroke (24%); the prevalence of stroke in known diabetics is 8.5%[10] and some other studies found it to be 17%[11].

The study also shows a high prevalence of newly diagnosed diabetics (18%) in patients presenting with acute stroke. As showed by some studies, the incident of stroke is 16% and 12% in known diabetics and newly diagnosed diabetics respectively[6]. These are in agreement with the observations in other series[6, 11]. Previous studies have found a range of prevalence of undiagnosed diabetes in acute stroke population from 6% to 42%[13].

This study revealed a higher mortality with stress hyperglycaemics and diabetic groups (Table V) which are consistent with other series as reported by some authors[14,15]. However, some other studies did not show any significant increase in diabetic stroke deaths in diabetics compared to non-diabetics[16].

Various pathophysiogical mechanisms have been described to explain the effects of blood sugar level on stroke, such as impaired auto-regulation of cerebral blood flow in diabetics[17]. Patients of stroke with hyperglycaemia are more prone to develop cerebral oedema[18]; patients with stroke and hyperglycaemia had higher lactate content in their ischaemic brain compared to normoglycaemics[19]. Hyperglycaemia is harmful to calcium recoverey during early recirculation period following focal cerebral ischaemia[20].

It was stated that there was increased adhesiveness of erythrocytes in diabetes with stroke[21]. This effect was found to be associated with increased activity of fibrinogen and non-enzymatic glycosylation haemolysis and a reduced red cell life span have been observed in a few patients with severe microangiopathy.

Recovery of cerebral ATP generation following cerebral ischaemia is impaired when the ischaemia occurs in the setting of hyperglycaemic patients, particularly above blood glucose level of 225 mg/dl[22].

In general, the brain has been considered as an insulin independent organ; moreover, insulin receptors have been identified in rat brain. Insulin also regulates ornithine decarboxylase activity, which regulates the synthesis of polyamines in the brain. Recently, insulin receptors have been found on the endothelium of cerebral microvessels, on platelets, and throughout the brain. Therefore, insulin may exercise beneficial effect on ischaemic stroke by enhancing the survival of neurons in the ischaemic zones[23].

Increased blood glucose concentration at or around the time of a brain ischaemic event may worsen outcome; even mild hyperglycaemia (125 mgm/dl) may result in

increased brain damage and delayed the recovery. Studies in rats showed that insulin improved functional recovery from brain ischaemia, probably through its effects on glucose and lactate levels, although there is no information on the benefit of this approach. It has one practical implication as stated by some studies[24]. Dextrose should not be provided to patients with acute ischaemic strokes. They indicated that moderate hyperglycaemia can exaggerate ischaemic brain damage by enhancing formation of lactic acid and impairment of normal phosphorous metabolism. However, hypoglycaemia should be avoided[25].

The main goal of fluid management in the acute phase of stroke is to establish and to maintain normovolaemia. Fluid depletion is best treated with isotonic saline or Ringer's solution. Except for the treatment of hypoglycaemia, no glucose-containing infusions should be used, in the early stroke patient. Fever also negatively influences outcomes after stroke. Lowering of elevated body temperature is strongly suggested[26].

Acute stroke, either ischaemic or haemorrhagic leads to a hypertensive reaction in the first hours and days after stroke. Anithypertensive drugs should be used only in rare exceptions in the early hours following acute ischaemic stroke, i.e., for hypertensive crisis or heart failure. Frequently it is suggested that in the early hours after stroke, arterial hypertension should only be treated if the diastolic blood pressure exceeds 120 mmHg. Drugs recommended for the treatment of such elevated hypertension vary from country to country. In essence, short-acting parenteral drugs that may be titrated over a venous line are to be used to control it best. Oral nifedipine is strongly discouraged[26].

Between 5 and 10% of patients develop enough cerebral oedema to cause obtundation or brain herniation. Oedema peaks on the second or third day but can cause mass effect up to the tenth day. Water restriction and intravenous mannitol may be used to raise the serum osmolality but hypovolumia should be avoided as this may contribute to hypotention and the worsening of infarction[1].

Neuroprotection is the concept of providing a treatment that prolongs brain's tolerance to ischaemia. Drugs that block the excitatory amino acid pathways have been shown to protect neurons and glia in animals, but despite multiple clinical trials they have not been proven to be beneficial in humans[1]. Serum glucose should be monitored and kept at 110 mg/dl using an insulin pump if necessary[27]. Blood pressure should be lower if there is malignant hypertension or myocardial ischaemia, or if blood pressure is > 185/110 mm of Hg and thrombolytic therapy is anticipated[27]. It is recommended to keep mean arterial pressure (MAP) < 130 mm of Hg in cases of cerebral haemorrhage unless an increased Intracranial pressure (ICP) is expected[28]. For patients with cerebral infarction who are not candidates for thrombolytic therapy, one recommended guideline is to initiate anti-hypertensive therapy only for patients with a systolic blood pressure > 220 mm Hg or a diastolic blood pressure > 130 mm Hg. In patients with haemorrhagic stroke the suggested guideline for initiating anti-hypertensive therapy are systolic blood pressure > 180 mm Hg or diastolic blood pressure > 130 mm Hg. Cautious reduction of blood pressure is indicated if mean arterial pressure is < 130 mm Hg[29].

Limitations of the study

1. Limited number of cases studied.
2. Exclusion of cases of stroke due to haematological disorders and intracerebral pathology existing from before.

Conclusion

Severity of stroke correlates with the glycaemic status of the patients in diabetics and non-diabetics. Hyperglycaemia in non-diabetic patients after acute stroke is a stress response reflecting more severe neurological damage. Management of hyperglycaemia in patients with diabetes and non-diabetes is an important aspect of the emergency management of stroke.

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"We shouldn't teach great books;
We should teach a love of reading."

– B. F. Skinner.

ORIGINAL ARTICLE

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Evaluation of upper gastrointestinal symptoms and effect of different modalities of treatment in patients of chronic kidney disease

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Abstract

Introduction: *Patients with chronic kidney disease (CKD) present with various clinical gastrointestinal (GI) symptoms and abnormalities in the GI tract. Studies on non-dialysed patients are very few and there is no Indian study to see the effect of yoga in these symptoms. This study was planned to evaluate upper GI symptoms in patients of CKD and evaluate the effects of haemodialysis, proton pump inhibitors (PPIs), and yoga on these symptoms.*

Material and methods: *The present study included 100 patients, of which 75 were patients of CKD with upper GI symptoms and 25 patients with upper GI symptoms without CKD served as controls. 75 cases of CKD were further subdivided into 3 groups – A, B, and C – to see effect of twice weekly haemodialysis, PPIs, and yoga, respectively at the end of 3 months. All cases were interviewed to obtain information regarding GI symptoms, and endoscopy was performed at the beginning and at the end of 3 months.*

Results: *In this prospective study, there were 66 males and 34 females. Nausea (93%), vomiting (57%), and anorexia (65%) were the most common symptoms; and erosive gastritis (21%) and hiatus hernia (15%) were the most common endoscopic findings in CKD patients. Effect of adequate haemodialysis caused reversal of both symptoms and endoscopic findings, whereas effect of PPIs and yoga had only symptomatic relief but no pathological change as the endoscopic findings remained unchanged due to continued presence of uraemic toxins.*

Conclusion: *Patients of chronic kidney disease frequently develop different GI symptoms and GI lesions. There was reversal of upper GI symptoms and endoscopic abnormality following adequate haemodialysis therapy. Persistence of endoscopic abnormality suggests that the improvement was not complete due to continued presence of uraemic toxins in non-dialysed patients.*

Key words: *Chronic kidney disease, haemodialysis, GI symptoms, GI endoscopy, proton pump inhibitors, yoga.*

Introduction

Patients of end-stage renal disease (ESRD) often suffer from co-morbidities like diabetes and cardiovascular diseases. The most common, non-renal, chronic disorders in patients with ESRD are GI disorders, necessitating the need to understand the GI disorders accompanying ESRD including those receiving renal replacement therapy. Some GI conditions are as a result of uraemia or the effects of renal replacement therapy or underlying disease or medications[1]. CKD is associated with several abnormalities in the gastrointestinal tract involving all its segments. The genesis of these complications is thought to be multifactorial. Most GI symptoms are readily reversed by haemodialysis[1]. However, with the advent of haemodialysis, the nature and distribution of disease appears to be changing, probably because these patients survive longer[2]. Patients with CKD on dialysis have a high consumption of proton pump inhibitors (PPIs)[3]. The effect of yoga on different diseases has been studied and its usefulness confirmed[4]. However, studies regarding effect of yoga in upper GI symptoms in CKD are lacking. Hence this study was planned to evaluate upper GI symptoms in CKD and to evaluate the effects of haemodialysis, proton pump inhibitors (PPIs), and yoga on these symptoms

Material and methods

The present study included 100 patients, of which 75 were patients of CKD with upper GI symptoms; and 25 with upper GI symptoms without CKD served as the control group. 75 cases of CKD were further subdivided into 3 groups – A, B, and C, as detailed below.

Group A consisted of 25 patients of CKD with upper GI symptoms. All these were regularly receiving twice a week haemodialysis and did not receive PPI for relief of symptoms. These patients continued to have GI symptoms despite haemodialysis. Group B consisted of 25 patients of CKD with upper GI symptoms and were given PPI (pantoprazole 40 mg once a day) for GI symptoms and none of them was receiving haemodialysis. Group C included 25 patients of CKD with upper GI symptoms. They received neither PPIs nor haemodialysis, but were advised to undertake yogic exercises. The yogic exercises

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were explained and demonstrated to these patients and training was provided by trained yoga teachers. All patients of this group were asked to do the selected yogic exercises daily in the morning. Group D included 25 patients with upper GI symptoms without CKD and they served as control group and were given symptomatic treatment according to symptoms including anti-emetics like domperidone for vomiting; antacids for heartburn; and appetisers for anorexia.

All patients were interviewed to obtain information regarding various gastrointestinal symptoms: Each symptom was scored according to its frequency and severity. Frequency was graded as 1 = occasional, 2 = frequent, and 3 = always or daily; and severity was graded as 1 = mild, 2 = moderate, and 3 = severe. The score for each symptom was obtained through summation of both frequency and severity scores. The dyspepsia score for each patient was the sum of the scores of all dyspeptic symptoms.

Upper gastrointestinal endoscopy was performed after overnight fasting using an Olympus endoscope. Pre-informed written consent was obtained from all patients before their inclusion into the study. All patients were regularly followed for a period of 3 months. Participants were evaluated at monthly intervals for upper GI symptoms, biochemical parameters, and upper GI endoscopy was done at the beginning and at the end of the study. At the end of the study, upper GI symptoms, endoscopic findings and effect of haemodialysis, PPIs and yoga on upper GI symptoms and endoscopic changes in patients of CKD were evaluated.

Stastistical analysis

Data was analysed using the Graphpad Instat V.3.0 software. Results are expressed as the mean ± SD. Differences in continuous variables were compared using a t-test or ANOVA, and differences in categorical variables were compared using a Chi-square test. P value less than 0.05 was considered statistically significant.

Results

In this prospective study of 100 patients (75 - CKD, 25 - control), males outnumbered females in all the groups. Nausea, vomiting, and anorexia were the most common symptoms in these patients. In group A, B, and C, nausea was present in 24 (96%), 23 (92%) and 23 (92%); vomiting in 20 (80%), 13 (52%) and 10 (40%); anorexia 21 (84%), 15 (60%) and 13 (52%); whereas in the control subjects heartburn 24 (96%) and nausea 19 (72%) were the most common symptoms (Table I). On analysis of upper GI symptoms, dyspeptic score was highest (10.20 ± 3.84) for group A followed by non-dialysed group B and C (8.36 ± 4.39), (7.48 ± 3.41), respectively (Fig. 1). It was least in group D (6.96 ± 3.97), showing group A had more symptomatics than groups B and C.

Table I: Baseline analysis of GI symptoms.

Symptoms	HD group A	PPIs group B	Yoga group C	Control group D
Nausea	24 (96%)	23 (92%)	23 (92%)	19 (72%)
Vomiting	20 (80%)	13 (52%)	10 (40%)	11 (44%)
Anorexia	21 (84%)	15 (60%)	13 (52%)	3 (12%)
Heartburn	8 (32%)	13 (52%)	9 (36%)	24 (96%)
Abd. distension	3 (12%)	4 (16%)	4 (16%)	2 (8%)
Abd. pain	1 (4%)	5 (20%)	3 (12%)	0
Haematemesis	1 (4%)	0	0	0
Dysphagia	1 (4%)	0	0	3 (12%)
Dyspepsia score	10.20 ± 3.84	8.36 ± 4.39	7.40 ± 3.47	6.96 ± 3.97

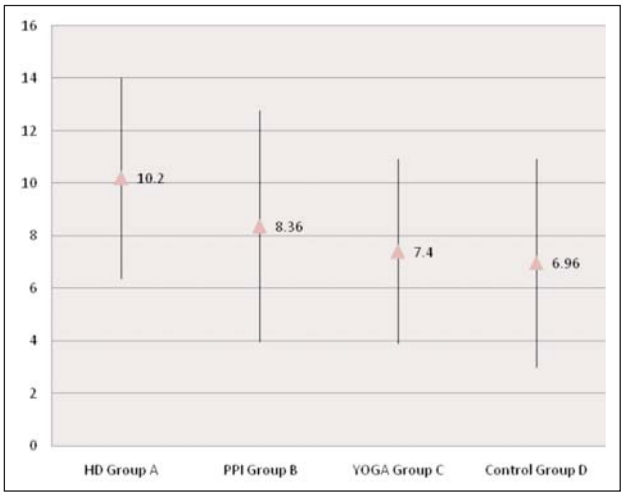

Fig. 1: *Baseline dyspepsia score in different groups.*

Table II: Baseline endoscopic findings.

Upper GI endoscopy	HD group A	PPIs group B	Yoga group C	Control group D
Normal	13 (52%)	17 (68%)	18 (72%)	19 (76%)
Abnormal	12 (48%)	8 (32%)	7 (28%)	6 (24%)
Erosive gastritis	8 (32%)	4 (16%)	4 (16%)	3 (12%)
Duodenitis	0	0	0	0
Oesophagitis	2 (8%)	1 (4%)	0	1 (4%)
Hiatus hernia	5 (20%)	3 (12%)	3 (12%)	3 (12%)
Gastroparesis	1 (4%)	1 (4%)	0	0
Peptic ulcer	0	0	0	0
Ca oesophagus	0	0	0	1 (4%)

Similarly, abnormal endoscopic findings were more common in dialysed group 12 (48%) followed by non-dialysed group B 8 (32%), group C 7 (28%) than control

group 6 (24%). Further, erosive gastritis 8 (32%) and hiatus hernia 5 (20%) were more common in the dialysed group than in the non-dialysed (group B and C), 4 (16%) had erosive gastritis, 3 (12%) had hiatus hernia in each group respectively, and were least in the control group. Peptic ulcer and duodenitis were not found in any group (Table II).

Analysis of symptoms and endoscopic findings after different therapies.

After 3 month of adequate haemodialysis there was a significant ($p < 0.05$) symptom frequency improvement in nausea (96% to 48%), vomiting (80% to 8%), and anorexia (84% to 44%), whereas heartburn improvement was not statistically significant ($p > 0.05$). Abdominal pain, abdominal distension, and dysphagia did not improve after haemodialysis in group A. In Group B after 3 months of pantoprazole medication, there was a significant ($p < 0.05$) symptom frequency improvement in nausea (92% to 48%), vomiting (52% to 20%), and heartburn (52% to 20%); whereas symptom frequency improvement in anorexia, abdominal distension, and abdominal pain was not statistically significant ($p > 0.05$). In group C there was statistically significant ($p < 0.05$) symptom improvement in nausea (92% to 64%); however symptom frequency improvement in vomiting, anorexia, heartburn, and abdominal distension was not statistically significant ($p > 0.05$). In control subjects, there was statistically significant ($p < 0.05$) improvement in vomiting and heart burn, whereas nausea, anorexia, and abdominal distension improvement was not statistically significant ($p>0.05$) (Table III, Fig. 2).

Therefore there was overall symptom frequency improvement more in the dialysed group as compared to others. Dyspeptic score decreased significantly for all the groups, but most for Group A (10.20 ± 3.84 to 3.08 ± 3.02) followed by B (8.36 ± 4.39 to 3.52 ± 3.75), C (7.40 ± 3.47 to 3.96 ± 3.04) and D (6.96 ± 3.73 to 3.16 ± 2.39) (Fig. 3).

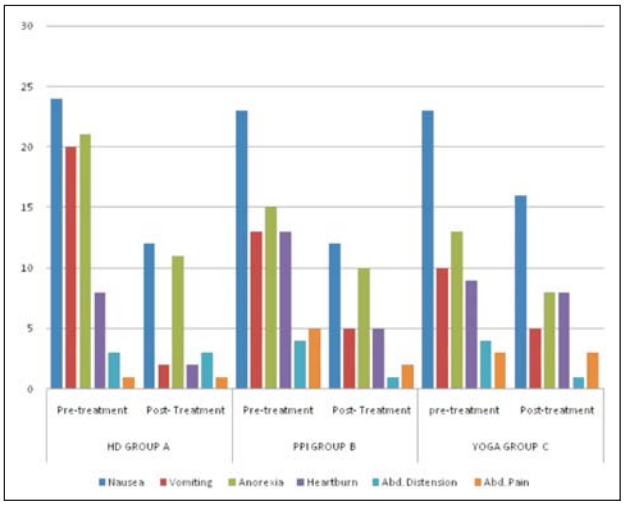

Fig. 2: *Pre- vs. post-treatment comparision of upper GI symptom frequency in different groups.*

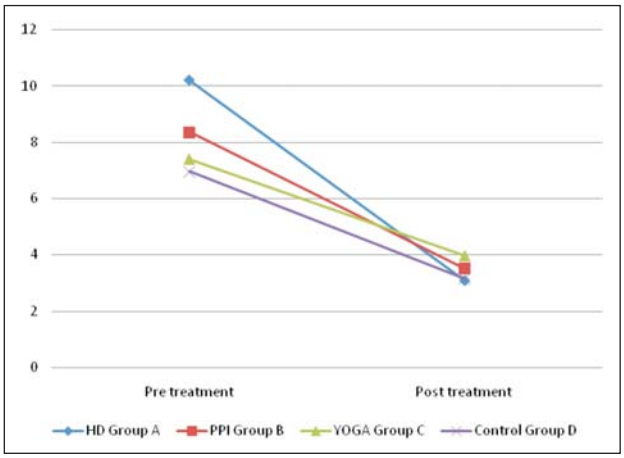

Fig.3: *Pre- vs. post-treatment comparision of dyspepsia score in different groups.*

In Group A, after 3 month of adequate haemodialysis, abnormal endoscopic findings decreased from 12 (48%) to 8 (32%), but this improvement was not statistically

Table III: Effect of different therapies on GI symptoms.

Symptoms	HD Group A			PPI Group B			Yoga Group C			Control Group D		
Therapy	Pre	Post	'p'	Pre	Post	'p'	Pre	Post	'p'	Pre	Post	'p'
Nausea	24	12	< 0.05	23	12	<0 .05	23	16	< 0.05	19	16	> 0.05
Vomiting	20	2	< 0.05	13	5	< 0.05	10	5	> 0.05	11	0	< 0.05
Anorexia	21	11	< 0.05	15	10	> 0.05	13	8	> 0.05	3	1	> 0.05
Heartburn	8	2	> 0.05	13	5	< 0.05	9	8	-	24	16	< 0.05
Abd. distension	3	3	-	4	1	< 0.05	4	1	> 0.05	2	0	> 0.05
Abd. pain	1	1	-	5	2	> 0.05	3	3	-	0	0	-
Haematemesis	1	0	-	0	0	-	0	0	-	0	0	-
Dysphagia	1	1	-	0	0	-	0	0	-	3	2	-
Dyspepsia score	10.2 ± 3.84	3.08 ± 3.02	< 0.05	8.36 ± 4.39	3.52 ± 3.75	< 0.05	7.40 ± 3.44	3.96 ± 3.04	< 0.05	6.96 ± 3.73	3.16 ± 2.39	< 0.05

For symptom frequency, data is represented as number: p = chi-square test; for dyspepsia score, data is represented as Mean^n ± S. D.: p = Paired student t test.

Table IV: Effect of different therapies on endoscopic findings.

Upper GI endocscopy	HD Group A			PPI Group B			Yoga Group C			Control Group D		
Therapy	**Pre-**	**Post-**	**'p'**	**Pre-**	**Post-**	**'p'**	**Pre-**	**Post-**	**'p'**	**Pre-**	**Post-**	**'p'**
Normal	13	17	> 0.05	17	18	> 0.05	18	20	> 0.05	19	20	> 0.05
Abnormal	12	8	> 0.05	8	7	> 0.05	7	5	> 0.05	6	5	> 0.05
Erosive gastritis	8	1	< 0.05	4	3	> 0.05	4	2	> 0.05	2	1	-
Duodenitis	0	0	-	0	0	-	0	0	-	0	0	-
Oesophagitis	2	1	-	1	0	> 0.05	0	0	-	1	1	-
Hiatus hernia	5	5	-	3	3	> 0.05	3	3	-	3	3	-
Gastroparesis	1	1	-	1	0	> 0.05	0	0	-	0	0	-
Peptic ulcer	0	0	-	0	0	-	0	0	-	0	0	-
Ca oesophagus	0	0	-	0	0	-	0	0	-	1	1	-

For endoscopic findings, data is represented as number: p = chi-square test.

significant (p > 0.05). Out of all gastrointestinal lesions, only erosive gastritis improved significantly as out of 8 cases only 1 patient had erosive gastritis (32% to4%) after 3 months of haemodialysis (p < 0.05). Oesophagitis decreased from 2 patients to 1 patient, and hiatus hernia and gastroparesis remained unchanged (Fig.4). In group B, abnormal endoscopic findings decreased from 8 (32%) to 7 (28%) (p > 0.05) which was insignificant. Out of all GI lesions, only erosive gastritis and gastroparesis had improved in one patient each. Similarly, in group C, abnormal endoscopic findings decreased insignificantly (p > 0.05) from 7 (28%) to 5 (20%). Out of all GI lesions, only erosive gastritis became normal in two patients which was statistically insignificant (p > 0.05). In control subjects none of upper GI lesions improved except in one patient erosive gastritis improved endoscopically following symptomatic therapy (Table IV).

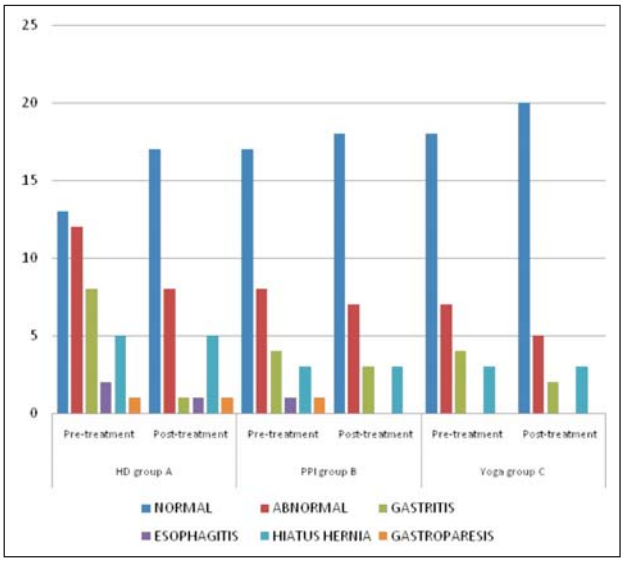

Fig. 4: *Pre- vs. post-treatment comparision of endoscopic findings in different groups.*

Discussion

Chronic renal disease is associated with several diseases, due to a multifactorial damage that leads to a loss in function of all systems of the organisms. Gastrointestinal alterations are very common in these patients leading to multiple symptoms and it is confirmed by endoscopy that shows a large range of pathological pictures. In the literature there are many studies of prevalence of GI symptoms and endoscopic findings, and different experiences and data have been documented. In this study, besides baseline evaluation of GI symptoms and endoscopic findings, effect of haemodialysis, PPIs and yoga on these symptoms, and endoscopic findings in both dialysed and non-dialysed patients of chronic renal disease was also studied.

In this study nausea, vomiting and anorexia were the most common symptoms in both dialysed and non-dialysed dyspeptic patients of CKD. Similar observations have been reported by Farasakh *et al* and Sivinovic *et al*[5,6]. Nausea, vomiting and anorexia symptom score was highest in the dialysed group, and followed by the non-dialysed group. Some of these symptomatology may be due to central effects of urea and other metabolic waste products which circulate in high concentrations in uraemic blood, as a part of dialysis disequilibrium syndrome, or as a manifestation of volume depletion explaining frequency higher in dialysed than non-dialysed[1].

In this study, erosive gastritis (32%) was the most common lesion followed by hiatus hernia (20%) in dialysed group. Whereas in non-dialysed group, 16% had erosive gastritis and 12% had hiatus hernia. Numerous studies have reported erosive gastritis and hiatus hernia are common in CK[5,6]. Elevated gastrin levels, *H. pylori* infection and toxic effect of urea and other toxic molecules on gastric mucosa are thought to be responsible for erosive gastritis. Potential causes for hiatus hernia in these cases may include protein malnutrition with defective collagen

synthesis, or altered muscle tone. Interestingly, despite the high incidence of hiatus hernia, oesophagitis was less common in these subjects, probably as a result of routine prescription of calcium carbonate[5]. No case of peptic ulcer was found in this study. Similarly, in two prospective studies, Morgalis *et al* and a recent study from Chennai on dialysis patients, did not find any case of peptic ulcer[7,8]. The high incidence of gastrointestinal symptoms in patients with renal failure may be induced by gastroparesis[9,10]. In this study, 2 patients had gastroparesis. Several studies have examined the duration of gastric emptying in patients with renal failure and have yielded conflicting results[11-13].

In this study, after 3 months of adequate haemodialysis, there was significant symptom frequency improvement in symptoms of nausea, vomiting and anorexia, because regular and adequate haemodialysis removed uraemic toxic molecules responsible for these symptoms but these symptoms may recur if dialysis becomes inadequate[14]. Furthermore, therapy with 3 months of pantoprazole showed there was a symptom frequency improvement in nausea, vomiting, and heartburn. In CKD patients there is gastric acid hypersecretion due to elevated gastrin level due to reduced renal clearance, the psychological stress of illness and haemodialysis, an increase in proton back-diffusion caused by high urea levels responsible for these symptoms. PPIs act irreversively on proton pump to reduce gastric acid secretion resulting in symptom improvement. In the yoga group, there was significant symptom improvement only in nausea, whereas symptom frequency improvement in vomiting, anorexia, heartburn, and abdominal distension was less. Effect of yoga has been studied in number of diseases affecting almost every system in the body[15]. The various effects of yoga in gastrointestinal symptoms may be through massage of internal organs, improved glandular function, decreased acid production, mental control and calm. The practice of yoga causes a shift of autonomic balance towards parasympathetic dominance with lowering of sympathetic activity resulting in decreased gastric acid production and mental control and calm[16]. Besides that, yoga decreases uropepsin levels resulting in decreased gastric acid production[17]. Therefore, there was overall symptom frequency improvement – more in the haemodialysis group as compared to others – indicating that after regular and adequate haemodialysis, symptom frequency decreased efficiently more than PPIs and yoga group because haemodialysis affects the main pathophysiological mechanism (uraemic toxins) responsible for GI symptoms in CKD whereas PPIs and yoga affect associated factors responsible for GI symptoms in CKD which includes hypergastrinaemia, increased gastric acid secretion, psychological factors, and stress. Dyspeptic score decreased significantly for all the groups including control subjects indicating different therapies useful in CKD patients, but most useful was adequate haemodialysis. Patients on good haemodialysis or those with functioning allograft experience a return of appetite and disappearance of nausea and vomiting.

Observations on endoscopic findings on these dyspeptic patients after different treatments had shown that there was insignificant improvement in endoscopic findings in all the groups except erosive gastritis in the haemodialysing group become normal significantly because adequate haemodialysis removes uraemic toxins, elevated gastrin levels due to reduced renal clearance and an increase in proton back-diffusion caused by high urea levels were responsible for gastric mucosal changes in CKD. It indicates that after 3 month of different therapies, PPIs and yoga had effect symptomatically but not mucosal changes of GI tract, whereas haemodialysis proved to be more effective symptomatically than other therapies, and also gastric mucosal changes become normal after 3 month of regular and adequate haemodialysis, but other endoscopic findings remain as such.

Conclusion

Patients of CKD frequently develop different GI symptoms and GI lesions. Endoscopic examination is a useful investigation in diagnosis of gastric mucosal lesions. There was reversal of upper GI symptoms and endoscopic abnormality following adequate haemodialysis therapy which would suggest that these symptoms were due to the presence of uraemic toxins. Yoga and PPIs group also showed significant symptom improvement; however, persistence of endoscopic abnormality in these cases would suggest that the improvement was not complete due to continued presence of uraemic toxins in non-dialysed patients. In the yoga group, the symptom improvement response was most likely to be subjective and symptomatic rather than pathological.

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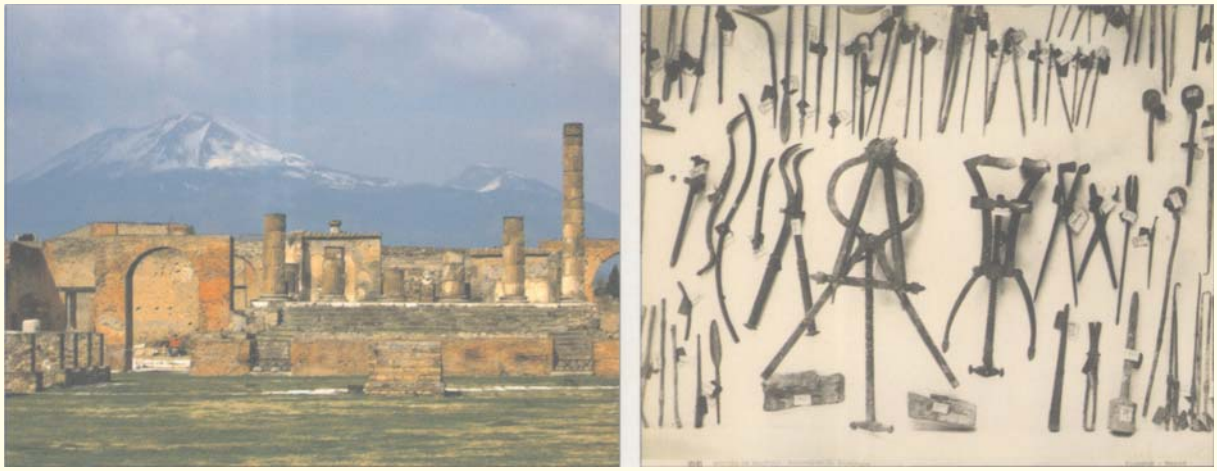

Medical Tools Of Antiquity
Pompeii 2000 Years Ago

When Pompeii (Italy) came under Roman rule over 2000 years ago, it was a town of great prosperity. It soon became an attractive location for wealthy Roman families to settle. In 79 A.D. (August 24 and 25) the booming city with a population of 25,000 was cut short by a sudden and terrible volcanic eruption of Mount Vesuvius. In a span of forty-two hours, Pompeii's streets, market places, homes, and public buildings were completely buried beneath a 23-foot layer of volcanic ash. The rediscovery of Pompeii that began in the eighteenth century has brought to limelight a lifestyle and culture that flourished in the ancient Roman world. Among the ruins of Pompeii are a range of surgical and medical tools. These were found in the remains of their original carrying cases. In one of the villas, medical tools including scalpels, probes, and gynaecological instruments were discovered. There were also pestles and mortars which would have been used to prepare drug treatments. Plaster cast models of the spaces left by roots in Pompeiian gardens have shown that many potentially beneficial herbs were commonplace. The level of medical care in the region is also demonstrated by the fact that some of the bodies found in the debris had well-set fractures.

(Courtesy: Journal of the Science of Healing Outcomes; Vol. 6, No. 22)

ORIGINAL ARTICLE

JIACM 2014; 15(3-4): 188-91

Trends in blood pressure with increasing plasma homocysteine levels

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Abstract

Background: It has been predicted that by 2020 there would be a 111% increase in cardiovascular deaths in India due to hypertension resulting in cardiovascular diseases (CVD). Mild elevations in serum homocysteine may contribute to elevations in blood pressure which may be one of the important causes for CVD.

Aim of study: Controversy remains as to whether the relation between homocysteine and CVD is causal or not? Our study comprises the relationship of homocysteine with blood pressure.

Methodology: Our study consists of 40 subjects diagnosed as hypertensive for the first time and 20 controls with normal blood pressure taken randomly from the OPD of Sunderlal Hospital, B.H.U., Varanasi, U.P. Most of the patients of both sexes were from Eastern Uttar Pradesh (Varanasi) and from Bihar. They were in the range of 25 to 60 years of age. Levels of homocysteine were measured in plasma by ELISA technique and blood pressure along with clinical history was observed separately for all subjects.

Results: It was observed that homocysteine was significantly elevated in hypertensive patients as compared to controls with p<0.001. It also bears a high degree of correlation with systolic blood pressure. It was also observed that the sex along with age and lifestyle plays a very important role for our study.

Conclusion: This study shows that homocysteine is significantly elevated in patients of hypertension and concludes that in every CVD patient, homocysteine plays a very important role.

Key words: BP, homocysteine levels.

Introduction

Essential hypertension, like obesity and diabetes, is one of the 'diseases of modern civilisation' that results from the collision of a modern lifestyle with palaeolithic genes. Cardiovascular diseases account for a large proportion of all deaths and disability worldwide. It has been predicted that by 2020 there would be a 111% increase in cardiovascular deaths in developing countries like India. Hypertension is a major cardiovascular risk factor and important public health problem in the Indian subcontinent and among the south Asians world-wide.

Blood pressure (BP) is directly associated with risks of several types of cardiovascular disease, and the associations of blood pressure with disease risk are continuous[1]. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart deaths. This fact is important because hypertension is a controllable disease[1-3].

High blood pressure is a major risk factor for cardiovascular disease. Although its aetiology has not been fully elucidated mostly because of as yet unknown genetic variation, multiple non-hereditary factors including dietary and other lifestyle factors have been identified that have important and modifiable influences on blood pressure.

Recent studies suggest that mild elevations in plasma homocysteine may contribute to elevations in blood pressure[4,5]. Although controversy remains as to whether the relation between homocysteine and cardiovascular disease is causal or not, the association of homocysteine with blood pressure deserves attention because blood pressure may mediate part of the cardiotoxic effect of homocysteine. The correlation has also been found to be significant in specific age groups like 'small for gestational age' babies[6-9].

Homocysteine is a sulfur-containing, non-proteinogenic amino acid biosynthesised from methionine that takes a key place between the folate and activated methyl cycles. It is present in plasma in four forms: a free thiol (1%); disulfide (5 - 10%); mixed disulfide (5 - 10%) and protein-bound thiol groups (80 - 90%). The combined pool of all four forms of homocysteine is referred to as "total plasma homocysteine"[10]. The total homocysteine level in plasma has been reported to be in the range of 5 - 15 micromoles/litre in healthy individuals[11]. A causal link between homocysteine and blood pressure is supported by experimental studies. In cell culture studies, homocysteine-induced oxidative stress to endothelium and reduced available nitric oxide (NO). Homocysteine may elevate blood pressure through multiple mechanisms, including its effect on vascular endothelial integrity.

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The vascular risk associated with hyperhomocysteinaemia has been observed to be stronger in hypertensive individuals. More recently, attention has been focussed on the direct relations of plasma homocysteine to blood pressure and hypertension because of the suggestion that the adverse risk associated with hyperhomocysteinaemia might be mediated in part by the positive association of homocysteine with hypertension[12].

As these biochemical agents have strong implications in the causation and pathogenesis of hypertension, we estimated the levels of homocysteine in hypertensive individuals who were otherwise free from any other underlying disease, as well as in normotensive individuals, and to see if any correlation does exist in our context.

Material and methods

The present study was carried out in the Department of Biochemistry, Institute of Medical Sciences, B.H.U., Varanasi, U.P.

Selection of patients and controls

The study included 40 patients of essential hypertension, and age and sex matched 20 healthy control subjects. Diagnosis of the patients with essential hypertension was done on the basis of history and clinical examination. BP was measured by standard protocol given by JNC VII. They were newly diagnosed hypertensives and were not on antihypertensive medication and had not taken any medicines for at least a week. Before selecting the patients it was ensured that they were not suffering from any other underlying disorder like renal or hepatic disease.

All control subjects selected for the study were healthy, non-diabetic, normotensive, and showed no evidence of any acute or chronic infection. All the healthy subjects ensured that they had not taken any type of medication for at least a week.

Estimation of homocysteine

Fasting blood was collected from the patients and also from healthy subjects. All subjects gave their informed consent. Plasma was separated using EDTA coated tubes. The estimation of homocysteine was done by homocysteine microtitre plate assay method. It is an EIA-assay for the determination of tHcy in blood. The assay employs a genetically engineered Homocysteine Binding Protein (HBP) as the capturing agent (Diazyme laboratories). Plasma samples are pretreated in vials with a reducing agent, TCEP, to reduce the protein bound Hcy that is subsequently converted to S-adenosyl-L-homocysteine (SAH) by SAH hydrolase and quantiated by the HBP in a competition assay between free SAH from samples and tracer SAH-HRP conjugate.

The sample size and mean was calculated by using Jandel Sigma Stat Statistical software version 2.

Results

Table I shows that the mean homocysteine level in hypertensive patients was found to be 38.340 ± 0.2411 µmol/l while that in controls was 7.360 ± 0.224 µmol/l. The range of homocysteine in cases was 21.1 µmol/l to 61.8 µmol/l while that in controls was 6.3 µmol/l to 10.1 µmol/l. This indicates that plasma homocysteine was significantly elevated in hypertensives. The range of homocysteine in the plasma of male controls was 6.3 µmol/l to 10.1 µmol/l while that in female controls it was 6.4 µmol/l to 7.9 µmol/l. It has been found that 55% of the patients were in the age group of 37 - 59 years, 37.5% were between 60 - 74 years and the remaining 7.5% were aged above 75. Among 60 subjects, 35 patients (70%) were male and 25 patients (30%) were female. In the control group, there were 12 males and 8 females whereas the test group consisted of 30 males and 10 females.

Mean systolic blood pressure in cases was 160 while that in controls was 124. Mean diastolic blood pressure in cases was 94 and that in controls was 82. Family history was found to be very significant in this study as it was found that 20 patients in the test group gave a history of hypertension in their first order blood relations. So family history in 50% patients again supports the familial predisposition of the disease.

On the contrary, only 5 patients in the control group (25%) gave a history of hypertension in their first-order relations.

In the history of addiction, it was found that tobacco chewing is more common than smoking in this population. 24 patients gave history of tobacco chewing whereas 13 patients were smokers and only 3 patients were alcoholic.

Though cardiologists always advise regular exercises/ morning walk, in our study group only 17 males were found to follow the advice. In females, the picture is much worse where only 4 patients were doing exercises and others thought that their daily household activity was sufficient for their health.

To calculate the number of overweight patients, both the WHO and Asia Pacific guidelines were followed.

According to the WHO classification (1997), 45% patients of the study group were found to be having BMI > 25 and classified as overweight. Among them, 33.33% patients are pre-obese, 8.33% are in Obese Class I and 3.33% are in Obese Class II.

Table I: Correlation between homocysteine and blood pressure.

S. No.	Groups	Homocysteine		SBP (a)		DBP (b)			'r'	á	r^2	C.I.
		Mean ± SEM	SD	Mean ± SEM	SD	Mean ± SEM	SD					
1	Case	38.340 ± 2.411	15.2	160 ± 2.067	13.071	93.90 ± 1.04	6.5	a	0.6741	0.05	0.4544	0.4589 – 0.8146
								b	0.3309	0.05	0.1095	0.2153 – 0.5824
2	Control	7.360 ± 0.224	1.00	124 ± 1.841	8.233	82.40 ± 1.404	6.2	a	0.6515	0.05	0.4244	0.2935 – 0.8492
								b	0.5210	0.05	0.2714	0.1019 – 0.7830
3	Case (m)	36.387 ± 2.748	15.0	158.2 ± 2.113	11.571	93.2 ± 1.285	7.0	a	0.7082	0.05	0.5015	0.4670 – 0.8513
								b	0.2281	N.S.	0.05247	(-) 0.1431 – 0.5445
4	Case (f)	44.2 ± 4.766	10.0	165.8 ± 5.107	16.151	96 ± 1.461	4.6	a	0.5564	N.S.	0.3096	(-) 0.1128 – 0.8784
								b	0.6812	0.05	0.4641	0.09018 – 0.9174
5	Control (m)	7.5338 ± 0.346	1.1	123.00 ± 2.714	9.4	82.667 ± 1.831	6.3	a	0.7432	0.05	0.5523	0.2950 – 0.9233
								b	0.4541	N.S.	0.2062	(-) 0.1622 – 0.8155
6	Control (f)	7.10 ± 0.209	0.5	125.5 ± 2.26	6.392	82.00 ± 2.33	6.5	a	0.5830	N.S.	0.3398	(-) 0.2068 – 0.9127
								b	0.8445	0.05	0.7132	0.3451 – 0.9712

According to the Asia Pacific Guidelines 2000, 70% patients were found to be overweight. Among them, 25% patients are pre-obese, 33.33% are in Obese Class I and 11.67% are in Obese Class.

In this study group, BMI has been found to have a significant ($p < 0.05$) positive correlation with both systolic and diastolic blood pressure (Table II).

Table II: Correlations of BMI.

Correlation between	Co-efficient of correlation (r)
BMI and systolic blood pressure	0.524*
BMI and diastolic blood pressure	0.413*

The above finding has been also supported by the following scatter diagrams where the trend lines shows increase in blood pressure with increase in BMI (Figures 1 and 2).

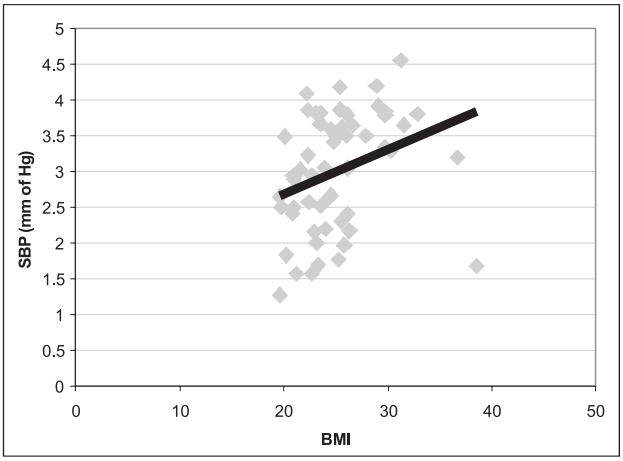

Fig. 1: *1 BMI vs SBP.*

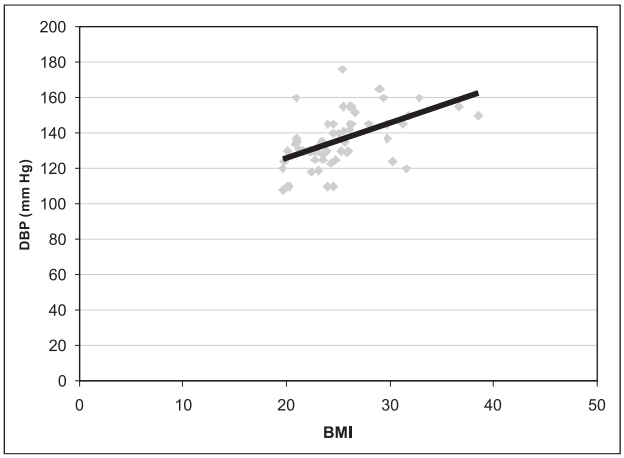

Fig. 2: *BMI vs DBP.*

In our study group, waist circumference has been found to have a significant ($p < 0.05$) positive correlation with both systolic and diastolic blood pressure (Table III).

Table III: Correlations of waist circumference.

Correlation between	Co-efficient of correlation (r)
Waist circumference and SBP	0.345*
Waist circumference and DBP	0.334*

Discussion

BP is directly associated with risks of several types of cardiovascular diseases, and the associations of blood pressure with disease risk are continuous, indicating that large proportions of most populations have non-optimal BP values[1]. More recently, attention has been focussed on the direct relations of plasma homocysteine to blood

pressure and hypertension because of the suggestion that the adverse risk associated with hyperhomocysteinaemia might be mediated in part by the positive association of homocysteine with hypertension. In the third National Health and Nutrition Examination Survey (NHANES III), persons in the highest quintile of plasma homocysteine had a 2- to 3-fold increased prevalence of hypertension relative to those in the lowest quintile[4]. These observations have been confirmed in other cross-sectional reports and in experimental studies[13,14]. Additionally, a potential causal role for homocysteine in the pathogenesis of elevated blood pressure is raised by the demonstration that homocysteine-lowering treatment is associated with a reduction in systolic and diastolic blood pressures[15]. Thus, a considerable body of evidence suggests a role for plasma homocysteine in the pathogenesis of hypertension[16].

The findings of this study indicate the importance of measuring homocysteine levels and using homocysteine lowering treatment to decrease cardiovascular risks.

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"Happiness is to be found in sources deeper than man-made things."

– LAWRENCE OF ARABIA.

ORIGINAL ARTICLE

JIACM 2014; 15(3-4): 192-5

A study of lipid profile levels in diabetics and non-diabetics taking TC/HDL ratio and LDL/HDL ratio into consideration

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Abstract

Objective: The aim of our study was to evaluate changes in lipid profile levels in diabetic and non-diabetic males and females with special emphasis on the role of TC/HDL ratio and LDL/HDL ratio in assessing the cardiovascular risk.

Study design: A hospital-based cross-sectional study was conducted on patients attending the out-patient department of medicine of MMC, Muzaffarnagar (U.P.), during a period of 8 months from April 2012 to Nov 2012. 500 patients (250 males and 250 females) in the age group 25-75 yrs were selected randomly for the study. Of the 250 males and 250 females, 125 were diabetic (blood sugar more than 110 mg/dl) and 125 were non-diabetic. All the participants underwent a biochemical analysis of fasting blood sugar, lipid profile (total cholesterol, triglyceride and HDL cholesterol). LDL and VLDL were calculated according to computational procedures. Ratios of TC/HDL and LDL/HDL were also calculated to assess the cardiovascular risk.

Methodology: Biochemical and statistical analysis was done on all the selected 500 pts (250 males and 250 females). FBS was estimated using glucose oxidase method. TC and HDL cholesterol were determined by an analytical method based on the sequence of reactions described by Fossati et al.

Statistical analysis of each parameter was done and values were expressed as mean ± S.D. ± S.E. Comparisons of male and female diabetics were made with their non-diabetic counterparts. TC/HDL and LDL/HDL ratios were calculated to assess the cardiovascular risk factors.

Results: The mean values of fasting blood sugar, total cholesterol, triglyceride and LDL cholesterol for diabetic males and females were higher than their non-diabetic counterparts, and HDL cholesterol values were found to be lower than the non-diabetics. Even the TC/HDL ratio and LDL/ HDL ratios were found to be much higher in diabetics than non-diabetics in both males and females.

Key words: Diabetes, cholesterol, HDL and LDL cholesetrol, triglyceride.

Introduction

Diabetes mellitus arises when insufficient Insulin is produced or when the available insulin does not function correctly. With the deficiency of insulin, the amount of glucose in the bloodstream is abnormally high, causing unquenchable thirst and frequent urination. The body's inability to store or use glucose causes hunger and weight loss[1].

There are 2 main types of diabetes – IDDM (type I diabetes) and NIDDM (type II diabetes) occurs due to lack of insulin since destruction of beta cells of Langerhans. Type II diabetes occurs when the body does not produce enough insulin and the insulin that is produced becomes less effective, occurs in people over the age of 40. 90% diabetes are non-insulin dependent[2].

According to the International Diabetes Federation Diabetes Atlas, it is estimated that 194 million people had diabetes in the year 2003 and about 2/3rd of the people lived in developing countries[3].

Type II diabetes mellitus is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities that are all recognised as predictors for coronary heart disease, including reduced plasma levels of HDL and elevated plasma levels of TG[4]. It is also associated with an elevation of total cholesterol, VLDL cholesterol, and LDL cholesterol[5].

The underlying pathophysiology of type II DM is mainly insulin resistance[6]. Triglyceridaemia has been associated with the risk of coronary heart disease both in type II diabetic and non-diabetic subjects[7,8]. LDL cholesterol is related to lifestyle factors such as diet and exercise[9].

In India diabetes is no more an epidemic. Infact, it has turned into a pandemic according to the *International Journal of diabetes in Developing Countries*, which labelled India the diabetes capital of the world. The International Diabetes Federation estimates that the number of diabetic patients in India has doubled from 19 million in 1995 to 40.9 million in 2007 and it is projected to increase to 69.9 million by 2025.

Lipid abnormalities are commonly found in persons with

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DM. Besides, Indian population is at a high risk for DM and its complications. Keeping in mind the increased incidence and the risk factors of diabetes mellitus together with paucity of recent literature, we thought of conducting this study.

Material and methods

A hospital-based cross-sectional study was conducted on patients attending the out-patient department of medicine, MMC, Muzaffarnagar (UP), during a period of 8 months from April 2012 to Nov 2012. 500 patients (250 males and 250 females) in the age group 25 - 75 years were selected randomly. Exclusion criteria was age less than 25 years or more than 75 years. Of the 250 males and 250 females, 125 were diabetic (blood sugar more than 110 mg/dl) and 125 were nondiabetic in each class.

All the subjects underwent a biochemical analysis of Fasting blood sugar, lipid profile (total cholesterol, HDL cholesterol and triglycerides). Serum LDL cholesterol was calculated according to the computational procedures of Friedwald *et al*[10]. Ratios of TC/HDL and LDL/HDL were also calculated to assess the cardiovascular risk factors. Fasting blood sugar was estimated using glucose oxidase method[11]. Total cholesterol and HDL cholesterol were determined by enzymatic methods[12,13], TG was estimated by an analytical method based on the sequence of reactions described by Fossati *et al*[14].

Computerised statistical analysis was done using SPS 11 software, and values were expressed as mean + SD + SE. Values of male and female diabetics were compared with their non-diabetic counterparts.

Results

A total number of 500 subjects (250 males, 250 females) in the age group 25 - 75 years were selected randomly. Of the 250 males and 250 females, 125 each were diabetic with fasting blood sugar more than 110 mg/dl and 125 each were having normal FBS levels. Patients below 25 yrs and above 75 yrs were not included in this study.

The mean values of FBS for diabetic males and females were (175 ± 66.97 ± 13.39 mg/dl) and (174.56 ± 63.11 ± 12.6 mg/dl) respectively which were quite high as compared to no-ndiabetic males (88.2 ± 11.43 ± 2.29 mg/dl) and non-diabetic females (89.28 ± 12.74 ± 2.55 mg/dl).

All the diabetic subjects both male and females had higher cholesterol, TG, and LDL cholesterol values as compared with their non-diabetic counterparts. The mean values of serum total cholesterol, TG, HDL cholesterol and TC/HDL and LDL/HDL ratios for diabetic males and females and normal non-diabetic males and females are tabulated in Table I and II and depicted graphically in Fig. 1 and 2.

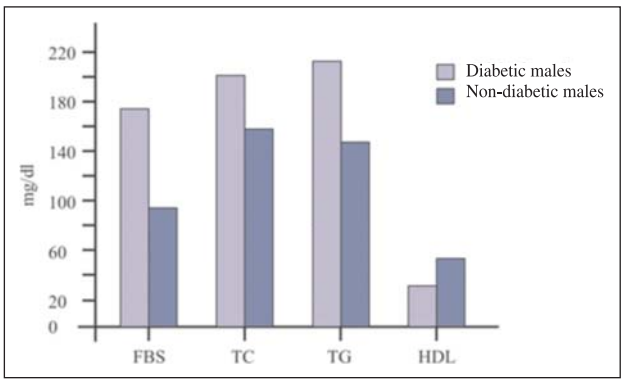

Fig : 1: *Dyslipidaemia in diabetic and non-diabetic males.*

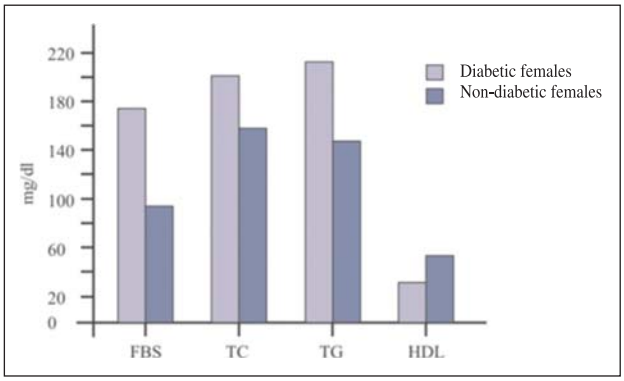

Fig : 2: *Dyslipidaemia in diabetic and non-diabetic females.*

The TC/HDL ratio for diabetic males was 6.3 and for diabetic females was 6.2, which was much higher as compared with non-diabetic males (3.5) and non-diabetic females (3.2). The LDL/HDL ratio for diabetic males and females were 4.0 and 3.9 respectively, which was again higher than the non-diabetic males and females - 2.5 and 1.6 respectively. The raised indices of TC/HDL and LDL/HDL prove that hyperglycaemia is responsible for the dyslipidaemia and that diabetics, both males and females, have a higher degree of atherosclerotic burden.

Table I:

	Diabetic males Mean ± SD ± SE	**Non-diabetic males Mean ± SD ± SE**
Fasting blood sugar (mg/dl)	175 ± 66.97 ± 13.39	88.2 ± 11.43 ± 2.29
Total cholesterol (mg/dl)	202.2 ± 45.56 ± 9.11	157.92 ± 21.71 ± 4.34
Triglyceride (mg/dl)	210 ± 75.27 ± 15.05	148.24 ± 37.16 ± 7.43
HDL cholesterol (mg/dl)	31.68 ± 7.78 ± 1.56	48.08 ± 7.97 ± 1.6
TC/HDL ratio	6.3 ± 2.45 ± 0.49	3.3 ± 0.65 ± 0.13
LDL/HDL ratio	4.0 ± 1.96 ± 0.39	1.75 ± 0.44 ± 0.09

Table II:

	Diabetic females Mean ± SD ± SE	Non-diabetic females Mean ± SD ± SE
Fasting blood sugar (mg/dl)	174.56 ± 63.11 ± 12.6	89.28 ± 12.74 ± 2.55
Total cholesterol (mg/dl)	214.36± 84.52 ± 16.9	161.44 ± 21.9 ± 4.38
Triglyceride (mg/dl)	211.6 ± 106.16 ± 21.23	150.52 ± 30.18 ± 6.04
HDL cholesterol (mg/dl)	38.72 ± 10.74 ± 2.14	49.88 ± 8.63 ± 1.72
TC/HDL ratio	6.2 ± 4.32 ± 0.86	3.2 ± 0.45 ± 0.09
LDL/HDL ratio	3.9 ± 3.45 ± 0.69	1.6 ± 0.34 ± 0.07

Discussion

The study revealed that lipid profile and lipoprotein profiles of type II diabetics were elevated as compared to their non-diabetic counterparts. The results also revealed an increase in TC/HDL ratio and LDL/HDL ratio in both diabetic males and females when compared with males and females having normal fasting blood sugar levels. We also conclude that TC/HDL ratio and LDL/HDL ratio are more specific and accurate indices for assessing coronary artery disease than considering only TC, TG, HDL, and LDL levels alone.

Many studies have shown altered lipid profile in diabetes mellitus[15] and it has been further shown that the dyslipidaemia predisposes the diabetic patients to cardiovascular complications, specially coronary heart disease[16-18].

HDL acts by enhancing the removal of cholesterol from the peripheral tissues and so reduces the body's cholesterol pool. Type II diabetes mellitus was usually associated with low plasma levels of HDL cholesterol. Low HDL concentrations are often accompanied by TG levels as seen in this study and this combination has been strongly associated with an increased risk of CHD[19].

The relative insulin deficiency that occurs in type II diabetes mellitus impairs the action of lipoprotein lipase and results in lower HDL cholesterol levels and higher TG levels, which may improve with improved glycaemic control[20].

Results of prospective studies also suggest that a high LDL/HDL ratio combined with hypertriglyceridaemia is associated with highest CHD risk. This dyslipidaemic state (lipid triad) has been described as atherogenic dyslipidaemia[21]. This approach could be further simplified by using TC/HDL and LDL/HDL ratios as markers of CHD. The TC/HDL ratio is a specific and sensitive index of cardiovascular risk and predictor of CHD especially with values above 6. Because of this overwhelming evidence that an elevated LDL concentration in plasma is atherogenic, whereas a high HDL level is cardioprotective[22,23], the measurement and interpretation of LDL and HDL levels is emphasised in the US National Cholesterol Education Programme Guidelines. According to these guidelines, LDL concentration should be considered primary therapeutic target, whereas HDL levels may also be critical in the assessment of CHD risk.

Conclusion

We conclude that dyslipidaemias and DM go hand in hand, so all type II diabetic patients should undergo lipid profile as a routine test. Since prevention is always better than cure, all persons with impaired glucose tolerance should switch over to a healthy lifestyle and diet, exercise regularly, avoid sedentary habits, increase fibre intake, and get regular check-ups of FBS and lipid profile to reduce the risk of coronary artery disease.

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INSTRUCTIONS TO AUTHORS

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REVIEW ARTICLE

JIACM 2014; 15(3-4): 196-8

Nephrogenic systemic fibrosis

Jashan Sandhu, JS Sandhu***

Abstract

Nephrogenic systemic fibrosis is a systemic fibrosing disease that occurs in patients with chronic kidney disease and acute renal failure and is linked to the administration of gadolinium-based contrast. Predominantly there is progressive hardening of the skin of the extremities. Systemic involvement also has been described. The disease is progressive and may lead to disabling joint contractures. Prevention plays the major role as therapeutic options are limited and mostly ineffective. Reversal of renal function to normal is the only effective modality.

Key words: Gadolinium, renal failure, magnetic resonance imaging.

Introduction

Since its first description by Cowper *et al* in 2000 as a scleromyxoedema-like illness in 14 patients on chronic haemodialysis[1], more than 500 cases have been reported in literature. Although NSF is possibly under-recognised and under-reported, its incidence is on a decline[2]. Because of the prominent cutaneous involvement, initially it was described as nephrogenic fibrosing dermatitis. However in view of subsequent evidence of systemic involvement of the heart, lung, diaphragm, skeletal muscle, and other organs with fibrosing disease, the disease is termed as nephrogenic systemic fibrosis (NSF)[3,4].

Clinical features

There is no predilection for a geographic region, race, or gender. Nephrogenic systemic fibrosis has been reported in all age groups in those with renal failure and exposure to gadolinium contrast.

The time to onset of symptoms ranges between a few days to a few years following exposure to gadolinium. The majority of published cases occurred within 3 months.

Early NSF may present as a pruritic erythrematous rash that appears shortly after exposure to gadolinium-containing contrast agent. Thickening and hardening of the skin that is usually symmetrical and typically of the upper and lower extremities is the hallmark of NSF. The skin surface appears brawny and woody and can have a cobblestone or "peau d´orange" texture. The face is usually spared and is an important distinction from scleroderma. Occasionally, the skin of the trunk may be involved[4,5].

Clinical course is relentlessly progressive in most of the cases. Decreased mobility of periarticular skin may lead to fixed flexion deformity making ambulation difficult.

Exra-cutaneous manifestations of NSF also occur. In many patients, there may be yellow plaques on the sclera typically, not compromising the vision. Visceral fibrosis involving heart, lungs, skeletal muscle, and other organs have been reported contributing to cardiomyopathy, pulmonary hypertension, and skeletal muscle weakness. Often there may be vascular thrombosis especially of the vascular access for haemodialysis[3,6].

Pathogenesis

Gadolinium use in patients with chronic kidney disease and acute renal failure, especially in patients with creatinine clearance less than 30 ml/min is implicated in causing nephrogenic systemic fibrosis. Gadolinium has an atomic number of 64 and has seven unpaired electrons. The exact mechanism is not known but seems to be stimulation of circulating fibrocytes following gadolinium. Out of the gadolinium-containing contrast materials, 90% of cases of NSF have been related to gadodiamide (Omniscan) and some to gadopentetic acid (Magnevist)[7].

It has long been known that free gadolinium is toxic and therefore it is chelated with a ligand. These chelates are divided into ionic and nonionic forms and linear and macro-cyclic forms. There are two generally recognised categories of gadolinium chelates: macrocyclic molecules where Gd^{3+} is caged in pre-organised cavity of the ligand, and the linear open chain molecules. Gadolinium chelates differ in their thermodynamic stability. In general, pre-clinical and *ex vivo* studies have suggested that macro-cyclic molecules are more stable than linear molecules[8].

Gadolinium-containing contrast agents have been categorised into three groups:-

- High risk: gadoversetamide (OptiMARK), gadodiamide (Omniscan) and gadopentetic acid (Magnevist).

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- Medium risk: gadofosveset (Vasovist), gadoxetic acid (Primovist) and gadobenic acid (MultiHance).
- Low risk: gadoteric acid (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).

The t ½ of gadolinium in healthy individuals is 1.6 hours and is markedly increased to > 30 hours in renal failure. This increases the potential for gadolinium-chelates dissociation through prolonged circulation. One haemodialysis treatment removes 2/3rd to 3/4th of gadolinium and three dialysis sessions of 4 hours each remove 99%. Peritoneal dialysis is not effective[8].

The cell responsible for fibrosis seen in NSF is a recently characterised cell involved in wound healing and tissue remodelling. This cell – a circulating fibrocyte (CF) – is distinct from a fibroblast in that it has CD34/procollagen dual positive profile and is blood borne[9].

In NSF, circulating fibrocytes are thought to leave the circulation and differentiate in the dermis into cells that functionally and histologically resemble normal dermal fibroblasts. Because of the presence of these circulating cells, NSF is a systemic disorder. Several reports and autopsy data have verified the presence of fibrosis in other organs in NSF[3, 10].

The factors responsible for differentiation of CFs into terminal fibroblast-like cells are not clear but are likely directly related to the underlying dysfunction of kidney.

Diagnosis

There is no clinical diagnostic criterion. The diagnosis is based on the presence of characteristic clinical features and is confirmed by skin and muscle biopsy.

A deep skin biopsy, preferably a deep wedge biopsy that includes fascia is needed. A deep punch biopsy at least 3 mm diameter may suffice.

The most characteristic histological features of NSF on skin biopsy are increased dermal fibroblast number and collagen, thickened collagen bundles, increased elastic fibres, and mucin deposition. Proliferation of dermal fibroblasts and dendritic cells is also evident [5].

Early lesions (within 20 weeks of clinical onset) demonstrate reticular, dermal, large, and epithelioid or stellate spindle cells. These cells can extend into and widen the subcutaneous fat lobule septa. The spindle cells are diffusely arranged among thickened collagen bundles. Clefts can encompass some spindle cells. Most of the spindle cells are CD34/procollagen dual-positive cells that form a dense interconnecting network.

Late lesions (> 20 weeks of clinical onset) typically have less prominent clefting, less mucin, and fewer CD34/procollagen-positive cells. Calcification, which is described in some patients and which has been interpreted as dystrophic in nature, can be present[11].

Demonstration of gadolinium in tissue by spectrometry provides further support for the diagnosis of NSF, though the amount of gadolinium deposition in tissue does not correlate with the extent of the clinical involvement[12, 13].

Differential diagnosis

The differential diagnosis of NSF is quite broad and includes several sclerosing and mucin deposition disorders. The major differential diagnosis includes scleroderma, eosinophilic fasciitis, scleromyxoedema, and calciphylaxis[14].

The characteristic anatomic distribution of skin involvement in NSF helps to differentiate from other fibrosing diseases. Out of all conditions, scleroderma is the most difficult to differentiate. Lack of facial involvement, absence of Raynaud's phenomenon and absence of antinuclear antibodies and antibody to Scl-70 in NSF helps it to differentiate from scleroderma and scleromyxoedema.

Calciphylaxis – rarely observed in patients of chronic kidney disease – can be easily distinguished from NSF by focal skin lesions with vascular calcification and tissue necrosis.

Treatment

Till date no therapy has been proven effective in NSF. Trials with corticosteroids, photopheresis, plasmapheresis, thiosulfate, methotrexate, and low-dose oral imatinib mesylate have not had consistent success. Some improvement has been reported with thalidomide in NSF of short duration. A favourable response to medical intervention is anecdotal. Of all treatments, extracorporeal photopheresis seems to provide the best, albeit mild and extremely expensive, treatment modality for nephrogenic systemic fibrosis. Haemodialysis is effective in removing gadolinium contrast media from the body. However, initiating haemodialysis solely to prevent nephrogenic systemic fibrosis is not recommended. Resolution of acute renal failure and the renal transplantation in chronic kidney disease have been associated with NSF resolution[14-16].

Prognosis

Nephrogenic systemic fibrosis almost always progresses relentlessly and does not usually regress spontaneously.

With normalisation of kidney function after renal transplantation and recovery from acute renal failure, improvement in skin lesions have been reported in several patients[17].

NSF is associated with increased mortality with a 3-fold increased risk of dying within 2 years of diagnosis.

Prevention

Since there is no effective treatment available, prevention of nephrogenic systemic fibrosis is the best practice [14,17]:

- Gadolinium-based contrast (GBC) agents are contraindicated in patients on dialysis.
- Avoid MRI with GBC agents in patients with GFR < 30 ml/minute, i.e., stage 4 and 5 chronic kidney disease.
- If exposure to gadolinium occurs in patients with renal failure, haemodialysis should be performed promptly after exposure, and repeated on consecutive days.
- There is no prophylactic agent that can be administered prior to gadolinium-containing contrast agent to prevent NSF.

Conclusion

NSF is a new disease, characterised by hardening and thickening of skin, leading over time, to flexion contractures of involved joints. Systemic involvement may occur. There is evidence that gadolinium may play a role. There is no therapy. Prevention is the mainstay treatment. It is recommended to avoid gadolinium-containing contrast in patients with stage 4 and 5 chronic kidney disease and acute kidney injury.

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"Often the test of courage is not to die but to live."

– VITTORIO ALFIERI.

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Peripartum cardiomyopathy: A condition physicians should be aware of

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Introduction

Peripartum cardiomyopathy (PPCM) is a poorly characterised, rare form of cardiomyopathy. The aetiology of PPCM is unknown, but viral, autoimmune, and idiopathic causes may contribute[1]. Risk factors include multiparity, age > 30 years, multiple pregnancies, obesity, hypertension, and toxaemia. The presentation is similar to other forms of congestive heart failure. Signs and symptoms of PPCM resemble systolic heart failure, and it is diagnosed by exclusion. The diagnosis of PPCM should not be considered until other causes of cardiac dysfunction are ruled-out. Echocardiography is central to diagnosis. An echocardiogram typically reveals an ejection fraction of < 45% and/or fractional shortening of < 30%, along with a left ventricular end-diastolic dimension > 2.7 cm/m^2 of body surface area[2]. Treatment consists of diuretics, vasodilators, digoxin. Patients with PPCM are at high risk of thromboembolism, and therefore anticoagulation therapy should be considered. The prognosis is variable, ranging from complete recovery to worsening heart failure requiring cardiac transplantation, or death. Future pregnancies are often discouraged because of the high mortality rate and risk of recurrence. Prognosis is related to recovery of ventricular function[3,4,5].

Pathophysiology and aetiology

The exact cause of peripartum cardiomyopathy (PPCM) is unknown, but the usual causes of systolic dysfunction and pulmonary oedema should be excluded. Many nutritional disorders have been suggested as causes, but other than salt overload, none has been validated by epidemiologic studies.

An increased prevalence of myocarditis has been found in case series and in a small case-control study. Abnormal myocardial biopsy findings were associated with a worse long-term prognosis for recovery. More recent data have found a similar incidence of myocarditis in women with PPCM, compared to those with the idiopathic type. However, a study that found myocarditis in 62% of 44 women with PPCM found that the finding did not correlate with survival[6].

Lower levels of selenium have been found in patients with PPCM. Autoantibodies against myocardial proteins have been identified in patients with PPCM but not in those with idiopathic cardiomyopathy[7].

Case reports and anecdotal experience have documented ejection fractions as low as 10 - 15% in patients with severe pre-eclampsia, with subsequent normalisation of echocardiograms within 3 - 6 months. Pre-eclampsia has been listed as a risk factor, but it may be the cause in some cases. Noncardiogenic pulmonary oedema has many causes, all of which must be considered. A study in 2005 found that 8 of 26 patients had parvovirus B19, human herpes virus 6, Epstein-Barr virus, and human cytomegalovirus detected after molecular analysis of myocardial biopsy specimens[8,9].

Clinical findings

The clinical presentation of PPCM is most often dyspnoea (90%), tachycardia (62%), and oedema (60%)[10]. Some case studies also cite unusual presentations, including multiple thromboembolic events[11] and acute hypoxia[12]. Onset occurs one month prior to delivery and up to five months after delivery. However, the majority of women present post-partum. The most common clinical presentation (dyspnoea, tachycardia, and oedema) can be mistaken for another disorder, such as pneumonia or depression. Therefore, when a woman presents in the puerperium with these findings, an echocardiogram should be considered. Cardiac biomarkers, including B-type natriuretic peptide (BNP), are elevated in patients presenting with PPCM although these markers are not unique to PPCM. Elevations of troponin T (TnT) appear to have prognostic significance in this group. A Tnt 0.04 ng/ml at presentation predicts persistence of systolic dysfunction with a sensitivity of 55% and specificity of 91%[13]. Inflammatory cytokines (IL-2, TNF, and IL-6) are elevated in women with PPCM compared to pregnancy controls[14,15]. However, these cytokines are elevated in patients with other cardiomyopathies. ECG abnormalities are often noted on presentation, most commonly sinus tachycardia, nonspecific ST-T segment changes, LV hypertrophy, premature ventricular contractions, and bundle branch block[16].

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Diagnosis

Patients with peripartum cardiomyopathy present with the typical signs and symptoms of left ventricular failure. The majority of cases occur after delivery and the immediate postpartum period. However, when the disease develops during the last month of pregnancy the diagnosis of cardiac failure is difficult to make by signs and symptoms alone since some of those symptoms, such as fatigue, orthopnoea, and pedal oedema, are common among normal parturients during late pregnancy. Further testing is required to establish the presence of cardiac failure. A chest x-ray consistently demonstrates cardiomegaly and pulmonary oedema. Echocardiography confirms ventricular failure with increased left ventricular end-diastolic dimensions and decreased ejection fraction. Once cardiac failure is identified, peripartum cardiomyopathy must be differentiated from other disease processes that lead to heart failure, such as valvular heart disease[17].

Echocardiography will rule-out other valvular diseases and at the same time diagnose reduction in the left ventricular ejection fraction (LVEF) and dilatation of cardiac chambers. Most of the cardiologists would consider PPCM if left ventricular ejection fraction is less than 50% and in the presence of the other two mentioned criteria for diagnosis of PPCM (see, hereinunder). Other nonspecific echocardiography findings in PPCM are left atrial enlargement, mitral regurgitation (MR) and a small pericardial effusion. The endomyocardial biopsy may show features of myocarditis, but the decision for biopsy should be taken after thorough discussion between patient and treating physicians. Viral and bacterial culture as well as coxasckie B titre should be considered in selected cases. Invasive haemodynamic monitoring will show elevated right and left heart filling pressures with low cardiac index[18].

The National Heart, Lung and Blood Institute (NHLBI), with the National Institutes of Health (NIH), USA, published diagnostic criteria for PPCM to direct more accurate research on epidemiology, pathophysiology, and outcomes. The criteria include:-

1. Onset of heart failure signs and symptoms in the last month of pregnancy or within 5 months postpartum;
2. LV systolic dysfunction with ejection fraction (EF) measured ≤45% or LV end-diastolic dimension ≥ 2.7 cm/m^2;
3. No evidence of pre-existing heart disease prior to peripartum symptom onset;
4. No other identifiable causes of heart failure[19].

An objective measurement of LV function excludes women with normal cardiac function with postpartum volume overload, which is common due to normal physiologic changes of pregnancy. Finally, PPCM is a diagnosis of exclusion[20].

Invasive evaluation, such as cardiac catheterisation or endomyocardial biopsy, is often unnecessary for diagnosis or treatment. The pathology identified on endomyocardial biopsy is often nonspecific oedema, inflammation, hypertrophy, and fibrosis. Inflammation consistent with myocarditis is present in up to 50% of specimens[21,22].

Who makes the diagnosis of PPCM?

Patients with PPCM most commonly present to gynaecologists or primary care physicians. Where pneumonia is suspected, a referral to a respiratory physician is often made. It would be desirable, however, for patients presenting postpartum with signs of cardiac failure such as shortness of breath, oedema or general lassitude, or with peripheral emboli or cardiac arrhythmias, to receive an urgent echocardiogram to exclude PPCM[23].

Treatment

When considering tests or treatments in pregnancy, the welfare of the foetus is always considered along with that of the mother. Coordinated management with specialists (an obstetrician and maternal-foetal medicine team) is essential, with foetal heart monitoring[24].

Angiotensin-converting enzyme (ACE) inhibitors and ARBs are contraindicated in pregnancy because they cause birth defects, although they are the main treatments for postpartum women with heart failure. The teratogenic effects occur particularly in the second and third trimester, with foetopathy characterised by foetal hypotension, oligohydramnios-anuria, and renal tubular dysplasia[25]. However, a recent study suggested a risk of malformations even after the first trimester exposure to ACE inhibitors[26].

Digoxin, beta-blockers, loop diuretics, and drugs that reduce afterload such as hydralazine and nitrates have been proven to be safe and are the mainstays of medical therapy of heart failure during pregnancy. Beta-blockers have strong evidence of efficacy in patients with heart failure, but they have not been tested in peripartum cardiomyopathy. Nevertheless, beta-blockers have long been used in pregnant women with hypertension without any known adverse effects on the foetus, and patients taking these agents prior to diagnosis can continue to use them safely.

Heart failure treatment postpartum

After delivery, the treatment is identical to that for a

nonpregnant women with dilated cardiomyopathy.

ACE inhibitors and ARBs: The target dose is one-half the maximum antihypertensive dose.

Diuretics are given for symptom relief.

Spironolactone or digoxin is used in patients who have New York Heart Association class III or IV symptoms. The goal with spironolactone is 25 mg/day after dosing of other drugs is maximised. The goal with digoxin is the lowest daily dose to obtain a detectable serum digoxin level, which should be kept at less than 1.0 ng/ml. In the Digitalis Investigation Group trial serum digoxin levels of 0.5 to 0.8 ng/ml (0.6 - 1.0 nmol/l) were most beneficial, and levels of 1.1 to 1.5 ng/ml (1.4 - 1.9 nmol/l) were associated with an increase in deaths related to heart failure.

Beta-blockers are recommended for peripartum cardiomyopathy, as they improve symptoms, ejection fraction, and survival. Nonselective beta-blockers such as carvedilol (Coreg) and selective ones such as metoprolol succinate (Toprol XL) have shown benefit. The goal dosage is carvedilol 25 mg twice a day (50 mg twice a day for larger patients) or metoprolol succinate 100 mg once a day[27].

During pregnancy, the risk of thromboembolic complications increases due to higher concentrations of coagulation factors II, VII, VIII, and X, and of plasma fibrinogen. The risk may persist up to 6 weeks postpartum. Cases of arterial, venous, and cardiac thrombosis have been reported in women with peripartum cardiomyopathy, and the risk may be related to the degree of chamber enlargement and systolic dysfunction and the presence of atrial fibrillation.

Patients with evidence of systemic embolism, with severe left ventricular dysfunction or documented cardiac thrombosis, should receive anticoagulation. Anticoagulation should be continued until a return of normal left ventricular function is documented.

We await the results of the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction trial, which should determine which drug will best prevent death or stroke in patients with ejection fractions of less than 35%.

Warfarin can cause spontaneous foetal cerebral haemorrhage in the second and third trimesters and therefore is generally contraindicated during pregnancy. However, guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) on the management of patients with valvular heart disease say that "warfarin is probably safe during the first 6 weeks of gestation, but there is a risk of embryopathy if warfarin is taken between 6 and 12 weeks of gestation. The guidelines also say warfarin is "relatively safe" during the second and third trimesters but must be stopped and switched to a heparin preparation several weeks before delivery. Unfractionated heparin or low-molecular-weight heparin can be used during pregnancy. However, should warfarin be needed for any reason, we believe a caesarian section should be performed to reduce the risk to the infant[28].

Patients with severe heart failure despite maximal drug therapy need cardiac transplantation to survive and to improve their quality of life. However, fewer than 3,000 hearts are available for transplantation worldwide per year. Therefore, ventricular assist devices are indicated as a bridge to transplantation. Patients with symptomatic ventricular arrhythmias should be considered for defibrillator implantation[29].

New treatments

Pentoxifylline improved outcomes, left ventricular function, and symptoms when added to conventional therapy in a small prospective study[30].

Intravenous immunoglobulin improved the ejection fraction in several studies and also markedly reduced the levels of inflammatory cytokines, namely thioredoxin[31].

Immunosuppressive therapy does not yet have a fully proven role, but it could be considered in patients with proven myocarditis. Given the various aetiologic mechanisms of peripartum cardiomyopathy, it is unlikely that immunosuppression will help all patients. Furthermore, without a large randomised trial, treatment successes may merely reflect the natural course of the disease.

Investigators have emphasised the need to rule-out viral infection before starting immunosuppressive treatment, as the treatment may activate a latent virus, with subsequent deterioration in myocardial function[32].

Bromocriptine (Parlodel). Peripartum cardiomyopathy develops in mice bred to have a cardiomyocyte-specific deletion of stat 3, leading to enhanced expression and activity of cardiac cathepsin D and promoting the formation of a 16-kD proapoptotic form of prolactin. Therefore, drugs that inhibit prolactin secretion may represent a novel therapy for peripartum cardiomyopathy. Based on this concept, two patients with peripartum cardiomyopathy were treated with bromocriptine, an inhibitor of prolactin secretion, and they showed a good recovery. We require large prospective randomised controlled studies to prove the beneficial effect of blocking prolactin in patients with peripartum cardiomyopathy[33].

Tale I: Major studies that have investigated prognosis in peripartum cardiomyopathy.

Authors	Study type	No. of pts.	Mean age year	Enrolment period	Mortality rate %	Findings
Karaye KM *et al*[65]	Cross-sectional	56	26	2008 - 2009	–	Peripartum cardiomyopathy associated with decreased QRS interval and decreased atrial arrhythmias. Mean age of peripartum cardiomyopathy lower than in other causes of cardiomyopathy.
Goland S *et al*[64]	Retrospective	182	29	2009*	28	Major adverse events are more common in nonwhites and with LVEF < 0.25.
Gentry MB *et al*[18]	Retrospecitve	28	25	2003 - 2008	–	Black women had 15.7% higher relative risk of peripartum cardiomyopathy than nonblacks. Other risk factors include hypertension history, > 2 previous pregnancies, and unmarried status.
Duran N *et al*[67]	Retrospective and prospective	33	33	1995 - 2007	30	LVEF > 0.27 and LVESD < 5.5 cm may predict LV recovery.
Safirstein JG *et al*[68]	Survey	55	32	2005 - 2007	–	Gesttational hypertension positive, LVEF < 0.35 at diagnosis, breastfeeding history, and postpartum diagnosis are associated with peripartum cardiomyopathy recovery.
Hassan JA *et al*[65]	Retrospective	32	32	2003 - 2007	–	Chronic hypertension, long-term tocolysis, pre-eclampsia, and multiple pregnancies were risk factors for peripartum cardiomyopathy.
Hu CL *et al*[33]	Prospective	106	28	2007*	–	LV dysfunction more persistent in pts with cardiac troponin levels > 0.04 ng/mL.
Brar SS *et al*[70]	Retrospective	60	34	1996 - 2005	3.3	Peripartum cardiomyopathy incidence highest in black and lowest in Hispanic populations.
Sliwa K *et al*	Prospective	80	30	2005*	10 (6 month) 28 (2 yrs.)	Peripartum cardiomyopathy mortality rate remains high after 6 months
Sliwa K *et al*	Prospective	100	32	2003 - 2005	15	C-reactive protein level correlated with LVEDD and LVESD and inversely with LVEF. High Fas/Apo-1 and low mean LVEF at presentation predicted death.
Fett JD *et al*[8]	Prospective	92	32	2003 - 2005	15	Mean LVEF and fractional shortening at diagnosis higher in recovered pts than in unrecovered pts.
Elkayam U *et al*[8]	Survey	100	31	2005	9	Subsequent pregnancy in peripartum cardiomyopathy pts is associated with decrease in LV function.
Isezuo SA, Abubakar SA	Cross-sectional	65	28	2003 - 2005	12	Peripartum cardiomyopathy outcome influenced by cardiothoracic index, LVEF, and diastolic pressure. Patients who died had lower diastolic pressure and higher cardiothoracic index.
Modi KA *et al*	Retrospective	44	25	1992 - 2003	16	In black pts, LV function and recovery rates comparable to those in studies reported from Haiti and South Africa.
Mielniczuk LM *et al*	Retrospective	171	30	1990 - 2002	1.36 - 2.05	Peripartum cardiomyopathy pts more likely to be older, black, and with pregnancy-associated hypertensive disorder.
Fett JD *et al*	Retrospective and prospective	47	32	1994 - 2001	14	Very high incidence of peripartum cardiomyopathy in Haiti (1 case/ 400 live births).
Chapa JB *et al*	Retrospective	32	27	1988 - 2001	10	LV fractional shortening < 20% and LVEDD > 6 cm at diagnosis is associated with 3-fold risk of poor LV recovery.
Felker GM *et al*[76]	–	51	29	1983 - 1998	6	Patients with peripartum cardiomyopathy have better prognosis than do pts with other forms of cardiomyopathy.
Silwa K *et al*[77]	Prospective	29	29	1996 - 1997	28	TNF-α, IL-6, and Fas/Apo-1 levels are elevated in peripartum cardiomyopathy pts. Fas/Apo-1 levels were higher in non-survivors.
Witlin AG *et al*	Prospective	28	–	1986 - 1994	18	Commonly associated disorders including preeclampsia of chronic hypertension (19 pts), alcohol abuse (2), positive family disorder (2), adn multiple tocolytic therapy (2).
Desai D *et al*[79]	Retrospective	99	29	1986 - 1989	14	Increasing age and multiparity did not favour adverse outcomes, but late presentation predicted adverse outcomes.
Carvalho A *et al*	Prospective	19	26	1982 - 1988	16	Death is predicted by increased LVEDD and late onset of symptoms.

*Fas/Apo-1 = Fas/apoptosis antigen 1; IL-6 = interleukin; LV = left ventricular; LVEDD = left ventricular end-diastoilc diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; Pts = patients; TNF-α = tumour necrosis factor-α. * Year in which recruitment began.*

Prognosis

Recovery from peripartum cardiomyopathy is defined as recovery of LVEF to $\geq$ 0.50 or improvement by > 0.20. As already mentioned, recovery usually occurs between 3 and 6 months postpartum, but might occur as late as 48 months postpartum[34]. Delayed diagnosis, higher NYHA functional class, black ethnicity, LV thrombus, multiparity, and coexisting medical illnesses are associated with delayed recovery. In a 2-year, long-term follow-up study in 123 peripartum cardiomyopathy patients, mean LVEF increased from 0.28 to 0.46, and in just over half of these cases, reached > 0.50[35]. Furthermore, recovery was greatest when baseline LVEF was > 0.30 and impaired when baseline LV end-diastolic diameter (LVEDD) was > 5.6 cm[5]; patients exhibiting low levels of recovery often required a heart transplant[36]. Also, high troponin levels at baseline were predictive of poor LVEF at 6 months[11]. Inflammatory markers such as CRP correlate positively with baseline LVEDD and LVESD, but negatively with LVEF in patients with peripartum cardiomyopathy[37].

Even after complete recovery from peripartum cardiomyopathy, the risk of recurrence in subsequent pregnancies remains high, and LVEF, once improved, can worsen again. In a study of 44 women who recovered from peripartum cardiomyopathy and subsequently became pregnant, LVEF deterioration was more frequent in those with partial recovery than in those with complete recovery (44% vs 21%)[39]. In a prospective study of 61 post-peripartum cardiomyopathy pregnancies, relapse occurred more often in patients who had a prior LVEF < 0.55 than in those who had a prior LVEF $\geq$ 0.55 (46% vs 17%)[40]. Generally, post-peripartum cardiomyopathy pregnancies are marked by a decline in LVEF[41]. Exercise stress echocardiography to estimate contractile reserve can uncover subtle residual cardiac dysfunction that might be exacerbated during a pregnancy[42]. At present, it is difficult to predict outcomes of a post-peripartum cardiomyopathy pregnancy, and current peripartum cardiomyopathy guidelines advise against future pregnancies[43]. Table I shows major studies that have investigated prognosis in peripartum cardiomyopathy.

Conclusion

Peripartum cardiomyopathy is a rare but serious condition of unknown cause that affects childbearing women. Diagnosis of peripartum cardiomyopathy requires heightened awareness among multidisciplinary patient care teams and a high degree of suspicion. Management of peripartum cardiomyopathy should aim first at improving heart-failure symptoms through conventional therapies, and then at administering targeted therapies. Targeted therapies (for example, intravenous immunoglobulin, pentoxifylline, and bromocriptine) show promise but need further clinical evaluation before they can be widely adopted. The prognosis is best when peripartum cardiomyopathy is diagnosed and treated early. Fortunately, despite a high risk of recurrence in subsequent pregnancies, many patients with peripartum cardiomyopathy recover within 3 to 6 months of disease onset. A large multicenter, prospective, randomised trial is currently needed to evaluate the incidence, the pathophysiology (which would include setting up a bio-repository for genetic and translational studies), and the current therapies for peripartum cardiomyopathy.

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"Cheerfulness is health,
its opposite melancholy is disease."

– William Shakespeare.

REVIEW ARTICLE

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Nutrition in critically ill patients

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Abstract

Malnutrition is a persistent problem in hospitals and intensive care units (ICUs) worldwide. The concept of therapeutic nutrition has replaced supportive nutrition in critically ill patients. Iso-energetic feeding improves outcome in ICU patients. Ideally, enteral nutrition should be initiated as early as possible and pro-kinetic agents can be used to improve gastric tolerance in critically ill patients. If enteral nutrition is not feasible, parenteral nutrition can be given to optimise the patient's energy requirements. Parenteral nutrition needs specialised care and monitoring. Newer pharmaconutrients and gut hormones are available, but further studies are needed before their routine use can be recommended.

Key words: Enteral nutrition, parenteral nutrition, pharmaconutrients.

Introduction

Critically ill patients quickly develop malnutrition, or pre-existing malnutrition is aggravated due to the inflammatory response, metabolic stress and bed rest which cause catabolism[1]. This response is combined with complications of increased morbidity due to infection, multi-organ dysfunction (MOD) and prolonged hospitalisation.

The persistence of this problem – despite existing guidelines – is partly explained by the absence of immediately visible consequences of acute malnutrition. 15 - 70% of patients admitted in hospitals are malnourished. Malnutrition remains undiagnosed in 70% of hospitalised patients, and among these, 70 - 80% patients do not receive any nutritional support in the hospital.

Importance of nutrition in the intensive care unit

Approximately 60% of intensive care unit (ICU) patients suffer from gut dysfunction due to impairment in gastro-intestinal (GI) motility, digestion, or absorption. GI dysfunction along with inadequate intake of calories leads critically ill patients to develop an energy deficit and lose lean body mass.

Malnourished ICU patients experience immune dysfunction, weakened respiratory muscles, lowered ventilation capacity and reduced GI tolerance. Hence, they are at risk of developing complications like ventilator dependence, gastro-oesophageal reflux, pulmonary aspiration, and infections that can lead to sepsis, multi-organ failure, and even death.

Goals of nutrition in the ICU

Nutritional support in critically ill patients was considered as an adjunctive care to provide exogenous fuels to support the patient during the period of stress. This support had 3 main goals:-

1. To preserve the lean body mass.
2. To maintain the immune function.
3. To avoid metabolic complications.

Feeding an ICU patient now extends beyond choosing the right feeding route, the rate and the caloric density. In modern critical care, the concept of 'therapeutic nutrition' is replacing traditional 'supportive nutrition'[2].

Assessment of nutritional status of a patient

Patients at risk for developing malnutrition are:-

1. Underweight patients (body mass index < 18.5) and/ or a recent loss of > 10% of usual body weight.
2. Patients with poor intake for more than 5 days.
3. Patients having protracted nutrient losses due to the presence of fistula, abscess, or wound.
4. Hyper-metabolic states.
5. History of alcohol abuse, use of drugs with catabolic properties.
6. Impoverishment, isolation, and advanced age.

Screening Tools for assessment of nutrition are[3]:-

1. Malnutrition Universal Screening Tool (MUST)
2. Subjective Global Assessment (SGA)
3. Mini Nutritional Assessment (MNA)
4. Malnutrition Screening Tool (MST)

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5. Nutritional Risks Screening 2002 (NRS-2002)
6. Nutrition Risk Index (NRI)
7. Short Nutritional Assessment Questionnaire (SNAQ)

Assessment of nutritional status is done by:-

1. Physical examination

   Weight, height and body mass index (BMI) are assessed along with examination for signs of any nutrient deficiency. Unintentional weight loss during illness often reflects loss of lean body mass.

   Measurement of skin-fold thickness is useful for estimating body fat stores, because 50% of body fat is normally present in the sub-cutaneous region. Skin-fold thickness also permits discrimination of fat from muscle mass. Triceps skin fold (TSF) thickness is generally representative of the body's overall fat. A TSF thickness < 3 mm suggests exhaustion of fat stores.

2. Biochemical tests

   Albumin, transferrin, pre-albumin and retinol-binding protein (RBP) are negative acute phase proteins. C-reactive protein (CRP) and ceruloplasmin are positive acute phase proteins.

   Nitrogen balance assessment is the only biochemical parameter that truly reflects visceral and somatic protein pools.

Calculation of substrate requirements

The total intake of prescribed nutritional support should account for:-

1. Energy, protein, mineral, micro-nutrients, fibre, and fluid and electrolyte needs.
2. Levels of activity and the patient's underlying clinical condition.
3. Gastro-intestinal tolerance, potential metabolic instability, and risk of re-feeding problems.
4. The likely duration of nutritional support.

Energy requirements

The energy requirement of a patient is not static and keeps changing during the course of ICU stay. Measurement of resting energy expenditure by indirect calorimetry is the gold standard. But, this involves specialised expensive equipment, trained personnel, and cannot be measured in certain settings. For example, O_2 sensor is not reliable at FiO_2 > 50% (FiO_2- fraction of inspired oxygen).

Energy expenditure is measured from the volume of O_2 (VO_2) consumed, and the volume of CO_2 (VCO_2) produced. Resting energy expenditure (REE) is calculated by the Weir formula as given below[4]:-

REE (kcal/day) = $[(3.9 \times VO_2) + (1.1 \times VCO_2) - 61] \times 1440$

Basal energy expenditure (BEE)

Daily energy expenditure is expressed as BEE. BEE is defined as heat production by basal metabolism in the resting and fasting states.

Simple equation for BEE (kcal/day) = 25 x body weight in kilograms.

BEE is multiplied by 1.2 to allow for the thermal effect of food. Adjustments in BEE are made as follows:-

1. Fever — BEE x 1.1 (for each 1°C above normal body temperature)
2. Mild stress — BEE x 1.2
3. Moderate stress — BEE x 1.4
4. Severe stress — BEE x 1.6

Harris Benedict equation can also be used to calculate BEE:-

1. Males — BEE = 66.47 + (13.75 x weight) + (5 x height) – (6.76 x Age)
2. Females — BEE = 655.1 + (9.56 x weight) + (1.8 x height) – (4.68 x Age)

BEE – In kilocalories/day
Weight – In kilograms
Height – In inches
Age – In years

Substrates

a) Carbohydrates – They should provide approximately 70% of caloric requirements.

b) Proteins – Protein requirements are higher than normal in critically ill patients due to hyper-catabolism.

   Protein requirement = 1.2 to 1.6 g/kg/day.

c) Lipids – 30% of daily energy requirement should be provided by lipids.

d) Fluids – Fluid requirement is estimated to be 30 ml/kg of body weight + replacement for abnormal losses.

   But, this also depends on the patient's underlying clinical condition and has to be individualised.

e) Vitamins

Table I: Requirement of vitamins in critically ill patients.

Vitamin	Enteral dose	Parenteral dose
Vitamin A	1,000 μg	3,300 IU
Vitamin B_{12}	3 μg	5 μg
Vitamin C	60 mg	100 mg
Vitamin D	5 μg	200 IU
Vitamin E	10 mg	10 IU
Vitamin K	100 μg	10 mg
Thiamine	2 mg	3 mg
Riboflavin	2 mg	4 mg
Pyridoxine	2 mg	4 mg
Pantothenic acid	6 mg	15 mg
Biotin	150 μg	60 μg
Folic acid	400 μg	400 μg

μg = microgram; mg = milligram; IU = international units

Hypo-caloric feeds

They have the potential to provide nutritional support without increasing the stress response. Permissive hypo-caloric feeds are recommended in critically ill obese patients.

Large energy deficits are associated with poor patient outcome. The cut-off for the appearance of biological consequences of under-feeding was found to be between –50 and –60 kcal/kg body weight[5].

Types of nutritional support

1. Enteral – Enteral nutrition is feeding via a tube placed in the gut to deliver liquid formulas containing all essential nutrients.
2. Parenteral – It is infusion of complete nutrient solutions into the blood stream via peripheral/central venous access to meet nutritional needs of the patient.

1. Enteral nutrition

Enteral nutrition supports the functional integrity of the gut by maintaining tight junctions between the intra-epithelial cells, stimulating blood flow and inducing the release of trophic endogenous agents. It also maintains the structural integrity of the GI tract by maintaining height of villi and supporting the mass of secretory IgA producing immune cells of gut-associated lymphoid tissue. (GALT)

Enteral nutrition is the preferred route of feeding for the critically ill patient who requires nutritional support. Compared to parenteral nutrition, infectious morbidity is reduced with enteral nutrition along with reduction in hospital stay and reduced cost of hospitalisation[6].

Modes of enteral nutrition

1. Nasogastric (NG)
2. Nasojejunal (NJ)
3. Percutaneous endoscopic gastrostomy (PEG)
4. Percutaneous endoscopic jejunostomy (PEJ)
5. Radiologically inserted gastrostomy (RIG)
6. Surgical gastrostomy
7. Surgical jejunostomy

Indication for enteral nutrition

If the patient has an inadequate oral intake for 1 - 3 days, it calls for nutritional support by the enteral route.

Contra-indications for enteral nutrition

1. Circulatory shock
2. Complete mechanical bowel obstruction
3. Severe diarrhoea
4. Entero-cutaneous fistulas

Composition of enteral feeds[7]

1. Caloric density: 1 - 2 kilocalories/litre of feeding solution
2. Osmolality: 280 - 1,100 mOsm/kg H_2O
3. Proteins: 35 - 40 grams/litre of feeding solution
4. Lipids: They consist of long-chain triglycerides derived from vegetable oils
5. Fibre

Efforts should be made to provide 50 - 65% of the goal calories in order to achieve the clinical benefit of enteral nutrition during the first week of hospitalisation. Enteral nutrition should be initiated as soon as the patient is resuscitated and haemodynamically stable. However, this should not translate into force feeding a patient.

Feeding regimen

Tube feedings are infused for 12 - 16 hours in each 24 hour period. Gastric retention should be monitored in the patient. If 4-hour gastric residual volume (GRV) is less than 200 ml, gastric feeding can be continued.

An elevation of the back-rest to levels between 40° - 45° has a protective effect against aspiration[8]. Also, using erythromycin and metoclopramide in combination is more effective than either agent alone in improving the outcomes of enteral nutrition[9].

Glycaemic control

Aggressive glycaemic control (random blood sugar between 81 - 108 mg%) was initially found to be associated with a significant reduction in ventilatory support[10]. This view has been contradicted by the NICE SUGAR study that demonstrated an increase in 90-day mortality with strict blood glucose control[11].

Complications of enteral feeding

a) Tube occlusion

b) Aspiration

c) Diarrhoea

d) Refeeding syndrome:-

Refeeding syndrome refers to severe fluid and electrolyte shifts and related metabolic complications in malnourished patients undergoing enteral nutrition. This occurs due to insulin causing intra-cellular uptake of glucose and other electrolytes and is characterised by hypokalaemia, hypophosphataemia and hypomagnesaemia.

Patients who have poor oral intake for more than 5 days should be started on nutritional support at about 50% of their requirement for the first 2 days. Feeding can be started at 10 kcal/kg/day and rates can be increased gradually to reach energy targets over 4 - 7 days.

e) Feed Intolerance:-

This can occur in patients with diabetes, renal failure, sepsis, and in patients on drugs like opioid analgesics and anti-cholinergic agents.

2. Parenteral nutrition

Indications for parenteral nutrition

a) Short-term (< 14 days)
- Severe pancreatitis
- Post-chemotherapy mucositis
- Entero-cutaneous fistula
- Intractable vomiting

b) Long-term (> 30 days)
- Inflammatory bowel disease
- Radiation enteritis
- Chronic malabsorption

Intravenous nutrient solutions

a) Dextrose solutions:-

These are used for meeting the caloric requirements of the patient. Dextrose, being hyper-osmolar should be preferably given through a central venous line.

b) Amino acid solutions:-

These consist of 50% essential and 50% non-essential and semi-essential amino acids.

c) Lipid emulsions:-

These contain droplets of cholesterol and phospholipids surrounding a core of long-chain triglycerides. These emulsions can be given through a peripheral vein.

d) Electrolytes, minerals, and trace elements.

Complications of parenteral feeding

a) Catheter-related infections

b) Carbohydrate infusion-related:– Hyperglycaemia, hypophosphataemia, and fatty liver

c) Lipid infusion-related:– Oxidation induced cell injury

d) GI complications:– Mucosal atrophy and acalculous cholecystitis

Table II: Monitoring of patients on parenteral nutrition.

Laboratory parameter	Frequency of Investigation
Renal function test and serum electrolytes	Daily until patient becomes stable, then 1 - 2 times/week
Blood glucose	1 - 2 times/day until patient becomes stable, then weekly
Magnesium and phosphorous	Daily followed by 3 times/week until patient becomes stable then weekly
Liver function test with PT/INR	Twice weekly until patient becomes then stable, weekly
Calcium and albumin	Weekly
Haemogram	1 - 2 times/week until patient becomes stable, then weekly
Iron and ferritin	3 - 6 monthly
Folate and vitamin B_{12}	2 - 4 weekly
C-reactive protein	2 - 3 times/week till patient becomes stable

Pharmaconutrients

Critical illness is characterised by oxidative stress and inflammation, both of which cause cellular damage and impair function of vital organs. Feeding formulas with specific pharmaconutrients can help in controlling inflammation and decreasing tissue damage.

Dietary anti-oxidants stabilise free radicals in cells and decrease oxidative injury. Dietary fish oil and borage oil blunt inflammatory responses by modulating the synthesis of pro- and anti-inflammatory mediators.

a) Arginine supplemented enteral formulas – They are used in the peri-operative period.

b) Glutamine – It is a metabolic substrate for enterocytes

and immune cells and supports intestinal barrier function and immune responses.

c) Prebiotics – They are non-digestible food ingredients that stimulate the growth of beneficial bacteria in the GI tract.

d) Probiotics – They are micro-organisms of human origin which when administered in adequate amounts confer a health benefit to the host.

e) Gut hormones[12] – Fasting Ghrelin concentration is reduced in the early phase of critical illness. Exogenous Ghrelin is a potential therapy that could be used to accelerate gastric emptying and/or stimulate appetite.

Hormones like Cholecystokinin and Peptide YY increase the gastric emptying time.

Incretin therapies need further evaluation in the management of hyperglycaemia in the critically ill.

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"Sleep is the best cure for waking troubles."

– Miguel de Cervantes.

REVIEW ARTICLE

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Hereditary angioedema

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Abstract

Hereditary angioedema (HAE) is a rare disease characterised by recurrent, self-limiting episodes of swelling. It is an autosomal dominant disease caused by low levels of the plasma protein C1 inhibitor (C1-INH) resulting in reduced plasmatic levels (HAE type I) or a dysfunctional protein (HAE type II), affecting equally men & women of all ethnic backgrounds. Patients can present with any combination of painless, nonpruritic, nonpitting swelling of the skin (cutaneous angioedema), severe abdominal pain, or acute airway obstruction. Attacks of hereditary angioedema (HAE) are unpredictable and, if affecting the upper airways, can be lethal. The attacks may be frequent or rare and they may vary substantially in severity, causing stomach discomfort or periorbital swelling in mild cases and hypovolaemic shock due to abdominal fluid shift or asphyxiation in the most severe cases. Since the symptoms of hereditary angioedema may be caused by other disorders (such as an allergic reaction), blood tests or genetic tests are needed to confirm the diagnosis. Two specific blood tests for hereditary angioedema check the level and proper functioning of C1-INH. Genetic testing could look for one of the known gene defects of chromosome 11 associated with hereditary angioedema. The most reliable and cost-effective screening test for HAE is a serum C4 level. Prior to the development of effective therapy, the mortality rate from HAE was 20 - 30%. In HAE types I and II, the treatment of choice in acute attacks consists of replacement with commercially available C1 inhibitor (C1-INH) concentrates or kallikrein inhibitor or, if those are unavailable, recommended fresh-frozen plasma. In HAE type III, infusion of C1-INH has proven to be ineffective.

Key words: Hereditary angioedema, protein C1 inhibitor, Icatibant.

Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease caused by low levels of the plasma protein C1 inhibitor (C1-INH) characterised by episodes of swelling that typically affect the extremities, bowels, face, or genitals. Angioedema is defined as a vascular reaction of the deep dermis or subcutaneous/submucosal tissues with localised dilatation and increased permeability of blood vessels resulting in tissue swelling[1-5]. Angioedema can be mediated by bradykinin or mast cell mediators including histamine[6]. Bradykinin-mediated angioedema can occur either on a hereditary or acquired basis due to a deficiency/defect of C1 inhibitor (C1-INH) or not[7-9].

Three forms of HAE have been defined:-

1. HAE due to C1-INH deficiency (type 1 HAE, HAE-1), characterised by low antigenic and functional C1- INH levels;
2. HAE due to C1-INH dysfunction (type 2 HAE, HAE-2), characterised by normal (or elevated) antigenic but low functional C1-INH levels; and
3. HAE with normal C1-INH antigenic and functional levels (HAE-3). Acquired C1-INH deficiency refers to patients with angioedema due to C1-INH deficiency on an acquired basis[10-13]. Many of acquired types of angioedema are not only due to C1-INH deficiency but they may be bradykinin mediated [e.g., angiotensin-converting enzyme inhibitor (ACE-I)-induced angioedema] or mast cell mediator histamine mediated (e.g., urticarial angioedema, anaphylactic angioedema).

Pathophysiology

Type 1 HAE and Type 2 HAE

HAE - 1 and 2 are caused by different mutations of the SERPING1 gene, which codes for C1-INH. In approximately 20 - 25%, a *de novo* mutation of SERPING1 is responsible for the disease[13,14]. C1-INH is a member of the serine protease inhibitor (serpin) superfamily and the major inhibitor of several complement proteases and contact system proteases (plasma kallikrein and coagulation factor XIIa) and a relatively minor inhibitor of the fibrinolytic protease plasmin and the coagulation protease factor XIa[15-17]. Laboratory and clinical data have shown that bradykinin is the primary mediator of swelling in HAE 1 &2. The nanopeptide bradykinin is generated when active plasma kallikrein cleaves high-molecular weight kininogen. Plasma kallikrein is activated from its inactive zymogen by the protease factor XII and both plasma kallikrein and factor XII are normally inhibited by C1-INH. Bradykinin has a number of important effects on the body including normal homoeostasis, normal immune responses, inflammation, vascular tone, and vascular permeability. The vascular permeability increased by the

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effect of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor[18-20]. Type I HAE is caused by mutations in the C1 inhibitor gene that result in either truncated proteins or misfolded proteins which cannot be secreted[21]. Most of SERPING1 mutations associated with type II HAE involve residues at or near the active site on the reactive mobile loop resulting in a mutant C1 inhibitor protein that is secreted but is dysfunctional[22].

Type 3 HAE

HAE with normal C1-INH (HAE-3) is a very rare disease. The symptoms are very similar to HAE-1/2. A subset of HAE-3 patients exhibit mutations in factor XII, which are thought to be responsible for the disease. The genetic abnormality of most HAE-3 patients has not yet been defined. Because of the lack of a clear genetic definition of this type of HAE, the diagnosis requires a family history of angioedema. There is clinical evidence that bradykinin also plays a major role in HAE-3[23,24].

C1 inhibitor is a major inhibitor of many complement proteases and contact system proteases. During HAE attacks, each of these plasma proteolytic cascades is activated and many vasoactive substances are potentially generated. Two potential mediators of swelling in HAE were identified:-

1. C2 kinin, generated through activation of the classic complement pathway[25], and
2. Bradykinin, generated through activation of the contact system[26]. Bradykinin is a pluripotent nanopeptide that mediates a variety of physiologic and pathologic effects[27].

Binding of bradykinin to the bradykinin B2 receptor on vascular endothelial cells results in a marked increase in microvascular permeability. Clinical severity is influenced by a polymorphism in the noncoding first exon of the bradykinin B2 receptor which affects bradykinin B2 receptor expression[28]. Bradykinin activates phospholipase-C, leading to increases in intracellular calcium and diacylglycerol (DAG) and activating protein kinase C. Protein kinase C phosphorylates beta-catenin and leads to the internalisation and destruction of the VE-cadherin. It is also involved in the generation of the vasodilator nitric oxide[29].

Clinical presentation

In HAE, women are more severely affected due to fluctuating oestrogen levels[30] as documented by worsening symptoms while using oestrogen-containing oral contraceptives[31]. The three most common forms of angioedema are subcutaneous oedema, abdominal oedematous attacks, and laryngeal oedema. The frequency of attacks is highly variable and shows substantial interindividual variation. In severe cases, attacks can occur weekly; but some patients remain symptom free almost throughout their lifetime. Reflecting the hereditary nature of the disorder, family history is positive in 75% of patients. In the remaining 25%, HAE cannot be demonstrated in the parents, which suggests *de novo* mutation of the C1-inhibitor gene in the index cases[32].

The commonest triggering factors for HAE attacks are trauma and stress[33]. Swelling episodes due to HAE typically worsen over one to two days and then resolve within two days. More severe attacks may last 5 days[34]. Patients may experience prodromal symptoms that include tingling or burning in the area of an imminent attack. Erythema marginatum – a serpiginous, non-pruritic rash – may appear on the trunk and appendages as part of the prodrome in one-third of patients[35].

Subcutaneous angioedema developing in HAE is a circumscribed, nonpruritic and nonerythematous swelling of the skin. It is not accompanied by urticaria. It is mostly seen on the extremities but can also develop on the face, neck, genitals, and trunk[36]. Subcutaneous angioedema resolves spontaneously, usually within 2 to 4 days.

Abdominal HAE attacks ocurs in more than 90% of patients[33]. In most patients, the abdomen will be protuberant and tender. Bowel sounds may be decreased or increased with presence of guarding and rebound tenderness[30]. The pain associated with abdominal angioedema may have a severe acute onset or recur as chronic abdominal pain of moderate severity. In addition, 78% of patients complain of vomiting, and 65% complain of diarrhoea with abdominal pain[36]. Substantial fluid accumulation in the intestinal wall and lumen and in the peritoneal cavity will cause intestinal wall swelling and ascites. In rare cases, hypovolaemic shock may occur due to the volume of fluid migration[37].

Angioneurotic oedema of the larynx is rare (0.9% of all HAE attacks) and a life-threatening manifestation of C1-inhibitor deflciency because of the risk of impending suffocation[36]. Usually, it occurs for the first time in patients in their mid-20s, approximately half of the patients with HAE during their lifetime and has been reported as early as age three[38]. In children, oedema formation has a propensity for the face and neck and it can progress to involve the uvula, the soft palate, or the larynx. Because of the small diameter of the upper airways in children, relatively mild swelling of the mucosal lining causes substantial obstruction[38,39]. Clinical manifestations include

hoarseness, stridor, dyspnoea, globus sensation, dysphagia, and voice change. Establishing a definitive diagnosis usually requires consultation with an otolaryngologist because indirect laryngoscopy is usually dificult to perform in infants for presence of any evidence of laryngeal oedema. In 2% of HAE attacks, oedema may involve atypical sites like brain, urinary bladder, urethra, muscles, joints, and the kidney. Infrequently, pericardiac or pleural effusion can be detected during the attack[36].

Laboratory investigations

Baseline laboratory testing at diagnosis at any age and follow-up

Blood borne pathogen surveillance (haemovigilance) samples should be collected and stored at baseline and annually, e.g., hepatitis B, C, G; HIV; HTLV. C1INH may be required at any time on an emergency basis after diagnosis; haemovigilance and baseline chemistries and urinalysis are best done at diagnosis. As attenuated androgens may predispose to lipid abnormalities and liver disorders including liver cancer[40-48], serum lipid profile and liver function tests should be obtained prior to androgen administration and abdominal liver and spleen ultrasound must be performed prior to continuous androgen administration (repeated annually)[49]. Creatine kinase (CK), lactic dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine (Cr), complete and differential blood count, as well as urinalysis should be obtained at diagnosis[50].

Treatment and prophylaxis

There are three different treatment approaches in the medical care of HAE patients[51]:-

1. Acute therapy of attacks.
2. Short-term prophylaxis before surgical or dental procedures.
3. Long-term prophylaxis in cases with frequent and severe attacks.

1. Acute therapy

Acute therapy is particularly indicated in severe or life-threatening attacks in order to rapidly reduce swelling. This is especially the case for painful abdominal swelling as well as attacks in the head and neck and laryngeal regions, but also for cutaneous oedema that affect the patient's quality of life[51].

Antihistamines, corticosteroids or epinephrine are only effective in histamine-mediated angioedema. If this treatment given routinely in emergency situations does not lead to a response, angioedema of a nonallergic genesis must be suspected and therapy be changed promptly. Every HAE patient should receive an emergency alert card which should always be carried by him/her.

C1-INH concentrate

A purified, pasteurised and lyophilised C1-INH concentrate derived from blood plasma is used for the acute therapy of HAE attacks. The C1-INH concentrate replaces missing C1-INH activity[52]. The efficacy and tolerability of C1-INH in the treatment of skin oedema, abdominal attacks, and laryngeal oedemas has been demonstrated in several clinical applications and retrospective studies[51-55].

The IMPACT programme (**I**nternational **M**ulticenter **P**rospective **A**ngioedema **C**1-INH **T**rials) constituted a prospective clinical trial. The IMPACT-1 trial showed that the lower dosage (10 units C1-INH concentrate per kg) there was no significant advantage of C1-INH concentrate versus placebo. With the higher dosage (20 units C1-INH concentrate per kg), attack symptoms improved significantly more rapidly than with placebo, with a median of 0.5 versus 1.5 hours. After about five hours, signs and symptoms had disappeared completely, in the placebo group after 7.8 hours. Adverse effects occurred significantly less frequently in patients treated with C1-INH than with placebo. No seroconversion for HIV, hepatitis viruses, or parvovirus B19 was observed. A subsequent open study (IMPACT-2) examined the time until improvement of symptoms using the licensed dosage of 20 units C1-INH per kg. The time until complete disappearance of symptoms was between 2.5 hours (laryngeal attacks) and 30 hours (peripheral attacks as well as facial swelling)[56]. Side-effects of C1-IHN include fever, injection site reactions and allergic-anaphylactic reactions in rare cases. C1-INH has been established in the acute therapy of HAE for decades. In severe attacks it can be used in pregnancy and during delivery[51].

Icatibant

Since July 2008, the synthetic bradykinin B2 receptor antagonist icatibant is available for acute therapy of HAE attacks[57]. A study confirmed that selective antagonism of the bradykinin B2 receptor with icatibant reduces both the bradykinin concentration as well as oedema signs and symptoms in the HAE patients studied[58]. Icatibant has a favourable safety profile. Serious side-effects were not observed in clinical studies. Antibody production was not observed. Caution is warranted for the use of icatibant in patients with acute ischaemic myocardial disease, unstable angina pectoris, as well as in patients in the weeks following a stroke[59]. Icatibant is available as 30 mg in 3 ml solution as a ready-to-use syringe for immediate subcutaneous injection in an HAE attack. In almost all cases a single injection is sufficient[59].

Medications for the future

At present two other substances are under development for the acute therapy of hereditary angioedema. A recombinant human C1 inhibitor (Rhucin®) that is obtained from rabbit milk is intended to compensate the lack of the body's own C1-INH and be employed in the therapy of oedema attacks. Phase II and III studies have been completed and confirm its efficacy[60].

The recombinant protein is being tested in further studies. The recombinant kallikrein inhibitor DX-88 (ecallantide) reduces the release of bradykinin, the final product of the kallikrein-kinin cascade. In the USA, ecallantide is already licensed under the name Kalbitor® for acute therapy of HAE patients.

2. Short-term prophylaxis

Short-term prophylaxis may be indicated before surgical or traumatic dental procedures in HAE patients for whom these events are known triggers of attacks. For small procedures it is sufficient to have C1-INH concentrate or icatibant available for immediate use. Many authors recommend oral prophylaxis with androgen derivatives. Danazol should be administered 5 days before and 2 days after the procedure at a dose of 2.5 - 10 mg/kg daily (100 - 600 mg daily, not in the first two trimesters of pregnancy), stanozolol 48 hours before and after the procedure (2 - 6 mg daily)[51,52].

Before larger surgical procedures especially in the vicinity of the airways and swallowing apparatus, C1-INH concentrate can (in case of intubation) infused 1 - 1½ hours before the procedure at a dose of 500 units for each 50 kg body weight. Tranexamic acid can be administered 48 hours before and after procedure at a dosage of 1 g qid in adults and 0.5 g qid in children[51].

3. Long-term prophylaxis

A long-term prophylactic strategy may be indicated to reduce frequency and severity of oedema attacks. For prophylactic therapy very often androgen derivatives and antifibrinolytics are used.

Androgen derivatives

Androgen derivatives are also used for the prophylaxis of HAE attacks. They can be administered orally and are considered despite not being licensed as first-line therapy for long-term prophylaxis as they more effectively reduce the frequency and severity of HAE attacks than antifibrinolytics[51]. As they have delayed onset of action, they are not suitable for therapy of acute attacks[61].

The exact mechanism of action is still unclear. In principle, only 17 alkylated androgens are effective in the prophylaxis of HAE attacks. Only these androgen derivatives elevate the concentration of C1-INH, which is increased synthesis of C1-INH in the liver. The most experience for HAE prophylaxis exists for danazol[62-64]. Consensus recommendations consider the dosage necessary for prophylaxis to be 200 mg once or twice daily with the individual required dose also possibly higher. Side effects include virilisation, amenorrhoea, infertility, loss of libido, acne, and depression, etc. The risk of side effects increases with the dose. Androgenic effects make long-term therapy especially in women, children, and adolescents problematic. During pregnancy, androgens are absolutely contraindicated. Androgen prophylaxis should be avoided in children and adolescents[51].

Antifibrinolytics

The effectiveness of antifibrinolytics is lower than that of androgen derivatives. Both agents are contraindicated in thromboembolic diseases and visual disturbances. Side effects include nausea, dizziness, diarrhoea, fatigue, and muscle cramps. A possible tendency for thrombosis must be considered during therapy with antifibrinolytics[34]. The initial dose for tranexamic acid is 1 - 1.5 g two to three times daily with a stepwise reduction depending on clinical findings to 0.5 g once or twice daily[51].

C1-INH concentrate

Some authors recommend using C1- INH concentrate prophylactically for patients frequently affected when androgens or antifibrinolytics are insufficiently effective, have too strong side-effects, or are contraindicated[51].

Conclusion

Hereditary angioedema (HAE) is a relatively rare disease with significant morbidity and mortality. The frequent failure is to make an accurate and timely diagnosis. What is required is to make an accurate and timely diagnosis before the start of therapy.

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"Reading is to the mind what exercise is to the body."

– Joseph Addison.

REVIEW ARTICLE

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Hiccups

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Abstract

Hiccup is a repeated involuntary spasm of the diaphragm followed by sudden rush of air into the lungs causing closure of the glottis which chokes the inflow of further air and produces a characteristic sound. This condition is common and transient and rarely intractable.

Hiccup is said to be the result of irritation of afferent and/or efferent diaphragmatic nerves or medullary centre that controls the respiratory muscles – particularly the diaphragm. The exact aetiology is not known, but is supposed to be often caused by gastric distension, alcohol consumption, or swallowing of hot or irritating substances. Various other causes include metabolic, posterior cranial fossa tumours, and psychological disorders, etc. The exact mechanism is not known though various mechanisms have been described.

Hiccup is usually benign, transient, and self limiting, with a duration of less than one hour without any complication.

Hiccup will need only routine history, physical examination, and routine investigations, rarely requiring specific specialised investigations.

Hiccups are managed easily with home remedies and avoiding predisposing factors, but occasionally may need pharmacological or other types of management. Pranayama and yogic exercises are useful in their management. Drugs often used in prolonged cases are baclofen, lidocaine, GI motilator drugs, antacids, antidepressants, etc.

Complications are rare except for causing social embarrassment, distress, insomnia, etc.

Key words: Hiccup, diaphragmatic irritation, sudden closure of glottis, obstruction of inflow of air, characteristic sound HIC, home remedies.

Hiccups (hiccough, singulus) are repeated involuntary spasms of the diaphragm followed by sudden rush of air into the lungs causing closure of the glottis, which chokes the inflow of further air and produces the characteristic sound.

Transient episodes are very common. Persistent (> 2 days) and intractable (> a month) hiccups are uncommon but quite distressing. The longest recorded attack is 6 decades. Prolonged attacks are a more serious phenomenon and often a diagnostic dilemma, and are associated with significant morbity and may even be fatal. The term "hiccup" derives from the sound of the event. "Hiccough" erroneously implies an association with respiratory reflexes. The medical term "Singulus" is thought to have originated from the Latin "Singult" which translates roughly as the "act of catching one's breath while sobbing".

A benign hiccup is very common and affects all ages including the foetus. Males (82 %) are affected more than females with a ratio of up to 4:1. Persistent intractable hiccups are rare and affect both males and females equally. Females develop hiccups more frequently during early adulthood than males of the same age, and are supposed to be of psychogenic origin. Some studies revealed predominance of males in hiccups of organic aetiology.

Aetiology

- Hiccup is the result of irritation of afferent or efferent diaphragmatic nerves or of the medullary centre that control the respiratory muscles – particularly the diaphragm. Aetiology is generally not known but supposed to be often caused by gastric distension, alcohol consumption, or swallowing hot or irritating substances. Gastro-oesophageal reflux disease and often other oesophageal disorders may result in persistent and intractable hiccups. Other causes are bowel disorders, pancreatitis, pregnancy, gall bladder disease, hepatic metastasis, hepatitis, subphrenic abscess. Thoracic and mediastinal causes include diaphragmatic pleurisy, lobar pneumonia (especially of the lower lobe), pericarditis, or surgery.
- Among metabolic disorders uraemia, chronic alcoholism, gout, hyponatraemia, hypocalcaemia, and alkalosis can cause hiccups.
- Posterior cranial fossa tumours and infarcts can cause hiccups stimulating centres at medullary reticular formation.
- Psychological disorders, e.g., personality disorder, conversion reaction, hysterical neurosis, anorexia

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nervosa, sudden shock and grief reaction can lead to the development of persistent intractable hiccups.

Pathophysiology

The exact mechanism underlying hiccups remains unknown. It can result from abnormalities of both the central and peripheral nervous system. The afferent limb of hiccup reflex involves the phrenic and vagus nerves as well as the sympathetic chain, while the efferent limb consists of the phrenic nerve, efferent nerve to the glottis, and accessory respiratory muscles, e.g., intercostals, scalenus muscle. Reflex arc centre is located at 3rd, 4th, and 5th cervical segment.

In the process of hiccups there is an abrupt inspiration which usually involves unilateral diaphragmatic contraction (mainly the left hemidiaphragm), although bilateral contractions occur, but one side usually dominates. The accelerated movement of air leads to a sudden closure of the glottis producing a typical sound, i.e., hiccup just 35 msec later. This can repeat frequently even upto 4 - 60 times in a min. The arterial PCO_2 level has an impact on the frequency of hiccups. PCO_2 increasing level will decrease whereas hyperventilation leading to reduced level of PCO_2 will increase the frequency.

Clinical features

Hiccup is a complex reflex pattern characterised by a sudden contraction of the diaphragm, inspiratory muscles, and is terminated with abrupt closure of glottis resulting in a characteristic hiccup sound. It can be:-

- Benign, i.e., self-limiting with a duration of less than one hour and no associated complications.
- Persistent, intractable hiccup is not self-limiting, with a prolonged duration, and associated with an underlying organic or psychogenic cause, and may lead to complications.
- Benign hiccups can be averted by avoiding predisposing factors such as excessive spicy and chilly food, alcohol consumption, carbonated beverages, sudden change in ambient or gastrointestinal temperature, e.g., cold showers, drinking hot and cold beverages, sudden excitement, and emotional stress.
- There is a single or series of diaphragmatic spasms of variable spacing and duration.
- Brief, unexpected jerky movements of the shoulder, abdomen, throat, and whole body tremors.
- Hiccups are easily heard as a chirp, squeak "hupp" or – if controlled – a quick inhaling gasp, sigh, or sniff.
- The patient may complain of brief but distracting or painful, frequent or occasional interruption in normal breath, sudden momentary pain of throat, chest, or abdomen.
- The patient may complain of sudden gastric distension after rapid ingestion of hot or very cold meals, food, alcohol, or air preceding hiccup.
- The patient with secondary causes of hiccups will have manifestations of the organic cause of primary disease.
- The hysterical and psychogenic hiccups will stop during sleep.

Diagnostic characteristics

- Presence of predisposing factors.
- Production of the distinctive characteristic "hic" sound as a result of sudden closure of glottis interrupting an abrupt inhalation secondary to diaphragmatic spasm.
- Duration is mostly less than one hour (benign) and self-limiting. But persistent hiccup may last for a long time and is not self-limiting and may even be present during sleep (uncommon). This has some organic cause and may lead to insomnia, fatigue, and exhaustion. It may cause impairment of alertness and concentration, etc.
- A severe form of persistent intractable hiccups can complicate eating and drinking leading to malnutrition, fluid and electrolyte imbalance, etc.

Evaluation

No specific evaluation is required for acute hiccups if routine history and physical examination are within normal limits. Routine laboratory investigations of blood, urine, and stool will suffice.

Hiccup of longer duration and with no obvious cause should have laboratory investigations for serum electrolytes, BUN, serum creatinine, chest X-ray PA view, liver function tests, serum enzymes, and ECG. Upper gastrointestinal endoscopy and oesophageal pH monitoring may be needed for GERD, oesophageal stricture and dilatation.

If all the aforementioned investigations are unremarkable, and hiccups are intractable, then MRI of the brain, CT of the chest, and ultrasonography for hepato-biliary system and other abdominal problems may be done.

Management

In most cases, hiccups are benign and self-limiting, not requiring any medical therapy, and relieved by home remedies. Pharmacological and more invasive methods should be reserved for the rare cases of persistent intractable hiccups. For the symptomatic relief and avoidance of potential complications, treatment should be guided by the duration and intensity of the hiccups and initiated by a physician. The risk of invasive therapy should be weighed against the benefits to avoid a benign condition resulting in serious treatment-related complications. Valid scientific data regarding the management of hiccup are difficult to find as relevant studies are rare or scarce.

Home remedies

Factors known to predispose to hiccups, e.g., excessively spicy, chilly food, alcohol consumption, sudden excitement, emotional stress, etc., should be avoided. Home remedies alone or in combination are:-

- Breath holding, the Valsalva manoeuvre, i.e., forced expiration against a closed glottis, breathing into a paper bag, pulling of the tongue, sneezing, swallowing a teaspoonful of granulated sugar, sipping of iced water, milk, or eating ice cream.
- *Kapalbhati pranayama*, *bharstika,* and *anulom vilom* are useful.
- *Yogasana* in which compressing the diaphragm by pulling the knees upto the chest and trying to touch the knee with the nose tip, is helpful.
- Swallowing large amount of water while closing the nose and ears, and a sudden fright situation are also known to be effective.

Alternative therapies

In addition, various methods and treatment with alternative therapies such as acupuncture, hypnosis, and psychotherapies can be useful.

Pharmacologic treatment

Most treatments are based on anecdotal experience or case reports, as the infrequent occurrence of prolonged hiccups preludes large controlled clinical trials.

Baclofen – a centrally acting muscle relaxant – has emerged now as a safe and acceptable first-line drug in most situations. It is effective in doses as small as 5 - 10 mg/day, although occasionally 20 mg three times a day may be needed. Intravenous lidocaine in a loading dose of 1 mg/kg followed by an infusion of 2 mg/minute has proved useful.

Chlorpromazine widely used previously as a first-line drug, almost always works (probably by a diffuse depressant effect on the reticular formation), but does not correct gastric distension. For gastric distension which could be a cause of hiccups, defoaming antiflatulents, e.g., simethicone and/or prokinetics, e.g., metoclopramide (10 - 20 mg) or itopride may be used. Adverse drugs reactions are commonly seen with chlorpromazine, e.g., hypotension, marked sedation, dryness of mouth – especially in the elderly. It can be given in a test dose of 10 - 20 mg orally and repeated BD/TDS or as and when required. Parenteral route of administration of chlorpromazine should be used very cautiously because of a fall in BP.

Haloperidol (tranquiliser) is effective in doses of 2 - 5 mg.

Several anticonvulsants have been used to treat intractable hiccups. Phenytoin, valproic acid, and carbamazepine have been effective when used in typical anticonvulsant doses. Gabapentine has been shown to be effective where CNS lesions are present, or in some other aetiological or non-specific groups.

Anaesthetic agents, e.g., ketamine, has been successful in a dose of 0.4 mg/kg i.e., one-fifth of the usual anaesthetic dose.

Other agents reported to be beneficial are sedative antidepressant (amytriptylline) except benzodiazepines which exacerbate or precipitate hiccups. Miscellaneous group of medicine include nifedipine, amantadine, midazolam, glucagon, edrophonium, etc.

Invasive therapy

Anaesthesia to block the phrenic nerve and surgical implantation of an electronic stimulator to the vagus nerve has been effective. Surgery to disable the phrenic nerve (the nerve that controls diaphragm) is the treatment of last resort.

Leg traction used by osteopaths relaxes the ipsilateral psoas muscle and terminates the spasm of diaphragm.

Breathing pacemaker devices control excursions of the diaphragm by electric stimulation of the phrenic nerve.

Complications

Hiccups may cause social embarrassment and distress and interfere with ventilation, medical procedures, and cause wound dehiscence. Hiccups may even lead to oesophagitis, weight loss, cardiac arrhythmias, and insomnia.

Prognosis

Benign hiccups can be annoying or sometimes embarrassing but are rarely of clinical significance. In healthy people, hiccups usually go away by themselves with no serious effects. Persistent hiccups can last longer and may result in speech, eating, and sleep disorders.

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"Faith is the force of life."

– LEO TOLSTOY.

REVIEW ARTICLE

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Understanding glycosylated haemoglobin

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Abstract

Glycosylated/glycated Haemoglobin (HbA1c) can be directly correlated to glucose levels and complications, and has long been used to assess adequacy of the treatment regimen and the stability of glycaemic control in diabetes. It has recently been introduced for the diagnosis of diabetes mellitus. This review article seeks to summarise the concept of glycosylated haemoglobin, and its current status in the management of diabetes mellitus.

Key words: Haemoglobin A1c protein.

Glycosylated haemoglobin/glycated haemoglobin

HbA1c can be directly correlated to glucose levels and complications[1,2], and is recommended by international guidelines as the preferred measure when evaluating the overall control of diabetes and the patient's risk for complications[3].

HbA1c is formed by a post-translational, non-enzymatic, substrate-concentration dependent irreversible process of combination of aldehyde group of glucose and other hexoses with the amino-terminal valine of the β-chain of haemoglobin. In the normal lifespan of the red blood cell, glucose molecules react with haemoglobin forming glycated haemoglobin. As the average amount of plasma glucose increases, the fraction of glycated haemoglobin increases in a predictable way. While glycation of haemoglobin occurs over the entire 120-day life span of the red blood cell, within these 120 days recent glycaemia has the largest influence on the HbA1c value[2,3]. Thus, mean blood glucose of past 1 month, 2 months and 3 months contributes 50%, 40% and 10% respectively to the final result. By mathematical modelling, the t1/2 of HbA1c is estimated to be 35.2 days[4]. This means that half of the glycation seen during estimation has occurred in the previous 35.2 days[5]. HbA1C is first recognised as a reliable marker for the overall glucose exposure and its direct consequence, an excessive rate of glycation[5,6], and second, as an integrator of both fasting and post-prandial glycaemic disorders. As a consequence, it is not surprising that fasting and post-prandial hyperglycaemia were identified separately or concomitantly as major risk factors for diabetes complications. The U.K. Prospective Diabetes Study (UKPDS) demonstrated that reductions in HbA1C and FPG (fasting plasma glucose) levels were accompanied by substantial decreases in the risk of all diabetes-related end-points, particularly the risks for myocardial infarction and microvascular complications, which were diminished by 14% and 37% respectively, for each 1% reduction in HbA1C (1,25). The IDF (International Diabetes Federation) and the American College of Endocrinology (ACE) recommend HbA1c values below 6.5%, while ADA (American Diabetes Association) recommends control below 7.0% for most patients[23]. The patient's health, risk of hypoglycaemia, and his/her specific health risks must be given due consideration when setting a target HbA1c level in an individual patient. Patients at high-risk of microvascular complications may further benefit from reducing HbA1c below 7% as long as hypoglycaemia can be avoided because the patients themselves are responsible for averting or responding to their own hypoglycaemic episodes. The patient's input and the doctor's assessment of the patient's self-care skills are also important in deciding the target HbA1c in individual patients as per the recent Position Statement of ADA[6]. The approximate mapping between HbA1c values and eAG (estimated Average Glucose) measurements is given by the following equation[7]:-

$$eAG\ (mg/dl) = 28.7 \times A1C - 46.7$$

$$eAG\ (mmol/l) = 1.59 \times A1C - 2.59$$

The ADA guidelines are similar to others in advising that the glycosylated haemoglobin test be performed at least twice a year in patients with diabetes who are meeting treatment goals (and who have stable glycaemic control), and quarterly in patients with diabetes whose therapy has changed or that are not meeting glycaemic goals[5].

Pitfalls of HbA1C

1. Abnormal haemoglobins: Patients with

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haemoglobinopathies and associated anaemia can also have altered red cell survival which will influence all HbA1c measurements. Any condition that changes red cell turnover, such as haemolytic anaemia, chronic malaria, major blood loss, glucose-6-phosphate dehydrogenase deficiency, sickle cell anaemia.

It has been demonstrated that erythrocyte survival is shorter at chronic high glucose levels and that this hyperglycaemia-related decrease in erythrocyte survival, which improves on control of hyperglycaemia, results in exponential underestimation of the severity of hyperglycaemia at higher HbA1c levels[9,10]. Major blood loss or blood transfusions also lead to spurious HbA1c results.

2. Ageing and ethnicity: It has been identified that older non-diabetic subjects appear to have higher HbA1c values than younger individuals, being approximately 0.4% higher at 70 years than at 40 years, even after adjusting for fasting and 2-hr glucose. Differences in the HbA1c have also been consistently found between individuals from different races[11].
3. Analytical considerations: There are still clinically significant differences between laboratories using different instruments from different manufacturers for estimating HbA1c. The most accepted method is the one used in the UKPDS trial. HbA1c estimation does not require a fasting state, and analytical variability is < 2%.
4. High-dose salicylates, vitamins C and E, have been reported to be interfering substances in the measurement of HBA1c.

HbA1c in the diagnosis of DM

Historically, the measurement of plasma glucose has been the means of diagnosing diabetes. An HbA1c level of ≥ 6.5% (to be reconfirmed on a subsequent day) has been introduced recently for diagnosis of diabetes mellitus. The diagnostic HbA1c cut-off point of 6.5% is associated with an inflection point for retinopathy prevalence, as are the diagnostic thresholds for FPG and 2-hr PPG (post-prandial glucose). The section previously known as pre-diabetic has been renamed as "Categories of increased risk for diabetes". In addition to IFG (impaired fasting glucose) and IGT (impaired glucose tolerance), an HbA1c range of 5.7-6.4% has been included in this category. An international expert committee[8], after an extensive review of both established and emerging epidemiological evidence, recommended the use of the HbA1c test to diagnose diabetes, with a threshold of > 6.5%. In selecting this diagnostic HbA1c level, the committee has balanced the stigma and costs of mistakenly identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis. ADA (2010) in its revised clinical practise guidelines for diabetes diagnosis has also recommended HbA1c as an easier test that could potentially reduce the number of patients with undiagnosed diabetes.

In conclusion, HbA1c is an increasingly important marker of glycaemia in the management of diabetes mellitus, and its utility cannot be stressed enough.

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"Good deeds are the best prayer."

– ANONYMOUS.

CASE REPORT

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Thyroid storm: An unusual presentation

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Abstract

A 23-year-old female patient was hospitalised with complaints of fever, diarrhoea, altered sensorium for 3 days with a rapidly declining mental status. Before admission to the hospital, her relatives gave history of her being restless, markedly irritable with generalised tonic-clonic seizures and a positive history of palpitations. Suspecting the diagnosis of thyroid storm clinically, she was started on aggressive antithyroid treatment following which she showed marked clinical improvement. Thyroid storm is a rare endocrine emergency with increased mortality risk in this otherwise fatal entity. The aim of reporting this case is to make the physicians aware of this fatal medical disease necessitating prompt intervention. A case of thyroid storm presenting with predominant neurological manifestations is being presented here for its rarity.

Key words: Thyroid storm, unusual presentation.

Introduction

Thyroid storm (accelerated hyperthyroidism) is a rare manifestation of thyrotoxicosis with a wide spectrum of clinical presentations involving multiple systems. It generally occurs in females from the third to the sixth decade of life, especially with Grave's disease. It is usually a life-threatening medical emergency and is fatal if left untreated. The classic clinical presentation includes fever, tachycardia, hypertension, tremors, nausea, vomiting, diarrhoea, dehydration, arrhythmias, delirium, and coma[1]. It usually develops in an undiagnosed hyperthyroid patient who has a major stress or continues without antithyroid treatment in addition to other precipitating factors like surgery, radio-iodine therapy, trauma, acute infection toxaemia of pregnancy, labour, excessive palpation of the thyroid gland in hyperthyroid patients, pulmonary thromboembolism, severe drug reactions, or myocardial infarction, etc[2]. Its early recognition and treatment is essential in reducing the morbidity and mortality rate in this potentially fatal disease. Only 1 - 2% of hyperthyroid cases manifest as thyroid storm and the mortality ranges between 20 - 30% despite treatment[3].

Case report

A 23-year-old unmarried female was brought to the hospital with complaints of fever, diarrhoea, light headedness, altered sensorium for 3 days with a rapidly declining mental status. Before admission, she was reported to be restless, markedly irritable with generalised tonic clonic seizures as well as positive history of palpitations as narrated by relatives.

There was no history of previous illness or hospital admission, major surgery, or antipsychotic drugs intake. On examination, she was febrile (temp 101°F), pulse rate 126/min and regular, BP 110/70 mmHg, respiratory rate 29 breaths/mm, oxygen saturation 98% on 3L. Her pupils were slightly dilated, mucous membranes were moist and the she had an abrasion on the tongue consistent with biting. JVP was normal; there was no lymphadenopathy. Examination of the neck revealed bilateral thyroid enlargement with diffuse toxic goitre with systolic bruit heard over it. She had a stare with a typical anxious look. There were no signs of meningeal irritation. Fundus examination was normal. On neurological examination, she responded to painful stimuli, with brisk deep tendon reflexes and plantar flexor response. CVS examination revealed tachycardia with regular rhythm but no murmurs. Respiratory system and abdominal examination was unremarkable. ECG showed sinus tachycardia. Her laboratory results showed no abnormality of haemogram, blood glucose levels, CSF, serum electrolytes, renal and liver function tests. X-ray chest showed no active disease. CT brain was normal. Blood cultures were negative. EEG revealed bilateral frontal slow waves. Technetium scan of thyroid showed hyperfunctioning gland with diffuse tracer uptake (36% at 20 minutes). The constellation of signs and symptoms suggested that this could be a case of thyroid storm. Based on the diagnostic criteria of Burch and Wartofsky[4], she had a total score of 60, which was strongly suggestive of thyroid storm (a score > 25 is suggestive of thyroid storm). The patient was put on antithyroid drugs awaiting thyroid function tests – T3, T4, and TSH. She was started on propylthiouracil 400 mg tid and propranolol 40 mg tid, IV fluids, hydrocortisone IV (later changed to oral steroids). Her thyroid profile revealed TSH 0.02 mIU/ml, T4 28 µg/dl (N 4 - 14 µg/dl); T3 40 ng/dl (N = 0.8 - 2 ng/dl). Thyroid peroxidase autoantibody was negative. Based on

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clinical presentation and later on confirmed by results, Lugol's iodine 8 drops 8 hourly was given for 3 days. The fever subsided, diarrhoea improved, and agitation decreased. After considerable improvement in her condition in about 8 days time, she was discharged in an euthyroid state, conscious, well oriented, without tremors and fever, and advised to continue on propylthiouracil and propranolol. On follow-up at 3 months, she was carrying our all routine activities with a positive frame of mind.

Discussion

Thyroid storm – a dramatic exacerbation of existing hyperthyroidism, of sudden onset associated with fever, tachycardia, and CNS symptomatology – remains a life-threatening medical emergency if left untreated. Being a rare endocrine emergency, all clinicians must be aware of its clinical features and treatment so that morbidity and mortality can be avoided. About 1 - 2% of patients with hyperthyroidism progress to thyroid storm and the 100% mortality reported earlier has now come down to 20 - 30% with better recognition and treatment. It might be difficult to distinguish between thyroid storm and infection in thyrotoxic patients as tachycardia and fever might be present in both. On account of an overlapping of the symptoms, precipitating conditions and complications, a clinical diagnosis is not easy and is often made too late. The definitive criteria of thyroid storm laid down by Burch and Wartotsky[4] are useful. The triggering factors for thyroid storm include surgery, major stress, noncompliance to antithyroid drugs, infection, radio-iodine, etc[2]. Treatment of thyroid storm should not be delayed if there is a high index of suspicion, and empirical treatment should be started on clinical grounds awaiting laboratory reports, which was evident in our case[5]. Urgent thyroid function tests is a confirmatory diagnosis. Hyperglycaemia, hypercalcaemia, leucocytosis may co-exist. Deranged liver functions mainly alkaline phosphatase – may occur due to increased osteoblastic activity in response to high bone resorption. Serum thyroid hormone levels would typically show hyperthyroidism, but due to an abrupt rise of thryoid hormone secondary to triggering factors, the patient can no longer adapt to the sudden metabolic stress[6]. An acute elevation of FT3 or FT4 in thyrotoxic patients may produce acute decompensation. However, no absolute levels of serum T3 or T4 exist above which thyroid storm develops inevitably.[7] Earlier, cases of thyroid storm have been well reported where treatment of thyroid storm was started immediately awaiting thyroid function tests[8,9]. T4 may rarely be normal or even decreasing because of co-existing nonthyroidal illness[10].

In our case, the patient presented with altered sensorium without signs of raised intracranial tension and focal neurological deficit. Differential diagnosis includes neuroleptic malignant syndrome, anticholinergic poisoning, sympathomimetic toxicity, alcohol withdrawal syndrome, toxic/metabolic encephalopathy, hypertensive encephalopathy, meningitis, etc. But the clinical features of our patient in the form of hypermetabolic state made thyroid storm a definitive diagnosis; and possibly the triggering factor for thyroid storm in this case could be febrile illness. Predominant neurological manifestation in the form of altered mental status and history of tonic clonic generalised seizures was an unusual feature in our case.

Treatment of thyroid storm includes correction of severe thyrotoxicosis, precipitating illness, and associated active thyroid eye disease. Patients should be monitored in the intensive care units in the early phase. Diuretics may be given for congestive cardiac failure (CHF). Drugs like thionamides block hormone synthesis; iodine solution blocks the release of thyroid hormone, beta-blockers control adrenergic symptoms, and steroids reduce T4 to T3 conversion. Beta-blockers should be used cautiously in the presence of CHF. Among thionamides, propylthiouracil is preferred over methionazole as it blocks peripheral T4 to T3 conversion. Iodinated radiocontrast iopanoic acid, cholestyramine can also be used. Peritoneal dialysis and plasmaphresis are used to reduce the high levels of circulating T4 and T3 in a thyroid storm[5,9,10].

Conclusion

Diagnosis may be missed on account of variable presentation. Treatment should never be delayed. A high index of suspicion is required for prompt recognition and effective management of unusual presentation of thyroid storm in order to reduce the morbidity and mortality of this life-threatening medical disorder.

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CASE REPORT

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A case of Kikuchi-Fujimoto disease

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Abstract

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotising lymphadenitis is a rare, benign, self-limited cervical lymphadenitis of unknown aetiology. Kikuchi first described the disease in 1972 in Japan. Fujimoto and colleagues independently described Kikuchi's disease in the same year. It predominantly affects young women and can closely mimic infective and immunological disorders. In this article a case of KFD in a young female is described.

Introduction

Kikuchi's disease is an uncommon, idiopathic, generally self-limited cause of lymphadenitis[1]. The condition was first described by Kikuchi in 1972 in Japan. The cause of Kikuchi-Fujimoto disease is unknown. Some kind of viral or post-viral aetiology has been proposed. KFD affects female patients under the age of 30 years in a 4:1 ratio. It presents with unilateral painless or painful lymphadenopathy along with fever. Symptoms may persist for a few weeks to 6 months. There have also been reports of a possible link between KFD and systemic lupus erythematosus (SLE). Its incidence has been reported worldwide with a higher prevalence among Japanese and other Asiatic individuals. KFD should be kept in the differential diagnosis of fever with cervical lymphadenopathy in a young female along with lymphoma and tuberculosis, to avoid unnecessary investigations.

Case report

History

A 14-year-old female from Kolkata presented to us with a 3 weeks history of fever, polyarthritis, and left-sided neck swelling for 2 weeks. There was no history of tuberculosis or contact with a case of tuberculosis. She did not have any history of weight loss, rash, mouth ulcers, drug intake, or atopy. The fever was intermittent in nature and used to subside after paracetamol intake. She had polyarthritis involving the wrists, ankles, and small joints of the hands and feet. One week after the onset of fever she noticed a painful swelling on the left side of her neck. She did not complain of any dental problem or odynophagia at that point of time.

Examination

She was febrile without any other feature of systemic inflammatory response. Multiple 2 × 2 cm nonmatted, tender, mobile lymph nodes were palpable along the left posterior and anterior triangle of neck. No other sites of lymphadenopathy, sternal tenderness or rash were noted. She had no hepatosplenomegaly.

Investigations

Her Hb was 10.4 gm%, TLC 5,030/cumm with a normal differential count. Her platelet count was 232,000/cumm and ESR 100 mm/hr. No abnormal cells were seen on peripheral smear. Malaria and dengue serology were negative. Widal test was negative at all dilutions. FT3 3.410 pg/ml, FT4 1.440 ng/dl, and TSH 1.820 µIU/ml were normal. CXR and USG abdomen were normal. ANA by hep 2 cell line was negative. Echocardiogram did not reveal any vegetation. USG neck revealed enlarged hypoechoic lymph nodes with loss of hilar architecture. Surgical referral was done for lymph node biopsy.

Histopathology

The excised lymph nodes show effacement of architecture by large areas of necrosis admixed with abundant karyorrhectic debris. Collection of mononuclear cells, clusters of foam cells, and plenty of phagocytic histiocytes with crescentic nuclei were present. Intervening areas show reactive hyperplasia and polymorphic population of lymphoid cells. No granuloma or malignancy was seen. This was consistent with necrotising histiocytic lymphadenitis (Kikuchi lymphadenitis).

Treatment

She was given prednisolone 1 mg/kg/d and naproxen 250

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mg bd. Her symptoms started resolving a week after. She got afebrile and her constitutional symptoms went away. Her lymph node swellings are resolving slowly.

Discussion

Kikuchi fir st reported KD or histiocytic necrotising lymphadenitis without granulocytic infiltration in Japan in 1972. Though it has been reported worldwide, it still remains a poorly recognised clinicopathologic entity and is confused with lymphoma and systemic lupus erythematosus. There are only few case reports of this disease in children[2].

Kikuchi's disease most often presents with cervical lymphadenopathy which may be tender and can be accompanied by fever, upper respiratory tract symptoms. Other possible affected lymph node groups are axillary, supraclavicular, mediastinal, retroperitoneal, or inguinal. Less common symptoms include arthralgia, skin rashes, weakness, and night sweats. Weight loss, diarrhoea, anorexia, chills, nausea, vomiting and abdominal pain have also been reported. Some patients may also have hepatosplenomegaly[3].

The exact aetiology of Kikuchi's disease is not known. Viral agents such as Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), Parvo virus B 19 and human T-cell lymphotropic virus (HTLV 1) have been suggested as possible aetiological agents, but none have been confirmed so far. Toxoplasma and other bacterial agents like *Yersinia enterocolitica*, Bartonella, and Brucella have also been implicated[4]. An autoimmune mechanism has also been proposed because KFD is seen in conjunction with SLE[5].

Routine laboratory investigations usually do not aid in the diagnosis except for ESR and CRP which might be elevated in some patients, and many patients have a low white count. Moreover, 25 to 31% of patients have atypical peripheral blood lymphocytes. Diagnosis is based on histopathological findings of lymph node biopsy. Morphologically, it is characterised by irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris which can distort the nodal architecture and large number of different types of histiocytes at the margin of necrotic areas. The karyorrhectic foci are formed by different cell types, predominantly histiocytes and plasmacytoid monocytes, but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are either absent or scarce[6]. The immunophenotype of Kikuchi's disease is primarily composed of mature CD 8 positive and CD 4 positive T lymphocytes. High rate of apoptosis is also seen among lymphocytes and histiocytes.

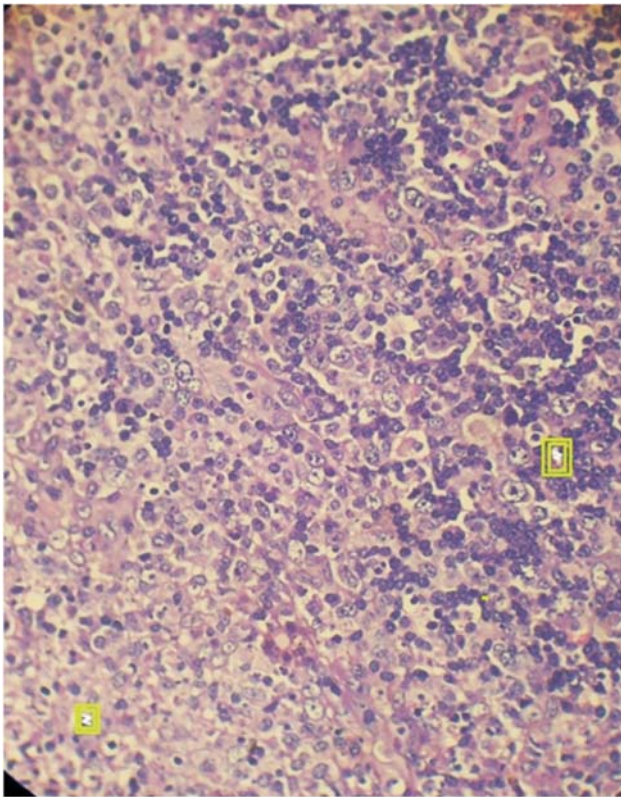

Fig. 1: *Photomicrograph depicting necrotising histiocytic lymphadenitis. N stands for necrosis and H for histiocytes.*

Clinically, Kikuchi's disease may mimic systemic lupus erythematosus (SLE) or lymphoma (especially T-cell non Hodgkin's lymphoma). Careful histopathologic examination will help us to distinguish KFD from otherdiseases. Antinuclear antibodies (ANA) were absent in our patient. Histological feature that helps in differentiation of KFD from SLE is almost total absence of plasma cells in the nodal tissue. Histological feature that helps in differentiation of KFD from lymphoma includes incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates, and absence of Reed-Sternberg cells[7].

No specific treatment is available for Kikuchi's disease. Treatment is generally supportive. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate lymph node tenderness and fever. The use of corticosteroids has been recommended in severe disease[8]. Intravenous immunoglobulin has also been tried with some success[9]. The disease runs a benign course usually and resolves in several weeks to months. The disease has a recurrence rate of 3 to 4 %[10].

Conclusion

In conclusion, this case highlights the importance of

keeping KFD in the differential diagnosis of fever with cervical lymphadenopathy, especially in a young female.

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CASE REPORT

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A rare case of pontine NCC presenting as abducens nerve palsy

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Abstract

The cerebral manifestations of cysticercosis are diverse, related to the encystment and subsequent calcification of the larvae in the cerebral parenchyma, subarachnoid space, and ventricles. Neurocysticercosis most commonly presents with seizure disorders, the lesions are most often multiple. We report a patient with solitary pontine NCC presenting with isolated abducens nerve palsy. The case report highlights an uncommon location of NCC, and also draws attention to an unusual cause of sixth nerve palsy in patients from tropical regions.

Introduction

Neurocysticercosis (NCC), the infection of the human brain by the larvae of the parasite *Taenia solium*, is the most common parasitic infection of the nervous system. In Central and South America and in parts of Africa and the Middle East, cysticercosis is a leading cause of epilepsy and other neurologic disturbances[1]. Most NCC cysts are located in the subarachnoid spaces, typically the basal cisterns and deep within the sulci. Other common locations include the hemispheric parenchyma at the gray-white matter junctions and the fourth ventricle; rarely, cysts are found in the brain stem. We report an unusual manifestation of NCC in a young tribal teenager who presented with isolated sixth cranial nerve palsy.

Case report

A seventeen-year-old tribal boy of low socioeconomic status, presented with inability to move his right eyeball laterally, and double vision on looking towards the right side for the last one week. There was no history of fever, headache, vomiting, seizure, diminution of vision, ptosis, deviation of angle of mouth, difficulty in swallowing, or nasal regurgitation. There was no history of weakness or incoordination of limbs. His general physical and systemic examination was unremarkable. There was a limited eye movement of right eyeball on lateral direction. He had diplopia – particularly on looking towards the right side. Bilaterally, the pupils were of normal size and reacting to light. There were no signs and symptoms of fifth and seventh cranial nerve palsy (all other cranial nerves were tested and found normal). There were no other neurological deficits. His gait and tandem walking was normal. A presumptive diagnosis of isolated sixth nerve palsy was made and a magnetic resonance imaging (MRI) with MR spectroscopy (MRS) was asked for; it showed a ring-enhancing SOL in the porterior part of pons (11 x 11 mm) with perifocal oedema. On MRS, there in near-normal NAA , Cho: Cr ratio < 1, and no lipid peak; thus it suggests neurocysticercosis.

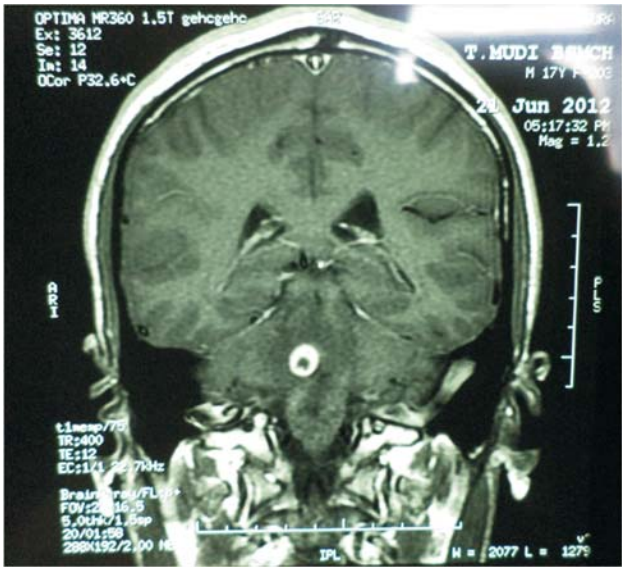

Fig. 1: *MRI brain showing ring-enhancing lesion with an eccentric dot in the pons.*

His other investigations including haemogram, ESR, skiagram of chest, liver and renal function tests were normal. HIV 1 and 2 and the Mantoux test was negative. The ELISA for IgG antibody against *T. solium* glycoprotein in serum was positive. We treated him with cysticidal drug (Albendazole 15 mg/kg/day) for 15 days alongwith a steroid. His symptoms gradually improved, and by the end of two weeks he was totally asymptomatic. A repeat MRI brain was done after one month during follow-up, it showed complete resolution of the pontine lesion.

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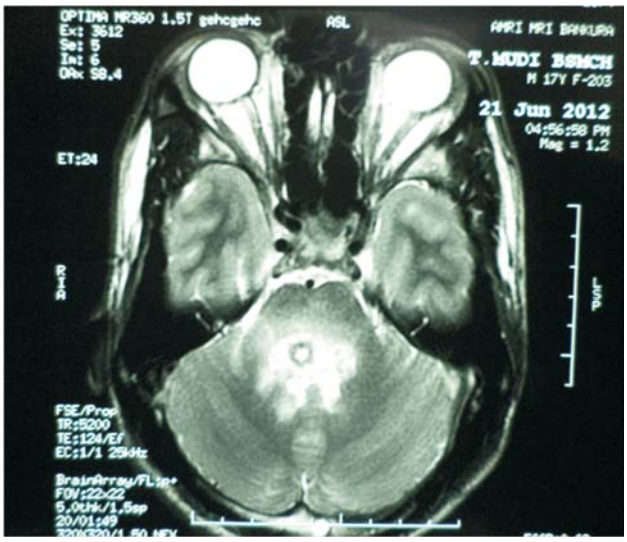

Fig. 2: *MRI brain showing ring lesion with perilesional oedema in posterior pons.*

Discussion

Neurocysticercosis is the most frequent parasitic disease of the nervous system, and is a growing problem in industrialised countries because of immigration of tapeworm carriers from areas of endemic disease. NCC has varied presentations. NCC is a pleomorphic disease and the pleomorphism is due to variations in the locations of the lesions, the number of parasites, and the host's immune response. The main clinical manifestations of neurocysticercosis are seizures, headache, and focal neurological deficits, and it can have sequealae such as epilepsy, hydrocephalus, and dementia[2].

Dewan and Kaushik[3] reported a 10-year-old girl who presented to the paediatric emergency department of Guru Teg Bahadur Hospital, a tertiary care hospital in Delhi, India, with complaints of abnormal choreiform movement along with slurring of speech and emotional lability for a period of 4 days. Magnetic resonance imaging (MRI) of the brain revealed a 5.2 x 4.8 mm ring-enhancing lesion involving the right paramedian midbrain with mild perilesional oedema suggestive of active NCC.

Anand and Prasad[4] reported the case of a sixteen-year-old boy who presented with inability to move his right eyeball laterally, and double vision on looking towards the right side for two months duration. Magnetic resonance imaging showed a discrete rounded lesion in the posterior aspect of the pons in the midline. After treatment with cysticidal drugs for 30 days, a follow-up MRI after three months revealed complete resolution of the lesion.

Bhatia and Desai[5] reported the case of a 45-year-old healthy man who presented with a 2-weeks history of continuous rippling and quivering movements of the right side of his face and neck, suggestive of myokymia. MRI scan of the head revealed neurocysticercus in the pons. Treatment with steroids and carbamazepine produced a significant benefit.

In our case we had a tribal boy of low socio-economic background, who presented with isolated abducens nerve palsy and MRI brain suggestive of NCC, which responded very well to antihelminthic drug and steroid.

Conclusion

We should always have a suspicion of NCC in all ring-enhancing CNS lesions even if the sites are unusual or the lesion is solitary, because early diagnosis and drug treatment can lead to total cure of this condition as in our case. Apart from the effective drug treatment, the control of disease depends on preventive measures. It is important to recognise this treatable disease in order to avoid unnecessary neurosurgical intervention and empirical antituberculous chemotherapy.

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"Nothing in life is to be feared.
It is only to be understood."

– Marie Curie.

CASE REPORT

JIACM 2014; 15(3-4): 229-31

A case of rapid second-line anti-retroviral treatment failure – An analysis of possible causes and preventives

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Abstract

A 45-year-man presented with fever, persistent cough, and diarrhoea. Routine screening of his symptoms revealed infection with HIV. But poor improvement was evidenced by his failing CD4 and viral load counts after initiation of ART. In resource-limited settings, we are not able to assess the drug resistance profile of patients to ART prior to initiation of regimens, hence we are left with no other choice than to assess efficacy from clinical outcomes. An unexpected and rapid switch of failing regimens aroused suspicion as to the causes which might have contributed and their prevention.

Key words: Rapid second-line ART failure, drug resistance.

Introduction

Combination anti-retroviral therapy (ART) against human immunodeficiency virus (HIV) infection is developing rapidly, with potentially more effective treatment options emerging every year. However, clinical, immunological and virological failure after using first-line therapy, resulting in switch to second-line therapy is not uncommon. In fact, the PLATO II project team and COHERE group, at the end of their study, have concluded that the rate of virologic failure of the three original drug classes [i.e. nucleos(t)ide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI)] is low, but not negligible, and does not appear to diminish over time from starting ART[1]. Fortunately, such cases are becoming more and more rare[2]. In fact, patients not responding to second-line therapy, even after a rapid switch, are extremely rare.

The case

A 45-year-old married man, presented with history of cough, fever, and irregular episodes of diarrhoea. In March 2002, HIV-1 infection was diagnosed. Initial CD4 count was 71 cells/μL and RNA viral load was 283,431 copies/ml. First-line therapy was initiated with Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP) in April 2002.

Even after 12 months of therapy, CD4 count failed to improve significantly (130 cells/μL). Non-adherence to protocol was detected. Due to lack of proper education, the patient had failed to follow the instructions and had taken the medicine once daily, instead of the recommended twice daily schedule.

However, after another year of treatment, he showed signs of gradually worsening anaemia. He was shifted to a regimen with Stavudine/Lamivudine/Nevirapine (d4T/3TC/NVP).

Almost at the same time, he had developed persistent cough, haemoptysis, and cervical lymphadenopathy, which did not respond to Co-trimoxazole and other conventional antibiotics. Repeated sputum examinations for acid-fast bacilli were negative. Fine needle aspiration of cervical lymph node biopsy showed nonspecific lymphadenitis, sputum Bactec cultures yielded no growth. Suspecting pulmonary tuberculosis from radiological imaging, he was started on Category I DOTS regimen against *M. tuberculosis* in April 2004, and NVP was substituted with EFV (Efavirenz). Anti-tubercular therapy was completed after nine months with an extended continuation phase, following which his symptoms showed clinical improvement.

Throughout these years of therapy, his CD4 count remained low. In September 2005, CD4 level dropped to its nadir value, i.e., 15 cells/μL.

Protease inhibitors were started as SQV (Saquinavir) with RTV (Ritonavir) boostering.

Revised ART Regimen was AZT/3TC/SQV/r. AZT was continued till December 2005, but had to be substituted as the patient developed severe anaemia (Hb - 5.5 gm%) and gastritis.

Despite this switch to protease inhibitor therapy, his CD4

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level failed to show significant improvement. CD4 counts ranged between 210 cells/µL (June, 2006) and 166 cells/µL (June, 2007), associated with a high viral load (3,60,387 copies/ml). By this time, he started having complaints of frequent anginal pain and was diagnosed to be suffering from cardiomyopathy with gross mitral regurgitation. He also had frequent episodes of diarrhoea, which were treated symptomatically. Evaluation of medication adherence revealed severe underdosing of Saquinavir, and this was possibly the reason of poor response inspite of prolonged treatment with it for around 2 years.

In August 2007, in view of high viral load he was switched to regimen with Abacavir/Tenofovir/Lopinavir with Ritonavir boost (ABC/TDF/LPV/r). Following this his CD4 count went up to 308 cells/µL.

In November 2009, his repeat CD4 was 236 and viral load was still high at 1,35,000 copies/ml. His case was presented at State AIDS Clinical Expert Panel for evaluation of failing regimen and he was started on AZT/3TC/TDF/LPV/r.

In May 2011, in keeping with ongoing changes in guidelines, he was switched on to Atazanavir with Ritonavir boost/Tenofovir /Lamivudine (ATV/r/TDF/3TC). In July 2011, his CD4 level was 244 cells/µL and viral load was 44,000 copies/mL, which was again suggestive of treatment failure (Figure 1).

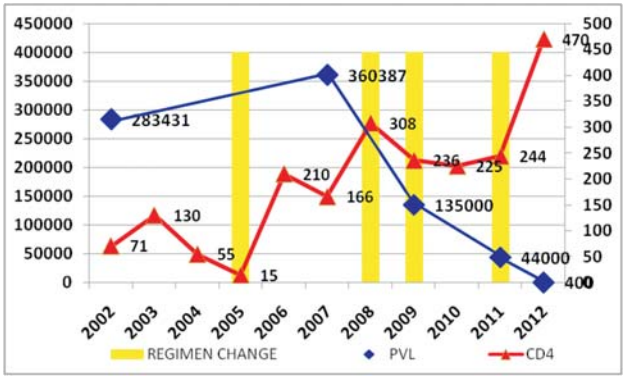

Fig. 1: *Graphical representation of changes of PVL and CD4 with switch of regimens.*

In October 2011, the patient opted for a drug resistance testing which revealed resistant mutations to M41L, D67N, T69D, L74I, M184V, L210W, T215F indicative of NRTI resistance, and L10I, K43T, M46L, F53L, I54V, A71V, T74P, V82A, L90M suggestive of resistance to most PI regimens. Partial sensitivity was seen to NNRTI which were used quite a few years back. Report showed sensitivity to Darunavir and partially to Tenofovir.

From December 2011, he was started on a fresh regime with Darunavir+Ritonavir boost/Raltegravir/Tenofovir/Lamivudine. After three months of therapy, in March 2012, for the first time in almost ten years of his antiretroviral treatment, he showed good response. His CD4 level improved to 470 cells/µL, and his viral load went down to an undetectable level (Table I).

Table I: Detailed course of ART treatment.

Date of starting ART	Ongoing regimen	Substitution/ switch/stop	Revised regimen	Reason
April, 2002	AZT/3TC/NVP	-	-	-
March, 2004	AZT/3TC/NVP	AZT > d4T	d4T/3TC/NVP	Anaemia
April, 2004	d4T/3TC/NVP	NVP > EFV	d4T/3TC/EFV	ATD started
September, 2005	d4T/3TC/EFV	Switchover	AZT/3TC /SQV/r	Immunological failure
December, 2005	AZT/3TC/SQV/r	AZT > d4T	d4T/3TC/ SQV/r	Anaemia
August, 2007	d4T/3TC/SQV/r	Switchover	ABC/TDF/LPV/r	High viral load
November, 2009	ABC/TDF/ LPV/r	Switchover	AZT/3TC/TDF/ LPV/r	Treatment failure
May, 2011	AZT/3TC/TDF/ LPV/r	Switchover	TDF/3TC/ATV/r	Change of National guidelines
December, 2011	TDF/3TC/ATV/r	Switchover	Darunavir/r/ Raltegravir/ TDF/3TC	Treatment failure - DR testing done regimen continuing

Conclusions

Present day anti-retroviral regimens tend to lead to sustained viral suppression in the majority of patients but rates of virologic failure (failure to continue to suppress viral load) remain appreciable. Virologic failure is thought to occur as the result of an uncertain mixture between sub-optimal adherence, inadequate treatment preparedness, poor counselling, and adherence monitoring. Prolonged intake of subtherapeutic dosage of medications led to the development of HIV drug resistance, while in some rare cases infection with a resistant virus strain was found to be contributory. Funtional monotherapy with SQV/r as the same NRTI backbone of AZT/3TC and d4T/3TC were used in succession for a substantial length of time[1].

Though Deeks *et al* observed that the incidence of second virological failure was gradually coming down, mortality rates among patients who suffered such failure were higher[2]. Also, although we go by the data from controlled trials, unselected patients in whom ART is started in a clinic setting achieve viral suppression substantially less frequently than do patients in controlled clinical trials[3]. The timing of switch to second-line therapy, after failure with the first-line protocol, might be of importance, as, according to a study reported from South Africa, delayed

start of 2nd-line ART after 1st-line ART failure was associated with an increased risk of lack of virologic suppression[4]. In limited resource setting, such as ours, we cannot go for genotypic and phenotypic assays whenever virologic failure is detected. Still, where such facilities are available, suboptimal adherence accounts for a lot of failure[1, 3]. Co-morbidities (e.g., diarrhoea leading to less drug absorption) and drug interactions (e.g., Rifampicin, Digoxin, etc.) might lead to treatment failure.

However, the PLATO II project team and COHERE group have recently completed their cohort study and have concluded that the substantial improvement in viral load suppression and accompanying decrease in the rates of AIDS in people after extensive failure to drugs from the three original anti-retroviral classes in present days is probably mainly driven by availability of newer drugs with better tolerability and ease of use and small cross-resistance profiles. They argued for introduction and availability of newer drugs for patients undergoing treatment failure, as this would be a major public health benefit[5]. Our reported case possibly justifies their argument.

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"Perseverance will prevail where all others will fail."

– ANONYMOUS.

CASE REPORT

JIACM 2014; 15(3-4): 232-3

Macrophage activation syndrome

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Abstract

Macrophage activation syndrome (MAS) is a potentially fatal systemic disorder which results from uncontrolled activation and proliferation of T cells and excessive activation of macrophages, which invariably leads to clinical and haematological alterations in the absence of treatment.

Here we report a case of a young male who came with complaints of fever and joint pains of 3 months. He was initially managed as a case of sepsis but was later detected to have macrophage activation syndrome.

Key words: Fatal systemic disorder, activation of macrophages, activation of T cells, fever and joint pains, macrophage activation syndrome.

Case report

A 22-year-old male hailing from Kerala, who was an accountant by profession, came with the complaints of fever and joint pains of 3 months and yellowish discolouration of eyes of 4 days duration. Fever was high grade, intermittent, and was associated with chills. The patient used to get 2 - 3 episodes of fever every day. It was accompanied by joint pains, predominantly involving the large joints that is the knee, elbow, and shoulder joints. There was no swelling of the involved joints, nor restriction of movements of the same.

The patient was put on aspirin and penicillin therapy for the above complaints which produced negligible improvement. Four days prior to admission to our hospital, the patient noticed yellowish discoloration of the eyes, which was accompanied by high coloured urine. The patient had a history of rheumatic fever at 10 yrs of age, for which he had taken prophylactic treatment till 20 yrs of age.

On examination, the patient was conscious, febrile (103 degree F) and had tachycardia (116/min). Blood pressure was 110/80 mm Hg. He had icterus, bilateral pitting pedal oedema and macular, purpura-like rashes all over the body, predominantly in the lower limbs. He also had cervical lymphadenopathy. Lymph nodes were small, discrete, 1 x 2 cm in dimension and non-tender on palpation. Patient was not pale or cyanosed and had no demonstrable asterixis.

On systemic examination, our patient had non-tender hepatomegaly. His chest was clear. Heart sounds were normally heard and no murmurs were audible. There were no signs of neurological deficit, and no signs of meningeal irritation.

On investigations, blood examination showed Hb - 9.5 gm%, TLC - 1,300/cmm, DLC - P36 L48 E2 M6, ESR - 9 mm in 1st hr. His platelet count was 129,000/cmm. Peripheral smear showed normocytic normochromic anaemia, WBCs were markedly reduced and the platelet count was reduced. No haemoparasites were seen. An impression of pancytopenia was made from the peripheral smear. ECG was within normal limits. Chest X-ray was normal. USG abdomen showed hepatosplenomegaly, bilateral minimal pleural effusion, and minimal ascites. Liver function tests revealed total bilirubin of 11.0 mg/dl of which unconjugated bilirubin was 5.0 mg/dl and conjugated bilirubin was 6.0 mg/dl. AST/ALT levels were 430/800 U/L respectively. Renal function tests showed a blood urea of 22.0 mg/dl and serum creatinine of 1.2 mg/dl. Serial monitoring of INR showed 1.62, 1.52, 1.53 and 1.46. APTT was 148.2 sec in comparison to a control of 30.0 sec. ABG report was normal. Anti-nuclear antibody (ANA) was negative. Viral markers for human immunodeficiency virus, hepatitis B and hepatitis C were negative. Serology for Weil's, dengue, and rapid malarial test were all negative. Echocardiography showed trace pericardial effusion. Blood culture and sensitivity showed no growth. Serum ferritin was > 100,000 ng/ml (Normal - 0 to 150 ng/ml). S. triglycerides was 542.0 mg/dl. In view of fever, tachycardia, pancytopenia, and liver dysfunction, a diagnosis of severe sepsis was considered and the patient was treated for the same in the medical intensive care unit. In view of pancytopenia, bone marrow aspiration study was done which showed that the marrow was hypercelluar, erythroid, and myeloid series were suppressed and megakaryocytic series and lymphoplasmacytes were within normal limits. Sheets and clusters of histiocytes

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were seen showing abundant vacuolated cytoplasm, with large nucleus showing mild variation in size and shape with prominent nucleoli. Cells were showing platelets and erythrophagocytosis.

An impression of a histiocytic disorder, macrophage activation syndrome/histiocytic malignancy was made. A final diagnosis of haemophagocytic lympho-histiocytosis (macrophage activation syndrome) was made in view of fever, rash, hepatosplenomegaly, liver dysfunction, pancytopenia, raised serum ferritin and serum triglyceride levels in addition to the erythrophagocytic picture.

After a diagnosis of MAS was made, the patient was treated with dexamethasone injections and was started on oral cyclosporine. The patient's condition gradually improved and he was discharged after 2 weeks.

Discussion

Macrophage activation syndrome (MAS) is a potentially fatal systemic disorder that results from uncontrolled activation and proliferation of T cells and excessive activation of the macrophages. It usually results from various adult and childhood systemic inflammatory rheumatic diseases; most commonly systemic onset juvenile idiopathic arthritis. MAS has also been associated with systemic lupus erythematosus, Kawasaki's disease and adult-onset Still's disease.

It is thought to be closely related and pathophysiologically similar to reactive or secondary haemophagocytic lymphohistiocytosis (HLH). HLH is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes that commonly appears in infancy, although it has been seen in all age groups. Active haemophagocytosis by normal appearing macrophages is the pathognomonic feature of MAS. Primary HLH which is familial erythrophagocytic lymphohistiocytosis, an inherited form of HLH, is a heterogeneous autosomal recessive disorder.

Secondary HLH (acquired haemophagocytic lymphohistiocyosis) occurs after immunological activation, such as that which can occur with systemic infection, immunological deficiency, and underlying malignancy. Both forms are characterised by the overwhelming activation of normal T lymphocytes and macrophages, invariably leading to clinical and haematological alterations and death in the absence of treatment. There is uncontrolled activation and proliferation of macrophages and T lymphocytes with a marked increase in circulating cytokines, such as IFN gamma and GM-CSF.

The diagnostic criteria proposed by the histiocyte society for inclusion in the international registry for haemophagocytic lymphohistiocytosis is as follows:-

1. Fever of 7 or more days with a temperature as high as 38.5 degree F.
2. Splenomegaly.
3. Cytopenia: Counts below the specified range in at least 2 of the following cell lineages:-
   a. Absolute neutrophil count less than 1,000/ml.
   b. Platelets less than 100,000/ml.
   c. Haemoglobin less than 9.0 g/dl.
4. Hypofibrinogenaemia or hypertriglyceridaemia.
5. Demonstration of haemophagocytes in the bone marrow, spleen, or lymph nodes.
6. Rash.

At least 5 of the above criteria have to be satisfied to make a definitive diagnosis. For confirmation, tissue diagnosis is required.

Treatment of secondary HLH is mainly supportive. More specifically, the underlying disease has to be treated. Treatment includes appropriate antibiotics, chemotherapeutic agents, corticosteroids, and immunosuppressive agents such as cyclosporine, cyclophosphamide, and IV immunoglobulins.

Two types of agents are used:-

1. To interrupt the function of activated macrophages and histiocytes. These are etoposide, steroids, and high dose IV immunoglobulins.
2. To interrupt the function of activated lymphocytes (T cells). These are steroids, cyclosporine; and antithymocyte globulin.
3. Since TNF-alpha levels are elevated in MAS, anti-TNF alpha agents have been used to achieve quick symptomatic relief.

A more commonly followed protocol consists of corticosteroids and etoposide with or without cyclosporine A. In MAS, corticosteroid treatment (high dose oral prednisolone or methyl prednisolone pulses) is usually effective. Cyclosporines A, as also other therapeutic measures for secondary HLH, have been used. Indications for these would be uncontrolled fever, progressive pancytopenia, and impending organ failure.

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CASE REPORT

JIACM 2014; 15(3-4): 234-39

Touraine-Solente-Gole' syndrome, Crohn's disease, and primary hypothyroidism presenting as anaemia

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Abstract

Pachydermoperiostosis or TSGS is a rare familial inherited autosomal dominant disorder characterised by digital clubbing, subperiosteal new bone formation with pain, polyarthritis, cutis verticis gyrata, seborrhoea, hyperhidrosis, thickened skin of the face with furrowing, thick and corrugated scalp with primary hypertrophic osteoarthropathy. Rheumatological manifestations in form of joint pain, effusion, acroosteolysis, and periosteal calcification are also seen. Association with various systemic diseases has been reported. Penetrance is variable, though autonomic recessive forms have also been reported. Three forms of the disease, i.e., complete, incomplete, and the fruste form are described. A rare case of TSGS in a 40-year-old young male who was admitted for evaluation of severe anaemia is presented. Detailed evaluation revealed iron deficiency anaemia, Crohn's disease, and primary hypothyroidism. The case is highlighted and presented for its rarity of association which probably is the first such reported case from India.

Key words: Idiopathic hypertrophic osteoarthropathy, pachydermia, periostosis, clubbing, Crohn's disease, hypothyroidism.

Introduction

TSGS or pachydermoperiostosis (PDP) is a familial disorder inherited as an autosomal dominant trait with variable expression[1]. Freidreich described – in 1868 – a familial case of hypertrophic osteoarthropathy (HOA) that he called hyperostosis of the entire skeleton[2]. Touraine, Solente, and Gole in 1935 first individualised the PDP as the primary form of HOA. They proposed a classification, namely, the complete form, the fruste form, and the incomplete form. The complete form includes pachydermia, clubbing, and periostosis. The fruste form includes prominent pachydermia with minimal skeletal changes, and the incomplete form has no pachyderma[3].

Case report

A 40-year-old young male born of a consanguineous marriage presented to the medical emergency of SMHS Hospital, Srinagar, Jammu & Kashmir State, India, with complaints of loss of appetite, easy fatiguability, palpitations, constipation, and a history of occasional evening rise of temperature of six months duration. There was no history of weight loss, haematemesis, haemoptysis, bleeding per rectum, mucus with stools, loose motions, jaundice, vomiting, or drug intake. No addiction to cigarette, *hookah*, alcohol, or *ganja* was recorded. General physical examination revealed a pale, young male of average build with coarse facial features

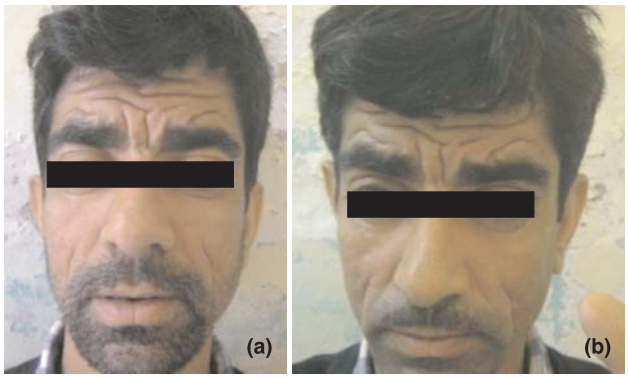

***Fig. 1: (a)** and **(b)** reveal coarse facial features and increased wrinkling of the folds of the skin of forehead, narrowed palpebral fissures with thick eyelids, mechanical ptosis with hyperaction of frontalis muscle.*

and increased wrinkling of the folds of the skin of forehead, narrowed palpebral fissures with thick eyelids, mechanical ptosis with hyperaction of frontalis muscle (Fig. 1 a, b). Scalp examination revealed a typical gyrate appearance with prominent multiple ridges. The patient had grade V clubbing with osteoarthropathy of both hands. The skin of both palms and soles was rough and thickened particularly on both hypothenar eminences (Fig. 2 a, b, c, d). Hands and feet were spindle shaped with thickened extremities. No palpable enlarged lymph nodes were found. Vitals were: Pulse 100/minute, regular. BP was 120/70 mm Hg. Abdominal examination revealed a palpabale lump in the right iliac fossa 3 x 3 cm in size,

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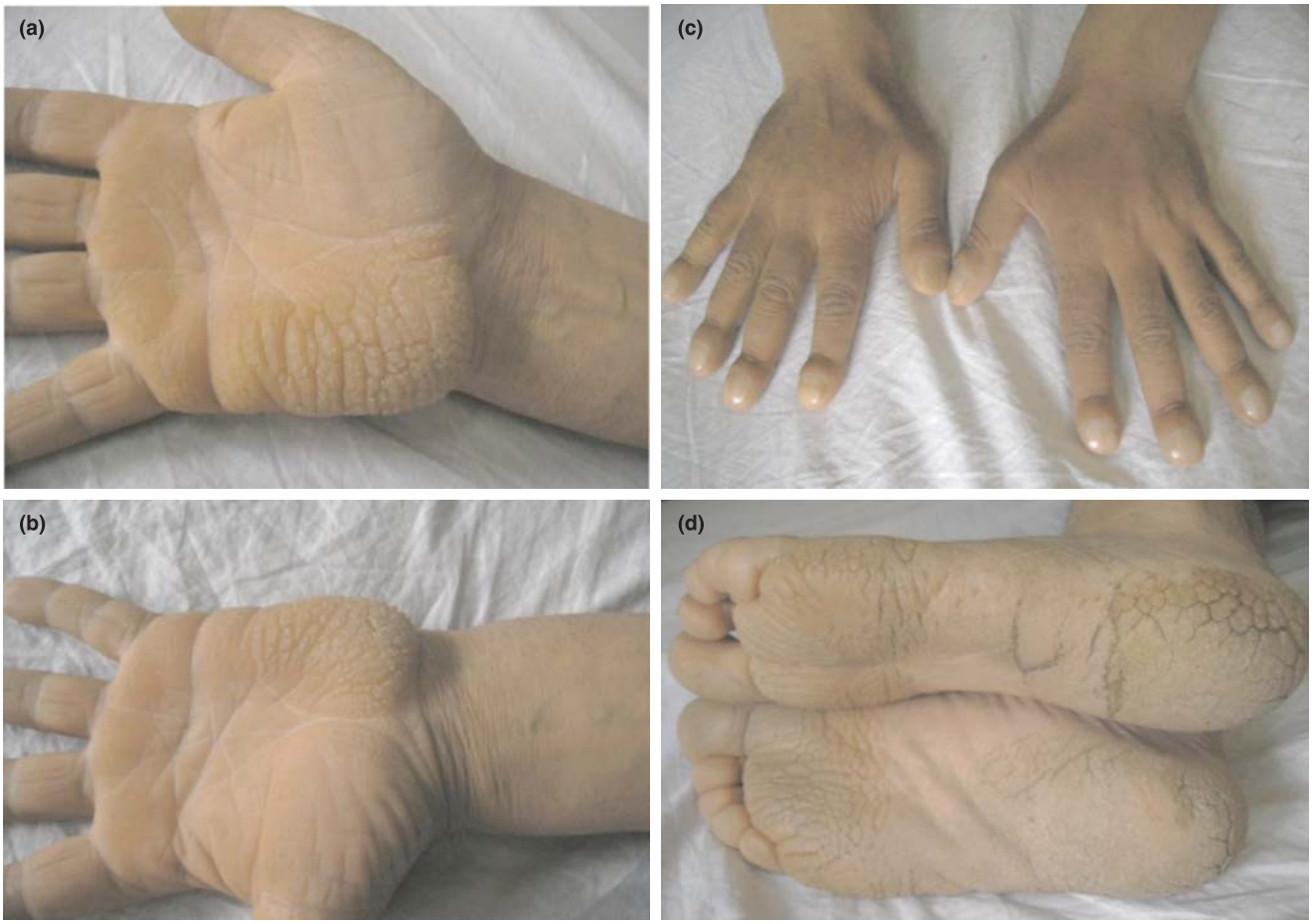

Fig. 2: (a), (b), (c), and (d) *reveal grade V clubbing with osteoarthropathy of both hands. Skin of both palms and soles was rough and thickened – particularly on both hypothenar eminences.*

non tender, without any enlargement of the liver and spleen. CNS examination was normal except for bilateral hung up ankle jerks. A provisional diagnosis of anaemia, pachydermoperiostosis, and an abdominal lump was made. Investigations revealed: Haemoglobin 6 gm%, TLC 5,100/cmm, DLC (Poly 66, Lym 21, Mix 13), Hct 23%, MCV 76, MCHC 27, MCH 20, platelets 2,90,000/cmm, ESR 40 mm/1st hr, reticulocyte count 5%. Peripheral blood film revealed a microcytic hypochromic type with no abnormal cells. Iron profile was: Serum iron 54 µg%, TIBC 328 µg% and transferrin saturation of 16%. Biochemical investigations including kidney function tests, liver function tests, blood sugar, electrolytes, and uric acid were normal. Routine urine examination was normal. ELISA for HIV, hepatitis serology, and VDRL for syphilis were negative. Stool for occult blood done thrice after proper preparation was positive. ECG showed sinus tachycardia. X-ray chest PA view was normal. Upper GI endoscopy was normal. Ultrasonography of the abdomen showed an ill-defined caecal mass of 2.7 x 3.0 cm with absence of para-aortic nodes or ascites. A

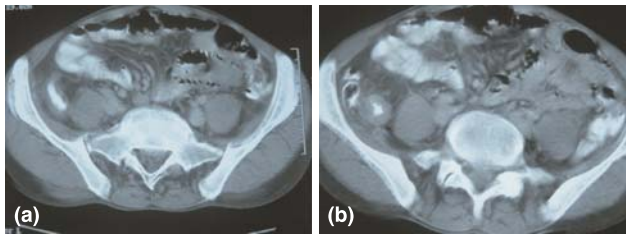

Fig. 3: (a) *and* ***(b)*** *reveal thickening of the terminal ileum and ileo-caecal junction with adjacent nodes.*

contrast-enhanced CT scan of the abdomen revealed thickening of the terminal ileum and ileo-caecal junction with adjacent nodes suggestive of ? ileocaecal TB, ?? Crohn's disease, ??? Behcet's disease (Fig. 3 a, b) Full length colonoscopy revealed a deformed caecum, ulceration around the ileo-caecal valve, a narrowed ileo-caecal valve with a fistulous opening suggestive of ? Ileo-caecal TB, ?? Crohn's disease (Fig. 4 a, b). Colonic biopsy of the tissue from the ileo-caecal region showed ulcerated ileal mucosal fragments with chronic inflammatory granulation tissue suggestive of a chronic

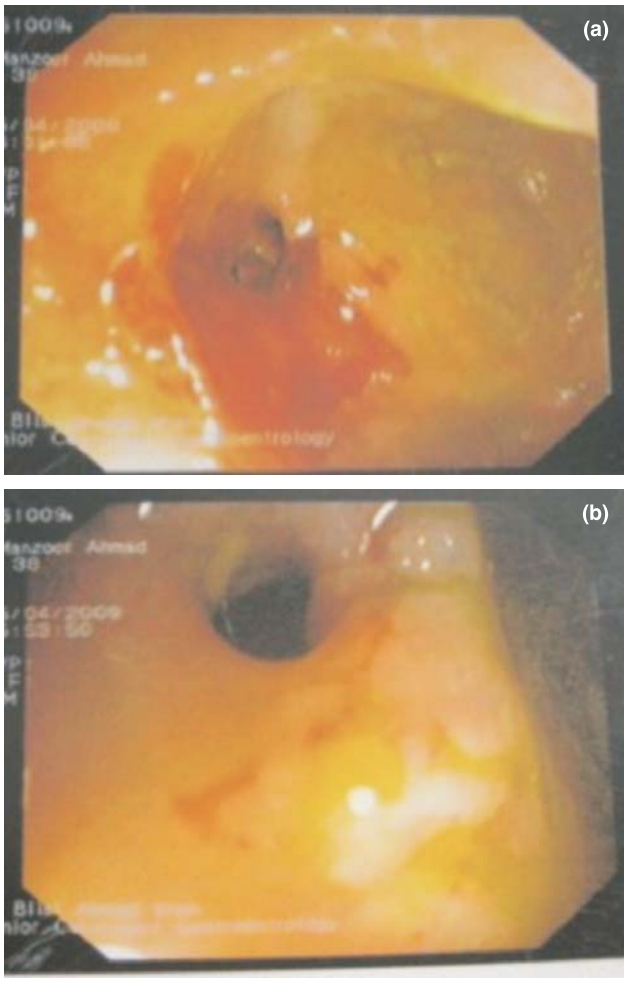

***Fig. 4: (a)** and **(b)** reveal a deformed caecum, ulceration around the ileo-caecal valve, a narrowed ileo-caecal valve with a fistulous opening.*

inflammatory disease likely to be ileo-caecal TB. Sputum for AFB done thrice was negative. TSH was 18 µIU/ml with negative anti-TPO antibodies. Skin biopsy revealed epidermal hyperkeratosis with follicular plugs with round cell infilteration, hypertrophied sebaceous glands, and dilated infundibuli in the dermis. X-ray skull including the pituitary fossa was normal. X-rays of both forearms and wrists revealed periosteal reaction at the lower ends of both radial bones without erosions. Diaphyseal thickening of radius/ulna, metacarpals and phalanges associated with cortical soft tissue swelling was also seen (Fig. 5 a, b, c, d). Serological evaluation for antineutrophil cytoplasmic antibodies, and human leukocyte antigen as well as genetic testing for tumour necrosis factor were negative. Since ileo-caecal TB is common in the third world countries, particularly India, it was decided to treat the patient empirically with the standard anti-tubercular regimen which was given for nine months. The patient was started on replacement therapy with iron, folic acid, l-thyroxine, and calcium. Anti-

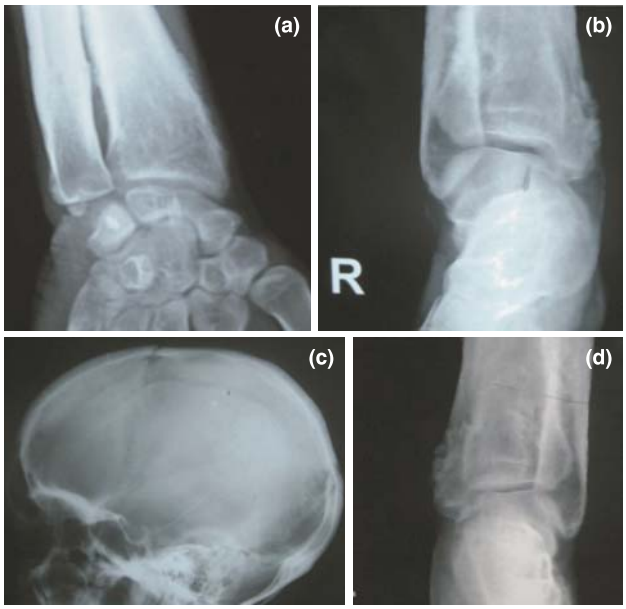

***Fig. 5: (a), (b), (c),** and **(d)** reveal X-ray skull including the pituitary fossa was normal. X-rays of both forearms and wrists revealed periosteal reaction at the lower ends of both radial bones without erosions. Diaphyseal thickening of radius/ulna, metacarpals and phalanges associated with cortical soft-tissue swelling was also seen.*

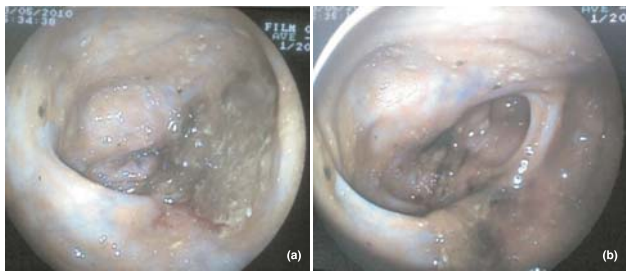

***Fig. 6: (a)** and **(b)** reveals a partially healed ulcer around the ileo-caecal valve with a deformed narrowed caecum.*

tubercular treatment with a four-drug regimen of INH, rifampicin, PZA and ethambutol along with pyridoxine was also given. The patient continued to be on regular follow-up with improvement of anaemia, constipation, and lassitude. Haemoglobin at the end of the 2-month intensive phase of ATT was 10 gm% with normal MCV and a decrease in reticulocyte count to 1.5%. Features of PDP could not be controlled though there was an overall improvement in his general condition. A repeat colonoscopy done at the end of one year treatment with anti-tubercular drugs showed a partially healed ulcer around the ileo-caecal valve with a deformed narrowed caecum (Fig. 6 a, b). A colonic biopsy taken at this point of time revealed a focal ulcer in the caecum with patchy, moderate, non-specific typhilitis and focal pyloric metaplasia. No granuloma was seen in the biopsy (Fig. 7). A revised diagnosis of pachydermoperiostosis (Touraine-Solente-Gole' syndrome), Crohn's disease,

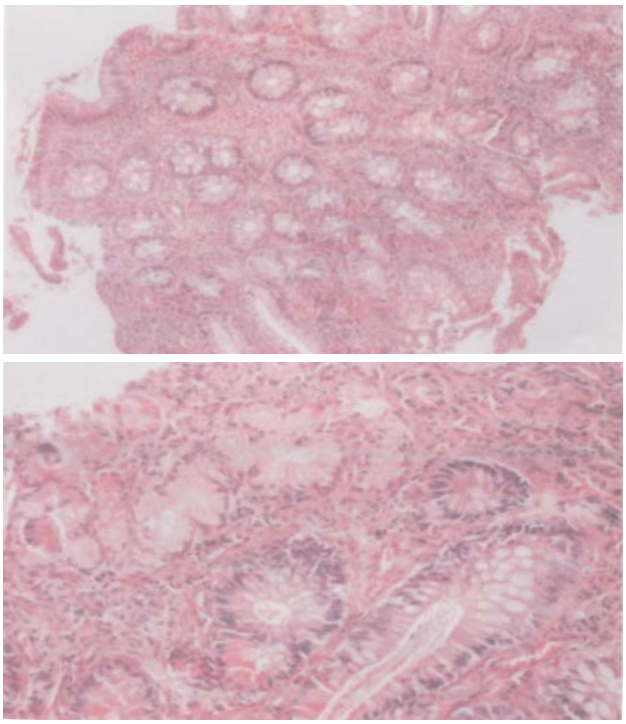

Fig. 7: *HPE of the biopsy reveals a focal ulcer in the caecum with patchy moderate non-specific typhilitis and focal pyloric metaplasia. No granuloma was seen in the biopsy.*

primary hypothyroidism, and anaemia was made keeping in view the history, investigations, and response to treatment . Sulphasalazine and corticosteroids were added to the patient's treatment with marked improvement in symptoms on follow-up as evidenced by normalisation of TSH, rise in the haemoglobin level, and normalisation of complete blood count, and no bleeding with stools. A detailed family survey of the patient's siblings, children, and relatives failed to reveal a similar disorder in any of them.

Discussion

TSGS or pachydermoperiostosis (PDP) is a familial disorder inherited as an autosomal dominant trait with variable expression[1]. Freidreich described – in 1868 – a familial case of hypertrophic osteoarthropathy (HOA) that he called hyperostosis of the entire skeleton[2]. Touraine, Solente, and Gole in 1935 first individualised the PDP as the primary form of HOA. They proposed a classification, namely, the complete form, the fruste form, and the incomplete form. The complete form includes pachydermia, clubbing, and periostosis. The fruste form includes prominent pachydermia with minimal skeletal changes, and the incomplete form has no pachyderma[3]. *Cutis verticis gyrata* or *cutis verticis et frontalis gyrate* – a form of pachydermia of the face and scalp – was described by Unna and Jadassohn in 1906-1907[4,5]. PDP is a rare syndrome and the precise incidence is unknown. According to one study its prevalence is 0.16%[6]. It usually manifests in adolescence occurring almost exclusively in males with a male: female ratio of 9:1[7,8] and has been reported in many races with significant morbidity at advancing ages. Rarely, as happened in our case, it may remain undiagnosed for long until there are significant facial, joint, digital deformities, or systemic manifestations which prompt the patient to seek medical attention. HOA is a syndrome characterised by finger clubbing, periostosis, and mono-or polyarthritis. PDP is a rare form of HOA with no known cause and is hence called as idiopathic or primary HOA to distinguish it from secondary osteoarthropathy or pulmonary osteoarthropathy which occurs in association with several diseases and sometimes as a part of the para-neoplastic syndromes. PDP occurs in 3 - 5 % of cases of hypertrophic osteoarthropathy[9].

Diagnostic criteria for primary PDP

Major: Pachydermia, periostosis, finger clubbing.

Minor: Hyperhidrosis, arthralgias, gastric ulcer, *cutis verticis gyrate*, blepharoptosis, joint effusion, oedema, seborrhoea, acne, and flushing.

Secondary form of hypertrophic osteoarthropathy

The secondary form of hypertrophic osteoarthropathy results from cardiopulmonary diseases (bronchiectasis, cystic fibrosis, congenital heart diseases, tuberculosis), hepatic diseases (portal and biliary cirrhosis), gastrointestinal diseases (inflammatory bowel disease and polyposis), malignancies (Hodgkin's disease, carcinoma nasopharynx, and chronic myeloid leukaemia)[1,9,10]. Secondary form of HOA occurs predominantly in men aged 30 - 70 years with bone changes that develop rapidly and are painful.

PDP is often familial in up to 1/3rd of patients, and hereditary affecting several members of the same family with autosomal dominance and variable penetrance[11]. PDP has been described in siblings of consanguineous marriages[12,13]. Some case reports suggest that it may be an X-linked disease. There is no difference in the severity of sympyoms but growth retardation, early ulcers, and acrolysis of distal parts of the extremities have been reported[14]. PDP is associated with thickening of the facial and scalp skin (pachydermia), periarticular and subperiosteal periostosis, or bone formation with consequent enlargement of hands and feet with joint deformities and neurological manifestations. Associated clinical manifestations like clubbing, seborrhoeic dermatitis, mechanical ptosis of thickened eyelids, periodontal disease, palmoplantar keratosis, and

hyperhidrosis have also been described and which were found in our case also, reflecting it as a classic complete form of the disease as described by Touraine *et al*[3]. Facial involvement in late stages causes prominence of folds on the forehead and cheek giving a leonine look. Thickening and undulating appearance of the scalp resembling sulci and gyri of the the brain (the so-called 'bulldog appearance' or *cutis verticis gyrata*) affecting 24% of patients is a prominent feature which was seen in our case also[4]. *Cutis verticis gyrata* is also seen in a variety of other disorders like neurofibromatosis, diabetes mellitus, myxoedema, cretinism, amyloidosis, acromegaly, tuberous sclerosis, and in syndromes like Noonan's, Turner's, and therefore is not pathognomonic for PDP[15]. Skeletal findings include symmetric shaggy subperiosteal bone formation in long bones (forearms/legs), metacarpals, metatarsals, and phalanges. Epiphyseal involvement is seen in primary HOA to distinguish it from secondary HOA where it is absent [9] as seen in our case also. Widening of the ends of bones due to increased bone formation with histological evidence of increased collagen formation and increased urinary hydroxyproline excretion have been attributed to osteoblast and osteoclast stimulation by various growth factors explaining the osteoporosis and osteolysis seen in this condition. A prominent feature is enlargement of digits and calcification of ligaments and interosseous membranes. Other features include enlargement of sinuses, hyperostosis of calvaria, skull base bones, and increased tracer uptake of the cortex in diaphyseal and metaphyseal regions. Joint effusion, periarticular erosions, reduction in joint space, narrowing of intervertebral disc spaces/foramina, ligamentous ossification/calification with secondary spondylolisthesis are also seen[9,16,17].

Anaemia in PDP seems to be multifactorial with myelofibrosis, gastrointestinal bleeds with peptic ulcer disease/erosions, gastric hypertrophy, gastric adenocarcinoma, polyposis, atrophic gastritis, and Crohn's disease accounting for the blood loss found in patients with PDP[17-19]. Reports of PDP associated with gastric involvement have been described in families and in sporadic cases with gastrointestinal symptoms being more severe in the early twenties with gastric and duodenal ulcer. Levels of pepsinogen I and II are elevated[20-23]. PDP has been found associated with inflammatory bowel disease in particular with Crohn's disease[24-25]. Primary hypothyroidism in PDP has not been found associated with the disease from the literature available till now. PDP precedes the Crohn's disease usually by 6 - 20 years as has also been seen with our patient. A new syndrome of Crohn's disease and pachydermoperiostosis associated with antineutrophil cytoplasmic antibodies has been described in the literature by Compton *et al*. No genetic link has been found to account for the same[26]. The authors believe that the patient described in this case report had primary HOA accompanied by Crohn's disease. Association of Crohn's disease and primary hypothyroidism as seen in our case is a very rare association thus making this case unique which has probably not been reported from India till now.

Squamous cell carcinoma, papular mucinosis, pyoderma gangrenous, basal cell carcinoma, and acromegaly are other associations described with PDP[16].

Treatment of PDP is multifactorial with NSAIDs, colchicine being the mainstay of treatment for articular: symptoms. Pamidronate for rheumatological symptoms, isotretinoin for seborrhoea, acne, folliculitis, and pachydermia. Retinoids inhibit procollagen formation by decreasing procollagen mRNA in fibroblasts and inhibit production of collagenase. Proton pump inhibitors (PPIs) for gastric symptoms like gastrointestinal bleeds are helpful. Plastic surgery like frontal rhytidectomy, correction of ptosis and finger clubbing reduction, besides symptomatic treatment of various associated diseases as seen in our case is helpful[16].

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"It is never too late to be what you might have been."

– George Eliot.

CASE REPORT

JIACM 2014; 15(3-4): 240-2

Parasitic zoo of *Fasciolopsis buski*, *Gastrodiscoides hominis*, *Giardiasis intestinalis*, and *Entamoeba histolytica*

HS Sunil, B Prashanth Gandhi**, Balekuduru Avinash***, DR Gayathri Devi****, U Sudhir******

Abstract

Polyparasitism of protozoans (Entamoeba histolytica and Giardia intestinalis) and trematodes (Fasciolopsis buski and Gastrodiscoides hominis) is not reported. A young lady presented with bilateral pitting pedal oedema of 2 months duration. Laboratory evaluation showed microcytic anaemia, low total protein and albumin. Endoscopy and colonoscopy revealed multiple motile worms which were retrieved for species identification. She benefitted with praziquantel, albendazole, along with metronidazole, and collected stools revealed all the four parasites. Poor hygiene, consumption of undercooked food, the climatic compatibility for the parasites, swine population, and usage of faecal manures for farming maintain the endemicity. A simple use of anti-helminthic/anti-protozoal in areas of high endemicity can prevent poor outcome in these patients.

Key words : Polyparasitism, co-infestation.

Introduction

Intestinal parasitic infections are a major public health problem in the developing world. This is a report of simultaneous infestation with trematodes – *Fasciolopsis buski*, the largest fluke parasitising humans; *Gastrodiscoides hominis*, an intestinal fluke infecting people and their livestock; protozoan anaerobic parasites *Entamoeba histolytica* and *Giardia intestinalis* which have high endemicity in the developing countries causing malabsorption. Chief pathways of human infection include ingestion of untreated sewage, a phenomenon particularly common in many developing countries. Re-emergence of polyparasitism indicates poor hygienic conditions that are still prevalent in the developing world.

Case report

A 20-year-old lady from Bihar, India, tailor by occupation, presented with bilateral progressive pitting pedal oedema without any abdominal distension or facial puffiness for the last 2 months. She also complained of mild abdominal discomfort and nausea without any vomiting or diarrhoea. She developed brownish pigmentation on the extensor aspect of legs. She had no other systemic symptoms. There were no similar complaints in her family. She consumes mixed diet which includes fish about twice a month. She had no history of eating any aquatic plants or dish made from it. She had an uneventful vaginal delivery 1 year back. Physical examination was unremarkable except for pedal oedema. Her height was 153 cm, and weight of 40 kg with a BMI of 17.1 kg/m^2. Healed rashes of partially treated *Tinea corporis* are appreciable on her neck and back. Hyperpigmented rash was noted on both legs (Fig. 1).

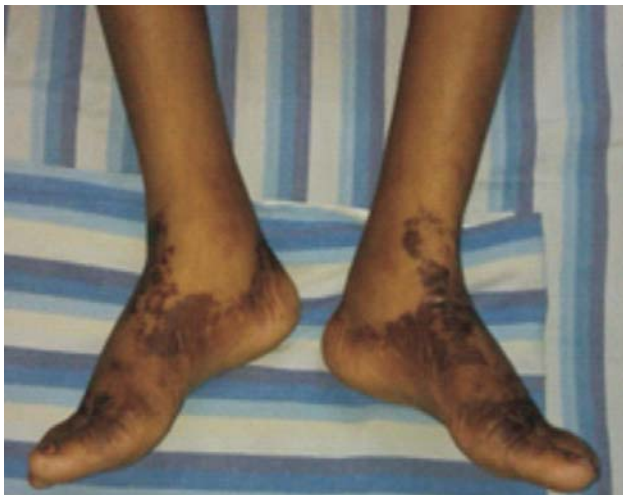

Fig. 1: *Hyperpigmented rashes over both legs.*

While the work-up was being done, during her stay in the ward she vomited out pink worms after mild post-prandial abdominal discomfort. She had no prior constipation or history of passing worms in stools.

Laboratory evaluation showed that she had microcytic anaemia (haemoglobin of 10.8 g/dl), and low total protein (4.2 g/dl) and albumin (1.8 g/dl). There was no peripheral blood eosinophilia. Her cardiac, thyroid, and renal functions were normal. Ultrasound of abdomen revealed mild ascites. Viral markers were negative. Doppler study of both lower limbs revealed normal arterial and venous

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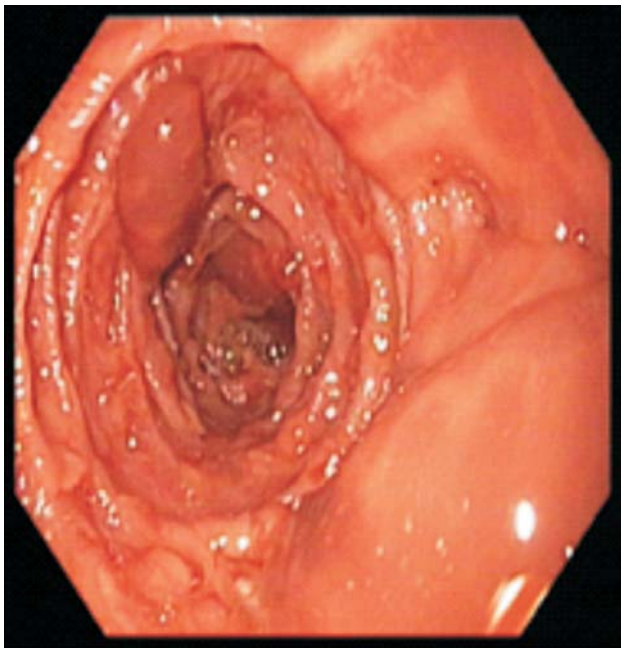

Fig. 2: *Endoscopic image of second part of duodenum (D2) showing adult flukes.*

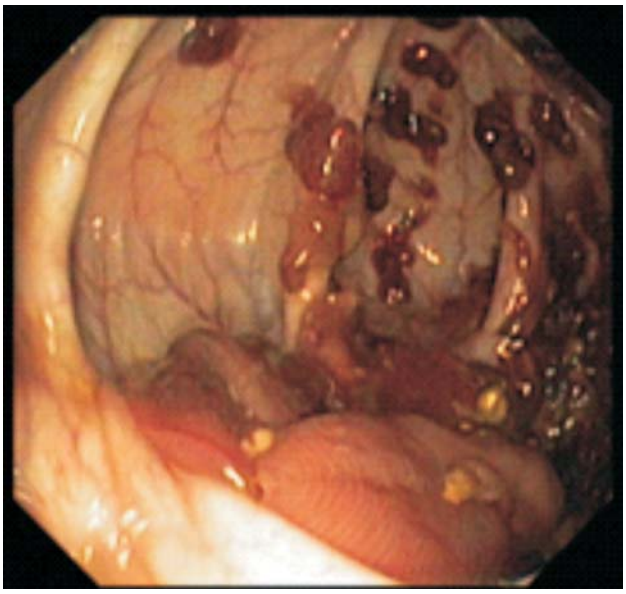

Fig. 3: *Colonoscopic image of caecum with fluke infestation.*

system with diffuse soft-tissue oedema. Upper GI endoscopy was done which multiple motile worms ranging from 1 - 5 cm long and 0.5 - 2 cm wide (Fig. 2). Few adult worms were retrieved and sent for species identification. Colonoscopy was done which also revealed infestation in the terminal ileum and in the right colon (Fig. 3).

The larger-sized (5 - 6 cm x 1 - 2 cm) parasites were provisionally identified as *Fasciolopsis buski*, based on the

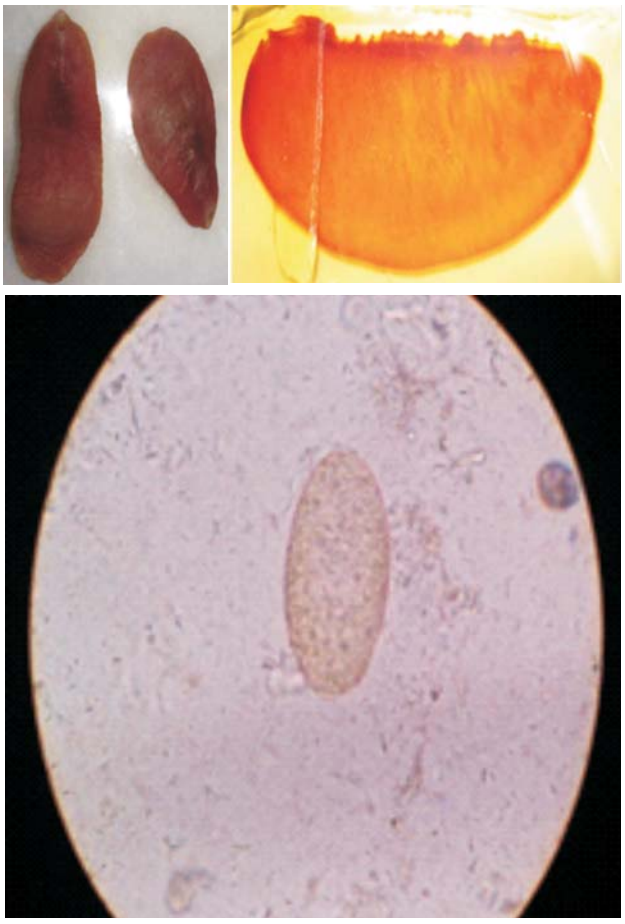

Fig. 4, 5 *and* ***6:*** *Fasciopsis buski in gross morphology, permanent mounting, and bile stained oval operculated egg of F. buski.*

gross morphology. Identification was later confirmed by permanent mounting (Fig. 4 and 5). Few of the samples were also confirmed to be of *Gastrodicoides hominis* (Fig. 7 and 8) by the Department of Veterinary Parasitology, Veterinary College, Bangalore. The Centers for Disease Control and Prevention (USA) also agreed with the same. Stool examination showed bile stained as well as non bile stained operculated eggs (Fig. 6 and 9) ova along with numerous trophozoites and cysts of *Giardia intestinalis* and *Entamoeba histolytica*. The family members were screened and did not harbor the infection.

The patient was treated with praziquantel (25 mg/kg) single dose, metronidazole (400 mg tid for 5 days) and albendazole 400 mg/day for 3 days. In view of hyperinfestation, she was given anti-helminthic under polyethylene glycol preparation to purge the dead worms, thus preventing obstruction. She passed many dead worms for three consecutive days. She became symptomatically better; serum albumin improved and she was discharged. Unfortunately, she was lost to follow-up.

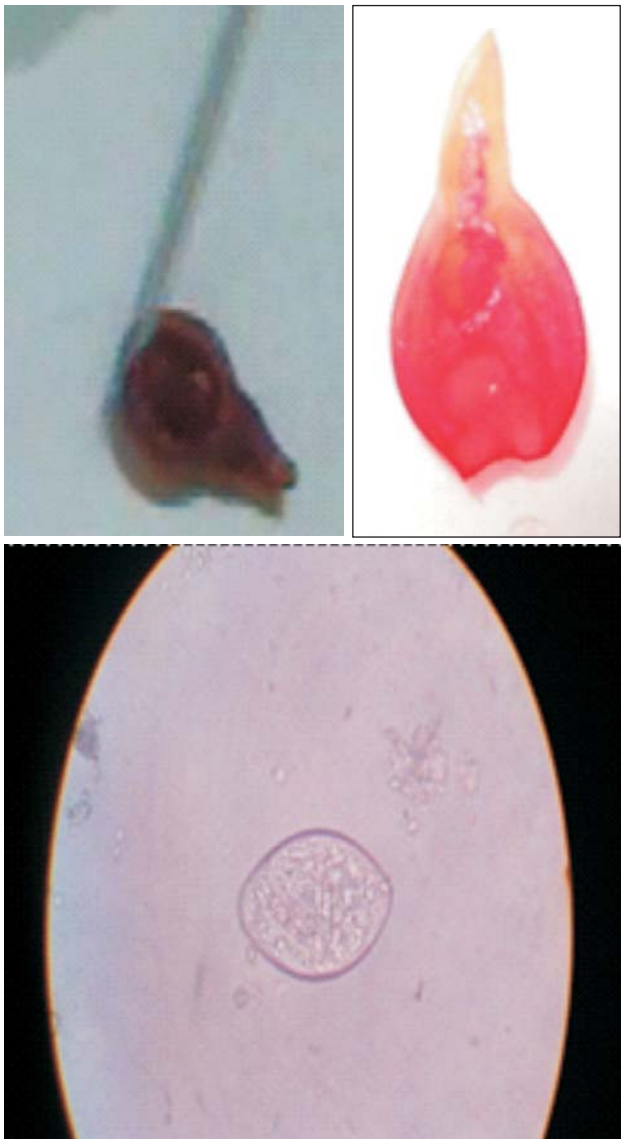

***Fig. 7, 8** and **9:** Gastrodiscoides hominis (clockwise) in gross morphology, permanent mounting, and the rhomboid non bile stained operculated egg of G. hominis.*

Discussion

Fasciolopsis buski is the largest intestinal fluke that parasitises humans and pigs with prevalence in India up to 60%[1]. Aquatic plants with metacercariae on their surface from snails is the major mode of human infection[2]. Pigs are the main source of eggs and drainage of pig excreta in farms is an important factor for maintaining high endemicity[3]. Usually asymptomatic, heavy infection causes diarrhoea, vomiting, malabsorption, intestinal obstruction, perforation, and eosionophilic leucocytosis[4,5].

Gastrodiscoides hominis is a common parasite of humans and pigs in India. The planorbid freshwater snails shed the cercariae, and the cercariae encyst to metacercariae on aquatic plants, or in tadpoles, frogs, and crayfish[3]. Ingested metacercariae excyst to flukes which reside in the caecum and colon causing mucoid diarrhoea.

Gastrodiscoides hominis and *Fasciolopsis buski* use the same molluscan intermediate host species. In Bareilly, India, 27% of a total of 233 slaughter-pigs were infected with *G. hominis* and in 50% of these cases the infection was concomitant with *F. buski*[6]. The same reason could also explain similar results obtained in human surveys, i.e., prevalences of 41% by *G. hominis* and of 59.7% by *F. buski* in the same population of 221 human subjects analysed[7]. Severe Fasciola and Gastrodiscoides infestation is due to repeated consumption of the metacercaria larva from aquatic plants. Praziquantel is the drug of choice for both trematodiasis .

Prevention of intestinal trematode infections requires preventing faecal contamination of water where fish and aquatic plants breed. Education regarding the risks associated with ingestion of raw or insufficiently cooked molluscs and fish is also important. Freezing, smoking, and pickling of fish do not destroy metacercariae[8].

Giardia intestinalis and *Entamoeba histolytica* were concomitant protozoan parasites due to similar faeco-oral contamination. Infestation with multiple parasites is common in endemic areas. Poor hygiene, lack of education and awareness, use of night soil are important factors in maintaining endemicity. A high index of suspicion is required to detect parasitic infestations when a patient presents with features of malnutrition and protein-losing enteropathy especially from endemic areas.

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CASE REPORT

JIACM 2014; 15(3-4): 243-4

An unusual case of insect bite presenting as acute respiratory distress syndrome

Manoj Kumar, PS Singh**, Arun Tyagi***, Ramakant Rawat**

Abstract

Local and self-limited reaction following insect bite is common. But severe reaction following single insect bite is very uncommon. We are presenting a case of insect bite that developed severe reaction in the form of anaphylaxis and acute respiratory distress syndrome.

Keywords: Epinephrine, arterial blood gas analysis, angioedema, mechanical ventilation, PEEP.

Introduction

Insect bite is not an uncommon problem. Most bite produce insignificant signs and symptoms and patients usually do not seek medical care. Few cases present with local signs in the form of erythema or vesicles. But in rare instances the insect bite may lead to severe anaphylactic reactions, and if not treated timely it may lead to death in a few hours.

Case report

A 40-year-old-male presented with complaints of breathlessness and choking sensation in the throat approximately 15 minutes following insect (wasp) bite below his left eye. There was pain around the left eye. There was no prior history of any illness. Examination revealed BP 90/60 mm Hg, pulse 116/min, respiratory rate 25/min. Local examination revealed that there was bite mark below the left eye (Fig. 1) with periorbital oedema; and on chest examination there were coarse crepitations mainly on the lower and mid-chest areas. Oxygen saturation was 95% on ventimask oxygen. We suspected anaphylaxis. Patient was nebulised with salbutamol. Intravenous (IV) 2.5 ml epinephrine, diluted 1:10,000, hydrocortisone100 mg and pheniramine 25 mg was given. Dopamine was started in the dose of 5 µg/kg/min along with IV dextrose normal saline. The patient's condition improved over a few hours. Ceftriaxone 1 gm IV 12 hourly, metronidazole 100 ml (500 mg) IV infusion 8 hourly, ranitidine 50 mg IV 12 hourly, intravenous fluid (dextrose normal saline) 80 ml/hr were added to the treatment. Nebulisation with salbutamol 6 hourly, oxygen by face mask, hydrocortisone100 mg IV 6 hourly and pheniramine 25 mg IV 8 hourly, ranitidine 50 mg IV 12 hourly and dopamine along with antibiotic were continued. History was reviewed. There was no history of trauma. There was no history of fever, diabetes, hypertension, or any other chronic illness. There was no history suggestive of any cardiac or respiratory illness before this event. Cardiovascular and nervous system examination was normal. The next day the patient's condition started deteriorating. His oxygen saturation started falling and reached up to 82% on ventimask oxygen. His arterial blood gas analysis revealed pH - 7.48, $PaCO_2$ - 26.7 mm of Hg, HCO_3^- 19.3 mmol/l, PaO_2 52 mm of Hg, PaO_2/FIO_2 -130. The patient was intubated and mechanical ventilation was initiated with ACMV mode, FiO_2 100%, tidal volume 450 ml, PEEP - 8 mm of Hg, respiratory rate 25/min. Patient required FiO_2 of 100% and PEEP of 10 mm of mercury to maintain oxygen saturation > 90%. Intravenous fluid (dextrose normal saline) was reduced to 40 ml/hr. X-ray chest showed bilateral diffuse opacities mainly in mid-zone and lower zone (Fig. 2). His biochemical investigation revealed serum creatinine - 1.4, urea - 44.2, total bilirubin - 0.4 mg/dl, SGOT - 65 IU/l, SGPT - 30 IU/l, alkaline phosphatase 51 IU/l, serum sodium - 136 mmol/l, potassium - 3.5 mmol/

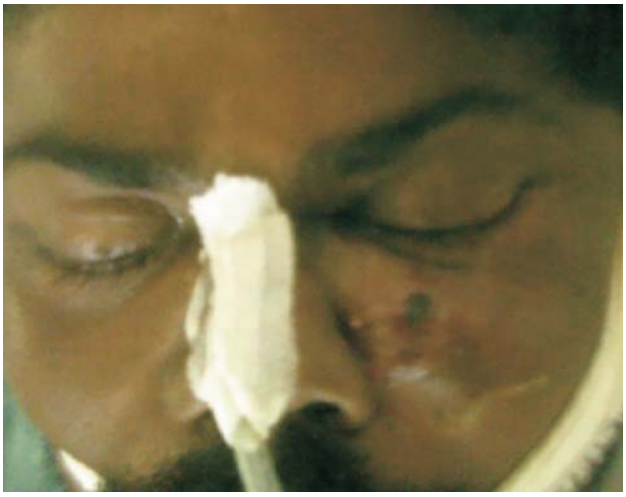

Fig. 1: *Insect bite mark below the left eye.*

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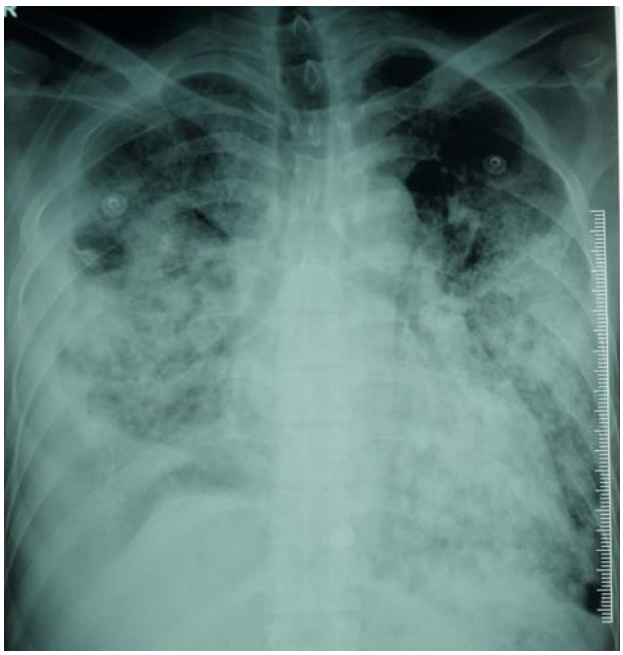

Fig. 2: *X-ray chest showing bilateral diffuse opacities mainly in mid-zone and lower zone.*

L, haemoglobin 14.5 gm%, total leukocyte count - 11,900, differential count - neutrophils - 64%, lymphocytes - 30%, monocytes - 2%, eosinophils - 4%, platelet count - 160,000/cmm. Urine routine and microscopic examination was normal, D-dimer 0.46 feu/ml, APTT patient value was 35.80 sec control 34.20 sec. ECG was normal, troponin-T was negative. Ultrasound abdomen was normal. Bedside echocardiography was normal. His blood culture and endotracheal aspirate culture was sterile.

The patient's condition improved in a few days and the weaning process was completed by the 10th day.

Discussion

The most common response to insect bite is a local reaction manifested by a sharp, stabbing pain followed within several minutes by intense, burning pain, erythema and a circumferential white ring and oedema. In most patients, the oedema usually resolves within several hours. Pruritus and a warm sensation may persist for several hours. In a report from the United States, approximately 0.4 - 4% of a random adult population report systemic allergic responses after stings by an insect (winged Hymenoptera)[1]. Systemic symptoms of immediate hypersensitivity reaction range from mild (urticaria, diffuse erythema, angioedema, nausea, vomiting, pruritus, anxiety) to severe (hypotension, laryngeal oedema, severe bronchospasm, dyspnoea). Fatalities from massive Hymenoptera envenomations usually involve multiorgan failure including intravascular haemolysis, respiratory distress syndrome (ARDS), hepatocellular necrosis, acute renal failure with myoglobinuria and haemoglobinuria, focal subendocardial necrosis, and disseminated intravascular coagulation. Systemic symptoms usually begin within 10 minutes after envenomation[2]. The clinical features of a massive envenomation are similar to anaphylaxis, and symptoms include fatigue, headache, weakness, fever, muscle spasm, diarrhoea, nausea, vomiting, lightheadedness, and transient loss of consciousness. Rarely, convulsions may occur usually along with multiorgan failure[3]. Within 24 hours, haemolysis, haemoglobinuria, rhabdomyolysis, and elevation of serum hepatic aminotransferases can develop[4].

Many cases of insect bite causing severe reactions in the form of acute myocardial injury and rhabdomyolysis[5], disseminated intravascular coagulation, acute renal failure, thrombotic microangiopathy[6], multiple organ dysfunction syndrome (MODS) [7] and encephalopathy[8] has been reported from India.

Our case presented with a history of breathlessness and choking sensation following insect bite. Initial examination revealed a bite mark below the left eye with periorbital swelling, hypotension and crepitations in chest with hypoxaemia. There was initial response to adrenaline, hydrocortisone, and pheniramine. Later on, the patient's condition worsened, and he developed a severe hypoxaemia despite oxygen supplementation by mask. Investigations revealed respiratory alkalosis with PaO_2/FiO_2 ratio 130. X-rays suggested bilateral extensive opacities in the mid and lower zones. This feature was consistent with a diagnosis of acute respiratory distress syndrome. The patient responded to positive pressure ventilation with high PEEP. Initial event of respiratory distress and breathlessness might be due to anaphylaxis as there was initial response to adrenaline, pheniramine, hydrocortisone, and β_2-agonist. Our case is atypical because of presentation with acute respiratory distress syndrome due to insect bite.

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CASE REPORT

JIACM 2014; 15(3-4): 245-8

Case series of pancreatic pleural effusion with pancreatico-pleural fistula

Anil Sontakke, BO Tayade***

Abstract

Pleural effusion secondary to chronic pancreatitis is an uncommon condition accounting for less than 1% of patients. Patients are alcoholic but only 50% of patients have clinical symptoms and signs of previous pancreatitis. Raised pleural fluid amylase level in haemorrhagic fluid is diagnostic of pancreatic pleural effusion. Presence of pancreatico-pleural fistula can be demonstrated by CT imaging or MRCP.

In this case series of three patients, all were presented with massive recurrent haemorrhagic or cola-coloured pleural effusion. All were alcoholic and having past history of abdominal pain. Pleural fluid was exudative with markedly raised levels of pleural fluid amylase. Computerised tomography of abdomen and thorax was able to demonstrate pancreatico-pleural fistula in all the cases. Conservative treatment was given in the form of intercostal chest tube drainage, somatostatin analogues, antibiotics, low fat diet for two to six weeks. Two patients responded to conservative treatment and one patient developed pancreatic abscess during the course after two weeks of conservative therapy.

Pancreatic pleural effusion with pancreatico-pleural fistula is difficult to diagnose and at times difficult to treat. Symptoms are predominantly respiratory than abdominal. Early pleural fluid amylase testing will avoid delay in diagnosis; CT imaging or MRCP will confirm the diagnosis. Surgery is to be considered when medical measures fail or if there is associated or complicated pseudocyst.

Key words : MRCP - Magnetic Resonance Cholangio-Pancreatography.

Background

Pancreatic pleural effusion due to pancreatico-pleural fistula is an unusual complications of acute or chronic pancreatitis or pancreatic trauma accounting for less than 1% of cases. Pleural fluid is haemorrhagic with markedly increased amylase activity. Presence of fistula can be demonstrated by CT imaging or MRCP. Because of low incidence, we are presenting three cases of pleural effusion secondary to chronic pancreatitis managed conservatively. Pancreatic pleural effusion usually presents on the left side, rarely on right side[1,2,3].

Case report (I)

A 56-year-old man was admitted for left-sided recurrent pleural effusion. He complained of left-sided chest pain, dry cough, and dyspnoea since one month which progressed to dyspnoea at rest over the last 15 days. The patient had history of intermittent left-sided colicky abdominal pain since 6 months which did not require hospitalisation. He had undergone thoracocentesis from left side at a general hospital one week back. In multiple sittings 3.5 litres of blood-tinged pleural fluid was tapped.

The patient was a non-smoker, alcoholic, consuming country liquor 180 ml/day since 20 years. He was a farmer by occupation.

On physical examination, the patient had signs of left-sided massive pleural effusion which was confirmed with

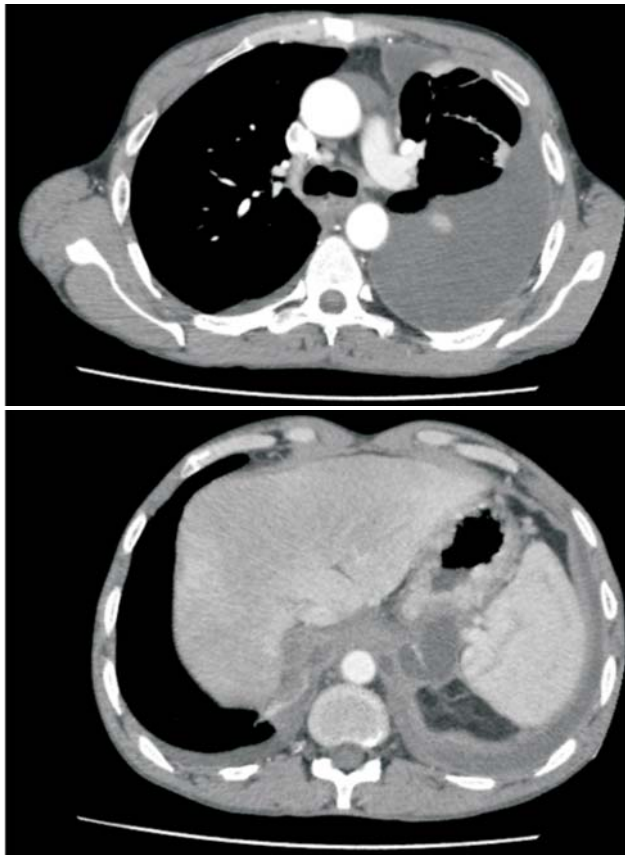

Fig. 1 and 2: *Left-sided pleural effusion communicating with fluid collection in the lesser sac.*

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chest X-ray. Thoracocentesis revealed haemorrhagic exudative pleural effusion. The pleural fluid had 3,000 white blood cells per high power field with 90% lymphocytes and plenty of RBCs. Pleural fluid cytology was negative for malignant cells; pleural biopsy revealed no abnormality; and pleural fluid amylase levels were markedly raised, i.e., 4,250.8 units/litre.

CT abdomen and thorax revealed left-sided pleural effusion communicating with a collection in the left pancreatic region which in turn was communicating with a collection in the lesser sac without evidence of pancreatitis (Figures 1 and 2).

An intercostal drain (ICD) was inserted in the left pleural cavity. The patient was given octreotide 50 micrograms by subcutaneous route 8 hourly and antibiotics for two weeks. The patient was given a low-fat diet. After two weeks, the intercostal drain was removed. Octreotide was continued up to six weeks. Pleural effusion had not recurred after 6 months.

Case report (II)

A 28-year-old man was admitted for severe dyspnoea associated with abdominal pain since 7 days. The patient was a labourer by occupation, an alcoholic but non-smoker. No significant clinical history of past medical illness was available except hospitalisation once for acute abdomen.

On physical examination, the patient had right-sided massive pleural effusion with shift of mediastinum which was confirmed on chest X-ray. Thoracocentesis revealed haemorrhagic exudative pleural effusion with ADA level 28 units/litre, pleural fluid WBC count 750/cu mm (all lymphocytes) and 70 - 75 RBCs per high power field. Pleural fluid amylase was 36,650 units/litre with raised serum amylase 686 units/litre and serum lipase 409 units/

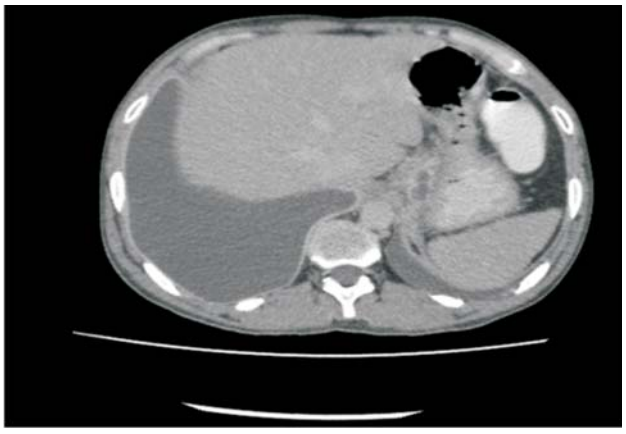

Fig. 3: *CECT upper abdomen and thorax s/o bilateral pleural effusion with pancreatic pseudocyst.*

Fig. 4: *Haemorrhagic pleural effusion.*

litre. USG thorax revealed bilateral collection in the pleural cavity.

In view of rapid re-filling of the right pleural cavity, intercostal chest tube drainage was done. CT abdomen and thorax revealed chronic pancreatitis with pancreatic pseudocyst with right-sided massive pleural effusion with left minimal pleural effusion (Figures 3 and 4).

The patient was started on low-fat diet, octreotide 50 micrograms by subcutaneous route 8 hourly and third generation cephalosporins. Intercostal drainage was continued for 4 weeks. However, octreotide was continued up to 2 months. The patient responded well to treatment with residual minimal pleural thickening.

Case report (III)

A 35-years-old male was admitted for left-sided haemorrhagic pleural effusion. The patient had an 8 days history of dry cough and progressive dyspnoea which worsened to dyspnoea at rest. The patient had left-sided abdominal pain not associated with vomitting or diarrhoea. He also had a past history of intermittent left-sided abdominal pain since 4 months which did not require hospitalisation. He was a chronic alcoholic too.

On physical examination, the patient had signs of left-sided massive pleural effision which was confirmed on chest X-ray. Thoracocentesis revealed a cola-coloured exudative pleural effusion. Pleural fluid white cell count was 200/cu mm with predominent lymphocytes and ADA level 35 units/dl. Serum amylase and serum lipase were raised to 427.7 U/l and 326.2 U/l respectively. Pleural fluid amylase was raised 30,250 U/l. Intercostal chest drain was inserterd in view of severe dysnoea on the left side. CT scans of abdomen and chest revealed moderate pleural

effusion on the left side with ICD *in situ* with bulky pancreas in the tail region with few small hypodense areas in the tail region. Main pancreatic duct was dilated, suggestive of pancreatitis.Thin streaks of fluid were passing from the tail of pancreas to the splenic tissue,then piercing through the lateral wall of left diaphgramatic crura in the pleural cavity (Figures 5 and 6).

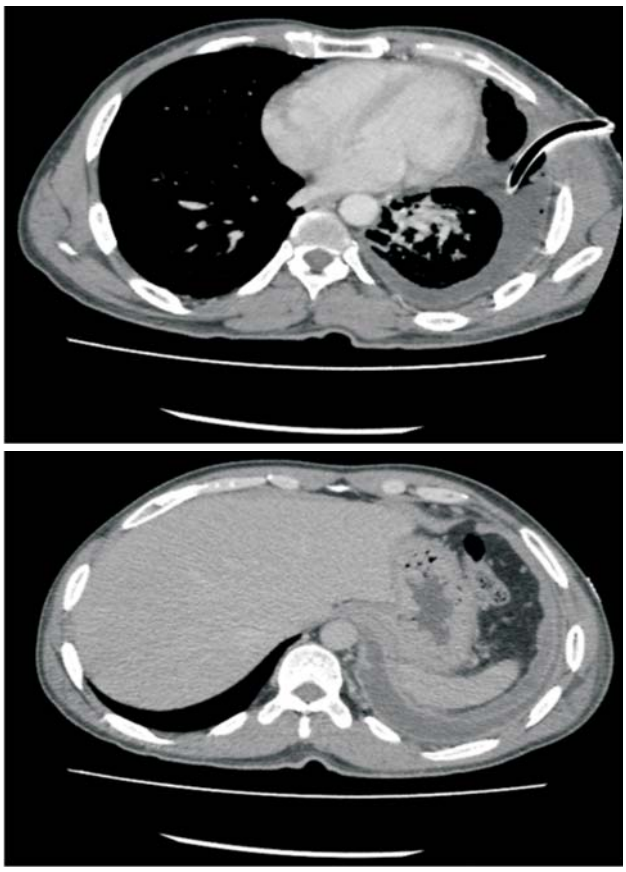

Fig. 5 and 6: *Left-sided pleural effusion with ICD in situ and a collection in the tail of pancreas respectively.*

Apart from ICD drainage of the left pleural cavity, the patient was given octreotide 50 microgram by subcutaneous route every 8 hourly, third generation cephalosporins and analgesics for two weeks. ICD drainage was reduced to 30 ml clear fluid daily but the patient had high grade fever and recurrence of pain in abdomen after two weeks of conservative management. Sonography of abdomen revealed a collection in the region of the tail of pancreas, suggestive of pancreatic abscess.Due to development of complications the patient was referred for surgical intervention.

Discussion

Most of the patients with pancreatic pleural effusion are alcoholics; only 50% of them have a clinical history and signs of previous pancreatitis.Pancreatico-pleural fistula is an unusual complication of chronic pancreatitis and estimated to occur in only 0.4% of patients with chronic pancreatitis and 4.5% of patients with pancreatic pseudocysts. In one series, approximately half (51%) of the patients had left-sided pleural effusion, 32% had right-sided pleural effusion, and 16% had bilateral pleural effusion; while another study showed that 14% of patients had bilateral pleural effusion[4]. Pancreatic pathologies can be complicated by two types of pleural effusion.The first is usually a small left-sided effusion and characterised by normal amylase activity (below 100 U/l) and low protein concentration (below 3 gms/dl); this type is associated with acute pancreatitis and resolves during recovery. The second type of pleural effusion is related to the presence of pancreatico-pleural fistula in the course of chronic or recurrent pancreatitis; this effusion is usually large, single-sided, recurrent, and contains high level of amylase above 100 U/l and protein above 3 gms/dl[4-6]. In published cases of PPF, the pleural fluid amylase activity ranged between 400 and 446,600 units/litre[7]. These two forms of pleural effusion should be clinically recognised in view of their different complication rates, progress, and treatment[2,5]. Pleural effusion due to pancreatitis is recurrent and requires repeated thoracocentesis or intercostal drainage; however, pancreatic pseudocysts have been found in 69 to 77% of patients with pancreatico-pleural fistula. Clinically, the massive pleural effusion with strongly increased activities of amylase and increased protein concentration in a patient with pancreatitis suggests a diagnosis of pancreatico-pleural fistula. Direct demonstration of the fistula may be difficult in a number of cases; CT imaging was able to diagnose fistula only in 33 - 47% of cases[2,7]. MRCP (magnetic resonance cholangio-pancreatography) a non-invasive test has 80% sensitivity to demonstrate PPF while ERCP (endoscopic retrograde cholangio-pancreatography) which is an invasive test, can demonstrate PPF in 46 - 78% of cases.

No systematic studies have yet been done to evaluate medical versus surgical therapy. Available treatment modalities include: 1) Conservative/medical management; 2) ERCP – with or without endoscopic pancreatic stent placement; 3) Surgery.

The aim of medical treatment is to reduce stimulation of pancreatic exocrine secretions[2,4,6,10,11]. Medical treatment constitutes thoracocentesis and/or tube thoracostomy and administration of somatostation analogues[4,11]. Thoracocentesis or tube thoracostomy gives symptomatic relief to the patient. Duration of conservative management varies from 2 to 4 weeks. However,

octreotide can be given for 2 to 5 months, chest tube drainage can be done from 6 to 24 days. Octreotide is given as an initial dose of 50 mg three times a day up to maximum dose of 250 mg three times daily. Octreotide significantly reduces fistula output and decreases the time of fistula closure. Measures like prohibition of oral intake, nasogastric tube insertion and parenteral nutrition used in the past are no longer necessary[4-6, 11]. ERCP with endoscopic pancreatic stenting is an effective therapeutic option for fistulas present in the head and body of the pancreas. The principal aim of the treatment with stent is to achieve drainage of ducts with fistulae in the short term, and drainage of stenosed pancreatic duct in the long term. Surgical treatment is safe, effective, and appropriate either when medical management fails or where the underlying condition requires surgical intervention. Surgical treatment options include either pancreatic resection or enteropancreatic anastomosis to the site of pancreatic duct leakage or to the pseudocyst.

Conservative treatment of pancreatico-pleural fistula has a success rate of 30 to 60% with a recurrence rate of 15%, and mortality of 12%. In contrast, operative therapy has a success rate of 90% with up to 18% recurrence rate.

Conclusion

Pancreatic pleural effusion with pancreatico-pleural fistula is difficult to diagnose and at times difficult to treat. It requires a high index of suspicion to diagnose, particularly in the settings of recurrent pleural effusion with co-existing history of pancreatitis or alcohol abuse. Symptoms are predominantly respiratory than abdominal. Early pleural fluid amylase testing will avoid delay in diagnosis; CT imaging or MRCP will confirm the diagnosis. The initial line of treatment includes drainage of effusion, inhibition of pancreatic secretion with octreotide and ERCP with stenting of pancreatic duct. Surgery is to be considered when medical measures fail or if there is associated or complicated pseudocyst.

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"Happiness is the best antidote for disease."

– C. F. Bates.

CASE REPORT

JIACM 2014; 15(3-4): 249-51

Epidermoid cyst of the spleen: A rare case report with review of the literature

Divya Dahiya, Prithviraj**, Lileswar Kaman***, Arunanshu Behera*****

Abstract

Epidermoid cyst is a rare non-parasitic cystic lesion of the spleen. We report the case of a 20-year-male who presented with abdominal discomfort in the left hypochondrium. He had splenomegaly on examination. Ultrasound and CT scan of the abdomen showed two simple cysts within the spleen. Patient underwent splenectomy, and histopathological findings were consistent with epidermoid cyst of the spleen. Aetiopathogenesis, diagnosis, and treatment modalities of true non-parasitic splenic cyst are discussed.

Key words: Spleen, epidermoid cyst of spleen, cystic lesion of spleen, benign splenic cyst.

Introduction

Cystic diseases of spleen are infrequent causes of splenomegaly with a reported incidence of 0.07% in a review of 42,327 autopsies[1,2]. More than two-third of these splenic cysts are due to parasitic infection with *Echinococcus granulosus*[1], and remaining are either pseudocysts or true cysts. Reported incidence for true non-parasitic benign splenic cysts is about 10%[1], and an epidermoid splenic cyst is rarest among these. Herein we report a case of benign epidermoid cyst of the spleen.

Case report

A 20-year-male presented with abdominal discomfort in the left hypochondrium for two years. The patient had no other complaint. There was no previous history of trauma or GI bleed. On abdominal examination, there was non-tender splenomegaly extending six cm below costal margin. Baseline laboratory investigations were normal. Hydatid serology was negative. Ultrasonography of the abdomen revealed a splenic cyst. CT scan of abdomen revealed two simple cysts, one at the upper pole and another near the hilum of the spleen sparing a small area of splenic parenchyma near the lower pole. There was no calcification in the cyst wall and no feature suggestive of hydatid cyst (Fig. 1). At laparotomy, there was a huge tense cyst occupying most of the spleen, sparing only part of the lower pole (Fig. 2). Splenectomy was done and the patient had an uneventful post-operative recovery.

On cut section there were two cysts – one at the upper pole measuring 6 x 3 x 2 cms containing ~400 ml of clear fluid; it was thick walled, and the inner surface of the cyst wall was white in colour with presence of many stria. Another cyst was at the hilum measuring 10 x 6 x 2 cms

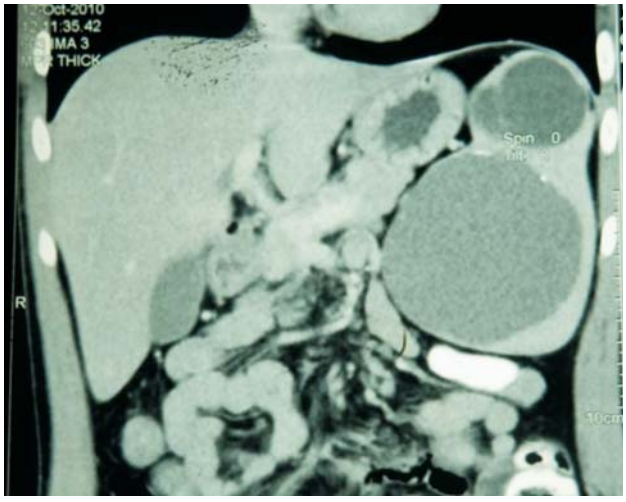

Fig. 1: *Computerised tomographic scan of spleen, showing two low density non-enhancing cystic lesions.*

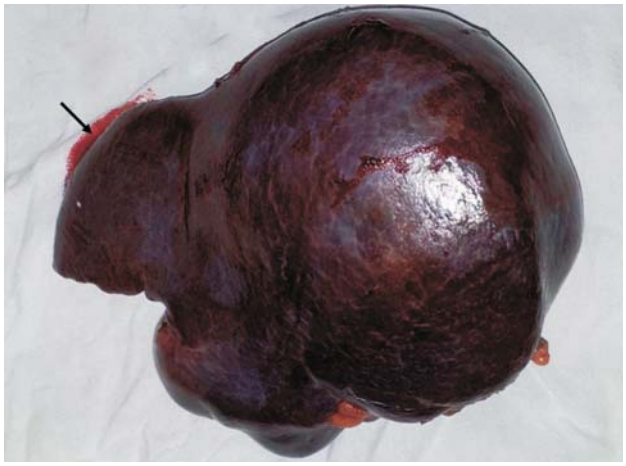

Fig. 2: *Splenic epidermoid cyst with compressed normal splenic parenchyma at the lower pole (arrow).*

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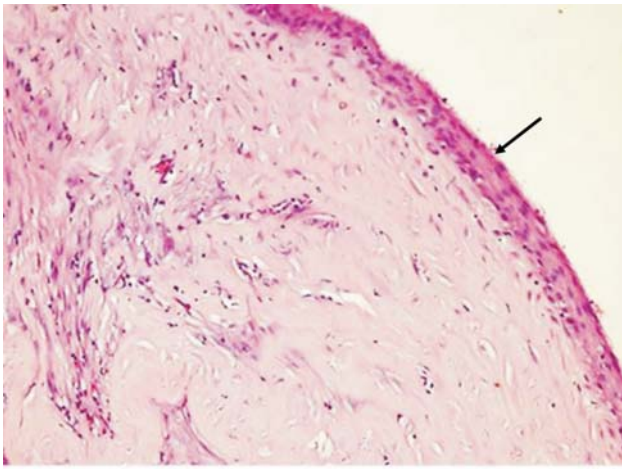

Fig. 3: *Microscopic view of true epidermoid cyst demonstrating a loose fibrous wall and stratified squamous epithelial lining.*

containing ~700 ml of clear fluid; it was thin walled, white in colour but without any stria. Microscopic examination showed a cyst with cuboidal-to-stratified squamous epithelium, with fibrosis in the wall (Fig. 3). Surrounding splenic parenchyma shows capillarisation and congestion of sinusoids with preservation of the white pulp.

Discussion

Non-parasitic cysts of spleen are exceptional and they can be divided into true (primary) or false (secondary) type based on the presence or absence of a cellular lining. True cysts can be congenital or neoplastic. Congenital cysts are epidermoid (lined by stratified non-keratinising squamous epithelium) in 90% of cases[3]; however they can be dermoid (having lining of squamous epithelium with skin appendages, hair follicles or sebaceous glands) or endodermoid (lined by columnar epithelium). Secondary cysts can be traumatic, or infective secondary to mononucleosis, malaria, or tuberculosis. The lining of the cyst in the index case was stratified squamous suggesting it to be epidermoid.

The first case of an epidermoid cyst was reported in 1829 by Andral at autopsy[4]. About 1,000 cases have been reported in the literature so far. There are various hypotheses about the aetiopathogenesis of splenic epidermoid cyst, and the most widely accepted is that there is inclusion of splenic surface mesothelium into the splenic parenchyma during embryogenesis which gradually grows in size either from proliferation of lining cells or by secretion from lining epithelium[1]. Another hypothesis is that it may originate from the normal lymph spaces. Cyst fluid is usually thin and serous, but it may be turbid or viscid.

Majority (nearly two-third) of true non-parasitic splenic cysts have female predominance and are unilocular and solitary. Splenic cysts grow slowly and remain asymptomatic until they are five cm or larger in size. Therefore, most of the patients become symptomatic in the second or third decade of life. Symptoms are non-specific and upper abdominal fullness and boring pain are frequent presenting complaints. Rarely, there may be symptoms secondary to intra-peritoneal rupture, infection, or haemorrhage within the cyst, hypersplenism, or malignant degeneration. They may cause extrinsic compression of stomach, gastro-oesophageal junction, splenic flexure, kidney, ureteropelvic junction, or left renal artery. They may present with reversible hypertension, or segmental portal hypertension or restricted movement of the left hemidiaphragm.

Diagnosis of true non-parasitic cyst is usually made while carrying out investigations for other diseases. It can be established by ultrasonography (US), computed tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen. Calcification of the cyst wall is uncommon in a true cyst, but it may be present in 10% of long-standing cases. US shows commonly an echo-free, well circumscribed lesion, although a few internal echoes secondary to haemorrhage may be present. CT scan is better for delineation of septation or calcification within the cyst. Echinococcal serology should be done to rule out hydatid cyst. In patients with negative serology and inconclusive findings on US or CT scan, MRI (MR diffusion and MR spectroscopy) has shown promising results in differentiation of parasitic, traumatic, or true splenic cysts[5,6].

The conventional treatment of a splenic cyst is splenectomy. Identification of the role of the spleen in immunogenic functions has led to the development of unconventional treatments with the aim to preserve the maximum splenic parenchyma. Splenic cyst which is asymptomatic at the time of diagnosis, i.e., less than five cm in size, has a regular wall without solid component on imaging, is best managed conservatively with a regular follow-up in the outpatient clinic. Cysts which are larger than five cm in size, located at the hilum of spleen, infective, with intra-cystic haemorrhage or compressive symptoms on adjacent organs, should be treated.

Treatment options include percutaneous aspiration of cyst and injection of sclerosant, marsupialisation, fenestration, partial splenectomy, or total splenectomy[7]. Percutaneous aspiration along with injection of a sclerosing agent is associated with a high risk of recurrence and perisplenic inflammation, which makes a later surgical intervention difficult. Marsupialisation was first described by Millar in 1982[8] by separating the cyst wall from the spleen. This

procedure is suitable for peripherally located cysts. Fenestration is also suitable for superficially located lesions and it includes partial cystectomy and de-roofing, which causes a communication of cyst with the peritoneal cavity. This is also associated with the high risk of recurrence. Partial splenectomy can be tried for polar lesions where more than 25% of the spleen can be preserved by using harmonic scalpel or radiofrequency haemostatic devices. Total splenectomy should be done for polycystic lesions, very large cyst occupying most of the spleen, cysts at the hilum, cyst which is inaccessible for fenestration or marsupialisation, or uncontrolled bleeding during spleen preserving procedures. Procedure can be done either by open or laparoscopic technique, depending on the location and size of the cyst and the availability and competence of the surgeon.

Conclusion

Clinically, epidermoid cyst of spleen cannot be distinguished from other benign cystic lesions. Symptomatic splenomegaly is an indication for surgical intervention. The aim of a pre-operative evaluation should be to exclude the secondary splenic involvement, hydatid cyst of spleen, and to localise the site of lesion within the spleen. The aim of surgery should be to preserve functional splenic parenchyma, and avoidance of recurrence. Treatment options should be based on the age of the patient, size, location, and nature of the lesion.

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What Is Pleasure?

Pleasure is a subjective state of mind that speaks of the good life. But until now nobody has been able to precisely define what pleasure is.

Pleasure is an emotion which is primarily associated with sensory elements, bodily feelings, and physiological drives. Pleasure is also absence of pain.

Pleasure is a sensation of happiness centred on the present. Sources of pleasure are broadly listed as follows:-

- Sexuality
- Eating
- Addictive substances
- Exercise
- Hobbies
- Recreational activities

Certain 'pleasure centres' in the brain need to be activated to experience pleasure. Studies show that there are no age differences in the levels of pleasure. But younger-age people tend to consider pleasure as a more important component of their well-being than older people.

The pursuit of pleasure is understood to be a fundamental impetus for human behaviour. Moral philosophers and ethicists, however, do not think high of the hedonist approach to pleasure. They say inner happinesss is more important than outer pleasure.

The perception of pleasure varies with difference in the culture of people. What is pleasure to 'A' need not be so for 'B'. However, pleasure seems to be a mixed blessing for mankind as it is capable of taking us to great heights.

(Courtesy: Journal of the Science of Healing Outcomes; Vol. 6, No. 23)

CASE REPORT

JIACM 2014; 15(3-4): 252-4

Variable atrio-ventricular block in dengue fever

JK Sharma, S Zaheer***

Abstract

Cardiac rhythm abnormalities – including ventricular arrhythmia, atrial fibrillation, and atrio-ventricular (AV) block – have been observed during the acute stage of dengue haemorrhagic fever. Atrio-ventricular or complete heart block can be fatal and may require a temporary pacemaker. We report an 18-year-old boy who presented with fever, hepatomegaly, thrombocytopenia and signs of extravascular leakage, and was diagnosed as dengue fever. He developed Mobitz type 1 atrio-ventricular block and atrio-ventricular dissociation that had a spontaneous resolution. There was no other abnormality in the 12-lead ECG, and echocardiogram showed normal ventricular systolic function. Transient AV block during recovery from dengue haemorrhagic fever may be a transient functional impairment of the AV node, in which altered autonomic tone may play a role.

Key words: Dengue haemorrhagic fever, Mobitz type 1 atrio-ventricular block, complete heart block, echocardiogram.

Introduction

Dengue is the most common arboviral disease transmitted by the mosquito, *Aedes aegypti*, infected by one of the four dengue virus serotypes: dengue-1, -2, -3, and -4 . The dengue virus, a member of the flavivirus group in the family Flaviviridae, is a single-stranded, enveloped RNA virus, 30 nm in diameter, which can grow in a variety of mosquitoes and tissue cultures. It is endemic in South-East Asia, the Pacific, East and West Africa, the Caribbean, and the Americas. More recently, dengue disease has spread geographically to many previously unaffected areas. Dengue haemorrhagic fever (DHF) epidemics occur annually with major outbreaks occurring every 3 years. Factors responsible for dengue's spread include explosive population growth, unplanned urban development and overpopulation with inadequate public health systems, poor vector control, and increased international recreational, business and military travel to endemic areas. Indeed, dengue and DHF is fast emerging as a global health problem.

Dengue infections may be asymptomatic, may lead to undifferentiated fever (or viral syndromes), dengue fever, or DHF. Mild dengue disease is characterised by biphasic fever, several types of skin rash, headache, retro-orbital pain, photophobia, cough, vomiting, myalgia, arthralgia, leukopenia, thrombocytopenia, and lymphadenopathy. However, DHF is an often fatal disease characterised by haemorrhages and dengue shock syndrome (DSS). Other common symptoms include sore throat, altered taste sensation, colicky pain and abdominal tenderness, constipation, dragging pain in the inguinal region, and general depression. A variety of cardiac complications have been reported in dengue-affected patients[1-7] which include atrio-ventricular conduction disorders[3], supra-ventricular arrhythmia[4] and myocarditis[5] (usually resulting in a benign and self-limited disease), ST segment abnormalites, low QRS voltage sinus bradycardia, first degree AV block, premautre atrial contraction (PAC), and premature ventricular contraction (PVC). We report here a patient who developed variable AV block (Mobitz type 1 second degree atrio-ventricular block and AV dissociation) during acute dengue fever.

Case report

An 18-year-old male was admitted through the emergency in Sir Ganga Ram Kolmet Hospital, Pusa Road, New Delhi, on 17th September, 2013, with a history of fever since 5 days, vomiting, generalised bodyache, pain abdomen, and dizziness. A dengue diagnosis was performed based on clinical and investigational grounds.

On clinical examination, his blood pressure was 100/70 mm Hg and heart rate was 52/min, and erythematous

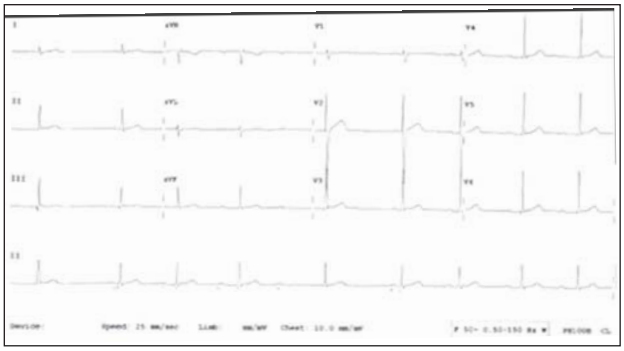

Fig. 1: *ECG showing Mobitz type 1 block on day 1 of admission.*

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rashes were present over both hands. Also, the patient had bilateral pleural effusion, mild hepatomegaly and free fluid in the peritoneal cavity. The 12-lead electrocardiogram detected intermittent Mobitz type 1 second degree atrio-ventricular block and AV dissociation. Laboratory investigations showed Hb -12.7; TLC – 16,300; DLC – P-66, L-24, M-6, E-2; platelet count - 10,000/cu mm. Urinalysis showed specific gravity 1.030, pH 6.5, albumin 2+, pus cells 4-6, RBCs 1-2, sugar- negative. Renal function tests were normal, LFT showed SGPT - 174, SGOT - 546, ALP - 62, GGT - 93, total protein - 5.2. Serum electrolytes showed Na^+- 142, K^+- 4.1, Ca^+-8.3 and Cl^- - 107. Dengue serology was positive, malaria antigen and Widal test were negative.

Treatment consisted of maintenance intravenous fluid,

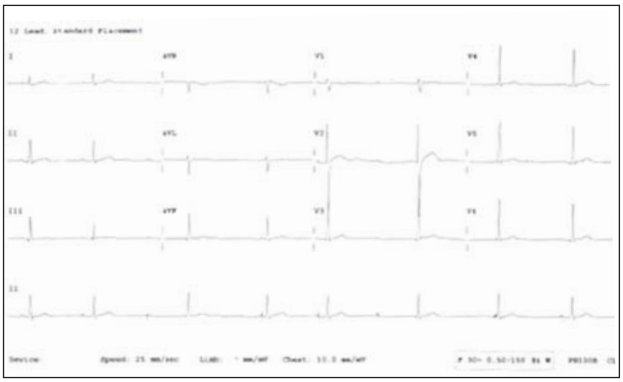

Fig. 2: *ECG showing AV dissociation (day 1 of admission).*

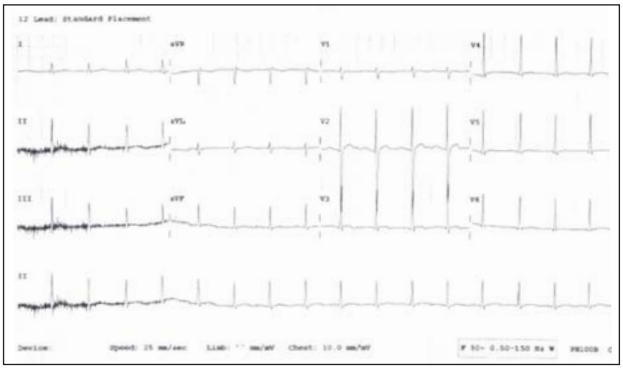

Fig. 3: *ECG recording after atropine administration.*

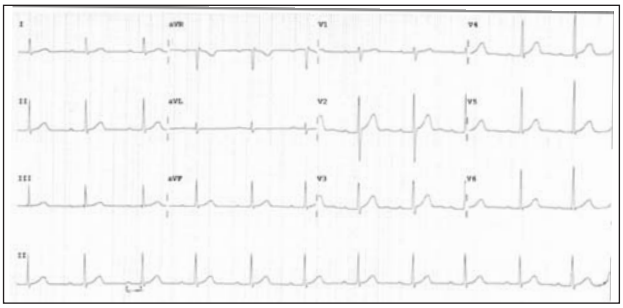

Fig. 4: *ECG showing normal sinus rhythm (NSR) on day 7 of admission.*

supportive care, and platelet transfusions. In view of variable AV block, continuous cardiac monitoring was done, but as the patient was asymptomatic no additional treatment was given. Bedside echocardiogram showed normal LV and RV functions, EF - 65%, and mild MR. Serum CPK was slightly raised. On the sixth day of admission, first degree AV block was recorded and normal sinus rhythm (NSR) was restored on the seventh day of admission.

His repeat investigations on the seventh day of admission were: Platelet count - 140,000, GGT - 97, SGOT - 118, SGPT - 106. The patient was discharged and followed 5 days later when his all blood reports were normal and ECG showed normal sinus rhythm.

Table I: Laboratory test results obtained during hospital admission.

Laboratory tests	Hospital admission	Normal range
Haemoglobin	12.7 g/dl	13-17
PCV	38.6 %	40 - 50
TLC	16,300/ dl	4,000 - 10,000
Platelets	10,000/dl	150,000 - 450,000
Creatinine	0.8 g/dl	0.67 - 1.17
Creatine kinase (CK)	254 U/l	0 - 171
SGOT (ALT)	174 U/l	0 - 50
SGPT (ALP)	546 U/l	0 - 50
GGT	93 U/l	0 - 55

Discussion

Electrocardiographic abnormalities have been observed in as many as 44 - 75% of patients with viral haemorrhagic fever. Although sinus bradycardia and prolongation of the PR interval were commonly observed, atrio-ventricular block beyond first degree appeared to be rare in these reports. In one review[7], varying degrees of nodal block during convalescence was said to be frequently seen, although descriptions of the patients were not given in this review.

Recently, Khongphatthallayothin *et al* reported two cases of Mobitz type 1 second degree atrio-ventricular block during recovery from haemorrhagic dengue[4]; both had spontaneous resolution. Previously, Donegani and Briceño had reported four patients with dengue who developed complete atrio-ventricular block, which required a permanent pacemaker[8].

Our patient was admitted with fever, diagnosed as a case of dengue fever, and during stay in hospital developed Mobitz type 1 AV block; and on continuous cardiac monitoring, AV dissociation was also found. While the mechanism for this phenomenon is still unclear and needs

further investigation, we believe that a clinical implication exists from this observation. These transient abnormalities may represent a transient functional (rather than anatomical) impairment. Among them are abnormalities in the autonomic tone, adenosine metabolism, or other abnormalities in the cells that use predominantly calcium current for depolarisation. Alternatively, localised pathology such as minute bleedings in the areas of SA and AV nodes may be responsible. Subendocardial haemorrhage, mostly in the interventricular septum has been reported in 47% of autopsy cases of patients who died from dengue haemorrhagic fever[9]. It is possible that haemorrhages in the vicinity of the AV node may result in transient AV block. Salgado *et al* in 2010 demonstrated in a study that derangements in calcium storage in infected cells of dengue patients may directly contribute to cardiac manifestations in paediatric patients[10]. AV block in an asymptomatic patient during the recovery phase of dengue fever may be benign, and careful observation alone in such a patient may be justified. Further study of the incidence and clinical courses of this phenomenon may prevent unnecessary transferring of these patients to tertiary centres.

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"If I have seen further, it is by standing on the shoulders of giants."

– Isaac Newton.

CASE REPORT

JIACM 2014; 15(3-4): 255-7

Large pulmonary embolism – Wind down the ambiguity

Sudeep Pathak, Rajeev Gupta**, Renu Sharma****

Abstract

Pulmonary embolisms are frequent in our country due to the large number of road traffic accidents and malignancies. Diagnosing PE in our setup is very difficult because of a paucity of high resolution multi-detector 64-slice CT scans along with financial limitations of patients. In this study of large pulmonary embolisms, we diagnosed a large pulmonary embolism with the help of d-dimer assay, electrocardiography, echocardiograph, chest X-ray, along with symptoms which were highly suggestive of pulmonary embolism. The reason and need for this approach in our country because either most hospitals do not have a CT scan facility or the patient is not financially sound to afford it. We can still diagnose a pulmonary embolism – as we observed in this study – with the help of d-dimer assay, ECG, chest X-ray, echocardiography in a patient who has symptoms highly suggestive of PE, and thus in turn can treat most of the patients with a moderate-to-large pulmonary embolism.

Key words: Pulmonary embolism, PE, acute pulmonary embolism, large PE.

Introduction

Pulmonary embolism (PE) accounts for millions of hospitalisations annually worldwide. Although d-dimer testing for exclusion of PE, and chest computed tomography (CT) for imaging PE have revolutionised the diagnostic approach, PE remain difficult to detect unless a high index of clinical suspicion in kept in the management of critically ill patients.

Our understanding and awareness of the precipitants of PE has improved: especially the role of hypercoaguable states and potentially modifiable risk factors such as long-haul air travel and obesity.

Specialists in critical care, and cardiologists must provide expertise in the treatment of haemodynamically compromised patients with PE as well as those with right ventricular failure who maintain a stable blood pressure and heart rate. This requires rapid and accurate risk stratification, often with echocardiography, test for detecting elevated troponin levels, brain natriuretic peptide (BNP) levels, so that those patient with adverse prognosis can be identified as early as possible, and treated with thrombolysis or embolectomy.

Case report

An elderly male aged 68 years who came to Narmada Trauma Centre on 10th March, 2013 at 7.40 pm with history of fall from two-wheeler, presented with sudden onset breathlessness, restlessness, and perspiration. He sustained mild abrasions on the face, scalp, and bruises on the chest without any major obvious external injury and internal organ injury. There was no evident fracture of the hip, femur, or spine. He had a blunt injury of the chest.

On examination, the patient was conscious, restless, tachypnoeic, with a respiratory rate of 38/minute, diaphoresis, mild cyanosis with SpO_2 of 70%. His pulse rate was 130 per minute, blood pressure was 90/60 mm Hg, and he was afebrile. He had a drop of blood pressure and saturation (70 systolic with oxygen saturation of 68%).

His investigations were:-

Haemogram	
Haemoglobin	11.8 gm%
Total erythrocyte count	4.08 x 10^6/cu mm
Erythrocyte sedimentation rate	17 mm in 1st hr
Total leucocyte count	12,300/cu mm
Differential leucocyte count:	
Neutrophils	81%
Lymphocytes	18%
Monocytes	1%
Eosinophils	0%
Basophils	0%
Platelet count	195,000/cu mm

Biochemistry	
Random blood glucose (RBG)	224 mg/dl
Urea	64 mg/dl
Creatinine	1.5 mg/dl
Calcium	9.0 mg/dl
Total billirubin	0.91 mg/dl
Direct	0.38 mg/dl
Indirect	0.53 mg/dl
AST	50 U/l

Narmada Trauma Centre, Bhopal, Madhya Pradesh.

ALT	40 U/l
Total protein	6.8 mg/dl
Albumin	3.6 mg/dl
Globulin	3.2 mg/dl
CK-MB	05 U/l
Troponin	Negative
Amylase	53 U/l
Lipase	80 U/l

d-dimer assay was positive by ELISA method.

Chest X-ray:

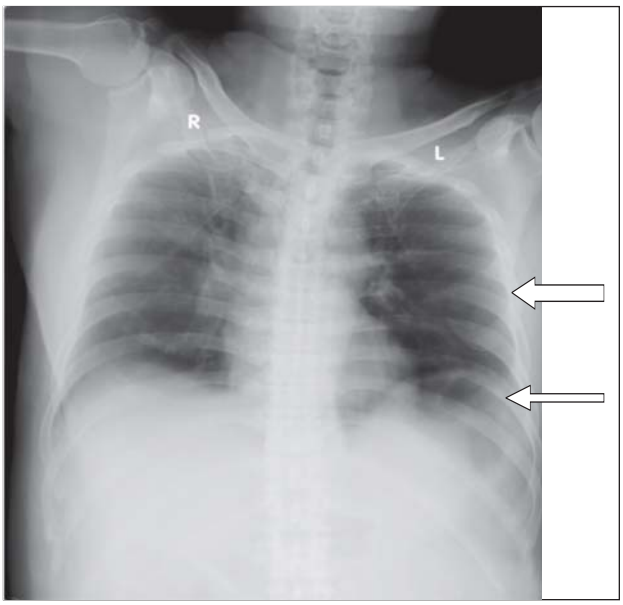

Fig. 1: *Chest X-ray of patient showing wedge shape opacity (thin arrow) at left base and prominent left pulmonary vascular markings (thick arrow) respectively.*

Electrocardiography:

There was evidence of enlarged right ventricle with size of 3.10 cm, and reduced right ventricular free wall movement. Left ventricle function was normal and there was no regional wall motion abnormality. Pericardium was normal. No evidence of RA/RV/LA/LAA/LV clot, thrombus, or vegetation. All cardiac valves were normal. There was grade-2 tricuspid regurgitation with a peak TR gradient of 45 mm Hg. There was mild pulmonary artery hypertension.

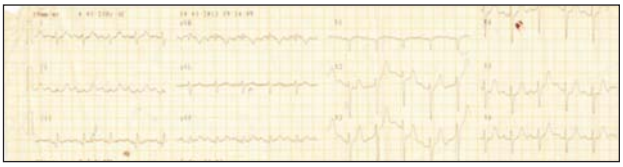

Fig. 2: *The patient's ECG was done in which he had sinus tachycardia with a heart rate of 156 per minute, axis was +80 and he had S1Q3T3.*

CT scan of the brain was normal.

Management

The patient was started on low molecular weight heparin (Enoxaparin) with a dose of 1 mg/kg body weight twice a day, IV fluids, antibiotics. His oxygen saturation by the next 6 - 8 hours had dropped to 68% and he developed hypotension with blood pressure of 80/60 mm Hg. Naso-trachea intubation was done and the patient was put on assisted ventilation – CMV-ACMV – mode with a tidal volume of 6 litres/kg, PEEP of 7 - 10, respiratory rate of 12/minute, FiO_2 of 70 which was subsequently reduced to 30 over the next 10 - 12 hours. He was also started on dopamine at the rate of 15 microdrops/kg per minute, and noradrenaline at the rate of 0.1 mg/kg/minute. Low molecular weight heparin was continued for 10 days; during this period the patient was on assisted ventilation and inotropic support, which were gradually tapered and stopped by the tenth day; and ventilator was gradually weaned to pressure support by the eight day, and weaned-off completely by the 9 th day. During the second post-admission day, the patient was started on oral anticoagulation (warfarin 5 mg once a day) and he continued to maintain INR between 2 - 2.5. The patient made a complete recovery by the 15th day, and was discharged on 28th March, 2013.

Discussion

There are various precipitating factors for venous thrombosis which in turn can cause PE.

A - Inherited factors

Hypercoagulable states

1. Mutation in factor V gene (factor V Leiden)
2. Resistance to activated protein C
3. Prothrombin gene mutation
4. Mutation in protein C gene
5. Protein S deficiency
6. Antithrombin 3 deficiency
7. Hyperhomocysteinaemia
8. Anti-phospholipid antibody

B - Acquired conditions

Acquired conditions may precipitate venous thrombosis

1. Long-haul air travel
2. Surgery/immobilisation/trauma
3. Hospitalisation with medical illness such as pneumonia or congestive heart failure, stay in medical or surgical intensive care unit.

4. Obesity
5. Increasing age
6. Cigarette smoking
7. Systemic arterial hypertension
8. Diabetes mellitus
9. Use of oral contraceptives/pregnancy/post-partum state
10. Cancer and cancer chemotherapy
11. Stroke/spinal cord injury
12. Indwelling central venous catheter, pacemakers, and internal cardiac defibrillators

Conclusion

In critical care and trauma units there is paucity of time for a complete investigational approach in rapidly deteriorating patients where clinical explanation of haemodynamic compromise is not acceptable. A high index of suspicion of pulmonary embolism can resolve the issue in certain patients and lead to a definitive diagnosis of pulmonary embolism. Therapy of pulmonary embolism is tailored according to the patient's clinical presentation, the anatomical extent of the embolus, presence of underlying cardio-pulmonary disease, cardiac biomarkers such as troponin, d-dimer, and detection of right-sided heart dysfunction by physical examination, electrocardiogram, and echocardiogram. High-risk patients warrant thrombolysis or embolectomy as primary therapy to dissolve or remove the embolus, in addition to anticoagulation to prevent recurrent venous thromboembolism. In low-risk patients, anticoagulation should suffice. The patient in our study had a large embolus, along with a positive d-dimer, ECG changes as sinus tachycardia and S1Q3T3. His chest X-ray had prominent pulmonary vascular markings and echocardiography was highly suggestive of pulmonary embolism, with features like enlarged right ventricle, hypokinetic free right ventricular wall and grade-2 tricuspid regurgitation. He was managed by anticoagulation, inotropes, and assisted ventilation. The patient made a complete recovery and was discharged thereafter.

The important aspect of this study is that we know there are less than 2% hospitals in our country which have in-house multidetector 64-slice CT scan which is the gold standard for diagnosis of PE. Therefore it is important for the critical care specialist and cardiologist to detect and recognise massive PE that can be timely investigated aggressively with multidetecter CT and managed by thrombolysis or embolectomy. On the other hand we can manage other grades of PE with anticoagulation and supportive treatment without CT scan and thrombolysis effectively, as we did in this study, and can save a large number of patients who form the majority of ambiguous PE.

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"He who asks is a fool for five minutes,
but he who does not ask remains a fool forever."

– CHINESE PROVERB.

CASE REPORT

JIACM 2014; 15(3-4): 258-59

Concomitant leptospirosis and dengue infections

KA Chopdekar, SS Patil**, SP Lilani*, AA Joshi**, A Chowdhary****

Abstract

Two cases of leptospirosis and dengue co-infection in paediatric patients are reported. Their co-existence is infrequently reported in literature. As both the conditions mimic each other, diagnosis is difficult for the physician. Serological testing for both the conditions in acute febrile illness plays a crucial role in diagnosis.

Key words: Leptospirosis, dengue, dual infections.

Introduction

Leptospirosis and dengue are infectious diseases of worldwide distribution especially in the tropics and subtropics[1]. Both the conditions often present as acute febrile illness, characterised by sudden onset of fever, headache, and myalgia[2,3]. Hence their co-existence can present a diagnostic dilemma to the treating physician. Leptospirosis and dengue co-infection is infrequently reported in the literature[4,5,6]. Here we report two paediatrics patients with dual infection of leptospirosis and dengue.

Case 1

A 4-year-old male child was admitted to the hospital with an 8 days history of fever and abdominal pain. There was no history of chills, headache, vomiting and diarrhoea. On physical examination, the patient was febrile and multiple petechial lesions were present on the face, buttocks, and scrotum. Conjunctival suffusion was present. The liver was palpable 2 cm below the right costal margin and the spleen was palpable 1 cm below the left costal margin. Urine output was decreased. Routine haematological investigations showed 9,600 WBC/cu mm^3 and decreased platelet count – 15,000/cu mm. Haematocrit was decreased to 31.3%. Liver enzymes were raised. A peripheral blood smear for malaria and the Widal test for enteric fever were negative. HBsAg, anti-HAV, anti-HEV were negative. Serum for leptospira by IgM ELISA (Indirect ELISA, J. Mitra) was positive. Dengue IgM capture ELISA (MAC ELISA, PanBio, Australia) was also positive. The patient was treated with inj. crystalline Penicillin and supportive line of therapy. At the time of discharge – after 9 days – the patient was free of symptoms and all his systems were normal.

Case 2

A 7-year-old female child was admitted with a 5 days history of fever with intermittent chills, vomiting, and diarrhoea. There was no history of abdominal pain, headache, myalgia, and conjunctival suffusion. On physical examination, the patient was febrile and the spleen was palpable 2 cm below the left costal margin. Other systems were normal. Routine haematological investigation showed 5,000 WBC/cu mm and decreased platelet count – 53,000/cu mm. Liver function tests were normal. A peripheral blood smear for malaria and Widal test for enteric fever were negative. HBsAg, anti-HAV, anti-HEV were negative. Serum for leptospira by IgM ELISA (Indirect ELISA, J. Mitra) was positive. Dengue IgM capture ELISA (MAC ELISA, PanBio, Australia) was also positive. The patient responded to inj. Monocef and supportive line of therapy.

Discussion

In an overcrowded city like Mumbai, overflow of waste water and heaps of garbage attract a large number of mosquitoes and rodents, which play an important role in spreading infections like leptospirosis and dengue. Although these two infections are commonly seen in Mumbai, co-infection with these two pathogens is not often documented. Very few cases of co-infections are being reported in the literature from India[5,6,7]. Because of several overlapping clinical features of leptospirosis and dengue, clinical diagnosis is challenging for the treating physicians. Even the lab findings including leucopenia, thrombocytopenia, and elevated aminotransferases are seen in both the conditions[2,3].

Due to the strong similarity in clinical presentation and

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epidemiology between dengue and leptospirosis and reported occurrence of the dual infections, it is advisable to conduct serological testing for both the infections in patients presenting with acute febrile illness so as to reduce the morbidity and mortality in such cases.

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Tibetan Medicine

A traditional medical system that employs a complex approach to diagnosis, Tibetan medicine incorporates techniques such as pulse analysis and urine analysis, and utilises behaviour and dietary modifications, medicines composed of natural materials (e.g., herbs and minerals) and physical therapies (e.g., Tibetan acupuncture, moxabustion, etc.) to treat illness. The Tibetan medical system is based upon a synthesis of the Indian (Ayurveda), Persian (Unani), Greek, indigenous Tibetan, and Chinese medical systems, and it continues to be practised in Tibet, India, Nepal, Bhutan, Laddakh, Siberia, China, and Mongolia, as well as more recently in parts of Europe and North America. It embraces the traditional Buddhist belief that all illness ultimately results from the "three poisons" of the mind: ignorance, attachment, and aversion.

Like other systems of traditional Asian medicine, and in contrast to biomedicine, Tibetan medicine first puts forth a specific definition of health in its theoretical texts. To have good health, Tibetan medical theory states that it is necessary to maintain a balance in the body's three principles of function, i.e., rLung (*pron.* Loong), mKhris-pa (*pron.* Tree-pa), and Bad-kan (*pron.* Pay-gen).

(Courtesy: Journal of the Science of Healing Outcomes; Vol. 6, No. 23)

CASE REPORT

JIACM 2014; 15(3-4): 260-1

Artemether-lumefantrine combination causing ventricular bigeminy

Nitin Sinha, Naresh Gupta**, Kaustubh Mahamine***, Shadab Samad****

Abstract

A 45-year-old gentleman presented with complaints of fever for six days and was diagnosed as having uncomplicated P. falciparum malaria. He was started on artemether-lumefantrine combination. On the 2nd day of admission, he had an irregular pulse. His electrocardiogram (ECG) revealed ventricular bigeminy with a normal corrected QT interval (QT_c). ECG on admission was normal. Serum potassium, calcium and magnesium and a transthoracic echocardiogram (TTE) were normal. The artemether-lumefantrine combination was stopped and the ECG on 3rd day was normal. In view of the onset of bigeminy after initiating the drug combination and subsequent reversal to normal sinus rhythm after stopping the drug made us conclude that ventricular bigeminy was per se due to the artemether-lumefantrine combination.

Key words: Venticular bigeminy, artemether-lumefantrine side effects, P. falciparum malaria.

Case details

A 45-year-old gentleman, shopkeeper by occupation and resident of Delhi, India presented to our emergency with complaints of high-grade fever associated with chills, rigors, headache, generalised body aches, and vomitings for the last six days. There were no other associated systemic complaints along with fever. He had no significant past history of any systemic illness. His examination revealed 105°F fever with a regular pulse of 108/minute. Blood pressure was 112/68 mm of Hg and respiratory rate was 24/min. He had a palpable liver (2 centimeters below the right costal margain) and a palpable spleen (3 centimeters below the left costal margain). Rest of the systemic examination was essentially normal. He had thrombocytopenia (platelet count was 1.25,000/cu mm) with the rest of haematological parameters being within normal limits. His biochemical investigations were normal. Baseline ECG (Figure 1) showed normal QRS axis with a heart rate of 107/minute and QT_c of 0.43 seconds (Normal: ≤0.44 seconds)[1]. His capillary blood smear examination showed trophozoites of *P. falciparum*. Therefore, a diagnosis of uncomplicated *P. falciparum* malaria was made. Treatment with artemether-lumefantrine combination (1 tablet: 80 milligrams artemether + 480 milligrams lumefantrine) was started in a dose of 1 tablet BD for three days. Tablet paracetamol (500 milligrams) was given for control of fever. He received just two tablets of paracetamol on day 1. He became afebrile from day 2. However, on the second day, on routine examination, his pulse appeared irregular. He had taken three tablets of the artemether-lumefantrine combination by the time of examination. He had become afebrile and the rest of his examination including the cardiovascular system was normal. An ECG at that moment showed ventricular bigeminy (Figure 2). Serum magnesium, potassium, and calcium levels were measured subsequently. Serum magnesium was 2.0 milligram/deciliter (mg/dl) (Normal: 1.5-2.3 mg/dl), serum potassium was 4.2 meq/l (Normal: 3.5 - 5.0 meq/l) and serum total calcium was 9.1 mg/dl (Normal: 8.7 - 10.2 mg/dl), respectively. The transthoracic echocardiogram was also normal. We stopped artemether-lumefantrine combination and started him on artesunate in combination with doxycycline. The pulse rate on the third day was 84/min and regular. The ECG on the third day (Figure 3) was essentially normal. The patient was

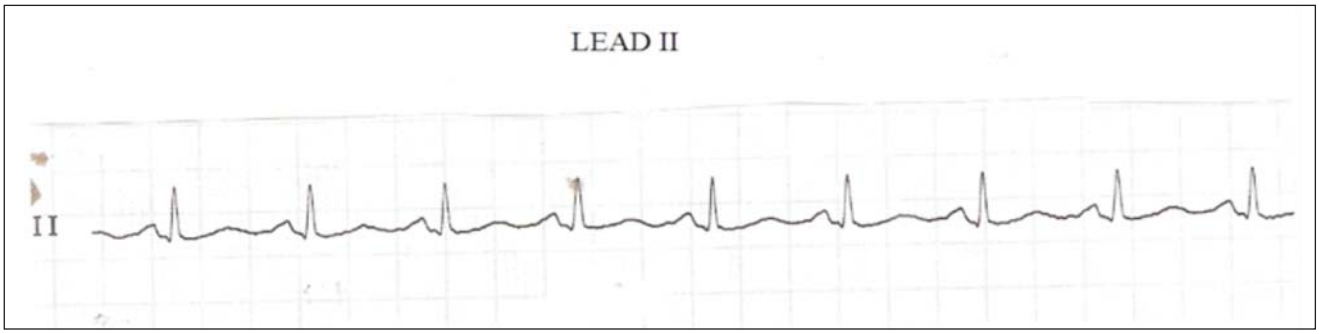

Fig. 1: *Normal ECG at baseline with normal QT_c interval.*

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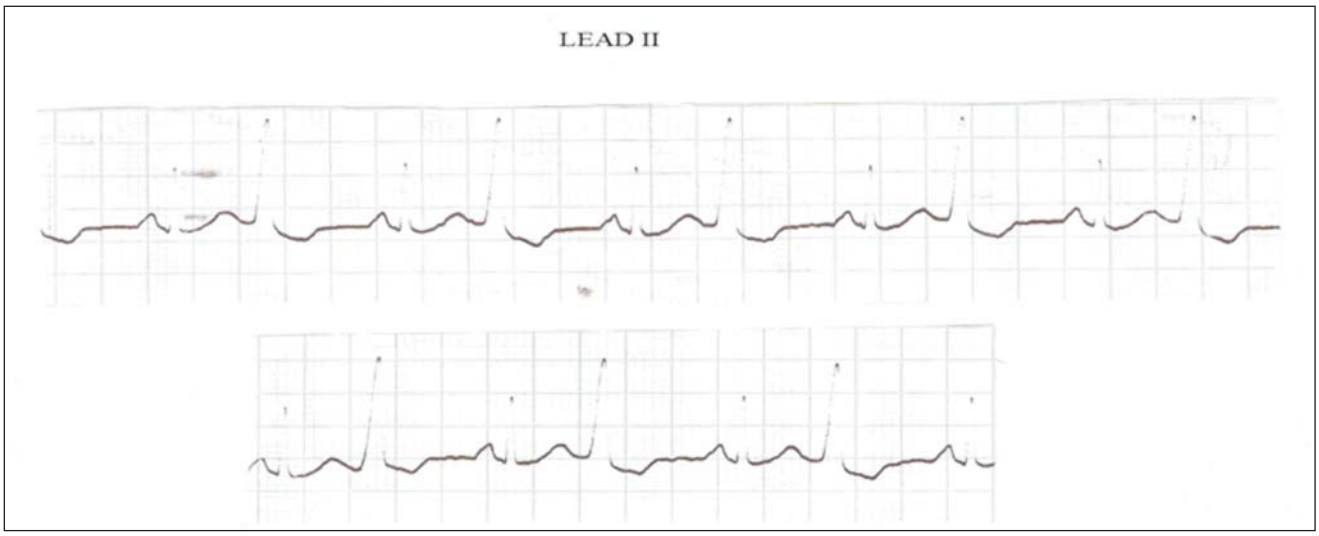

Fig. 2: *ECG showing ventricular bigeminy with normal QT_c after receiving three doses of artemether-lumefantrine.*

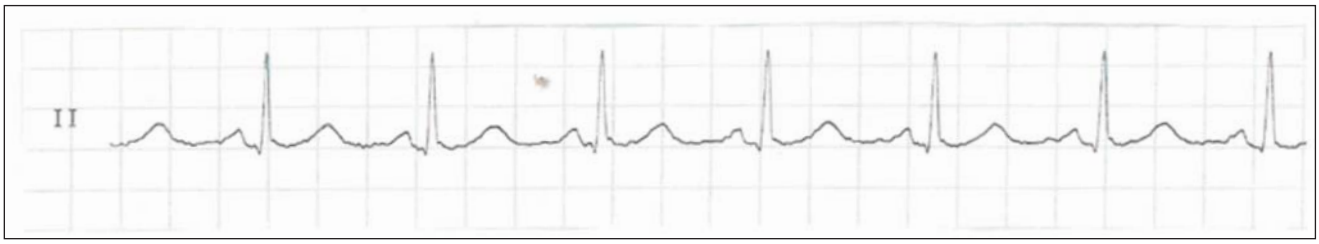

Fig. 3: *Normal ECG on day 3 after stopping the drug.*

discharged on the fourth day and is currently doing well.

Discussion

Artemether-lumefantrine drug combination is an Artemisinin based Combination Therapy (ACT) which is recommended by the World Health Organisation (WHO) as the first-line treatment of uncomplicated *P. falciparum* malaria[2]. The side effects noted with this drug combination are headache, dizziness, fatigue, myalgia, muscle stiffness, loss of appetite, vomiting, diarrhoea, abdominal pain, allergic reactions, and QT_c prolongation[3,4]. Our patient however, did not develop any of these side effects. Rather, he developed ventricular bigeminy on the second day of starting the medication. By the time he developed bigeminy he had taken three tablets of the artemether-lumefantrine combination (each tablet contains 80 milligrams of artemether and 480 milligrams of lumefantrine). We discontinued the combination and shifted the patient to artesunate and doxycycline. Repeat ECG on the third day showed ECG with normal sinus rhythm. Ventricular bigeminy can be seen in structural heart diseases, drug toxicities (e.g., digoxin), ischaemia, and in the elderly[5]. Our patient was middle-aged and had no evidence of any dyselectrolytaemia or any structural heart disease. He was also not on any other drugs which could lead to development of ventricular bigeminy. Since this abnormality occurred after initiating artemether-lumefantrine combination and resolved immediately after stopping the drug, we assume that ventricular bigeminy occurred due to this drug combination. This is probably the first time such a rhythm disturbance has been noted with this drug combination. This case also highlights the fact that this drug combination can lead to cardiac rhythm disturbances and the treating physician must keep a hawk's eye for picking up these abnormalities and use the drug judiciously in cardiac patients.

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CASE REPORT

JIACM 2014; 15(3-4): 262-5

Scrub typhus: Keep high index of suspicion and treat early

Nitin Sinha, Ashok Grover**, NP Singh***, Pankaj Nand Choudhry*****

Abstract

We present a 59-year-old lady who presented to the emergency with complaints of fever, headache, recurrent vomitting, and occasional dry cough for six days. She had thrombocytopenia. Investigations for dengue, malaria, and typhoid fever were negative. She was given symptomatic treatment. On fifth day of hospitalisation she developed interstitial pneumonia. Suspecting Rickettsial disease, Rickettsial serology was sent and doxycycline was added to the treatment. She developed jaundice on eighth day of hospitalisation, and on the same day IgM for scrub typhus came positive. Doxycycline was continued and she improved. Rickettsial diseases can be fatal and a high index of suspicion should be kept. Treatment should be instituted even on suspicion.

Key words: Scrub typhus, diagnosis of scrub typhus, treatment of scrub typhus.

Introduction

Scrub Typhus is caused by *Orientia tsutsugamushi*, a Rickettsia, spread by the bite of the larva of trombiculid mite. Humans are accidental hosts. Scrub typhus is the most common Rickettsia in India and is endemic in various regions of the country. Index of suspicion should be high in appropriate settings as the serological tests to detect scrub typhus become positive only in second week. Treatment should be instituted on suspicion as the disease can be fatal.

Case summary

Our patient is a 59-year-old homoeopathic doctor from Delhi, India. She presented to the emergency with complaints of fever, headache, recurrent vomitting and occasional dry cough for the last 6 days. Her temperature was 101° F with rest of vitals and systemic examination being normal. Her investigations revealed thrombocytopenia (platelet count - 130,000/cu mm), along with elevated liver enzymes [aspartate transaminase (AST) - 140 U/l, alanine transaminase (ALT) - 115 U/l, alkaline phosphatase (ALP) - 230 U/l, gamma glutamyl transpeptidase (GGTP) - 113 U/l], hypoalbuminaemia [serum albumin (S. Alb) - 3.1 g/dl] and normal haemoglobin (Hb) - 12.3 g/dl, total leucocyte count (TLC) - 4,200/cu mm, total bilirubin - 1.1 mg/dl and direct bilirubin - 0.6 mg/dl. Her blood urea, serum creatinine, urine routine examination, electrocardiogram, and chest X-ray (Figure 1) were also normal. NS1 antigen, dengue serology IgM, malaria antigen and typhidot IgM were negative. Blood culture was sent. She was started on ceftriaxone along with other supportive medications. Over the next four days, her fever and headache persisted though her vomitting and cough got relieved.

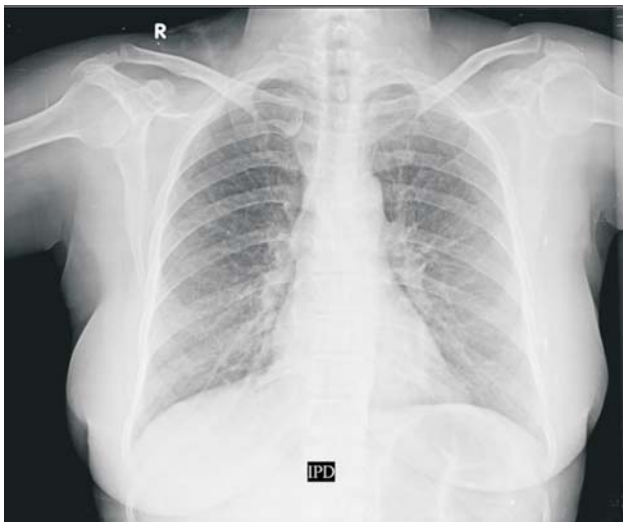

Fig. 1: *Normal chest X-ray at the time of admission.*

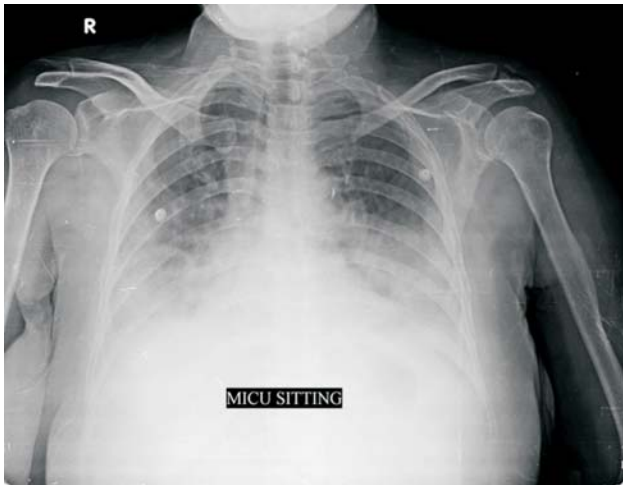

Fig. 2: *Chest X-ray on day 5 of hospitalisation showing bilateral interstitial pneumonia.*

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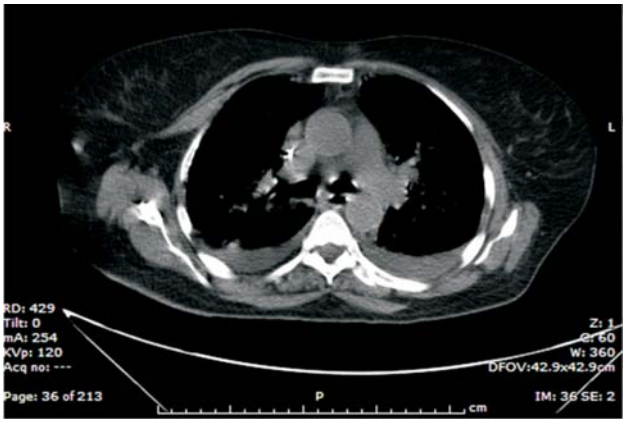

Fig. 3: *CECT chest showing bilateral pleural effusion with basal atelectasis with middle and lower zone peribronchial thickening.*

Her platelet counts decreased to 60,000 by day two of hospitalisation and continued to be between 60,000 - 70,000/cu mm over the next two days. Blood culture showed no growth. MRI brain with contrast was done to look for the cause of persisting fever with headache and was normal. On day five of hospitalisation, she developed breathlessness and desaturated. Chest examination revealed bilateral infrascapular crepitations with the rest of her systemic examination being normal. Her investigations now revealed leucocytosis (TLC - 13,890/ cu mm), anaemia (Hb - 9.9 g/dl), thrombocytopenia (plt. ct - 62,000/cu mm) along with bilateral lower lobe haziness on chest X-ray (Figure 2) and a normal echocardiogram. Due to the development of this adverse event, she was shifted to ICU, was put on high flow oxygen and BiPAP support. CECT chest (Figure 3) showed bilateral pleural effusion with basal atelectasis and middle and lower zone peribronchial thickening.

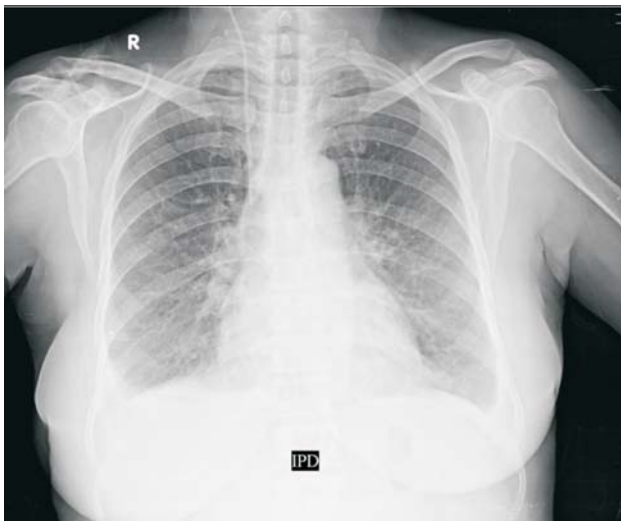

Fig. 4: *Chest X-ray showing near complete resolution of bilateral interstitial pneumonia.*

Ceftriaxone was stopped and piperacillin-tazobactam was started. In view of having suspicion of Rickettsia and Leptospira, respective serologies were sent and doxycycline was added. Over the next two days her fever subsided and her breathlessness improved, her TLC became normal but her anaemia (Hb - 9.5 g/dl) and thrombocytopenia (plt. ct - 71,000/cu mm) persisted. On the eighth day of hospitalisation, she developed jaundice. Her liver function tests showed t. bil - 9.85 mg/ dl, (D) - 8.49 mg/dl, AST - 301 U/l, ALT - 137 U/l, ALP - 325 U/l, GGTP - 203 U/l and albumin - 2.7 g/dl. Leptospira serology was negative. Rickettsial serology revealed positive IgM for scrub typhus. Chest X-ray showed mild improvement. It was here that on further probing she disclosed that she had travelled to a village in Haridwar, a town in Uttarakhand State, India around two weeks prior to her illness where she frequently visited a farm land. Over the next five days she became asymptomatic, platelet count normalised (plt. ct - 201,000/cu mm), chest X-ray (Figure 4) showed almost complete resolution and liver function tests showed marked improvement. She was discharged on haematinics and was advised to take doxycycline for seven more days. She was followed after one week and her liver function tests became normal. Her haematinics were continued, and after one month of discharge her haemoglobin was 11.1 g/dl.

Discussion

Scrub typhus is caused by bacteria of the family Rickettsiaceae, genus *Orientia* and species *tsutsugamushi*. It was first described by Hashimoto from Japan in 1899. The term scrub is used because of the type of vegetation (terrain between woods and clearing) that harbours the vector; however, recently it has been found that the disease can be prevalent in areas such as sandy beaches, mountain deserts, and equatorial rain forests. Therefore, it has been suggested that the names, mite borne typhus, or chigger borne typhus, are more appropriate. It is endemic in tsutsugamushi triangle which is a geographically distinct area extending from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan and Afghanistan in the west[1]. It also occurs in Nepal, northern Pakistan, Papua New Guinea and the Australian states of Queensland and Northern New South Wales[2]. It is the most common Rickettsial infection in India and is present in the whole of Shivalik ranges from Kashmir to Assam, Eastern and Western Ghats and Vindhyachal and Satpura ranges in the central part of India[1]. Outbreaks of scrub typhus have been reported in India from Sikkim, Himachal Pradesh, Haryana, Darjeeling, and southern India in the last ten years suggesting the re-emergence of the disease in the

Indian sub-continent[1,3]. The most important vector for the disease throughout the world is *Leptotrombidium deliense* (Trombiculid mite). Besides this, the other Leptotrombidium species, viz., *dihumerale*, *akamushi*, *subintermedium*, *pallidum* and *scutellare* have also been incriminated as vectors of scrub typhus. *Schoengastiella ligula* in addition to *Leptotrombidium* has also been incriminated as vector of scrub typhus, especially in India[3]. These mites grow in large numbers in a conducive environment to form "mite islands". Rodents are natural hosts. The mites feed on the infected rodents and acquire the organism and maintain the infection throughout their life stages. The larva of mite also called as "chigger" is the one that feeds on the host. Since neither the rodents nor the mites die of *Orientia*, they also act as reservoirs. Human infection takes place when they come in contact with the mite islands and are bitten by chiggers[1]. Illness can be mild and self-limiting to severe and fatal. Incubation period is 6 - 21 days and the onset of disease is characterised by fever, headache, myalgia, cough, and gastrointestinal symptoms. An eschar is present at the site where chiggers bite but is seldom seen in indigenous patients and only 50% of Westerners develop it[4]. Eschar starts as a papule which breaks down to form an ulcer and gets covered by a black crust and has an erythematous halo. It is located mainly in the lower extremities, axilla, and groins; and tender regional lymphadenopathy may be present[5,6]. A maculopapular rash may appear on the 6th day on the trunk and may later spread to the arms and legs but is seen in less than 40% of the patients[4,5]. Generalised lymphadenopathy and hepatosplenomegaly are also commonly found on examination. A small number of patients may develop tremors, delirium, or nuchal rigidity in the second week of the illness. Complications which occur due to vascular involvement leading to cellular infiltration and congestion in various organs include interstitial pneumonia, respiratory distress syndrome, myocarditis and heart failure, acute renal failure, gastrointestinal haemorrhage, hepatits, gall bladder oedema, encephalitis, and disseminated intravascular coagulation (DIC)[5]. Mortality rates in untreated patients range from 0 - 30%[5]. In a case series of 30 patients from Taiwan, 29 had liver abnormalities and among them 89.3% had elevated aspartate aminotransferase (AST) levels, 91.7% had elevated alanine aminotransferase (ALT) levels, 84.2% had elevated alkaline phosphatase (ALP) levels, and 38.5% had elevated total bilirubin levels[7]. In the same series, among the 16 patients who underwent ultrasonography, nine had acute hepatitis-like imaging including minimal ascites, mild splenomegaly, oedematous gall bladder wall, and two had right-sided pleural effusion. In a recently published case series of eight patients of scrub typhus, fever was the chief symptom followed by headache, myalgia, and cough, with hepatosplenomegaly and lymphadenopathy being detected on examination, and eschar being present in all cases. Also, hepatic dysfunction was seen in all cases, and thrombocytopenia, hypoalbuminaemia, haematuria, and proteinuria were also observed[8]. IgM antibodies to *O. tsutsugamushi* appear at the end of the first week, and IgG antibodies appear at the end of the second week. Weil-Felix, complement fixation, indirect haemagglutination, latex agglutination, enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence antibody (IFA), indirect immunoperoxidase (IIP), microimmun-ofluorescence, and Western blot are the various serological tests available. Weil-Felix being the cheapest and most easily available is most commonly performed. It is based on the principle of sharing of OX K antigen of *Proteus mirabilis* and *O. tsutsugamushi*. Agglutinating antibodies, especially of IgM type are detected after 5 - 10 days of onset of symptoms. If agglutination is weak, repeat testing can be done after 10 days. IFA is considered the gold standard. It does not depend on seroconversion. Here, biopsy samples from petechial lesions or from around the eschar are obtained and fluorescent antibodies are used to detect the organism but it requires special microscopes and is expensive. IIP uses peroxidase rather than fluorescein and the advantage is that its result can be read with a light microscope. *O. tsutsugamushi* can be cultured from blood or skin rash lesions or lymph nodes on Vero, L929, HEL or MRC5 cells and diagnosis can be made before seroconversion. Polymerase chain reaction (PCR) from blood, lymph nodes, and skin rash lesions to detect 56 kDa antigen producing gene of *O. tsutsugamushi* is also available[9]. Treatment consists of giving doxycycline (100 milligram bid orally for 7 - 15 days) or chloramphenicol (500 milligram qid orally for 7 - 15 days). In areas where doxycycline resistance is present, rifampicin is used. Azithromycin and clarithromycin have been used successfully in some patients but further studies are required. Studies are also required for finding regimens for severe disease, for example, comparing intravenous chloramphenicol with intravenous tetracycline[4,10].

Our patient also had fever, headache, recurrent vomitting but also had mild dry cough. She had thrombocytopenia and elevated liver enzymes at the time of admission. In the second week of her illness she developed interstitial pneumonia with bilateral pleural effusion and jaundice with elevation of liver enzymes, which, as discussed above are well known complications of scrub typhus. Her IgM serology for scrub typhus was positive in the second week of illness which is consistent with the fact that IgM response occurs after the first week. She responded well

to doxycycline given orally and broad spectrum antibiotics along with other supportive medications, and her platelet count, liver function tests and chest x-ray normalised.

Scrub typhus should be suspected in all cases of fever and thrombocytopenia with elevated liver enzymes in endemic areas and in appropriate clinical settings (a person with a history of recent travel to an endemic area, farmers, military personnel, forest officials, etc.). Treatment should be started presumptively and early to prevent complications as serological tests to detect *Orientia* become positive only in the second week of the illness. In non-endemic areas, a history of travel to an endemic area should be sought in suspected cases. Our patient was residing in Delhi (India) which is not endemic for scrub typhus but she probably caught the infection when she visited a village in Haridwar (Uttarakhand State, India) where this disease is endemic.

Learning points from the case:-

- Rickettsial diseases should be suspected in any fever of more than 6 - 7 days duration where there is history of travel to an endemic area or there has been exposure to the vector or reservoir.
- High index of suspicion and prompt institution of treatment is the key. This is because the serological tests commonly available for the diagnosis show positivity only in the second week.
- Doxycycline is the drug of choice and should not be deferred due to deranged LFTs.

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"Good people are good because they've come to wisdom through failure."

– William Saroyan.

CASE REPORT

JIACM 2014; 15(3-4): 266-8

Gall bladder tuberculosis with bilateral pleural effusion – A rare presentation of disseminated TB

Pooja Agarwal, Prashant Prakash**, Ashutosh Gupta***, Deepa Rani**

Abstract

Tuberculosis of gall bladder is rare with approximately 50 cases reported in the literature so far. The reason for this low incidence could be the presence of inhibitory substances in the bile. Imaging is non-specific and in most cases is similar to that of chronic cholecystitis. Most cases are diagnosed accidentally on histopathological examination. We report one such case of gall bladder tuberculosis associated with bilateral tubercular pleural effusion.

Key words: Gall bladder, tuberculosis.

Introduction

Tuberculosis (TB) of the gall bladder (GB) is rare. The first case of GBTB was described in 1870 by Gaucher. To date, approximately 50 cases have been reported with most of these being diagnosed only on histological examination after cholecystectomy[1,2]. We report a case of gall bladder tuberculosis (GBTB) which was accidentally detected on histopathological examination of gall bladder in conjunction with bilateral (B/L) tubercular pleural effusion. One case of GBTB was reported by Akhtar *et al* in 2009[3].

Case report

A 37-year-old female reported to the Medicine OPD of S.N. Medical College, Agra with complaints of mild pain in the right upper abdomen radiating to the right shoulder; and fatty dyspepsia of 1 month duration, along with mild grade off-and-on fever. There was history of breathlessness since 8 months. Chest X-ray revealed B/L pleural effusion which was moderate on the left side and minimal on the right side (Fig. 1). Aspirated pleural fluid was sent for biochemical analysis which revealed a cell count of 2,480 cells/µl with 70% lymphocytes; glucose level was 50 mg/dl; pleural fluid protein was 3.8 gm%, and ADA level was 78 U/l. These findings were suggestive of tuberculosis, and ATT was started. There was no history of haematemesis, malena, jaundice, rigors, or chills. There was no past or family history of tuberculosis.

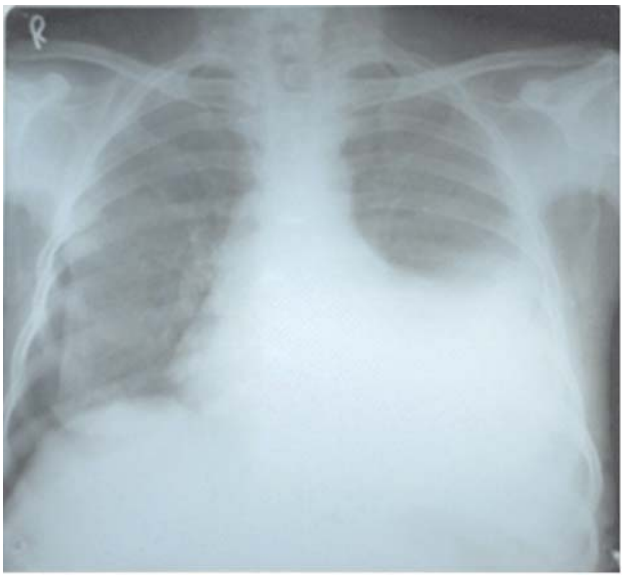

Fig. 1: *Chest X-ray showing bilateral pleural effusion.*

On examination, the patient was of average built and well nourished. She had no cyanosis, jaundice, or oedema. There was no generalised lymphadenopathy. Her pulse and blood pressure were within normal limits. The examination of her abdomen revealed mild tenderness on deep palpation in the right hypochondrium. There was no rigidity or rebound tenderness, and no lump was palpable. There was no organomegaly and no free fluid was present in the abdomen. The rest of the systemic examination did not reveal any abnormality. A provisional diagnosis of chronic cholecystitis was made and the patient was admitted for investigations.

Investigations revealed normal haemogram and normal urine analysis. Blood sugar, blood urea, and serum creatinine were within normal limits. Liver function tests showed serum bilirubin to be 0.6 mg%, serum total proteins 6.4 gm%, serum albumin 4 gm%, serum total globulins 2.4 gm%, and serum alkaline phosphatase 10 KA units. ECG was normal. Plain X-ray of the abdomen did not show any radio-opaque shadow in the gall bladder or common bile duct areas. On USG, the diagnosis of chronic cholecystitis along with minimal right-sided

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pleural effusion and moderate left-sided pleural effusion was confirmed and the patient was advised to undergo surgery (Fig. 2).

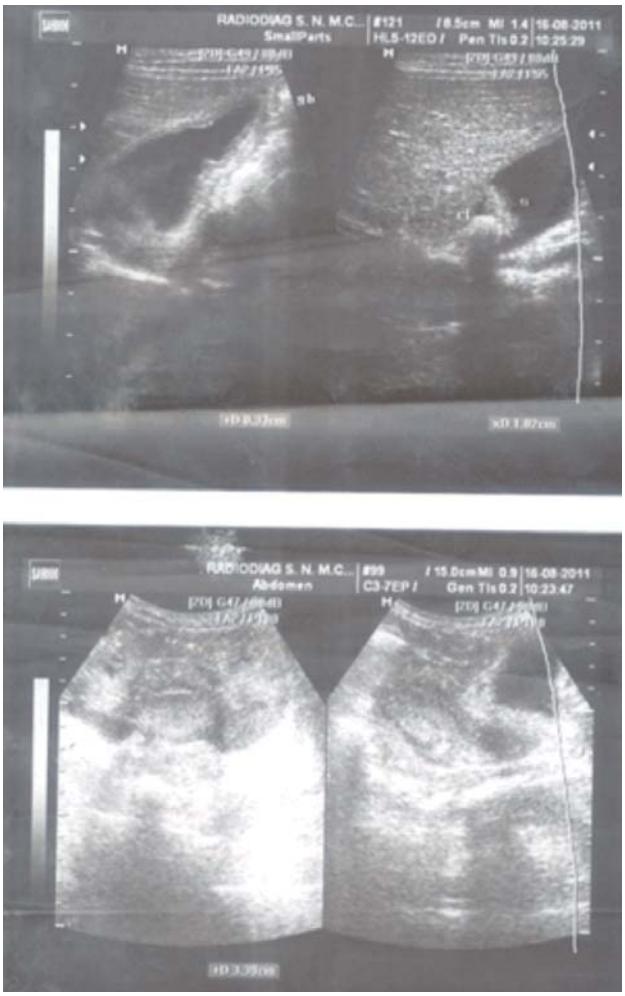

Fig. 2: *USG of gall bladder showing thickened walls and multiple stones.*

Laparotomy was done under general anaesthesia. The gall bladder was found to be small and fibrosed with a thick wall. Stones were felt within the gall bladder. The common bile duct was normal. Cholecystectomy was performed, and the gall bladder when cut open, showed no growth or tubercles on its mucosal surface. The serosal layer was also normal. The patient had a very smooth and uneventful post-operative period. The extirpated gall bladder was examined. On gross examination, there was no evidence of caseation or any other lesion. Microscopic examination revealed caseating granulomatous lesions with Langhan's giant cells in the serosal layer. The mucosa was atrophic, and the muscle layer showed mild chronic inflammatory infiltrate (Fig. 3, 4). The picture was consistent with tuberculosis of the gall bladder. The patient was discharged on antitubercular treatment. Since then, she is regularly attending the follow-up clinics and is symptom-free.

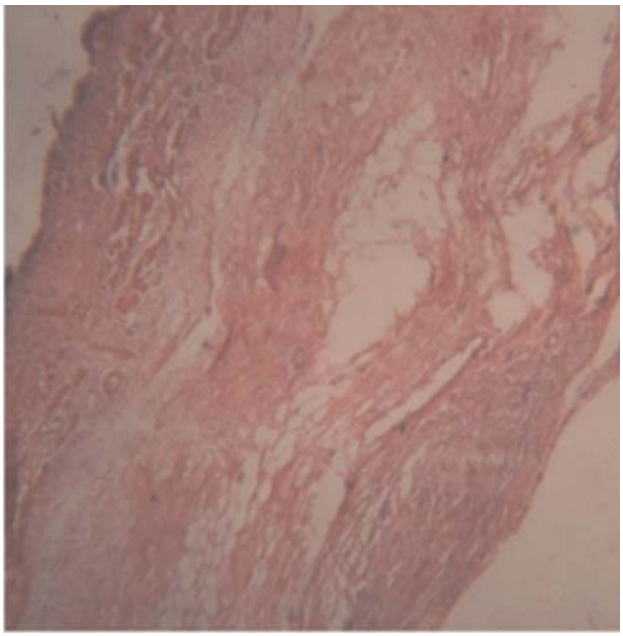

Fig. 3: *Microphotograph showing atrophic gall bladder mucosa with granuloma in the serosa.*

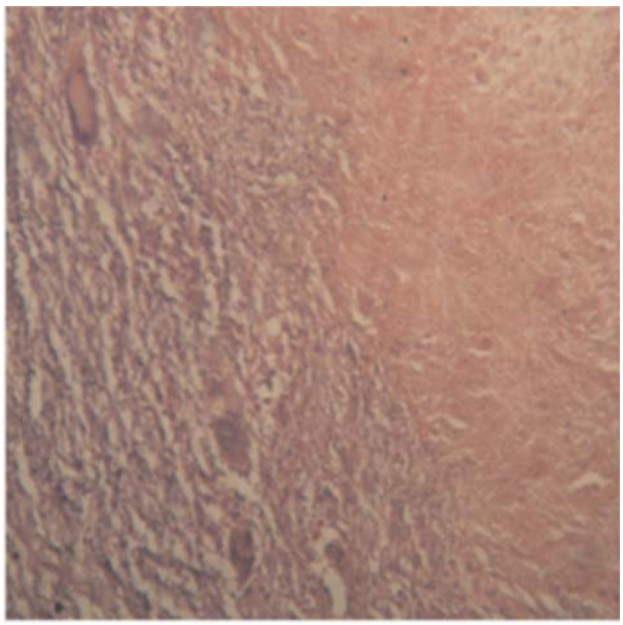

Fig. 4: *Microphotograph showing granuloma with necrosis.*

Discussion

The incidence of gall bladder tuberculosis is very low although the frequency of cholecystitis has increased during the past decades[4,5]. Various reasons for the low incidence of gall bladder tuberculosis are failure to

recognise the condition or the presence of inhibitory substances in the bile[1]. It is not clearly known whether the infection can occur in a normal gall bladder. Kettler has proposed that the absence of tubercles from the mucosa indicates a haematogenous or lymphogenic spread of infection; whereas tubercles mainly localised in the mucosa denote canalicular dissemination, and tubercles scattered over the serosal layer of the gall bladder might indicate dissemination via the peritoneal cavity[1,5].

Clinical studies denote that stones or cystic duct obstruction may be of pathogenic significance for the development of tuberculosis in the gall bladder[1,2]. Most of the cases of tuberculosis of gall bladder reported in the literature had stones in the gall bladder or had obstruction of the cystic duct or common bile duct. In our case, stones were seen in the gall bladder.

TB is especially rampant in the developing and the underdeveloped parts of the world. Despite this massive prevalence of TB, only about 50 cases of GBTB have been reported in the literature so far. Gulati *et al* reported a case of GBTB in conjunction with adrenal TB[6].

Four types of GBTB have been described:–

A. Miliary TB in children with ulcerating tubercles in the gall bladder.

B. GBTB in association with severe generalised TB.

C. Isolated GBTB.

D. Gall bladder involvement in association with TB in other intra-peritoneal organs[1]. The fourth group is said to be the commonest type[2].

Our case did not conform to the above-mentioned groups as it was associated with only tubercular pleural effusion with no evidence of TB in any other organ. This association of GBTB with tubercular pleural effusion, to the best of our knowledge, has not been reported in the literature so far.

The route of infection in GBTB can be canalicular, lymphatic, or haematogenous. The clinical presentation is often vague and non-specific. Anorexia, fever, weight loss, abdominal pain, diarrhoea with or without jaundice has been described[1,2,7]. The notable feature in our case was the breathlessness accompanied by a vague right upper quadrant pain in the absence of any biliary symptoms.

Imaging morphology of GBTB has rarely been described. GB with abnormally thickened walls with underlying cholelithiasis has been described in the available surgical reports[1]. Jain *et al* have reported a case wherein the GB was enlarged with thickened walls, presence of gall stones and an intraluminal mass simulating a GB carcinoma was present[7]. A dilated GB with a large stone located in the neck simulating acute cholecystitis has also been reported[8]. Presence of features like portal, mesenteric, and retroperitoneal adenopathy, mesenteric thickening, and ascites if present favour the diagnosis of TB[7,8]. None of these described features were present in our case. In conclusion we emphasise that GBTB has no pathognomonic diagnostic imaging features. Our case report aims to add to the existing spectrum with the appearance of a thick walled GB. There are no pathognomic features for the preoperative diagnosis of gall bladder tuberculosis, and accidental reporting on histopathology has been a common occurrence. We also highlight the role of histopathology to confirm the diagnosis.

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"Silence is a good medicine for the heart."

– Chinese proverb.

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Victor A McKusick: From "musical murmurs" to "medical genetics"

*M Mahesh**

A self-styled medical nomad, Victor A McKusick was a clinical cardiologist who became an interventional cardiologist and then finally went on to become the doyen of medical genetics.

Introduction

Many medical students of the earlier generation must have studied the book on heart sounds and murmurs *"Cardiovascular Sound in Health and Disease"* during their undergraduate or postgraduate days. That authoritative and comprehensive treatise authored by Victor McKusick has played a major role in molding the knowledge bank and auscultatory skills of scores of physicians.

This article aims to remind readers of this great soul. His career illuminates several outstanding qualities a doctor is expected to possess. His efforts and success in getting a publication early in his career ought to show the way to present young medical professionals in India where research is the urgent need of the day. His versatility in excelling in two major branches of medicine is commendable. His deeds are certainly inspiring, worthy of emulation by our younger generation — medical colleagues and medical students. A noble figure in medicine indeed.

Victor A. McKusick – "Father of Genetic Medicine."

Victor McKusick is widely considered to be the founding father of medical genetics. An innovative clinician, medical educator, and researcher, he established the first medical genetics programme and clinic at Johns Hopkins in 1957, conceived and compiled *Mendelian Inheritance in Man*, a catalogue of human phenotypes, and conducted landmark studies of hereditary disorders. He was closely involved in the Human Genome Project, and served as Founding-President of the Human Genome Organization.

Early schooling

Victor McKusick was born in 1921. Raised on the family dairy farm, he attended a one-room school and graduated from a local high school. In his teens, he considered becoming a minister, but a close encounter with medicine changed his plans: he developed an abscess under one arm, and the infection (caused by an unusual streptococcus strain) spread and would not heal. McKusick spent 10 weeks in hospital at Massachusetts General in Boston, where he was treated successfully with the then new antibiotic sulfanilamide. Inspired by the experience, he chose to pursue a career in medicine.

Medical career

McKusick began his medical studies in 1943 at Johns Hopkins, received his MD in 1946. He joined the faculty at Johns Hopkins in 1951 as an instructor, and was promoted to professor in 1960. From 1973 to 1985, he served as Physician-in-Chief and Chairman of the Department of Medicine. From 1985, he was University Professor of Medical Genetics, and remained active in teaching and research till the end.

McKusick took his first step into medical genetics during his internship. A teenager with intestinal polyps and curious pigmented spots on his lips became his patient. McKusick had seen four other patients with this combination, three of them in the same family, indicating a hereditary condition. Hearing that a Boston physician, Harold Jeghers, had seen five such cases,

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McKusick contacted him, and the two wrote up their cases for the *New England Journal of Medicine*. This became McKusick's first medical publication. Because the syndrome had been noted many years earlier by Peutz, a Dutch physician, it was named the Peutz-Jeghers syndrome (PJS).

Cardiology days

Medical genetics was not a specialty at that time, and in his residency, McKusick was drawn to cardiology. He worked for two years in the cardiovascular unit at the U.S. Marine Hospital, doing cardiac catheterisations and studying the heart borders with a new imaging method called electrokymography.

During his early faculty years at Johns Hopkins, he pursued a study of heart sounds and murmurs using sound spectrography, which had been developed at the Bell Telephone Laboratory for studying speech sounds. The technology could pick up and record the frequency spectrum of heart sounds, allowing physicians to visualise what they were hearing with their stethoscopes. McKusick renamed it spectral phonocardiography, and used the studies as the basis for a comprehensive treatise on heart sounds titled *Cardiovascular Sound in Health and Disease*, published in 1958. He also published papers on chronic constrictive pericarditis, ventricular fibrillation, the electrocardiographic effects of lithium chloride, and other topics.

He carried out a comprehensive study of Marfan syndrome and four similar disorders, collecting patients and family histories from his own practice and from many other clinical departments at Johns Hopkins. This work produced his first book, *Heritable Disorders of Connective Tissue*, first published in 1956.

Genetics

Medical genetics as a distinct clinical and academic discipline at Johns Hopkins began in 1957, when McKusick was asked to serve as director of the multifaceted chronic disease clinic. McKusick accepted the position, on the condition that he could develop a Division of Medical Genetics within the Department of Medicine.

Arguing that genetic disease is the ultimate chronic disease, he envisioned the new division carrying out teaching, research, and patient care related to hereditary disorders. Increased understanding of rare genetic disorders would vastly improve differential diagnosis and treatment, and enable physicians to better counsel affected patients and their families.

His research focussed on nosology (defining the multiple distinct forms of genetic diseases) and on gene mapping. The centre became a premier post-doctoral training ground for specialists from many areas of medicine, and its alumni helped propagate the new field of medical genetics in the United States and abroad.

Soon after the medical genetics programme was founded, McKusick and his colleagues began doing comprehensive annual reviews of the relevant medical and scientific literature, which were published in the *Journal of Chronic Diseases* from 1958 to 1963. The catalogue, titled *Mendelian Inheritance in Man*, was first published in 1966. in collaboration with the National Library of Medicine, the *Online Mendelian Inheritance in Man* became available in 1987, and remains a standard reference work.

McKusick played a leading role on the committee charged with assessing the feasibility of what became the Human Genome Project. In 1988, he became Founding-President of the Human Genome Organisation (HUGO), an international coordinating agency for the global mapping and sequencing efforts.

Publications

McKusick was a prolific writer throughout his career and published over 500 medical articles and 7 books in addition to the ongoing compilation of *Mendelian Inheritance in Man*. Other projects included a study of haemophilia in colonial New England.

History of medicine

He also pursued a lifelong interest in the history of medicine. Many of his clinical publications included historical components, and he wrote a history of medical genetics for a standard textbook in the field.

In a paper in 2005, McKusick was quoted: "I have always told my students, residents, and fellows, if you want to really get on top of some topic, you need to know how it got from where it was to how it is now. I was always strong on eponyms, too – like Marfan syndrome, Freeman-Sheldon syndrome, Down syndrome, Tay-Sachs disease, etc. On rounds, the resident or student would present a patient with some particular condition, and I would always ask, so who is so and so for whom the disease was named. This prompts thought and research into the disease or condition itself to find out who first described it and, therefore, for whom it was named."

"A historical background is an essential part of research in any field of medicine."

– Victor McKusick.

Awards

McKusick's work earned him many honours and awards, including the Award of the American College of Physicians for distinguished contributions in internal medicine (1972); election to the National Academy of Sciences (1973); the Lasker Award for Special Achievement in Medical Science (1997); the National Medal of Science (2002), along with more than 20 honorary doctorates.

Victor McKusick died on July 22, 2008, at the age of 86.

"I became known as a cardiologist before I became known as a geneticist. Some thought I was committing professional suicide in leaving cardiology to focus on rare and "unimportant" genetic disorders. They asked why I switched from cardiology to genetics. Actually it was a matter of phasing down cardiology and ramping up genetics after 1957."

– Victor McKusick.

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Relaxed Deep-Breathing

Pranayama – the breathing practices of yoga – is found to shift the overall basal authonomic balance to the parasympathetic direction. In actual practice, it involves slow diaphragmatic breathing. This process reduces the adverse psycho-physiological and psychological effects of chronic stress and reactivity in stressful situations. Relaxed deep breath practices have now become a valuable component of many integrated treatment programmes. The patients with heart disease, hypertension, and asthma have found these breathing practices beneficial in stress reduction.

Deep breathing is closely related to the movement of the diaphragm – the dome-shaped muscular structure that separates the chest from the abdomen. When we breathe deeply, our diaphragm moves downward as we inhale, and upward as we exhale. The more the diaphragm moves, the more our lungs can expand. It means that more oxygen can be taken in and more carbon dioxide released with each breath.

Breathing is the rhythm of life. Pranayamic breathing exercises are more than deep-breathing practices. Pranayama allows the body to regain its natural rhythm. It thus promotes holistic healing.

Regular practise of Pranayama throws out physical and mental toxins. We can use our breath to free the mind of blocks. This leads to greater clarity of thinking. Pranayama is considered to be the highest form of purification and self-discipline for our mind.

Says Patanjali (ca B.C. 300), the Indian sage and the foremost exponent of Pranayama, "When we practice Pranayama, the veil of lethargy and ignorance is slowly taken away from the mind."

Through Pranayama techniques, the blood stream, heart, lungs, brain, tissues, and other organs get enriched with vital energy. It brings about a change in the coordination of physical functions and mental attitudes.

The practice of Pranayama reinforces the findings of modern medical science which has come to accept the role of the mind in physical diseases. With the judicious practice of Pranayama we can attain a sound healthy body and a steady peaceful mind.

A Taoist physician from China, Shen Chai-tsu (17th century A.D.) has also pointed out the benefits of breathing practices. "Breathing exercises are a hundred times more effective than any drug," says he.

The Pranayama – the relaxed deep-breathing exercise – is a definite journey to good health.

(Courtesy: Journal of the Science of Healing Outcomes; Vol. 3, No. 10)

PICTORIAL CME

JIACM 2014; 15(3-4): 272-3

Retinal haemorrhages in *Plasmodium falciparum* malaria

AP Singh, MK Multani**, S Singh****

A 20-year-old female presented with complaints of fever with chills, easy fatiguability, jaundice since four days, and blurring of vision since one day. Fever was high-grade, without history of rashes. She had dyspnoea on exertion NYHA grade II. Jaundice was associated with yellowness of eyes and urine. On examination, she was febrile, had pallor (+++), icterus (+), and splenomegaly. Fundus examination showed multiple superficial haemorrhages, multiple dot blot haemorrhages, and a large pre-retinal haemorrhage (Fig. 1 and 2). On investigation, her Hb was 2.7 gm % and *Plasmodium falciparum* ring was seen on the peripheral smear; TLC – 4,600 cells/mm; DLC – $P_{34}L_{61}M_{3}$; ESR – 75 mm; serum bilirubin – total – 6.8, SGOT – 62 IU/l, SGPT – 54 IU/l; and USG abdomen showed mild hepatosplenomegaly.

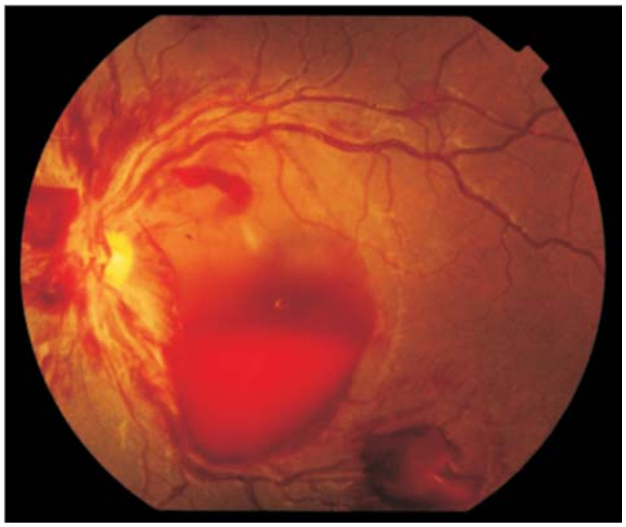

Fig. 1: *Fundus photograph of left eye showing a large pre-retinal haemorrhage of 3 disc diameters, multiple superficial haemorrhages present around the disc (nasally, and along the superior and inferior temporal arcade).*

Based on the above findings, it appears that blurring of vision in this patient was because of malarial retinopathy. The patient was given intravenous artesunate 2.4 mg/kg and was transfused two units of packed RBCs. Thereafter, the patient improved symptomatically and was discharged on haematinics.

Retinal haemorrhage is a frequently observed sign in *Plasmodium falciparum* infection. Malarial retinopathy has been frequently associated with severe malaria, particularly cerebral malaria[1,2]. But in patients with complicated non-cerebral malaria it is uncommon[3,4,5].

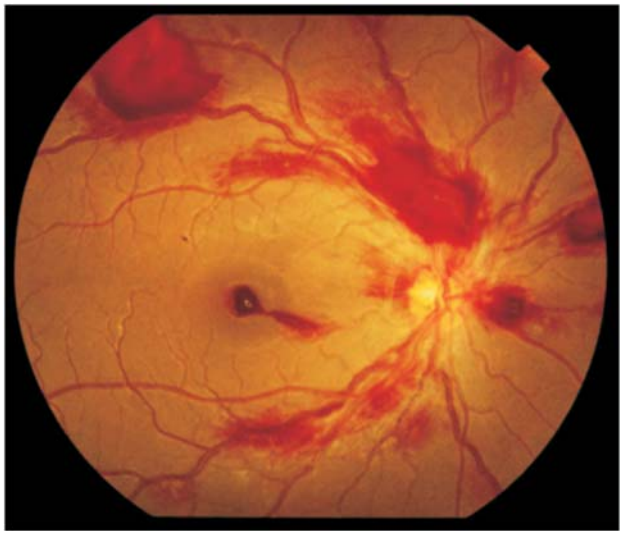

Fig. 2: *Fundus photograph of right eye macular haemorrhage, pre-retinal haemorrhage of 1.5 disc diameter and multiple superficial haemorrhages along supero-temporal arcade.*

Malarial retinopathy consists of four components: retinal whitening (macular or peripheral), vessel discoloration (white or orange), retinal haemorrhages (particularly with white centres), and papilloedema. These findings have been used for diagnostic purposes in high transmission areas in sub-Saharan Africa, where it is difficult to distinguish severe malaria from other causes of severe febrile illness[1,6]. The key processes of retinal haemorrhage in *Plasmodium falciparum* are likely to be sequestration of parasitised red blood cells (RBCs) and cytoadhesion with rosetting. Retinal haemorrhages in malaria patients are usually absorbed spontaneously, but a permanent decrease in visual acuity is possible in rare cases[7].

Apart from this, various studies have correlated retinal haemorrhages with prognosis of cerebral malaria. Increased association has been seen with anaemia in malaria, and retinal haemorrhages[1,3]. To conclude, malarial retinopathy should be kept in mind while managing cases of complicated noncerebral malaria.

Key words: Falciparum malaria, retinal haemorrhages, malarial retinopathy.

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