LETTER FROM THE EDITOR

Prof. Dr. M.C. Gupta
Founder-President, IACM

A Person to Remember

The *Journal*, *Indian Academy of Clinical Medicine* deeply regrets to report the passing away of our beloved Professor Dr. M.C. Gupta, MD, FRCP (Edinburgh) – Founder and Founder-President of the *Journal*'s parent body, the 'Indian Association of Clinical Medicine (IACM)' – on 27th March, 2013 at Agra, Uttar Pradesh.

A Physician-Cardiologist, Dr. M.C. Gupta was a unique, quiet, and unassuming personality who was keenly interested in the advancement of internal medicine both as a science and an art. A graduate and post-graduate of King George's Medical College, Lucknow, Dr. Gupta first taught medicine at the Medical College at Jhansi; thereafter, he joined the Sarojini Naidu Medical College, Agra, from where he retired as Director, Professor and Head of the Department of Medicine in December, 1992. In fact, after retirement, Dr. Gupta made himself busier and more useful – academically as well as clinically. Immensely passionate about the IACM and all its activities, he was ever-appreciative of the *JIACM*'s content. Sadly, the last time I met him was just briefly – at the Governing Body Meeting of the IACM held at Agra in early 2012 – where, like a father-figure he took me aside, and spoke some kind and encouraging words for the *Journal*.

Professor Gupta had long, eventful, and fruitful innings with innumerable achievements to his credit. He was President of the Association of Physicians of India (API), and Chairman of the Indian College of Physicians (ICP) in 1991. He served as President of the Hypertension Society of India (HSI), the Indian Society of Electrocardiology (ISE), and the U.P. Chapter of the Association of Physicians of India (API). As a dedicated and gifted medical teacher, Professor Gupta was unique – and his contribution to the teaching of clinical medicine was outstanding. He was conferred the prestigious 'Dr. B.C. Roy National Award' by the then President of India, Dr. Shankar Dayal Sharma. He was a recipient of the 'Eminent Teacher Award' by the Association of Physicians of India. He was honoured with the 'Lifetime Achievement Award' by the API-UP Chapter. He was also bestowed the 'Rashtriya Gaurav Award', 'Millennium Gold Medal of Achievers (2004)'. He received the 'Best Citizen of India Award' in 2005. On 21st February, 2005, he was conferred the 'International Gold Star Medal' and 'Certificate of Excellence' for his services to the minorities by the Hon'ble Union Minister of India Shri Priya Ranjan Das Munshi and H.E. Sir Michael Arthur, British High Commissioner to India. Dr. M.C. Gupta's name also figures in the *Who's Who* book. Apart from this, Dr. Gupta had many national and international publications to his credit. He had also written chapters in various textbooks of Medicine. The IACM and the *JIACM* shall always miss his sagacious presence and guidance.

Dr. Gupta leaves behind his Advocate son Anurag Gupta and daughter-in-law Dr. (Mrs.) Nidhi Gupta, and grandchildren. May his noble soul rest in eternal peace!

As the *JIACM* enters the 15th year of incessant publication, I wish to thank wholeheartedly our readers, contributors, and patrons for their indulgence – valuable suggestions, criticism, and unwavering support. Finally, time to bid *adieu* to our outgoing Associate Editor Dr. Alladi Mohan, Professor & Head, Department of Medicine, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, who served the *Journal* for three years (2011-13). I shall always value his skills as a keen academician who – I am pleased to inform – shall continue to serve the *JIACM* as a peer reviewer. In the same breath, I am happy to welcome Dr. M.P.S. Chawla, Senior Consultant, Department of Medicine, PGIMER & Dr. Ram Manohar Lohia Hospital, New Delhi, as Associate Editor (2014-16) alongwith Dr. Sumit Singla, Assistant Professor, Department of Medicine, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, as Joint Secretary (2014-16) of the *Journal*. I am sure that our new team shall enjoy bringing out the *Journal* with the same regularity and – as always – in the best interests of the teaching and practice of internal/clinical medicine and its allied specialities in the Indian subcontinent. Team *JIACM* wishes you a clinically fruitful and academically enriching new year sprinkled with abundant peace and happiness!

– Dr. D.G. JAIN

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CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 15, Number 1, January-March, 2014

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VIEWPOINT

JIACM 2014; 15(1): 7-8

Barefoot walking and running

*BM Hegde**

"No matter how complex or affluent, human societies are nothing but subsystems of the biosphere, the Earth's thin veneer of life, which is ultimately run by bacteria, fungi, and green plants."

– Vaclav Smil.

Barefoot walking in 2013? The writer must have gone mad! That would be your first reaction as you are sold to the idea of running without shoes is impossible up until this minute, right? Read on to know the truth as is known now. We were walking barefoot for millio/ns of years until very recently when we invented foot wear. Even then our ancestors were using biological material for the foot wear like animal hide. It is only very recently that we have invented artificial material like rubber and many other plastic like stuff to make expensive fancy foot wear and running shoes. In the so called developed countries babies almost from the time they start walking use footwear avoiding any contact with mother earth. In addition we were also sleeping on uncovered ground for some time every day where a large area of the skin used to come in contact with the earth.

Mother earth contains innumerable bio-positive free electrons which are human immune-boosters. The National Library of Medicine's online resource PubMed lists 7,021 studies and 522 review articles from a search of "antioxidant+electron+free radical". The influx of free electrons absorbed into the body through direct contact with the Earth is likely to neutralise reactive oxygen species and thereby reduce acute and chronic inflammation. When we insulate ourselves from those healthy electrons we are pushing ourselves towards illnesses. Walking in itself has now been shown to be a very healthy activity. The famous Ohasaki Cohort Study in Japan showed that walking regularly reduces the risk of premature mortality in addition to reducing one's medical bills in the long run.

Now that the leading science journal *Nature* (2010; 463: 531) has published a good study that has shown barefoot walking in good light, my plea might be acceptable to the westernised Indians (RNIs – Resident Non-Indians) who think they have a scientific temper. Our mistaken notion that lack of evidence is equal to evidence of absence has been proved to be wrong in all sciences. I better quote that study summary in detail without editing it here below:-

"Humans have engaged in endurance running for millions of years, but the modern running shoe was not invented until the 1970s. For most of human evolutionary history, runners were either barefoot or wore minimal footwear such as sandals or moccasins with smaller heels and little cushioning relative to modern running shoes. We wondered how runners coped with the impact caused by the foot colliding with the ground before the invention of the modern shoe. Here we show that habitually barefoot endurance runners often land on the fore-foot (fore-foot strike) before bringing down the heel, but they sometimes land with a flat foot (mid-foot strike) or, less often, on the heel (rear-foot strike). In contrast, habitually shod runners mostly rear-foot strike, facilitated by the elevated and cushioned heel of the modern running shoe. Kinematic and kinetic analyses show that even on hard surfaces, barefoot runners who fore-foot strike generate smaller collision forces than shod rear-foot strikers. This difference results primarily from a more plantarflexed foot at landing and more ankle compliance during impact, decreasing the effective mass of the body that collides with the ground. Fore-foot- and mid-foot-strike gaits were probably more common when humans ran barefoot or in minimal shoes, and may protect the feet and lower limbs from some of the impact-related injuries now experienced by a high percentage of runners."

Mounting evidence suggests that the Earth's negative potential can create a stable internal bioelectrical environment for the normal functioning of all body systems. Moreover, oscillations of the intensity of the Earth's potential may be important for setting the biological clocks regulating diurnal body rhythms, such as cortisol secretion. Human body is immaterial; it is energy vibrations, seen as a solid structure. Hence energy vibrations of the healthy variety from outside might set right many an aberration in the body physiology. Professor Robert Becker, a doyen of an orthopaedic surgeon from New York University has shown that each body cell is but

Padma Bhushan; Former Vice-Chancellor, Manipal University; Editor-in-Chief, The Journal of the Science of Healing Outcomes (JSHO); Chairman, State Health Society's Expert Committee, Govt. of Bihar, Patna; Visiting Professor of Cardiology, The Middlesex Hospital Medical School, University of London, U.K.; Affiliate Professor of Human Health, Northern Colorado University, U.S.A.

a semi-conductor. We also generate plenty of static body electricity which needs to be earthed. Direct body contact with the earth is a good way of accomplishing that task as well.

Shoes alter our gait. That would result in minor damage to the various lower limb joints as also the lower spine. So many of our aches and pains are due to this minor change that we have brought on us of wearing the fashionable shoes. We do not feel that till the pains become severe and the injury uncorrectable except with quick fixes like drugs or surgery. Correcting that early, if not avoiding it in the first place, should be our aim. So hit the ground on bare feet. There are certain precautions one has to take before barefoot running though. If one is used to shoes right from childhood, it will take some time to get used to walking barefoot even. Our soles of the feet are built for barefoot walking but we alter that by using shoes right from childhood. So do it gradually. We should try to walk on sand, wet sand would be still better, on the beach for a few days before walking barefoot on rough ground or roads. Running barefoot requires longer period of such training, but running is bad for health anyway. We are concerned about barefoot walking here. Another good place to walk barefoot would be a well-kept lawn.

If one cannot avoid footwear one has to choose such shoes that do not alter the physiology of the sole. In fact, barefoot walking will correct many of the changes that have been caused by shoes. Heal landing shoes that we have in the market are the worst enemies of the human sole. "Shoes affect the gait of children. With shoes, children walk faster by taking longer steps with greater ankle and knee motion and increased tibialis anterior activity. Shoes reduce foot motion and increase the support phases of the gait cycle. During running, shoes reduce swing phase leg speed, attenuate some shock and encourage a rearfoot strike pattern. The long-term effect of these changes on growth and development are currently unknown," feel the Harvard researchers in their study quoted above.

A previous study demonstrated that connecting the human body to the earth during sleep (earthing) normalises the daily cortisol rhythm and improves sleep. A variety of other benefits were reported, including reductions in pain and inflammation. I am sure that even the sceptics among us will now start thinking about bare feet walking!

"What a joy it is to feel the soft, springy earth under my feet once more, to follow grassy roads that lead to ferny brooks where I can bathe my fingers in a cataract of rippling notes, or to clamber over a stone wall into green fields that tumble and roll and climb in riotous gladness!"

– Helen Keller.

A Teacher's Task

"If we work upon marble, it will perish,
If we work upon brass, time will efface it,
If we rear temples, they will crumble to dust,
But if we work upon men's immortal minds,
If we imbue them with high principles,
With the just fear of God and love of fellow men,
We engrave upon those tablets something which time can never efface,
And which will brighten to all eternity."

– Daniel Webster.

ORIGINAL ARTICLE

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A study of drug resistance in malaria

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Abstract

Introduction: Malaria is a major public health problem in South-East Asian and African countries – especially India. It is a protozoan disease transmitted by a vector, i.e., female anopheles mosquito in various states of India. The prevalent species of malarial parasite are Plasmodium vivax and P. falciparum. The present study has been undertaken to evaluate the efficacy of various drugs – chloroquine, quinine, doxycycline, and artimisinin (artesunate) combined therapy (ACT) – in uncomplicated vivax and falciparum malarial infection.

Material and methods: A total of 120 hospitalised patients in Dr D.Y. Patil Medical College and Hospital, Navi Mumbai; smear-positive cases – 60 each of P. vivax (group A) and P. falciparum or mixed malaria (Group B) – were included. Complicated cases were excluded, i.e., those with target organ damage; complete blood count and parasitic index were done on day I, 4, and 7, in addition to liver, kidney, pulmonary, and cardiac functions

Results: The observations revealed that patients of group A responded early to treatment as compared to group B (regarding fever and parasitic index disappearance). The group A did respond partially to chloroquine and statistically significantly to other drugs combinations; whereas group B did not respond to satisfactorily to chloroquine, but had reasonable statistically significant effect with other drugs.

Conclusions: The best medications were artesunate and quinine in combination with doxycycline in both the groups (A and B), whereas chloroquine with doxycycline did not fare as well in either group. Thus the artesunate combination therapy (ACT) is emerging as the first-line treatment in drug resistant malaria under the present circumstances.

Key words: World Health Organization, artimisinin (artesunate) combined therapy (ACT).

Introduction

Malaria ranks among the top 10 killer diseases on this earth and has been a global[1] health hazard for centuries. Nearly 100 countries in the world account for this dreaded disease especially in sub-Saharan Africa where one-half (i.e., 3.3 billion) of the malarial patients are living in fear of transmission. South-East Asian countries (e.g., Thailand, Indonesia)[2] and Western Pacific regions (~ 1.2 billion) are the other half to harbour this ailment and thus account for 1.1 to 2.7 million deaths annually in the world according to the WHO. The maximum casualty is in children. The Indian scenario accounts for 77% of total malaria in South-East Asia[3], being a part of tropical countries with mortality of 20,000 deaths/year though 13-times less (under-reported). South-East Asian Regional Office[4-6] (WHO SEARO) estimates 15 million cases. 1.5 million cases are reported annually by the National Vector Borne Diseases Control Programme (NVBDCP) and 40% - 50% are due to *P. falciparum*. North-Eastern states are the areas reporting 50% cases of falciparum malaria. The sub-Saharan African[5] continent also accounts for 50% falciparum malaria. The construction work where stagnant water accumulates for breeding mosquitoes is the main cause. Vivax malaria thus accounts for the remaining 50% of this disease in the Asian continent.

The emergence of uncontrolled malarial disease is attributed to multiple factors (misuse and ineffective, cheap, duplicate antimalarial drugs; particularly use of artesunate alone).

In the 1970s, the incidence of falciparum malaria increased by 50%. As per NVBDCP data[7] in 2007, when there were reportedly 14,76,562 malaria cases, half of these were due to falciparum species.

In India, Orissa[8] tops the list accounting for 25% of total cases in India, with the majority being falciparum malaria. 18.2% of deaths in the country occurred here in 2007 (Fig. 1)[9,10].

Antimalarial drug resistance has emerged as one of the greatest challenges for malaria control due to collapse of vector control and waning efficacy of existing drugs. Chloroquine and quinine were effective drugs till 2001, but lately, the effect of chloroquine is fading. The other drugs like sulfadoxine pyrimethamine did well for the next five years but have started showing resistance lately due to genetics and to mutations in some enzymes in its

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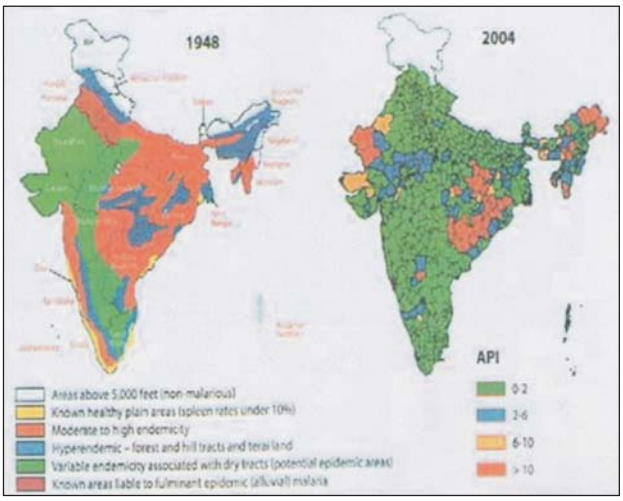

Fig.1: *Malaria endemicity in India.*

metabolism. Mefloquine came next in use in resisting malaria, but lasted for only a short time. Finally the artemisinin derivatives (artemether, arteether, and artesunate) appeared on the scene and are being used increasingly in Asia, Africa, and Europe. These drugs have shown potency and efficacy in reducing parasitaemia in multidrug resistant malaria[11-14] with lack of side effects, thus a better option for chloroquine resistant cases[15-20]. Three grades of resistance exist according to the WHO: Low grade R1 – Recrudescence of infection between 7 and 28 days of completing the treatment with initial resolution of symptoms and parasite clearance; High grade R2 – Reduction of parasitaemia by > 75% at 48 hours but failure to clear the parasites within 7 days; High grade R3 – Parasitaemia does not fall by > 75% within 48 hours (Fig. 2).

Fig. 2: *Distribution of Plasmodium falciparum resistance to antimalarial drugs in South-East Asia.*

Considering the above criterion of suspicion of drug resistance prevailing in our country, this study was assigned with use of newer artimisinin drugs, i.e., artesunate, chloroquinine, and quinine, with doxycycline (tetracycline) with their comparison in combined therapy, after review in various randomised trials done earlier in various parts of the country showing good results with ACT.

Aims of the study

The aims and objectives of the study were to find out the uncomplicated vivax and falciparum +/– vivax mixed malaria patients in our medical ward hospital admission and to find out the resistance to various antimalarial drugs in these patients.

Material and methods

A total of 120 adult patients (60 cases of *P. vivax* and 60 cases of *P. falciparum* or mixed malaria) were undertaken for the study. A pre-informed consent was obtained in every case. The inclusion criterion was smear-positive cases only. The exclusion criteria were smear-negative cases, target organ damage in complicated malaria, paediatric age group < 12 years, pregnant women, evidence of infection in either systems, e.g., respiratory, urinary, HIV, etc., patients with smear-positive reports who had received antimalarial drugs, and a past history of allergy to doxycycline. They were subjected to complete blood count, peripheral blood film (PBF) for malarial parasites, parasitic index (on day 1, 4 for all patients, and on day 7 for refractory ones), renal, liver function, x-ray chest, urine examination.

The patients were divided in two groups (Table I):

Table I:

Group A *P. vivax* infestation			Group B *P. falciparum* and mixed infestation		
Subgroup (a)	**Subgroup (b)**	**Subgroup (c)**	**Subgroup (a)**	**Subgroup (b)**	**Subgroup (c)**
Chloroquine + Doxycycline	Quinine + Doxycycline	Artemisinin (Artesunate) + Doxycycline	Chloroquine + Doxycycline	Quinine + Doxycycline	Artemisinin (Artesunate) + Doxycycline

Results

A total of 120 cases of positive malaria (*P. vivax*, *P. falciparum,* and mixed varieties) were studied. The series included 97 male and 23 female patients.

Clinical features

The 120 patients were divided into 2 groups depending on the malarial parasite manifestations and drug combinations. Fever, chills and rigors, headache, vomiting,

abdominal pain, abnormal behaviour, oliguria, breathlessness were more pronounced in group B patients. Similarly, physical signs like hypotension, hyperpyrexia, icterus, pallor, petechiae, abdominal tenderness, and hepatosplenomegaly were also predominant findings in group B as compared to group A patients.

Specific investigations

Peripheral smear (PS) both thick and thin for malarial parasite (MP) with parasite index (number of MP/1,000 RBCs) were evaluated as shown in Table II.

Table II:

Stages				Parasitic index (No. of MP/1000 RBC's)	
	Ring	Gametocyte	Ring and Gametocyte	< 1%	> 1%
Group A					
No. of patients	24	20	16	30	30
Group B					
No. of patients	8	29	23	28	32

The 120 subjects in group A and B were also allotted at random into three subgroups to the combination of antimalarial drugs as in group A. It is as follows:

Subgroups: **a** – Choroquine and doxycycline; **b** – Quinine and doxycycline; **c** – Artesunate and doxycycline. After the medication, the disappearance of fever was observed from day 1 to day 28 along with parasitic index and absence of malarial parasites in peripheral smears. If the response to the group of drugs was not satisfactory, the patient was switched on to the next alternative group respectively as shown in Table III.

Routine investigations

All the 120 patients underwent following investigations:- Table IV reveals the range of haemoglobin (Hb), white blood cells (WBCs), and platelets.

There was an early disappearance of fever and parasitic index in patients of *P. vivax* (Group A) as compared to those of *P. vivax* and *P. falciparum* mixed infections (Group B).

Table IV:

Investigations	Group A (60 patients)	Group B (60 patients)
Haemoglobin (Hb) < 10.0 gm%	26	34
Haemoglobin (Hb) > 10.0 gm%	34	26
White blood cells (WBCs)		
< 4,000/cmm (UL)	10	9
> 4,000-11,000/cmm (UL)	50	51
Platelet counts		
< 30,000 to 50,000 (UL)	20	11
> 51,000 to 1,50,000 (UL)	40	49

Discussion

One hundred and twenty cases of smear-positive (60 cases of uncomplicated *P. vivax* Group A, and 60 cases of uncomplicated *P. falciparum* or mixed malaria Group B) were taken into study. Patients of group A were subdivided in subgroups a, b and c; and of group B were subdivided in subgroups a, b and c. Subgroup a, b, c of both groups were given chloroquine + doxy; Subgroup b – quinine + doxy; Subgroup c – artesunate + doxy, respectively.

Table III:

Group A (60 patients)					
No. of patients (subgroup a) 20	Disappearance of fever		Parasitic index clearance		Switch on to alternative combination
	< / = Day 4	> Day 4	< / = Day 4	> Day 4	
Chloroquine plus doxycycline – 20 patients	13/20 (65%)	7/20 (35%)	5/20 (25%)	15/20 (75%)	7/20 to artesunate plus doxy
No. of patients (20) Subgroup b quinine and doxycycline combination	8/20	12/20	7/20	13/20	Nil
No. of patients (20) Subgroup c (artesunate and doxycycline combination)	18/20	2/20	8/20	2/20	2/20 to quinine + doxy
Group B (60 patients)					
No. of patients (20) Subgroup a chloroquine + doxycycline combination	4	16	4	16	8/8 to artesunate + doxy; quinine + doxy
No. of patients (20) Subgroup b quinine and doxycycline combination	18	2	18	2	2/20 to artesunate + doxy
No. of patients (20) Subgroup c (artesunate and doxycycline combination)	19	1	19	1	1/20 to quinine + doxy

Group A

Subgroup a (chloroquine & doxycycline – 20 patients). It was detected that this group had 65% success rate. The remaining 35% were shifted to other drugs, i.e., artesunate/ quinine with doxycycline. In subgroup b no patients were shifted and this group had 100 per cent success rate. In Subgroup c, 18 out of 20 recovered fully and within 3 days (90 per cent success rate). Two patients had to be switched on to quinine and doxycycline combination for recovery.

Group B

Subgroup a (chloroquine + doxycycline – 20 patients): There was 80 per cent failure rate. 4 patients responded to this combination and 16 had to be switched over to other combinations, i.e., artesunate and quinine with doxycycline. This study is similar to the one conducted in Arunachal Pradesh with 83% failure rate.

Subgroup b: 18 out of 20 patients recovered fully with disappearance of fever within next 3 days and only 2 patients had to be switched on to artesunate and doxycycline combination for complete recovery. This subgroup had 90% success rate.

Subgroup c: 19 out of 20 patients recovered fully with disappearance of fever within 3 days. Only 1 patient had to be switched over to quinine and doxycycline and he responded within 7 days. This subgroup had 95% success rate.

This study reveals that the best combination of drugs in *P. vivax* group infections and *P. falciparum* mixed malarial infection are artesunate followed by quinine along with doxycycline combination as compared to chloroquine with doxycycline. However, in *P. vivax* (subgroup a of group A), the patients did show a response (65%) to chloroquine and doxycycline drugs combination. They all were given primaquine 15 mg daily x 14 days for prevention of relapse. Artesunate or quinine with doxycycline combination proved to be the ideal choice in mixed infection of *P. falciparum* and *P. vivax* cases and in drug resistance cases with chloroquine.

Conclusions

1. In group A (*P. vivax*; subgroup a) with chloroquine and doxycycline combination therapy, 65% of patients responded well and 35% had to be switched to other groups.
2. In group A (subgroup b and c), quinine and doxycycline combination, and artesunate and doxycycline combination had 100% and 90% success rate respectively. Artesunate should have limited use in uncomplicated *P. vivax* so that resistance does not occur.
3. In group B (subgroup a) on chloroquine and doxycycline combination, patients with falciparum malaria had 80% failure rate and had to be switched to other drugs like artesunate or quinine to which they responded. Falciparum malaria responds poorly to chloroquine due to resistance to this drug.
4. In group B (subgroup b and c) on quinine and artesunate with doxycycline combinations had 90% and 95% success rate respectively. Artesunate followed by quinine are the most effective drugs in uncomplicated falciparum and mixed (vivax and falciparum) malaria.
5. Artesunate and quinine have earlier onset of action and do very well with other combination of drugs, i.e., doxycycline having longer duration of action in killing and eradicating the malarial parasites. Total duration of treatment being 3 - 7 days.

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ORIGINAL ARTICLE

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Insulin resistance in patients of end-stage renal disease (ESRD) on haemodialysis: Effect of short-term erythropoietin therapy

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Abstract

Aim: Insulin resistance is a potentially modifiable cardiovascular risk factor and it can be considered as a therapeutic target in patients of chronic kidney disease (CKD), especially those undergoing haemodialysis. The present study was conducted to assess insulin resistance (IR) in patients of end-stage renal disease (ESRD) on haemodialysis and to evaluate effect of short-term treatment with recombinant human erythropoietin therapy.

Material and methods: It was a prospective case control study which was carried out at a tertiary care hospital in North India, from May 2010 to September 2011. Adult patients of CKD (both diabetic and non-diabetic) were enrolled in the study and were randomly assigned into two groups. Study group consisted of 20 patients (10 diabetics and 10 non-diabetics) with ESRD who were on regular twice weekly haemodialysis and were given subcutaneous erythropoietin (80 to 120 U/kg/wk) after each session of dialysis. Control group included 10 patients with ESRD on regular haemodialysis but did not receive erythropoietin.

Results: Mean baseline fasting insulin levels and insulin resistance as reflected by homeostasis model assesment of insulin resistance (HOMA-IR) were similar in the two groups. HOMA-IR was 5.48 ± 10.43 in the study group and 3.11 ± 2.16 in the control group.The levels decreased significantly to 0.51 ± 0.36 (P < 0.001) in the study group and increased insignificantly to 3.84 ± 4.08 (P >0.05) in the control group after 6 months.

Conclusion: Fasting insulin level and insulin resistance is increased in CKD patients. Recombinant human erythropoietin therapy has a favourable effect on insulin sensitivity in addition to its role in the treatment of anaemia in cases of CKD on dialysis.

Key words: Insulin resistance, chronic kidney disease, fasting insulin levels, homoeostasis model assessment of insulin resistance (HOMA-IR).

Introduction

Insulin resistance is a characteristic feature of uraemia. As long as hyperinsulinaemia is adequate to overcome insulin resistance, glucose tolerance remains normal[1]. In addition to abnormalities in carbohydrate metabolism, the IR syndrome is accompanied by an elevation in non-esterified fatty acid, abnormalities in visceral fat metabolism, elevated uric acid, endothelial dysfunction, and abnormalities in glucocorticoids, all leading to the development of atherosclerosis[2]. The influence of insulin resistance on cardiovascular risk is independent of age, body mass index (BMI), concomitant hypertension, dyslipidaemia, or C-reactive protein (CRP) levels. Numerous factors implicated in the aetiology of insulin resistance include uraemic toxins, chronic metabolic acidosis, intracellular ion homoeostasis disequilibrium, and qualitative as well as quantitative disturbances of insulin receptors on adipocytes, skeletal muscles and hepatocytes, cytokines produced by adipocytes (adipokines), chronic inflammation as well as low physical activity[3]. Definitive evidence for the efficacy of some of these interventions on clinical outcomes such as cardiovascular end-points or mortality is still lacking. However, management of insulin resistance in patients on haemodialysis is multifaceted. Treatment of insulin resistance in CKD patients can be achieved by haemodialysis, angiotensin-converting enzyme (ACE) inhibitors, thiazolidinedione, treatment of calcium and phosphate disturbances and recombinant human erythropoietin[4]. Few studies have shown favourable effect of erythropoietin in decreasing insulin resistance[1,5,6,7,8]. However, no Indian study is available on this issue.The present study was therefore conducted to assess insulin resistance in patients of CKD irrespective of diabetic status, to evaluate the effect of short-term human erythropoietin therapy on insulin resistance.

Materials and methods

This was a prospective case control study carried over a period from May 2010 to September 2011. It included 30 patients of end-stage renal disease (both diabetic and non-diabetic) on regular twice weekly haemodialysis. Patients taking drugs like angiotensin converting enzyme inhibitors, thiazolidinedione, steriods, or patients with diseases like congestive heart failure, end-stage pulmonary disease, cancer, which are known to affect fasting insulin levels, were excluded from the study. Pre-informed consent was obtained in each case and patients were divided into two

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group. Group I (study group) consisted of 20 patients (10 diabetics and 10 non-diabetics) with ESRD on regular Haemodialysis which were given subcutaneous erythropoietin in a dose of 80 to 120 U/kg/week. Group II (control group) included 10 patients with ESRD on regular haemodialysis but were not receiving erythropoietin and had either Hb > 8 gm% or refused to take erythropoietin due to financial constraints or those who did not tolerate erythropoietin or had accelerated hypertension secondary to erythropoietin – where erythropoietin had to be discontinued. All the patients were examined in detail and all basic laboratory investigations were done with a special emphasis on renal and various metabolic parameters. Serum fasting insulin was measured at baseline and at 6 months along with other renal parameters. Patients were evaluated every month for adherence to treatment, adverse effects, and clinical outcome. Serum fasting insulin levels were measured by ADVIA CENTAUR CP model using Siemens kit[9]. Insulin resistance was calculated by HOMA-IR because of its simplicity. Data was analysed by using student 't' test (paired and unpaired) and Pearson's correlation coefficient (r).

Results

Baseline biochemical parameters of the two groups were alike/comparable and are shown in Table I. The baseline mean fasting insulin levels in study participants showed a mean value of 11.40 ± 16.58 mU/L and at six months it decreased to 2.30 ± 1.40 mU/L and the fall was significant ($p < 0.05$) showing that twice weekly erythropoietin had a significant effect on lowering fasting insulin levels in CKD patients. On the other hand, the control participants showed a significant increase in serum fasting insulin levels (Table II) from baseline value of 9.72 ± 8.36 mU/L to mean value at six months of 12.79 ± 11.31 mU/L. ($p < 0.05$). Homoeostasis model assessment of insulin resistance (HOMA-IR) levels in study group treated with erythropoietin significantly decreased from baseline value of 5.48 ± 10.43 to 0.51 ± 0.36 at end of study ($p < 0.05$). But, there was no significant change in levels of HOMA-IR in control group participants from baseline levels of 3.11 ± 2.16 to 3.84 ± 4.08 at the end of the study ($p > 0.05$). This study found that erythropoietin therapy significantly improved insulin resistance. Erythropoietin had a favourable effect on serum lipid profile (Table III) in the study group. Mean triglyceride decreased significantly at end of six months vs baseline value ($p < 0.05$) in study group. Similarly, mean VLDL decreased significantly at six months as compared to baseline value ($p < 0.05$). Mean HDL increased significantly at six months as compared to baseline value ($p < 0.05$). The control group had no significant decrease in mean triglyceride, cholesterol, LDL during the course of study ($p > 0.05$). There was a significant increase in mean HDL values at sixth months as compared to baseline value ($p < 0.05$). Mean fasting blood sugar and post-prandial blood sugar values decreased significantly in the study group after sixth months ($p < 0.05$). There was no significant improvement in fasting blood sugar and postprandial blood sugar levels at six months vs baseline value in control group ($p>0.05$).

Table I: Biochemical parameters at baseline in two groups.

Investigation	Study group (Mean ± S.D.)	Control group (Mean ± S.D.)	p Value (Unpaired)
Blood urea (mg%)	173.4 ± 67.48	215 ± 53.80	**> 0.05**
Serum creatinine (mg%)	7.83± 3.46	9.65 ± 3.55	**> 0.05**
Serum sodium (mE/L)	139.65 ± 12.31	147.3 ± 6.93*	**< 0.05**
Serum potassium (mE/L)	4.55 ± 0.75	4.74 ± 0.74	**> 0.05**
Serum uric acid (mg%)	7.30 ± 3.23	7.89 ± 3.20	**> 0.05**
Serum calcium (mg%)	8.16 ± 1.36	8.36 ± 1.20	**> 0.05**
Serum phosphate (mg%)	6.29 ± 2.44	7.42 ± 1.86	**> 0.05**
SGOT (IU)	34.45± 22.48	68.8± 141.35	**> 0.05**
SGPT (IU)	33.55± 21.04	85.8 ± 167.60	**> 0.05**
Alkaline phosphatase (IU)	184.2± 112.81	175.1 ± 94.86	**> 0.05**
Serum protein (g/dL)	5.86±1.03	6.1 ± 0.68	**> 0.05**
Albumin:globulin ratio	1.05 ± .20	1.08 ± 0.09	**> 0.05**

**P < 0.05 is significant*

Tabele II: Comparison of fasting insulin levels and HOMA-IR of both groups before and after study.

	Study group (Mean ± S.D.)	Control group (Mean ± S.D.)	Unpaired 'p' value
Fasting insulin levels (mU/L)			
0 month	11.40±16.58	9.73±8.36	**> 0.05**
6 month	2.30±1.40	12.79±11.31	**< 0.05**
Homoeostasis model assessment of insulin resistance (HOMA-IR)			
0 month	5.48±10.43	3.11±2.16	**> 0.05**
6 month	0.51±0.36	3.84±4.08	**< 0.05**

**P < 0.05 is significant*

Table III : Comparison of the metabolic profile at baseline.

Investigation	Study group (Mean ± S.D.)	Control group (Mean ± S.D.)	p Value (Unpaired)
Blood sugar fasting (mg%)	154.9 ± 62.97	153 ± 84.09	**> 0.05**
Blood sugar post prandial (mg%)	213.1 ± 91.62	234.6 ± 106.33	**> 0.05**
Serum triglycerides (mg%)	145.45 ± 53.69	125.9 ± 35.02	**> 0.05**
Serum cholesterol (mg%)	145.8 ± 50.39	149 ± 47.32	**> 0.05**
Serum HDL (mg%)	33.40 ± 12.44	35.3 ± 12.82	**> 0.05**
Serum LDL (mg%)	89.25 ± 45.19	88.6 ± 38.40	**> 0.05**
Serum VLDL (mg%)	26.8 ± 9.42	28.6 ± 9.24	**> 0.05**
Serum ferritin (ng/l)	587.1 ± 582.49	828.41 ± 706.27	**> 0.05**
HBA_1C (%)	6.43 ± 1.39	6.27 ± 1.48	**> 0.05**

**P < 0.05 is significant*

Discussion

Insulin resistance and the metabolic syndrome are common in patients with diabetes mellitus and CKD and they predict subsequent cardiovascular events and mortality. Insulin resistance results from a combination of genetic and environmental factors and contributes to type 2 diabetes mellitus, dyslipidaemia, hypertension, central obesity, and cardiovascular disease[1]. Although traditional risk factors such as hypertension are more prevalent in this population, there has been increasing emphasis on the role of nontraditional risk factors such as anaemia, hyperparathyroidism, dyslipidaemia, divalent ion abnormalities, increased oxidant stress, inflammation, hyperhomocysteinaemia, neurohormonal overactivity, malnutrition, and insulin resistance[10]. Insulin resistance, as a potentially modifiable cardiovascular risk factor, is currently considered as a therapeutic target in patients of CKD undergoing haemodialysis. It is because of the nearly universal presence of insulin resistance and concomitant hyperinsulinaemia in patients with diabetic and non-diabetic chronic kidney disease in the early stage of renal disease[11]. The epidemiologic correlation between insulin resistance and cardiovascular risk in the chronic kidney disease population has been documented. It has been found that erythropoietin also decreases insulin resistance in few studies conducted for short-term[1,5-8].

In this study, insulin resistance was calculated by HOMA-IR (homoeostasis model assessment), a computer generated model; because of its simplicity it requires only measurement of the fasting plasma insulin and plasma glucose. Other investigators have also calculated insulin resistance by HOMA-IR[1,5]. This study showed a significant improvement in fasting insulin levels as well as insulin resistance in the study group. And in the control group, serum fasting insulin level increased significantly whereas insulin resistance increased insignificantly. This study would suggest that haemodialysis patients, receiving erythropoietin therapy, are insulin sensitive as compared to those not receiving erythropoietin therapy. A couple of other studies have also reported similar observations[1,5-8]. Improved insulin resistance by erythropoietin therapy has been postulated to be due to decreasing plasma cell differentiation antigen 1 (PC-1) activity which has been found to be elevated in the insulin resistant state. PC-1 inhibits insulin signalling either at the level of receptor or downstream at the post-receptor site[12]. Improvements in oxygen supplementation and overcoming tissue hypoxia may explain improvement in insulin action[13]. Erythropoietin corrects anaemia and improves appetite and nutritional status of patients with ESRD, thereby improving insulin resistance[14]. Improvement of insulin resistance with erythropoeitin has also been explained through repair of chronic inflammation, as reduced level of inflammatory cytokines, particularly TNF-α, and iron overload or ferritin level have been found in patients with ESRD on haemodialysis.[15]

In this study there was a significant reduction in mean fasting and post-prandial blood sugar in the study group, indirectly suggesting reduction in insulin resistance. There was a significant fall in lipids in the study group and rise in HDL levels. While in control group, lipids increased. HDL levels decreased significantly. This observation may be related to an improved response to insulin resistance in the study group, because it is known that patients with increased insulin resistance have diminished lipoprotein activity, while triglyceride production remains the same. An excess PTH and hypoalbuminaemia has also been implicated in the pathogenesis of insulin abnormalities in uraemia[16]. However, in this study serum calcium, phosphorous, and albumin were not significantly different in the two groups. Apart from treatment with erythropoietin, insulin resistance, hyperinsulinaemia, and glucose intolerance in uraemic patients has been shown to improve with the use of angiotensin converting enzyme inhibitor[17] (ACE inhibitors), thiazolidenedione. However, their role can be easily excluded as part of improvement in insulin resistance as in this study all patients treated with ACE inhibitors or thiazolidinedione were excluded.

The observations made in this study show that serum fasting level and insulin resistance measured by HOMA-IR decreased significantly in the study participants on twice weekly erythropoietin therapy as compared with control group. Also, erythropoietin therapy had a favourable effect on triglyceride and HDL levels in haemodialysed patients. Therefore, a long-term further study should be performed to confirm the relationship between erythropoietin therapy and the possible causes of insulin resistance in haemodialysis patients. However, regular erythropoietin therapy is advised in all haemodialysis patients because of its favourable effect on insulin sensitivity and lipid profile, in addition to its role in the treatment of anaemia in these populations.

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"There is no greater wealth than wisdom;
no greater poverty than ignorance;
no greater heritage than culture."

– Nahjul Balagha.

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ORIGINAL ARTICLE

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Clinico-epidemiological profile of HIV positive patients attending ART centre at a tertiary care centre of north India

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Abstract

This composite study enrolled a total of 584 HIV positive patients that included 42 (7.14%) in the paediatric age group (≤ 13 years). 34.6% patients were females. 65.5% of the patients more than 13 years of age were widowed, and 17.5% divorced/separated. The average age at presentation was 35.32 years among adolescents and adults, and 7.00 years among the paediatric age group. 44.6% of the patients older than 13 years were illiterate; female illiteracy being 64.25%. For 60.8% patients, heterosexual route was the probable route of transmission. For other routes of transmission, the figures were: IDU (4.3%), blood transfusion (11.5%), perinatal transmission (7.4%) and probable unsafe injections (10.3%). 39% of patients presented in WHO clinical stage III, and 9.9% in stage IV. Average CD4 count among males at presentation was 208.96/μL, while it was 247.14/μL among females. 48.7% of patients older than 13 years of age presented with CD4 count ≤ 200/μL. Only 3.7% had CD4 counts more than 500/μL. The most common opportunistic infection was tuberculosis (18.45%) followed by chronic diarrhoea (14.94%) and recurrent respiratory infections (12.73%). Eighty-seven patients aged 13 years and above expired after a mean follow-up of 3.6 months. This subgroup of patients had lower average CD4 count (132.73 vs. 139.97/μL) and lesser average body weight (44 vs. 49.3 kg) at presentation, and higher incidence of opportunistic infections. Comparison of weight, haemoglobin, and CD4 count between the baseline and 6 month values showed that there were significant improvements in weight, haemoglobin, and CD4 count, most markedly in the first-time recipients of ART, less markedly in the ART-experienced patients, and least markedly in the patients who were managed only for opportunistic infections or complications without ART.

Key words: HIV (human immunodeficiency virus), CD4 count, opportunistic infection, ART (antiretroviral therapy).

Introduction

The global HIV/AIDS pandemic now ranks alongside the influenza pandemic of the early 1900s and the Bubonic plague of the 14th century in terms of fatalities. Absence of a curative therapy or an effective preventive vaccine till now compounds the complexity of the problems encountered in our endeavour to tackle the pandemic. However, antiretroviral therapy (ART) has been able to reduce mortality and morbidity, improve quality of life, and increase life expectancy of HIV positive individuals. Early diagnosis, antiretroviral therapy, chemoprophylaxis, and treatment of opportunistic infections remain the four pillars for the control of HIV replication, disease progression, and ultimately the containment of the epidemic. The epidemiological and clinical features differ greatly from country to country, from region to region in the same country, and even from patient to patient. Though *Pneumocystis carinii* pneumonia (PCP) remains the commonest AIDS-defining illness in the western population[1], the incidence of PCP is much lower in India[2]. Disseminated *Penicillium marneffie* infection is being increasingly found among HIV positive patients in SE Asia and in the North-East India (Manipur)[3,4]. Similarly, Kaposi's sarcoma, atypical mycobacterial infection, and disseminated cytomegalovirus disease, common in western literature, are not frequently seen in India[1,5,6]. Due to poor socio-economic conditions, absence of awareness and lack of facility for diagnosis in the rural set-up, the incidence of HIV infection is highly under-reported from these areas[2]. Bringing about positive changes in health-related behaviour of the people, so they take the requisite preventive precautions or readily seek access to healthcare for early diagnosis and treatment, requires a realistic understanding and assessment of the various local factors and practices. Keeping these facts in mind, this study was undertaken to elucidate the epidemiological, clinical, and laboratory profiles of HIV positive patients attending an ART centre located in the rural western region of Uttar Pradesh State.

Materials and methods

This study was conducted between August 2009 and July 2010 at the ART Centre, JN Medical College Hospital, AMU, Aligarh. Our centre serves Aligarh and adjoining rural districts of western Uttar Pradesh. It was a **composite** study with a descriptive arm and an analytical arm. The ***descriptive*** arm dealt with epidemiological, clinical, and laboratory profiles at presentation of the HIV positive patients registered with the ART centre, JNMCH, AMU, Aligarh. The ***analytical*** arm involved the comparative

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study of changes in weight, haemoglobin, and CD4 count after 6 months of follow-up with ART or 6 months of follow-up without ART, but with appropriate management of complications/opportunistic infections.

A. For patients who presented for the first time during the period (August 2009 to April 2010): Diagnosis of HIV infection confirmed by ELISA using two different antigens and a rapid antigen test (as per NACO guidelines). Confirmed patients are registered. Demographic parameters are recorded. The patients are clinically assessed keeping in mind symptoms and signs of immune-compromise and opportunistic infections. Baseline clinical parameters recorded for further reference. Baseline CD4 count is done at the ART Centre with Cyflo Counter (Partec). Baseline investigations including haemogram, LFT, RFT, lipid profile, VDRL, HBsAg and anti-HCV are requisitioned. Patients were started on ART if their CD4 count is < 200-250 cells/µl. For others, opportunistic infections/ complaints are appropriately managed. Follow-up visits are planned at intervals of one month for patients on ART, and 4 months for pre-ART patients. More frequent follow-up visits were planned as necessary. At each follow-up visit, patients are evaluated for relevant clinical and laboratory parameters. Opportunistic infections are diagnosed on the basis of standard clinical definitions and laboratory procedures, and treated. Chemoprophylaxis and ART are advised as indicated. At the completion of 6 months of follow-up, either on ART or not, CD4 count, haemogram, LFT, RFT and lipid profile are repeated.

B. For patients registered before the beginning of the study: respective case records were accessed, and demographic parameters, and clinical and laboratory parameters at baseline (and at 6 months if they had completed 6 months of follow-up) were recorded. The patients who are still actively attending ART centre are also assessed in the same way as above at each follow-up visit.

Data analysis was done using SPSS for Windows version 17.0. Mean was used as the measure of central tendency and standard deviation (SD) was used as measure of dispersion for the descriptive arm. Paired t-test with two tailed significance was used to analyse the difference between the means in case of the analytical arm.

Observations

Descriptive data (Tables I-IV): A total of 584 patients were eligible for enrolment into the study. That included 42 patients below the age of 13 years, and 542 patients aged 13 years or above. 174 patients aged 13 years or older and 2 below the age of 13 years were already on ART at the time of presentation to the centre. 408 patients were ART naive. Of them, 20 patients below the age of 13 years and 231 patients aged 13 years or more went on to receive ART later on. Altogether, 190 out of 542 patients aged 13 years or more completed at least 6 months of ART by the end of the study period. Out of the 542 patients aged more than 13 years, 87 patients had expired by the close of the

Table I: Epidemiological parameters.

Epidemiological parameters		Number	Percentage (%)
Sex	Male	382	65.4
	Female	202	34.6
Age	0 -20	62	10.6
	21 - 40	413	70.7
	41 - 60	103	17.6
	Above 60	6	1.0
Marital status (for 542 pts. ≥ 13 yrs)	Married	81	14.9
	Widowed	355	65.5
	Single	11	2.0
	Divorced/separated	95	17.5
Education	Illiterate	242	44.6
	Primary school	153	28.2
	Secondary school	112	20.7
	College and above	35	6.5
Probable mode of transmission	Heterosexual	355	60.8
	MSM	0	0.0
	Injecting drug use	25	4.3
	Blood transfusion	67	11.5
	Mother to child	43	7.4
	Unsafe injection	60	10.3
	Unknown	34	5.8

Table II: Clinical and laboratory parameters.

Clinical and laboratory parameters		Total	Percentage (%)
WHO clinical stage at presentation	I	163	27.9
	II	135	23.1
	III	228	39.0
	IV	58	9.9
CD4 count at presentation	0 - 200	264	48.7
	201 - 350	194	35.8
	351 - 500	64	11.8
	501 and Above	20	3.7
Opportunistic infections or diseases among adult patients (N = 542)	Tuberculosis	100	18.4
	Chronic diarrhoea	81	14.9
	Recurrent RTI	69	12.7
	Candidiasis	23	4.2
	UTI	21	3.9
	Herpes Zoster	7	1.3
	PCP	2	0.4
	Crypt. meningitis	1	0.2
	SLE	1	0.2
Co-infection	HBV	10	1.8
	HCV	0	0.0
ART regimen (N = 405)	AZT + 3TC + EFV	34	8.3
	AZT + 3TC + NVP	172	42.5
	d4T + 3TC + EFV	39	9.6
	d4T + 3TC + NVP	161	39.7

Table III: Serum cholesterol (Chol), triglyceride (TG), and SGOT in patients on ART.

Variables	No. of patients	Average ART duration	Minimum	Maximum	Mean
Chol > 200 mg/dl	28	6.0 months	200.00	465.00	225.07 mg/dl
TG > 200 mg/dl	9	9.1 months	203.00	316.00	235.67 mg/dl
SGOT ≥ 50 IU/L	47	7.2 months	50.00	376.00	97.08 IU/L

Table IV: ART regimen and SGOT, TG, and total cholesterol levels.

	AZT+3TC+EFV (Mean value)	AZT+3TC+NVP (Mean value)	d4T+3TC+EFV (Mean value)	d4T+3TC+NVP (Mean value)
SGOT ≥ 50 IU/L N = 47	6 (98.6 IU/L)	17 (76.2 IU/L)	6 (131.5 IU/L)	18 (108.0 IU/L)
TG > 200 mg/dl N = 9	3 (230.3 mg/dl)	0 (0.0 mg/dl)	1 (219.0 mg/dl)	5 (108.0 mg/dl)
Chol > 200 mg/dl N = 27	2 (241.5 mg/dl)	15 (217.0 mg/dl)	3 (201.6 mg/dl)	7 (247.7 mg/dl)

Table V: Comparison between the expired and the rest of the population.

Characteristics	Among the expired (n = 87)	Among the rest of the population (n = 455)
Age (average) (years)	34.5	35.5
Weight (average) (kg) at presentation	44	49.3
CD4 count (/μL) at presentation	132.73	239.97
HBV infection (number of cases)	4 (4.6%)	6 (1.3%)
P. tuberculosis (number of cases)	19 (21.8%)	67 (14.7%)
EP tuberculosis (number of cases)	8 (9.2%)	6 (1.3%)

study period (Table V). Analytical data (Table VI): Three patient groups who were followed-up for a minimum of 6 months were selected and designated A, B, and C. Group A: 102 patients who were already receiving ART from outside at the time of registration and who were continued on ART. Group B: 67 patients who were not receiving ART at registration, but were started on ART at the centre. Group C: 76 patients who were neither receiving ART at the time of registration nor started on ART during the study period.

Discussion

A total of 584 patients were enrolled for the descriptive arm of the study, out of which 42 patients (7.14%) were in the paediatric age group (<13 years), and 202 patients (34.5%) were females. The figures compare well with the NACO figures (3.5% and 39% respectively)[7] although the percentage of paediatric patients is double the NACO average that may be an indication of the fact that the incidence of HIV infection is rising and the epidemic is relatively young and fast catching its speed of spread. This is borne out by another finding of a younger age at presentation (35.32 years among adolescents and adults, and 7.00 years among the paediatric age group) as against the Western studies that give an average age of presentation at 39 years[8,9]. The lower number (34.5 %) of females is not a true representation of the proportion of females as financial constraints, gender bias, and social stigma and neglect attached with the disease decrease the number of females attending the HIV clinics. However, this number is higher than reported (19.2%) in other studies in regions with similar socio-economic milieu in India[2]. Hence, in actuality, this may indicate a rising trend even among the females – hence among the general population. In our study, 158 patients had HIV positive spouses. Fourteen of them had at least one HIV positive child.

NACO estimates that 86% of transmissions are due to sexual risks, 2.4% due to IVDU, 2.0% due to receipt of blood/blood products and 3.6% due to perinatal transmission[10]. In our study, for 355 patients (60.8%) out of the total 588, heterosexual route was the probable route of transmission. The lower contribution by this route of transmission is because of a more than expected contribution from other routes of transmission: IDU (4.3%), blood transfusion (11.5%), perinatal transmission (7.4%) and probable unsafe injections (10.3%). This assumes significance for many reasons. One, injection drug use has been traditionally considered the major mode of transmission in North-East India. The almost double contribution from the IDU means that western UP needs

Table VI: Change in weight, CD4, and haemoglobin in different patient groups.

Variable	Group	Baseline (Mean ± SEM)	Follow-up (Mean ±SEM)	't' Value	'p' Value
Weight (kg)	B	49.48 ± 1.00	53.73 ± 0.89	-5.213	< 0.001
	A	48.80 ± 0.67	50.89 ± 0.65	-4.266	< 0.001
	C	49.74 ± 1.08	52.00 ± 0.89	-3.809	< 0.001
CD4 (/μL)	B	201.24 ± 12.82	349.31 ± 11.35	-16.147	< 0.001
	A	203.03 ± 8.51	301.42 ± 9.51	-12.636	< 0.001
	C	300.03 ± 8.29	361.00 ± 10.43	-6.133	< 0.001
Haemoglobin (g/dl)	B	9.9 ± 0.22	11.0 ± 0.20	-9.098	< 0.001
	A	9.86 ± 0.251	10.31 ± 0.218	-3.202	0.002
	C	10.17 ± 0.22	10.43 ± 0.21	-1.624	0.109

't' value = paired student 't' test value; SEM = standard error of mean; 'p' value = power of study.

to focus on this high-risk group as well. Two, contribution of blood transfusion as a mode of transmission is also more than 5 times the national average. This is a reflection of the rampant illegal private commercial blood banks in this part of the country. Three, unsafe injections because of various forms of quackery widespread in this part of the country is a menace that needs to be tackled properly. Four, more than double the national average of perinatal transmission means either the epidemic of HIV is imploding in this part of the country, or that improper obstetric and perinatal practices due to the rampant quackery are being compounded by illiteracy among the people (44.6% illiteracy among the total patients and 64.25% among the females). 48.9% of patients presented in the WHO clinical stage III and IV. Only 3.7% had CD4 counts above 500/μL. This again shows the extent of the gap between the optimum level of health and HIV awareness and the reality. The average CD4 count among males at presentation is 208.96/μL, while it is 247.14/μL among women. Most of the females acquire the infection through their husband, who in turn got it from commercial sex workers as evident from other studies in India[11,12]. The higher average CD4 in females at the time of presentation is an indirect indication of the later contact of infection by females.

Among the 169 patients who had completed 6 months of ART, 47 patients were detected to have SGOT level two times the upper limit of normal or more (≥ 50 IU/L) after an average of 7.27 months of ART, out of which 4 patients were also HBsAg positive. NVP was a component of the ART regimen in 35 of those 47 patients, EFV in the remaining 12 patients. 24 patients had SGOT level 3 times the upper limit of normal or more (≥ 75 IU/L), out of which 16 had NVP in their regimen while 8 took EFV as part of their regimen. 10 patients had SGOT level 5 times the upper limit of normal, and had to discontinue the medication (6 with NVP and 4 with EFV). This correlates with the reputation of NVP being the most hepatotoxic drug followed by EFV. However, no major derangement could be demonstrated in the SGPT or serum bilirubin levels as is the case with blood glucose or renal function. 27 patients had documented serum cholesterol ≥ 200 mg/dl after an average of 6.00 months of ART. 6 patients had EFV in their regimen with an average cholesterol level of 217.6 mg/dl. 22 patients had NVP in their regimen with average serum cholesterol of 226.77 mg/dl. Ten patients had d4T in their ART regimen with average serum cholesterol of 233.89 mg/dl. Thus, while d4T as expected has the maximum effect on serum cholesterol, NVP is more hypercholesterolaemic than EFV. Or this may be because of the more significant selective elevation of HDL-cholesterol fraction by NVP as compared to EFV[13]. This needs further verification in larger and well-controlled trials involving Indian patients. When it comes to the serum TG level, only 9 patients out of the 169 had a level ≥ 200 mg/dl after an average duration 9.1 months of ART. Of the 9 patients, 4 took EFV with an average serum TG level of 227.50 mg/dl. 5 patients had NVP in their regimen with an average serum TG level of 208.04 mg/dl. Similarly, in one study, effects on serum lipid abnormalities prompted by prior PI-based HAART were improved after switching to nevirapine compared with efavirenz[14]. A total of 87 patients out of the 542 aged 13 years and above were documented to have expired after a follow up of 3.6 months on average. As expected, this subgroup of patients had (as compared to the rest of the population) lower average CD4 count (132.73/μL vs. 139.97/μL) and lesser average body weight (44 kg vs. 49.3 kg) at presentation, and higher prevalence of HBV infection, pulmonary tuberculosis, extra-pulmonary tuberculosis and other severe opportunistic infections or complications. This finding is in tune with the Antiretroviral Therapy (ART) Cohort Collaboration that demonstrated that among the factors measured at the time of starting HAART, the CD4 count is the strongest predictor of progression to AIDS or death during a 3-year period, whereas the HIV RNA level measured at the same time is a weaker predictor, being associated with an increased risk of progression only when the level is greater than 100,000 copies/mL[8].

Because prior treatment exposure is associated with a poorer response to ART[15], in the analytical arm of the study, the patients who received ART were divided into two groups: group A comprising patients who had already taken ART, and group B comprising patients who were newly started on ART at the centre. Comparison of haemoglobin, weight, and CD4 count between the baseline and 6-month values showed that there were significant improvements in all the three parameters in all three groups, most markedly in group B, less markedly in group A, and least markedly in group C that comprised patients who did not receive ART, but were followed up and their complications and/or opportunistic infections properly managed.

Conclusion

There may be a marked under-estimation of the magnitude of the HIV epidemic in India, especially in areas which are educationally and socio-economically backward, like the western UP. The HIV epidemic in the country, though described by NACO as "concentrated" among the high-risk populations, is fast spreading into the general population as evidenced by the high incidence of perinatal transmission and paediatric HIV, and the generally younger age at presentation but later stages of presentation. HIV epidemic control measures should

also involve promoting education/literacy among the general population, specially the females, so they can make informed choices regarding health-related behaviour. Illegal private blood banks and quackery should be abolished with strict implementation of the rules of law. Since the response to ART depends on initial CD4 count, it may be reasonable to start ART at higher CD4 counts (higher than the WHO recommended threshold of 350/μL) as has been proposed by in DHSS Panel's 2009 guidelines. Upgrading of ART centres with well-equipped laboratories and close interlinking with other clinical disciplines at a tertiary care centre are a must if ART is to be properly monitored, if the opportunistic infections and complications are to be properly managed, if accurate data are to be maintained, and if accurate and timely assessment of the problem is to be done.

Population-specific studies are needed since we need to look for ways to manage patients efficiently in a resource-limited setting like ours.

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Catheter-associated urinary tract infection: Aetiology, ESBL production, and risk factors

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Abstract

The present study was undertaken with the objective to know the ESBL production among the Gram-negative isolates from catheter-associated urinary tract infections (CAUTI) and the risk factors for the same. 100 urine samples were collected from patients with in situ urinary catheters. Rate of ESBL production among the Gram-negative bacilli (GNB) was 27.86%. Klebsiella pneumoniae (43.75%) was the commonest ESBL producer, followed by Escherichia coli (20.68%). Age beyond 40 yrs, female sex, duration of catheterisation of 6 or more days, and exposure to ciprofloxacin and betalactam antibiotics were found to be the probable risk factors for CAUTIs with ESBL producing GNB. Temporary stoppage of ciprofloxacin and cephalosporins as empirical therapy is suggested. Treatment strategies like antibiotic cycling and appropriate combination therapies should be explored further.

Key words: Risk factors, ESBL, catheter-associated UTI.

Introduction

UTIs accounts for more than 100,000 hospital admissions annually and at least 40% of all hospital acquired infections, which, in the majority of cases are catheter-associated[1]. Nosocomial bacteriuria develops in up to 25% of patients requiring a urinary catheter for > 7 days with a daily risk of 5%[2]. Majority of infections are caused by *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, other Enterobacteriaceae, Pseudomonas, and Acinetobacter species. Although easily treatable, complicated UTI and multidrug resistant uropathogens do pose a therapeutic challenge and may warrant an array of investigations and higher antibiotics.

Production of extended spectrum beta-lactamases (ESBLs) and Amp C beta-lactamases are the most common mechanisms of antimicrobial resistance in GNB[3]. Microorganisms such as *Escherichia coli* (*E. coli*), Klebsiella species and Citrobacter species have the ability to produce ESBL in large quantities[4]. The incidence of ESBL among uropathogens is reported to range from 8.9% to 71.5%[5, 6, 7, 8]. Periodic review of the antibiotic resistance pattern and the extent of ESBL infections is therefore crucial to make/change strategies to combat these infections.

Material and methods

A total of 100 urine samples were obtained from patients with *in situ* urinary catheters. 2 ml urine sample was collected from the catheter tube under aseptic precautions and processed on blood agar and Mac-Conkey's agar by semiquantitative technique using nichrome loop delivering 0.004 ml of urine. Interpretation of cultures and identification of isolates was done as per standard protocol[9] and antimicrobial susceptibility testing was done as per CLSI guidelines[10]. The Gram-negative isolates were further tested for ESBL production by phenotypic confirmatory test by disc diffusion method[10].

Phenotypic confirmatory test

Ceftazidime (30 µg) and ceftazidime with clavulanic acid (30 µg + 10 µg) discs were placed on a lawn culture on Mueller Hinton agar and incubated overnight at 37°C. An isolate was considered to be an ESBL producer if the zone of inhibition around the ceftazidime/clavulanic acid disc was > 5 mm than the zone around the ceftazidime disc alone.

The antimicrobial susceptibility and the ESBL production in Gram-negative uropathogens was then analysed with various parameters. Statistical analysis was done using Chi square test.

Results

A total of 76 isolates were obtained from 100 urine samples, which comprised of 61 Gram-negative bacilli, 6 Gram-positive cocci of which 3 were coagulase-negative staphylococcus species (CONS) and 3 were enterococci. 9 candida species were isolated. Among the GNB, *E. coli* was found to be the predominant bacteria 29 (47.54%), followed by *Klebsiella pneumoniae* 16 (26.22%), *Pseudomonas aeuroginosa* 8 (13.11%), Enterobacter Spp

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2 (3.27%), Citrobacter Spp 2 (3.27%), Acinetobacter Spp 3 (4.9%), and Providencia Spp 1 (1.63%) (Table I). Overall 17 (27.86%) of GNB were ESBL producers, predominant among them were *Klebsiella pneumoniae* 43.75% and *E. coli* 20.68%. The only providencia species isolated was an ESBL producer making it 100% (Table I).

Table I: Distribution of ESBL producing Gram-negative isolates.

Isolate	Total No (%) N = 61	ESBL Producing GNB
E. coli	29 (47.54%)	06 (20.68%)
Klebseilla pneumoniae	16 (26.22%)	07 (43.75%)
Pseudomonas aeruginosa	08 (13.11%)	02 (25%)
Enterobacter species	02 (3.27%)	00
Citrobacter species	02 (3.27%)	01 (50%)
Acinetobacter species	03 (4.91%)	00
Providencia species	01 (1.63%)	01 (100%)
Total	**61**	**17 (27.86%)**

ESBL production was more often associated with infection in patients more than 40 years of age, female sex, and in patients with in situ catheters for 6 or more days (Table II). Majority of the patients were on combination therapy prior to sample collection, ciprofloxacin and ceftriaxone being the commonest combination used. ESBL production was more often associated with patients who had received ciprofloxacin and beta-lactam antibiotics (Table III).

Table II: Correlation of duration of catheterisation and CAUTI (n = 61).

Duration in days	Total samples	Isolates	ESBL production
3	03	00	00
4	03	00	00
5	60	34 (56.66%)	7 (20.58%)
6	12	10 (83.33%)	4 (40%)
> 6	22	17 (77.27%)	6 (35.29%)
Total	**100**	**61**	**17 (27.86%)**

Table III: Percentage of antibiotics received prior to sample collection among ESBL producers and non-ESBL producers.

Antibiotic	ESBL positive (N = 17)	ESBL negative (N = 44)
Ceftriaxone	10 (58.82%)	15 (34.09%)
Amikacin	02 (11.7%)	02 (4.54%)
Gentamicin	00	02 (4.54%)
Ampicillin	03 (17.64%)	02 (4.54%)
Amoxy/Clav	03 (17.64%)	05 (11.36%)
Ciprofloxacin	11 (64.70%)	25 (56.81%)
Piperacillin/tazobactam	00	01 (2.27%)

Overall resistance was relatively less for gatifloxacin (40.90%) and amikacin (49.18%), and least for piperacillin/tazobactam (1.6%). Amikacin, ciprofloxacin, and gatifloxacin exhibited a higher resistance among the ESBL producers. Resistance to other antibiotics was comparable in both the groups (Table IV).

Table IV: Per cent resistance to antibiotics among ESBL producers and non-ESBL producers.

Antibiotics	ESBL producers (n = 17)	Non-ESBL producers (n = 44)
Ampicillin	17 (100%)	44 (100%)
Gentamicin	14 (82.35%)	36 (81.81%)
Amikacin	10 (58.82%)	17 (38.63%)
Cefazolin	16 (94.11%)	42 (95.45%)
Ceftazidime	15 (88.23%)	38 (86.36%)
Ceftriaxone	16 (94.11%)	41 (93.18%)
Ciprofloxacin	16 (94.11%)	33 (75%)
Gatifloxacin	14 (82.35%)	17 (38.63%)
Piperacillin/tazobactam	01 (5.88%)	00

Discussion

The epidemiology of antibiotic resistant bacteria varies with the type of infection, medical speciality, region, and with time[11]. Development of newer antibiotics counter this to some extent, but often fail as new modes of resistance develop in the bacteria. The most common mode of transmission is through ESBL production.

In the present study of the 76 isolates, the 9 *Candida albicans* isolated were considered as transient colonisers/contaminants as repeat cultures yielded no growth; Gram-positive organisms were excluded from the analysis of data as the focus of the study was ESBL production among GNB. 61 isolates were gram-negative bacilli (GNB). Identification of these GNB predictably revealed a predominance of *E. coli* 29 (47.54%) and *Klebsiella pneumoniae* 16 (26.22%) (Table I). A predominance of *E. coli* (50% and 30.26%) and Klebsiella (16.58% and 22.06%) has also been reported by other authors[8,12].

ESBL production among these routinely isolated bacteria is well documented. Several studies have reported the incidence of ESBL among uropathogens ranging from 8.9% to 71.5%[5,6,7,8]. ESBL production was moderate in the present study (27.86%) (Table I). Our results are comparable to a study that reported 25.65% ESBL production[8]. Some authors have reported a higher rate (40% - 41%)[7], others have reported 71.5% with a predominance in Acinetobacter species (95.23%)[8]. Occasionally there are reports of lower prevalence too, i.e., 8.9%[5]; however, the patient population in this study

included out-patients, in-patients, and those in long-term care wards. The predominance of ESBL production in *Klebsiella pneumoniae* (43.75%), and *E. coli* (20.68%) in the present study also correlated well with other studies[8].

Male sex, treatment in subacute care unit, recent antimicrobial treatment, pressure sores, endoscopic gastrostomy, PEG tube, anaemia, hypoalbuminaemia, permanent urinary catheters, and recent invasive procedures have been reported to be associated with ESBL production[4]. Fluoroquinolones are reported to be strongly associated with development of ESBL producing bacteria[8]. Ceftazidime or aztreonam exposure is also reported to be a risk factor[13].

In the present study, ESBL production was more often associated with infection in patients above 40 years (> 50%), and female patients (31.25%) compared to males 24.13%. Duration of catheterisation of 6 or more days was found to be associated with higher rates of ESBL production, i.e., 40% and 35.29% (Table II). All the patients had received antibiotic therapy for the disease that they were admitted for, prior to collection of samples. 64.70% of ESBL positive group and 56.81% of ESBL negative group had received ciprofloxacin. Similarly the percentage of betalactam antibiotics received was more among ESBL positive group ceftriaxone 58.82%, ampicillin 17.64% compared to 34.09% and 4.54% in non-ESBL producers (Table III). Although these results suggest that exposure to ciprofloxacin and betalactam antibiotics were the risk factors for infection with ESBL producing GNB, the same was not statistically significant. A case control study with larger number of patients is likely to throw more light on this.

ESBL positive isolates also carry multiple resistant genes which confer on them multiple drug resistance[5]. Similarly, 67% to 100% resistance to ampicillin, gentamicin, ciprofloxacin, cefazolin, ceftriaxone, and ceftazidime was noted.

When resistance rates were compared between ESBL producer and non-ESBL producers (Table IV), both showed high and comparable resistance to ampicilin (100% and 100%), gentamicin (82.35% and 81.81%), cefazolin (94.11% and 95.45%), ceftazidime (88.23% and 86.36%) respectively. However, non-ESBL producers showed relatively less resistance to amikacin (38.63%), ciprofloxacin 75%, gatifloxacin (38.63%) compared to ESBL producers (58.82%, 94.11%, 82.35%). This was statistically significant with a p value of < 0.05. Piperacillin/tazobactam was the most effective antibiotic in both the groups with the exception of one ESBL producing isolate that was resistant.

Bacteria exhibit an enormous repertoire of different resistance mechanisms. Unspecific mechanisms such as reduced permeability or efflux alter the tolerance to antibiotic substances less than mechanisms such as inactivation of the antibiotic[11]. In our study, ESBL production could explain only 27.86% cases of drug resistance suggesting that other modes of resistance could be responsible in the remaining cases.

Besides the problem of drug resistance, the pharmacodynamics of the antibiotic used in particular infections needs to be considered in order to prescribe an appropriate antibiotic and to achieve a positive outcome. For instance, the urinary excretion for fluroquinolones differs widely between substances. A high urinary excretion > 75% can be observed with gatifloxacin (80%), levofloxacin (84%), lomefloxacin (75%), and ofloxacin (81%). An intermediate excretion rate of 40% - 74% is seen with ciprofloxacin[14]. However, in case of catheter associated UTI (CAUTI), the patients are already on antibiotics for the disease that they are admitted with, which may not be specifically targeted at UTI. Similarly, in the present study too, majority of the patients were on ceftriaxone and ciprofloxacin – both of which are not the best choices for UTI. These factors further complicate the treatment of CAUTI and may result in treatment failures.

Conclusion

In our study we observed a moderate rate of ESBL producing CAUTI. Antibiotic resistance among both the ESBL producers and non-producers was similar, barring amikacin, ciprofloxacin, gatifloxacin. Female sex, duration of catheterisation of > 6 days, prior antibiotic usage like ciprofloxacin and beta-lactams were the probable risk factors for CAUTI by ESBL producing GNB. The disparity of resistance rates and ESBL production among different hospitals is reflective of their practice of empirical therapy and policies. In our hospital there is a high rate of resistance to cephalosporins and quinolones which could confer a selective advantage to these resistant bacterial clones, thus necessitating the temporary stoppage of use of these antibiotics empirically. Treatment strategies like antibiotic cycling and appropriate combination therapies should be explored further. Periodic review of beta-lactamase including ESBL, Amp-C, and metallobeta-lactamase rates in the hospital will help in the struggle between man and microbes.

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"Knowledge and wisdom, far from being one,
Have oft-times no connection.
Knowledge dwells
In heads replete with thoughts of other men;
Wisdom in minds attentive to their own.
Knowledge is proud that he has learned
So much;
Wisdom is humble that he knows no more."

– Sir William Osler (1849-1919).

ORIGINAL ARTICLE

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Poor adherence to treatment: A major challenge in diabetes

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Abstract

Objectives: Multiplicity of therapeutic components and the need for lifelong adherence to the prescription makes diabetes management a hard task. We undertook this study to evaluate the patient adherence to the treatment prescription and to analyse the reasons for non-adherence.

Methods: A four-question preformed questionnaire – the Morisky's instrument – was used to assess the level of adherence to the prescribed anti-diabetic drugs in 600 patients with type 2 diabetes mellitus, and the results were analysed using standard statistical methods.

Results: Only 16.6% of the patients were considered adherent to the prescribed anti-diabetic drugs. Only 23.3 and 31.7% of the participants followed diet restrictions and moderate exercise respectively. 63.3% of the patients wished to receive medications free of cost.

Conclusion: The results showed that the rate of non-adherence to the treatment prescription was high. It stresses the need for constant motivation and one-to-one level education at frequent intervals to ensure better adherence.

Key words: Type 2 diabetes mellitus, medication non-adherence, Morisky's instrument, patient non-compliance, anti-diabetic medication, therapeutic cost.

Introduction

"Drugs don't work in patients who don't take them". It is clear that full benefit of many of the effective medications that are available will be achieved only if patients follow prescribed treatment regimen reasonably closely. Our health care system has been designed in such a way that acute diseases are taken care of in a better way than chronic diseases. Adherence rates are typically higher among patients with acute conditions as compared to those with chronic conditions[1]. Adherence is defined as the extent to which patients take medications as prescribed by their health care providers.

Studies on this subject show that adherence for medications in chronic diseases averages only 50%[2,3].

Diabetes is a challenging disease to be managed successfully. It requires frequent self-monitoring of blood glucose (SMBG), dietary modifications, exercise, and administration of medications as per schedule. So regimen adherence problems are common in individuals with diabetes, thus making glycaemic control difficult to attain[4,5,6].

Recent data from the American Diabetes Association targets HbA1c level less than 6%[7]. It is widely used as the standard biomarker for the adequacy of glycaemic control that further associates with reduced mortality[8] and reduced incidence of complications in patients with type 2 DM[9].

Ensuring that patients take oral anti-diabetic medications as prescribed and achieve normal or near normal blood glucose control is among the most common challenges encountered by the physicians and other health care providers involved in the treatment of diabetes. Failure to attain the desired therapeutic goal might be related to inadequate adherence. Instead of changing the prescription, increasing the drug dosage, or adding a new drug, adherence assessment to the treatment should be considered first in most patients.

In the present study, a short, validated patient questionnaire the – Morisky instrument[10] – is used to measure adherence to anti-diabetic treatment. Adherence studies are being carried out extensively in developed countries though the scenario of adherence in most chronic diseases in the Indian subcontinent is still unknown.

There is a progressive increase in the incidence of type 2 diabetes globally and among Indians. These numbers are projected to increase significantly to ~366 million worldwide and ~80 million in India by the year 2030[11]. As a group patients with diabetes are especially prone to substantial regimen adherence problems[12]. It is in line with this background the present study was carried out to assess the level of adherence to anti-diabetic treatment among type 2 diabetes patients who attend the routine diabetes clinic of Doon Government Hospital and identify the factors contributing to non-adherence, if any.

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Material and methods

A cross-sectional research design was used to study the adherence of patients to anti-diabetic treatment regimens over a period of eight months (June 2009 to January 2010) at the Doon Government Hospital, Dehradun, Uttarakhnad, India. An ethical approval was obtained from the ethics committee at the hospital prior to the initiation of this study.

Patient inclusion criteria: Type 2 diabetes patients aged 30 years and above with fasting blood glucose level $\geq$ 126 mg/dl, post-prandial blood glucose $\geq$ 200 mg/dl, and glycosylated haemoglobin (HbA1C) $\geq$ 7% despite being on anti-diabetic treatment for over a month were included in the study. Patients who were attending the diabetes clinic at the hospital and consented to participate were included in the study.

Treatment included oral hypoglycaemic drugs along with an appropriate diet and exercise regimen. The objective of the study was explained to the individual patients and voluntary informed consent of the patients was also taken.

The selected patients were interviewed regarding their socio-demographic characteristics, income, frequency of drug intake, and reasons for non-adherence to both pharmacotherapy and non-pharmacological therapy (exercise and dietary restriction) by using a preformed questionnaire.

Adherence was assessed through the specific four-question patient questionnaire, the Morisky's instrument[10] that has high reliability and validity, and the patient was considered to be adherent if he answered in the negative to all four questions. Simple percentage was used to describe different variables. The chi-square test was used to assess the significance of association between the groups. A p-value of 0.05 or less was considered statistically significant.

Results

A total of 4,470 patients attended the medicine OPD of the hospital during the period of eight months of which 600 (13.42%) type 2 diabetes patients were enrolled in the study group following the defined inclusion criteria.

Table I shows the socio-economic and demographic parameters among the study group.

Only 16.6% of the patients answered 'no' to every question and were considered adherent according to the Morisky's instrument (Table II), while 83.3% of the patients were non-adherent.

The various factors for non-adherence that were assessed have been tabulated in Table III.

Table I: Socio-demographic outcome variables in non-responders to anti-diabetic medication.

Variable	Category	Frequency (n = 600)	Percentage (%)
Age (Yrs)	31-40	40	6.6
	41-50	120	20
	51-60	145	24.1
	61-70	180	30
	71-80	60	10
	81-90	55	9.1
Gender	Women	195	32.5
	Men	405	67.5
Occupation	Business	155	25.8
	Govt. services including professionals	280	46.7
	House wives	60	10
	Retired	70	11.7
	Manual workers	35	5.8
Income (monthly)	> Rs.10,000 (US$195)	275	45.8
	$\geq$ Rs.10,000 (US$195)	325	54.2

Table II: Morisky's instrument: Assessment of adherence among non-responders to anti-diabetic medication.

Four-question patient questionnaire (Morisky's instrument)	No. of patients who said 'No'	Percentage (%)
1. Did you ever forget to take your medication?	110	18.3%
2. Were you careless at times about taking your medication?	365	60.8%
3. When you felt better, did you sometimes stop taking your medication?	430	71.6%
4. Sometimes, if you felt worse when you took your medicine did you stop taking it?	510	85%
The number of patients who said 'No' to all four questions were considered adherent to the prescribed anti-diabetic treatment	100	16.6%

Table III: Reasons for non-adherence to anti-diabetic drugs in non-compliant patients.

Factors	Non-compliants who said 'Yes'	Compliants who said 'No'
If the drug was provided free of cost would have taken it more regularly	380 (63.3%)	220 (36.6%)
Dietary restriction was difficult to maintain	460 (76.7%)	140 (23.3%)
Lack of time for exercise	410 (68.3%)	190 (31.6%)
Self-monitoring of blood glucose cumbersome	480 (80%)	120 (20%)
Too many drugs	360 (60%)	240 (40%)
Not aware of the consequences of missing the doses	310 (51.6%)	290 (48.3%)
Multiple dosing	345 (57.5%)	255 (42.5%)
Missed the drug very often	135 (22.5%)	465 (77.5%)
Self-discontinuation of prescribed anti-diabetic drugs	160 (26.6%)	440 (73.3%)
Shifted to alternative treatment (ayurvedic, homoeopathic, etc.) after self-discontinuation of prescribed anti-diabetic drugs	90 (15%)	510 (85%)
Side effects of medication	80 (13.3%)	520 (86.6%)

A statistically significant association was observed between participants who missed their drugs very often and the monthly income of ≤ Rs. 10,000 ($p < 0.05$). Majority of these non-compliants were from the lower socio-economic strata who also possessed a poor educational background and/or literacy levels, were self-employed, or held low-income designations in work places. Female patients who were chiefly non-occupational housewives were significant in this group.

Non-adherence was highly significantly ($p < 0.001$) associated with frequent dosing and multiple drugs in the prescription, especially attributed to the 'forgetfulness' in the older/occupationally retired age groups. Patients would deliberately take drug holidays without the knowledge of their physician. More than half of the patients desired a decrease in the number and the frequency of medications.

51.6% of patients were not aware of the consequences of missing the drugs and 13.3% of patients experienced a number of side effects contributing to medication non-adherence ($p < 0.05$). As the country offers alternative systems of medicine which are affordable in comparison, many non-compliants preferred to shift to such remedies off and on, chiefly blaming the side-effects for this change in medication regimen.

Discussion

Poor medication adherence seems to be a significant barrier to attainment of positive clinical outcome among type 2 diabetes patients. Paes *et al*[13] had found that most deviations in medication taken by patients occur as omission of the doses. Fear of inconvenience of daily ingestion of too many drugs has been observed to constitute hindrance to medication adherence among patients with chronic diseases in general and diabetes patients in particular. Our results are consistent with the results of the above-mentioned study that patients want less number of drugs and preferably long-acting ones. Minimising the number of daily doses has been found to be important in improving adherence to the anti-diabetic treatment.

We noted a significant association between patients with low-income and non-adherence to drugs. This was supported by other studies of non-adherence and high cost of the prescribed drugs[14]. High cost of newer oral hypoglycaemic agents hindered optimal adherence to the treatment, so one should ensure that cost effective as well as beneficial oral hypoglycaemic drugs are prescribed to the patients.

Moderate exercise and dietary restrictions were a part of the treatment recommendation for the participants in this study, but many of them do not understand the relevance of these non-drug therapies in the management of type 2 diabetes.

Only 23.3% and 31.7% of the participants were found to be adherent to diet and exercise regimen. Thus it is a matter of necessity to educate the patients of type 2 diabetes at their every visit to their physician about the importance of self-monitoring of blood glucose (SMBG) and lifestyle modifications[15]. These dietary modifications, physical activity, foot care, and ophthalmology check-ups have been shown to be effective in reducing complications and disability and improved patients' quality of life (QOL) and life expectancy[16].

Studies have reported that adherence can be improved by patient education, motivational strategies, improving doctor-patient relationship, and also considering the cost of oral hypoglycaemic drugs, and simplifying the dosage regimen[17,18].

Conclusion

Type 2 diabetes mellitus being a chronic disorder requires multiple therapeutic approaches including dietary and lifestyle modifications. Furthermore, patient adherence rates to these therapeutic regimens tend to be generally low. In view of the adverse effects of hyperglycaemia leading to severe morbidity and increased mortality among the diabetic subjects, a tight control of blood glucose level is mandatory. Therefore, patient education and motivation are important components of diabetes care regimen[19]. The results of the study showed that the patients' adherence rates were generally poor.

Socio-economic states also had an important role in deciding adherence rate. It was also noted that 51% of the patients did not understand the need for strict adherence to the prescription.

All the effort, time, and expenses taken to diagnose the disease and prescribe medications are wasted if the patient does not adhere to the prescribed treatment regimen. The Morisky's instrument was adopted as a method of measuring adherence because of its simplicity, economic feasibility, and as one of the most useful methods in clinical settings.

Such a short and time saving Morisky instrument questionnaire allows the physician to assess the level of adherence so as to improve clinical outcome.

Increasing the effectiveness of adherence interventions might have a far greater impact on the health of the population than any improvement in specific medical treatment[20]. Also, a collaborative relationship between patient and provider may improve patient adherence and

outcomes in chronic medical illnesses[21].

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" Fear not! Life still
Leaves human effort scope.
But, since life teems with ill,
Nurse no extravagant hope."

– Mathew Arnold: Empedocles on Etna.

REVIEW ARTICLE

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Low back pain – Signs, symptoms, and management

*RK Arya**

This review of low back pain and sciatica over the past 3,500 years tries to put our present epidemic of low back disability into historical perspective. Backache has affected human beings throughout recorded history. Despite greater knowledge, expertise, and health care resources for spinal pathologies, chronic disability resulting from nonspecific low back pain is rising exponentially in modern society. Recurrences and functional limitations can be minimised with appropriate conservative management, including medications, physical therapy modalities, exercise, and patient education. Radiographs and laboratory tests are generally unnecessary, except in the few patients in whom a serious cause is suspected based on a comprehensive history and physical examination[2].

Pain in the lower back or low back pain is a common concern, affecting up to 90% of people at some point in their lifetime[1]. Up to 50% will have more than one episode. Low back pain is not a specific disease, rather it is a symptom that may occur from a variety of different processes. In up to 85% of people with low back pain, despite a thorough medical examination, no specific cause of the pain can be identified. America spends approximately $50 billion a year on low back pain[3].

Low back pain is second only to the common cold as a cause of lost days at work. It is also one of the most common reasons to visit a doctor's office or a hospital's emergency department. It is the second most common neurologic complaint in the United States, second only to headache. Low back pain accounts for approximately 15% of the sick leave, and is the most common cause of disability in persons less than 45 years of age. The prognosis for most cases of low backache is good. For 90% of people, even those with nerve root irritation, their symptoms will improve within two months no matter what treatment is used, and even if no treatment is given.

An historic review shows that there is no change in the pathology or prevalence of low back pain: What has changed is our understanding and management. There are striking differences in health care for low back pain in the United States and the United Kingdom, although neither delivers the kind of care recommended by recent evidence-based guidelines. A study in the US reported that 65% patients with low back pain sought care from family physicians as compared against 22% in Australia[31]. Interestingly, there is an eight-fold difference in the likelihood of undergoing surgery for low back pain depending on the specific region in which one resides in the USA. Despite the different health care systems, treatment availability, and costs, there seems to be little difference in clinical outcomes or the social impact of low back pain in the two countries. There is growing dissatisfaction with health care for low back pain on both sides of the Atlantic. Future health care for patients with nonspecific low back pain should be designed to meet their specific needs. Moreover, there are many specialists who claim expertise at treating these symptoms. This includes orthopaedic surgeons, chiropractors, neurosurgeons, physical therapists, rheumatologists, acupuncturists, neurologists, pain management specialists, osteopaths, physical medicine and rehabilitation specialists, internists, and family physicians. Naturally, the education, training, skills, and experience of this diverse group vary considerably when it comes to treating low back pain. Thus there exists a great deal of variance in expertise and opinion within each health profession and subspeciality that treat low back pain.

Causes

Back pain is a symptom. Common causes of back pain involve disease or injury to the muscles, bones, and/or nerves of the spine. Pain arising from abnormalities of organs within the abdomen, pelvis, or chest may also be felt in the back. This is called referred pain. Many disorders within the abdomen, such as appendicitis, aneurysms, kidney diseases, kidney infection, bladder infections, pelvic infections, ovarian disorders, uterine fibroids, and endometriosis among others, can cause pain referred to the back. Normal pregnancy can cause back pain in many ways, including stretching ligaments within the pelvis, irritating nerves, and straining the low back. Additionally, the effects of the female hormone estrogen and the ligament-loosening hormone relaxin may contribute to loosening of the ligaments and structures of the back.

- Mechanical:
  - Apophyseal osteoarthritis
  - Diffuse idiopathic skeletal hyperostosis
  - Degenerative discs
  - Scheuermann's kyphosis
  - Spinal disc herniation ("slipped disc")

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- Thoracic or lumbar spinal stenosis
- Spondylolisthesis and other congenital abnormalities
- Fractures
- Leg length difference
- Restricted hip motion
- Misaligned pelvis-pelvic obliquity, anteversion or retroversion
- Abnormal foot pronation

- Inflammatory:
  - Seronegative spondylarthritides (e.g., ankylosing spondylitis)
  - Rheumatoid arthritis
  - Infection – epidural abscess, or osteomyelitis
- Neoplastic:
  - Bone tumours (primary or metastatic)
  - Intradural spinal tumours
- Metabolic:
  - Osteoporotic fractures
  - Osteomalacia
  - Ochronosis
  - Chondrocalcinosis
- Psychosomatic
  - Tension myositis syndrome
- Paget's disease
- Referred pain:
  - Pelvic/abdominal disease
  - Prostate cancer
  - Posture
- Depression
- Oxygen deprivation

Nerve root syndromes are those that produce symptoms of nerve impingement (a nerve is directly irritated), often due to a herniation (or bulging) of the disc between the lower back bones. Sciatica is an example of nerve root impingement. Impingement pain tends to be sharp, affecting a specific area, and associated with numbness in the area of the leg that the affected nerve supplies.

Herniated discs develop as the spinal discs degenerate or grow thinner. The jelly-like central portion of the disc bulges out of the central cavity and pushes against a nerve root. Intervertebral discs begin to degenerate by the third decade of life. Herniated discs are found in one-third of adults older than 20 years of age. Only 3% of these, however, produce symptoms of nerve impingement.

Spondylosis occurs as intervertebral discs lose moisture and volume with age, which decreases the disc height. Even minor trauma under these circumstances can cause inflammation and nerve root impingement, which can produce classic sciatica without disc rupture.

Spinal disc degeneration coupled with disease in joints of the low back can lead to spinal-canal narrowing (spinal stenosis). These changes in the disc and the joints produce symptoms and can be seen on an X-ray. A person with spinal stenosis may have pain radiating down both lower extremities while standing for a long time or walking even short distances.

Cauda equina syndrome is a medical emergency whereby the spinal cord is directly compressed. Disc material expands into the spinal canal, which compresses the nerves. A person would experience pain, possible loss of sensation, and bowel or bladder dysfunction. This could include inability to control urination causing incontinence or the inability to begin urination.

Musculoskeletal pain syndromes that produce low back pain include myofascial pain syndromes and fibromyalgia. Myofascial pain is characterised by pain and tenderness over localised areas (trigger points), loss of range of motion in the involved muscle groups, and pain radiating in a characteristic distribution but restricted to a peripheral nerve. Relief of pain is often reported when the involved muscle group is stretched. Fibromyalgia results in widespread pain and tenderness throughout the body. Generalised stiffness, fatigue, and muscle aches are reported.

Occasionally, the source may be the sacroiliac joints or the hip joints and musculature.

Infections of the bones, pyogenic or tubercular (osteomyelitis) of the spine are an uncommon cause of low back pain.

Noninfectious inflammation of the spine (spondylitis) can cause stiffness and pain in the spine that is particularly worse in the morning. Ankylosing spondylitis typically begins in adolescents and young adults.

Tumours – benign or malignant, primary or metastatic – can be a source of skeletal pain.

Inflammation of nerves from the spine can occur with infection of the nerves with the herpes zoster virus that causes shingles. This can occur in the thoracic area to cause upper back pain or in the lumbar area to cause low back pain.

As can be seen from the extensive, but not all inclusive, list of possible causes of low back pain, it is important to have a thorough medical evaluation to guide possible diagnostic tests. Psychological and emotional factors, particular depression, can play a role[14].

Back pain is also classified into three categories based on the duration of symptoms[13]:-

i. Acute back pain – pain that has been present for

six weeks or less.

ii. Subacute back pain – pain that has a 6 to 12-week duration.

iii. Chronic back pain – pain present for more than 12 weeks.

Table I[2]: Differential diagnosis of acute low back pain.

Disease or condition	Patient age (years)	Location of pain	Quality of pain	Aggravating or relieving factors	Signs
Back strain	20 to 40	Low back, buttock, posterior thigh	Ache, spasm	Increased with activity or bending	Local tenderness, limited spinal motion
Acute disc herniation	30 to 50	Low back to lower leg	Sharp, shooting or burning pain, paraesthesia in leg	Decreased with standing; increased with bending or sitting	Positive straight leg raise test, weakness, asymmetric reflexes
Osteoarthritis or spinal stenosis	> 50	Low back to lower leg; often bilateral	Ache, shooting pain, "pins and needles" sensation	Increased with walking, especially up an incline; decreased with sitting	Mild decrease in extension of spine; may have weakness or asymmetric reflexes
Spondylolisthesis	Any age	Back, posterior thigh	Ache	Increased with activity or bending	Exaggeration of the lumbar curve, palpable "step off" (defect between spinous processes), tight hamstrings
Ankylosing spondylitis	15 to 40	Sacroiliac joints, lumbar spine	Ache	Morning stiffness	Decreased back motion, tenderness over sacroiliac joints
Infection	Any age	Lumbar spine, sacrum	Sharp pain, ache	Varies	Fever, percussive tenderness; may have neurologic abnormalities or decreased motion
Malignancy	> 50	Affected bone(s)	Dull ache, throbbing pain; slowly progressive	Increased with recumbency or cough	May have localised tenderness, neurologic signs, or fever

Low back pain symptoms

Pain in the lumbosacral area (lower part of the back) is the primary symptom of low back pain.The pain may radiate down the front, side, or back of the leg, or it may be confined to the lower back. The pain may become worse with activity. Occasionally, the pain may be worse at night or with prolonged sitting such as on a long car trip.

One may have numbness or weakness in the part of the leg that receives its nerve supply from a compressed nerve. This can cause an inability to plantarflex the foot. This means one would be unable to stand on one's toes or bring the foot downward. This occurs when the first sacral nerve is compressed or injured. Another example would be the inability to raise the big toe upward. This results when the fifth lumbar nerve is compromised.

When to seek medical care

The Agency for Healthcare Research and Quality has identified 11 red flags[32] that doctors look for when evaluating a person with back pain.The focus of these red flags is to detect fractures (broken bones), infections, or tumours of the spine. Presence of any of the following red flags associated with low back pain should prompt a visit to one's doctor as soon as possible for complete evaluation.

Red flags

1. Recent significant trauma such as a fall from a height, motor vehicle accident, or similar incident.
2. Recent mild trauma in those older than 50 years of age: A fall down a few steps or slipping and landing on the buttocks may be considered mild trauma.
3. History of prolonged steroid use: People with asthma, COPD, and rheumatic disorders, for example, may be given this type of medication.
4. Anyone with a history of osteoporosis: An elderly woman with a history of a hip fracture, for example, would be considered high risk.
5. Any person older than 70 years of age: There is an increased incidence of cancer, infections, and abdominal causes of the pain.
6. Prior history of cancer.
7. History of a recent infection.
8. Temperature over 100° F.
9. IV drug use: Such behavior markedly increases risk of

an infectious cause.

10. Low back pain worse at rest: This is thought to be associated with an infectious or malignant cause of pain, but can also occur with ankylosing spondylitis.
11. Unexplained weight loss.

The presence of any of the above would justify a visit to a hospital.

The presence of any acute nerve dysfunction should also prompt an immediate visit. These would include the inability to walk or inability to raise or lower your foot at the ankle. Also included would be the inability to raise the big toe upward or walk on the heels or stand on the toes. These might indicate an acute nerve injury or compression. Under certain circumstances, this may be an acute emergency. Loss of bowel or bladder control, including difficulty starting or stopping a stream of urine, or incontinence, can be a sign of an acute emergency and requires urgent evaluation in an emergency department.

If the patient cannot manage the pain using the medicine currently prescribed, this may be an indication for a re-evaluation or visit to a hospital.

The history and review of systems include the patient's age, constitutional symptoms, and the presence of night pain, bone pain, or morning stiffness (Table II). The patient should be asked about the occurrence of visceral pain, symptoms of claudication and neurologic symptoms such as numbness, weakness, radiating pain, and bowel and bladder dysfunction.

It is also important to inquire about the specific characteristics and severity of the pain, a history of trauma, previous therapy and its efficacy, and the functional impact of the pain on the patient's work and activities of daily living. An assessment of social and psychologic factors (e.g., depression) may yield information that affects the treatment plan.

Table II: Key aspects of the history and physical examination in the patient with acute low back pain[2].

History

- Onset of pain (e.g., time of day, activity)
- Location of pain (e.g., specific site, radiation of pain)
- Type and character of pain (sharp, dull, etc.)
- Aggravating and relieving factors
- Medical history, including previous injuries
- Psychosocial stressors at home or work"Red flags": age greater than 50 years, fever, weight loss

Physical examination

- Informal observation (e.g., patient's posture, expressions, pain behaviour)
- Comprehensive general physical examination, with attention to specific areas as indicated by the history
- Neurologic evaluation
- Examination of the back:

  Palpation
  - Range of motion or painful arc
  - Stance
  - Gait
  - Mobility (test by having the patient sit, lie down, and stand up)
  - Straight leg raise test

Physical examination

As part of the initial evaluation, the physician should perform a thorough neurologic examination to assess deep tendon reflexes, sensation, and muscle strength (Table II). Peripheral pulses should also be assessed, and the abdomen should be palpated to search for organomegaly. The physician should assess joint and muscle flexibility in the lower extremities, examine the entire spine and assess stance, posture, gait, and straight leg raising. Pain with forward flexion is the most common response and usually reflects mechanical causes. If pain is induced by back extension, spinal stenosis should be considered. The evaluation of spinal range of motion has limited diagnostic use[15], although it may be helpful in planning and monitoring treatment. A patient unable to walk heel to toe, and squat and rise may have neurologic compromise.

Red flags for physical examination

1. Saddle anaesthesia.
2. Loss of anal sphincter tone.
3. Major motor weakness in lower limbs.
4. Fever.
5. Vertebral tenderness.
6. Limited spinal range of motion.
7. Neurologic findings persisting beyond one month.
8. Structural spinal deformity.

Physical examination findings associated with specific nerve root impingment[33]

Nerve root	Strength	Sensation	Reflex
L2	Iliopsoas	Anterior thigh, groin	None
L3	Quadriceps	Anterior/lateral thigh	Patellar
L4	Quadriceps, ankle dorsiflexion	Medial ankle, foot	Patellar
L5	First toe dorsiflexion	Dorsum of foot	None
S1	Ankle plantarflexion	Lateral plantar foot	Achilles

Nonorganic signs

Functional overlay, or sign of excessive pain behaviour, should be assessed. Non-organic signs of physical

impairment have been described[16]. The presence of three or more of these signs are thought to suggest a non physiologic element of the patient's presentation. In this situation, further psychological testing and/or behavioural intervention may be warranted.

Waddell signs: Non-organic signs indicating the presence of a functional component of back pain –

1. Superficial, non-anatomic tenderness.
2. Pain with simulated testing (e.g., axial loading, or pelvic rotation).
3. Inconsistent responses with distraction (e.g., straight leg raises while the patient is sitting).
4. Nonorganic regional disturbances (e.g., non-dermatomal sensory loss).
5. Over-reaction.

Laboratory tests

The comprehensive evaluation may include a complete blood count, determination of erythrocyte sedimentation rate and other specific tests as indicated by the clinical evaluation. In particular, these tests are useful when infection or malignancy is considered a possible cause of a patient's back pain.

Radiographic evaluation

Why we need imaging?

- To provide precise anatomical information.
- To perform clinical diagnosis.
- To plan an effective treatment.
- To assess the efficacy of treatment.
- To plan and perform a diagnostic or therapeutic intervention.

Plain-film radiography

Plain-film radiography is rarely useful in the initial evaluation of patients with acute-onset low back pain. At least two large retrospective studies have demonstrated the low yield of lumbar spine radiographs[4, 5]. In one of these studies, plain-film radiographs were normal or demonstrated changes of equivocal clinical significance in more than 75 per cent of patients with low back pain. The other study found that oblique views of the spine uncovered useful information in fewer than 3 percent of patients. At the first visit, anteroposterior and lateral radiographs should be considered in patients who meet any of the criteria listed in Table IV[6,7,8]. Exposure to unnecessary ionising radiation should be avoided. The issue is of particular concern in young women because the amount of gonadal radiation from obtaining a single plain radiograph (2 views) of the lumbar spine is equivalent to being exposed to daily chest radiograph for more than one year[17].

Indications for radiographs in the patient with acute low back pain

- History of significant trauma.
- Neurologic deficits.
- Systemic symptoms.
- Temperature greater than 38°C (100.4°F).
- Unexplained weight loss.
- Medical history:
  - Cancer
  - Corticosteroid use
  - Drug or alcohol abuse
- Ankylosing spondylitis suspected.

Two major drawbacks to radiography are difficulty in interpretation and an unacceptably high rate of false positive findings. Plain films provide following specific information:

- Uni-segmental (like in tuberculosis) or multi-segmental involvement as seen in lumbar degenerative disc disease.
- Acute or chronic process. Chronic changes include decreased inter-vertebral height, vacuum phenomenon as in disc herniation, end-plate remodelling with spur and sclerosis, and spinal mal-alignment.
- Congenital or acquired pathology.
- Mal-alignment as in scoliosis or kyphosis.
- Destruction and erosion as seen in tumours or infection.

Plain films have high sensitivity and specificity for bony pathologies like acute fractures, spondylosis, or spondylolisthesis, scoliosis, kyphosis, gross degenerative disease. They have a low or no sensitivity and specificity for soft-tissue pathologies like disc herniation, marrow infiltration, spinal infection, and tumours.

Myelogram

It is an X-ray study in which a radio-opaque dye is injected directly into the spinal canal. Its use has decreased dramatically since MRI scanning. A myelogram nowadays is usually done in conjunction with a CT scan. CT myelography has become the investigation of choice to study disc herniation and/or arachnoiditis in post-operative spine with metal hardware in place. It is also useful when clinical findings are compelling and are not

adequately explained by CT and/or MRI. This study is however unable to differenciate disc herniation from bony, mal-alignment, infectious or other extradural lesions. The most important limitation of myelography is its inability to visualise entrapment of nerve root lateral to the termination of nerve root sheath. It is thus unable to detect any far lateral disc herniations. Rarely used nowadays as better non-invasive radiological investigations are available. Complications are headache, nausea, vomiting, back pain, and seizures.

Computed tomographic (CT) scanning

The principal value of CT is its ability to demonstrate the osseous structures of the lumbar spine and their relationship to the neural canal in an axial plane. A CT scan is useful in diagnosing tumours, fractures, and partial-to-complete dislocations. In showing the relative position of one bony structure to another, CT scan is also helpful in the diagnosis of spondylolisthesis. The limitation of CT includes less detailed images and possibility of obscuring non displaced fractures or simulating false ones. In addition, radiation exposure limits the amount of lumbar spine that can be scanned, and the results are adversely affected by patient movement. Spiral CT addresses these weaknesses because it is more accurate and faster, which decreases a patient's exposure to radiation.

Magnetic resonance imaging (MRI)

MRI has emerged as the procedure of choice for diagnostic imaging of neurologic structures related to low back pain. MRI is better than CT in showing the relationship of the disc to nerve, and at locating soft-tissue and non-bony structures. For this reason, it is better than CT at detecting early osteomyelitis, discitis, and epidural type infection or haematomas.

MRI provides high resolution multiaxial, multiplanar images of tissues with no known biohazard effects. The only contraindication to MRI is the presence of ferromagnetic implants, cardiac pacemaker, intracranial clips, or claustrophobia.

Magnetic resonance imaging (MRI) and computed tomographic (CT) scanning have been found to demonstrate abnormalities in "normal" asymptomatic people[9,10]. Thus, positive findings in patients with back pain are frequently of questionable clinical significance. In one study, MRI scans revealed herniated discs in approximately 25 per cent of asymptomatic persons less than 60 years of age, and in 33 per cent of those more than 60 years of age[11]. Clearly, the presence of abnormalities does not correlate well with clinical symptoms. Therefore it is very important to correlate clinical findings with MRI findings. Their routine use is discouraged in acute back pain unless a condition is present that may require immediate surgery, such as with cauda equina syndrome or when red flags are present and suggest infection of the spinal canal, bone infection, tumour, or fracture. Compared with MRI, CT scanning is less sensitive to patient movement and is also less expensive. MRI may also be considered after one month of symptoms to rule out more serious underlying problems. MRIs are not without problems. Bulging of the discs is noted in up to 40% of MRIs performed on people without back pain. Other studies have shown that MRIs fail to diagnose up to 20% of ruptured discs that are found during surgery.

MRI or CT studies should be considered in patients with worsening neurologic deficits or a suspected systemic cause of back pain such as infection or neoplasm. These imaging studies may also be appropriate when referral for surgery is a possibility.

Bone scintigraphy

Bone scintigraphy, or bone scanning, can be useful when radiographs of the spine are normal but the clinical findings are suspicious for osteomyelitis, bony neoplasm or occult fracture. However, this technique is unlikely to demonstrate bone changes when radiographs and the erythrocyte sedimentation rates are normal.

Physiologic assessment

Electrodiagnostic assessments such as needle electromyography and nerve conduction studies are useful in differentiating peripheral neuropathy from radiculopathy or myopathy. If timed appropriately, these studies are helpful in confirming the working diagnosis and identifying the presence or absence of previous injury. They are also useful in localising a lesion, determining the extent of injury, predicting the course of recovery and determining whether structural abnormalities (as seen on radiographic studies) are of functional significance.

The physician needs to be aware of the limitations of electrodiagnostic studies. Because the tests depend on patient cooperation, only a limited number of muscles and nerves can be studied. In addition, the timing of the studies is important, because electromyographic findings may not be present until two to four weeks after the onset of symptoms. Hence, electrodiagnostic studies have only a limited role in the evaluation of acute low back pain.

Electrodiagnostic studies may not add much if the clinical

findings are not suggestive of radiculopathy or peripheral neuropathy. These tests should not be considered if they will have no effect on the patient's medical or surgical management.

Because electrodiagnostic studies are examiner-dependent, they should ideally be performed by physicians who are specialists in electrodiagnostic medicine[14,15].

Self-care at home

General recommendations are to resume normal, or near normal activity as soon as possible. However, stretching or activities that place additional strain on the back are discouraged. Sleeping with a pillow between the knees while lying on one side may increase comfort or lying on your back with a pillow under your knees.

Ibuprofen, available over the counter, is an excellent medication for the short-term treatment of low back pain. Because of the risk of ulcers and gastrointestinal bleeding, avoid this medication for a long time.

Acetaminophen has been shown to be as effective as ibuprofen in relieving pain.

Topical agents such as deep-heating rubs have not been shown to be effective.

Some people seem to benefit from the use of ice or heat. Their use, although not proven effective, is not considered to be harmful. Take care: Do not use a heating pad on "high" or place ice directly on the skin.

Most experts agree that prolonged bed rest is associated with a longer recovery period. Further, people on bed rest are more likely to develop depression, blood clots in the leg, and decreased muscle tone. Very few experts recommend more than a 48-hour period of decreased activity or bed rest. In other words, advise patients to get up and get moving to the extent they can.

Medical history

Because many different conditions may cause back pain, a thorough medical history will be performed as part of the examination.

Questions regarding the onset of the pain:

Were you lifting a heavy object and felt an immediate pain? Did the pain come on gradually? What makes the pain better or worse? Ask questions referring to the "red flag" symptoms and about recent illnesses and associated symptoms such as cough, fever, urinary difficulties, or stomach illnesses. In females, about vaginal bleeding, cramping, or discharge. Pain from the pelvis, in these cases, is frequently felt in the back.

What are the points to be noted in the patient with backache?

- Age of the patient.
- Any history of cancer (like prostate or breast carcinoma).
- Unexplained weight loss.
- Long-term use any steroidal drugs or drugs for AIDS.
- Duration of back pain.
- Any pain. or worsening of pain. at rest.
- Drug abuse.
- Numbness or weakness of legs.
- History of injury to the back.
- Urinary disturbance (difficulty in passing urine).
- Work status.
- Educational level of the patient.
- Any pending cases in court against the patient.
- Worker's compensation issues.
- Previous failed treatment for backache.
- Depression.

Physical examination

To ensure a thorough examination, ask the patient to put on a gown. Watch for signs of nerve damage while patient walk on heels, toes, and soles of the feet. Reflexes are usually tested using a reflex hammer. This is done at the knee and behind the ankle. Make the patient lie flat on the back, one leg at a time is elevated, both with and without the assistance. This is done to test the nerves, muscle strength, and assess the presence of tension on the sciatic nerve. Sensation is usually tested using a pin, paper clip, broken tongue depressor, or other sharp object to assess any loss of sensation in legs.

Depending on these findings, it may be necessary to perform an abdominal examination, a pelvic examination, or a rectal examination. These examinations look for diseases that can cause pain referred to the back. The lowest nerves in the spinal cord serve the sensory area and muscles of the rectum, and damage to these nerves can result in inability to control urination and defaecation. This becomes very important if cauda equina syndrome is suspected.

Rest

Previously, bed rest was frequently prescribed for patients with back pain. However, several studies have shown that this measure has an adverse effect on the course and outcome of treatment. One randomised clinical trial found

that patients with two days of bed rest had clinical outcomes similar to those in patients with seven days of bed rest[20]. The group with a shorter rest period missed 45 per cent fewer days of work and presumably avoided the effects of deconditioning and the fostering of a dependent sick role.

Laboratory and radiographic findings in selected causes of low back pain

Disease or condition	Laboratory tests	Radiographs
Back strain	No abnormalities	Usually negative Radiographs may show incidental spondylotic changes.
Acute disc herniation	If testing is timed properly, positive findings for electrodiagnostic studies in the presence of root entrapment	Possibly, narrowed intervertebral disc spaces on radiographs. CT and MRI can reveal level and degree of herniation. Myelography localises site of disc herniation and the presence of root entrapment.
Osteoarthritis	ESR and WBC count plus differential typically normal	Asymmetric narrowing of joint space. Sclerotic subchondral bone. Marginal osteophyte formation.
Spondylolisthesis	No abnormalities	Abnormal intervertebral movement on radiographs obtained with spine in flexion and extension. Radiographs may reveal pars defect. Bone scans can reveal pars defect not visible on radiographs.
Ankylosing spondylitis	ESR may be elevated Mild anaemia possible Positive human leukocyte antigen-B27 assay in 90 per cent of affected patients	Radiographs of pelvis are positive for sacroiliac joint sclerosis and narrowing. Bone scans are useful for demonstrating increased activity in sacroiliac joints, facets, or costovertebral joints.
Infection	Elevated ESR; WBC count may be normal Blood culture or tuberculin test may be positive	Radiographs may show vertebral end-plate erosion, decreased intervertebral disc height, changes indicative of bony erosion and reactive bone formation. Gallium citrate scanning or Indium-labelled leukocyte imaging may be positive.
Malignancy	Anaemia Increased ESR Prostate-specific antigen or alkaline phosphatase level may be elevated	Radiographs may show bony erosion or blastic lesions. Bone scans are useful for early demonstration of blastic lesions. CT localises cortical lesions earlier than radiographs. MRI is useful for demonstrating soft-tissue tumours involving the spinal cord.

The current recommendation is two to three days of bed rest in a supine position for patients with acute radiculopathy[21, 22]. The biomechanical rationale for bed rest is that intradiscal pressures are lower in the supine position. However, rolling over in bed may result in increased intradiscal pressures. Sitting, even in a reclined position[23], actually raises intradiscal pressures and can theoretically worsen disc herniation and pain. Activity modification is now the preferred recommendation for patients with non-neurogenic pain. With activity restriction, the patient avoids painful arcs of motion and tasks that exacerbate the back pain.

Physical therapy modalities

Superficial heat (hydrocolloid packs), ultrasound (deep heat), cold packs, and massage are useful for relieving symptoms in the acute phase after the onset of low back pain. These modalities provide analgesia and muscle relaxation. However, their use should be limited to the first two-to-four weeks after the injury. The use of deep heat may be subject to a number of restrictions[21].

No convincing evidence has demonstrated the long-term effectiveness of lumbar traction[22] and transcutaneous electrical stimulation[23] in relieving symptoms or improving functional outcome in patients with acute low back pain. Therapy should emphasise the patient's responsibility for spine care and injury prevention.

Corsets

The role of corsets (lumbosacral orthoses, braces, back supports, and abdominal binders) in the treatment of patients with low back pain is controversial at best[24]. Use of a corset for a short period (a few weeks) may be indicated in patients with osteoporotic compression fractures.

Exercise

Aerobic exercise has been reported to improve or prevent back pain[25]. The mechanism of action is unclear, and the relationship between cardiovascular conditioning and rate of recovery is not universally accepted. Excess weight, however, has a direct effect on the likelihood of developing low back pain, as well as an adverse effect on recovery[26].

In general, exercise programmes that facilitate weight loss, trunk strengthening, and the stretching of musculotendinous structures appear to be most helpful in alleviating low back pain. Exercises that promote the strengthening of muscles that support the spine (i.e., the oblique abdominal and spinal extensor muscles) should be included in the physical therapy regimen. Aggressive exercise programmes have been shown to reduce the need for surgical intervention[27].

Selected therapies for low back pain

Therapy	Indications	Contraindications	Prescription
Superficial heat (hydrocolloid packs)	Analgesia Reduction in muscle spasm Increased tolerance for exercise	Impaired sensation, circulation cognition Oedema Bleeding diathesis	Apply to affected area for 20 to 30 minutes; inspect skin frequently during therapy; repeat application every 2 hours as needed.
Ultrasound (deep heat)	Analgesia Increased length of periarticular ligaments and tendons	Same as for superficial heat Never use deep heat near cardiac pacemaker or fluid-filled cavities (e.g., eyes, uterus, testes, aminectomy sites)[21]. Avoid use of deep heat near open epiphyses, malignancies, or joint arthroplasties[21].	Apply 0.5 to 2.0 W per cm^2 to affected area for 10 to 15 minutes before range-of-motion exercises are performed.
Cold packs	Analgesia Limitation of oedema formation in acute musculoskeletal injury	Impaired sensation, circulation, cognition History of cold intolerance	Apply to affected area for 20 to 30 minutes; inspect skin frequently during therapy; repeat application every 2 hours for 48 hours after injury as needed.

Chiropractic

Patients with acute or chronic back pain frequently seek chiropractic intervention. The Agency for Healthcare Research and Quality (AHRQ), previously the Agency for Health Care Policy and Research (AHCPR)[28], and the Clinical Standards Advisory Group (CSAG)[29] acknowledge the potential value of a short course of spinal manipulation in patients with acute low back pain. However, further research is needed to clarify the subgroup of patients most likely to benefit from this intervention[30].

Patient education

It is critical to solicit the active participation of patients in spine care. Successful treatment depends on the patient's understanding of the disorder and his or her role in avoiding re-injury. Many hospitals and large businesses offer programmes on back protection. These programmes emphasise measures for avoiding spinal injury and review appropriate postures for sitting, driving, and lifting. Weight loss and healthy lifestyle classes are also widely available.

Psychologic evaluation

Psychosocial obstacles to recovery may exist and must be explored. Studies have shown that workers with lower job satisfaction are more likely to report back pain and to have a protracted recovery[31]. Patients with an affective disorder (e.g., depression), or a history of substance abuse are more likely to have difficulties with pain resolution. It is important for the physician to find out whether the patient has any pending litigation, because this can often adversely affect the outcome of therapy[32].

Indications for surgical evaluation

Of all industrialised nations, the United States of America has the highest rate of spinal surgery (e.g., five times that of Great Britain)[33]. Studies examining the outcomes of conservative and surgical treatment of back pain have revealed no clear advantage for surgery. In one prospective study of 280 patients with herniated nucleus pulposus diagnosed by myelography[34], the surgical group demonstrated more rapid initial recovery than the medical treatment group. However, after approximately four years, outcomes appeared to be roughly equivalent in both groups; by 10 years, no appreciable differences in outcome were found.

Select groups of patients with acute low back pain should undergo immediate surgical evaluation. Patients with suspected cauda equina lesions (characterised by saddle anaesthesia, sensorimotor changes in the legs and urinary retention) require immediate surgical investigation. Surgical evaluation is also indicated in patients with worsening neurologic deficits or intractable pain that is resistant to conservative treatment.

Medications

Medication treatment options depend on the precise diagnosis of the low back pain. Medication in several classes have been shown to have moderate, primarily short-term benefits.

Nonsteroidal anti-inflammatory medications: (NSAIDs) are the mainstay of medical treatment for the relief of back pain[25]. Ibuprofen, naproxen, ketoprofen, and many others

are available. No particular NSAID has been shown to be more effective for the control of pain than another. However, you may switch from one NSAID to another to find one that works best for your patient.

COX-2 inhibitors: Such as celecoxib (Celebrex), are more selective members of NSAIDs. Although increased cost can be a negative factor, the incidence of costly and potentially fatal bleeding in the gastrointestinal tract is clearly less with COX-2 inhibitors than with traditional NSAIDs. Long-term safety (possible increased risk for heart attack or stroke) is currently being evaluated for COX-2 inhibitors and NSAIDs.

Acetaminophen: It is considered effective, safe, and less costly for treating acute pain as well[26]. NSAIDs do have a number of potential side effects, including gastric irritation and kidney damage with long-term use[27].

Muscle relaxants: Paraspinous muscle spasm associated with acute back injuries of various aetiologies responds well to these medications. Muscle relaxants are effective in the management of non-specific low back pain, but the adverse effects require that they be used with caution[29].

Opioid analgesics: These drugs are considered an option for pain control in acute, severe, and disabling back pain that is not (or unlikely to be) controlled with acetaminophen or NSAIDs. The use of these medications is associated with serious side effects, including dependence, sedation, decreased reaction time, nausea, and clouded judgment[28]. One of the most troublesome side effects is constipation. This occurs in a large percentage of people taking this type of medication for more than a few days. A few studies support their short-term use for temporary pain relief. Their use, however, does not speed recovery.

Depression is common in patients with chronic low back pain and should be assessed and treated appropriately[24].

Tricyclic antidepressants: Are an option for pain relief in patients with chronic low back ache. Gabapentin is associated with a small, short-term benefit in patients with radiculopathy.

Steroids: Systemic steroids are not recommended for the treatment of low back pain with or without sciatica[30]. Steroid injections into the epidural space have not been found to decrease duration of symptoms or improve function and are not currently recommended for the treatment of acute back pain without sciatica. Benefit in chronic pain with sciatica remains controversial. Injections into the posterior joint spaces, the facets, may be beneficial for people with pain associated with sciatica. Trigger point injections have not been proven helpful in acute back pain. Trigger point injections with a steroid and a local anaesthetic may be helpful in chronic back pain. Their use remains controversial.

Low back pain surgery

Surgery is seldom considered for acute back pain unless sciatica or the cauda equina syndrome is present. Surgery is considered useful for people with certain progressive nerve problems caused by herniated discs.

Other therapies

Spinal manipulation

Osteopathic or chiropractic manipulation appears to be beneficial in people during the first month of symptoms. Studies on this topic have produced conflicting results. The use of manipulation for people with chronic back pain has been studied as well, also with conflicting results. The effectiveness of this treatment remains unknown. Manipulation has not been found to benefit people with nerve root problems.

Acupuncture

Current evidence does not support the use of acupuncture for the treatment of acute back pain. Scientifically valid studies are not available. Use of acupuncture remains controversial.

Transcutaneous electric nerve stimulation (TENS)

TENS provides pulses of electrical stimulation through surface electrodes. For acute back pain, there is no proven benefit. Two small studies produced inconclusive results, with a trend toward improvement with TENS. In chronic back pain, there is conflicting evidence regarding its ability to help relieve pain. One study showed a slight advantage at one week for TENS but no difference at three months and beyond. Other studies showed no benefit for TENS at any time. There is no known benefit for sciatica.

Exercises

In acute back pain, there is currently no evidence that specific back exercises are more effective in improving function and decreasing pain than other conservative therapy. In chronic pain, studies have shown a benefit from the strengthening exercises. Physical therapy can be guided optimally be specialised therapists.

Follow-up

After their initial visit for back pain, patients are recommended to follow their doctor's instructions as carefully as possible. This includes taking the medications and performing activities as directed. Back pain will, in all

likelihood, improve within several days. Tell patients not to be discouraged if they do not achieve immediate improvement. Nearly everyone improves within a month of onset of the pain.

Low back pain prevention

The prevention of back pain is, itself, somewhat controversial. It has long been thought that exercise and an all-around healthy lifestyle would prevent back pain. This is not necessarily true. In fact, several studies have found that the wrong type of exercise such as high-impact activities may increase the chance of suffering back pain. Nonetheless, exercise is important for overall health and should not be avoided. Low-impact activities such as swimming, walking, and bicycling can increase overall fitness without straining the low back.

Specific exercises

Patients should learn from their doctor about how to perform these exercises.

Abdominal crunches, when performed properly, strengthen abdominal muscles and may decrease the tendency to suffer back pain.

Although not useful to treat back pain, stretching exercises are helpful in alleviating tight back muscles.

The pelvic tilt also helps alleviate tight back muscles.

Lumbar support belts

Workers who frequently perform heavy lifting are often required to wear these belts. There is no proof that these belts prevent back injury. One study even indicated that these belts increased the likelihood of injury.

Standing

While standing, keep your head up and stomach pulled in. If you are required to stand for long periods of time, you should have a small stool on which to rest one foot at a time. Do not wear high heels.

Sitting

Chairs of appropriate height for the task at hand with good lumbar support are preferable. To avoid putting stress on the back, chairs should swivel. Automobile seats should also have adequate low-back support. If not, a small pillow or rolled towel behind the lumbar area will provide adequate support.

Sleeping

Individual needs vary. If the mattress is too soft, many people will experience backaches. The same is true for sleeping on a hard mattress. Trial and error may be required. A piece of plywood between the box spring and mattress will stiffen a soft bed. A thick mattress pad will help soften a mattress that is too hard.

Lifting weights

Patients should not lift objects that are too heavy for them. If they want to attempt to lift something they should keep their back straight up and down, head up, and lift with the knees. One should keep the object close by, and not stoop over to lift. One should tighten the stomach muscles to keep the back in balance.

Low back pain prognosis

The prognosis for people with acute back pain associated with red flags (described earlier) depends on the underlying cause of the pain. Up to 90% of people experience an episode of back pain without other health concerns, and their symptoms will go away on their own within a month. For about half, back pain may return.

About 80% of people with sciatica will eventually recover, with or without surgery. The recovery period is much longer than for uncomplicated, acute back pain.

One can improve one's chances of early recovery by staying active and avoiding more than two days of relative bed rest.

Quick tips to a healthier back

Following any period of prolonged inactivity, begin a programme of regular low-impact exercises. Speed walking, swimming, or stationary bike riding 30 minutes a day can increase muscle strength and flexibility. *Yoga* can also help stretch and strengthen muscles and improve posture. Patients should ask their physician or orthopaedist for a list of low-impact exercises appropriate for their age and designed to strengthen lower back and abdominal muscles.

Advice to patients

- Always stretch before exercise or other strenuous physical activity.
- Do not slouch when standing or sitting. When standing, keep your weight balanced on your feet. Your back supports weight most easily when curvature is reduced.
- At home or work, make sure your work surface is at a comfortable height for you.
- Sit in a chair with good lumbar support and proper position and height for the task. Keep your shoulders back. Switch sitting positions often and periodically walk around the office or gently stretch muscles to relieve tension. A pillow or rolled-up towel placed behind the small of your back can provide some lumbar support. If you must sit for a long period of time, rest your feet on a low stool or a stack of books.

- Wear comfortable, low-heeled shoes.
- Sleep on your side to reduce any curve in your spine. Always sleep on a firm surface.
- Ask for help when transferring an ill or injured family member from a reclining to a sitting position or when moving the patient from a chair to a bed.
- Do not try to lift objects too heavy for you. Lift with your knees, pull in your stomach muscles, and keep your head down and in line with your straight back. Keep the object close to your body. Do not twist when lifting.
- Maintain proper nutrition and diet to reduce and prevent excessive weight, especially weight around the waistline that taxes lower back muscles. A diet with sufficient daily intake of calcium, phosphorus, and vitamin D helps to promote new bone growth.
- If you smoke, quit. Smoking reduces blood flow to the lower spine and causes the spinal discs to degenerate.

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REVIEW ARTICLE

JIACM 2014; 15(1): 42-6

Factors affecting severity, functional parameters, and quality of life in COPD patients

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a major cause of health care burden worldwide, and the only leading cause of death that is increasing in prevalence[1]. Although most of the available data on the disease are reported from the Western world, a recent study from India estimated the burden from chronic diseases to account for 53 per cent of all deaths and 44 per cent of DALYs lost in 2005[2].

Aims of the study: To study the factors affecting the severity, functional parameters, and quality of life (QOL) in COPD patients, and to study the physicians' awareness of the modalities of diagnosis and treatment.

Methodology: A total of 100 patients aged between 40 and 70 years either admitted or attending the clinics of Internal or Pulmonary Medicine, Safdarjung Hospital & Vardhman Mahavir Medical College (VMMC), New Delhi were included in the study. The data from these patients were collected by detailed history and physical examination as per the pre-designed proforma. The quality of life was accessed using the St. George's respiratory questionnaire and physician awareness about COPD and its various modalities was also evaluated through a specially designed questionnaire.

Results: Of the total patients 25 males and 4 females had moderate COPD, 23 males and 5 females had severe COPD and 35 males and 8 females had very severe COPD. Smoking , domestic smoke exposure, female sex and poor nutritional status were associated with more severe disease and worse quality of life. 84.7% of the doctors who participated in the study were aware of the GOLD guidelines for diagnosis and management of COPD and 60.5% doctors were aware of the modalities of physical rehabilitation in COPD.

Conclusion: Our study concluded that severity of COPD depends on a variety of factors with smoking being the most important. Also domestic smoke exposure, female sex and poor nutritional status were associated with more severe disease and worse quality of life. Physician awareness about COPD and its various modalities was also found to be below the desirable levels.

Introduction

Definition

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases[3].

Chronic obstructive pulmonary disease (COPD) is a major cause of health care burden worldwide and the only leading cause of death that is increasing in prevalence[1]. The largest increase in the tobacco related mortality is estimated to occur in India, China, and other Asian countries[4].

Although most of the available data on the disease are reported from the Western world, it is being equally recognised from Asia and Africa.

Unlike Europe and the United States of America, the Asian continent is rather large and heterogeneous with marked disparities in social and health care infrastructure in different countries.

Risk factors

Several risk factors have been reported in different epidemiological studies. *Tobacco smoking* is the most important identifiable factor in almost all the reports. Exposures to exhausts of fuel combustion are also important especially amongst non-smoker patients and women.

Male sex, advancing age, lower socio-economic grouping, and urban residence are also associated with an increased occurrence of COPD.

Tobacco smoking in India in different States and regions is highly variable from 13.3 to 59.4 per cent in men, and 0.2 to 22.0 per cent in women[5].

There are several different forms of tobacco products

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indigenously available in India and other Asian countries. *Bidi* smoking, in particular, is a more common habit than cigarette smoking in India. The present study was carried out to ascertain factors determining disease severity in COPD patients and to determine the impact of functional status on quality of life in these patients. It also aimed to study physicians' awareness towards diagnosis and management of COPD patients.

Materials and methods

A total of 100 male and female patients of COPD aged between 40 to 70 years attending the general/internal medicine and respiratory clinics and admitted in the medical or respiratory medicine wards of Safdarjung Hospital, Vardhman Mahavir Medical College (VMMC), New Delhi were recruited. COPD was diagnosed clinically with signs and symptoms of COPD, that is, cough, sputum production, and dyspnoea on exertion. The severity of disease was categorised as per the GOLD criteria by spirometry. Patients already diagnosed and on treatment were also included.

Patients refusing consent, with other co-existing pulmonary diseases, with congestive heart failure, with other co-morbidities like malignancies, renal failure, hepatic failure, or taking drugs, other than those for COPD, which cause alternation in lung function were excluded from the study.

The patients were subjected to a detailed history and physical examination as per the specially designed proforma. To assess the factors affecting the severity of disease, a detailed history of smoking, occupational exposure, indoor and outdoor air pollution, acute exacerbation-emergency visits/hospital admissions was elicited. Socio-economic status was calculated using the Kuppuswamy's socio-economic status scale updated for 2007[6].

The functional disability and quality of life was evaluated through the St. George's respiratory questionnaire which is a validated and accepted instrument for the assessment of quality of life in COPD patients.

Physician-related factors were evaluated through predesigned proforma. Physicians included were doctors working in the departments of general/internal medicine and pulmonary and critical care medicine, Safdarjung Hospital & VMMC, New Delhi.

The data was analysed and the correlation was calculated by Pearson's co-efficient and p-value was calculated using students t-test and non parametric Kruskal-Wallis test. P-value ≤ 0.05 is significant and a p-value ≤ 0.001 is highly significant.

Results

A total of 100 patients were included in the study out of which 83 patients were male and 17 were female. 80 out of the total 83 males and 9 out of the total 17 females were smokers. Of the total patients 25 males and 4 females had moderate COPD, 23 males and 5 females had severe COPD, and 35 males and 8 females had very severe COPD. No patients in this study belonged to mild (GOLD Stage 1) COPD category.

In the study group the mean age was 61.06 ± 4.95 years, the mean FEV1% was 36.34 ± 16.41 and the mean total SGRQ score was 55.62 ± 16 .02. The correlation co-efficient for age and FEV1% was -0.80 (p value = 0.428; not significant) The correlation between age and total SGRQ score was 0.81 (p value = 0.421; not significant).

In the study group female patients had lower mean FEV1% of 32.71 ± 14.01 as compared to males 37.08 ± 16.84 (p value = 0.36 ; not significant).

Females had a higher mean SGRQ scores of 62.32 ± 14.24 as compared to males 54.24 ± 16.1 (p value = 0.02 which is significant) indicating that females had poorer quality of life in COPD.

In our study group the mean body mass index was 20.28 ± 1.57 kg/m^2. The correlation co-efficient for BMI and FEV1% was 0.348 (p value = 0.000; highly significant). Similarly, BMI and total SGRQ score showed a correlation of - 0.271(p value= 0.006; moderately significant)

The correlation between socio-economic class, accessed by the Kuppuswamy scale, and FEV1 had a p value of 0.095 (not significant).

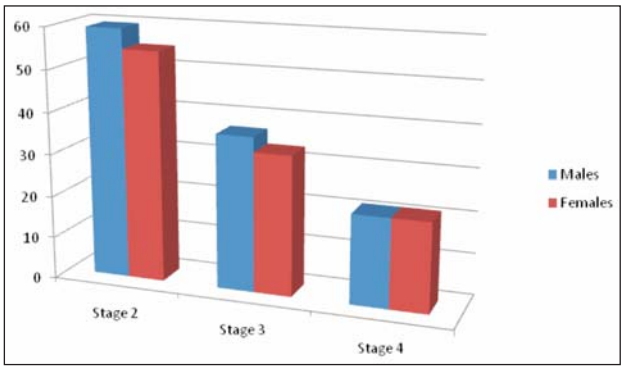

Fig. 1: *Graph showing mean total scores in males and females within different stages of COPD.*

The correlation between socio-economic class and total scores had a p value of 0.212 (not significant).

Of the total 100 patients, 71% had severe to very severe disease and 89% of all patients included were smokers. The remaining 11% had history of exposure to smoke from

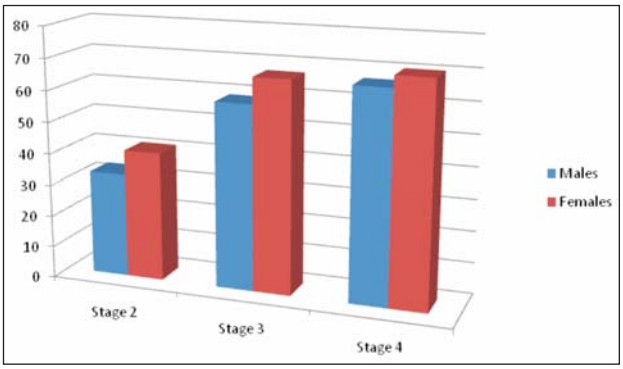

Fig. 2: *Graph showing mean FEV1% in males and females within different stages of COPD.*

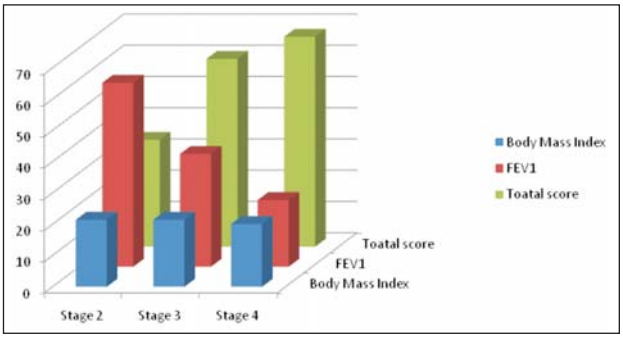

Fig. 3: *Graph showing body mass index, FEV1, and SGRQ scores in patients of different stages.*

biomass fuel consumption at home or outdoor pollution.

Among the 89 patients who smoked, 61 were bidi smokers, 24 were cigarette smokers, and 4 patients had smoked tobacco in multiple forms (*hukkah, chillum,* etc.).

These differences in the form of tobacco smoking were found to be highly significant for FEV1 (p value = 0.001) and also for total SGRQ scores (p value = 0.001) with those smoking in multiple forms being worst followed by *bidi* and cigarette smokers respectively (Table I).

Table I: Showing mean FEV1 and SGRQ (St. George's respiratory questionnaire) scores among patients with different forms of tobacco smoking.

	Bidi	Cigarette	Multiple
FEV1% predicted	32.34 ± 14.76	46.58 ± 18.15	27.50 ± 6.45
SGRQ Total score	58.30 ± 15.03	45.80± 16.50	67.20 ± 4.19

The quality of life was accessed by the St. George's respiratory questionnaire. The symptoms, activity, impacts, and total scores correlated significantly with the FEV1% predicted.

Physician awareness about COPD and its modalities was accessed by a specially designed questionnaire (Table II). A total number of 38 doctors working in various capacities in the department of general/internal medicine, Safdarjung Hospital were included in the study. Of these, 32, i.e., 84.2% were aware of the GOLD guidelines for diagnosis and management of COPD. However only 24 out of 38 doctors, i.e., 63.1% obtained a PFT in suspected cases to confirm the diagnosis. The remaining relied on the clinical features for diagnosis. Also, only 81.3 % (26 out of 32) reported treating patients as per the GOLD guidelines, stating ill-affordability of treatment by the patients and hence their non-compliance as the reason. Only 23 out of 38, i.e., 60.5% doctors were aware of the modalities of physical rehabilitation in COPD. All the doctors recruited in the study were aware of the role of smoking (both active and passive), and nutrition of the patient in COPD.

Table II: Showing physician awareness of various aspects of COPD.

	Yes	No
Aware of GOLD guidelines	32	6
Obtained PFT for diagnosis	24	14
Treating as per GOLD guidelines	26	12
Aware of physical rehabilitation in COPD	23	15
Aware of role of smoking in COPD	38	0

Discussion

The Asian continent is rather large and heterogeneous with marked disparities in social and health care infrastructure in different countries. While some of the countries have very high fiscal indices, the others are either poor or in different stages of economic development. Although these factors are likely to significantly affect the disease prevalence, COPD, interestingly is a problem of great magnitude in almost all these countries.

India can be projected as a classical example with reference to the rising burden of chronic diseases. In a recent estimate, the burden from chronic diseases was estimated to account for 53 per cent of all deaths and 44 per cent of DALYs lost in 2005[2]. Chronic respiratory disease was shown to account for 7 per cent of deaths and 3 per cent of DALYs lost[2].

In our study, correlation between age and disease severity, and age and quality of life, was not found to be statistically significant. However, an analysis of the distribution of patients of different age groups in the GOLD stages showed that majority of patients belonging to lower age groups had less severe disease. Similarly, as the age group increased, the number of patients having more severe disease increased. Therefore there was a trend towards worsening disease with advancing age, though statistical significance could not be established. This may be due to the cumulative effects of smoking with increased age and

the age-related physiological deterioration in lung function. Similar results were obtained in a study done by Charalampos Dimitropoulos *et al* (2009)[7] in 137 Greek patients to study the impact of age on quality of life wherein no significant correlation was obtained between age and health-related quality of life.

In our study, sex of the patient was not significantly correlated to the severity of the disease; however, female patients had worse quality of life as compared to male patients. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men[8-10]. Also, studies have shown that women with COPD have poorer disease outcome as accessed by the health-related quality of life instruments[11]. The PLATINO study[12], a cross-sectional, population-based study which studied the sex-related differences in COPD patients across five Latin American cities also reported increased perception of dyspnoea and physical limitation in females as compared to males .

In our study we measured the body mass index (BMI) of patients as a measure of their nutritional status and BMI was found to be significantly affecting the disease severity and the quality of life of the patients. In the past, studies on BMI and its correlation with COPD have shown that a lower BMI is an independent risk factor for mortality in COPD. Landbo *et al* (1999)[13] in a study of 1,218 men and 914 women concluded that low BMI is an independent risk factor for mortality in subjects with COPD, and that the association is strongest in subjects with severe COPD. However there is no clear evidence as to whether a low BMI is a result of the general debility of patients with severe disease or is an independent risk factor in the causation of the disease.

In our study no significant correlation was found between the socio-economic status of patients and the disease severity and quality of life of patients. Perhaps a larger study group with patients drawn from all socio-economic classes and with detailed adjustments for other risk factors like smoking and occupational/domestic smoke exposure is required to demonstrate the statistical significance of socio-economic status in affecting the disease severity and quality of life in COPD patients.

Studies done in the past have shown that the risk of developing COPD is inversely related to socio-economic status[14]. It is not clear, however, whether this pattern reflects exposures to cigarette smoke, indoor and outdoor air pollutants, crowding, poor nutrition, or other factors that are related to low socio-economic status[14].

In our study, 89% of the subjects had significant history of smoking with 80 out of the total 83 males and 9 out of the total 17 females being smokers. The remaining 11 subjects had positive history of being exposed to indoor pollution – mainly in the form of biomass fuel consumption – underlining the small but definite role of indoor and outdoor air pollution as a risk factor for COPD[15,16-22]. Among smokers, those indulging in multiple forms of smoking had the most severe disease and the worst quality of life followed by *bidi* smokers and cigarette smokers respectively.

These results assume significance as *bidi* smoking is the more prevalent form of tobacco smoking especially among the lower socio-economic classes as it is cheaper as compared to cigarettes. Moreover, the *bidi* bundles do not carry the statutory warning against smoking which is mandatory for cigarette packets.

Exposure to indoor pollution mainly from solid fuel combustion has been shown to be an important cause of chronic bronchitis and COPD in women in studies from India, Nepal, China, South Africa, Turkey, and some other countries. In a study by Behera and Jindal from India, respiratory symptoms were reported in 13 per cent of 3,608 non-smoking women involved in domestic cooking[15].

Therefore, provision of clean domestic fuel and properly ventilated houses may prove to be an important measure in the reduction of the burden of COPD.

Physician awareness about COPD and its modalities which was accessed by a specially designed questionnaire showed that only 81.3% physicians reported treating patients as per the GOLD guidelines. This queistionnaire also highlights the role of the socio-economic status of the patient, and may infact be one of the factors contributing to disease severity and poor quality of life in patients belonging to lower socio-economic strata who were found to be non-compliant to the prescribed treatment.

Another surprising finding was the low awareness about the modalities of physical rehabilitation in COPD with only 60.5% doctors reporting awareness. In India where majority of the patients belong to low socio-economic group and hence affordability and hence compliance to medications is a vexing issue. Physical rehabilitation could serve as an important tool in the management of COPD. All the doctors recruited in the study were aware of the role of smoking (both active and passive), and nutrition of the patient in COPD.

Conclusions

The following conclusions were drawn from the study:-

1. Tobacco smoking, the most important risk factor, was the most common in our study group with 89% of

patients reporting to be smoking.

2. Occupational/domestic smoke exposure also appears to be an important risk factor for COPD with 11% of patients who were non-smokers reporting exposure to domestic biomass fuel smoke.
3. Amongst smokers, *bidi* smokers have more severe disease and a poorer quality of life as compared to cigarette smokers. Patients indulging in multiple forms of tobacco smoking had the most severe disease and the worst quality of life.
4. Although majority of the patients in the higher age groups had more severe disease, no significant correlation was found between age and disease severity and quality of life (QOL).
5. Female patients of COPD had more severe disease and poorer quality of life as compared to males.
6. Nutritional status of the patients is an important factor, and patients with a lower BMI had more severe disease and poorer quality of life as compared to those with higher BMI.
7. In our study, majority of patients belonged to lower socio-economic classes, and as the socio-economic status decreased, the disease severity increased and the quality of life deteriorated. However, a significant correlation between socio-economic status and disease severity or quality of life could not be established in our study.
8. Disease severity was inversely related to the quality of life in COPD patients and this holds true for both males and females and for all stages of disease severity.
9. 84.7% of the doctors who participated in the study were aware of the GOLD guidelines for diagnosis and management of COPD.
10. 81.3% of doctors were treating patients as per the GOLD guidelines with the ill-affordability of medicines by the patients being the desisting factor in the majority.
11. Only 60.5% doctors were aware of the modalities of physical rehabilitation in COPD.

Hence we may conclude that severity of COPD depends on a variety of factors with smoking being the most important. Hence initiatives to spread awareness about the harmful effects of smoking are required and may help in reducing the burden of this disease. Domestic biomass fuel consumption is another important factor which assumes significance in the Indian context where a large proportion of the population resides in rural areas and availability of clean fuel is limited. Physician awareness about COPD and its various modalities was also found to be below the desirable levels. Hence active initiatives may be taken to keep the doctors armed with adequate knowledge to deal with this increasingly prevalent disease.

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CASE REPORT

JIACM 2014; 15(1): 47-8

Chiari network-induced paroxysmal atrial fibrillation

Monika Maheshwari, SK Kaushik***

Abstract

An interesting case report of paroxysmal atrial fibrillation triggered by Chiari's network is reported herein.

Key words: 2D echocardiography, Chiari network, atrial fibrillation.

Introduction

The Chiari network is a reticulated network of fibres originating from the Eustachian valve connecting to different parts of the right atrium. Its presence results from incomplete reabsorption of the right valve of the sinus venosus. We report herein an unusual case of paroxysmal atrial fibrillation precipitated by prominent Chiari network in right atrium.

Case report

An 61-year-old male presented in the emergency room with the complaint of a 2-months history of shortness of breath, palpitation, dizziness, and recurrent fainting attacks lasting for a few seconds. He had no significant past history of ischaemic/valvular heart disease. Physical examination revealed regular pulse at rate of 86/minute with blood pressure of 96/68 mmHg. Clinically, no structural or functional lesion was established on cardiovascular examination. Bilateral chest fields were clear with no adventitious sounds. Blood tests including thyroid functions were normal. Chest skiagram showed a normal-sized cardiac shadow and electrocardiogram revealed normal sinus rhytum. Finally, Holter monitoring (Figure 1) was done for 24 hours which demonstrated paroxysmal atrial fibrillation and transthoracic echocardiographic scan (Figure 2) showed a mobile

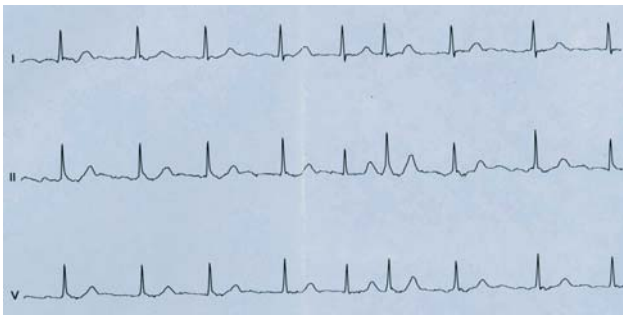

Fig. 1: *Electrocardiogram showing atrial fibrillation.*

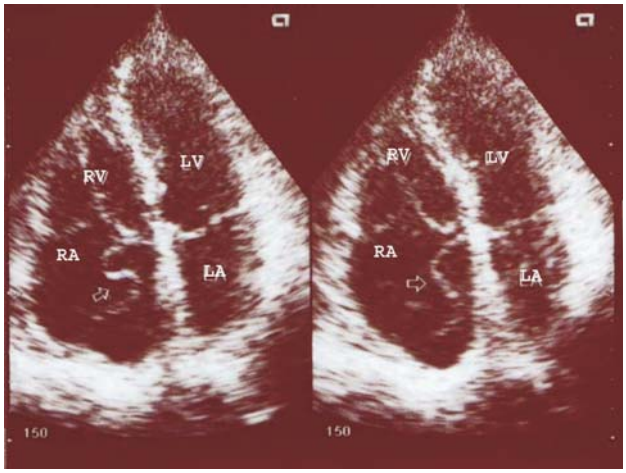

Fig. 2: *Echocardiogram (apical four chamber view) showing Chiari network in right atrium, with whip-like motion (arrow).*

structure in the right atrium, with the characteristic whip-like motion, suggestive of a prominent Chiari's network. There was no atrial septal defect or additional valvular lesion. Left ventricular systolic and diastolic functions were normal. Later on, an electrophysiology study was done which induced no arrhythmias abnormality. Hence, none other than the presence of Chiari's network could explain these episodes. Our patient was advised surgical excision, which he underwent, and till date no recurrence of arrhythmia or syncope has been detected during 2 years of follow-up.

Discussion

The Chiari network was first described in 1897 in an autopsy series by the German pathologist Dr Hans Chiari. Overall prevalence of this network is 2%[1]. This normal anatomic variant maintains an embryonic right atrial flow pattern into adult life and directs the blood from the inferior vena cava toward the inter-atrial septum. It can be confused with some pathological masses in the right atrium like thrombus, vegetation, and myxoma. However,

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thrombus is usually an echogenic mass with well-defined margins, attached to asynergic myocardium with stagnant blood. Chiari's network is usually of no clinical significance. Recently some authors have reported it to be involved in the pathogenesis of arrhythmias[2], athero-embolic disease[3], endocarditis[4], and entrapment of catheters upon percutaneous intervention[5]. It seems that supraventricular arrhythmias are connected with prolonged atrial conduction[6]. Till date, only one case of atrial fibrillation induced by Chiari network has been reported in literature[7]. Hence it was worth reporting this case so as to create awareness among treating cardiologist of this rare clinical entity which can precipitate atrial fibrillation and can be cured successfully by surgical excision of the Chiari network .

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CASE REPORT

JIACM 2014; 15(1): 49-52

Adult Henoch-Schönlein purpura and its clinical implications at a tertiary care centre in the Garhwal hills

Monika Pathania, Kalam Singh Butola**, Vyas Rathaur****

Abstract

Henoch-Schönlein Purpura (HSP) is a small vessel vasculitis mediated by lgA-immune complex deposition. It is characterised by the clinical tetrad of non-thrombocytopenic palpable purpura, abdominal pain, arthritis, and renal involvement. Though it is the most common vasculitis affecting children (over 90% of cases), the occurrence in adults has been rarely reported. There have been no case series in adults presenting with HSP from the hilly regions of Garhwal. We hereby report three cases of HSP in adult residents of Garhwal hills with some typical and atypical signs and symptoms alongwith treatment outcome.

Key words: Leukocytoclastic, tetrad, rash, small vessel vasculitis.

Introduction

Henoch-Schönlein purpura (HSP) is a systemic, generalised vasculitis of unkown aetiology which mainly affects children but can also occur in adult patients. Diagnosis is based on a constellation of physical findings, including: (1) characteristic non-thrombocytopenic petechial or purpuric rash, (2) migratory polyarthralgia, (3) renal involvement, and (4) gastrointestinal involvement[1]. Though it primarily affects children (over 90% of cases), the occurance in adults has been rarely reported (3.4 to 14.3 cases per million)[2]. We analysed the clinical presentation, management, and outcome of three cases with HSP. The diagnosis was made based on the proposed American College of Rheumatology criteria – 1990. All the three patients had a good recovery.

Case 1

A 40-year-old male smoker, a resident of the hills, presented with altered sensorium following headache and two episodes of generalised tonic clonic seizures. His attendants told us that he was apparently well five days back when he had complained inability to walk due to pain and swelling in his ankles and knees bilaterally followed by sudden onset progressive rashes over his ankles which had extended upto his knees over a period of two days. There was a history of sore throat 15 days back which was self-limiting. There was no history of fever, vomiting, drug intake, vaccination, jaundice, insect bite, bleeding manifestation, trauma. There was no past history of hypertension or renal disease. Physical examination revealed temperature 98.5°F, BP - 190/110 mm Hg, PR - 96/min regular; facial puffiness was present. Neurological examination revealed patient to be drowsy when examined in post-ictal phase. On examination after 2 hours, the patient was conscious with normal neurological examination and no signs of meningeal irritation. Fundus was normal bilaterally. Skin examination revealed non-

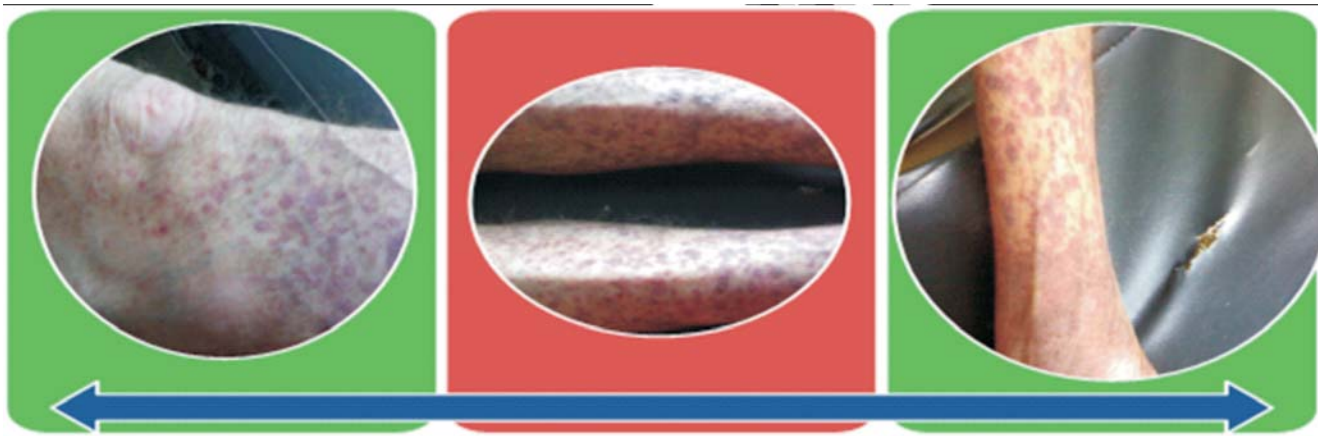

Fig. 1: *Skin rash: Bilateral, symmetrical, non-blanching, palpable purpura with petechiae and ecchymosis in legs up to knees. Colour ranging from deep red to purple.*

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blanching palpable purpuric rash with petechiae and ecchymosis in both lower limbs up to his knees (Fig.1). Joint examination revealed bilateral tender and swollen knee and ankle joints. All other systems were normal. Laboratory values (Table I: Case 1) were normal except for a raised ESR, ASO titre, and proteinuria with haematuria. Imaging study i.e., CT head was normal.

In the presence of characteristic palpable non-thrombocytopenic purpura, arthralgia, and proteinuria with haematuria, a provisional diagnosis of HSP was made. He was treated, as a case of HSP with hypertensive encephalopathy secondary to glomerulonephritis, with IV nitroglycerin, phenytoin sodium, methyl prednisolone 0.5 g for 5 days and continued with oral steroids. He was also started on ACE inhibitors for his proteinuria. There were no seizures afterwards, and his blood pressure was fairly controlled during his course at the hospital. He showed significant improvement in the resolution of skin lesions and arthralgias.

After a 6-week follow-up, the rash had disappeared, hypertension persisted which was controlled by antihypertensives, there was no proteinuria or features suggestive of progressive renal disease.

Case 2

A 31-year-old male smoker, a resident of the hills, presented during the winter season with a week-long history of pain and swelling in his right wrist joint which progressed to involve his left wrist, both elbows, knees, and ankles respectively over one day. He took some over-the-counter (OTC) analgesics from a medical store. The next day he noticed a skin rash which appeared in reverse order as that of his joint involvement. The skin rash extended up to the trunk mainly over his backside over a period of two days, for which he came to our hospital. He denied any history of fever, abdominal pain, bleeding manifestations, or upper respiratory tract infection. Physical examination revealed normal vitals, systemic examination was normal. Skin rashes ranged from erythematous macules to large palpable purpura predominantly over his back, similar lesions were present on the extensor aspect of his lower limbs (Fig. 2). Swelling was noted on his left wrist and both elbows; however, typical rash was absent in the upper limbs. His laboratory investigations (listed in Table I: Case 2) revealed a normal haematological profile except for raised CRP and microalbuminuria with normal renal function tests. He was initially given a single dose of a steroid in the emergency room as management of a drug-induced reaction; later it was stopped and he was managed conservatively. His arthralgia subsided over one week; but skin biopsy was sent to the lab keeping HSP in mind due to the typical rash; and thereafter, the diagnosis of leukocytoclastic vasculitis was confirmed.

His hospital stay was uneventful, and repeat serology was normal. The drug that caused the rash could not be identified.

Case 3

A 25-year-old male smoker presented with a 24-hour history of severe joint and muscle pains. He had intermittent abdominal pain for the previous two weeks and a sore throat for 1 week. He had given history of blackish stool since the last four days. Physical examination revealed a temperature of 98°F and examination of the

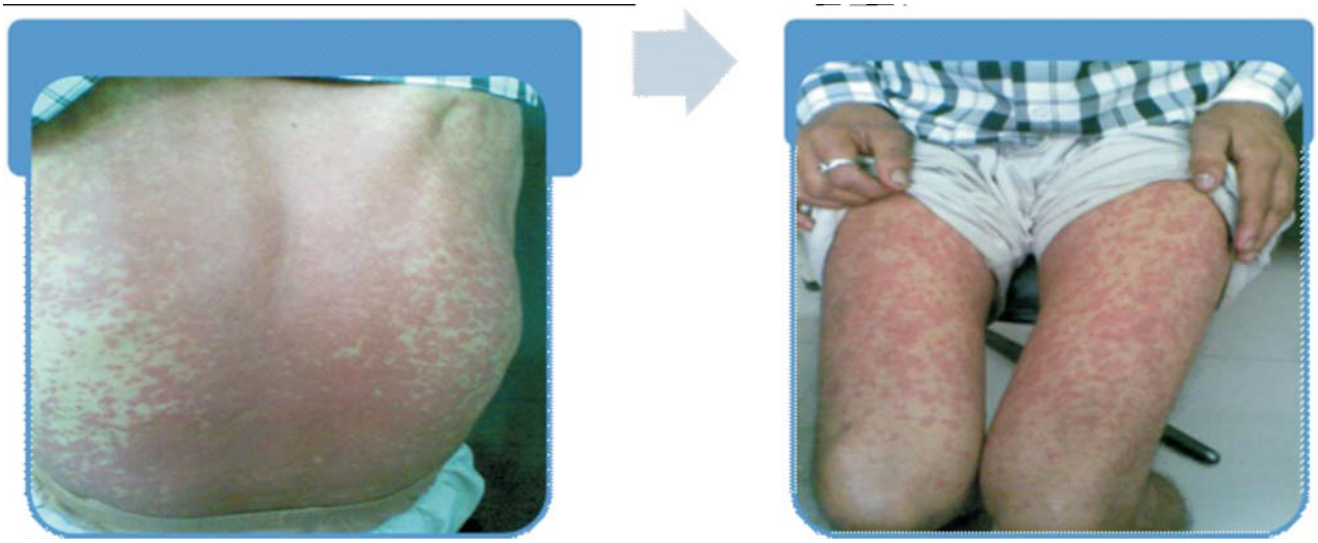

Fig. 2: *HSP (Henoch-Schönlein purpura) rash with predominance on the trunk.*

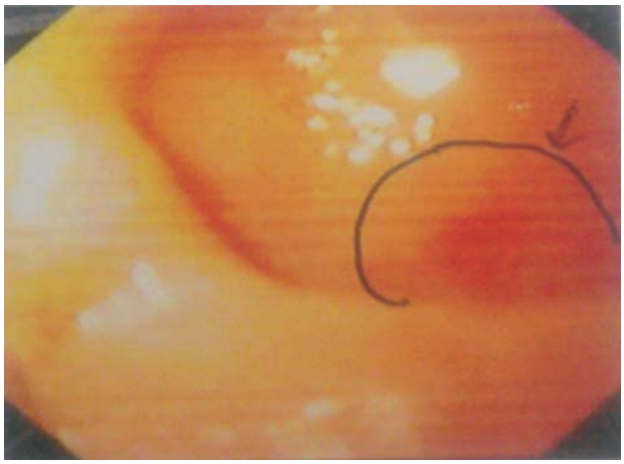

Fig. 3: *Upper GI endoscopy showing duodenal erosions.*

joints showed tenderness and swelling of his elbow and metatarso-phalangeal joints bilaterally. All other joints were normal. On the first hospital day, several 1-cm red macules were noted only over the ankles. On the third day, these lesions had increased in number, and were palpable. Additional lesions in the form of palpable purpurae were noted on the back of the legs and the buttocks. Examination of the gastrointestinal system revealed mild epigastric tenderness but no rebound tenderness; bowel sounds were normal. Other systems were normal. Routine laboratory investigations were normal (Table I: Case 3). Plain radiograph of the abdomen and USG abdomen were normal. Stool was positive for occult blood. Upper GI endoscopy was performed to rule out the source of upper GI bleed. The endoscopy revealed *Helicobacter pylori*-negative gastritis and multiple duodenal erosions (Fig. 3). Treatment with a proton pump inhibitor (PPI) failed to alleviate his symptoms. Based on the physical findings and the palpable purpura, the patient's condition was diagnosed as HSP. Steroids were started on the second day as his pain was not responding to PPIs. Abdominal pain responded dramatically after starting steroids. There was dramatic improvement noted not only in abdominal pain, but also in his joint pains and general well-being. Skin rash also disappeared gradually. Steroid dose was tapered and stopped. Repeat stool examination after one week – when patient was pain free – revealed negative Guaiac test for occult blood.

Discussion

HSP is a multisystem disorder mainly affecting the skin, joints, gastrointestinal tract, and kidneys; but sometimes other organs may be involved. The cases described in this series demonstrate several typical features of HSP but also bring to light several atypical features. HSP is usually considered a disease of children. Three-fourth of all patients with this condition are under the age of seven[3]. Our patients, aged more than 18 years, are atypical in that respect. HSP occurs primarily in males (2:1 ratio), with an incidence of 14 cases per 100,000 population[1]. All our cases were males,

Table I: Clinical presentation, laboratory findings, treatment, and outcome of cases in the study.

Case	Case 1	Case 2	Case 3
Age (years)	40	31	25
Symptoms	Rash, arthralgia, encephalopathy	Rash, arthralgia	Rash, arthralgia, abdominal pain
Eruptions	Lower limbs	Trunk > lower limb	Lower limb, buttocks
White blood cells (/cumm)	10,000	9,500	11,500
Platelet count (/mm^3)	2,30,000	2,00,000	2,52,000
PT/INR	Nl	Nl	Nl
ESR (mm)	45	43	24
CRP (Mg/L)	23 (0-9.9)	18 (0-9.9)	5 (0-9.9)
LFT[a]	Nl	Nl	Nl
S. creatinine (mg/dl)	1.9	1.2	0.9
RA factor[b]	Negative	Negative	Negative
ANA[c]	Negative	Negative	Negative
Hepatitis serology[d]	Negative	Negative	Negative
Proteinuria	2+	1+	Nil
Haematuria	+ ve	Nil	Nil
Imaging	CT head - Normal	Chest X-Ray - Nl	Chest X-Ray - Nl
Skin biopsy	Leukocytoclastic vasculitis, i.e., HSP	HSP	Na
Treatment	Steroids (1mg/kg/day)	Symptomatic	Steroids (1mg/kg/day)
Outcome	Recovery with hypertension persisting	Complete recovery	Complete recovery

a = Liver function test; b = Rheumatoid factor; c = Anti-nuclear antibody; d = Hepatitis B, C, and D.

and all of them were smokers. HSP occurs most frequently in the spring and fall[4]. All three of our patients presented in the winter season, i.e., December and January. The disease is preceded by an upper respiratory or pharyngeal infection in up to two-third of the patients[5,6]. Two of our cases had preceding history of upper respiratory tract infection, while one had a history of drug intake. All our patients had symptoms that are considered classic of HSP: rash, joint involvement, and abdominal pain, except Case 1, who had rare manifestation of seizure along with classic features of HSP. The patient had facial puffiness, hypertension, sub-nephrotic range proteinuria, haematuria which was suggestive of associated glomerulonephritis secondary to HSP. It was this association that probably had led to the hypertensive emergency that precipitated seizures and transient encephalopathy. Skin lesions in this case gradually faded within 2 weeks. Acute kidney injury and proteinuria also improved following steroid therapy. The patient was symptom-free on his follow-up visit. Renal disease has been reported in 20%-100% of patients[7,9]. Two of our patients had transient non-progressive renal involvement[10,12] detected as proteinuria and raised serum creatinine. The short-term outcome of renal disease in HSP is favourable in most patients, with complete recovery reported in 94% of children and 89% of adults[6]. Renal outcome in this patient was good and he is still under regular follow-up to rule out any progressive renal disease. Case 2 had an unknown over-the-counter analgesic drug as a precipitating factor of HSP rash. Rash of HSP in this case was unusual as it had predominance over the trunk, unlike typical HSP rash which occurs over extensor aspect of lower limbs[2]. Cases 2 and 3 had unusual involvement of joints of upper limb mainly elbow, unlike involvement of lower limb joints that is commonly seen in HSP[8]. In addition, case 3 had GI involvement in the form of severe abdominal pain and endoscopically demonstrated duodenal lesions. The reported frequency of gastrointestinal involvement in HSP varies between 57% and 75%[9]. Gastrointestinal symptoms most frequently include abdominal pain[7]. GI bleeding occurred more frequently in adults (59.1%) compared to children (28.3%, p = 0.01)[6]. Case 3 in our study had melaena secondary to the GI bleed.

Conclusion

HSP is the most common childhood vasculitis but it can present in adults as well. There is no specific serologic test to diagnose HSP and diagnosis is made on the basis of clinical suspicion. Physicians should be suspicious of HSP in adult patients who present with clinical manifestations of the disease comprising the characteristic tetrad. Patients with renal involvement should be closely followed. Early recognition of multiorgan involvement, especially outside of the typical age group and proper intervention can mitigate the disease and limit organ damage.

Limiting factors of this case series were its size and short duration follow-up of the patients.

Consent

Written and informed consent was obtained from the patients for publication of their case reports and any accompanying images.

Abbreviations

USG: Ultrasonography; ACE: Angiotensin converting enzyme; GI: Gastrointestinal; CRP: C-reactive protein.

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CASE REPORT

JIACM 2014; 15(1): 53-5

Symmetrical peripheral gangrene and scrotal gangrene in a falciparum malaria case

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Abstract

Peripheral gangrene, characterised by distal ischaemia of the extremities, is a rare complication in patients with falciparum malaria. Though many case reports have been published regarding association of peripheral gangrene and falciparum malaria, in this report, we describe a 40-year-old male who presented with high-grade fever for 6 - 9 days, jaundice, and gangrene which developed at all four limbs; and besides this he also developed scrotal gangrene. Blood smears revealed hyperparasitaemia with Plasmodium falciparum. The most common pathophysiology is disseminated intravascular coagulation (DIC) secondary to malaria infection, although other mechanisms are also involved. In our case there was no any evidence of sepsis, disseminated intravascular coagulation, Raynaud's phenomenon.

Key words: Falciparum malaria, symmetrical peripheral gangrene (SPG), scrotal gangrene.

Introduction

Symmetrical peripheral gangrene is characterised by distal ischaemic damage in 2 or more extremities, without large vessel obstruction. This syndrome has been reported in several conditions such as infections, disseminated intravascular coagulation (DIC), low cardiac output states, and rarely associated with falciparum malaria[1-8]. The microcirculation is compromised in *Plasmodium falciparum* malaria as a result of the adhesion of infected erythrocytes to the vascular endothelium. Rare causes include paraneoplastic syndromes, polymyalgia rheumatica, Raynaud's phenomenon, and sickle cell disease. Vasopressor therapy may be an aggravating factor in septic shock patients. No modality of treatment is universally effective in managing SPG, nor can any single aetiology apply to all cases.

Though falciparum malaria is known for its various pernicious and atypical manifestations, peripheral vascular manifestations are rarely seen[9]. Most of cases reported in the past have found DIC as a common mechanism in the development of SPG in severe malaria. However, several other possible mechanisms may play their role in the development of peripheral ischaemia and subsequent necrosis in severe malaria with heavy parasitaemia. Here we report a case of SPG and scrotal gangrene in severe malaria without any evidence of shock, Raynaud's phenomenon, or DIC[1-9].

Case report

A 40-year-old male patient presented to us with sudden onset blackish discolouration of all toes and fingers and scrotum (Fig. 1, 2, 3). He gave history of high-grade fever associated with chills and rigors 9 days before the onset of discolouration of toes and fingers and scrotum. The patient became unconscious after 2 days and was diagnosed as a case of falciparum malaria and was treated with combination artesunate and clindamycin therapy, after which he regained consciousness on the 5th day. Fever subsided from the 7th day onwards. On the 7th day he noticed swelling over his fingers and toes and scrotum associated with some burning sensation, which, within a period of 2 days progressed to a blackish discolouration involving all toes and fingers and scrotum. There was no history of any underlying disease, alcohol consumption, or smoking. There was no history of ulcer over the toes, Raynaud's phenomenon, oral ulcer, malar rash, chest pain, joint pain, dyspnoea, convulsion, or stroke. Afer complete demarcation of the dry gangrene, the patient was transferred to the surgery department where he had to undergo amputation of the involved digits.

On physical examination, pallor, icterus, dehydration, cyanosis, oedema were absent. Pulse rate was 88/min., regular, normal in volume and character, without radio-radial or radio-femoral delay, all peripheral pulses including the radial and dorsalis pedis were palpable. Blood pressure was 118/68 mm Hg.

His clinical cardiovascular, respiratory, neurological, and abdominal examinations revealed no abnormality. On local examination of hands and feet, there was blackish discolouration of all toes and fingers which were cold, shrunken, and dry, with a definitive line of demarcation, without any local rise in temperature and ulceration. The skin over the scrotum turned dark, shrunken, dry which

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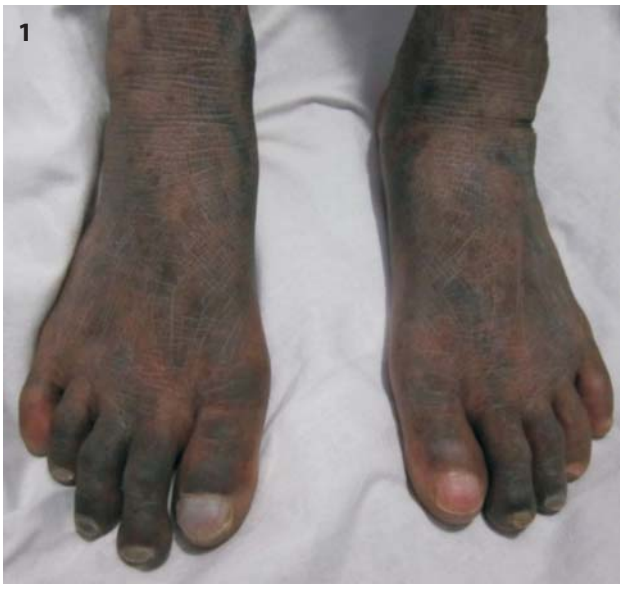

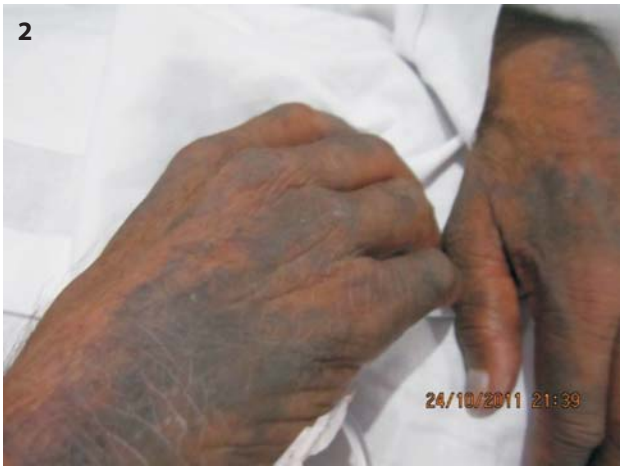

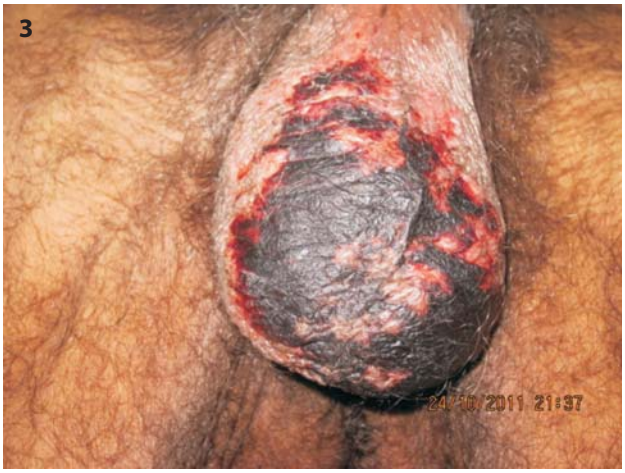

Fig. 1-3: *Symmetrical peripheral gangrene (1, 2) and scrotal gangrene (3) in this case of falciparum malaria.*

was increasing progressively without any ulceration or pus formation.

On investigations, peripheral blood smear for *Plasmodium falciparum* trophozoites was positive. Other laboratory investigations included: Hb - 8.3mg%, total WBC - 6,400 (N66, L28, E2, M4), ESR - 10 mm, platelet count – 2,30,000/cumm, RBS – 106 mg%, S. creatinine - 0.8 mg/dl, total protein - 7.54 mg/dl, AST - 29.8 IU/L, ALT - 33.4 IU/L, alk. phosphatase – 144 IU/L, BT – 1 min, CT - 2 min 20 secs, PT (patient) - 13.5 secs, D Dimer < 0.5. He had cholestatic jaundice (total bilirubin 2.8 mg/dl, direct bilirubin 2.0 mg/dl). Radiography of the chest was normal. Blood and urine cultures, Rh factor, VDRL, Coombs' test were negative. Antinuclear antibody (ANA) test was negative. Doppler study upto radial artery and dorsalis pedis artery demonstrated normal flow. Patient was later transferred to surgery department for further management of scrotal gangrene and peripheral gangrene.

Discussion

Symmetrical peripheral gangrene is an uncommon complication of falciparum malaria reported mainly in Asian countries. The exact pathogenesis for bilateral gangrene remains uncertain and may be multifactoral. Most of the cases reported in the literature were associated with DIC[1-4, 7]. Infected red cells may play an important role in initiating protocoagulant activity or the indirect effects of clotting cascade activation may lead to the blockage of small capillaries and DIC[1, 10, 12]. The presence of tight packing of the parasitised erythrocytes by decreased deformability of red cells or adherence of infected red cells to microvascular endothelium will initiate a microcirculatory obstruction[13]. In *P. falciparum* infections, erythrocyte membrane adhesive protein (PfEMP1) mediates attachment to receptors on venular and capillary endothelium (ICAM-1, VCAM-1, and CD36) – an event termed *cytoadherence*. Thus, the infected erythrocytes stick inside and eventually block capillaries and venules. The processes of cytoadherence, rosetting, and agglutination are central to the pathogenesis of falciparum malaria. They result in the sequestration of RBCs containing mature forms of the parasite particularly in vital organs as well as peripheries in case of SPG where they interfere with microcirculatory flow and metabolism. Heavy parasitaemia causing activation of complement system and activation of coagulation cascade is the triggering factor. Severe malaria is also associated with reduced deformability of the uninfected erythrocytes, which compromises their passage through the partially obstructed capillaries and venules and shortens RBC survival.

Sharma (1987)[2] first described the possibility of vasculitis of cutaneous capillaries of the periphery by the malaria

parasite in addition to an immune vasculitic reaction to the malaria antigen, which resulted in capillary occlusion and epidermal gangrene. Various autoantibodies, such as ANA and antineutrophil cytoplasmic antibodies (ANCA) develop in the presence of falciparum malaria infection (Yahya *et al*, 1997).

The patient described in this report exhibited many clinical similarities. He was heavily parasitised enough to develop cerebral malaria, symmetrical peripheral gangrene, and scrotal gangrene developed in association with microcirculatory obstruction due to malarial infection.

From the study of Edwards (1980)[11], the early management of this condition with heparin or streptokinase was successful specially where tests for disseminated intravascular coagulation were positive. However, bleeding is a complication from anticoagulant therapy, so the patients should have careful monitoring of all clotting factors, and platelet concentrations should be given as soon as they are indicated[11, 12]. In proven cases of malaria, the treatment for severe malaria with intravenous artesunate or quinine should be promptly started. Intravenous nitroprusside, IV prostaglandins (e.g., epoprostenol), topical nitroglycerine ointment, papaverine, reserpine, streptokinase, dextran, hyperbaric oxygen, and sympathetic blockers are tried but with little success. Amputation should be deferred till clear demarcation of the healthy and diseased part takes place; otherwise viable tissue may be sacrificed. Preservation of joint mobility and range of motion is achieved by early physiotherapy. Although development of SPG may be irreversible, further progression can be prevented with early identification and treatment of the cause[10-16].

Conclusion

Symmetrical peripheral gangrene and scrotal gangrene which developed in our case was due to microcirculatory obstruction as a result of *Plasmodium falciparum* infection.

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CASE REPORT

JIACM 2014; 15(1): 56-9

Thrombotic thrombocytopenic purpura in pregnancy: As grave as it comes

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Abstract

Thrombocytopenic thrombotic purpura (TTP) is a microangiopathy affecting the circulation of multiple organ systems. It is a rare entity with an incidence of about 2 to 11 cases per million in the general population. Thrombotic microangiopathies affect about 1 in 25,000 pregnancies. Classical pentad of haemolytic anaemia, thrombocytopenia, fever, alongwith neurological and renal involvement is rare. Herewith, we report the case of an 18-year-old primigravida of 26 weeks gestation diagnosed as TTP, who had a stormy course with posterior reversible encephalopathy syndrome (PRES) alongwith fever, thrombocytopenia, microangiopathic haemolytic anaemia, and acute kidney injury.

Key words: Thrombotic thrombocytopenic purpura, posterior reversible encephalopathy syndrome, classical pentad of TTP.

Introduction

Thrombocytopenia complicates up to 10% of all pregnancies. It occurs in gestational thrombocytopenia, idiopathic thrombocytopenic purpura, pre-eclampsia, malignant hypertension, HELLP (haemolysis, low platelets, elevated liver enzymes) syndrome, sepsis with disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP) - haemolytic uremic syndrome (HUS). A large overlap of clinical features and laboratory parameters in these disease conditions makes an early diagnosis of TTP difficult. Of the three varieties of TTP – idiopathic, secondary, and genetic – secondary is the commonest (up to 60%). And of the various triggers of secondary TTP, none is as potent as the gravid state. Women – either pregnant or postpartum – make up 10 - 25% of cases, suggesting an inter-relationship between the two. However, despite a diagnosis, treatment remains a challenge in view of high maternal and foetal mortality seen in TTP, especially with delayed treatment.

Case report

An 18-year-old, previously healthy, primigravida of 26 weeks gestation was admitted late night with complaints of mild fronto-temporal throbbing headache with scanty clear vomit and low-grade fever since two days. Clinical examination revealed fever of 99°F, mild pallor, and a gravid uterus, but was otherwise unremarkable. Early morning she had an episode of generalised tonic clonic seizure lasting 2 to 3 minutes followed by loss of consciousness. Her blood pressure remained 170/110 mm Hg inspite of giving nifedipine and alpha-methyldopa. Both pupils were equal, reacting to light; bilateral plantars were extensor. Other systems were normal. Scanty cola-coloured urine suggestive of haemoglobinuria was noted upon Foley's catherisation. Urgent MRI brain with venogram revealed features suggestive of PRES (Fig. 1).

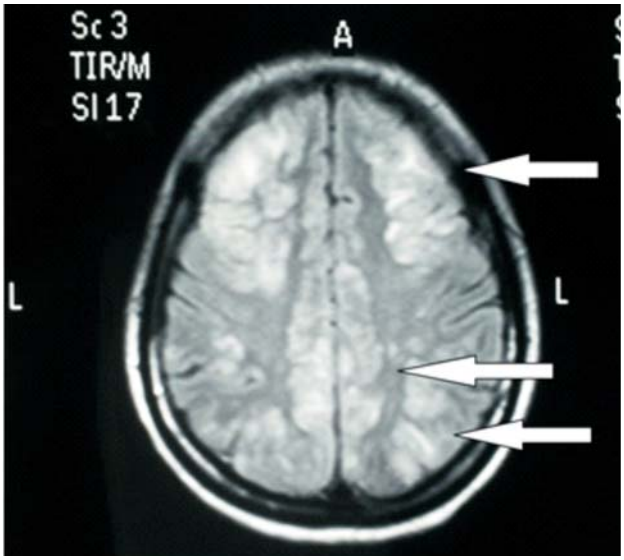

Fig. 1: *MRI Brain showing bilateral high signals in frontal, temporal, parietal and occipital lobes, lentiform nucleus, caudate nuclei (arrows) suggestive of PRES (posterior reversible encephalopathy syndrome).*

Pre-term vaginal delivery was done the same day in view of severe oligohydramnios and intra-uterine growth retardation during which a fresh stillbirth was delivered. The procedure was uneventful. Serial haemograms revealed severe haemolysis (Fig. 2) with thrombocytopenia. Negative blood culture, negative urine culture, reduced urine output and a normal DIC screen (serum fibrinogen, fibrinogen degradation products like D-dimer; prothrombin time and activated partial thromboplastin time) ruled out sepsis and consumptive coagulopathy.

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Typical pentad including microangiopathic haemolytic anaemia (evidenced by schistocytes), thrombocytopenia, fever, renal impairment (oliguria, haemoglobinuria) and neurological involvement (seizures due to PRES) supported the diagnosis of TTP. Elevated lactate dehydrogenase (LDH) levels were corroborative evidence. She underwent 5 sittings of plasmapheresis (therapeutic plasma exchange) with fresh frozen plasma (FFP). Table I shows serial investigations from admission up to discharge. Once clinically stable, she was discharged on day 12.

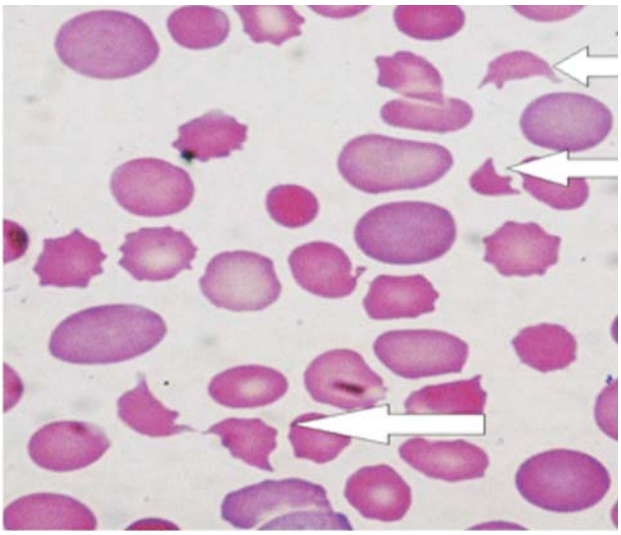

Fig. 2: *Peripheral blood smear showing severe haemolysis and schistocytes (arrows).*

Discussion

TTP or Moschcowitz syndrome, first described by Dr Eli Moschcowitz in 1925, occurs due to deficiency of ADAMTS13. Thus, ultra-large multimers of von Willebrand factor (ULVWF) released from endothelium are not cleaved appropriately, and cause spontaneous platelet aggregates in conditions of high shear, such as in the microvasculature of the brain, heart, and kidneys[1].

Classified as idiopathic, secondary, and familial, TTP (secondary variety) has a strong relation to pregnancy. The reason for this is that pregnancy is associated with increasing concentrations of procoagulant factors, decreasing fibrinolytic activity, loss of endothelial cell thrombomodulin, and decreasing activity of ADAMTS-13. All of these abnormalities worsen through the course of pregnancy until delivery and immediately post-partum[2].

Classic pentad is rare. However, the triad of Coombs'-negative microangiopathic schistocytic haemolytic anaemia, consumptive thrombocytopenia causing severe haemorrhagic diathesis, and fluctuating neurological symptoms can be observed in up to 75% of patients[3]. Due to the high mortality of untreated TTP, a presumptive diagnosis of TTP is made even when only microangiopathic haemolytic anaemia and thrombocytopenia is present. Table II[4] suggests a rational clinico-pathological approach to ruling-out entities with remarkably similar presentations as TTP.

Despite this, the distinction between TTP and HELLP is very difficult. Delivery generally leads to a rapid resolution of pre-eclampsia and HELLP syndrome; however, if no improvement is seen after 48 to 72 hours of delivery, possibility of thrombotic microangiopathies should be considered. The differentiating features between the three are as shown in Table II[5].

Posterior reversible encephalopathy syndrome (PRES) is the predominant brain neuroimaging abnormality in patients with TTP. There is no association between degree of hypertension, haematocrit or platelet count, D-dimer, fibrinogen, lactate dehydrogenase, or total bilirubin levels and occurrence of PRES. The presenting feature can be benign – like headache, vomiting; or severe – like confusion, seizures, visual abnormalities, and motor signs. However, this pathology is completely reversible if the underlying cause is treated early. PRES in TTP is associated with worse renal function.

Plasmapheresis (or therapeutic plasma exchange – TPE) has reduced mortality in TTP from over 90% to 10 - 20%. Earlier initiation correlates with a better prognosis. TPE allows removal of autoantibody, and repletes ADAMTS-13. Large volume plasma infusions are indicated if there is to be a delay in TPE. Daily exchange should continue for minimum 2 days after complete remission, defined as normal platelet count (> 1,50,000/dl). More intensive exchange, such as twice daily TPE, may be required in resistant cases especially with neurological or cardiac events[4]. Immunosuppressive therapy with rituximab may be used singularly or as an adjunctive to plasmapheresis. Recently, intravenous immunoglobulins have been successfully used alone to treat a case of TTP with PRES with other co-morbidities[6]. Maternal mortality in TTP is related to widespread microvascular thromboses and multiple organ dysfunction. Placental infarction leads to foetal intra-uterine growth retardation and/or mortality. Women with previous history who wish to conceive should be counselled and closely monitored for platelet count, haemoglobin, LDH, and peripheral smear throughout the course of pregnancy. Plasma therapy should be started at the earliest evidence of a relapse of TTP. Prophylactic plasma infusion in a pregnant woman with a history of relapsing TTP may be considered[7]. No association of TTP in subsequent pregnancies in women presenting with TTP in an earlier pregnancy can be made. Thus assurance is required for anxious women.

Table I: Showing serial investigations from admission up to discharge.

Investigation	Day 1	Day 3	Day 5	Day 12
Haemoglobin	9.9 gm/dl	6.6 gm/dl	7.6 gm/dl	10.8 gm/dl
Mean corpuscular volume	80.6 fL	76.1 fL	97.7 fL	92.6 fL
Total leucocytic count	22,800 cells/cmm	18,400 cells/cmm	28,300 cells/cmm	11,300 cells/cmm
Differential count	Neutrophils 87% Lymphocytes 7%	Neutrophils 75% Lymphocytes 19%	Neutrophils 72% Lymphocytes 24%	Neutrophils 72% Lymphocytes 24%
Platelets	50,000 cells/cmm	10,000 cells/cmm	30,000 cells/cmm	2,93,000 cells/cmm
Peripheral smear	Normocytic, normochromic picture with no evidence of haemolysis	Microcytic, hypochromic picture; anisopoikilocytosis with schistocytes, and evidence of severe haemolysis	Occasional anisopoikilocytosis, microcytes, macrocytes, polychromatic cells and helmet cells, occasional spherocytes, schistocytes	Normocytic normochromic picture with occasional anisopoikilocytosis
Reticulocyte count		1.5 %		
Urea	35 mg/dl		45 mg/dl	30 mg/dL
Creatinine	0.9 mg/dl		1.1 mg/dl	0.8 mg/dL
Bilirubin				
- Direct	0.5 mg/dl	0.78 mg/dl	0.73 mg/dl	
- Indirect	1.1 mg/dl	1.67 mg/dl	1.93 mg/dl	
Aspartate transaminase	484 IU/L	455 IU/L	69 IU/L	38 IU/L
Alanine transaminase	311 IU/L	268 IU/L	76 IU/L	41 IU/L
Prothrombin time	19.5sec /1.5	215.6sec /1.18	13.1sec /0.97	
APTT activated partial thromboplastin time	27.9 sec	29.9 sec	21.5 sec	
Fibrinogen			344.80 mg/dl (Normal)	
D-dimer	Negative	Negative		
Lactate dehydrogenase	4,687 IU/L	1,187 IU/L	700 IU/L	550 IU/L
ANA			Negative	
Antiphospholipid antibody (IgG/IgM)			Negative	
Blood culture		No growth		
Urine routine	Haemoglobinuria		RBCs 6 - 8/hpf	
Urine culture		No growth		
Chest X-ray	Normal	Normal		
USG abdomen	Single live intra-uterine pregnancy of 25 weeks 6 days with oligohydramnios and asymmetric intra-uterine growth retardation.		Coarse hepatic echotexture with moderate to gross ascites and bilateral pleural effusion. Bulky uterus.	
MRI brain with venogram	Venogram normal. Bilateral high signals are seen in frontal, temporal, parietal and occipital lobes, lentiform nucleus, caudate nuclei, cerebellar hemispheres and brainstem, suggestive of PRES.			

Table II: Typical features in pregnancy-associated micro-angiopathies.

Entity	MAHA	Thrombocytopenia	Coagulopathy	High BP	Abdominal symptoms	Renal impairment	Neurological symptoms
PET	+	+	+/-	+++	+/-	+/-	++
HELLP	+	++	+/-	+	+++	+	+/-
TTP	++	+++	-	+/-	+	++	+++
HUS	+	++	+/-	++	+	+++	+/-
SLE	+	+	+/-	+	+/-	++	+

PET = Pre-eclampsia; HELLP = Haemolysis, elevated liver enzymes, and low platelets; TTP = Thrombotic thrombocytopenic purpura; HUS = Haemolytic uraemic syndrome; SLE = Systemic lupus erythematosus; MAHA = Micro-angiopathic haemolytic anaemia; BP = Blood pressure.

Table III: Differentiating features between TTP, HUS, and HELLP.

Feature	TTP	HUS	HELLP
Neurological features	+++	±	±
Fever	+++	±	-
Hypertension	±	±	±
Renal dysfunction	±	+++	±
Purpura with bleeding	++	-	-
Platelets	Markedly reduced	Moderately reduced	Reduced
PT/APTT	Normal	Normal	Prolonged
Fibrinogen	Normal	Normal	Reduced
BUN/Creatinine	Increased	Increased	Increased
Liver enzymes	±	±	+
LDH	Markedly increased	Moderately increased	Can be increased

TTP = Thrombotic thrombocytopenic purpura; HUS = Haemolytic uraemic syndrome; HELLP = Haemolysis, elevated liver enzymes and low platelets; PT = Prothrombin time; APTT = Activated partial thromboplastin time; BUN = Blood urea nitrogen; LDH = Lactate dehydrogenase.

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"I wish to say what I think and feel today, with the proviso that tomorrow probably I shall contradict it all."

– Ralph Waldo Emerson.

CASE REPORT

JIACM 2014; 15(1): 60-1

Congenital aortic stenosis and patent ductus arteriosus in an adult: A rare combination

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Abstract

One case of aortic stenosis and patent ductus arteriosus is presented. The combination is extremely rare and the clinical diagnosis of aortic stenosis may be missed as the murmur of aortic stenosis may be submerged by the murmur of PDA. Literature review attests to the rarity of the combination. This is the first such case being reported from India.

Key words: Aortic stenosis, patent ductus arteriosus, pressure gradient.

Introduction

Patent ductus arteriosus (PDA) accounts for 15% of all congenital heart defects and is the third most common congenital lesion in a combined series of children and adults[1]. Adult patients with PDA may remain quite asymptomatic for varying periods of time. The association of a PDA with left ventricular outflow tract is common in the neonatal period when the obstruction is critical[2]. However, the prevalence of a PDA in association with aortic stenosis beyond the neonatal period is unknown but appears to be extremely low[3]. We report a case of aortic stenosis in combination with PDA in an adult female.

Case history

One 33-year-old female presented with history of shortness of breath (Class II) since childhood with recurrent respiratory infections. She was being treated in a village hospital where the doctor used to give her intermittent antibiotics for chest infection. There was no history of rheumatic fever and endocarditis.

On examination, the patient was of average body build with a body mass index (BMI) of 22. There was no cyanosis. The pulse was 80/minute, regular and low volume with carotid shudder over the right carotid artery. There was no brachio-femoral delay. The jugular venous pulse was not raised. The blood pressure was 110/70 mm Hg.

Examination of the precordium revealed cardiomegaly with the apex beat at left 6th intercostal space, 2 cm lateral to the mid-clavicular line. There was a continuous thrill at the infra-clavicular and second intercostal space close to the sternum. There was a systolic thrill at the right second intercostal space. The first heart sound was of normal intensity. The second heart sound was buried in the continuous murmur and there was a third heart sound at the apex. There were eddy sounds. A continuous murmur of grade IV/VI was audible in the left infra-clavicular space. There was a mid-diastolic rumble at the cardiac apex. Auscultation of right second intercostal space revealed a harsh ejection systolic murmur (Grade IV/VI) radiating to the right carotid artery. Examination of other systems

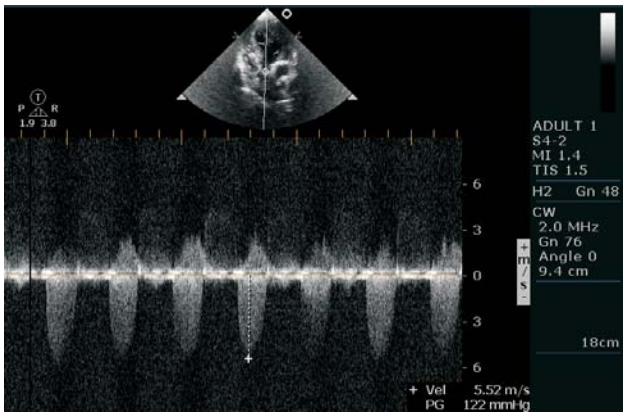

Fig. 1: *Continuous Doppler echocardiography showing gradient across LVOT.*

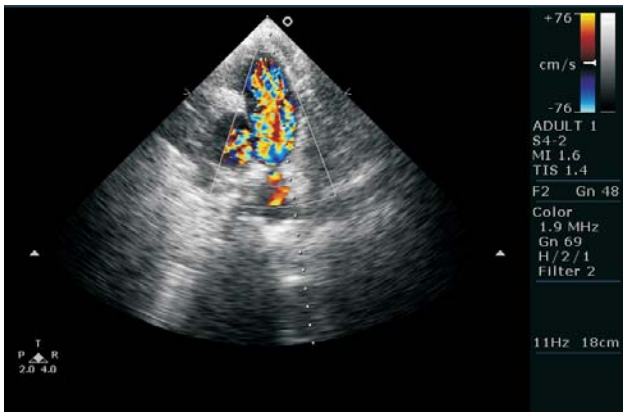

Fig. 2: *Colour Doppler echocardiography showing presence of ductus.*

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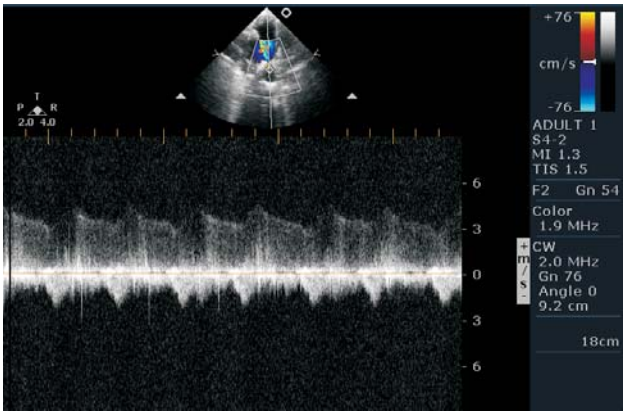

Fig. 3: *Continuous wave Doppler tracing across the ductus.*

revealed no abnormality. A provisional diagnosis of severe aortic stenosis and large patent ductus arteriosus (PDA) was made.

Investigations

The haemogram was normal. The ECG showed left ventricular hypertrophy with strain pattern and left atrial enlargement. X-ray of chest revealed cardiac enlargement (cardiothoracic ratio = 65%) and dilatation of ascending aorta. Pulmonary vascularity was increased.

Echocardiography revealed concentric hypertrophy of the LV with normal function. The aortic valve was thick and trileaflet having unequal cusps. Continuous Doppler echocardiographic examination revealed peak systolic gradient of 122 mm Hg at left ventricular outflow tract. There was no aortic regurgitation. Colour Doppler examination of right ventricular outflow tract revealed continuous signal suggestive of PDA. The aorta to pulmonary artery systolic gradient was 90 mm Hg and the diastolic gradient was 50 mm Hg. The calculated Qp : Qs was 2.2 : 1.

Discussion

A rare combination of severe aortic stenosis with PDA in adulthood is presented. The combination of aortic stenosis with PDA is distinctly uncommon[4]. One study of 146 patients referred for transcatheter closure of PDA reported 20 who had additional heart defects of whom only 3 had LVOT abnormality, 2 with a subaortic membrane and 1 with a bicuspid aortic valve[4]. Rarity of the combination of aortic valve disease and PDA in adults is further borne out by the fact that only nine cases of concomitant aortic valve replacement and closure of PDA in adults were reported till 1994.[4] A review of literature reveals a very small number of case reports of aortic stenosis with PDA[1,4,5].

While assessing the severity of AS by Doppler echocardiography by measuring the peak-to-peak systolic pressure gradient, one should bear in mind that this gradient is dependent on the aortic valve area and the amount of flow across the aortic valve[6]. Therefore, in high-output states, a less severe obstruction may be associated with severe pressure gradient with the converse being true for low output states. Thus, the severity of aortic obstruction may actually be overestimated in the presence of a large left to right shunt across the PDA. One faces the same dilemma while assessing aortic stenosis severity during cardiac catheterisation. That is why it is recommended that when faced with this rare combination of AS and PDA, one should first opt for closure of the PDA. Then, one should assess the severity of AS and decide for aortic valve replacement if the aortic stenosis is found to be severe even after ductal closure[4].

Conclusion

A rare combination of aortic stenosis and PDA is presented. Literature review shows sparse cases of such a combination. When faced with such a situation, the patient should first undergo closure of the PDA followed by reassessment of severity of aortic stenosis.

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"Some things have to be believed to be seen."

– Ralph Hodgson.

CASE REPORT

JIACM 2014; 15(1): 62-4

Pancreatic tuberculosis in an immunocompetent young female

S Prasad, R Manocha**, SK Mahavar***, R Kumar****, B Gupta*****, A Sharma****

Abstract

Pancreatic TB is a rare disease requiring a high index of suspicion for diagnosis in immunocompetent individuals. We report a rare case of pancreatic tuberculosis involving the tail region in an immunocompetent young female without miliary/pulmonary tuberculosis.

Keywords: Pancreatic tuberculosis, immunocompetent.

Introduction

Tuberculosis (TB) infection is a common disease and an important cause of morbidity and mortality, especially in underdeveloped and developing nations. TB infection can affect any body organ. Abdominal TB is one of the most prevalent forms of extra-pulmonary manifestations. Abdominal TB collectively refers to the involvement of the gastrointestinal tract, hepatobiliary system, pancreas, spleen, abdominal lymph nodes, and other abdominal organs[1]. Although extra-pulmonary tuberculosis is an emerging clinical problem, it rarely affects the pancreas alone. Pancreatic tuberculosis usually occurs as a complication of miliary tuberculosis in immunodeficient individuals. Pancreatic tuberculosis among immunocompetent individuals is a rare entity and can be clinically elusive. An experienced eye is required to diagnose peripancreatic tuberculosis based on clinical and laboratory features. There are no radiological features that are pathognomonic of tuberculosis. Fine needle aspiration cytology (FNAC) and definitive biopsy are the primary techniques used for reaching a definitive diagnosis and avoiding surgical complications. We report a rare case of pancreatic tuberculosis in an immunocompetent young female without miliary/pulmonary tuberculosis.

Case report

A 23-year-old young female, resident of Delhi, presented to our hospital with the complaints of non-colicky upper abdominal pain for the last 4 years. The pain was described as a continuous, dull ache, sited at the epigastric, left subchondral and left lumbar region, and was unrelated to meals. There were occasional episodes of dyspepsia. No recent change in bowel habits was reported.

There was a past history of tuberculous left cervical lymphadenitis (FNAC had revealed giant cells). However, the patient took treatment for only 2 months since she developed jaundice after starting ATT (treatment was stopped without consultation with the doctor and since the lymph node regressed she did not visit the doctor again). She also had history of contact with an open case of tuberculosis (first degree relative had pulmonary tuberculosis). There was no history of cough, fever, diarrhoea, constipation, haematemesis or melaena, anorexia, weight loss, or vaginal discharge.

On examination at the time of presentation, the patient was conscious and oriented, with a normal physical built. Patient was acyanotic, nonicteric, and had no evidence of oedema or clubbing. Her vitals were stable. Cardiac examination was unremarkable with normal first and second heart sounds and no added murmur. Chest auscultation revealed bilateral vesicular breath sounds. There was no organomegaly, no abdominal lump palpable, and normal bowel sounds were present on abdominal examination. There were no features of endocrine or exocrine pancreatic insufficiency.

Laboratory investigations revealed a haemoglobin of 11.0 gm%, leucocyte count of 6,500/dl (P70, L26, M2, E2) and a platelet count of 2,24,000/dl. Her ESR was 45 in the first hour. Her KFT, LFT, blood sugar, and serum electrolytes were within normal limits. Serological tests for HIV, hepatitis B and C were negative. A chest radiograph exhibited no abnormal findings. Her ultrasound abdomen was unrevealing. A CECT abdomen showed a bulky pancreatic tail with multiple small hypoechoic lesions and subtle peripancreatic shadowing along with multiple necrotic nodes with peripheral enhancement in peripancreatic, paraaortic and mesenteric areas. A FNAC done from the tail region of the pancreas revealed granulomas with epitheliod cells. The patient was started on anti-tubercular therapy (with regular monitoring of LFT) to which she responded

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favourably with a decline in ESR, weight gain, and is presently asymptomatic. A repeat CT examination of the abdomen revealed regression of the lymph nodes and resolution of the pancreatic lesions.

Discussion

Patients in immunocompromised states, such as those with human immunodeficiency virus (HIV), are particularly susceptible to TB infections, both pulmonary and extrapulmonary[2] and in this group of patients, extrapulmonary (especially abdominal TB) involvement predominates. Our patient was not immunocompromised and was previously diagnosed of extra-pulmonary tuberculosis but was noncompliant to treatment.

One study showed that among those with abdominal TB, the small bowel (especially ileocaecal region) was the most commonly affected site (33.8%), followed by the peritoneum (30.7%), large bowel (22.3%), liver (14.6%), and the upper gastrointestinal tract (8.5%)[3]. Tuberculosis of the pancreas is a rare disease and is sparsely reported in medical literature. In immunocompetent individuals with military tuberculosis, infection of the pancreas by *Mycobacterium tuberculosis* is rare. In the largest autopsy series of 1,656 tuberculosis patients, fourteen patients had pancreatic tuberculous involvement; however, all had widespread miliary tuberculosis. None of the patients had isolated involvement of the pancreas[4]. In a study from India, post-mortem analysis of 300 patients with miliary tuberculosis over a period of 12 years did not reveal a single patient with pancreatic involvement. Isolated pancreatic involvement in the absence of miliary tuberculosis is even rarer[5].

This low incidence has been attributed to the pancreatic enzymes which interfere with the seeding of *Mycobacterium tuberculosis*. Some possible mechanisms of pancreatic infection may be pulmonary disease leading to lymphatic and haematogenous spread to the pancreas, ingestion of infected material from an active pulmonary lesion, reactivation of latent tuberculosis in the pancreatic focus, a toxic-allergic reaction of the pancreas involving an inflammatory response to mycobacterial antigens and direct extension from adjacent organs such as the lymph nodes[6].

The evaluation of suspected cases can be divided into three stages. The first two stages involve clinical and radiological evaluations, and usually provide indirect evidence of the presence and location of the involvements. Confirmation is required in the more invasive third stage, where tissues samples are obtained for histological and microbiological evaluations.

Feng *et al* have summarised characteristics of pancreatic TB as follows:

1. Mostly occurs in young people, especially females;
2. Have a past history of TB, or come from an endemic zone of active tuberculosis;
3. Often present with epigastric pain, fever, and weight loss;
4. Ultrasound and CT scan show pancreatic mass and peripancreatic nodules, some with focal calcification[7].

Our patient too, had presented in this typical pattern.

Tuberculosis of the pancreas presents with nonspecific symptoms like fever, abdominal pain, weight loss, and anorexia[8,9]. It has been reported to present as obstructive jaundice, gastrointestinal bleed, acute or chronic pancreatitis, pancreatic mass mimicking malignancy, pancreatic abscess, portal venous thrombosis causing portal hypertension and even colonic perforation[10,11]. The diagnosis of pancreatic TB is a real challenge. The challenge is partly because of the rarity of the disease itself, and partly due to its insidious presentation, with nonspecific signs and symptoms. Hence there is often a need to request radiological investigations.

Ultrasonography reveals focal hypoechoic lesions or cystic lesions of the pancreas[12]. Findings on CT scan include hypodense lesions and irregular borders mostly in the head of the pancreas, diffuse enlargement of the pancreas, or enlarged peripancreatic lymph nodes[13]. Ring enhancement or low density areas within enlarged lymph nodes must raise suspicion of tuberculous lymph nodes.

Pancreatic tuberculosis most commonly involves the pancreatic head, followed by the body and the tail[13]. Our case had involvement of the tail region of pancreas and hence ultrasonography may have failed in our case to identify the site of infection due to poor visualisation of the tail region.

Nagar *et al*. reviewed 32 patients having pancreatic tuberculosis, of which 14 patients had a history of pulmonary tuberculosis while 18 had primary pancreatic/peripancreatic tuberculosis. Ultra-sonography, in their cases, showed a bulky inhomogeneous pancreas in five patients and solitary or multiple hypoechoic collections in 27 patients. Twenty-nine patients showed hypodense collections within the pancreas along with peripancreatic lymphadenopathy on CT scan. The remaining three patients had a complex pancreatic mass lesion[14].

Pancreatic tuberculosis is a well known masquerader, and the diverse clinical and radiological picture of this chronic infection may be revealed as a variable pancreatic lesion. There are no radiological pathognomic signs of pancreatic

tuberculosis. Extensive surgical procedures for this often misdiagnosed, medically treatable condition, are not unheard of. Owing to availability of curative pharmacotherapy, recognition of this disease process is vital before we embark on the tedious and risky surgery for treatment. The definitive diagnosis is based on histological and bacteriological evidence of disease.

Pre-operative FNAC and tissue biopsy help avoid unnecessary surgical interventions and the morbidity and mortality of serious operations. Endoscopic ultrasound (EUS) is being increasingly used these days for imaging and fine needle aspiration of solid or cystic pancreatic masses[15]. It is now considered the preferred imaging modality for the diagnosis of pancreatic masses[16]. However, it is a technically difficult procedure with a longer learning curve compared to CT or ultrasound guided percutaneous needle biopsies. In a recent randomised controlled study, comparing EUS-guided biopsy and CT- or US-guided biopsy for determination of pancreatic mass aetiology, no statistical difference was found in terms of accuracy[17]. In our case, USG guided FNAC served our purpose well.

The microscopic features suggestive of tuberculosis are the presence of caseating granulomatous inflammation and positive stain for acid-fast bacilli (AFB). Cultures for mycobacteria take up to 6 weeks to grow and are used to confirm the diagnosis. However, it must be remembered that bacteriological confirmation may not be possible in many patients[18]. The polymerase chain reaction (PCR)-based assay is a highly specific assay and may give a positive result even when special staining techniques and cultures of these tissues are negative[19].

Once the tissue diagnosis has been made, the management of TB rests on the medical treatment. The treatment of pancreatic tuberculosis comprises multi-drug anti-tuberculous chemotherapy. Response to therapy is predictable and complete.

Conclusion

Pancreatic TB is a rare disease requiring a high index of suspicion for diagnosis in immunocompetent individuals. Its indolent course and vague symptomatology along with non specific laboratory and radiological features call for greater vigilance. Because almost all cases of pancreatic TB are responsive to antituberculosis management, every effort should be made to arrive at an early diagnosis so as to avoid unnecessary interventions, including laparotomy.

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"When anger rises, think of the consequences."

– Confucius (c. 550 - c. 478 BC).

CASE REPORT

JIACM 2014; 15(1): 65-7

Extensive cortical venous thrombosis associated with protein S deficiency and hyperhomocysteinaemia

Susanta Kumar Das, Niloy Banerjee**, Sudarshan Khaskil**, Sabyasachi Mukhopadhyay***

Abstract

Thrombosis of the cerebral venous sinuses, particularly of the superior sagittal sinus and tributary of cortical and deep veins, gives rise to a number of important neurologic syndromes. Our patient, a 49-year-old male presented with severe right-sided headache for four months and was found to have normal CT brain parenchyma. High index of suspicion leads to detection of cortical sinus thrombosis by magnetic resonance (MR) venography. Subsequent evaluation revealed severe protein 'S' deficiency and hyperhomocysteinaemia. Such an uncommon combination of protein 'S' deficiency and hyperhomocysteinaemia causing cortical venous thrombosis has never been reported.

Keywords: Cortical venous thrombosis (CVT), protein S deficiency (PSD), hyperhomocysteinaemia.

Introduction

Cortical venous thrombosis (CVT) is a distinct cerebrovascular disorder that mostly affects young adults. The estimated annual incidence is 3 to 4 cases per 1 million, with 75 per cent of the adult cases occur in women[1]. The clinical symptoms vary and may include severe headache (90%), focal lateralised signs (50%), seizures (40%) as well as behavioural symptoms such as delirium, amnesia, and disturbances in consciousness[1]. In about 70% of the CVT cases, the causes are secondary, and in 30% cases, it is associated with genetic prothrombotic conditions, such as deficiency of antithrombin III, protein C, or protein S, mutation of factor 'V' or prothrombin genes, resistance to activated protein C and hyperhomocysteinaemia.

Case report

A 49-year-old male non diabetic, non hypertensive, non alcoholic but chronic smoker and strict vegetarian presented with right-sided headache and heaviness since the last four months. Initially it was intermittent in nature without any specific aggravating or relieving factors and not relieved by medication. There were no history of nocturnal awakening due to headache, head trauma, convulsion, vomiting, weight loss, or prolonged fever, or any history of endocrinopathy. Patient also complained of transient visual obscuration at the onset of illness with rapid recovery. There was no history suggestive of significant bladder, bowel, motor, sensory system involvement. Past, personal, and family history were non-contributory. General examination was within normal limits. On nervous system examination, no abnormality was detected except bilateral papilloedema on fundoscopy, other systemic examination was within normal limits.

Investigations revealed mild anaemia (haemoglobin 11.5 gm%), haematocrit, platelet count, white cell count, and ESR were within normal limits. Mean corpuscular volume (MCV) was 109 fl. Serum B_{12} was low (value 120 ng/L; normal 160 - 200 ng/L). RBC folate and serum ferritin were normal. Lipid profile, urea, creatinine, plasma sugar, liver function tests, urine were within normal limits. CT scan brain (plain + contrast) revealed no parenchymal abnormality but empty delta sign (a triangular area of non-enhancement

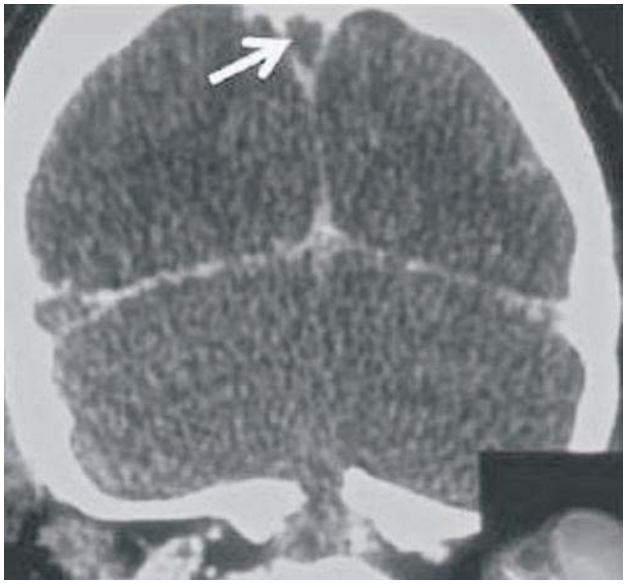

Fig. 1: *Contrast CT brain (coronal section) shows non-enhancing triangular area (white arrow) surrounded by enhancing dura – empty delta sign.*

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surrounded by enhancing dura in contrast CT brain) was present (Fig. 1). CSF study showed high pressure (more than 200 mmH_2O), but was otherwise normal. Therefore, we strongly suspected a case of pseudo-tumour cerebri (benign intracranial hypertension) and did MR venography. MR venography revealed (Fig. 2) non-visualisation of superior sagittal sinus, inferior sagittal sinus, sigmoid sinus, and straight sinus. Peripheral venous Doppler study of both upper and lower limbs were normal. Both internal jugular veins were thrombosed at the level of hyoid bone. USG abdomen and CT scan thorax were within normal limits. Then we did coagulation profile for hereditary or acquired coagulopathies six weeks after initial presentation. Investigations revealed antithrombin III was 22.5 mg/dl (normal: 0.5 - 35 mg/dl), protein C was 94.7% (normal: 70 - 130%), protein S was 10% (normal: 93.5 - 126.5%), homocysteine was 33.2 µmol/L (normal: 3.7 - 13.9 µmol/L), anticardiolipin antibodies IgG and IgM were 5.6 GPL and 2 MPL respectively (within the normal limit). Lupus anticoagulant and ß$_2$GPI were negative. Factor V Leiden mutation was absent. Serum protein electrophoresis was within normal limits. Family screening for hereditary thrombophilia was performed and was found to have protein S deficiency (35%) in his only son of 25 years age.

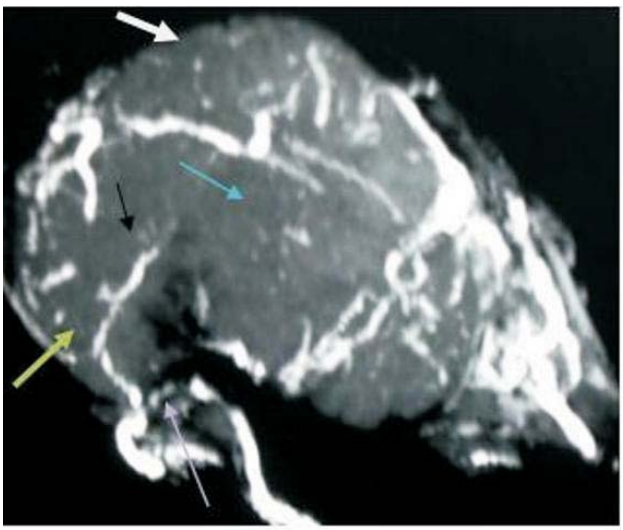

Fig. 2: *MR venography brain (coronal section) revealed non visualisation of superior sagittal sinus (white arrow), inferior sagittal sinus (blue arrow), straight sinus (black arrow), transverse (yellow arrow) and sigmoid sinus (purple arrow).*

From the above investigations, a diagnosis of hereditary severe protein S deficiency along with hyperhomocysteinaemia causing CVT was made.

Discussion

Thrombosis of the cerebral venous sinuses, particularly of the superior sagittal sinus and tributary of cortical and deep veins, give rise to a number of important neurologic syndromes. Cerebral vein thrombosis may develop in relation to infections of the adjacent ear and para-nasal sinuses[2]. Other causes include severe dehydration, medication, hereditary coagulopathies, systemic diseases, trauma, or idiopathic causes. They usually present with venous infarctive stroke. In case of sagittal sinus thrombosis, intracranial hypertension with headache, vomiting, and papilloedema are the usual presenting features. Contrast-enhanced CT scan, arteriography (venous phase), MR venography greatly facilitate the diagnosis by directly visualising the venous occlusion. In veno-occlusive stroke, a large vasogenic oedema forms and it appears early (1 hour). This vasogenic oedema influences the formation of new collateral vessels and neovascularisation. In this way, large parenchymal changes can be dissolved completely with or without recanalisation of thrombosed veins and sinuses[3]. This can explain normal brain parenchyma in CT scan in CVT, as seen in our case.

Hereditary PSD is an autosomal dominant condition, resulting in a 50 per cent chance of passing the disease to one's offspring[4]. Less than half of those diagnosed with PSD will experience thrombosis and those who do, usually are affected only from the age of the late teens onwards. His only son also has protein 'S' deficiency but without any past history suggestive of any thrombotic event and was advised a regular follow-up.

Hyperhomocysteinaemia occurs due to either genetic mutation or secondary causes. The secondary causes of hyperhomocysteinaemia are chronic renal failure, deficiencies of vitamin B_{12} and folate, hypothyroidism, smoking, excessive coffee intake, inflammatory bowel disease, psoriasis, and rheumatoid arthritis. Our patient was a strict vegetarian and chronic smoker and his serum B_{12} level was low. These factors could have caused hyperhomocysteinaemia in our patient. Hyperhomocysteinaemia has not been known to cause CVT directly, but it is an established risk factor for CVT. When it is associated with other inherent anticoagulant deficiencies like protein C, protein S (as in our case), it inhibits the activation of protein C and protein S, so the chances of developing CVT increase manyfold[5].

Testing of coagulation profile should not be done immediately after an event. In general, thrombophilia testing should be delayed by at least 4 - 6 weeks to allow acute-phase reactant proteins to return to the baseline[6]. Family screening is necessary to determine hereditary thrombophilia. Most often, the treatment for CVT includes prevention or reversal of cerebral herniation with IV mannitol, or decompressive hemicraniectomy and/or removal of haemorrhagic infarct with surgical

procedures. In addition, oral acetazolamide (500 to 1,000 mg daily) – a carbonic anhydrase inhibitor, may be administered to reduce the intracranial pressure. Anticoagulation therapy with heparin may be used to arrest the thrombotic process and to prevent haemorrhagic infarction. Thrombolysis (endovascular thrombolysis) by administration of a thrombolytic enzyme, urokinase, into the sinus has also been tried in some CVT cases with limited success[7]. Our patient was managed with IV heparin for several days, followed by warfarin for lifelong along with folic acid (1mg/day), vitamin B_6 (10 mg/day), vitamin B_{12} (0.4 mg/day) and acetazolamide (750 mg/day).

Two months after his discharge, all the symptoms were subsided. Serum homocysteine level was decreased (20 µmol/L). Further imaging study could not be possible as patient was not willing for it.

Late age of presentation of hereditary thrombophilia, normal CT brain parenchyma despite extensive cortical sinus thrombosis and an uncommon combination of protein 'S' deficiency and hyperhomocysteinaemia causing cortical venous thrombosis has never been reported to the best of our knowledge.

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"It requires wisdom to understand wisdom;
the music is nothing if the audience is deaf."

– Walter Lippman.

CASE REPORT

JIACM 2014; 15(1): 68-70

Osteomalacia: An unusual presentation and a brief overview

S Sompura, R Jain**, A Pandey**, AK Gupta***, P Jain*****

Abstract

Osteomalacia is the softening of bones caused by defective bone mineralisation secondary to inadequate amount of available phosphorous and calcium or because of overactive resorption of calcium from bone as a result of hyperparathyroidism. The most common cause of this disease is a deficiency of vitamin D which is normally obtained from diet and/or exposure to sunlight. A 22-year-old female presented to us with complaints of backache and multiple bone pains since the last 1-1.5 years. X-ray skull showed multiple punched-out lesions suggestive of the possibility of multiple myeloma or secondaries. On further evaluation, this patient was diagnosed as a case of osteomalacia with iron deficiency anaemia. Possibility of multiple myeloma, secondaries, and oncogenic osteomalacia was ruled out. The patient improved remarkably with vitamin D3 and calcium supplementation. In reporting this case we tried to observe any differences in the clinical presentation other than those mentioned in literature and highlight the need for a proper diagnostic work-up and treatment in such cases.

Key words: Osteomalacia, multiple myeloma, diagnostic work-up.

Introduction

Osteomalacia is softness of bones most commonly due to lack of vitamin D or any problem with body's ability to activate and use this vitamin. Softer bones seen in persons with osteomalacia have a normal amount of collagen – which gives the bone its structure – but lack proper amount of calcium. In children, this condition is called rickets. Dietary deficiency of vitamin D, malabsorption, and poor exposure to sunlight are common causes. Some cancers (oncogenic osteomalacia), kidney failure, liver disorders, phosphate depletion, hereditary disorders of vitamin D metabolism, antiepileptics drugs excess can also cause osteomalacia. The patient presents with multiple bone pains, muscle weakness, bone fractures. Characteristic radiological findings are Looser's zones, pseudo-fractures, and protrusio acetabuli[1-4]. Oncogenic osteomalacia is a tumour-induced osteomalacia due to tumours in sinuses, bone, skin that resolves after removal of the tumour. Phosphatonin peptide is released from the tumour that leads to phosphaturia resulting in osteomalacia. Multiple myeloma with light-chain nephropathy, hypo-phosphataemia or as a part of Fanconi syndrome can lead to osteomalacia. Vitamin D 10,000 U per week for 4 - 6 weeks along with calcium supplementation is the treatment modality used in cases of osteomalacia[11-17].

Case report

A 22-year-old female came to our clinic with complaints of backache, multiple bone pains, generalised weakness since last 1 - 1.5 years. Her family, medical, surgical, drug history was unrevealing. The patient's LFT, RFT, serum uric acid, urine (routine & microscopic exam.), thyroid profile were within normal limits. She was found to be anaemic with Hb - 9.1 gm% and ESR - 38 mm. RA factor was negative, iron profile was in favour of iron deficiency anaemia. S. calcium - 8.12mg/dl, S. phosphate-2.29 mg/dl (both were low) with alk. phosphatase in higher range, i.e., 489.4 U/l. X-ray skull showed multiple punched-out lesions suggestive of multiple myeloma and secondaries (Fig. 1). X-ray of lumbo-sacral spine and pelvis showed fish-shaped intervertebral disc with pseudo-fractures of

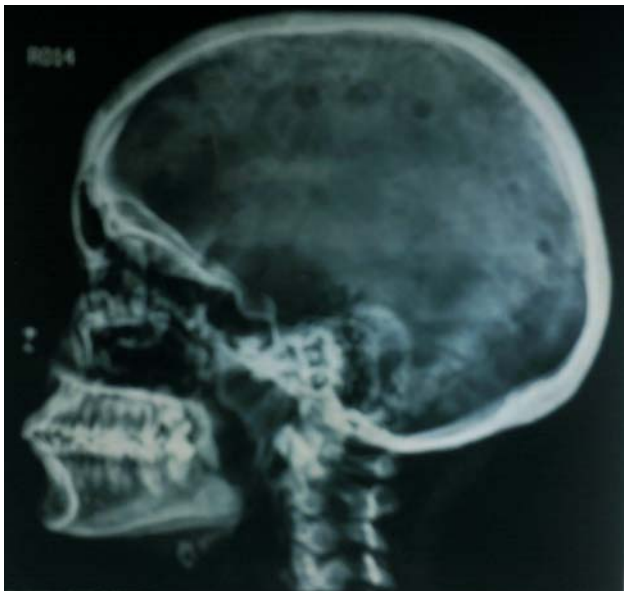

Fig. 1: *X-ray of skull showing multiple punched-out lesions suggestive of multiple myeloma or secondaries.*

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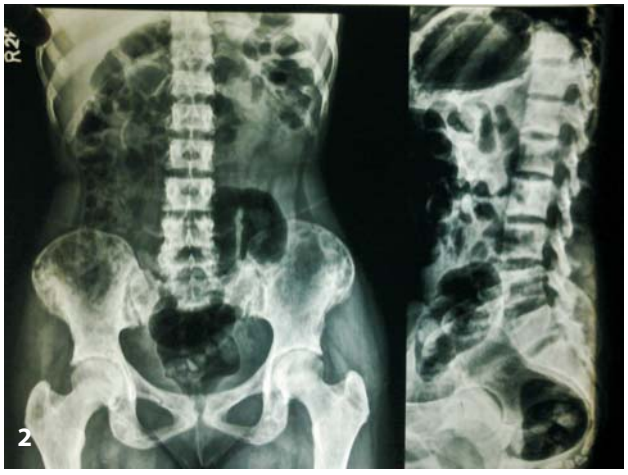


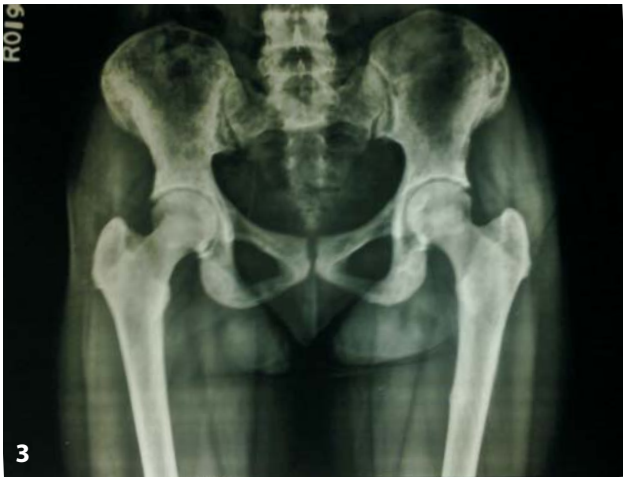
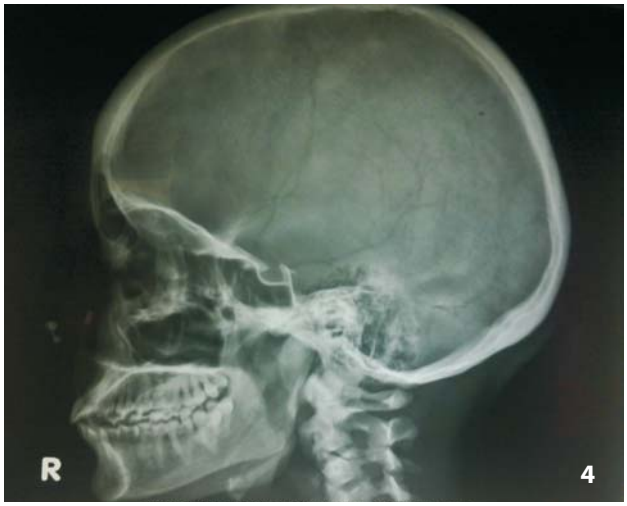


Fig. 2 & 3: *X-rays of pelvis showing typical changes of osteomalacia prior to treatment.*



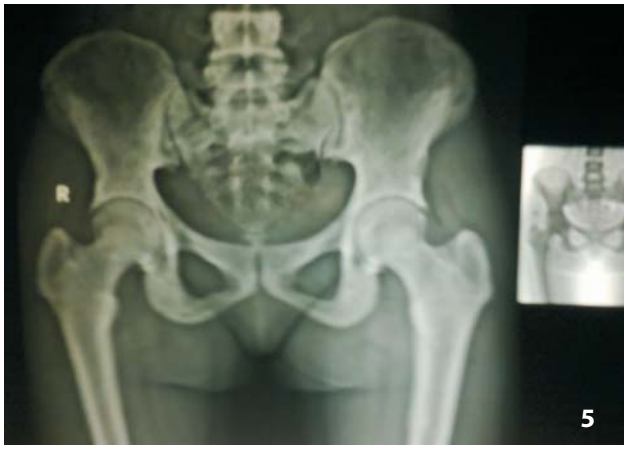


Fig. 4 & 5: *X-rays of skull and pelvis showing remarkable improvement after vitamin D and calcium supplementation.*

superior ramus of right pubic bone, cystic rarefaction in either side of iliac bone/pubic rami, partial lumbarisation of S1 giving probability of osteomalacia (Fig. 2, 3). Bone mineral density was normal with a T score of 0.9. Technetium bone scan showed increased uptake. The patient's vitamin D3 level was very low (10.9 ng/ml) and PTH leval was high (78 pg/ml), further confirming a diagnosis of osteomalacia. To exclude multiple myeloma, serum protein electrophoresis was done which was normal; Bence-Jones protein was absent in urine. To exclude the possibility of tumour, CT head, X-ray Water's view, chest X-ray, and USG whole abdomen and pelvis were done, but no abnormality was detected in any of these (Figure 6). The patient was given vitamin D3 10,000 U per week for 6 weeks along with calcium supplementation. During subsequent investigations, calcium and phosphate level improved and alkalne phosphatase returned to normal; also, radiological parameters improved and the patient showed remarkable clinical improvement (Fig. 4, 5).

Discussion

Osteomalacia means "soft bones". Osteoid is the bone protein matrix, composed primarily of type 1 collagen. When there is insufficient mineral or osteoblast dysfunction, the osteoid does not mineralise properly, and it accumulates. When the newly formed bone of the growth plate does not mineralise, the growth plate becomes thick, wide, and irregular. This results in the clinical diagnosis of rickets, and is seen only in children because adults no longer have growth plates. When the remodelled bone does not mineralise, osteomalacia occurs, and this happens in all ages. Most of the hereditary causes of osteomalacia appear during childhood and cause rickets. Osteomalacia is usually caused by a lack of vitamin D. Vitamin D regulates the bone-building process and the way the body handles calcium and phosphate which are used in the formation of strong, hard bones. Vitamin D deficiency is actually very common, but it must be severe and prolonged for osteomalacia to develop. The lack of vitamin D also leads to muscle weakness, which is also a part of osteomalacia.

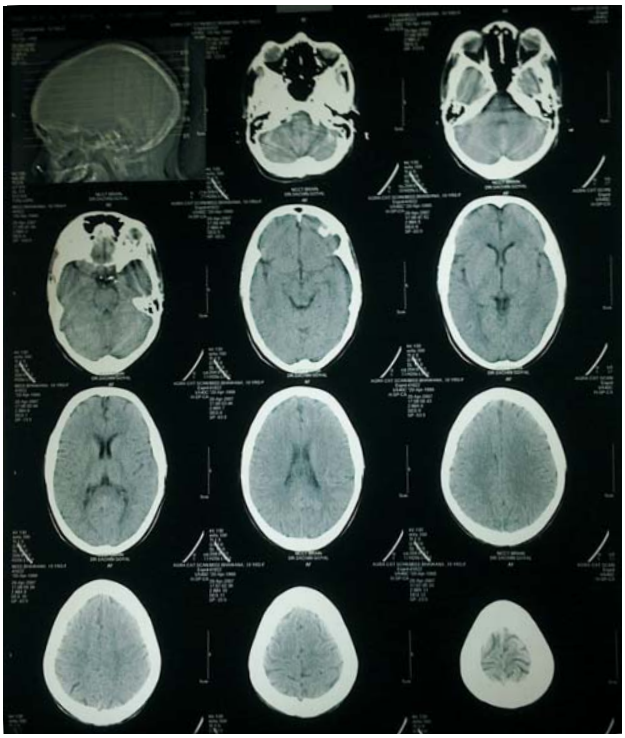


Fig. 6: *CT Head-normal done to rule out any tumour leading to oncogenic osteomalacia.*

Most of our vitamin D is made in the body by the action of sunlight on the skin. This means that people who stay inside or who cover up their skin, struggle to make enough vitamin D. Black and Asian people need more sunlight exposure to their skin to make vitamin D. The elderly and housebound are particularly at risk. Lack of sunlight on the skin is the *main* reason that people get osteomalacia. Very little vitamin D is found in our food, although some foods do contain a little. Examples of foods relatively rich in vitamin D include: oily fish (such as herring, sardines, pilchards, salmon, tuna, and mackerel) and egg yolk. Some of our foods are fortified with vitamin D, such as infant formula milk, margarine, and some cereals. Certain groups of people need more vitamin D than others. For example, pregnant and breast-feeding women. Some medical conditions and some medicines increase the likelihood of vitamin D deficiency and consequent osteomalacia. There are some rare inherited conditions that affect bone mineralisation and cause osteomalacia. Aluminium poisoning is another rare cause. Osteomalacia may be suspected from one's medical history, symptoms, or lifestyle (risk factors for vitamin D deficiency). A blood test can check vitamin D levels. Liver function blood tests and calcium and phosphate levels are also measured as they may detect problems with the liver or bone that are linked to osteomalacia. Sometimes osteomalacia shows up on an X-ray, but X-rays are not usually necessary. Usually, the symptoms plus blood tests are enough to make the diagnosis. Extra tests may be needed if the cause of the osteomalacia is in doubt, or if there are other vitamin or mineral deficiencies. More tests may be needed if one has another medical condition which is contributing to the problem. The usual treatment is vitamin D supplements. This is a form of vitamin D called ergocalciferol or calciferol. Rarely, if osteomalacia is not caused only by vitamin D deficiency, other treatments may be needed. In our case multiple punched-out lesions seen on the skull X-ray confused the picture between multiple myeloma/secondaries and osteomalacia; but on further work-up this proved to be a case of osteomalacia and the patient responded to calcium and vitamin D supplementation. Also, punched-out lesions seen in a skull X-ray are an alert that osteomalacia can have such varied clinical presentation[5-10].

Conclusion

Presenting this unusual case of osteomalacia we emphasise that such a varied clinical presentation (other than that given in literature) needs further diagnostic work-up and appropriate treatment.

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CASE REPORT

JIACM 2014; 15(1): 71-2

Empty sella syndrome with co-existent arachnoid cyst in a case of hypopituitarism: Co-incidence or association?

M Manjula, BC Mithra*, NK Seetharam***

Abstract

Empty sella syndrome (ESS) may remain asymptomatic or present with neurological, endocrine, or systemic manifestations. We present a 38-year-old female patient presenting with features of hypopituitarism and magnetic resonance imaging of brain showing empty sella turcica with co-existent arachnoid cyst.

Introduction

In empty sella syndrome (ESS) – though not uncommon – fewer than one-third of individuals ever develop symptoms. ESS accounts for 4% cases of hypopituitarism. The presenting complaints may be neurological, endocrine, or systemic. Panhypopituitarism is encountered in 10% cases of ESS. Pituitary failure occurs if more than 90% of the tissue is compressed/atrophied. ESS may be primary (pituitary/arachnoid cyst, incompetent diaphragm causing herniation, raised intracranial pressure) or secondary (infarction of pituitary adenoma, post-surgery, post- radiation).

Case report

A 38-year-old female patient presented with the chief complaints of loss of appetite, generalised weakness, loss of weight, and vomiting – all of 3 months duration. There was history of irregular menstrual cycles (2 - 3 days/5 - 6 months) with her last menstrual period 6 months back. There was no history of lactational failure following previous childbirth. There was no history of fever, headache, visual disturbances, rhinorrhoea or galactorrhoea.

On examination, our patient was conscious, oriented, emaciated, and lethargic. Pulse - 60/min, regular, blood pressure – 80/60 mm Hg. Cardiovascular system, respiratory system, and per abdomen examination revealed no abnormality. Optic fundoscopy was normal.

Her investigations revealed Hb of 10 gm%, total count of 6,000, platelet count of 2,00,000, ESR – 50 mm, RBS < 50 mg/dl, urea = 26 mg/dl, creatinine = 0.9 mg/dl.

Serum bilirubin = 0.9 mg/dl (direct = 0.4), SGOT = 23 mg/dl, SGPT = 19 mg/dl.

Ultrasonography of abdomen – Normal study.

HIV and HBsAg – Negative.

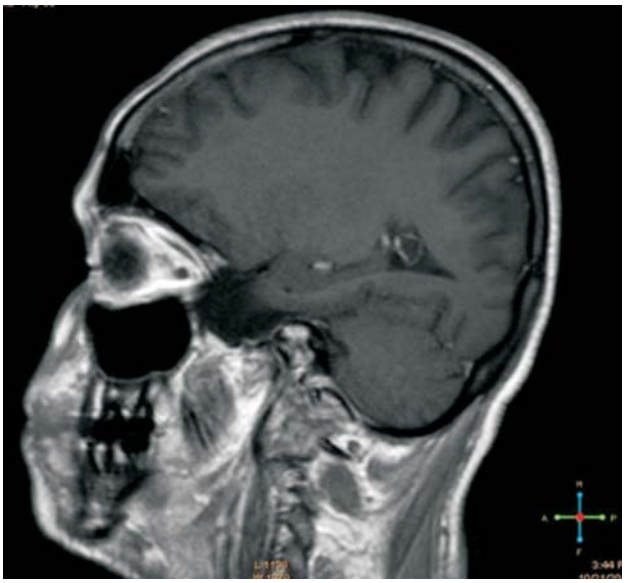

Fig. 1: *MRI of brain showing arachnoid cyst.*

FBS – 30 mg/dl, PPBS – 35 mg/dl (the next day).

Serum electrolytes revealed persistent hyponatraemia (< 125 mEq/L).

There was no response to IV fluids, anti-emetics, and antacids.

Serum cortisol (8 AM sample) was 3.60 µg/dl (NR = 6.7 - 22.6 µg/dl).

T3 = 0.14 ng/ml (NR = 0.5 -1.85 ng/ml), T4 = 0.16 µgm/dl (NR = 4.8 -11.6 µgm/dl).

Serum thyroid stimulating hormone (TSH) = 2.94 µU/ml (NR = 0.28 - 6.82 µU/ml).

Growth hormone (GH) was 0.07 ng/ml (very low).

Adreno-corticotrophic hormone (ACTH) was < 5 pg/ml (Normal-range = 0 - 46 pg/ml).

Follicular stimulating hormone (FSH) = 6.07 IU/l (NR = 8 - 22).

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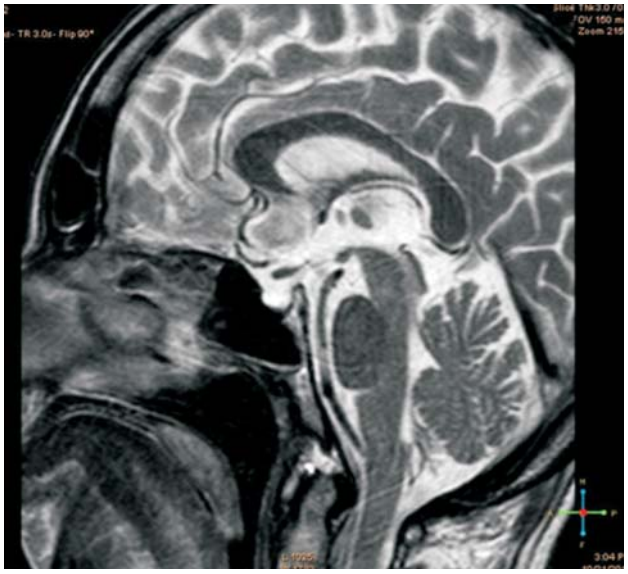

Fig. 2: *T1W MRI of brain showing empty sella turcica.*

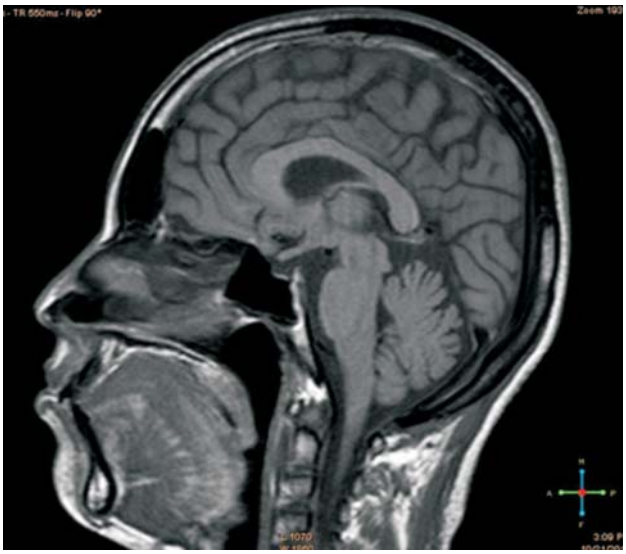

Fig. 3: *T2W MRI of brain showing empty sella turcica.*

Luteinising hormone (LH) = 2.28 IU/l (NR = 18.4 - 61.3 IU/l).

Prolactin (PRL) = 4.92 µg/l (NR = 1.2 - 19.2 µg/l).

In view of two trophic hormones being reduced, growth hormone stimulation tests carried little value.

In view of low serum cortisol, low ACTH, low GH, inappropriate TSH for the very low T3/T4 levels, a diagnosis of hypopituitarism was established.

MRI brain (Fig. 1-3) showed:

1. Severely thinned-out pituitary gland with prominent CSF in the pituitary fossa s/o empty sella.
2. Arachnoid cyst (3.5 x 1.1 x 2.4 cm) along anterior and medial aspect of the left temporal region.

Discussion

Clinical studies of patients with ESS have revealed a variety of associated features and it seems likely that several aetiologic factors are involved. Most common hormone deficiency is GH (30%) followed by TSH (15%), LH (15%) and ACTH (11%). PRL may be high due to functional stalk compression. 50% patients of primary ESS present with features of benign intracranial hypertension. Causes for secondary ESS may be hypertension, raised intracranial pressure, burnt-out pituitary adenoma, ruptured arachnoid cyst in intrasellar location, post-inflammation, or post-radiation. Arachnoid cyst may remain asymptomatic and may be only an incidental finding. However, 20% are associated with symptoms. They may be primary (congenital) or secondary (acquired, post- arachnoiditis). The symptoms may vary by the size and location of the cyst. Beneditti *et al* in 1977 reported co- existence of ESS and arachnoid cyst. Since then, 22 such cases have been reported which raises the possibility of raised intracranial pressure in the aetiology. Whether the co-existence is inter-linked or incidental, still remains unclear.

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CASE REPORT

JIACM 2014; 15(1): 73-4

Multiple wasp stings – An unusual cause of reversible akinetic Parkinsonism

B Sehgal, N Malhotra**, J Dhanoa**, V Loomba**

Abstract

Wasp stings are a common occurrence especially in people living in close proximity of forested areas all over the world. The clinical manifestations of wasp sting are varied – ranging from mild local reaction to severe anaphylaxis. The rare but serious manifestations comprise of myocardial infarction, pulmonary oedema, bleeding manifestations, haemolytic anaemia, renal failure,stroke, encephalitis, acute disseminated encephalomyelitis, Parkinsonism, polyneuritis, Guillain-Barré syndrome. We report a rare case of wasp sting induced extra-pyramidal manifestations in the form of akinetic rigid Parkinsonism which developed 2 days after multiple wasp stings.

Keywords: Wasp sting, neurological manifestations, reversible Parkinsonism.

Introduction

The clinical manifestations of wasp sting are variable, generally causing local reactions in the form of pain, wheal, flare and swelling, which are usually self-limiting. The other severe manifestations include myocardial infarction, pulmonary oedema, bleeding manifestations, renal failure and life-threatening anaphylactic shock[1]. Neurological manifestations of wasp sting are uncommon and delayed in onset (Sachdev *et al*)[1]. Various central and peripheral nervous system presentations have been described including wasp sting encephalopathy, cerebral infarction, optic neuropathy, polyradiculopathy, neuromuscular junction disorders[1].

Case report

An 85-year-old lady presented to the emergency department with history of being stung by numerous (described by onlookers as 50 - 100) wasps while passing through a rural semi-forested district in Himachal Pradesh, India. She was stung predominantly on the scalp, face, neck, upper limbs, and trunk which was followed by a local reaction in the form of swelling, pain, and redness. Following this, she received antihistaminics and analgesics at a local hospital. About 48 hours later she developed difficulty in speech, stiffness, and abnormal posturing of all four limbs. There was no history of altered sensorium, convulsions, weakness of limbs, sensory symptoms, and bowel or bladder disturbances. A previous history of wasp sting could not be confirmed.

On admission, she was conscious and oriented, her vital parameters were normal. General physical examination was normal except for an erythematous rash over her left hand, neck, face, and upper trunk. She also had macular lesions on the face, and periorbital puffiness. Higher mental functions and cranial nerve examination were normal. She had extra-pyramidal dysarthria. Motor system examination revealed normal power and preserved reflexes, lead pipe rigidity and dystonic posturing without tremors in all four limbs. Sensory and cerebellar system

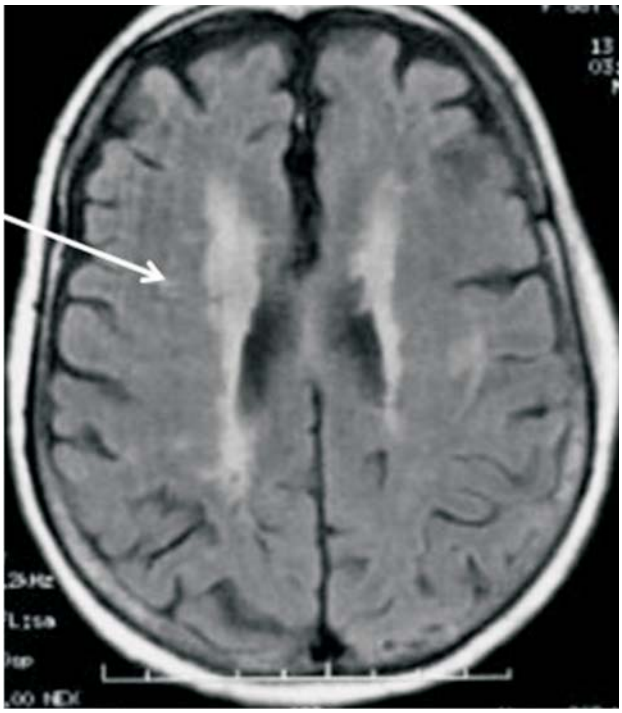

Fig. 1: *Magnetic resonance imaging of brain showing bilateral periventricular hyperintensitites in the region of corona radiata and basal ganglia on T2 FLAIR.*

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examination was normal. There were no signs of meningeal irritation.

A thorough laboratory evaluation was undertaken which revealed haemoglobin 12.4 gm%, total leucocytes count 15,500 cells/cumm, (differential leukocyte count – polymorphs 79, lymphocytes 18, monocytes 2, eosinophils 1), erythrocyte sedimentation rate 38mm in first hour, platelet count 1,34,000/cumm, fasting blood sugar 94 mg/dl, urea 120 mg%, serum creatinine 2.9 mg%, Na^+ 138 meq/L, K^+ 4.1 meq/L, Cl^-101 meq/L. Liver function tests, lipid profile, electrocardiogram, and chest X-ray were normal. Enzyme-linked immuno-sorbent assay (ELISA) for HIV was negative. Her magnetic resonance imaging (MRI) of brain in T2W and FLAIR images showed hyper-intense signals in bilateral periventricular white matter and brain stem (Fig. 1). Electroencephalography (EEG) was normal. She was administered injection methylprednisolone intravenously for three days and all symptoms and signs resolved promptly and renal parameters became normal.

Discussion

Hymenoptera stings occur quite frequently. The Hymenoptera family includes the Apidae (honeybees and bumblebees) and the Vespidae (wasps, hornets, and paperwasps), which usually stay in colonies[2]. The venom contains several chemical compounds which have been postulated to be responsible for its clinical features. It includes enzymes (phospholipases, hyaluronidase), polypeptides or protein toxins (e.g., apamin, melittin, kinins), and amines (histamine, serotonin, dopamine, norepinephrine, and acetylcholine)[3]. Epidemiology studies have found the peak incidence of wasp stings in the month of August. Two types of reactions are usually associated with wasp stings: local or systemic. A local reaction is generally characterised by pain, swelling, redness, itching, and a wheal surrounding the wound made by the stinger – this is mainly mast cell mediated type 1 anaphylactic reaction[4]. Some allergists believe that about 0.4 - 0.5% of the general population is hypersensitive to Hymenoptera venom[5]. A substance known as precipitin is the cause of life-threatening laryngeal oedema, or anaphylactic shock in stings and is of rare occurrence[8]. Life-threatening anaphylaxis accounts for most deaths from Hymenoptera stings and are a result of dysfunction of the body's immune system whereby the venom allergens react principally with cell-bound specific IgE to induce massive release of anaphylotoxins[6]. Multiple stings can lead to vomiting, diarrhoea, generalised oedema, dyspnoea, rhabdomyolysis, intravascular haemolysis, and renal failure. The various neurological manifestations are presumed to be immune-mediated and are late complications of Hymenoptera envenomation[1]. These include Guillain-Barré syndrome, multiple sclerosis, optic neuritis, Parkinsonism, and transverse myelitis. The possible mechanisms of the CNS involvement include immunologically mediated damage or the direct affection of the apamin receptors by the venom[7].

Regarding the treatment of the acute episode, antihistaminics along with analgesics and supportive care is enough. But systemic involvement warrants the use of steroids, so we used methyl-prednisolone in the present case, and the patient responded to the therapy very promptly.

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"Learn, learn, learn... otherwise you get soft and stupid.
Stay vibrantly alive."

– Alden James.

CASE REPORT

JIACM 2014; 15(1): 75-7

Coumarin-induced skin necrosis

A Bansal, P Melmane***

Abstract

Coumarin-induced skin necrosis is an uncommon, catastrophic complication of oral anticoagulant therapy. A substantial number of cases occur in association with a familial protein C or S deficiency. An acquired protein S deficiency secondary to development of antiphospholipid antibodies has also been reported. We describe the case of a 40-year-old male patient who developed skin necrosis during warfarin treatment for cerebral venous thrombosis. A gradual approach, using low-dose warfarin and achieving a therapeutic INR in 10–12 days would lessen the risk without compromising the treatment. The necrotic skin areas, sometimes heal spontaneously with or without scarring, but usually require surgical intervention.

Key words: Warfarin, anticoagulation, protein S, thrombus.

Introduction

Coumarin-induced skin necrosis (CISN) is usually an unpredictable complication of warfarin therapy, occurring in 0.01 - 0.1% of warfarin treated patients, occasionally leading to death[1]. It was first described in 1943. It is also known as warfarin-induced skin necrosis (WISN). A small number of cases occur in association with familial deficiency of protein C[2] or protein S[3]. An acquired deficiency of protein S secondary to development of antiphospholipid antibodies has also been implicated[4]. Onset is usually between the third and eighth day of warfarin therapy, with development of frank necrosis 36 - 72 hours after onset of the initial skin lesion. The patient most commonly complains of pain in a region of abundant subcutaneous fat, with progression to erythema, petechiae, and gangrenous necrosis. Thrombosis of the dermal and the subcutaneous veins is demonstrated pathologically. Differential diagnoses include purpura fulminans, necrotising fasciitis, microembolisation and pressure sores. With the increasing number of patients anticoagulated as out-patients for thromboprophylaxis, we are concerned that the incidence of skin necrosis may increase. If skin necrosis does occur, prompt remedial action may be of benefit in preventing permanent tissue damage. We describe a case and review the pathogenesis, treatment, and prevention of this lesion.

Case report

A 40-year-old male weighing 55 kgs with a BMI of 21.9, presented with weakness of bilateral lower limbs with headache and vertigo for 4 days. The patient had no significant premorbid risk factors and illnesses. Neurological examination revealed a conscious, cooperative patient with intact higher functions with deficit only in the form of right lower limb monoparesis (power grade 4) with right plantar reflex being extensor. MRI brain revealed early subacute thrombosis of superior sagittal sinus and left transverse and sigmoid sinus. He was started on enoxaparin (0.4 ml s.c. twice daily) and warfarin (5 mg daily) therapy. On the 3rd day of initiating the treatment, the patient developed erythematous lesions on the back, arms, and legs (Figure 1), which progressed to necrotic lesions over the next 2 days (Figure 2). Dermatological reference revealed the possibility of CISN. Warfarin was discontinued immediately. Functional protein C level was normal (79%), but both functional protein S (29%), and antithrombin III level (72%) were decreased. Biopsy results two weeks later showed necrosis, haemorrhage, epithelial degeneration, damage to precapillary arterioles, dermal and subcutaneous vessels thrombosis, and tissure oedema, thus suggesting the diagnosis of CISN. The necrotic areas were treated with hydrogel and later by topical antimicrobials to prevent infections. Subsequently, the lesions healed with scab formation. Keeping in view the gravity of the

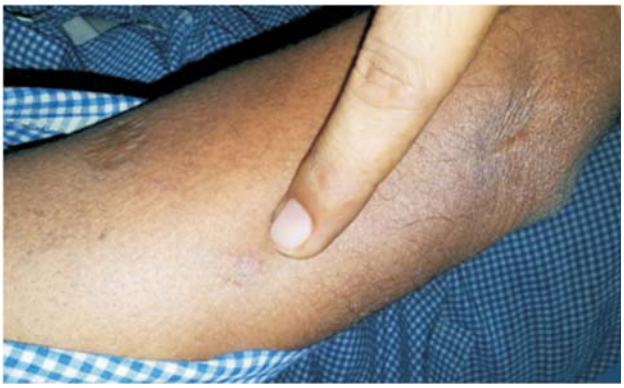

Fig. 1: *Erythematous lesion over right arm on day 3 of initiating warfarin.*

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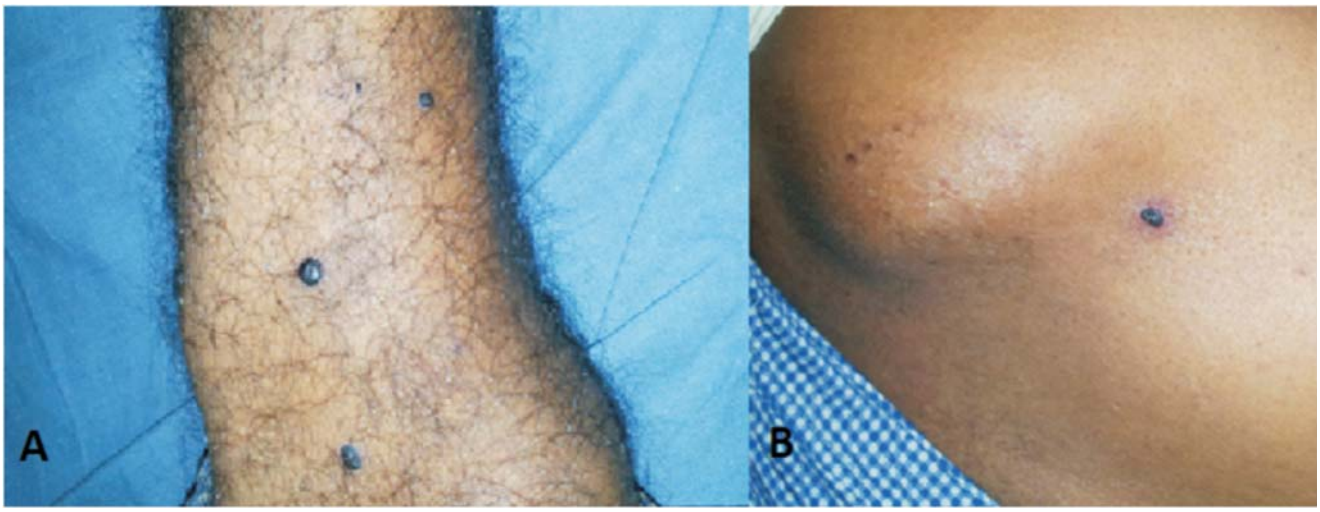

Fig. 2: *Necrotic eschars appeared on day 4 on (A) left leg and (B) back.*

neurological problem, the patient was rechallenged with low dose warfarin (2 mg daily) with further increase to 3.5 mg daily. During the last 6 months of anticoagulation with the said dose, the patient is clinically stable, with no recurrence of the lesions, and INR being in the therapeutic anticoagulation range.

Discussion

CISN usually appears 3 - 8 days after initiating warfarin treatment in susceptible individuals, although it may appear later. It is more common in females and frequently affects areas with abundant subcutaneous fatty tissue such as breasts, thighs, and buttocks. In males, the penis is affected while the breasts are spared. Biopsy of the skin shows fibrin and platelet thrombi in small dermal vessels with no evidence of inflammatory infiltration. Haemorrhagic necrosis and subepidermal bullae may also occur. Protein C is a vitamin K dependent protein that, in association with protein S, inactivates activated factors V and VIII, down-regulating thrombin formation and coagulation. They also promote fibrinolysis through TPA inactivation. The pathogenesis is believed to be secondary to a more rapid initial reduction in blood levels of vitamin K-dependent anticoagulants (proteins C and S) than the procoagulants (factors II, IX, X) during the warfarin anticoagulation, although other factors may also be involved. The lowering of protein C level occurs much earlier, as the half-life of protein C is much shorter compared with most of the procoagulant factors (protein C, 6 - 8 hours vs. factor VII, 6 hours; factor IX, 24 hours; factor X, 40 hours; factor II 60 hours)[5]. This would paradoxically render a temporary hypercoagulable state in the patient. In those patients already deficient in the natural anticoagulants, i.e., protein C, protein S and antithrombin III, this hypercoagulable state is further amplified resulting in the development of thrombi in the microvasculature of the skin. Notably, the prothrombin time (or international normalised ratio, INR) used to test the effect of warfarin is highly dependent on factor VII, which explains why patients can have a therapeutic INR (indicating good anticoagulant effect) but still be in a hypercoagulable state. This results in the clinical picture of CISN. Late onset CISN is accompanied by inflammatory infiltrate, its localisation is different, and treatment depends on discontinuation of the drug and administration of steroids. Although protein C deficiency has been implicated in less than 50% of cases, the association of protein S and antithrombin III deficiency has been reported[6]. Lupus anticoagulant has also been associated with skin necrosis. Skin necrosis usually occurs after warfarin therapy with large loading doses (i.e., > 10 mg)[6]. Low-dose heparin administration for a few days to gain a good anticoagulation (PTT = 60 - 80) and then giving low-dose oral warfarin in CISN patients is possible.

Conclusion

CISN is a rare but serious complication of coumarin therapy, associated with high morbidity and mortality rates, and often requires surgical intervention. Early recognition has important implications for treatment and reduction in severity of complications. It is suggested that a more gradual approach, using low-dose warfarin and aiming to achieve a therapeutic INR in 10 - 12 days would lessen this risk without compromising the treatment of patients who are being electively anticoagulated[7]. Patients known to be at risk of CISN (those with a previous episode, protein C or S deficiency and antiphospholipid antibodies) should also be warfarinised in this gradual

way[8]. Conventional heparin and low molecular weight heparin act by a different mechanism than warfarin, so these drugs can also be used to prevent clotting during the first few days of warfarin therapy and thus prevent warfarin necrosis (this is called 'bridging').

Since the clot-promoting effects of warfarin are transitory, patients with protein C deficiency or previous warfarin necrosis can still be re-started on these drugs if appropriate measures are taken. These include gradual increase in dosage of warfarin starting from low dose, and supplemental administration of protein C (pure or from fresh frozen plasma), if required.

Direct thrombin inhibitors such as rivaroxaban, apixaban, dabigatran have been found to be equally potent as warfarin with decreased incidences of intracranial bleed, reduced need of monitoring and no risk of CISN. Increased awareness and timely action about this complication may prevent devastating necrotising dermatological complications.

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"Friendship improves happiness and abates misery,
by the doubling of our joy, and the dividing of our grief."

– Marcus Tullius Cicero.

CASE REPORT

JIACM 2014; 15(1): 78-9

Progressive disseminated histoplasmosis in an immunocompetent patient misdiagnosed as disseminated tuberculosis

R Kashyap, D Gupta**, Neelam Gupta*, P Machhan***, Ranvijay****, Preyander*****

Abstract

Progressive disseminated histoplasmosis is common in immunocompromised patients, but in an immunocompetent individual infection is either asymptomatic or mild and self-limiting. Diagnosis is through clinical suspicion; fungal culture remains the gold standard diagnostic test, which is often negative in less severe cases. We report the case of a 48-year-old immunocompetent male patient with progressive disseminated histoplasmosis with unilateral adrenal involvement.

Key words: Histoplasmacapsulatum, disseminated histoplasmosis, tuberculosis, immunocompetent, Himachal Pradesh.

Introduction

Histoplasmosis is caused by a dimorphic fungus – Histoplasmacapsulatum. The disease is worldwide in distribution. Sporadic cases have been reported so far in India[1]. Progressive disseminated histoplasmosis is rare in adults who are immunocompetent. Progressive disseminated histoplasmosis occurs in 1 in 2,000 cases of adults who are immunocompetent. Hepatosplenomegaly is a significant mode of presentation as reported by some Indian authors[1]. We report the case of a 48-year-old male who presented with progressive disseminated histoplasmosis as a result of prolonged exposure to dust soiled with pigeon droppings masquerading as disseminated tuberculosis and treated with anti-tubercular drugs for three months.

Case report

A 48-year-old male diagnosed as a case of disseminated tuberculosis three months back – by FNAC of cervical lymph node – who was on regular anti-tubercular drugs since then, presented with worsening of his symptoms in the form of progressive breathlessness, low grade fever, loss of appetite and weight. His history was reviewed and it was found that there was continuous exposure to dust soiled with pigeon droppings right in front of his room windows which were opening outdoors.

On clinical examination, our patient had a pulse rate of 94/min regular, BP of 120/80 in right arm, respiratory rate 16/min, temperature 100 degrees F, and pallor was present. The cervical lymph nodes were enlarged, about 1 - 1.5 cms size. The abdominal examination showed a non-tender firm spleen 6 cms below the costal margin, and liver was just palpable and firm. Routine haematological investigations revealed anaemia, leucopenia, and thrombocytopenia. His ESR was 30 mm in the first hour. On biochemical investigations, renal functions, liver functions were normal. ELISA for HIV was non-reactive. Urine and blood cultures were sterile. Chest skiagram and ECG were normal. On CT scan and ultrasonography, there was hepatosplenomegaly, left adrenal mass, and suggestion of mediastinal lymphadenopathy. On further evaluation, bone marrow aspiration showed graulomatous lesion. CT scan confirmed the above findings and on guided fine needle aspiration cytology of left adrenal mass (Fig. 1) when stained with Giemsa stain showed intracellular yeast cells. Fungal culture from splenic aspirate was sterile after one month. He was started on liposomal amphotericin-B 5mg/kg body weight daily for a period of two weeks with regular monitoring of hepatic and renal functions. The patient improved clinically, his body weight increased from 40 kg to 45 kg, size of spleen and liver

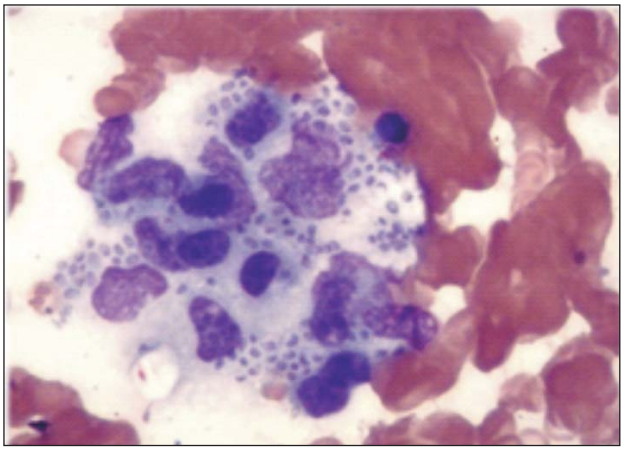

Fig. 1: *FNAC of adrenal gland showing intra- and extra-cellular yeasts of H. capsulatum.*

****Associate Professor, **Professor, Department of Pathology, ***Assistant Professor, ****Resident, Department of Medicine, Indira Gandhi Medical College, Shimla - 171 001, Himachal Pradesh.***

regressed. The anaemia, thrombocytopenia and leucopenia resolved. Patient was discharged on Itraconazole 200 mg bid for one year with regular follow-up.

Discussion

Histoplasmosis is an intracellular infection of reticuloendothelial system caused by the dimorphic fungus Histoplasmacapsulatum. The causative fungus is present in soil, rotting trees, and is particularly abundant in bird faeces. The soil in endemic areas provides an acidic, damp environment with high organic content good for mycelial growth. Birds cannot be infected by the fungus and don't transmit the disease; however, bird excretions contaminate the soil, thereby enriching the growth medium for mycelium. Contaminated soil can be potentially infective for years[2].

In our case, the patient had a history of prolonged exposure to pigeon droppings that could have served as a source of infection. He was diagnosed as a case of disseminated tuberculosis which may mimic disseminated histoplasmosis as both diseases can have almost similar mode of presentation and both are granulomatous diseases. Histoplasma in the immunocompetent individual is mild, self-limiting, or asymptomatic in 95% of cases. In immunocompetent individuals it usually manifests as self-limited respiratory infection comprising of fever, malaise, cough, and chest pain. Chest radiographs may show focal infiltrates and hilar or mediastinal lymphadenopathy[3]. Chronic progressive disseminated histoplasmosis is a term used to describe the slowly progressive and generally fatal infection due to H. capsulatum that occurs mostly in elderly who are not overtly immunosuppressed[4]. Disseminated histoplasmosis is a less common manifestation and mainly infects immunocompromised individuals and accounts for 70% of cases[4]. Our patient had hepatosplenomegaly with unilateral adrenal involvement and bone marrow involvement. Adrenal involvement has been found in over half of the patients with disseminated histoplasmosis who undergo abdominal CT scan, ultrasound, or die of histoplasmosis. The patient was diagnosed as progressive disseminated histoplasmosis on the basis of involvement of liver, spleen, bone marrow, adrenal and histomorphological features. The patients who are seriously ill, tissue biopsy with histopathological evaluation for fungi is a rapid means to establish the diagnosis. Subramanian *et al*[5]. suggested the diagnosis of histoplasmosis by histopathology and/or culture from bone marrow, adrenal gland, lymph node, and spleen to be confirmatory. While differentiating the tuberculosis from other granulomatous diseases, we should be very particular about asking the history of exposure to dust and bird droppings.

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out of such trifling investment of facts."

– Mark Twain (1835-1910): Life on the Mississipi, 1883.

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