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JIACM 2014; 15(2): 86

Dirty electricity

*BM Hegde**

"Each morning when I open my eyes I say to myself: I, not events, have the power to make me happy or unhappy today. I can choose which it shall be. Yesterday is dead, tomorrow hasn't arrived yet. I have just one day, today, and I'm going to be happy in it."

– Groucho Marx.

Last time I wrote something on the above lines, a good hearted Mumbai doctor was so upset that he abused me in a comment. This word – dirty electricity – has now become a respectable word for Indians as their intellectual masters in the West do use it. I am sure the doctor would be nice to me this time round. Much more dangerous than the ghost called cholesterol, dirty electricity has become a dangerous killer risk factor for myriad illnesses and many daily discomforts like tiredness, aches and pains, dizziness which might cost the hapless sufferer thousands of rupees if he goes to mainline neurologists who would want to rule out everything using all their gadgets without finding the cause though, e.g., lethargy, insomnia AND EVEN DEPRESSION AND PANIC ATTACKS.

A more dignified name for this dirty electricity would be electro-smog, worse than the usual water vapour smog that we worry about. The dirty electricity emanates from all the latest gadgets that have become second nature to modern man. Computers, Wi-Fis, smart phones, cordless phones, moneysaving new bulbs (not LCD), mercury filled bulbs, cell phone towers, heavy electricity lines above your house, microwave ovens, refrigerators, cell phones, electric blankets, hair dryers, water beds, electric blankets and such "life comforting" gadgets of our advanced civilization. All these gadgets work on an unhealthy 40 - 60 Hz frequency while the Schumann and other healthy energies work between 0 - 30 Hz. Body tissues need this healthy range for their good health – 2 Hz for nerve regeneration, 7Hz for bone growth, 10 Hz for ligament growth, and 15 - 20 Hz for capillary growth stimulation. "Everything in life is vibration", wrote Albert Einstein.

Holistic health includes the most important 6th element – the earth. In addition to food, water, oxygen, exercise, mental tranquillity, the vital sixth element is the earth. The healthy vibrations of the earth, the electromagnetic energy from the geomagnetic field, are what sustain life on earth. We should be plugged in to it to be healthy. Earth gives energy to our body, organs, cells, and atoms. Our health and even longevity depend on our environment. Our genes have very little to do with either our health or our longevity. Epigenetics now tells us that genes could be managed with the mind. Of course, we also know that matter and mind are but the two faces of the same coin. Positive thoughts have been shown to change the winding and unwinding of the genetic coil!

When we are not connected to the earth as happens in people who are not earthed at all, our health suffers. They live in high rise buildings and rarely walk on earth. Several studies have shown significantly increased incidence of psychological illnesses in high rise dwellers like anxiety, depression, agitation, and even suicides. They travel in metal vehicles or planes where geomagnetic energy cannot reach. They are totally unplugged from their energy source. In addition they drain their own body energy faster and feel fatigued easily.

Jet lag is one such simple example where long distance travel in closed metal jet aircraft the body's energy does not get replenished. The static energy of the body does not get drained either. Together these make the person feel tired. The time zone change and the dehydrating pressurised cabin put extra burden on the human physiology. Lack of exercise and altered sleep rhythm add to the burden.

Human sole of the feet are built with very thick superficial layer (stratum corneum) for barefoot walking. Our ancestors in the forests did not use shoes. The thick soled layer becomes thicker by walking bare foot. Earlier chappals were made of animal hide which is but a poor conductor of electricity. Leather chappals and shoes are in that sense better than the artificial soled shoes. Bare foot walking is very good for health but our roads and walkways are not conducive to barefoot walking. Those who can afford would do well to walk on wet sand on the seashores. Rest of us can make do with walking and working with our bare hands in our own back yard kitchen gardens.

Live with nature and live well. Live with others in society and be healthy. Replace the super ego of "I" with that altruistic "We" concept and avoid debilitating diseases.

"The best feeling in the world is realising that you're perfectly happy without the thing you thought you needed".

– Marxie.

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.

ORIGINAL ARTICLE

JIACM 2014; 15(2): 87-90

Cognitive function in elderly population – An urban community based study in north-west Rajasthan

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Abstract

Background: Improvements in health care have extended the average life expectancy causing a substantial increase in the elderly population. Cognitive impairment is becoming more prevalent with changing demography.

Aims of study : To obtain data on different domains of cognition in elderly population (≥ 60 years) of the north-west part of Rajasthan using Kolkata cognitive screening battery and the effect of risk factors on cognition in elderly.

Methodology: It is a randomised urban population based study conducted in the north-west part of Rajasthan. Cognitive test battery based on Consortium to establish a Registry for Alzheimer's Disease and mini mental state (hindi version) was used to evaluate apparently non-demented subjects. CDR (Clinical Dementia Rating) scale and GDS (Geriatric Depression Scale) were used to exclude severe cognitive impairment and dementia respectively.

Results: 270 elderly participants were included; there were 189 males and 81 females. Mean age of male & female population was 68.38 ± 6.08 & 65.56 ± 4.61 years respectively. In the < 75 years age groups, there was no significant difference between male & female performance in cognitive domains (p > 0.05). In the > 75 years age groups, males were better performers than females in global cognitive function. On comparing age groups there was uniform decline in all domains of cognitive functions (p<0.001). On comparing illiterate vs graduate, and primary vs graduate, there was uniform decline in all modalities of cognitive function and was statistically significant (p<0.001).

Conclusion: Cognitive functions in elderly were affected by age and education. In older elderly, male performance was better than female.

Key words: Cognition, Elderly, Education.

Introduction

Cognition can be defined as a mental process in which higher level functions are carried out by the human brain including comprehension, use of speech, visual perception and construction, calculation ability, attention, memory, and executive functions .

Demographic trends of India[1] and other developing countries are leading to an unprecedented rise in the Indian elderly population. In 1961 it was 5.63%, numbering around 24.7 million, whereas on 2001 it rose to 7.4% (76.6 million). Considering the current demographic trend, it is projected that by the middle of this century the geriatric population will go up to 324 million, i.e., four-times the current aged population. It would be the 21% of the total population of that time. Cognitive impairment and dementia are becoming increasingly prevalent because of these demographic changes.

The Mini-Mental State Examination (MMSE)[2] is an often used instrument to evaluate a patient's cognitive status. MMSE when applied alone has low sensitivity and is insufficient for the detection of early dementia.

More comprehensive test batteries such as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[3], Cambridge Examination of Mental Disorders of the Elderly (CAMDEX)[4] and the Structured Interview for Diagnosis of dementia of Alzheimer-Type, multi-infarct dementia and dementia of other aetiology (SIDAM)[5] have been developed and applied in various settings, generally in the developed world, to obtain more elaborate analyses of cognitive function.

In India, there are only a few studies on evaluation of cognitive status and on prevalence of mild cognitive impairment in elderly population. Due to ethnic, lingual, cultural, educational, and economic differences in various regions in India, we conducted this study in an urban population of the north-west part of India..

Methods

The study was conducted within the municipal area of Bikaner – a city in the state of Rajasthan in western India.The predominant ethnic group speaks Hindi and Marwadi languages. The municipal area of Bikaner has

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been divided into 55 wards based on geographic location and every tenth ward was selected. We included 5 largest wards of Bikaner city for our study. List of individuals ≥ 60 years of age was prepared using voters ID list. Individuals to be interviewed were selected by systematic random sampling method; every second individual from the list was selected. In this way, 336 individuals were included. The house-to-house survey was then conducted in selected households. Written consent was taken before an interview.

The evaluation of the subjects included collecting information on age, sex, literacy level, religion, occupation, family income, addictions (smoking, chewing tobacco, alcohol, drugs), and any deterioration of memory over a period of six month preceding the test. Behavioural functions, language and orientation difficulties, past history of medical/neurological disorders (hypothyroidism, epilepsy, stroke, hypertension, diabetes, loss of consciousness, abnormal movements, disturbed sensation, weakness, head injury, chronic medication use), and psychiatric illnesses (schizophrenia, depression, mania, mental retardation) as well as relevant family history were also probed. A general physical and neurological examination was also carried out. Biochemical evaluation included CBC, blood sugar, complete lipid profile, serum creatinine, and thyroid function test. Radiological investigation used was CT scan of head. A structured proforma was used to capture all information. The study was carried out over a period of one year – from June 2010 to May 2011. HMMSE (Hindi Mini-Mental State Examination) score was applied to screen for dementia. Persons with score ≤ 20 were excluded from any further evaluation. CDR score was used to confirm and stage the cognitive status. Geriatric depression scale was applied to detect the presence of depression and to assess the activities of daily living. 66 subjects were excluded in this way from the further study. The excluded individuals were as follows: refused cognitive evaluation (22 females, and 3 males), hearing and visual problem (females 3, and males 2), CVA (females 4, and males 2), seizure disorder (female 1, and males 2), head injury (female 1, and male 1), Parkinsonism (female 1, and male 1), hypothyroidism (females 2), depression (females 5, and male 2), severe cognitive impairment and dementia (females 7, and males 3), acutely ill (females 3, and male 1). Hence, 270 participants ≥ 60 years, apparently non-demented were included for the detailed cognitive test. Kolkata cognitive test battery[4] consisted of category-based verbal fluency tests (fruits and animals), a 15-item version of the object-naming test (based on the visual presentation of the objects), mental state examination, calculation tests, visuo-constructional ability (which included circle, diamond, overlapping rectangles, and box), and a set of memory tests (immediate memory, delayed memory, and recognition of a ten-item wordlist). We removed fruits naming and memory recognition test items from the original kolkata cognitive battery.

Data were analysed using SPSS version 10. The normative data have been presented in the form of mean (± SD), 10th and 90th percentile scores. The 10th percentile score was taken as the operational cut-off point for identifying the cognitively impaired section of the population. The 90th percentile score on the GDS assessment (11 in our case) was taken as the cut-off point for identifying participants with significant depression.

Results

The total study population was 270 elderly persons living in an urban community. There were 189 males (70%) and 81 females (30%). The proportion of female elderly was around half of the male population (Male: Female ratio = 2.3:1). The mean age of study population was 67.53 ± 5.81 years. The mean ages of male and female were 68.38 ± 6.08 and 65.56 ± 4.61 years respectively. The maximum number of persons were in 60 - 64 year age group (36%) and minimum number of persons were in > 75 years age group (13%). The number of females were less as compared to males in all age groups.

Literacy rate in males and females were 80.42% and 80.24%. The female literacy rate of our study population was quite high compared to overall female literacy rate of India. The mean year of education of overall study population was 6.92 ± 5.4. In males and females, the mean years of education were 7.52 ± 5.25 and 6.55 ± 5.58. The persons with secondary education constituted 28.5% and it was more than other educational groups (Table I).

Table I: Distribution of study population by sex, age, and education.

	N	Mean age (SD)	Mean years of education (SD)
Total participants	270	67.53 ± 5.80	6.92 ± 5.4
Male	189	68.38 ± 6.08	7.52 ± 5.25
Female	81	65.56 ± 4.61	6.55 ± 5.58
Age groups			
60 - 64	97	61.97 ± 1.45	7.51 ± 5.56
65 - 69	79	66.63 ± 1.33	6.88 ± 5.52
70 - 74	59	71.23 ± 1.33	6.74 ± 5.27
> 75	35	78.74 ± 3.43	6.52 ± 4.91
Education groups			
Illiterate	63	67.86 ± 6.40	0 ± 0
Primary	68	67.59 ± 5.96	4.55 ± 0.65
Secondary	77	67.66 ± 5.17	9.79 ± 1.11
Graduation & above	62	66.98 ± 5.61	14.47 ± 1.43

There were 44.80 % hypertensive cases, 19.60% diabetic

cases, and 7% CAD (coronary artery disease) patients in our study population. Chronic smokers and alcoholics constituted 31.10% and 2.20% respectively. The majority of elderly persons were staying in a joint family (83%).

In the study population, 16.30% (4.80% female and 11.50% male) complained of memory decline while the remaining 83.70% (25.20% female and 58.50% male) did not complain of memory decline.

Mean score values of females were better than males in all parameters of cognition except on global cognitive function. In global cognitive function, males had better mean score value than females. But it was not statistically significant. Statistically, females were better performers than males on object naming test only (P value < 0.05) (Table II).

Table II: Sex-wise comparison of test scores on Kolkata cognitive battery applied to persons aged ≥ 60 years in urban area.

Cognitive tests	Sex	N	Mean ± (SD)	Median	10th percentile	90th percentile	P value
HMMSE (Hindi Mini-Mental State Examination)	M	189	27.36 ± 2.35	28	24	30	0.537 (NS)
	F	81	27.10 ± 2.50	28	23	30	
Verbal fluency (VF)	M	189	10.94 ± 2.69	11	7.2	14	0.786 (NS)
	F	81	10.97 ± 2.49	12	7	14	
Object naming (ON)	M	189	14.43 ± 0.74	15	13	15	0.036
	F	81	14.62 ± 0.70	15	14	15	
Calculation	M	189	4.71 ± 0.68	5	4	5	0.859 (NS)
	F	81	4.73 ± 0.59	5	4	5	
Immediate memory recall (IMR)	M	189	14.10 ± 3.39	14	9	19	0.750 (NS)
	F	81	14.21 ± 3.20	14	10	19	
Delayed memory (DM)	M	189	4.37 ± 1.46	4	2	6	0.650 (NS)
	F	81	4.40 ± 1.43	4	2	6	
Visuo-constructional ability (VCA)	M	189	10.28 ± 2.50	11	6	13	0.757 (NS)
	F	81	10.39 ± 2.52	11	6	13	

Table III: Statistical analysis between four age groups by Mann Whitney U test.

Tests	60 - 64 vs. 65 - 69 yrs.	60 - 64 vs. 70 - 74 yrs.	60 - 64 vs. > 75 yrs.	65 - 69 vs. 70 - 74 yrs.	65 - 69 vs. > 75 yrs.	70 - 74 vs. > 75 yrs.
HMMSE	0.034	< 0.001	< 0.001	0.097 (NS)	< 0.001	0.002
Verbal fluency	0.366 (NS)	< 0.001	< 0.001	0.002	< 0.001	0.012
Object naming	0.037	< 0.001	< 0.001	0.019	< 0.001	0.044
Calculation	0.976 (NS)	< 0.001	0.05	0.199 (NS)	0.059 (NS)	0.466 (NS)
IMR	0.037	< 0.001	< 0.001	0.004	< 0.001	0.048
Delayed memory	0.014	< 0.001	< 0.001	0.016	0.002	0.146 (NS)
VCA	0.003	< 0.001	< 0.001	0.110 (NS)	0.001	0.034

Table IV: Statistical analysis between four education groups by Mann Whitney U test.

Tests	Illiterate vs. primary edu.	Illiterate vs. secondary edu.	Illiterate vs. graduate	Primary vs. secondary edu.	Primary vs. graduate	Secondary edu. vs. graduate
HMMSE	< 0.001	< 0.001	< 0.001	0.038	< 0.001	0.002
Verbal fluency	0.072 (NS)	< 0.001	< 0.001	0.034	0.006	0.406 (NS)
Object naming	0.016	< 0.001	< 0.001	0.796 (NS)	0.032	0.026
Calculation	0.126 (NS)	< 0.001	< 0.001	0.026	< 0.001	0.079 (NS)
Immediate memory recall	0.001	< 0.001	< 0.001	0.031	< 0.001	0.016
Delayed memory	0.011	< 0.001	< 0.001	0.062 (NS)	< 0.001	0.005
VCA	< 0.001	< 0.001	< 0.001	0.113 (NS)	< 0.001	0.002

There was a progressive decline in performance on all domains of cognitive functions in both the sexes as age advanced. In the ≤ 75 years age groups, there was no significant difference between male & female performance in all cognitive domains (P value > 0.05). In the ≥ 75 years age groups, males were better performer than females in global cognitive function, calculation, and memory domains, and this was statistically significant (P value < 0.05).

On comparing between 60 - 64 years vs. 65 - 69 years and 65 - 69 years vs. 70 - 74 years age groups, the difference in cognitive performance was unevenly distributed. But the same was not true on comparison of two extremes of age groups like 60 - 64year vs. 70 - 74 vs. ≥ 75 years and 65 - 69 years vs. ≥ the 75 years age groups and there was a uniform decline in all domains of cognitive functions (P < 0.001) (Table III).

There was declining performance on all domains of cognitive functions in both the sexes in lower educational groups. There was no significant difference between males and females across all educational groups in other tests of cognitive function (P > 0.05).

On comparison between illiterate vs. primary, and primary vs. secondary educational groups, the statistical difference in cognitive performance was unevenly distributed. On comparison of illiterate vs. secondary, Illiterate vs. graduate, and primary vs. graduate, there was a uniform decline in all modalities of cognitive function and it was statistically significant (P < 0.001) (Table IV).

Discussion

Giuseppe Salemi[8] in 2002 studied the impact of socio-demographic characteristics on cognitive performance in an elderly population. In a bivariate analysis, age, sex, education, occupation were all significantly associated with cognitive impairment. In our study, there was no difference in cognitive performance between sexes in younger elderly. Males had better performance than females in ≥ 75 years age group. In our study, male participants were more in number than females. The reasons are attributable to social and religious customs; females did not participate in the study.

Das *et al*[10] (2006) conducted a study and evaluated cognitive function on non-demented elderly in an urban community. They noticed age-related decline in most parameters, though not uniformly. When two extreme educational groups were compared, the differences were clearly significant in all the parameters including the three domains of memory test.

In our study, females were better performers than males in object naming test only; and in other test of cognitive domain, there was no difference between males and females even after controlling age and education up to 75 years.

In an earlier Indian study by Ganguli[11], it was observed that men had better fluency in the animal category of the verbal fluency test than women. We found no difference on verbal fluency test between males and females.

Several studies of normal ageing have also reported more rapid cognitive and functional decline among persons with lower educational attainment[13-14]. In our study, declined cognitive performance on all domains of cognitive functions was observed in lower educational groups as compared to higher educational groups in both the sexes.

On comparison of our study results with similar Indian studies, mean scores on HMMSE, verbal fluency, object naming, and memory tests in our study were slightly lower. But, in calculation and visuo-constructional tests, mean scores of our study were better than Kolkata cognitive study.

References

1. Swain P, Raj TPS. Demography of ageing in India. *Indian Journal of Gerontology* 2005; 19 : 327-342.
2. Folstein MF, Folstein SE, McHugh PR. Mini Mental State: A practical method for grading the cognitive state of patients for the clinicians. *J Psychiatr Res* 1975; 12 : 189-98.
3. Welsh KA, Butters N, Mohs RC *et al*. The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology* 1994; 44: 609-14.
4. Roth M, Huppert FA, Mountjoy CQ *et al*. CAMDEX-R: The Cambridge Examination for Mental Disorders of the Elderly. *Psychiatric Bulletin* 2000; 24: 199.
5. Zaudig M, Mittelhammer J, Hiller W *et al*. SIDAM- A structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementias of other aetiology according to ICD-10 and DSM –III-R. *Psychological Medical Journal* 1991; 21: 225-36.
6. Sheikh JI, JA Yesavage. "Geriatric Depression Scale (GDS): Recent Evidence and Development of a Shorter Version." In Clinical Gerontology: A Guide to Assessment and Intervention, edited by TL Brink, 1986; 165-75.
7. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993; 43: 2412-4.
8. Reggio GSA, Letterio Morgante *et al*. Impact of Socio-demographic Characteristics on Cognitive Performance in an Elderly Sicilian Population. *Neuroepidemiology* 2002; 21: 44-9.
9. Christopher M, Callanhan, Hugh C *et al*. Documentation and Evaluation of Cognitive Impairment in Elderly Primary Care Patients. *Ann Intern Med* 1995; 112(6): 422-9.
10. Das SK, Banerjee TK, Mukherjee CS *et al*. An urban community based study of cognitive function among non demented elderly population in India. *Neurol Asia* 2006; 11: 37-48.
11. Ganguli M, Chandra V, Gilby JE *et al*. Cognitive test performance in a community – based nondemented elderly sample in rural India: The Indo-U.S. Cross-National Dementia Epidemiology Study. *Int Psychogeriatr* 1996; 8: 507-22.
12. Manly JJ, Jacobs DM, Sano M *et al*. Effect of literacy on neuropsychological test performance in non-demented, education-matched elders. *Journal of the International Neuropsychological Society* 1999; 5: 191-202.
13. Chodosh J, Reuben DB, Albert MS *et al*. Predicting cognitive impairment in high-functioning community-dwelling older persons: MacArthur studies of successful aging. *J Am Geriatr Soc* 2002; 50: 1051-60.
14. Butler SM, Ashford JW, Snowdon DA. Age, education and changes in the Mini-Mental State Exam scores of older women: findings from the Nun Study. *J Am Geriatr Soc* 1996; 44: 675-81.

ORIGINAL ARTICLE

JIACM 2014; 15(2): 91-5

Study on serum and urinary electrolyte changes in cerebrovascular accident

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Abstract

***Background:** Electrolyte disturbances are an important cause of mortality and morbidity in a cerebrovascular accident (CVA). Timely treatment is very effective and can decrease mortality significantly. However, studies showing the extent of dyselectrolytaemia in CVA patients are rare from India.*

***Materials and methods:** We studied the blood and urine sodium and potassium levels in CVA patients (excluding SAH), after proper exclusion of confounding factors like renal failure and infection. The measurements were done on days 1, 5, and 10. The data was then analysed for any correlation with mortality. Logistic regression analysis was also performed with mortality as dependent variable.*

***Results:** We had 50 patients in our study, with 76% having cerebral infarction. Maximum number of patients was in the 51 - 60 year age group (38%). Significant co-morbid factors included hypertension (72%), diabetes (66%) and dyslipidaemia. Especially, 62.5% of females had low HDL as a risk factor. We found hyponatraemia in 80% of cases at presentation, and on Day 10, hyponatraemia persisted in 46%. Urinary sodium excretion was also significantly high on Day 1. Hypokalaemia was not significant. Both hyponatraemia and urinary sodium excretion were significantly linked to mortality by regression analysis. High urinary excretion of sodium on D10 has an odds ratio of 1.57 ($p < 0.05$) in predicting mortality. There was no statistical difference between haemorrhage and infarct cases in terms of dyselectrolytaemia.*

***Discussion and conclusion:** This observational study found hyponatraemia as a significant factor in CVA mortality. Treatment of this hyponatraemia is essential to prevent further complications. Unlike other studies, we did not find any significant alteration in potassium homoeostasis. Further randomised trials are needed to delineate the treatment and prognosis of electrolyte disturbances in CVA.*

***Key words:** Cerebrovascular accident, hyponatraemia, urinary electrolytes, SIADH.*

Introduction

Cerebrovascular accident (CVA) is associated with high mortality and morbidity. Different factors like infection and pulmonary embolism are implicated in increasing mortality in CVA[1]. Electrolyte disturbances are also commonly found in CVA cases and may contribute to mortality of these patients unless corrected urgently[2].

Disorders of sodium and potassium concentration are the commonest electrolyte abnormalities found in CVA patients[2]. Hyponatraemia is quite common in these patients and is often precipitated by concomitant use of various drugs like diuretics[3].

Syndrome of inappropriate ADH secretion (SIADH) is a leading cause of electrolyte disturbance in these patients[3]. SIADH and the consequent hyponatraemia likely aggravate the brain oedema in CVA. The INTERSALT study has shown that in CVA patients there is increased renal excretion of various cations and this also contributes to the serum electrolyte disturbances[4]. In this study, a significant correlation was found between 24-hour urinary sodium excretion rates and CVA mortality[4].

Studies describing these electrolyte disturbances in CVA patients are rare from India. Timely diagnosis and treatment of electrolyte disturbances can decrease mortality of CVA patients to a large extent. Thus, there is scope for studying the electrolyte changes in Indian CVA patients to know the extent of the problem and plan treatment protocols in an acute care setting. We therefore undertook this study to observe the changes in serum and urinary sodium and potassium in CVA patients and to find any relation with other biochemical parameters.

Aims and objectives

1. To study various parameters in CVA patients, including serum and urinary sodium and potassium.

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2. To study for any correlation among these parameters.
3. To find any relation of the electrolyte changes with mortality

Patients and methods

This was an observational, hospital based, prospective study. The study was carried out among patients selected from indoors of Department of Medicine, Medical College Kolkata between 1st March, 2011 and 31st December 2011.

Patients of any age, diagnosed with CVA [infarct/ hemorrhage] by appropriate imaging, either CT scan or MRI, were included in the study by random sampling. However, patients with sub-arachnoid haemorrhage (SAH) were excluded. Patients with renal failure, those on previous diuretic or steroid therapy, and patients with documented infection were excluded from the study. Also, patients presenting with severe hyperglycaemia (> 300 mg/dl) and hypertriglyceridaemia (> 400 mg/dl) were excluded from the study to avoid the chance of pseudohyponatraemia.

All the patients were first clinically examined after proper consent from patient/next of kin. Then, laboratory tests including complete blood count, sugar, urea/creatinine, lipid profile, and sodium-potassium were done. Blood lipid profile and other tests were done within 24 hours of the CVA event. Blood sugar was done at presentation without regard to time of last meal. Any abnormal test result was rechecked instantly. All tests were done by automated instruments (ERBA XL 300) by the same set of technicians. Urine was checked for sodium and potassium concentrations. The urine electrolytes were done from a pooled 24-hour specimen.

Blood and urine sodium and potassium were checked thrice:

Immediately on admission (D1) and then on 5th (D5), and tenth day (D10) after admission. So, only patients of CVA who stayed for at least 10 days in our hospital could be included in the study. We did not order any dietary restriction on the patients, except any restriction they were already following before admission.

Data was at first arranged in Microsoft Excel 2007 (Redmond, WA) worksheet. Data are expressed as mean ± SD for continuously distributed variables, and in absolute numbers and percentages for the discrete variables. Tests of significance were done with unpaired student's t-test/ Chi square test as needed. Pearson correlation coefficient was used to find correlation between data. Logistic regression analysis was performed for mortality considering the serum electrolyte values as independent variables. Software used for statistical analysis included freely available online software like GraphPad and MedCalc. A *p* value of <0.05 was considered significant.

Normal values for electrolytes[5]: - (urine values for pooled specimen):-

Serum sodium: 135-145 mEq/l; serum K: 3.5-5 mEq/l

Urinary sodium: 40-220 mEq/l/day; urinary K: 25-125 mEq/ l/day

We could not do any osmolarity measurement due to lack of logistics.

The study was approved by the institutional ethical committee.

Results

At first we selected 73 patients for our study. But some patients needed to be excluded due to various reasons like lack of consent, development of nosocomial infection, and need for diuretic therapy while staying. So finally we had 50 patients of CVA in our study – 20% haemorrhage, 76% infarction, and 4% mixed lesions; most of the patients had unilateral lesion, only 4 (8%) of the patients had bilateral lesion on imaging.

32% (n = 16) of our patients were female. Table I shows the age distribution of the patients. It is seen that the maximum number of patients were in the 51 - 60 years age group (n = 19; 38%).

Table I: Age distribution of the patients.

Age group (years)	Male	Female	Total
< 50	3	1	4
51 - 60	14	5	19
61 - 70	8	6	14
> 70	9	4	13
Total	**34**	**16**	**50**

The general characteristics of the patients are shown in Table II. It is seen that hypertension as a pre-morbid condition was present in 72% of the patients (n = 36) and diabetes in 66%. Low HDL as a risk factor was present in 17 patients, but considering the gender-wise data, 62.5% of the female patients with CVA had low HDL, as compared with 20.6% males (p = 0.0088 by Fisher's exact test with 2-tailed correction). On the other hand, high triglyceride level was present in 61.7% males as compared to 25% female patients (p = 0.0322 by Fisher's exact test with 2-tailed correction). The total cholesterol levels were mostly normal (80% of the patients), but that may be because many of the patients were on statin therapy at the time of

the event.

Table II: General characteristics of the patients (n; %).

Parameter		Male (N = 34)	Female (N = 16)
Past history of hypertension		25; 73.5%	11; 68.7%
Past history of diabetes		20; 58.8%	13; 81.2%
Cholesterol (mg/dL)	≤ 200	29; 85.3%	11; 68.7%
	200 - 300	4; 11.8%	5; 31.3%
	> 300	1; 2.9%	0
HDL	Normal/High	27; 79.4%	6; 37.5%
	Low	7; 20.6%	10; 62.5%
Triglyceride	High	21; 61.7%	4; 25%
	Normal	13; 38.2%	12; 75%
Anaemia		6; 17.6%	3; 18.7%

Figure 1 shows the serum sodium (Na^+) values as measured on three days (D1, D5, and D10). It is seen that 80% of the patients had hyponatraemia (serum sodium < 135 mEq/l) on D1 as compared to 70% on day 5 and 46% on D10 (p = 0.0066 by chi-square test). Also, on checking by chi-square test for trend between D1 and D10, p = 0.0005, meaning the hyponatraemia improves significantly with time. The mean urinary excretion of Na^+ is shown in Figure 2. It is seen that there was significantly more excretion of Na^+ initially (150 ± 30.5 mEq/day on D1 as compared to 135 ± 20.5 on D10; p = 0.0082, t = 2.7006 by paired T Test between D1 and D10).

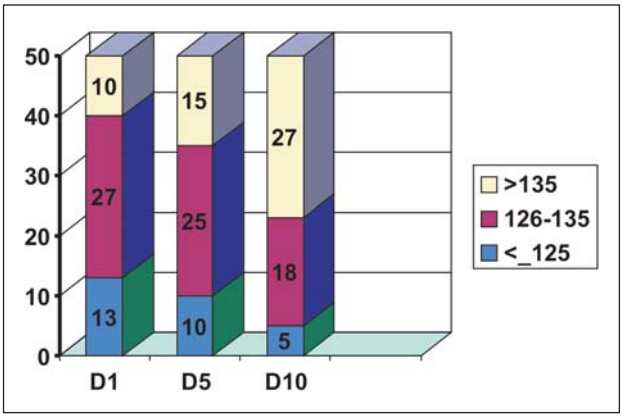

Fig. 1: *Showing the serum sodium values in the 10-day period (total no. of patients = 50).*

Serum potassium was also measured. Table III shows the serum and urinary potassium values on three days. However, there was no statistical difference between the values measured on the three days (p > 0.05 by one way ANOVA both for serum and urinary values). Correlation data of serum electrolytes with other parameters is shown in Table IV. It is seen that serum sodium on D1 was

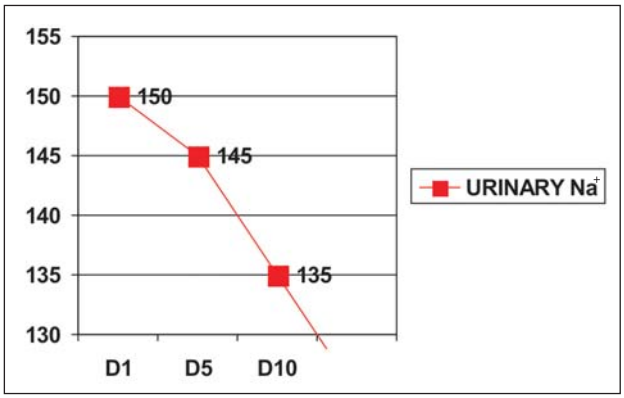

Fig. 2: *Showing the mean urinary excretion of sodium (mEq/day).*

significantly correlated to increased mortality. Also hyponatraemia at presentation was more likely in older patients (correlation coefficient with age = 0.47) and those with renal failure. Altogether, 12 (24%) patients died. Only patients expiring after 10 days were included in calculations. Performing logistic regression analysis for mortality, it is found that high urinary Na^+ excretion on D1 has OR of 1.13 and high urinary Na^+ excretion on D10 has OR of 1.57(P<0.0001) in predicting mortality.

Of the 40 patients presenting with hyponatraemia on D1, there were 10 cases of haemorrhagic CVA and the rest were infarct/mixed lesion (29 infarct, 1 mixed lesion). This means, 100% of the haemorrhagic CVA patients presented with hyponatraemia initially, compared to 76.3% of infarct CVA cases (p = 0.08 by Fisher's exact test). However, of the 23 patients who remained hyponatraemic on D10 (vide Figure 1), 3 were haemorrhagic CVA and 20 were infarct. This means, 30% of the haemorrhagic CVA cases remained hyponatraemic on D10 as compared to 52.6% in infarct cases (p = 0.29 by Fisher's exact test).

Table III: Serum and urinary potassium values (mean ± SD).

Day of measurement	Serum potassium (meq/l)	Urinary potassium (meq/day)
D1	4.66 ± 0.54	80 ± 15.1
D5	4.7± 0.6	77 ± 9.9
D10	4.35 ± 0.72	78 ± 10

Discussion

In our observational study, we found significantly high prevalence of hyponatraemia at presentation in CVA patients. Hyponatraemia and urinary excretion of sodium correlated significantly with mortality. Serum and urinary potassium values did not correlate significantly with mortality. There was not much difference between haemorrhage and infarct CVA cases in terms of

electrolyte values. For patients who survived, there was significant improvement in serum sodium values over 10 days.

In one observational study on CVA patients from Japan, significant alterations in serum sodium and potassium values was seen[2]. However, in that study, both hypo- and hypernatraemia were found. In our present study, we found only hyponatraemia as a co-morbid factor. Hyponatraemia in these patients can be due to various factors, including decreased intake, drug use, SIADH or decreased renal function[6]. In our study, we found significant hyponatraemia in patients with high creatinine (vide Table IV).

SIADH is considered an important reason for hyponatraemia in CVA[6]. These patients continue to secrete hyperosmolar urine in face of serum hypo-osmolarity. In our patients, we could not measure osmolarity of body fluids, but as figures 1 and 2 show, there was high urinary excretion of sodium (150 ± 30.5 mEq/day) on D1 associated with hyponatraemia. The treatment of this hyponatraemia should be gradual, to avoid osmotic demyelination[7]. Fluid restriction is an important step in treatment, and sometimes the newer drugs like vasopressin antagonists are used[7]. Some patients also develop the cerebral salt wasting syndrome after CVA, and in them fluid and electrolyte replacement is needed[7]. However, differentiation between these two conditions is often not possible and treatment is based on clinical impression. Usually, hypertonic saline is not needed in CVA[8]. Some authors have used hypertonic saline in CVA, not for correcting hyponatraemia, but as therapy to reduce ICP[9]. In our study, none of the patients needed hypertonic saline.

In the present study, there were no significant alterations in serum/urinary potassium values (Table III). The alteration in potassium homoeostasis after CVA is debated. Some authors have found hypokalaemia as a risk factor for mortality in stroke, independent of other risk factors like smoking[10]. But hypokalaemia does not show as strong an association with CVA as hyponatraemia in other studies.

We found significant correlation of serum/urine sodium values with mortality (Table IV).

In the CASTEL study, hyponatraemia has been found to be a predictor of CVA mortality with RR of 1.34[11]. In the same study, hyperkalaemia was also identified as a risk factor[11]. We found significant correlation of mortality with higher urinary excretion of sodium on D1 and D10 (Table IV). Also, the older patients were more prone to hyponatraemia (Table IV). Old age is itself a risk factor for hyponatraemia[6]. Thus in old patients with CVA, the chances of hyponatraemia are compounded. SIADH, which is characterised by high urinary sodium is associated with much mortality and even in survivors, there are sequelae like gait disturbance and attention deficit disorders[12]. Thus, hyponatraemia in CVA, whether due to SIADH or not, needs to be corrected properly.

Our study is limited by the small number of patients (n = 50) and short follow-up (10 days). Also, we excluded the sub-arachnoid haemorrhage cases. Our study was also observational and the effect of various interventions like fluid restriction on the final outcome was not checked. But still, this study shows that electrolyte disturbances in Indian CVA patients are as common as reported from other studies abroad. A larger randomised trial is needed to exactly characterise the spectrum of electrolyte disturbances in CVA.

Conclusion

Electrolyte disturbances, especially hyponatraemia, are highly prevalent in CVA patients. The cause may be SIADH or cerebral salt wasting. Early diagnosis is essential to prevent morbidity and mortality. Thus, serum electrolyte analysis should be a part of initial evaluation in all CVA patients. Urinary electrolyte values can be used also to

Table 4: Correlation of various parameters with electrolyte changes (coefficient r; p value).

Parameter	Mortality	Triglyceride	Cholesterol (total)	Creatinine	Age	Blood sugar
Serum sodium, D1	**-0.59; 0.0019**	0.08; 0.67	0.13; 0.51	**-0.46; 0.018**	**-0.47; 0.01**	**-0.46; 0.01**
Serum sodium, D10	0.05; 0.79	0.04; 0.83	0.1; 0.60	-0.36; 0.07	0.13; 0.53	-0.29; 0.15
Urinary Na^+, D1	**0.92; < 0.0001**	0.17; 0.39	0.34; 0.09	-0.19; 0.36	0.18; 0.37	0.26; 0.2
Urinary Na^+, D10	**0.84; < 0.0001**	0.27; 0.18	0.29; 0.15	0.03; 0.86	0.2; 0.33	0.09; 0.64
Serum K^+, D1	-0.07; 0.72	0.01; 0.95	0.39; 0.05	0.24; 0.23	0.05; 0.8	0.37; 0.06
Serum K^+, D10	-0.11; 0.59	0.01; 0.93	0.3; 0.14	-0.09; 0.65	0.08; 0.67	0.06; 0.75
Urinary K^+, D1	0.17; 0.41	0.26; 0.2	0.27; 0.18	0.25; 0.21	0.11; 0.58	0.41; 0.04
Urinary K^+, D10	0.19; 0.56	0.34; 0.09	0.01; 0.95	0.24; 0.22	0.16; 0.43	0.13; 0.51

differentiate the cause of hyponatraemia.

References

1. Viitanen M, Winblad B, Asplund K. Autopsy-verified causes of death after stroke. *Acta Med Scand* 1987; 222: 401-8.
2. Kusuda K, Saku Y, Sadoshima S *et al*. Disturbances of fluid and electrolyte balance in patients with acute stroke. *Nihon Ronen Igakkai Zasshi* 1989; 26: 223-7.
3. Moussa NA, Osman AR, Yahya TM. Acute hyponatremic encephalopathy after a cerebrovascular accident. *Am J Med Sci* 1998; 316: 56-9.
4. Xie JX, Sasaki S, Joossens JV *et al*. The relationship between urinary cations obtained from the INTERSALT study and cerebrovascular mortality. *J Hum Hypertens* 1992; 6: 17-21.
5. MedlinePlus [internet]. N.I.H.:U.S. National Library of Medicine. [About 4 pages]. [Updated 2011 Nov 17; Cited 2012 Mar 15]. Available online from http://www.nlm.nih.gov/medlineplus/ency/article/003600.htm
6. Kugler JP, Hustead T. Hyponatremia and hypernatremia in the elderly. *Am Fam Physician* 2000; 61: 3623-30.
7. Lath R. Hyponatraemia in neurological diseases in ICU. *Indian J Crit Care Med* 2005; 9: 47-51.
8. Ziai WC, Mirski MA, Bhardwaj A. Use of hypertonic saline in ischaemic stroke. *Stroke* 2002; 33: 1166-7.
9. Schwarz S, Georgiadis D, Aschoff A *et al*. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. *Stroke* 2002; 33: 136-40.
10. Gariballa SE, Robinson TG, Fotherby MD. Hypokalemia and potassium excretion in stroke patients. *J Am Geriatr Soc* 1997; 45: 1454-8.
11. Mazza A, Pessina AC, Pavei A *et al*. Predictors of stroke mortality in elderly people from the general population. The Cardiovascular Study in the Elderly. *Eur J Epidemiol* 2001; 17: 1097-104.
12. Hoorn EJ, van der Lubbe N, Zietse R. SIADH and hyponatraemia: why does it matter? SIADH and hyponatraemia: why does it matter? *NDT Plus* 2009; 2(suppl_3): iii5–iii11.

"Health is the greatest possession.
Contentment is the greatest treasure.
Confidence is the greatest friend.
NIRVANA is the greatest joy."

– The Dhammapada.

ORIGINAL ARTICLE

JIACM 2014; 15(2): 96-9

Passive smoking affects nasal mucociliary clearance

Jyoti Yadav, Gajraj Kaushik**, Rupender K Ranga****

Abstract

Background: The present study was undertaken to evaluate the effect of chronic smoking – active as well as passive – on nasal mucociliary clearance (NMC).

Method: The nasal mucociliary clearance was evaluated with Andersen's method, in which a saccharine particle of 1.5 mm diameter was used.

Result: Nasal mucociliary clearance was assessed in 50 healthy controls, 50 active and 50 chronic passive smokers of more than 5 years duration in the age group of 25 - 50 years. NMC time in control group was 8.57 ± 2.12, in active smokers 23.08 ± 4.60, and 20.31 ± 2.51 minutes in passive smokers. The difference in mean value of two samples was statistically significant as compared to controls.

Conclusion: This study explains that both active as well as passive smoking causes a decrease in the nasal mucociliary clearance time which predisposes to upper as well as lower respiratory tract infections.

Globally, smoking is not an uncommon practice. Passive smoke exposure is an independent risk factor for asthma, sinusitis, and is responsible for more severity of respiratory tract infections. Passive smoking emits both particulate and vapour contaminants which not only cause irritation but also adversely affect the respiratory defense mechanism including local humoral and cellular immunity[1]. On passive exposure to tobacco smoke, symptoms like sneezing, rhinorrhoea, post-nasal drip, nasal congestion, headache, chest discomfort or tightness, cough and irritation of eyes, nose, and throat are commonly observed[2]. As the duration of exposure to smoke increases, the hypersensitivity response of tracheobronchial passage increases, which leads on to mucous production, altered surfactant activity, and decreased mucociliary function[3].

Mucociliary clearance is a defense mechanism of upper as well and lower respiratory tract. The vital part of this mechanism is an adequate quantity of mucous with appropriate rhinological qualities and adequately functioning cilia, which beat in metachronous fashion towards the nasopharynx[4]. Any disturbance in the number and movement of cilia and mucous production leads to an altered nasal mucociliary clearance as occurs in smoking[5]. The present study was undertaken to evaluate the effect of chronic smoking – active as well as passive – on nasal mucociliary clearance time using Andersen's method as this method is very simple, reliable, reproducible, and economical[6].

Material and methods

The present prospective study was conducted in fifty active and fifty chronic passive smokers of more than five years duration in the age group of 25 - 50 years of either sex. The passive smokers suffered from hazards of passive smoking at home, work place, and social functions outside the home, e.g, parties, dinners, and weddings. Fifty age and sex matched healthy adults acted as controls. A detailed history was taken with special reference to sneezing, itching, nasal discharge, nasal obstruction, and hyposmia. A thorough clinical examination of ear, nose and throat was carried out. The diseases known to affect the mucociliary clearance like nasal polyps, deviated nasal septum (DNS), allergic and other chronic rhinitis were excluded from the study. Similarly, patients of lower respiratory diseases like bronchiectasis, and patients on drugs known to affect mucociliary clearance, were excluded from the study.

The nasal mucociliary clearance was evaluated with Andersen's method, in which a saccharine particle of 1.5 mm diameter was carefully placed on the floor of the nasal cavity approximately 1 cm behind the anterior end of the inferior turbinate. The subject consumed nothing orally at least 30 minutes before the test, to minimise the disturbance of taste perception. The subjects were asked not to sniff, sneeze, eat or drink during the test. They were asked to swallow every thirty seconds and to report any change in taste. The time taken by the subjects from placement of particle to perception of taste was taken as mucociliary clearance time. The nature of particle was not disclosed to the subject to ensure the reliability of the test. The test was carried out on both sides and the average of the two was taken to taken to minimise the effect, if any, of nasal cycle on the mucociliary time. The results were

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statistically analysed by using student's 't' test.

Results

The mean age in healthy controls (group A) was 38.7 years, in study group (B) i.e., active smokers it was 39.1 and in passive smokers (group C) was 35.1 years. In control group there were 44 (88%) males and 6 (12%) females, whereas in group B there were 42 (84%) males and 8 (16%) females, whereas in group (C) there were 24 (48%) males and 26 (52%) females, (Table I).

Table I: Age and sex distribution of controls and subjects.

Group	Age (in years)		Sex	
	Mean	Range	Male	Female
A) Control	38.7	25 - 50	44 (88%)	6 (12%)
B) Active smokers	39.1	25 - 50	42 (84%)	8 (16%)
C) Passive smokers	35.1	25 - 50	24 (48%)	26 (52%)

The mean value of nasal mucociliary clearance time in control group was 8.57 ± 2.12 minutes whereas in study group B and C it was 23.08 ± 4.60 and 20.31 ± 2.51 minutes respectively. The difference in the mean values of the two samples was statistically significant (Table II).

Table II: Nasal mucociliary clearance time in controls, active and passive smokers.

Group	N	NMC time value (in minutes)	Mean ± SED
A) Controls	50	5.09 - 13.02	8.57 ± 2.12
B) Active smokers	50	12.8 - 36.2	23.08 ± 4.60
C) Passive smokers	50	17.3 - 27.4	20.31 ± 2.51

A vs. B = P value < 0.0001; A vs. C = P value < 0.0001; B vs. C = P value = 0.03

Discussion

Nose is a complex structure that performs many functions including warming and humidifying ambient air as well as filtering particulate and gaseous pollutants in inhaled air. Its shape forces a change in the direction of airflow so that larger particles are removed by impaction and its substantial surface specially the plate-like turbinates serve as scrubber for water soluble gases[7]. Larger particles, greater than several micrometer in aerodynamic diameter, and very small particles < 100 µm in aerodynamic diameter, are filtered with high efficiency, while particles of intermediate size range tend to pass through and reach lower airways and lung. The particles of passive smoking, the mass median aerodynamic around 0.40 µm, are in this size range and hence reach the lungs, cause acute and chronic respiratory diseases[8].

In the present study, the mean value of normal nasal mucociliary clearance time in the control group was 8.57 ± 2.12 minutes. Yadav *et al*[9] reported the normal value of nasal mucociliary clearance in healthy subjects as 5.9 minutes, which is comparable to our results; however, a wide range from 3.3 - 35 minutes has been reported in adults in western countries[10,11]. The mean value of nasal mucociliary clearance time at Haryana, Chandigarh, Kolkata, and Nagpur are reported to be 5.9 minutes, 5.06 minutes, 4.4 minutes, and 7.1 minutes respectively[9,12-14]. At the place of the present study, the mean nasal mucociliary clearance time has been reported to be 7.5 minutes in adults. There is a considerable variation in the value at different places even in India. The nasal mucociliary clearance differs from place to place, habit, habitat, climate, and facial configuration[9].

The mean value of nasal mucociliary clearance in active smokers was found to be 23.08 ± 4.60 minutes. When this was compared with control group, the difference was found to be statistically extremely significant ($p < 0.0001$) by conventional criteria. This finding of increased value of nasal mucociliary clearance time in active smokers is due to the fact that smoking has ciliotoxic effect on nasal mucociliary clearance[15] which was also observed in the present study, i.e., increased nasal mucociliary time. Cigarette smoke is composed of volatile and particulate matter like nicotine, phenols, hydrocarbons, aldehydes, ketones, organic acids, and alcohols. Pure nicotine has been shown to stimulate the mucociliary activity but several other components of smoke are more or less ciliotoxic[3]. Agius *et al* showed that continine metabolite of nicotine causes significant decrease in the ciliary beat frequency of nasal mucosal cells *in vitro*[16].

The mean value of nasal mucociliary clearance in passive smokers was found to be 20.31± 2.51 minutes and when this was compared with the control group the difference was found to be statistically extremely significant ($p<0.0001$) by conventional criteria. This finding of increased value of nasal mucociliary clearance time in passive smokers is due to the fact that tobacco smoke has ciliotoxic effect on nasal mucociliary clearance, clearly indicating that passive smoking also depresses ciliary activity[2].

The mean value of nasal mucociliary clearance in active and passive smokers was compared, the difference using two-tailed P value was found equal to 0.03 by conventional criteria which is statistically significant. It has been observed that chronic passive exposure to smoke in the household has slightly higher serum continine which is a metabolite of nicotine which decreases ciliary activity[17] as was also observed in the present study. In fact chronic passive smokers have a more or less equal effect on nasal mucociliary function

as tobacco smoke is composed of volatile and particulate matter like nicotine, phenols, hydrocarbons, aldehydes, ketones, organic acids, and alcohols[18, 19]. This was also confirmed in our study as the nasal mucociliary time was increased in both active as well as passive smokers very highly significantly as compared to controls and there was significant difference between active and passive smokers.

It is also based on the hypothesis that passive smoking causes allergic rhinosinusitis-like symptoms and allergic inflammatory events involving the mucous membrane which leads on to increased mucous production. Environmental tobacco smoke has been shown to alter nasal mucociliary clearance in non smokers[20]. Impaired nasal mucociliary clearance with subsequent mucous retention contributes to pathophysiology of each of these diseases. Further, altered epithelial salts and water transport play an important aetiological role. Studies also show that smoke inhibits secretion of Cl^- and K^+ conductance in normal respiratory epithelium cells which causes altered salt and water transport due to allergic nasal mucosal reaction[21].

Exposure to smoke – either passive or active – is associated with profound changes in the mucous production mechanism. It also results in metaplastic changes to the respiratory mucosa with increase in the number and size of the goblet cells that leads on to increased production of respiratory airway secretions[3]. Histologically, smoke causes reduction in cells viability and induction of apoptosis, opposite mitogenic effect or pro-apoptotis depending on the concentration of smoke and impairment of cell regeneration in respiratory epithelium[22].

Animal studies have shown that chronic and intermittent exposure to cigarette smoke causes morphological alteration in the epithelium of the entire respiratory tract, in the form of hyperplasia in lower concentration to complete loss of cilia and metaplasia with keratinisation in higher concentration. There are many inflammatory processes submucosally like infiltration of inflammatory cells[23].

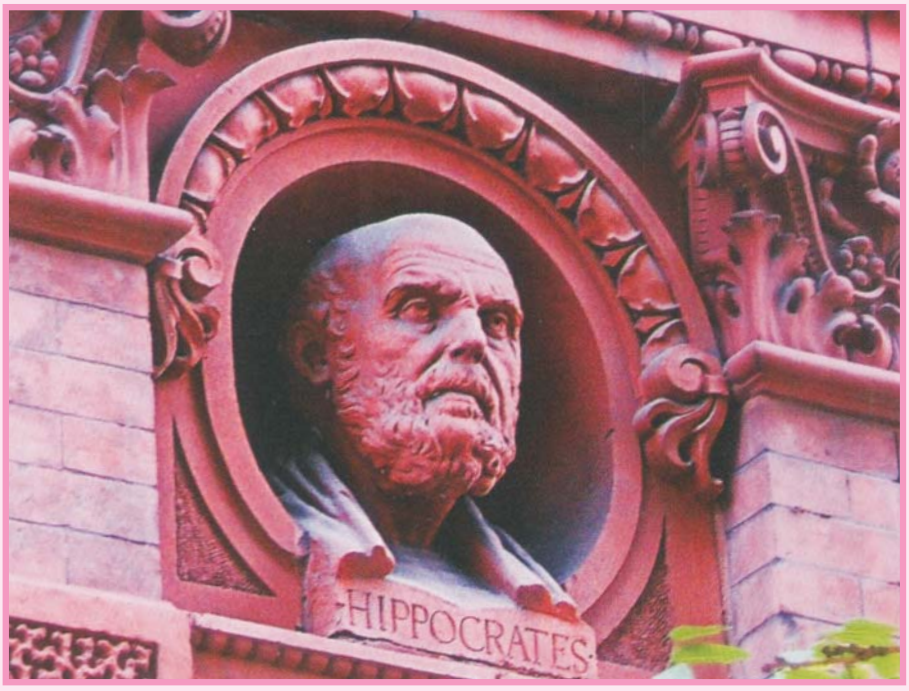
Mucociliary clearance may be disturbed by factors including increased mucous production, abnormal mucous quality and quantity and abnormal ciliary activity consequent to chronic smoking which causes stagnation of secretions in the sinuses[15]. The mucous layer which is present over the ciliated cells has two properties, i.e., viscosity and elasticity. The outer layer which is a thick, viscoelastic, semi-solid mucous layer where the cilia do not strike directly, is found over a layer of watery serous fluid. Low viscosity of the layer of watery serous fluid or sol layer facilitates the movement of cilia which moves the sol layer affecting the movement of the upper thick layer[5]. If the movement of the mucous is slowed, bacteria can multiply as the mucus thickens and stagnates; this plays a major role in pulmonary, sinonasal, and laryngeal diseases that leads on to substantial morbidity and increased cost to patients as well as society.

The risks for acute otitis media are also increased by passive smoking as much as 50% in some studies in children[15]. Exposure to passive smoking is related to an ever-increasing frequency of diseases among children and adults such as respiratory illness, asthma, otitis media, sudden infant death syndrome (SIDS), and cancer. These study findings have important clinical and public health implications, due to passive smoking.

References

1. Flouris AD, Vardavas CI, Metsios GS *et al*. Biological evidence for the acute health effects of second hand smoke exposure. *Am J Physiol Lung Cell Mol Physiol* 2010; 298: 3-12.
2. Bascom R, Kesavanathan J, Fitzgerlad *et al*. Sidestream tobacco smoke exposure acutely alters human nasal mucociliary clearance. *Environmental Health Perspect* 1995; 103: 1026-30.
3. Tamasbiro E, Coben NA, Palmer JN *et al*. Effect of cigarette smoking on the respiratory epithelium and its role in pathogenesis of chronic rhinosinusitis. *Braz J Otorhinolaryngol* 2009; 75: 903-7.
4. Waguespack R. Mucociliary clearance pattern following endoscopic sinus surgery. *Laryngoscope* 1995; 105: 1-40.
5. Singh I, Mehta M, Singh J *et al*. Nasal mucus clearance in chronic smokers. *Indian J Chest Dis Allied Sci* 1994; 36:133-6.
6. Andersen I, Lundquist G, Jensen PL *et al*. Nasal clearance in monozygotic twins. *Am Rev Respir Dis* 1978; 110: 301-5.
7. Auarback O, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking. *New Engl J Med* 1979; 300: 381-6.
8. Glasius M, Ketzel M, Wahlin P *et al*. Impact of wood combustion on particle level in residential area in Denmark. *Atmospheric Environ* 2006; 40: 7115-24.
9. Yadav J, Ranga RK, Singh J *et al*. Nasal mucociliary clearance in healthy children in a tropical country. *Int J Pediatr Otorhinolaryngol* 2001; 57: 21-4.
10. Stanley P, Macwilliam L, Greenstone M *et al*. Efficay of a saccharin test for screening to detect abnormal mucociliary clearance. *Br J Dis Chest* 1984; 78: 62-5.
11. Puchelle E, Aug F, Pham QT *et al*. Comparison of three methods for measuring nasal mucociliary clearance in man. *Acta Otolaryngol* 1981; 91: 297-303.
12. Mehra YN, Mann SBS, Mehra S *et al*. Cryosurgery in vasomotor rhinitis- an analysis of 156 patients. *Indian J Otolaryngol* 1990; 42: 95-8.
13. Mukherjee AL. Human nasal mucus flow rates. Indian J Otolaryngol 1977; 29: 174-5.
14. Golhar S. Nasal mucus clearance. *J Laryngol Otol* 1986; 100: 533-8.
15. Stanley PJ, Wilson R, Greenstone MA *et al*. Effect of cigarette smoking on nasal mucociliary clearance and ciliary beat frequency. *Thorax* 1986; 41: 519-23.

16. Agius AM, Wake M, Pahor AL *et al*. Smoking and middle ear ciliary beat frequency in otitis media with effusion. *Acta Otolaryngol* 1995; 115: 44-9.
17. Dye JA, Adler KB. Effects of cigarette smoke on epithelial cells of the respiratory tract. *Thorax* 1994; 49: 825-34.
18. Wanner A. State of the art: Clinical aspects of mucocili ary transport. *Am Rev Respir Dis* 1977; 116: 73-125.
19. Pakhale SS, Jayant K, Bhide SV. Chemical analysis of smoke of Indian cigarette, bidis, and other indigenous forms of smoking levels of steam- volatile phenol, hydrogen cynide and benzo(a)pyrene. *Indian J Chest Dis Allied Sci* 1990; 32(2): 75-81.
20. Benninger MS. The impact of cigarette smoking and environmental tobacco smoke on nasal and sinus disease: a review of literature. *Am J Rhinol* 1999; 13: 435-8.
21. Cohen NA, Zhang S, Sharp DB *et al*. Cigarette smoke condensate inhibits transepithelial chloride transport and ciliary beat frequency. *Laryngoscope* 2009; 119: 2269-74.
22. Van Winkle LS, Evans MJ, Brown CD *et al*. Prior exposure to aged and diluted sidestream cigarette smoke impairs bronchiolar injury and repair. *Toxicol Sci* 2001; 60: 152-64.
23. Gaworski CL, Dozer MM, Eldridge S *et al*. Cigarette smoke vapor-phase effects in rat upper respiratory tract. *Inhalation Toxicol* 1998; 10: 857-73.



Hippocrates: Father of Medicine and Medical Education

The Greek physician Hippocrates (460 - 370 B.C.) stood far above the rest of the physicians of his day for his down-to-earth curative practices. His belief that the human body was a single organism and each part of the body could be understood in relation to the whole body was a big breakthrough in medical knowledge. He believed that the power of healing existed within every person and the way a person lived affected his or her health. "Let food be your medicine and medicine be your food," he said. He advised his pupils to observe the patient's background, his way of life, job, age, mannerism, conversation, thoughts, and his silences. "It is our job to pay attention to all these things and see what they lead to," he used to say. No wonder he is revered as the 'Father of Medical Education' even today!

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

ORIGINAL ARTICLE

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Nutritional intervention in stable COPD patients and its effect on anthropometry, pulmonary function, and health-related quality of life (HRQL)

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Abstract

Objectives: COPD is a systemic disorder frequently associated with malnutrition. Our aim was to study the nutritional status of stable COPD patients and to study the effect of nutritional supplementation on anthropometry, pulmonary function, and health-related quality of life (HRQL).

Material and methods: 60 stable COPD patients were enrolled and equally divided into 2 study groups. A commercially available supplement (Nourish), providing 500 Kcals was given to 15 patients in the 1st group; and additional 20% carbohydrate and 20% protein from naturally available diet was given to 15 patients in the 2nd group by making appropriate diet charts. Both the study groups had an equal number of age and sex matched COPD patients as controls who were on their usual diet.

Results: There was significant increase in the weight and BMI of the patients in the 1st study group with nutritional intervention with p value of 0.002 and 0.019 respectively and with p value of 0.001 in the 2nd study group. However, there was insignificant increase in mid-arm circumference (MAC), skin fold thickness (SFT) and serum protein level . The study also showed significant improvement in the distance travelled in the 6-min walk test and HRQL scores after nutritional intervention with p values of 0.000 in both the study groups .

Conclusion: Malnutrition is prevalent in COPD patients and supplemental nutrition does bring about significant improvement in exercise capacity and quality of life, but not in pulmonary function.

Key words: COPD, health-related quality of life(HRQL), pulmonary function, nutritional intervention.

Introduction

COPD is a state of systemic inflammation that causes changes in body composition, metabolism, and immune status.These systemic effects contribute to weight loss and skeletal muscle wasting, limiting the exercise capacity of these patients,and worsening the prognosis,independent of their pulmonary function[1].Significant loss in fat-free mass (FFM) is related to impaired skeletal muscle strength and exercise capacity[2,3].Weight loss also reduces diaphragmatic muscle mass and depresses diaphragm contractility[4]. Various hypotheses proposed for the pathophysiologic mechanisms for weight loss in COPD include increased resting energy expenditure (REE),inadequate dietary intake, systemic inflammation,tissue hypoxia and medications.The factors that are implicated in the increase in REE include systemic inflammation causing hypermetabolism and increased respiratory muscle work due to increased oxygen consumption of the respiratory muscles secondary to an increased resistive load and an impaired respiratory muscle insufficiency. More specifically, muscle wasting is a consequence of an imbalance between protein synthesis and protein breakdown. Individuals with low weight have more gas trapping, lower diffusing capacity, and lower exercise capacity than those with similar pulmonary mechanics but with normal weight[5]. Several studies have shown an association between malnutrition and impaired pulmonary status among patients with COPD[5,6,7]. However, there is no clear relationship between measures of nutritional status and airflow obstruction. Malnourished subjects have worse scores on a respiratory disease-specific quality of life questionnaire than do adequately nourished individuals[8]. Malnutrition varies between 20% and 70% among different patient groups with COPD[9,10].

Although nutritional repletion in some ambulatory COPD patients resulted in improvements in respiratory and limb muscle function[10,11,12], this has not always been the case[13,14]. Furthermore, it remains unclear whether improvements in respiratory and peripheral muscle function will result in better functional exercise capacity or improvement in health-related quality of life. The literature, till a recent study by Schols and colleagues[15], provided evidence that for some patients with COPD, the negative effect of low body weight can be reversed by appropriate therapy. In a study, Landbo *et al*[16] concluded that low BMI is an independent risk factor for mortality in subjects with COPD, and that the association is strongest in subjects with

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severe COPD. Reported attempts to date have shown equivocal benefits from long-term (> 2 weeks) nutrition supplementation programme in COPD. Lewis *et al* examined the effect of nutritional supplementation for 8 weeks and did not find any improvement in anthropometric measures, pulmonary function studies, or respiratory muscle function[19]. Similar results were observed in the studies by Sridhar *et al*[18]. Even the meta-analysis by Ferreira[20] of nutritional support did not identify improvements in anthropometric measures or functional exercise capacity among patients with stable COPD, and it was advised that further studies should include the influence of supplementation on health-related quality of life. Hence, the present study was undertaken to see the effect of nutritional supplement in stable COPD patients on anthropometry, spirometry (PFT), exercise capacity and health-related quality of life (HRQL).

Material and methods

Clinically stable patients with COPD with FEV1 < 80% of predicted value and room air PaO_2 > 55 mmHg with age ≥ 35 yrs were included in this study. Patients of COPD with acute exacerbation and those suffering from any other chronic illness like diabetes mellitus, hypertension, chronic liver disease, tuberculosis, lung cancer or any other malignancy were excluded. This study had approval from the ethics committee of our institution, and all subjects gave written consent to participate in the study. The total number of patients included in the study was 60. The patients were divided into 2 study groups. These patients were evaluated via complete history and physical examination, pulmonary function tests, nutritional assessment including anthropometric measurement and serum protein levels, 6-min walk test and health-related quality of life assessment by the Seattle Obstructive Lung Disease Questionnaire (SOLDQ) at the start of the study and then repeated after 6 wks after initiating nutritional intervention. In the 1st study 15 patients were given oral nutritional supplement in the form of commercial food preparation (Nourrish), 114 gm per day for a period of 3 weeks on out-patient basis. This provides 500 Kcal and comprises of 31.4 gm carbohydrate, 9.7 gm fat, and 9.7 gm protein. Other contents were fibre, vitamins, and minerals. The other 15 patients matched for height, weight, and age were left on their normal diet which served as controls in this study. In the 2nd study group, 15 patients were given supplemental nutrition in the form of additional 20% carbohydrate and 20% protein-rich diet for a period of 6 weeks. Diet charts were made for the patients considering their present intake. Patients were followed up weekly and compliance checked by dietary recall method. The other 15 patients matched for height, weight, and age were left on their normal diet.

A stable regime of inhaled and oral bronchodilators and inhaled steroids was maintained during the study duration. Use of systemic steroids was not allowed during this period. Routine haematological and biochemical investigations were carried out. X-ray chest, ECG, and arterial blood gas (ABG) analysis were done for all patients.

Nutritional assessment

The body mass index (BMI) was calculated as weight (in Kg)/height^2 (in metres). Mid-arm circumference (MAC) measurement was done in the non-dominant arm of the patient using a flexible measuring tape. Skin fold thickness was calculated using the Holtain skin fold caliper. This was used to calculate triceps skin fold thickness in the non-dominant arm of the patients. Serum protein levels were determined using the Biuret method.

Pulmonary function tests

The Jaegers Master Screen Diffusion Spirometer was used for pulmonary function test. Room temperature of the laboratory was recorded. All measurements were done in a sitting position by the same technician to ensure the consistency of the technique. The calculation was done with Udwadia's formula. The best of three technically acceptable readings were included for analysis.

Exercise performance

The 6-minute walk test was used to assess the exercise capacity of the patient. These patients were asked to walk at their own pace while breathing room air for a duration of 6 minutes on level ground. The distance covered was then measured in metres. The patient was given constant encouragement and support during this time.

Health-related quality of life

This was assessed using the Seattle Obstructive Lung Disease Questionnaire (SOLDQ). This consists of 29 items measuring four health dimensions, i.e, physical function, emotional function, coping skills, and treatment satisfaction.

Results

We studied a total of 60 patients dividing them in two study groups. In each group half of the patients were given nutritional supplementation and the other half were left on their usual diet. Patients who were given supplementation served as cases and those who were left on their usual diet served as controls. Various parameters were compared before and after 6 weeks of starting nutritional intervention.

Table I: Baseline characteristics of patients (mean ± SD).

Variables	Case (1st group) (mean ± SD) (n = 15)	Control (1st group) (mean ± SD) (n = 15)	Case (2nd group) (mean ± SD) (n = 15)	Control (2nd group) (mean ± SD) (n = 15)
Weight (kg)	54.47 ± 10.439	53.80 ± 12.863	49.40 ± 9.72	50.47 ± 10.34
BMI (kg/m^2)	16.527 ± 3.1068	17.147 ± 4.0790	19.095 ± 3.1269	19.1259 ± 3.4203
MAC	25.633 ± 2.8502	24.667 ± 0.0237	24.867 ± 1.689	24.240 ± 2.269
SFT	9.947 ± 0.5125	9.980 ± 0.6155	10.013 ± 0.307	10.013 ± 0.694
S. protein	6.213 ± 0.3852	6.080 ± 0.2484	6.487 ± 0.669	6.207 ± 0.571
FEV_1 (%)	55.440 ± 8.5627	52.027 ± 14.5698	50.387 ± 9.860	50.593 ± 13.327
6-MWT (mt)	306.33 ± 18.942	297.33 ± 13.870	295.67 ± 18.41	297.00 ± 19.98
HRQL	112.00 ± 3.317	110.27 ± 5.800	112.27 ± 4.80	108.93 ± 4.83

Table II: Characteristics after nutritional supplementation (mean ± SD).

Variables	Case 1 (mean ± SD) (n = 15)	Control 1 (mean ± SD) (n = 15)	Case 2 (mean ± SD) (n = 15)	Control 2 (mean ± SD) (n = 15)
Weight (kg)	55.62 ± 10.697	53.27 ± 12.806	51.20 ± 10.16	50.67 ± 10.01
BMI	17.040 ± 3.2926	17.053 ± 4.2537	19.7996 ± 3.2822	19.2225 ± 3.3846
MAC	25.687 ± 2.8382	24.600 ± 1.9928	24.893 ± 1.693	24.220 ± 2.235
SFT	9.953 ± 0.5181	9.987 ± 0.6424	10.007 ± 0.306	10.027 ± 0.716
S. protein	6.253 ± 0.3292	6.013 ± 0.02167	6.753 ± 0.614	6.193 ± 0.473
FEV_1 (%)	57.813 ± 8.2342	52.440 ± 15.2950	53.875 ± 16.631	47.362 ± 14.502
6-MWT (mt)	324.0 ± 23.619	298.0 ± 11.464	320.33 ± 18.27	298.33 ± 16.97
HRQL	134.93 ± 6.341	112.80 ± 5.361	134.67 ± 6.70	109.80 ± 5.20

The baseline characteristics of the two study groups are shown in Table I. There was no significant difference in the cases and controls in both the groups at the start of the study.

Table II shows these characteristics after 6 weeks of starting nutritional supplementation and table 3 shows p-value for all the parameters in the study.

Table III : p-values after nutritional intervention.

Variables	Case 1	Control 1	Case 2	Control 2
Weight (kg)	.002	.192	.001	.714
BMI	.019	.517	.001	.668
MAC	.150	.164	.104	.486
SFT	.719	.670	.719	.334
S. protein	.450	.106	.236	.806
FEV_1 (%)	.190	.553	.269	.073
6-MWT (mt)	.000	.806	.000	.499
HRQL	.000	.058	.000	.313

There was a significant increase in the weight of patients in both the study groups as compared to control groups. There was a significant improvement in the BMI in both the study groups after the study period but not in the control groups after nutritional intervention. 48 patients (80%) out of 60 had BMI of less than 21 before the nutritional intervention, thereby suggesting a significant incidence of malnutrition in these stable patients. There was insignificant improvement in mid-arm circumference, skin fold thickness, or serum protein levels in both the study groups.

Pulmonary function: There was no significant improvement in FEV_1 (%) after 6 weeks in any of the groups after nutritional intervention.

6-minute walk test: The improvement in the distance travelled in the 6-min walk test was highly significant in the cases of both the study groups but not in the control groups.

HRQL: The improvement in the HRQL scores were highly significant in the cases in both the study groups after nutritional supplementation but not in the control groups.

Discussion

The aim of our study was to estimate the nutritional status of stable COPD patients and to study the effect of nutritional supplementation on anthropometric measures, pulmonary function and health-related quality of life (HRQL).

There was significant increase in weight and BMI of the patients in our study groups after nutritional intervention.

Studies done the world over show that as many as 25% of out-patients with COPD may be malnourished while almost 50% of patients with COPD admitted to the hospitals have evidence of malnutrition. This figure increases to 70% in patients with COPD with acute respiratory failure, i.e., malnutrition varies between 20% and 70% among different patient groups with COPD[9,10]. Sahebjami[5] showed that a substantial number of stable COPD patients (46.8%) have nutritional abnormalities and BMI is a simple and accurate indicator of nutritional status in these patients. The incidence of malnutrition in these stable patients was 80% in our study. This increased incidence could be because most of the patients in our study were from a low socio-economic background. In a systematic overview of nutritional intervention in COPD patients, Ferreira *et al* found that in studies where nutritional intervention was given for more than 2 weeks there was no consistent effect on weight[20]. Those who did gain weight, it was just under 2 kg (1.87 ± 1.06) whereas weight in the control group remained the same. This was also observed by Otte *et al*, who showed an improvement of 1.5 kg in the study group over a period of 13 weeks and Sridhar *et al* found a mean increase of only 0.3 kg after 4 months of supplementation[18,21]. A meta-analysis done by the same author showed no consistent improvement in anthropometric measures. Although Schweiz Rundsch *et al* found weight gain, which was statistically significant ($p = 0.003$) in the study group, the difference between the study and control group was statistically not significant ($p = 0.08$). Wilson[6] found that when given calories in excess of their needs, patients gained weight. They did a study on admitted COPD patients for 3 weeks and found significant improvement (p value < .001) in weight. Chailleux[22] *et al* found that lower body mass index (BMI) was an independent negative determinant of survival in patients with COPD. The inverse relationship between BMI and incidence of COPD is in agreement with results of Higgens[23] *et al* who reported that after an average follow-up period of 15 years, the incidence of COPD was highest in lean men and lowest in those who were overweight. Similarly, Schols[15] *et al* demonstrated the association between low body weight and increased respiratory disease mortality. Amongst a number of nutritional intervention studies done on stable COPD patients, some like by Whittaker[12] *et al* and Efthimiou[11] *et al* showed improvement in BMI while others like Lewis[19] *et al* and Shizgal *et al* failed to show much improvement. This could be because either the dietary intake was not increased sufficiently or the period of supplementation was not sufficient.

Mid-arm circumference and skin fold thickness reflect muscle mass and the body's fat stores respectively. A low triceps skin fold has been shown in patients with COPD patients, and it helps in early identification of a deteriorating clinical state. This measurement is not affected by fluid retention often seen in COPD patients, which might mask weight loss. Studies by Lewis[19] *et al* and Sridhar[18] *et al* had also shown no significant improvement in mid-arm circumference and skin fold thickness in patients. Although Schweiz *et al* showed an improvement in skin fold thickness, it was not significant in comparison to the control group. Otte[21] *et al* showed significant improvement in skin fold thickness after 13 weeks nutrition supplementation. The sum of four skin fold thickness increased 2.7 mm in the fed group, and decreased 0.9 mm in the control group – the difference being significant (p value < 0.01). Wilson[6] also showed a small but significant improvement in SFT in hospitalised patients (p value < 0.05). There was no significant improvement in mid-arm circumference (MAC), skin fold thickness or serum protein level in any of the study groups in our study. Song[25] *et al* showed a significant improvement in weight and serum protein level (p value < 0.05). They used parenteral nutrition (10% Intralipid and 5% Nutrisol) as nutritional supplement. Other studies[11,12] done for similar duration failed to show significant improvement in serum protein level. The absence of a response in mid-arm circumference and skin fold thickness to nutritional support likely reflected the multifactorial mechanisms in COPD by which an increased energy expenditure is not balanced by an adequate dietary intake. Also, the duration of study was only 3 - 6 weeks in our study whereas studies which showed significant improvement were done for a much longer period (13 weeks) or on admitted patients. There is always a possibility that the intervention itself was not of sufficient magnitude to produce an effect. Other explanations for a poor response to nutritional support include an increased metabolism, diet-induced thermogenesis, tissue hypoxia, and medications such as corticosteroids.

On classifying the patients according to severity of the disease, most of the patients in our study were in the moderate category (55%) with a few in the mild (16.6%), and 28.6% patients in the severe category of COPD as per the GOLD guidelines, and there was no significant improvement in pulmonary function parameter after nutritional intervention. Otte[21] *et al* in their study also did not find improvement in pulmonary function despite significant weight gain. The study by Wilson[6] *et al* too did not show significant improvement in lung function despite significant improvement in anthropometric measures. Ganzoni[5] *et al* conducted a study over 12 months but the improvement in FEV_1 was not significant in the study. Efthimiou[11] *et al* also did not get a significant improvement in lung function. Some statistically

significant differences in the FEV_1 are so small that they may not represent important differences in symptoms for the average patient with severe COPD; an awareness of the smallest difference in FEV_1 that is noticeable to patients can help clinicians interpret the effectiveness of symptomatic treatments. Redelmeier[26] *et al* showed that the FEV_1 needed to differ by 4% predicted for the average patient to stop rating his or her dyspnoea as "about the same", and start rating his or her dyspnoea as either "a little bit better" or "a little bit worse" relative to other patients (95% CI, 1.5 to 6.5). This was equivalent to the average patient's FEV_1 increasing by 112 ml (starting from 975 ml and ending at 1,087 ml). This means that although the improvement in the cases of study 2 was statistically significant, the increase in FEV_1 of only 0.082 ml and increase in FEV_1% of 2.373% were both not clinically significant. Even the meta-analysis of 9 randomised controlled trials of nutritional support in COPD patients failed to show any clinically important difference in FEV_1[20].

The 6-minute walk test is a useful test for seeing the functional status of COPD patients. Functional status measurements are often difficult to interpret because small differences may be statistically significant but not clinically significant. Redelmeier[27] *et al* found that the distances needed to differ by 54 m for the average patient to stop rating themselves as "about the same" and start rating themselves as either "a little bit better" or "a little bit worse" (95% CI: 37 to 71 m). They suggested that differences in functional status can be statistically significant but below the threshold at which patients notice a difference in themselves relative to others; an awareness of the smallest difference in walking distance that is noticeable to patients may help clinicians interpret the effectiveness of symptomatic treatments for COPD. Hence although the improvement in the study group was statistically highly significant, it was not clinically significant in any of the study as it was much less than 54 metres. Ganzoni[25] *et al* in their study showed improvement in distance covered by the study group patients, but it was not significant. Even the meta-analysis of effect of nutrition supplement on COPD patient showed changes in the 6-min walk test which did not exceed the minimum clinically important difference (defined as the smallest difference perceived as important by the average patient).

The HRQL measure provides independent and relevant information on the health status of COPD patients. Lower QOL is a powerful predictor of hospitalisation and mortality. The Seattle Obstructive Lung Disease Questionnaire is a useful tool for evaluating COPD patients. In our study, HRQL improved significantly in all the groups where nutritional intervention was done, but it did not improve in controls. During the 3 months of dietary supplementation, Efthimiou *et al*[11] did not see improvement in breathlessness and general well-being that fell gradually over the subsequent 3 months. In contrast, Otte *et al*[21], (using a different scale) did not identify changes in well-being associated with supplementation.

From the above observations, we may conclude that patients with COPD are generally malnourished and the prevalence is more in a developing country like India. Nutritional interventions in the form of dietary supplement has shown improvement in anthropometry, exercise capacity and HRQL but did not show any significant improvement in pulmonary function. However, the variable outcome may be due to a small study population, shorter duration, different modes of intervention, and variable COPD severity.

References

1. Schols AM, Slangen J, Volovics L *et al*. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791-7.
2. Baarends EM, Schols AMWJ, Mostert R *et al*. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 2807-13.
3. Palange P, Forte S, Felli A *et al*. Nutritional state and exercise tolerance in patients with COPD. *Chest* 1995; 107: 1206-12.
4. Thurlbeck WM. Diaphragm and body weight in emphysema. *Thorax* 1978; 33(4): 483-7.
5. Sahebjami H, Doers JT, Render MC *et al*. Anthropometric and pulmonary function test profile of outpatients with stable chronic obstructive pulmonary disease. *Am J Med* 1993; 94: 469-74.
6. Wilson DO, Rogers RM, Wright EC *et al*. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989; 139: 1435-38.
7. Arora, NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis* 1982; 126: 5-8.
8. Goris AHC, Schols AMWJ, Weling-Sheeoers CAP *et al*. Tissue depletion in relation to physical function and quality of life in patients with severe COPD. *Am J Respir Crit Care Med* 1997; 155: A498.
9. Schols A, Wouters E. Nutritional abnormalities and supplementation in chronic pulmonary respiratory disease. *Clinics in Chest Medicine* 200; 4: 753-62.
10. Donahoe MP. Nutrition in end-stage pulmonary disease. *Monaldi Arch Chest Dis* 1995; 50: 47-50.
11. Efthimiou J, Fleming J, Gomes C *et al*. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; 137(5): 1075-82.
12. Whittaker JS, Ryan CF, Buckley PA *et al*. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive disease patients. *Am Rev Respir Dis* 1990; 142: 283-8 .
13. Lewis MI, Belman MJ, Dorr-Uyemura L. Nutritional supplementation

in ambulatory patients with COPD. *Am Rev Respir Dis* 1987; 135: 1062-8.

14. Knowles JB, Fairbarn, M, Wiggs BJ *et al*. Dietary supplementation and respiratory muscle performance in patients with COPD. *Chest* 1988; 93: 977-83.
15. Schols AMWJ, Slangen J, Volovics, L *et al*. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791-7.
16. Landbo C, Prescott E, Lange P *et al*. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856-61.
17. Rogers RM, Donahoe M, Constantino J. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 146: 1511-7.
18. Shridhar MK, Galloway A, Lean MEJ *et al*. An out-patient nutritional programme in COPD patients. *Eur Respir J* 1994; 7: 720-4.
19. Lewis MI, Belman MJ, Dorr-Uyemura J. Nutritional supplementation ambulatory patients with COPD. *Am Rev Respir Dis* 1987; 135:1062-8.
20. Ferreira IM, Brooks D, Lacasse Y *et al*. Nutritional Support for Individuals with COPD: A Meta-analysis. *Chest* 2000; 117: 672-8.
21. Otte KE, Ahlburg P, D'Amore F *et al*. Nutritional repletion in malnourished patients with emphysema. *J Parenter Enteral Nutr* 1989; 13: 152-6.
22. Chailleux E, Fauroux B, Binet F *et al*. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation: a 10-year analysis of ANTADIR Observatory. *Chest* 1996; 109: 741-9.
23. Higgins MW, Keller JB, Becker *et al*. An index of risk for obstructive airways disease. *Am Rev Respir Dis* 1982; 125: 144-51.
24. Song Y, Kang XM, Xia XR. Clinical observation on short term nutritional support in the treatment of advanced chronic obstructive pulmonary disease. *Zhonghua Nei Ke Za Zhi* 1993; 32: 819-22.
25. Ganzoni A, Heilig P, Schonenberger K *et al*. High caloric nutrition in chronic obstructive lung disease. *Schweiz Rundsch Med Prax* 1994; 83(1): 13-6..
26. Redelmeier DA, Goldstein RS, Min ST *et al*. Spirometry and dyspnea in patients with COPD: when small differences mean little. *Chest* 1996; 109: 1163-8.
27. Redelmeier DA, Bayoumi, AM, Goldstein RS *et al*. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; 155(4): 1278-82.

"Wealth, youth and flowers are guests only for four days.
They wither and fade like leaves of the water-lily."

– Guru Nanak.

ORIGINAL ARTICLE

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A study on insulin and its analogues for control of abnormal glycosylated haemoglobin in controlled or near-controlled type II diabetes mellitus patients on oral hypoglycaemic agents

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Abstract

HbA1c values are known to be elevated even in well/near-controlled type II diabetes mellitus patients especially when they are only on oral hypoglycaemic agents. Elevated HbA1c values are known to be associated with microvascular and macrovascular complications. The present study was undertaken in two phases. In phase I (2007-2009) 105 cases of type II diabetes mellitus with controlled/near-controlled glycaemic status as per ADA criteria 2007 were seen for their HbA1c values. 47.62 % had elevated HbA1c values. In phase II study (2008-2010) 50 cases with oral hypoglycaemic agents having controlled/near-controlled diabetes mellitus but with abnormal elevated HbA1c values were put on insulin and insulin analogues for controlling HbA1c values. Statistically significant findings were observed after 3 months of insulin therapy irrespective of the type of insulin used. Estimated average glucose levels if carried out may avoid repeated fasting and post-prandial glucose estimations calculated by knowing the HbA1c values.

Key words: Glycosylated haemoglobin, insulin and analogues, estimated average glucose.

Introduction

India leads the world with the largest number of diabetic subjects, thus earning the dubious distinction of being termed the "diabetes capital of the world". According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India – currently around 40.9 million – is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. Even though the prevalence of microvascular complications of diabetes like retinopathy and nephropathy are comparatively lower in Indians, the prevalence of premature coronary artery disease is much higher in Indians compared to other ethnic groups. The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years and is mainly attributed to elevated glycosylated haemoglobin[1].

We have undertaken the present study in two phases. The first phase of study (2007-2009) focussed to know percentage of abnormal glycosylated haemoglobin levels in 105 type II diabetes mellitus patients on oral hypoglycaemic agents having controlled or near controlled FPG and PPG levels. The second phase of the study (2008-2010) was conducted to know effect of insulins on abnormal glycosylated haemoglobin in 50 type II diabetic patients on oral hypoglycaemic drugs having euglycaemic status. Newer insulin and insulin analogue preparations have greater effectiveness, safety, versality in providing flexible regimens to patients' needs and bring about control on both glycaemic homoeostasis and control over HbA1c. Response to insulin and its analogues for control of abnormal glycosylated haemoglobin values was carried out in the second phase of the study.

Materials and methods

In the first phase of the study, 105 cases of patients of type II diabetes mellitus having controlled or near-controlled glycaemic status were selected. In the second phase of the study, 50 cases of patients of type II diabetes mellitus who were receiving oral hypoglycaemic agents for 3 months or more and remained controlled or near-controlled but whose HbA1c remain abnormal, were selected. Fasting plasma glucose less then 130 mg%, post-prandial glucose less then 180 mg %, and glycosylated haemoglobin less then 7 % for controlled or near-controlled type 2 diabetes mellitus were included in the study as per ADA 2007[2] guidelines.

Patients of type I diabetes mellitus, patients of type II diabetes mellitus previously receiving insulin therapy, newly detected type II diabetes mellitus patients, well or near controlled diabetics receiving oral hypoglycaemic agents for less than 3 months, anaemic patients with Hb < 9 gm% were excluded from the study. Fasting and post-prandial plasma sugar levels were done by glucose oxidase dehydrogenase (GOD) method and pyruvate oxidase dehydrogenase (POD) method. Glycosylated haemoglobin levels was conducted from Affinity Boronate Assay by electronic HbA1c meter method. Those patients

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with elevated glycosylated haemoglobin levels meeting the inclusion criteria were selected and shifted to insulin or its analogue therapy and FPG, PPG and HbA1c values were repeated post-insulin therapy after 3 months in phase II study.

Statistical analysis was carried out for knowing the efficacy of insulin and its analogues in reducing elevated glycosylated haemoglobin in pre-insulin (on OHA) and post-insulin group. The study was further extended to record percentage contribution of fasting and post-prandial glucose levels in relation to HbA1c quintiles. Estimated average glucose levels were also calculated from HbA1c by an equation (Estimated average glucose = 28.7 × A1c - 46.7) proposed by Nathan *et al*[3].

Results

The first phase of the study included 105 cases with 63 males and 42 females. Mean age for males was 53.77 ± 10.18 years while that for females was 53.10 ± 9.50 years. Male to female ratio was 1.5: 1. Mean HbA1c of males and females was 7.386 ± 1.17 and 7.476 ± 1.08 respectively. Mean FPG for males and females was 101.09 ± 13.70 and 99.071 ± 12.14 respectively. Mean PPG for males and females was 149.76 ± 19.82 and 150.02 ± 18.68 respectively (Table I). The second phase of the study comprised age and sex matched 50 cases with 31 males and 19 females. Mean of age, HbA1c, FPG, PPG for males and females are provided in Table II.

Table I: Mean FPG, PPG, and HbA1c according to sex in 105 studied cases in phase I study.

Variable	Sex	
	Male	Female
No of patients	63	42
Mean FPG ± SD	101.09 ± 13.70	99.071 ± 12.14
Mean FPG ± SD	149.762 ± 19.82	150.024 ± 18.68
Mean HbA1c ± SD	7.386 ± 1.17	7.476 ± 1.08

FPG = Fasting plasma glucose; PPG = Post-prandial plasma glucose; HbA1c = Glycosylated haemoglobin; SD = Standard deviation.

Table II: Mean and SD of FPG, PPG, and HbA1c patients on OHA according to sex in 50 studied cases in phase II study.

Parameters	Sex	
	Male	Female
No. of patients	31	19
Mean FPG ± SD(mg%)	104.66 ± 16.13	104.89 ± 11.75
Mean PPG ± SD(mg%)	142.01 ± 26.80	146.79 ± 16.33
Mean HbA1c ± SD (%)	8.02 ± 0.65	8.44 ± 0.87

FPG = Fasting plasma glucose; PPG = Post-prandial plasma glucose; HbA1c = Glycosylated haemoglobin; SD = Standard deviation.

All the 50 selected cases in the second phase of the study were shifted to insulin therapy. 20 patients were provided with insulin isophane, 20 with insulin aspart, and 10 with insulin glargine. HbA1c in them was reassessed after 3 months of insulin therapy.

Patients of the first phase of study were future divided into six groups according to quintiles of HbA1c (from 6.5% to > 9.1% with six quintiles) to study for percentage contribution of FPG and PPG to overall euglycaemic status on OHA but with varing HbA1c values (Figure 1).

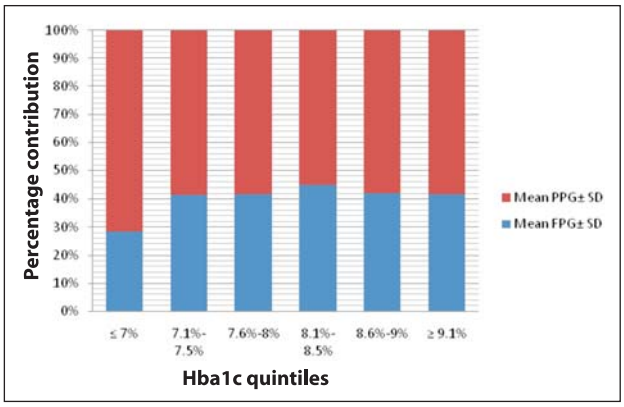

***Fig. 1**: Percentage contribution of FPG and PPG to overall euglycaemia depending on OHA on HbA1c quintiles in phase I of the study.*

In each of the HbA1c quintiles, PPG was contributing more to the overall euglycaemia than FPG. In the second phase of the study, 70% of the studied cases were below HbA1c 7.5% post-insulin therapy as compared to 18% of these same studied patients when they were on OHA, showing significant shift of patients towards controlled HbA1c (Figure 2).

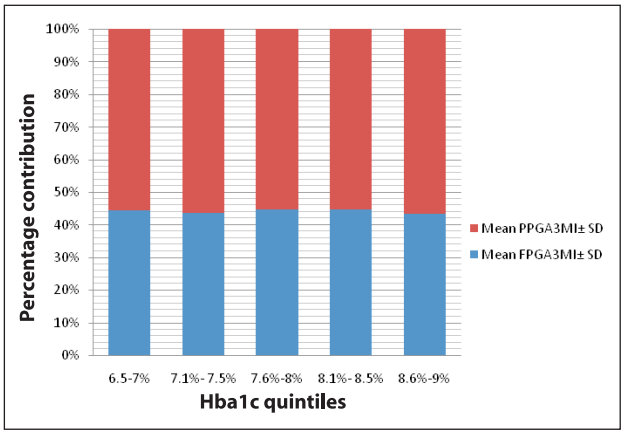

***Fig. 2**: Percentage contribution of FPG and PPG to overall euglycaemia after 3 months of post-insulin therapy on HbA1c quintiles in phase II of the study.*

In phase II of the study, estimated average glucose levels were below 200 mg% on insulin therapy as compared to OHA where most of the values were above 200 mg%. The

results were found to be statistically significant (p = 0.001) (Figure 3).

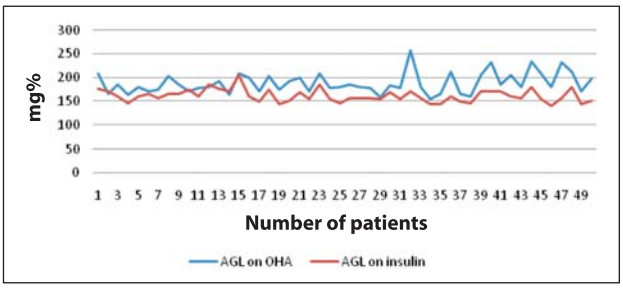

***Fig. 3**: Comparison between estimated average glucose level on OHA and after 3 months of insulin therapy.*

In phase II of the study, the mean HbA1c on OHA was 8.18 ± 0.76% while that after insulin therapy was 7.26 ± 0.47%. Thus mean reduction of HbA1c, 3 months post-insulin therapy was 1.12% (Table III).

Table III: Mean and SD of FPG, PPG, and HbA1c of patients on OHA and post-insulin therapy after 3 months in 50 studied cases in phase II study.

Parameter	Mean ± SD on OHA	Mean ± SD post-insulin therapy
FPG (mg%)	104.75 ± 14.45	113.16 ± 11.86
PPG (mg%)	143.82 ± 23.31	143.14 ± 17.11
HbA1c (%)	8.18 ± 0.76	7.26 ± 0.47

Statistical comparison of HbA1c on OHA and post-insulin therapy was significant (p = 0.001). Maximum decrease in mean HbA1c is seen in aspart group by 1.509% and lowest decrease in mean HbA1c is seen in glargine group by 0.918% as compared to OHA therapy. Among the insulin receivers no significant difference was noted (Table IV).

HbA1c of those 47.62% patients was elevated despite of controlled FPG and PPG levels (Table V). In the second phase of the study (2008 - 2010), insulin and its analogues for control of abnormal glycosylated haemoglobin in OHA controlled/near-controlled type 2 diabetics was studied in 50 studied cases with matched males and females.

Table V: Distribution of patients to sex and elevated HbA1c levels in 105 studied cases.

HbA1c (%)	Sex		Total no. of patients
	Male	Female	
Normal (≤ 7 %)	35	20	55
Elevated (>7%)	28	22	50
Total no. of patients	63	42	105

The use of biphasic insulin or its analogues, both as monotherapy and as an adjunct to other therapies, has been the subject of interest in a number of recent trials and reviews[4,5,6]. Biphasic human insulin have a more rapid and higher peak for more effective mealtime coverage as shown in their studies. In the present phase II study with 50 studied cases, statistical comparison between the three groups of insulin used for control of HbA1c revealed no statistical significant observation when compared with each other. (P values 0.194, 0.684, 0.926 for isophane, aspart and glargine insulin group users respectively). However, data for control of HbA1c pre-insulin (OHA therapy alone) and post-insulin (OHA off) had shown significant fall of HbA1c in post-insulin therapy group (Table IV). Thus this study revealed that insulin is more effective in controlling HbA1c than OHA irrespective of type of insulin therapy used. In the present study, maximum decrease in mean HbA1c was seen in aspart group by 1.509%. In 2000, Home[7] showed insulin aspart

Table IV: Distribution of patients according to HbA1c on OHA and its percentage reduction later after 3 months of insulin therapy in 3 different groups of insulin therapy.

Insulin	No. of patients	Mean HbA1c ± SD on OHA	Mean HbA1c ± SD on insulin	% reduction	S/NS	p-value
Isophane	20	8.16 ± 0.60	7.2 ± 0.347	1.173%	S	0.001
Aspart	20	8.62 ± 0.77	7.32 ± 0.59	1.509%	S	0.001
Glargine	10	7.98 ± 0.85	7.24 ± 0.45	0.918%	S	0.001

(p < 0.05, significant)

Discussion

The present study was conducted in two phases. In the first phase (2007 - 2009) HbA1c values were recorded of type II diabetes mellitus patients who were for more than 3 months on oral hypoglycaemic agents and had well or near-controlled glycaemic status. Out of the 105 patients included in the first phase of the study, 50 patients (47.62%) had uncontrolled HbA1c. It was noted that

superior to human insulin with respect to HbA1c. In 2005, the INITIATE (initiation of insulin to reach A1c target) study reported that initiating insulin therapy with twice daily aspart was more effective in achieving HbA1c targets compared to initiating insulin therapy with once daily glargine; however, mild hypoglycaemic episodes were not seen in the glargine group as compared to other groups[8]. Our observations are in agreement with observations noted earlier by these workers.

DECODE study in 1999[9] showed that HbA1c levels are more closely related to post-prandial than pre-prandial levels. In phase I of the study wherein 105 cases enrolled for knowing their percentage contribution of FPG and PPG status to HbA1c quintiles, the study revealed that in most cases PPG values were more contributing to overall euglycaemia then FPG values in each HbA1c quintiles (Figure 1). In phase II of the study, inspite of taking controlled or near-controlled diabetic patients, post-prandial glucose has shown rising trend although falling within the near-controlled status even after institution of insulin therapy (Figure 2). Uncontrolled glycaemic status with or without insulin would be more informative as has been worked out by other workers[10,11,12].

having euglycaemic status. The determination may be carried out if we know the value of HbA1c. Repeated fasting, post-meal could thus be avoided. Such practices may be undertaken in selected cases.

One has to analyse the reasons for elevated HbA1c values in near/well-controlled diabetes mellitus on OHA. Certain missing of occasional doses prior to estimation could be a factor for elevated HbA1c levels. Besides this fact, different OHAs are known to exhibit non-uniform decline in HbA1c levels. Lifestyle modifications are also a vital contributing factor known to reduce HbA1c (Table VI)[13].

We put this observation that euglycaemic patients on

Table VI: Summary of glucose-lowering interventions.

Intervention	Expected decrease in A1c with monotherapy (%)	Advantages	Disadvantages
Tier 1: Well-validated core			
Step 1: Initial therapy			
Lifestyle to decrease weight and increase activity	1.0 - 2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0 - 2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: Additional therapy			
Insulin	1.5 - 3.5	No dose limit, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycaemia, analogues are expensive
Sulfonylurea	1.0 - 2.0	Rapidly effective	Weight gain, hypoglycaemia (with glibenclamide orchlorpropamide)
Tier 2: Less validated			
TZDs	0.5 - 1.4	Improved lipid profile, decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5 - 1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established
Other therapy			
Glucosidase inhibitor	0.5 - 0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5 - 1.5	Rapidly effective	Weight gain, three times/day dose, hypoglycaemia
Pramlintide	0.5 - 1.0	Weight loss	Three injections daily, frequent GI side effects.
DPP-4 inhibitor	0.5 - 0.8	Weight neutral	Long-term safety not established, expensive

CHF = congestive heart failure; GI = gastrointestinal; MI = myocardial infarction. Source: Diabetes Care, Volume 32, Number 1, January 2009

We further stretched the phase II study with 50 studied cases to known relationship of estimated average glucose level to HbA1c as suggested by Nathan and workers[3]. The importance of average glucose with HbA1c values pre-insulin (OHA) and post-insulin shows highly significant results indicating average glucose levels all below 200 mg%. Thus the importance of glycosylated haemoglobin is also attributed to determine average sugar level. We therefore recommend that the average sugar level should be in the pre-diabetic range to label the individual as

oral hypoglycaemic agents are having elevated HbA1c to the tune of 47.62 %. When these patients were kept only on insulins, their glycosylated haemoglobin values improved irrespective of insulin type used in the study. We humbly believe that there is a paucity of published data in literature on abnormal elevated HbA1c despite their well/near-controlled glycaemic status in type II diabetes. To minimise micro and macrovascular complications early, use of insulin in such category of patients may be advocated.

References

1. Mohan V, Sandeep S, Deepa R *et al*. Epidemiology of type 2 diabetes: Indian Scenario. *Ind J Med Res* 2007; 125: 217-30.
2. American Diabetes Association: Standards of medical care in diabetes-2007 (Position Statement). *Diabetes Care* 2007; 31(1): S12–S54.
3. Nathan DM, Judith Kuenen, Rikke Borg *et al*. For The A1c Derived Average Glucose (Adag) Study Group: Translating the A1c assay into estimated average glucose values. *Diabetes Care* 2008; 31: 1473-8.
4. Halimi S, Raskin P, Liebl A *et al*. Efficacy of biphasic insulin aspart in patients with type 2 diabetes. *Clin Ther* 2005; 27: S57–74.
5. Rolla AR, Rakel RE. Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. *Clin Ther* 2005; 27: 1113-25.
6. Garber AJ, Wahlen J, Wahl T *et al*. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obes Metab* 2006; 8: 58-66.
7. Home PD, Barriocanal L, Lindholm A. Comparative pharmacokinetics and pharmacodynamics of the novel rapid-acting insulin analogue, insulin aspart, in healthy volunteers. *Eur J Clin Pharmacol* 1999; 55: 199-203.
8. Nazia Raja-Khan, Sarah S Warehime, Robert A Gabbay. Review of biphasic insulin aspart in the treatment of type 1 and 2 diabetes *Vascular Health and Risk Management* 2007; 3(6): 919-37.
9. Decode Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care* 2003; 26: 688-96.
10. Bonora E, Calcaterra F, Lombardi S *et al*. Plasma glucose levels throughout the day and HbA1c interrelationships in type 2 diabetes: implications for treatment and monitoring of metabolic control. *Diabetes Care* 2001; 24: 2023-9.
11. Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 1997; 20: 1822-6.
12. Bastyr EJ, Stuart CA, Brodows RG *et al*. (IOEZ Study Group): Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. *Diabetes Care* 2000; 23: 1236-41.
13. Nathan DM, John B Buse, Mayer B Davidson *et al*. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care* 2009; 32:193-203.

"That is a good book which is opened with expectation, and closed with delight and profit."

– Amos Bronson Alcott, American reformer & philosopher.

ORIGINAL ARTICLE

JIACM 2014; 15(2): 111-5

Fine needle aspiration cytology of HIV-related lymphadenopathy in Manipur

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Abstract

Background: A number of opportunistic infections and malignancies involving the lymph nodes are frequently encountered in human immunodeficiency virus (HIV) infection.

Aims of the study: To analyse the cytological patterns of lymph node lesions in HIV/AIDS patients in Manipur.

Methodology: The study was conducted in the department of pathology (cytology section) RIMS hospital for a period of 2 years from January 2009 to December 2010. Known cases of HIV with peripheral lymphadenopathy attending cytology OPD at RIMS hospital were enrolled for the study. Fine needle aspirations cytology (FNAC) was done and the smears were air-dried and stained with May-Grünwald Giemsa (MGG) routinely. Special stains were done whenever necessary.

Results: 64 aspirates from 62 HIV positive cases presenting with lymphadenopathy were performed. The commonest cytological diagnosis was tuberculous (TB) lymphadenitis with 27 cases (42.19%) followed by reactive lymphadenitis 18 cases (28.12%). The others were acute suppurative lymphadenitis 7 (10.94%), fungal infection 5 (7.81%), malignancy 3 (4.69%), and viral 1 (1.56%). Diagnosis could not be rendered in 3 (4.69%) cases due to inadequate material. Histopathological confirmations were available in 12 cases of tuberculous lymphadenitis and all the 3 cases of malignancy.

Conclusion: Tuberculous (TB) lymphadenitis was the commonest lesion detected. Lymph node aspiration cytology is a helpful tool for identification of opportunistic infections, neoplastic and non-neoplastic lesions in HIV related lymphadenopathy.

Key words: Human immunodeficiency virus (HIV), fine needle aspiration cytology (FNAC), tuberculous lymphadenopathy.

Introduction

Since the first positive case of HIV in Manipur was reported in February, 1990 from the blood sample of an injecting drug user (IDU), today it has become a number one killer among young adults in Manipur and a serious public health emergency. Manipur, a small state with a population of only 2.4 million in the northeast region of India, has the highest concentration of HIV infection in the country. The HIV prevalence in the state is 1.57%[1]. The emergence of the AIDS epidemic in recent years has presented lymph node pathology including cytology with formidable problems. The exclusion or confirmation of malignant lymphoma and other malignant processes by FNAC is of great of practical importance in these patients since it may obviate the need for surgical excision[2,3].

Lymphadenopathy is one of the earliest presentations in HIV infected persons[4]. A number of opportunistic infections and malignancies frequently involve the lymph nodes of HIV infected patients. FNAC as a diagnostic tool in the evaluation of lymphadenopathies is well known[4]. In a state like Manipur having high prevalence of HIV infection, a simple investigative technique for HIV infected lymphadenopathy is greatly needed. The purpose of the present study is to know the various cytological patterns of lymph node lesions in HIV patients in Manipur, India. Segregating lymphadenopathy cases that need further evaluation will help in the planning and management of HIV positive patients.

Materials and methods

The study was conducted at RIMS hospital, Manipur, India during the period January 2009 to December 2010. The material consists of 64 consecutive needle aspirations from 62 HIV positive patients with lymphadenopathy attending Cytology OPD/admitted to RIMS hospital. All the cases were proved to be HIV positive as per NACO guidelines. Ethical approval was taken for this study from the institutional ethical committee. Prior to FNAC, the patients were examined in detail, which included thorough physical examination regarding size and multiplicity of lymph nodes. After a brief explanation of the technique, an informed consent of the patient was obtained. Subsequently, FNAC was done using 23G needle attached to 20cc plastic disposable syringe with Cameco

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syringe piston. Smears were air dried and stained with May-Grundwald Giemsa (MGG) and Z-N stain for AFB. Periodic Acid Schiff (PAS) stain for fungi was performed whenever required. After staining, a detailed cytomorphological study was conducted.

Results

We performed 64 aspirations from 62 HIV positive patients presenting with lymphadenopathy. Among the cases, cervical lymphadenopathy was the commonest with 34 cases (54.8%) out of which 29 cases presented as multiple lymph nodes and 5 cases presented as single node. The next commonest presentation was generalised lymphadenopathy 13 (20.3%). The various sites and multiplicity of lymphadenopathy are summarised in Table I.

Table I: Showing sites and multiplicity of lymph nodes.

	Site	Single	Multiple	Total (62)	Percentage
1.	Cervical node	5	29	34	54.84
2.	Submandibular	3	1	4	6.45
3.	Supraclavicular	3	1	4	6.45
4.	Axillary	2	1	3	4.84
5.	Inguinal	2	2	4	6.45
6.	Generalised			13	20.97

Male to female ratio of the patients was 1:0.35. Patients age ranged from 2 years to 61 years. The age and sex-wise distribution of the patients are shown in Figure 1. The size of the lymph node varied from more than 3 cm in diameter to less than 1 cm. most of the lymph nodes were within the range of 1 - 2 cm (48.5%). Various sizes of node involvement are shown in Table II.

Table II: Showing various sizes of lymphadenopathy.

	Size (cms)	Number	Percentage
1.	> 3	6	9.38
2.	2 - 3	15	23.43
3.	1 - 2	31	48.44
4.	< 1	12	18.75
		Total = 64	

On the basis of cytomorphological analysis, diagnosis of various lymphadenopathies was made. The results were tuberculous (TB) lymphadenopathy with 27 (42.19%), reactive lymphadenopathy 18 (28.12%), suppurative lesion 7 (10.94%), fungal infection 5 (7.81%), malignancy 3 (4.69%), viral infection 1 (1.56%), – and 3 (4.69%) cases could not be diagnosed due to inadequate material (Table III). In our present study, tuberculous lymphadenitis – which was the commonest – showed four cytologic

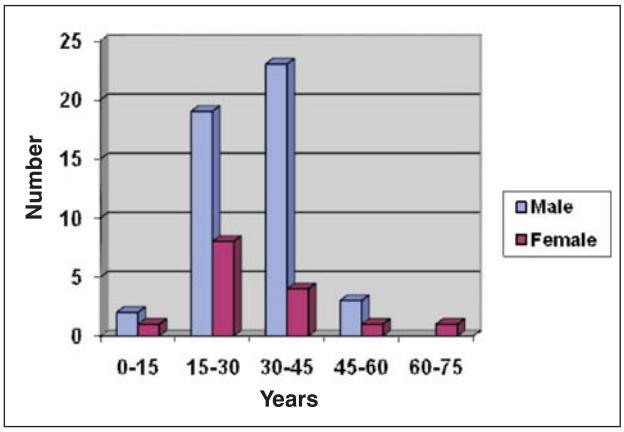

Fig. 1: *Age and sex-wise distribution.*

patterns. They were: 1) Caseating granuloma (8 cases) showing classical epithelioid granuloma, giant cells, and caseation in a milieu of lymphoid cells; 2) Granulomatous lymphadenitis (5 cases) showing only granulomas with or without giant cells (Figure 2); 3) Necrotising lymphadenitis (9 cases) which showed degenerating epithelioid cells in a necrotic background (Figure 3); and 4) Necrotising and Suppurative lymphadenitis (5 cases) where smears showed degenerating and viable neutrophils in a necrotic background. The diagnosis of tuberculous lymphadenitis could be considered in the first two patterns while the third and fourth patterns would be dismissed as suppurative lymphadenitis in the absence of Z-N stain. All the tuberculous suspected lesions were subjected to Z-N stain for acid-fast bacilli (AFB). Out of the 8 cases of caseating granulomas, 4 cases showed AFB. Among the granulomatous lesion, 2 out of 5 cases showed AFB. All the 4 AFB-negative cases of caseating granuloma and 3 cases of granulomatous lesions were put under tuberculous category after histopathological

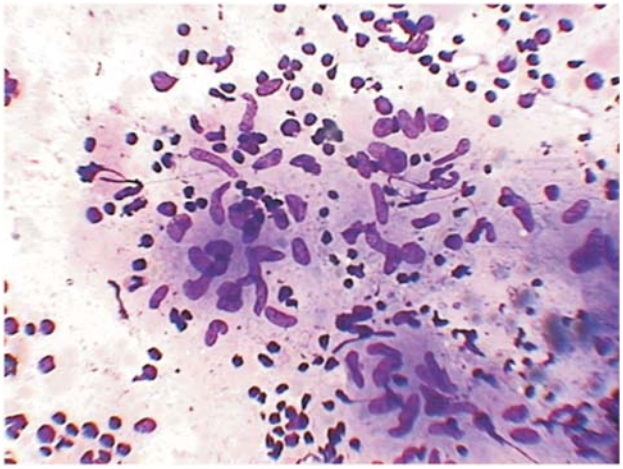

Fig. 2: *Microphotograph of FNAC lymph node smear showing granuloma (MGG stain, 40X).*

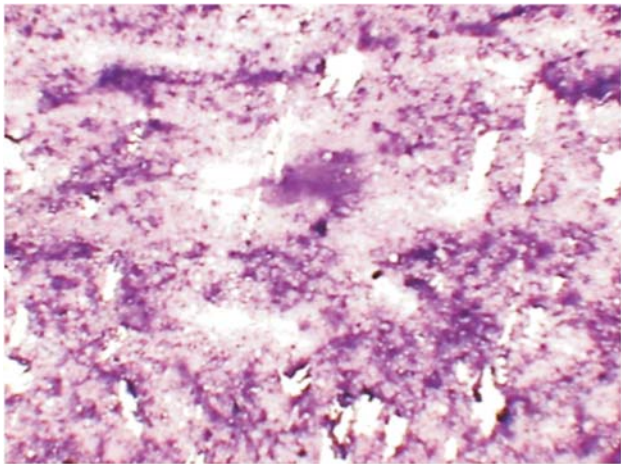

Fig. 3: *Microphotograph of FNAC lymph node smear showing caseation (MGG stain, 40X).*

confirmation. All the cases of necrotising and suppurative necrotising showed high positivity of AFB (Figure 4). 2 cases of necrotising and 3 cases of suppurative necrotising were also confirmed by histopathological examination. Out of the total 27 cases of tuberculous lymphadenitis, histopathological slides were available in 12 cases. Reactive lymphadenopathy was the second commonest with 18 cases (28.12%). They were placed in this group owing to the presence of reactive cytological picture, no clinically suspicious symptoms and clinical improvement on follow up. Of the 5 cases of fungal lymphadenopathies, two cases were of Histoplasma and *Penicillium marneffei* each and one case of Cryptococcus. The two cases of *Penicillium marneffei* were confirmed by culture on Sabouraud dextrose agar (SDA) showing wine red pigments diffusion. We encountered one case of infectious mononucleosis that presented with generalised lymphadenopathy. Among the malignant cases, one was metastatic adenocarcinoma; the other two were that of

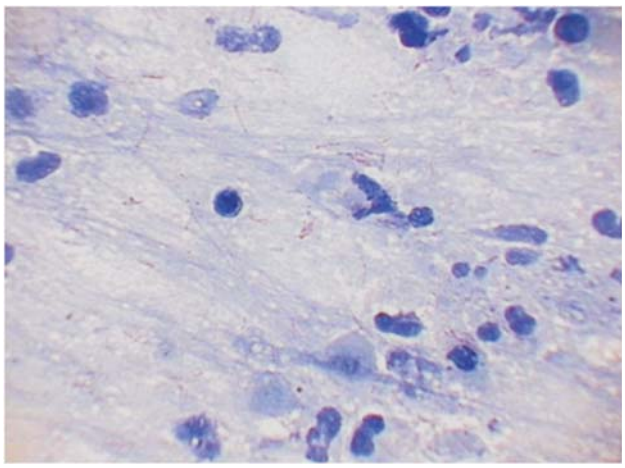

Fig. 4: *Microphotograph of FNAC lymph node smear showing AFB (Z-N stain, 100X).*

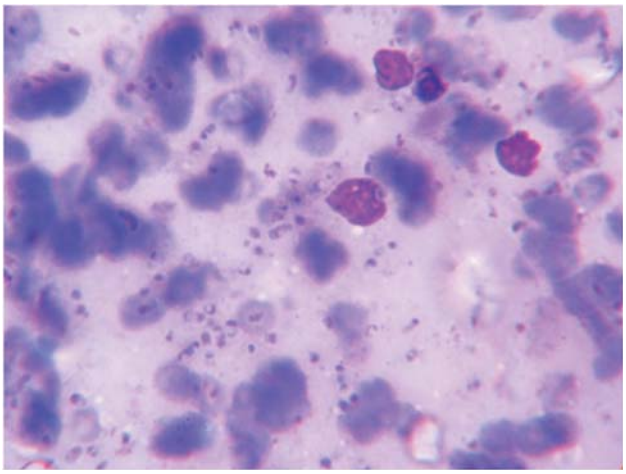

Fig. 5: *Microphotograph of FNAC lymph node smear showing Penicillium marneffei (MGG stain, 100X).*

non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) – both of which were confirmed with histopathological examination. 3 cases could not be diagnosed due to inadequate material.

Table III: Showing the FNAC diagnosis of the various lymph nodes.

Diagnosis	No. of cases	Total (64)	Percentage (%)
Tuberculosis:			
a) TB with caseating granuloma	8		
b) Granulomatous lesion	5		
c) Necrotising	9	27	42.9
d) Suppurative necrotising	5		
Reactive lymphadenitis		18	28.12
Suppurative lesion		7	10.94
Fungal infection:		5	7.81
a) Histoplasma	2		
b) *Penicillium marneffei*	2		
c) Cryptococcus	1		
Viral: Infectious mononucleosis		1	1.6
Malignancy:		3	4.7
a) Non-Hodgkin's lymphoma	1		
b) Hodgkin's lymphoma	1		
c) Metastatic adenocarcinoma		27	42.9
Inadequate material		3	4.7

Discussion

Lymph nodes are the usual target organs affected in HIV/AIDS[5]. FNAC has proven to be an easy, quick, reliable, and cost effective tool for lymphadenopathies. It is suitable for an initial rapid diagnosis in HIV positive patients with lymphadenopathies[6]. Among the peripheral lymph nodes involved, cervical lymphadenopathy was the commonest

Table IV: Showing comparison between the present study and other studies.

			Diagnosis						
	Study	No. of aspirates	TB	Reactive	Fungal	Suppurative	Viral	Malignancy	Inadequate material
1	Saikia *et al*[3]	25	9	10	3	-	-	2	1
2	Shenoy *et al*[5]	48	24	17	-	1	-	6	-
3	Nayak *et al*[11]	32	15	10	-	5	-	2	-
4	Kamana *et al*[9]	300	173	89	7	5	-	7	-
5	Vanisri *et al*[10]	36	21	13	-	-	-	1	-
6	Present study	64	27	20	3	7	1	3	3

site in the present study similar to the findings by Sawhney *et al*[7].

The maximum number of cases were found in the age group 30 - 45 years, followed by 15-30 years. In a study done by Shenoy *et al*[5], the age group commonly affected was between 25 - 30 years with cervical group of nodes being the most common site.

In India the most common opportunistic infection in AIDS patients is tuberculosis[8]. In our study, tuberculous lymphadenitis was the most encountered cause of lymphadenopathy constituting 27 cases (42.19%). Similar findings were also observed in various studies conducted by Shenoy *et al*[5] with 50% in Mangalore, Jayaram *et al*[4] (53.84%) in Malaysia, Kamanal *et al*[9] (57.67%) and Vanisri *et al*[10] with 58.3%. Nayak *et al*[11] found four patterns of TB lymphadenitis: a) Necrotising granulomatous; b) Granulomatous; c) Necrotising; and d) Necrotising suppurative. Llatjos *et al*[12] observed three cytological patterns in AIDS patients diagnosed as having tuberculous lymphadenitis: a) Granulomatous lymphadenitis; b) Necrotising granulomatous lymphadenitis; c) Necrotising lymphadenitis. A definite cytologic diagnosis of tuberculous lymphadenitis can be offered in smears with caseating granulomas with or without giant cells, while the necrotising suppurative smears would be dismissed as acute suppurative lymphadenitis in the absence of Zeihl-Neelsen stain. This pattern is found in purulent aspirates and shows the highest rate of acid-fast bacilli positivity[13,5]. Thus Zeihl-Neelsen staining should be performed on all aspirates from cases of suspected tuberculosis. Tuberculous lymphadenitis may be more common in HIV patients with superficial lymphadenopathy than is generally believed. Greater use of lymph node aspiration or biopsy may improve the diagnosis of suspected tuberculosis[14].

Reactive lymphadenitis was the second most common lesion in the present study (28.12%). Similar observations were also made by Saika *et al*[3] (40%), Vanisri *et al*[10] (36.1%) even though higher percentage were reported by Martin-Bates *et al*[6] (41%) and Reid *et al*[2] (51%).

We found 7 cases (10.94%) of acute suppurative lymphadenitis. ZN and PAS stains were negative with smears showing mostly neutrophils and scant lymphocytes in a necrotic background. Nayak *et al*[11] also reported suppurative lymphadenitis in 15.62%.

Among the fungal lesions, we found two cases of Histoplasma and *Penicillium marniffei* each. *Penicillium marniffei* is readily detected by direct microscopy. Lim *et al*[15] has documented the rapid diagnosis of *Penicillium marniffei* infection by FNAC and stated that demonstration of yeast cells with a distinctive central septum confirms the diagnosis. *Penicillium marniffei* measures 2 - 6 µm in diameter, oval and can be found either within the histiocytes or scattered throughout the tissue[16,17]. On the other hand yeast cells of Histoplasma are small in size (3 - 4 µm) and divide by budding[17]. Jayaram *et al*[4] encountered two cases of histoplasma, one cryptococcal lymphadenitis and one case of non-Hodgkin's lymphoma similar to the present study. Cryptococci were seen in lymphnodes of patients with marked immunosuppression. Saika *et al*[3] observed two cases in their study. Lymph node FNAC is a valuable investigation in HIV patients where most opportunistic infections (bacterial and fungal) can be correctly identified and high grade lymphoma can be diagnosed[4].

The comparison of various other similar studies with the present study is shown in Table IV. FNAC of lymph nodes in HIV/AIDS patients with clinical correlation can provide most useful information to physicians to determine the further mode of management. However, to obtain maximum benefit from the procedure, co-operation between a committed, trained cytopathologist and an experienced clinician is essential[18]. With today's increasing cost of medical practice, any technique which speeds up the process of diagnosis is of tremendous value.

Conclusion

Tuberculous (TB) lymphadenitis was the commonest lesion detected. Lymph node aspiration cytology in HIV patients helps in segregating cases which needs further

evaluation. Neoplastic lesions need biopsy and immunohistochemistry for typing especially in NHL. Detection of opportunistic infections in lymph nodes is also possible from aspirates along with culture.

References

1. National AIDS Control Organisation- HIV Sentinel Surveillance & HIV Estimation in India 2007- A Technical Brief. www.nacoonline.org.
2. Reid AJ, Miller RF, Kocjam GI. Diagnostic utility of FNAC in HIV-infected patients with lymphadenopathy; *Cytopathology* 1998; 9(4): 230-9.
3. Saikia UN, Dey P, Jindal B *et al*. Fine needle aspiration cytology in lymphadenopathy of HIV positive cases. *Acta Cytol* 2001; 45(4): 589-92.
4. Jayaram G, Chew MT. Fine needle aspiration cytology of lymph nodes in HIV infected individuals. *Acta Cytol* 2000; 44(6): 960-6.
5. Shenoy R, Kapadi SN, Pai KP *et al*. Fine needle aspiration diagnosis in HIV-related lymphadenopathy in Mangalore, India. *Acta Cytol* 2002; 46(1): 35-9.
6. Martin Bates E, Tanner A, Survana SK *et al*. Use of fine needle aspiration cytology for investigating lymphadenopathy in HIV positive patients. *J Clin Pathol* 1993; 46(6): 564-6.
7. Col Sawhney MPS. Lymphoreticular involvement in human immunodeficiency virus infection. *MJAFI* 2008; 64: 4-6.
8. Kumarasamy N, Solomon S, Jayakar Paul SA *et al*. Spectrum of opportunistic infections among AIDS patients in Tamil Nadu, India. *Int J STD AIDS* 1995; 6: 447-9.
9. Kamana NK, Wanchu A, Sachdeva RK *et al*. Tuberculosis is the leading cause of lymphadenopathy in HIV infected persons in India: results of a fine needle aspiration analysis. *Scand J Infect Dis* 2010; 42(11-12): 827-30.
10. Vanisri H R, Nandini N M, Sunila R. Fine needle aspiration findings in human immunodeficiency virus lymphadenopathy. *Indian J Pathol Microbiol* 2008; 51(4): 481-4.
11. Nayak S, Mani R, Kavatkar AN *et al*. Fine needle aspiration cytology in lymphadenopathy of HIV-positive patients. *Diagn Cytopathol* 2003; 29(3): 146-8.
12. Llatjos M, Romeu J, Clotet B *et al*. A distinctive cytologic pattern for diagnosing tuberculous lymphadenitis in AIDS. *J Acquir Immune Defic Synd* 1993; 6(12): 1335-8.
13. Metre MS, Jayaram Gita. Acid Fast bacilli in aspiration smear from tuberculous lymph nodes – An analysis of 255 cases. *Acta Cytol* 1987; 31: 17-9.
14. Bem C. Human immunodeficiency virus positive tuberculous lymphadenitis in Central Africa: clinical presentation of 157 cases. *Int J Tuberc Lung Dis* 1997; 1(3): 215-9.
15. Lim D, Lee YS, Chang AR. Rapid diagnosis of Penicillium marneffei infection by fine needle aspiration cytology. *J Clin Pathol* 2006; 59(4): 443-4.
16. Devi KR, Laishram RS, Rajkumari R *et al*. Penicillium marneffei- an indicator disease of AIDS: A case report. *Indian J Pathol Microbiol* 2007; 50(3): 674-6.
17. Cooper CR Jr, Mc Ginnis MR. Pathology of Penicillium marneffei: An emerging acquired immunodeficiency syndrome related pathogen. *Arch Pathol Lab Med* 1997; 121(8): 798-104.
18. Tilak V, Dhaded AV, Jain R. Fine needle aspiration cytology of Head and neck masses. *Indian J Pathol Microbiol* 2002; 45(1): 23-30.

"Two sorts of writers possess genius;
those who think, and those who cause others to think."

– Joseph Roux.

ORIGINAL ARTICLE

JIACM 2014; 15(2): 116-9

Hospital based study of carotid intima media thickness and high-sensitivity C-reactive protein in young hypothyroid patients

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Abstract

***Background and objective:** Hypothyroidism enhances atherosclerosis in multiple ways carotid intima media thickness is a risk determinant of atherosclerosis. The hsCRP (high-sensitivity C-reactive protein) is a marker of inflammation and has been incriminated as a risk factor for future cardiovascular events. The present study was conducted to assess carotid intima media thickness (CIMT) and hs CRP in young hypothyroid patients. It was also aimed to determine any relation of these variables to other risk factors of atherosclerosis in young hypothyroid patients.*

***Methods:** In a prospective observational hospital based study we consecutively included 50 patients (18-40 years) each in overt (thyrotropin level >10 miu/l) and sub-clinical hypothyroidism (thyrotropin level 4 - 10miu/l) group along with age, sex, BMI matched euthyroid controls. We compared CIMT and hs CRP in 3 groups along with other atherosclerotic risk factors.*

***Results:** Mean CIMT values in group 1, 2, and 3 were 0.72 ± 0.12, 0.66 ± 0.13, and 0.48 ± 0.09 mm respectively (p value was significant < 0.001). Mean hsCRP levels were 3.04 ± 0.8, 2.56 ± 0.65, and 1.81 ± 0.88 in 3 groups respectively, which was also found to be significant (p<0.001).CIMT and hsCRP also showed positive correlation with other atherosclerotic risk factors (diastolic hypertension and LDL cholesterol).*

***Conclusion:** This is the first study trying to correlate CIMT and hsCRP in patients of hypothyroidism. Hypothyroidism even in sub-clinical form leads to vascular alterations and is associated with increased cardiovascular risk. Therefore, efforts should be made to detect and treat hypothyroidism at an early stage.*

***Key words:** Sub-clinical hypothyroidism, cardiovascular risk factors, hsCRP, carotid intima media thickness.*

Introduction

There is incontrovertible evidence that overt hypothyroidism is associated with several functional cardiovascular abnormalities and increased risk of atherosclerosis[1]. Sub-clinical hypothyroidism – a mild degree of thyroid failure – is characterised by increase in thyroid stimulating hormone and normal total and free thyroxine levels[2]. The prevalence of sub-clinical hypothyroidism has been identified as 4 - 10% in different population groups without known thyroid disease and it increases with age[3]. The cardiovascular benefits of levothyroxine replacement are not questionable in overt hypothyroidism but no consensus has been reached so far about the adverse cardiovascular health outcomes of sub-clinical hypothyroidism and its treatment[4]. Despite some conflicting reports[5], many studies have found that sub-clinical hypothyroidism is also associated with increased risk of atherosclerosis as these subjects with sub-clinical hypothyroidism also share the same potential atherogenic factors such as higher total and low density lipoprotein cholesterol, increased hsCRP, hyperhomocysteinaemia, altered coagulation profile, increased arterial stiffness and endothelial dysfunction which are present in overt hypothyroidism[6-13].

The carotid intima media thickness (CIMT) is a close marker of early atherosclerotic changes and is a widely accepted surrogate end-point for cardiovascular events[14]. The association of carotid intima media thickness with major cardiovascular risk factors has been well demonstrated. Nagasaki *et al*[15] demonstrated carotid artery intima media thickening in patients with overt hypothyroidism and Kim *et al*[16] in sub-clinical hypothyroidism which was regressed after levothyroxine replacement. Similarly, chronic inflammation is associated with adverse cardiovascular outcomes and hsCRP has been proved to be the strongest and most significant predictor of the risk of future cardiovascular events[17]. Thus we conducted this study to assess the cardiovascular risk in young hypothyroid patients who have not been particularly studied so far using two important tools CIMT and hsCRP which have not been correlated with each other; and in this way our study is unique.

Study design and methods

This study was carried out as a prospective observational

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study in a tertiary care hospital associated with Era Medical College, Lucknow from January 2009 to June 2010. The young patients (18 - 45 years), who presented with history and clinical examination suggestive of hypothyroidism were subjected to thyroid stimulating hormone (TSH) and free thyroxin determination (normal range 0.3 - 4 miu/l, and 0.9 - 1.7 ng/dl respectively). On the basis of TSH they were divided into overt and sub-clinical hypothyroidism groups. Overt hypothyroidism was defined as an elevated TSH > 10 miu/l, sub-clinical hypothyroidism as TSH level > 4 miu/l but < 10 miu/l and euthyroidism was defined as TSH < 4 miu/l. 50 consecutive patients were enrolled in each group (overt and sub-clinical) and 50 euthyroid (age, sex, and BMI matched) controls were selected among hospital staff. Patients with diabetes mellitus, smokers, alcohol users, those with pituitary-hypothalamic disorders, pregnant, critically ill, those taking levothyroxine, oral contraceptives, statins within 3 months before enrollment, patients with concomitant inflammatory disease, coronary artery disease or cerebrovascular accidents were excluded from the study. The study was approved by the institutional ethics committee and all subjects gave written voluntary consent to participate in the study.

Methods

A general physical examination was performed including assessment of height in meters^2 (without shoes), weight in kg, waist circumference (minimum value between iliac crest and lateral costal margins) and hip circumference were measured in centimeters (cm), BMI was calculated as weight (in kg)/height (in m^2). Systolic and diastolic blood pressures were measured from the right brachial artery in supine position after 10 minutes of rest using pneumatic sphygmomanometer.

Biochemical evaluation

Venous blood samples were drawn after overnight fast of 12 hours. Serum was centrifuged and stored at –70 degrees until assayed. Serum TSH and free thyroxin levels were measured by Immunochemiluminescense (Diagnostic Corporation, USA). The intra-assay coefficients of variation were 3.8 - 12.6% and 4.2 - 7.8% while inter-assay coefficients of variations were 4.2 - 12.2% and 4.6 - 8% for TSH and free thyroxine respectively. Total cholesterol (TC), triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) were determined enzymatically (Boehringer Mannheim Systems, Germany) and low density lipoprotein cholesterol (LDL-C) was calculated by Friedwald equation LDL-C = (TC-HDL) - TG/5. The reference ranges for all lipid parameters were based on ATP III National Cholesterol Education Programme[18]. HsCRP was measured by ELISA (Diagnostics Biochem, Canada) in mg/dl; < 1mg/dl was considered as low risk, 1 - 3 mg/dl as moderate risk, and > 3 mg/dl was considered as high risk[17].

Carotid intima media thickness (CIMT) was measured by B mode ultrasound (Logiq 5 GE Medical Equipments, Mumbai) using a linear probe at frequency of 9-11 MHz. The common carotid arteries were scanned at the level of bifurcation on either sides or mean value was used for analysis. CIMT was assessed by single observer who was blinded for TSH values.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS 15.0 version). CIMT was expressed in quintiles. The lowest values were in I and highest values were in V quintile. Results were shown as number (%) and mean standard deviation. Analysis of variance (ANOVA) was used to compare patients of overt, sub-clinical hypothyroidism, and control group. Pearson linear correlation coefficient was used to define correlation between CIMT, hsCRP, lipid profiles, and TSH values. The value $p < 0.05$ was accepted as statistically significant.

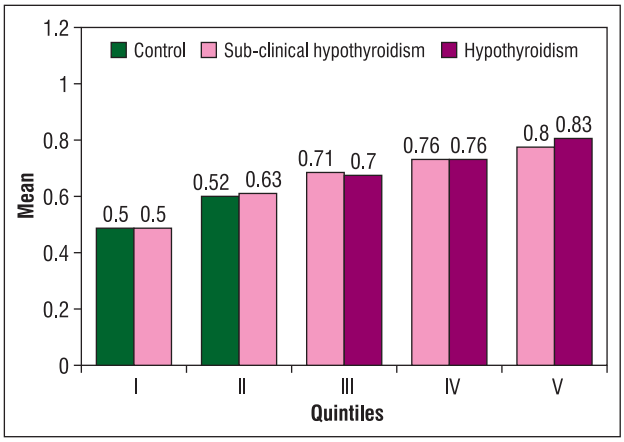

Fig. 1: *Quintile-wise distribution of all patients and controls according to CIMT.*

Results

The characteristerics of patients of sub-clinical and overt hypothyroidism and controls have been summarised in Table I. Mean age, sex, and BMI did not differ among overt, sub-clinical hypothyroidism and control groups. The mean TSH was 17.81 ± 9.6 in overt, 7.94 ± 1.45 in sub-clinical and 3.6 ± 0.51 in control group ($p < 0.001$). Mean diastolic blood pressure was 95.8 ± 11, 88.24 ± 13 and 82 ± 12 mmHg. Total cholesterol was 218.4 ± 42.3, 192.8 ± 16 and 180 ± 10.6 mg/dl respectively ($p < 0.01$), LDL cholesterol was 151 ± 34.8, 135 ± 23 and 112 ± 12 mg/dl respectively ($p < 0.001$). The values of mean CIMT were in highest

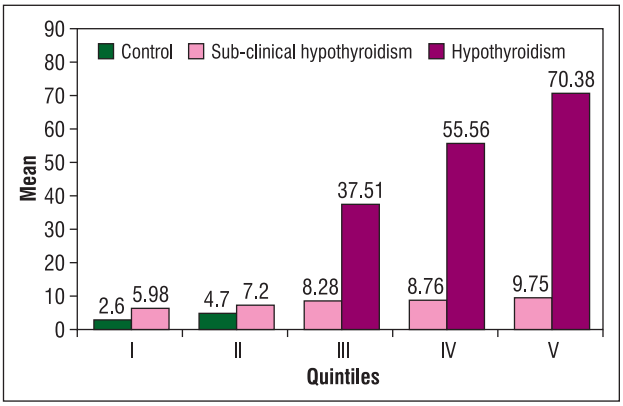

Fig. 2: *CIMT quintile wise distribution of patients according to TSH.*

quintile in overt hypothyroidism (0.71 ± 0.14 mm) followed by sub-clinical hypothyroidism (0.6 ± 10 mm) and lowest were in controls (0.5 ± 0.08 mm). The hsCRP levels were 3.04 ± 0.8, 2.56 ± 0.6 and 1.8 ± 0.6 mg/dl in three groups respectively ($p < 0.001$). There was positive correlation between TSH, CIMT and hsCRP. In the highest quintile of CIMT, patients had higher TSH and Hs CRP values.

Table I: Clinical characteristics of patients with sub-clinical and overt hypothyroidism and control subjects.

Variables	Control	Sub-clinical	Overt
Age (years)	29.92 ± 6.74	31.8 ± 8.57	31.36 ± 5.57
Female sex (%)	76%	72 %	78%
Duration of symptoms (days)	-	84 ± 21	780 ± 52
Waist/hip ratio	0.94 ± .08	0.94 ± 0.16	0.96 ± 0.09
Diastolic blood pressure (mmHg)	82 ± 12	88.24 ± 13	95.8 ±11*

*Data is shown mean ± SD; *p < 0.05 was considered significant.*

Table II: Biochemical parameters of patients with sub-clinical and overt hypothyroidism and control subjects.

Variable	Control	Sub-clinical	Overt
TSH (miu/L)	3.6 ± 0.5	7.94 ± 1.45	37.8 ± 19.6*
Total cholesterol (mg/dl)	180 ± 10.6	192.8 ± 16	218.4 ± 42*
HDL cholesterol (mg/dl)	44.6 ± 8	44.2 ± 7.6	42.2 ± 9.6
LDL cholesterol (mg/dl)	112 ± 12	135 ± 23	151 ± 34*
Triglyceride (mg/dl)	102.6 ± 14	108 ± 11.6	103.4 ± 14
HsCRP (mg/dl)	1.8 ± 0.6	2.56 ± 0.6	3.04 ± 0.8*
CIMT average (mm)	0.5 ± 0.08	0.62 ± 0.1	0.71 ± 0.14*

*Data are mean ± SD; *p < 0.05 was considered significant.*

Discussion

The onset of hypothyroidism is a progressive process starting from mild thyroid failure (sub-clinical hypothyroidism) to overt hypothyroidism and its effect on cardiovascular system have been well recognised since 1918 when Zondek described the 'myxoedema heart'. In overt hypothyroidism, increased risk of atherosclerosis is related to induction of hypercholesterolaemia, stiffening of central arteries, and diastolic hypertension.

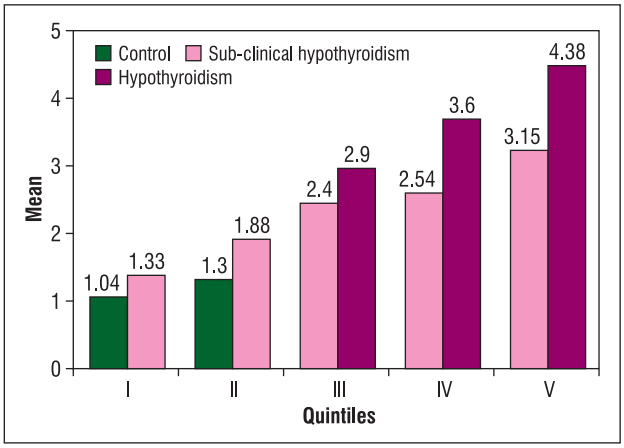

Fig. 3: *Quintile-wise distribution of all patients according to hsCRP.*

Recently newer nontraditional risk factors, such as high levels of highly sensitive CRP, homocystein, endothelial dysfunction, and altered coagulation parameters have also been incriminated in causation of atherosclerosis and it has been demonstrated by surrogate markers (CIMT) which was reversible after levothyroxin replacement. Controversy still remains as to the risk of cardiovascular disease associated with sub-clinical hypothyroidism although increased cardiovascular risk has been shown to be present even in this subgroup also.

Our study showed that patients of overt and sub-clinical hypothyroidism both had higher CIMT and hsCRP values than control subjects. There was a positive correlation between CIMT, hsCRP, and TSH levels. The highest quintile of CIMT included patients who had higher TSH and hsCRP levels. Patients with subclinical hypothyroidism had CIMT and hsCRP higher than controls. High total cholesterol and LDL cholesterol along with diastolic hypertension were present in both overt and subclinical hypothyroidism although HDL cholesterol did not differ.

Cakal *et al*[19] have similarly demonstrated higher CIMT in primary hypothyroid patients. They also found positive correlation between lipids, CIMT, and TSH levels. They concluded that CIMT is an objective sign of accelerated atherosclerosis in patients with primary hypothyroidism. Monzani and co-workers[20] found early carotid wall alterations in sub-clinical hypothyroid patients that showed improvement after levothyroxin replacement. They also observed positive correlation between mean CIMT and serum TSH levels. Since many studies except a

few, on the relationship between sub-clinical hypothyroidism and hyperlipidaemia or cardiovascular disease have been performed using elderly subjects[7] who do not represent the subject population of interest in terms of cardiovascular risk prevention, on the contrary they are actually benefited by the presence of sub-clinical hypothyroidism; therefore we chose young hypothyroid patients as study population.

This is the first time that we conducted this type of study to correlate hsCRP and CIMT both together in patients of hypothyroidism; although more number of studies with larger number of patients is required to study relative benefits of each of them and to conclude which tool is better to assess the cardiovascular risk.

Conclusion

Presence of even sub-clinical hypothyroidism poses a definite cardiovascular risk. There should be an active search for these and they should be considered for treatment. Further, large scale studies are needed to determine the superiority of different tools over one another for the assessment of cardiovascular risk.

References

1. Biondi B, Klein I 2004 Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine* 2004; 24: 1-13.
2. Surks MI, Ortiz E, Daniels GH *et al*. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; 291: 228-38.
3. Hollowell JG, Staehling NW, Flanders WD *et al*. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002; 87: 489-99.
4. Vanderpump MPJ, Tunbridge WMG, French JM *et al*. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol* (Oxf)1995; 43: 55-68.
5. Efstathiadou Z, Bitsis S, Milionis HJ *et al*. Lipid profile in subclinical hypothyroidism: is l-thyroxine substitution beneficial? *Eur J Endocrinol* 2001; 145: 705-10.
6. Kahaly G. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 2000; 10: 665-79.
7. Hak AE, Pols HA, Visser TJ *et al*. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infraction in elderly woman: the Rotterdam Study. *Ann Intern Med* 2000; 132: 270-8.
8. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. *J Clin Endocrinol Metab* 2002; 87: 1533-40.
9. Ozcan O, Cakir E, Yaman H *et al*. The effects of thyroxine replacement on the levels of serum asymmetric dimethylarginine (ADMA) and other biochemical cardiovascular risk markers in patients with subclinical hypothyroidism. *Clin Endocrinol* 2005; 63: 203-6.
10. Deicher R, Vierhapper H. Homocysteine: a risk factor for cardiovascular disease in subclinical hypothyroidism? *Thyroid* 2002; 12: 733-6.
11. Muller B, Tsakiris DA, Roth CB *et al*. Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. *Eur J Clin Invest* 2001; 31: 131-7.
12. Owen JD, Rajiv C, Vinereanu D *et al*. Subclinical hypothyroidism, arterial stiffness, and myocardial reserve. *J Clin Endocrinol Metab* 2006; 91: 2126-32.
13. Taddei S, Caraccio N, Virdis A *et al*. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab* 2003; 88: 3731-7.
14. O' Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. *Am J Cardiol* 2002; 90: 18L-21L.
15. Nagasaki T, Inaba M, Henmi Y Kumeda Y *et al*. Decrease in carotid intima media thickness in hypothyroid patients after normalisation of thyroid function. *Clin Endocrinol (Oxf*) 2003; 59: 607-12.
16. Kim SK, Kim SH, Park KS *et al*. Regression of the increased common carotid artery intima media thickness in subclinical hypothyroidism after thyroid hormone replacement. *Endocr J* 2009; 56: 753-8.
17. Ridker PM. C-reactive protein-A simple test to help predict risk of heart attack and sroke. *Circulation* 2003; 108: E81-E5.
18. National Cholesterol Education Programm(USA). Expert Panel on detection evaluation and treatment of high blood cholesterol in adults. Third report of the National Cholesterol Education Program (NCEP; adult treatment panel III): final report. Bethesda:National institutes of Health;2002.
19. Monzani F, Caraccio N, Kozakowa M *et al*. Effect of levothyroxine replacement on lipid profile and intima media thickness in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab* 2004; 89: 2099-106.
20. Cakal E, Turgut AT, Demirbas B *et al*. Effect of levothyroxin replacement therapy on caroltid intima-media thickness in patients with primary hypothyroidism. *Exp Clin Endocrinol Diabetes* 2009; 117(6): 294-300.

"Seek the friendship of the pure, and shake off the worthless even at a price."

– Tiruvalluvar, The Kural: 800.

REVIEW ARTICLE

JIACM 2014; 15(2): 120-4

Understanding the relation between COPD and coronary artery disease

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Abstract

Coronary artery disease (CAD) is one of the leading causes of mortality in chronic obstructive pulmonary disease (COPD). Right ventricular hypertrophy and ischaemia are known to occur in COPD due to secondary pulmonary hypertension, but there is a significant link between COPD and CAD, regarding aetiology, pathophysiology, and precipitating factors. There is a definite role of smoking, respiratory muscle strength and lung function (independent of the effect of smoking) and inflammatory markers, which predisposes the patient of COPD towards CAD. Even precipitating factors for acute exacerbation of COPD like infections, hyperglycaemia, or enzyme matrix metalloproteinase (MMP) have a role to play in acute coronary syndrome. Steroids given for COPD in long term can contribute to CAD and statins have a beneficial role to play in COPD also. We should look for CAD in patients of COPD before severe left ventricular dysfunction sets in.

Keywords: MMP (matrix metalloproteinase); PFT (pulmonary function test); FEV_1 (forced expiratory volume in 1 second).

Introduction

In hospital admissions, patients being admitted with acute exacerbation of COPD is a regular feature. Reynolds found that 50 per cent of patients with COPD past the age of 50 years had CAD, hypertension, or heart failure[1]. Also, in SPRINT study – a series of 5,800 patients with acute myocardial infarction – the incidence of COPD was roughly 50 per cent higher than in the general population[2]. In many such known patients of COPD usual presentation is congestive cardiac failure. However, a sizeable number present with biventricular failure or pure left ventricular failure. Breathlessness in such patients may be due to underlying CAD. The traditional paradigm is that COPD patients die from progressive respiratory failure, but the actual fact is that CAD is one of the leading causes of mortality in COPD cases. We should try to probe the following in relation to COPD:-

- Proportion of cardiac patients having concomitant COPD.
- Cause of acute breathlessness – whether respiratory or cardiac, or difficult to differentiate?
- Standard line of drugs we prescribe for COPD patients and their safety in underlying CAD.
- How frequently we go for spirometry and interpret its data in COPD and CAD (acute LVF).

It is surprising that a measure of respiratory function has not been included in health assessment programmes. Significantly, still many do not perceive respiratory functions having direct relation with underlying cardiac status.

Role of spirometry

This is underused. A severe obstructive or restrictive pattern would point to a respiratory cause. In borderline cases echocardiography can clinch the diagnosis. Similar symptoms of dyspnoea, chest pain, due to right ventricular ischaemia or secondary pulmonary hypertension in COPD, raised JVP, crepitations, rhonchi, and signs of cardiac failure, may not give a clear picture many a times. Non-specific ECG changes in COPD; mild rise in troponins; unequivocal echocardiographic study may understandably mask underlying CAD. Two conditions do masquerade as COPD with pulmonary hypertension. Important is a curable condition of chronic constrictive pericarditis; here, echocardiography using superior vena cava Doppler can assist in differentiation. The other condition, albeit historical, is reverse Bernheim's disease; here, a thickened interventricular septum of severe pulmonary hypertension bulges into the left ventricle compromising left ventricular function. Both cases may be considered to arise from CAD. Our article will focus on the definitive association between COPD and CAD, so as to highlight the fact that COPD is now a strong risk factor for CAD, and timely diagnosis of CAD will positively affect the prognosis of COPD patients.

We will try to analyse each and every known possible link between COPD and CAD one by one:-

A. Smoking: Undoubtedly, it is significantly related to causation of chronic bronchitis and emphysema and also is a major risk factor for CAD. Possible link is due to poor lung function and low FEV_1 which has a dose response relationship to the intensity of cigarette smoking – expressed as pack years. Low FEV_1 has a

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direct effect on CAD as explained below. Smoking deranges the lipid profile which becomes more atherogenic, induces changes in platelet function, and causes endothelial dysfunction by the mechanism of free radical injury, increases SICAM-1(soluble intracellular adhesion molecule-1), fibrinogen, monocytes, and CRP, which is the platform for atherogenesis[3]. Cessation of smoking has been shown to alter the lipid profile favourably and accelerate regression of plaque in vessels.

B. Right ventricular ischaemia: Long-standing COPD causes secondary pulmonary hypertension which leads to right ventricular hypertrophy (RVH). RVH along with hypoxaemia in COPD leads to a supply-demand mismatch and can cause angina due to RV ischaemia[4]. Right ventricular myocardial infarction is also seen in patients of COPD more due to this factor[5].

C. Inflammatory markers: COPD is a state of systemic inflammation and high levels of inflammatory markers are associated with severity of airflow obstruction and cardiac injury. Inflammatory process in airways parenchyma and pulmonary vasculature may spillover into systemic circulation promoting a generalised inflammatory reaction, i.e., a process of reverse causation. This inflammation was seen in COPD persons who were non current smokers; and once COPD develops, cessation of smoking may not fully attenuate the inflammatory process associated with this condition. Inflammatory markers set the stage not only for COPD but also for atherosclerosis and thus CAD. Apart from leucocytosis, CRP, fibrinogen, α_1 antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid were found to be associated with low FVC and increased chances of cardiovascular death. These inflammatory sensitive proteins (ISP) play a detrimental role in atherosclerosis[5]. These inflammatory markers not only predispose COPD patients to CAD but also to osteoporosis, muscle wasting, and malignancy[6,7]. Notably all these complications are observed in COPD[8] (along with CVA ischaemic stroke), Fibrinogen[9], TNF-α[10] and CRP were shown to be associated with decrease FEV_1 and FEV_1/FVC ratio. Interlukin-6 ELISA assay was found to be positively correlated with low lung functions and complications of COPD[11]. This relation was found even in non current smokers showing that once COPD develops, cessation of smoking may not fully attenuate the inflammatory process. COPD is characterised by intense inflammation of airways, parenchyma and lung vasculature. It is possible that there is an inflammatory spillover into the systemic circulation causing this to be a generalised process[12]. It is possible that common genetic and constitutional factors may predispose individuals with COPD to systemic and pulmonary inflammation. So COPD is responsible for systemic inflammation along with possibility of reverse causation, i.e., systemic inflammation causing injury to airways. Inflammatory markers cause accelerated decline in lung function, repeated hospital admissions, and acute coronary events[13] as airflow limitation doubles the risk of cardiovascular mortality independent of smoking[8,14].

D. Lung function in COPD and cardiovascular risk: Poor lung function is associated with risk of developing diabetes and high BP, fatal stroke, and cardiovascular disease[15]. Poor lung functions (FEV_1, FEV_1/FVC ratio, PO_2, $PaCO_2$ levels), respiratory muscle strength all have been shown to have strong association with CAD independent of the effect of smoking and atherogenic lipid profile[16]. Adverse effect of lung function on CAD was found more marked in women[17]. Lung function is strongly related with height and gender. Low FEV_1 is related to CAD and is independent of the confounding effect of smoking as findings were found to be consistent among never, current, and former smokers. Stronger relation among women was found to be either due to an artefact or the consequence of residual confounding, a chance finding, or may be due to unknown biological effect on lung function which is different in men and women[18]. Low FEV_1 apart from increased levels of inflammatory markers is associated with ventilation-perfusion mismatch, low PaO_2, high $PaCO_2$ – which in turn leads to higher pulmonary artery pressures and poor left ventricular function.

E. Respiratory muscle strength: It is also related to CAD[19]. Maximal inspiratory pressure (MIP) is a measure of diaphragm muscle strength and reduced MIP is a risk factor for respiratory and total mortality. A low MIP is a marker of generalised poor health. Inflammation, malnutrition, mechanical stress, metabolic stress and oxidative stress, and drugs are all related to low MIP and poor health. Thus, associated with[20] decreased FEV_1, FVC and PEF and cardiovascular morbidity and mortality, the effect of MIP on CAD is similar to that of decreased FVC. Inclusion of FVC (modestly) attenuated the effect of MIP on outcome. Interestingly, markers of inflammation do not appear to explain the effect of MIP on CAD and also decreased MIP does not appear to be a risk factor for incident CHF; although in prevalent CHF, decrease in MIP was an independent predictor of prognosis[21].

F. Risk of CAD in bronchial asthma: On the similar

above-mentioned risk factors like inflammatory markers, decreased lung function, not only COPD but also bronchial asthma is associated with modest but statistically significant increased risk of CAD among women[22] especially. Thus, association was seen both in never and in ever smoking younger and older women. By contrast, asthma was not found to be significantly associated with CAD among men.

G. Precipitating factors for acute exacerbation of COPD and ACS: There is a definitive link between AECOPD (acute exacerbation of COPD) and ACS at the level of precipitating factors – especially infections, hyperglycaemia, and raised levels of MMPS (matrix metalloproteinases).

i. Hyperglycaemia: It is known to be associated with poor outcomes[23]. Tight blood sugar control is advised in AECOPD, in ACS, and post-cardiothoracic surgery[24]. Administration of insulin benefits the patients due to its anti-inflammatory and anabolic properties and promotes better utilisation of glucose as a metabolic fuel which generates more molecules of ATP per molecule of oxygen than free fatty acids with observed potential benefits for ischaemic tissue[24]. The damaging effect of hyperglycemia is due to glucose toxicity as seen in autopsy study of surgical patients in whom mitochondrial damage was limited to tissues characterised by expression of glucose transporter GLUT-1 & 3, but not GLUT-4[25]. GLUT-1 & 3 are cell membrane transport proteins that allow equilibrium of intra- and extra-cellular glucose independently of insulin. Increased blood sugar causes many potentially damaging events like production of ROS (reactive oxygen species), superoxide and peroxinitrites, glycosylation of proteins[26], impairment of leucocyte functions, activation of pro-inflammatory genes through transcription factors like NF-kB(nuclear factor kappa B) and AP-1 (activator protein–1). Hyperglycemia causes deranged lipid metabolism, altered membrane function and endotoxin scavenging, raised level in tissues and bronchial aspirates leads to proliferation of bacteria (staphylococcus sp.), along with poor bacterial clearance and poor host response which can be effectively countered to some extent by insulin infusion. So the aim is to keep blood sugar should below 8 mmol/l in acutely ill patients, even in those who are non-diabetics[27]. Hyperglycaemia in COPD (> 11 mmol/l) on admission predicts failure of noninvasive ventilation and infection complications in ICU[28]. Blood sugar is high in acutely ill patients due to raised catecholamine concentration, oral steroids given in COPD, raised glucocorticoid hormone concentration, and increased peripheral insulin resistance[29].

ii. Role of MMPS in AECOPD and ACS: Several MMPS are involved in the pathogenesis of COPD. MMPS are a family of metalloproteases that contain a zinc atom at their active site and are able to degrade matrix molecules including collagen, elastin, and laminin[30]. In addition to their ability to degrade extracellular matrix components, some MMPS also cleave cytokines[31] and antiproteolytic molecules[32]. MMPS – especially MMP-9 & 12 – are found in mice; these play a crucial role in development of emphysema and were found in high concentration in alveolar macrophages[33]. MMP-12 knockout mice was found to be protected from emphysema. MMPS not only have a direct effect on extracellular matrix but also causes in activation of α_1 antitrypsin by MMP-12 mediated recruitment of neutrophils. Molet and colleagues found a high level of MMP-12 in BAL (bronchoalveolar lavage) fluid (Western Blot analysis), bronchial biopsy tissues, than in controls[34]. Thus, in the early stages of COPD, MMP-12 can be an important biomarker of the disease activity; the mechanism by which MMP-12 is induced in COPD may be due to local deficiency of TGF-β_1 or rise in IL-13 or γ-IFN which lead to the overproduction of MMP-12[35]. Grumelli showed that in human subjects, lung macrophages release MMP-12 in response to infection[36]. MMPS are not only secreted from alveolar macrophages but also from bronchial epithelial cells in response of cigarette smoking, and secretion is mediated by chemokine receptor-3 (CXCR-3) on macrophages in emphysema. In mice, potent inhibitor of both human and murine MMP-12 (RS-113456) prevented progression of emphysema in smoke-exposed animals[37]. MMPS thus have a role in acute exacerbation of COPD and also in ACS (plaque instability).

iii. Infections: These are very important precipitating factors for acute exacerbation of COPD, and some of them like *Chlamydia pneumoniae*, *Helicobacter pylori* and Cytomegalovirus (especially in post-transplant cases) can accelerate atherosclerosis and precipitate acute coronary syndrome by causing plaque instability[38]. AECOPD (acute exacerbation of COPD) is known to be precipitated

by bacterial infection (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus parainfluenza* and *Pseudomonas aeruginosa* and Gram-negative bacteria)[39]. Viruses such as rhinovirus, influenza, parainfluenza, coronavirus, adenovirus, respiratory syncytial virus, Picorna virus are shown to be a cause of AECOPD in 40% cases by PCR[40]. Atypical organisms, i.e., Mycoplasma and Chlamydiae, environmental pollutants, change of temperature, are also important causes. All these factors increase inflammatory markers, increase MPO (myeloperoxidase) in sputum and increase interleukin-8 (CXCL8), leukotriene (LTB4), tumour necrosis factor-α (TNF-α). Inflammatory environment causes decrease in FEV_1 so infections are common precipitating factors for AECOPD and ACS. AECOPD can also affect ventricular functions by reducing pre-load, high pulmonary artery pressures, hypoxaemia, V/Q mismatch increases right ventricular after-load. LV diastolic function are adversely affected due to ventricular interdependence, although systolic functions remain normal except in AECOPD, where due to increase LV after-load as a consequence of increased imposed transmural pressure gradient, LV systolic performance is impaired[41].

H. Drugs, COPD, and ACS: Oxygen inhalation plays a beneficial role in COPD and ACS if used judiciously. Oral steroids given for COPD for long terms have shown to cause hyperglycaemia which is a negative factor for both COPD and ACS. β_2-agonists, theophyllines and anticholinergics given in COPD with cardiac dysfunction may have a negative effect as they cause tachycardia and arrhythmia. Doxofylline is safer for cardiac patients instead of theophylline. However, inhalers have, to a large extent, reduced the risk of β-agonists and bronchodilators.

Statins are known to decrease mortality not only in ACS but also in COPD by improving endothelial functions[42].

I. Co-morbidities in COPD: Are defined as diseases co-existing with the primary disease of interest. In COPD, they are cardiovascular diseases, lung carcinoma, and osteoporosis – link is systemic inflammatory pathway[43].

Conclusion

A long duration of COPD is a major risk factor for CAD. Almost like diabetes, COPD is a major risk factor for CAD and the common link of inflammation and poor respiratory function mainly explains this association. We should try to rule out ACS or LV dysfunction in AECOPD and in ACS patients, look for the presence of COPD also, as only a combined approach of treatment including drugs will have an affect on outcome. Apart from the traditional investigations, echocardiography is now increasingly in use.

In COPD patients we should unmask the presence of underlying CAD and target it before the patient lands in ACS. In JNMCH, our team is doing a prospective study in patients of ACS who have COPD.

References

1. Reynolds RJ, Buford JG, George RB. Treating asthma and COPD in patients with heart disease. *J Respir Dis* 1982; 3: 41.
2. Behar S, Panosh A, Reicher-Reiss H *et al*. Prevalence and prognosis of chronic obstructive pulmonary disease among 5,839 consecutive patients with acute myocardial infarction. SPRINT Study Group. *Am J Med* 1992; 93: 637-41.
3. Howard G, Wagenknecht LE, Burke GL *et al*. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA* 1998; 279: 119-24.
4. Mahler DA, Brent BN, Loke J *et al*. Right ventricular performance and central circulatory hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 130: 722-29.
5. Gan WQ, Man SFP, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574-80.
6. Ross R. Atherosclerosis:an inflammatory disease. *N Engl J Med* 1999; 340: 115-26.
7. Kotler DP. Cachexia. *Ann Intern Med* 2000; 133: 622–34.
8. Agusti AG, Noguera A, Sauleda J *et al*. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 347-60.
9. Dahl M, Tybjaerg-Hansen A, Vestbo J *et al*. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1008-11.
10. Di Francia M, Barbier D, Mege JL *et al*. Tumor necrosis factor levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 150: 1453-5.
11. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: Data from the third national health and nutrition examination. *Am J Med* 2003; 114: 758-62.
12. van Eeden SF, Tan WC, Suwa T *et al*. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM_{10}). *Am J Respir Crit Care Med* 2001 ;164: 826-30.
13. Anthonisen NR, Connett JE, Kiley JP *et al*. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline FEV_1. The Lung Health Study. *JAMA* 1994; 272: 1497-505.
14. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; 107: 1514-9.

15. W B Kannel, Helen Hubert, EA Lew. Vital capacity as a predictor of cardiovascular disease: The Framingham Study. *American Heart Journal* 1983; 105: 311-5.

16. Schroeder EB, Welch VL, Couper D *et al.* Lung Function and Incident Coronary Heart Disease The Atherosclerosis Risk in Communities Study *Am J Epidemiol* 2003;158: 1171-81.

17. Hole DJ, Watt GC, Davey Smith G *et al.* Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711-5.

18. Holmen TL, Barrett-Connor E, Clausen J *et al.* Gender differences in the impact of adolescent smoking on lung function and respiratory symptoms: The Nord-Trøndelag Health Study, Norway, 1995-1997. *Respir Med* 2002; 96: 796-04.

19. van der Palen J, Rea TD, Manolio *TA et al*. Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax* 2004; 59: 1063-67.

20. Sliwinski P, Macklem PT. Inspiratory muscle dysfunction as a cause of death in COPD patients. *Monaldi Arch Chest Dis* 1997; 52: 380-3.

21. Meyer FJ, Borst MM, Zugck C *et al.* Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation* 2001; 103: 2153-8.

22. Carlos Iribarren, Irina V Tolstykh, Mark D Eisner. Are patients with asthma at increased risk of coronary heart disease? *International Journal of Epidemiology* 2004; 33: 743-8.

23. Finney SJ, Zekveld C, Elia A *et al.* Glucose control and mortality in critically ill patients. *JAMA* 2003; 290: 2041-7.

24. Malmberg K, Ryden L, Efendic S *et al.* Randomised trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; 26: 57–65.

25. Mesotten D, Swinnen JV, Vanderhoydonc F *et al.* Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab* 2004; 89: 219-6.

26. Mohanty P, Hamouda W, Garg R *et al.* Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab* 2000; 85: 2970-73.

27. Baker EH, Janaway CH, Philips BJ *et al.* Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006; 61: 284-9.

28. Moretti M, Cilione C, Tampieri A *et al.* Incidence and causes of non-invasive mechanical ventilation failure after initial success. *Thorax* 2000; 55: 819-25.

29. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues* 2004; 15: 45-62.

30. Parks WC, Wilson CL, Lopez-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. *Nat Rev Immunol* 2004; 4: 617-29.

31. Churg A, Wang RD, Tai H *et al.* Macrophage metalloelastase mediates acute cigarette smoke-induced inflammation via tumor necrosis factor-alpha release. *Am J Respir Crit Care Med* 2003; 167: 1083-9.

32. Banda MJ, Clark EJ, Werb Z. Limited proteolysis by macrophage elastase inactivates human alpha1-proteinase inhibitor. *J Exp Med* 1980; 152: 1563-70.

33. Russell RE, Culpitt SV, DeMatos C *et al.* Release and activity of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by alveolar macrophages from patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2002; 26: 602-9.

34. Molet S, Belleguic C, Lena H *et al.* Increase in macrophage elastase (MMP-12) in lungs from patients with chronic obstructive pulmonary disease. *Inflamm Res* 2005; 54: 31-6.

35. Orris DG, Huang X, Kaminski N *et al.* Loss of integrin alpha(v)beta6-mediated TGF-beta activation causes MMP-12 dependent emphysema. *Nature* 2003; 422: 169-73.

36. Grumelli S, Corry DB, Song LZ *et al.* An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. *PLoS Med* 2004; 1: e8.

37. Martin RL, Shapiro SD, Tong SE *et al.* Macrophage metalloelastase inhibitors. In: Hansell TT, Barnes PJ, eds. New drugs for asthma, allergy and COPD. Volume 31. Progress in Respiratory Research. Basel, Switzerland: Karger, 2001:177–80.

38. Anderson JL, Carlquist JF, Muhlestein JB *et al*. Evaluation of C-reactive protein, an inflammatory marker, and infectious serology as risk factors for coronary artery disease and myocardial infarction. *J Am Coll Cardiol* 1998; 32: 35-41.

39. Pela R, Marchesani FF, Agostinelli C *et al.* Airways microbial flora in COPD patients in stable clinical conditions and during exacerbations, a bronchoscope investigation. *Monaldi Arch Chest Dis* 1998; 53: 262-7.

40. Bogaert D, van der Valk P, Ramdin R *et al.* Host-pathogen interaction during pneumococcal infection in patients with chronic obstructive pulmonary disease. *Infect Immun* 2004; 72: 818-23.

41. Vizza CD, Lynch JP, Ochoa LL *et al*. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998; 113: 576-83.

42. Soyseth V, Brekke PH, Smith P *et al*. Statin use is associated with reduced mortality in COPD. *Eur Respir J* 2007; 29: 279-83.

43. Agusti AG, Noguera A, Sauleda J *et al.* Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 347-60.

"Every problem you have, you experience in your mind.
The solution to the problem lies in the same place."

– Gautam Buddha.

REVIEW ARTICLE

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Nutrition in diabetes

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Abstract

Medical nutrition therapy (MNT) plays a role in all three levels of diabetes-related prevention. Primary prevention interventions seek to delay or halt the development of diabetes in individuals with obesity and prediabetics (IGT and IFG). Secondary and tertiary prevention interventions include MNT for individuals with diabetes and seek to prevent (secondary) or control (tertiary) complications of diabetes. Clinical trials/outcome studies of MNT have reported decreases in HbA1c (AIC) of 1% in type 1 diabetes and 1 - 2% in type 2 diabetes, depending on the duration of diabetes. Metaanalysis of studies in non diabetic, free-living subjects and expert committees report that MNT reduces LDL cholesterol by 15 - 25 mg/dl. After initiation of MNT, improvements were apparent in 3 - 6 months. Meta-analysis and expert committees also support a role for lifestyle modification in treating hypertension.

Key words : Diabetes, diet, calorie.

Introduction

Diabetes mellitus is a rampantly growing metabolic disorder, emerging as a global epidemic with expected 300 million people by 2025. Harmful effects of diabetes are usually associated with poorly controlled blood sugar for which dietary management is a must. The present article describes the current scenario and gravity of dietary management in diabetic patients. The main concern of newly diagnosed diabetics and their families relates to dietary restrictions – when, what, and how?

In India, there are not many trained and skilled nutrition and exercise therapists, and their beneficiaries are only a few. This means that treating physicians are required to provide appropriate advice related to diet to most people with diabetes.

As diabetes is a lifelong disorder, nutrition therapy become a part of self-care education. People with diabetes have to understand the ways and means to alter their dietary habits and to adjust to deviations from their daily routine.

Before advising the diet plan

It is important to make people with diabetes understand the need for alterations in their dietary habits. An understanding of eating and cooking habits of the family, the type of food consumed, and the day-to-day pattern of meals, helps in planning nutritional therapy. Decisions must not be forced on the patient. The factors that need to be taken into consideration before giving dietary advice include:-

1. The type of diabetes mellitus, presence of co-morbid conditions, and complications.
2. The current drug regimen.
3. Treatment goals, e.g., weight loss, target blood glucose level, prevention of hypoglycaemia.
4. Educational and psychological background of the person with diabetes.

Medical nutrition therapy

Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes-related complications.The 2006 ADA (American Diabetes Association) update recommends:-

1. Lifestyle changes, including nutritional education and behaviour modification, reduced calorie and fat intake, and regular physical activity for overweight and obese individuals.
2. Daily fibre intake of 20 - 35 g/1,000 kcals.
3. Saturated fat intake of < 7% of total calories, minimal transfat intake, and cholesterol intake of < 200 mg per day for individuals with diabetes, plus carbohydrate monitoring to regulate blood glucose.
4. Normal dietary protein intake (15 - 20% of energy) and avoidance of high-protein weight-loss diets and micronutrient supplementation except for specific deficiencies.
5. Limited daily alcohol intake: one drink for women, and two drinks for men.
6. Specific nutritional interventions for individuals with diabetes who are experiencing microvascular complications, cardiovascular disease, hypertension,

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hypoglycaemia, and acute illness.

Goal for medical nutrition therapy in diabetes

Goals of medical nutrition therapy[7] that apply to all persons with diabetes are as follows:-

1. Attain and maintain optimal metabolic outcomes including
   - o Blood glucose levels in the normal range or as close to normal as is safely possible to prevent or reduce the risk for complications of diabetes.
   - o A lipid and lipoprotein profile that reduces the risk for macrovascular disease.
   - o Blood pressure levels that reduce the risk for vascular disease.
2. Prevent and treat the chronic complications of diabetes. Modify nutrient intake and lifestyle as appropriate for the prevention and treatment of obesity, dyslipidaemia, cardiovascular disease, hypertension, and nephropathy.
3. Improve health through healthy food choices and physical activity.
4. Address individual nutritional needs taking into consideration personal and cultural preferences and lifestyle while respecting the individual's wishes and willingness to change.

Goals of medical nutrition therapy that apply to specific situations include the following:

1. For youth with type 1 diabetes, to provide adequate energy to ensure normal growth and development, integrate insulin regimens into usual eating and physical activity habits.
2. For youth with type 2 diabetes, to facilitate changes in eating and physical activity habits that reduce insulin resistance and improve metabolic status.
3. For pregnant and lactating women, to provide adequate energy and nutrients needed for optimal outcomes.
4. For older adults, to provide for the nutritional and psychosocial needs of an ageing individual.
5. For individuals treated with insulin or insulin secretagogues, to provide self-management education for treatment (and prevention) of hypoglycaemia, acute illnesses, and exercise-related blood glucose problems.
6. For individuals at risk for diabetes, to decrease risk by encouraging physical activity and promoting food choices that facilitate moderate weight loss or at least prevent weight gain.

Planning the diet

The pharmacokinetics of a person's medications need to be understood while individualising the nutrition plan. People with diabetes should be explained the relationship between their medications and various nutrients to prevent them from overdoing any aspect of a dietary plan. Based on the drugs that a person is receiving, alterations need to be made to the dietary plan. Some of these are:-

1. Insulin sensitisers (metformin and glitazones): The total amount of macronutrients can be distributed over meals.
2. Insulin secretagogues (sulfonylureas) and conventional insulin therapy: They must be prescribed snacks or split meals patterns to match insulin levels in the body as well as to avoid hypoglycaemia in later hours.
3. Bedtime glargine or detemir insulin: While most people do not need a bedtime snack, this should not be ruled out.
4. People on insulin lispro or aspart as their premeal insulin do not need midmorning and afternoon snacks, but if bedtime insulin is NPH, they need complex or high fibre carbohydrates in their bedtime snacks.
5. People receiving drugs which retard the breakdown and/or absorption of carbohydrates (e.g., alpha glucosidase inhibitors) should be prescribed a lower amount of fibre for a major meal with which the drug is taken, and snacks with more fibre should be given.

Before prescribing macronutrients in diet, we must see the nutritive value of common Indian foods (National Institute of Nutrition) (Table I)

Table I: Nutritional values of different food items.

Name of food stuff (100 gm)	Proteins (gm)	Fats (gm)	Carbohydrates (gm)	Energy (K cal)
Cereals (grains)				
Wheat (whole)	11.8	1.5	71.2	346
Wheat, bread (brown)	8.8	1.4	49	244
Wheat, bread (white)	7.8	0.7	51.9	245
Rice (raw)	6.4	0.54	80	362
Rice (cooked)	1.9	0	24.3	101
Pulses				
Bengal gram (whole)	17.1	5.3	60.9	360
Bengal gram (dhal)	20.8	5.6	59.8	372
Green gram (dhal)	24.5	1.2	59.9	348
Red gram (dhal)	22.3	1.7	57.6	335
Vegetables				
Bathua leaves	3.7	0.4	2.9	30
Cabbage	1.8	0.1	4.6	27
Spinach	2	0.7	2.9	26
Carrot	0.9	0.2	10.6	48

Name of food stuff (100 gm)	Proteins (gm)	Fats (gm)	Carbohydrates (gm)	Energy (K cal)
Potato	1.6	0.1	22.6	97
Radish	0.7	0.1	3.4	17
Brinjal	1.4	0.3	4	24
Cauliflower	2.6	0.4	4	30
Cucumber	0.4	0.1	2.5	13
Nuts and oils				
Almond	20.8	58.9	10.5	655
Cashew nut	21.2	46.9	22.3	596
Coconut (dry)	6.8	62.3	18.4	662
Ground nut	25.3	40.1	26.1	567
Walnut	15.6	64.5	11	687
Water melon seeds	34.1	52.6	4.5	628
Fruits				
Apple	0.2	0.5	13.4	59
Banana	1.2	0.3	27.2	116
Dates (dried)	2.5	0.4	75.8	317
Dates (fresh)	1.2	0.4	33.8	144
Grapes	0.5	0.3	16.5	71
Guava	0.9	0.3	11.2	51
Lichi	1.1	0.2	13.6	61
Mango	0.6	0.4	16.9	74
Watermelon	0.2	0.2	3.3	16
Orange	0.7	0.2	10.9	48
Papaya	0.6	0.1	7.2	32
Pineapple	0.4	0.1	10.8	46
Pomegranate	1.6	0.1	14.5	65
Fish, meat, and poultry				
Fish	19.5	2.4	-	101
Buffalo meat	19.4	0.9	-	86
Goat meat	21.4	3.6	-	118
Pork meat	18.7	4.4	-	114
Chicken	31.4	3.4	-	162
Egg	13.3	13.3	-	173
Milk and milk products				
Milk (buffalo)	4.3	6.5	5	117
Milk (cow)	3.2	4.1	4.4	67
Milk (skimmed)	2.5	0.1	4.6	29
Curd	3.1	4	3	60
Cheese	24.1	25.1	6.3	348
Khoa (buffalo milk)	24.1	25.1	6.3	421
Khoa (cow milk)	20	25.9	24.9	413
Khoa (skimmed milk)	22.3	1.6	25.7	206
Skimmed milk				
Powder (cow milk)	38	0.1	51	357
Whole milk				
Powder (cow milk)	25.8	26.7	38	496
Fats and edible oils				
Butter	-	81	-	729
Ghee	-	100	-	900
Hydrogenated oil	-	100	-	900
Cooking oil (groundnut, mustard, coconut, etc.)	-	100	-	900
Sugars				
Sugarcane	0.1	-	99.4	398
Honey	0.3	-	79.5	319
Jaggery	0.4	0.1	95	383

Soft drinks	Quantity			Energy (K cal)
Orange juice	200 ml	-	-	30
Tomato juice	200 ml	-	-	30
Apple juice	200 ml	-	-	100
Grape juice	200 ml	-	-	80
Mango juice	200 ml	-	-	150
Cola	100 ml	-	-	40
Amul cool	100 ml	-	-	89
Amul masti	100 ml	-	-	29
Nimbu pani	100 ml	-	-	48
Fast foods				
Potato wafers	50 gm	-	-	430
Samosa	40 gm	-	-	130
Veg. cutlet	100 gm	-	-	140
Cakes & pastries				
Cake plain	50 gm	-	-	150
Chocolate	50 gm	-	-	250
Sponge cake	50 gm	-	-	150
Pastry	50 gm	-	-	250-400
Desserts				
Custard	150 gm	-	-	360
Fruit salad	150 gm	-	-	150
Fruit salad with cream	150 gm	-	-	300
Ice cream	150 gm	-	-	380
Gajar halwa	100 gm	-	-	600
Badam halwa	100 gm	-	-	570
Sweets				
Nariyal barfi	25 gm	-	-	110
Gulab jamun	25 gm	-	-	200
Laddu	30 gm	-	-	160
Rasgulla	150 gm	-	-	140
Jam	2 big spoons	-	-	80
Beverages				
Beer	150 ml	-	-	65
Wine (dry)	30 ml	-	-	30
Whisky / Brandy / Gin / Rum	30 ml	-	-	65
Vodka	30 ml	-	-	65
Others				
Paratha (40 gm)	1	-	-	185
Poori	2	-	-	100
Tandoori roti	1	-	-	147
Naan	1	-	-	191

Low carbohydrate diet

Although low fat diets have traditionally been promoted for weight loss , several randomised controlled trials (RCTs) found that subjects on low-carbohydrate diets (< 130 g/ day of carbohydrate) lost more weight at 6 months than subjects on low fat diet ; however, at 1 year, the difference in weight loss between the low-carbohydrate and low-fat diet was not significant and weight loss was modest with both diets. Another study of overweight women randomised to one of four diets showed significantly more weight loss at 12-months with the Atkins low-carbohydrate diet than with high carbohydrates diet[8].

Dietary fibres

Dietary fibres are a part of carbohydrates, but are considered non-nutritive as they do not provide any energy. A meta-analysis have recently concluded that increasing the daily intake of green vegetables could significantly decrease the risk of type 2 diabetes mellitus[9]. Soluble or insoluble, they have been proven to be useful in various ways:-

1. Delay the absorption of macronutrients and hence prevent a post-prandial blood glucose surge.
2. Help provide a feeling of satiety because of their bulk and thus prevent overeating.
3. Delay absorption and retard the breakdown of carbohydrates, thus maintaining blood glucose level evenly over a period in this manner; fibres help reduce hypoglycaemia episodes.
4. Reduce hyperinsulinaemia and hyperlipidaemia.

Micronutrients

There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes (compared with the general population) who do not have underlying deficiencies. Routine supplementation with antioxidants (such as vitamins E and C, and carotene) and chromium is not advised because of lack of evidence of efficacy and concern related to long-term safety. Optimum micronutrients can be derived from a diet with an optimal composition of macronutrients and minimally processed food items. In select groups, such as elderly individuals, pregnant or lactating women, strict vegetarians, or individuals on calorie-restricted diets, supplementation with a multivitamin preparation is advisable[10].

Snacks and split meals

In India, traditionally, people are used to larger meals. For many people with diabetes, splitting a large meal into 2 small meals spaced at 3 - 4 hour intervals is advised. Alternatively, a healthy snack at 3 - 4 hour intervals is advised. Alternatively, a healthy snack option (fruits, nuts, etc.) after a moderate meal can be introduced. The initial discomfort of "not feeling full" can be overcome by options of eating low or non-caloric food items such as vegetable salads, egg white, etc. A major meal and any snack following that meal should have a calorie and carbohydrate distribution in a ratio of 2 : 1. The system of split meals or snacks has many benefits:-

1. It improves post-pradial glycaemic response.
2. It improves insulin sensitivity.
3. It helps match the pharmacokinetics of insulin or other insulin secreting drugs and hence provides optimum glycaemia.

Calorie requirement

The diet of the diabetic patient should contain the minimum number of calories which the normal individual will require under similar conditions. The calories intake can be estimated as below:-

Basal calories: 22 Kcal/Kg desirable body weight. Add calories for activity, i.e.,

- If sedentary, add 10% of estimated basal calories.
- If moderately active, add 20% of estimated basal calories.
- If strenuously active, add 40% of estimated basal calories.

Desirable body weight

The desirable body weight can be achieved by reaching appropriate body mass index. BMI is the most widely used formula for relating height and weight.

BMI = Weight (kg) / Height (m^2)

The international classification of adult underweight, overweight, and obesity according to BMI as established by WHO (Table II):-

The WHO Expert Consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing WHO cut-off point for overweight (= 25 kg/m^2). However, the cut-off point for observed risk varies from 22 kg/m^2 to 25 kg/m^2 in different Asian populations; and for high risk, it varies from 26 kg/m^2 to 31 kg/m^2 [11].

Table II: BMI as established by WHO.

	BMI (Kg/m2)
Underweight	< 18.50
Severe thinness	< 16.00
Moderate thinness	16.00 - 16.99
Mild thinness	17.00 - 18.49
Normal	18.50 - 24.99
Overwieght	> 25.00
Obese	> 30.00
Obese Class I	30.00 - 34.99
Obese Class II	35.00 - 39.99
Obese Class III	> 40.00

Calorie reduction to achieve desirable body weight

National Heart Lung and Blood Institute evidence report

Table III: Standard daily meal chart (Vegetarian)

Time	Meal	Menu	Energy (K Cal)	% Value
7:30 AM	Morning	1 cup tea (without sugar)	60	4%
9:30 AM	Breakfast	Suji cheela/Upma, Sprouted moong, Cheese tomato sandwich Basen cheela, Salted dalia, Methi paratha with veg.) 1 serving Skimmed milk – 1 Cup (without sugar), or Butter milk – 1 Cup	250-300	20%
12:00 PM	Noon	One Fruit or mixed (Guava, Cucumber, Kakdi, Orange, Musammi, Papaya, Pineapple)	80	6%
2:00 PM	Lunch	Roti – 2 medium (without fat) 1 Katori cooked dal – 100gm 1 Katori dry veg – green leafy 150 gm Cooked rice ½ Cup Salad – 1 plate (Onion, Radish, Cucumber, Cabbage)	500	30%
5:00 PM	Evening Time	Lemon water, or Tea without sugar with Roasted Chana, or Roasted Peanuts, or any light snack (Dhokla, idli, wheat puffs)	160-180	10%
8:30 PM	Dinner	Roti – 2 medium (without fat), (wheat flour + chana flour) Curry veg – 1 Katori Blended curd or Raita – (Lauki, Kashiphal, Cucumbar, Tomato, Onion, etc.) = ½ Cup	500	30%

Table IV: Food exchange system (1 cup = 200 ml)

Exchange List	Serving Size/Raw Weight (gm)	Carbohydrate (gm)	Protein (gm)	Fat (gm)	Energy (k cal)
Vegetable					
Green leafy	½ Cup	6	-	-	40
Others	½ Cup	6-10	-	-	50-60
Fruit	Varies	10	-	-	40
Cereal	25	19-21	2-3	-	85
Legumes/pulses	25	15	6	-	85
Milk	½ Cup	4	3.5	4.0	65
Meat	75	-	7.5	6.0	85
Fat	10	-	-	10.0	90
Sugar	10	10	-	-	40

states that one can lose and maintain a loss of 10% from baseline weight.

Thus, the evidence suggests that it is better to aim for a slow, attainable and sustainable weight loss. One kilogram of lost weight, which will be part fat and part lean body mass, is equivalent to about 7,000 Kcal. A calorie deficit of 700 Kcal/day results is 1 Kg weight loss in 10 days; if calorie deficit is 500 Kcal/day, it will take 14 days. Initial weight loss may be a bit faster because water diuresis occurs. A nutritional and exercise regimen with a diet and exercise that creates a deficit of 500 to 1,000 Kcal/day is reasonable.

Patients generally plateau with regard to weight loss at about 6 months into their treatment programme. At that point, decreased calorie intake comes into a new equilibrium, and no more weight is lost.

The combination of physical activity and low calorie diet is effective in weight reduction. Exercise helps in weight reduction, and low-calorie diet helps to maintain body weight. One-year results of the intensive lifestyle intervention in AHEAD trial show an average of 8.6% weight loss, significant reduction of HbA1c, and reduction in several CVD risk factors[12]. In findings published in the May, 2007 issue of *Obesity*, the researchers report 80% of Eat Right participants maintain their weight loss during two years of follow-up and most do it primarily by sticking to a low calorie, low energy density diet. The multifactorial intensive lifestyle interventions used in the Diabetic Prevention Program (DPP), which included reduced intake of fat and calories, lead to weight loss averaging 7% at 6 months and maintainence of 5% weight loss at 3 years, associated with a 58% reduction in incidence of type 2 diabetes mellitus[13].

Food exchange

Food exchange, whereby one food item can be exchanged with another, provides variety and a balance of macronutrients in a fixed diet plan. Some examples are:-

1. One glass fat-free milk (without sugar) 200 ml can replace ¾ glass powder milk or 100 ml curd.

2. 30 gm meat can replace 1 egg on 30 gm fried fish.
3. One boiled egg can replace 50 gm boiled/grilled fish or 50 gm chicken.
4. 2 whole wheat chapati (60 gm each) can replace 1 chapati and cooked rice (120 gm)
5. A 110 gm jowar roti (about 2 medium size) or 1 nan/ thick roti can replace 2 chapati.
6. 2 slices bread in sandwich can replace 2 medium size Idlis (30 gm each) with vegetable sambhar.
7. 2 chapati (30 gm each) can replace one nan or one missi roti (30 gm).
8. 100 gm cooked vegetables can replace 200 gm raw vegetables.
9. 200 gm of edible part of a watermelon (about 5 - 6 slices) can replace 1 whole orange (about 120 gm) or 1 apple or 1 medium size banana or half a custard apple or a 90 gm (small) chicku.
10. 4 - 5 almonds and 4 dry dates can replace 1 cup of coffee and 4 biscuits.
11. 1 bowl of sprouts with some onion and tomato can be exchanged with 1 bowl of curd and some salad.

Food exchange for grains

Rice	30 gm (raw)
Wheat flour	30 gm
Bread	2 Slices
Roti	1 ½
Oat meal	30 gm (raw)
Corn flakes	30 gm (raw)
Sewain	½ katori (cooked)
Idli	2
Poha	½ katori (cooked)
Upma	½ katori (cooked)

Food exchange for fat

Butter	7.5 gm
Ghee	5.5 gm
Vanaspati	5.5 gm
Oil (coconut, mustard, groundnut)	5.5 gm

Food exchange for milk and dairy products

Curd	100 gm
Lassi	375 ml
Cheese	15 gm
Milk (buffalo)	45 ml
Milk (cow)	90 ml
Milk (skimmed)	130 ml

Non-vegetarian sedentary worker

Minor alteration

Breakfast –

1 boiled egg with 2 slices of bread, or

1 egg fry with skimmed milk

Major Meal –

Lunch & dinner

1 plate fish curry / chicken curry / roasted chicken instead of dal or curry (veg.).

Small amount of meal at frequent intervals.

Use of protein supplement with milk to meet daily protein need (high protein).

Conclusion

The diet for diabetes is the nutrition regimen developed to meet physical, metabolic, and lifestyle requirements of an individual. For patients with type 2 diabetes, reduction of total energy intake and increase in physical activity consistent with the patient's physical capabilities should be recommended in order to reduce body fat, decrease insulin resistance, and improve glycaemic and lipid control. Most dietary guidelines emphasise target intakes of specific macronutrients. But many individuals find it difficult to make dietary changes based on such numerical criteria. Recommending an overall pattern of dietary intake focussing on appropriate food choices meal-wise might be easy for the common man to interpret or translate into diets. Dietary recommendations for the management of diabetes should focus more on the quality and quantity of carbohydrates and fats in the diet in addition to balancing total energy intake with expenditure. Diet for people with diabetes should be individualised, with consideration given to each individual's usual food and eating habits, metabolic profile, treatment goals, and desired outcomes. Monitoring of metabolic parameters, including glucose, HbA1c, lipids, blood pressure, body weight, and renal function, when appropriate, as well as quality of life is essential to assess the need for changes in therapy and to ensure successful outcomes. Ongoing nutrition self-management education and care need to be available for individuals with diabetes[14].

References

1. Pastors JG, Warshaw H, Daly A *et al*. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002; 25: 608-13.

2. Pastors JG, Franz MJ, Warshaw H *et al*. How effective is medical nutrition therapy in diabetes care? *J Am Diet Assoc* 2003; 103: 827-31.
3. Yu-Poth S, Zhao G *et al*. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: A metaanalysis. *Am J Clin Nutr* 1999; 69: 632-46.
4. Grundy SM, Balady GJ *et al*. When to start cholesterol lowering therapy in patients with coronary heart disease: A statement for healthcare professionals from the American Heart Association Task Force on Risk Reduction. *Circulation* 1997; 95: 1683-5.
5. Chobanian AV, Bakris GL, Black HR *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003; 289: 2560-72.
6. Whitworth JA, Chalmers J. World Health Organisation–International Society of Hypertension (WHO/ISH) hypertension guidelines. *Clin Exp Hypertens* 2004; 26: 747-52.
7. Nutrition principles and recommendations in Diabetes. *Diabetes Care* January 2004 vol. 27 no. suppl 1 s36.
8. Gardener CD, Kiazand A, Alhassan S *et al*. Comparison of the Atkins, Zone, Ornish, and LEARN Diets for change in weight and related risk factors among overweight premenopausal women. *JAMA* 2007; 297: 969-77.
9. Culling Zhang *et al*. Dietary fibre intake, dietary glycemic load and risk of gestational diabetes mellitus. *Diabetes Care* 2006; 29: 2223-30.
10. U.S. Department of Agriculture, U.S. Department of Health and Human Services: *Nutrition and Your Health: Dietary Guidelines for Americans.* 5th ed. Home and Garden Bulletin No. 232, 2000.
11. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet* 2004; 157-63.
12. Look AHEAD Research Group, Pi-Sunyer X *et al*. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one year results of the look AHEAD trial. *Diabetes Care* 2007; 30: 1374-83.
13. Knowler WC, Barrett-Connor E *et al*. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM* 2002; 346: 393-403.
14. Franz MJ, Beebe CA, Chiasson J *et al*. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications; *Diabetes Care* 2002; 25(1): 148-98.

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REVIEW ARTICLE

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Cerebroprotein hydrolysate: Innovation in the treatment of neurodegenerative disorders

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Abstract

Neurodegenerative disorders are one of the leading causes of death and disability in both developing and developed countries. There are a number of neurotrophic drugs used in these disorders. Cerebroprotein hydrolysate is the latest one launched in more than 40 countries. Its superiorty is because of different actions which help in faster and more complete nerve repair and growth than other neurotrophic agents. Different mechanisms include regulation and improvement of the neuronal metabolism, modulation of the synaptic plasticity, neuronal differentiation and protection against ischaemic and neurotoxic lesions, cerebroprotein hydrolysate reduces excitotoxic damage, blocks over-activation of calcium dependent proteases, and scavenges free oxygen radicals.

Epidemiology

Ischaemic stroke, traumatic brain injury, vascular dementia and Alzheimer's disease (AD) collectively are responsible for a major part of morbidity and mortality in geriatric as well as young adult population.

Stroke ranks as the third leading cause of death in the United States. It is now estimated that there are more than 700,000 incident strokes annually and 4.4 million stroke survivors[1]. In the USA on an average, approximately 1.7 million people sustain a traumatic brain injury annually[2].

Roughly speaking, in the USA alone, 1,300/100,000 people suffer concussions each year. Of these, 300/100,000 are treated in emergency departments. Of these, 90/100,000 are retained in the hospital. Around 25/100,000 die[3]. AD and other degenerative diseases that affect the cognitive functions in the elderly compromise the quality of life for more than 24 million people across the world[4].

Besides the above-mentioned illnesses, other neurodegenerative disorders like amyotrophic lateral sclerosis, Friedreich's ataxia, Huntigton's disease, Parkinson's disease, and Lewy-body disease pose some of modern medicine's most difficult challenges. The common pathophysiologic feature in all these conditions is the same, i.e., functional loss of neurons.

Development, basic structure, and repair of neurons

Neuron is the basic structural and functional unit of the nervous system. Although there are some variations depending on the type of neurons, they all contain four parts: cell body, dendrites, axon, and axon terminal. They develop from the neural stem cells known as type 1 cells which produce progeny called amplifying neural progenitor cells (also known as type 2 cells) which proliferate and differentiate into mature neurons. Till recent past it was believed that there is no way to repair a damaged neuron.

One of the main goals of researchers is to develop drugs to stimulate areas of the brain to repair itself by replacing its own cells[5]. Several drugs like edaravone, citicoline, and piracetam have been developed based on these neurotrophic factors. Neurotrophic factors are small proteins that exert survival-promoting and trophic (derived from the Greek meaning "to nourish") actions on neuronal (or nerve) cells[6]. These neurotrophic factors are NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), NT-3 (neurotrophin-3), GDNF (glial cell-derived neurotrophic factor), GAP-43 (growth associated protein 43) and CNFT (cilliary neurotrophic factor).

Glial cells continue to undergo cell division in adulthood and their ability to proliferate is particularly noticeable after brain injury (e.g., stroke)[7]. This is not the case with neurons; they cannot divide, but they undergo a lot of activity after injury. Treatment of these neurodegenerative disorders is changing at a remarkable pace. Interestingly, studies demonstrate that neurons in the adult brain have an unappreciated capacity for remodelling away from the actual injury, and that these neurons are attempting to re-wire the brain following an injury[8].

Cerebroprotein hydrolysate is the latest weapon in the physician's armamentarium. It is a neurotrophic drug. It consists of short biological peptides which act like endogenous neurotrophic factors. Neurotrophic activity can be detected upto 24 hours after a single injection. It

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has been approved in a number of European and Asian countries.

Pharmacokinetics

It is given in a dose of 60 -180 mg once daily for 10 - 20 days. It should be slowly perfused in 250 ml saline in 60 - 120 minutes. Maintenance doses (30 mg) can be given by intramuscular route. It should not be mixed with balanced aminoacid solutions in an infusion. Dose of antidepressants should be reduced if used with cerebroprotein hydrolysate.

Adverse effects and contraindications

Studies[9,10] have revealed that most of the side effects are minor. Most common side effects include headache, nausea, vertigo, increased sweating, agitation, fever, hallucinations, confusion, and flu-like syndrome. Contraindications include hypersensitivity, epilepsy and severe renal impairment. Safety has not been established in pregnancy and lactation; so should be used cautiously in humans.

Indications

a) Acute ischaemic stroke.
b) Traumatic brain injury.
c) Vascular dementia.
d) Alzheimer's disease (AD).

Mechanism of action and pharmacological effects

Cerebroprotein hydrolysate acts by:-

a) Regulation and improvement of the neuronal metabolism.
b) Modulation of the synaptic plasticity.
c) Neuronal differentiation and protection against ischaemic and neurotoxic lesions.
d) Cerebroprotein hydrolysate reduces excitotoxic damage, blocks over-activation of calcium dependent proteases, and scavenges free oxygen radicals.

Cerebroprotein hydrolysate has been shown to counteract the negative effect of the elevated FGF-2 on neurogenesis and neuromodulation[11]. This could be the mechanism for its beneficial effect in Alzheimer's disease.

Cerebroprotein hydrolysate-augmented proliferation, differentiation, and migration of adult SVZ neural progenitor cells results in increased number of neural progenitor cells and neuroblasts to contribute to neurogenesis. This may be the mechanism for its beneficial effect in acute ischaemic stroke and traumatic brain injury.

Enhancement of neuronal survival is produced through effect on calpain. The hyper-activation of calpain is implicated in a number of neurodegenerative disorders.

Calpain is inhibited by Cerebroprotein hydrolysate.

Neuromodulatory effect is produced by increasing GLUT-1 expression which is responsible for more than 90% of glucose transport to brain[12].

Neuronal plasticity is produced by reduction of amyloid beta accumulation, increased MAP 2 and synaptophysin synthesis.

Neuro-immunotrophic activity is produced by inhibition of microglial activation and expression of IL-1 beta. This results in reduction of inflammation.

This drug can be given with other neuroprotective agents like edaravone, citicoline, and piracetam safely. Other neurotrophic drugs and nootropics are not having as much broad spectrum of different actions as possessed by cerebroprotein hydrolysate. The patients of neurodegenerative disorders can now be managed in a better way with the advent of cerebroprotein hydrolysate.

References

1. Goldstein LB, Adams R, Becker *K et al*. Primary Prevention of Ischemic Stroke. A Statement for Healthcare Professionals From the Stroke Council of the American Heart Association. *Stroke* 2001; 32: 280-99.
2. Injury Prevention & Control: Traumatic Brain Injury. http://www.cdc.gov/traumaticbraininjury/(last accessed on 30-nov-2011).
3. Introduction to traumatic brain injury. The Neurosurgeon's Handbook. In: Samandouras G, editor. Oxford: Oxford University Press; 2010. p. 207-8.
4. Thomas SV. Addressing problems of dementia in India. *Annals of Indian Academy of Neurology* 2011; 14(3): 147.
5. Introduction to neurogenesis. Available at http://neurogenesis.iord.org/ accessed on15th oct 2011.
6. http://www.ceregene.com/neurotrophic.asp) last accessed on 30 oct 2011.
7. Ganong's *et al*. Review of Medical Physiology. In: Physiology of nerve and muscle cells: Excitable Tissue: *Nerve* 23rd edi. 2010.
8. Gopalan T. India: Neurons Key To Healing Of Brain Injuries Identified. August 24, 2010. Research News [online] Available from: http://www.medindia.net/news/Neurons-Key-To- Healing-Of-Brain-Injuries-Identified-73058-2.htm][last accessed on Nov 28 2011.
9. Long J, Wei GZ, Xu ZB *et al*. Injection of cerebroprotein hydrolysate vs cerebrolysin in treating cerebrovascular diseases. [Available from:http://en.cnki.com.cn/Article_en/CJFDTOTAL-XYYL606.002.htm. Last accessed on March 07 2012.]
10. Sui CM, Kam WC, Jia-Hong L *et al*. Systematic Review on the Efficacy and Safety of Herbal Medicines for Vascular Dementia. [Available from:http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3250997. Last accessed on March 07 2012.]
11. Chen H *et al*. Trophic factors counteract elevated FGF-2-induced inhibition of adult neurogenesis. *Neurobiol Aging* 2007; 28(8): 1148-62.
12. *Neuroscience Research* 1999, 34: 217-24.

REVIEW ARTICLE

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Testosterone: An adjunctive therapy in heart failure

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Abstract

Chronic heart failure (CHF) is a serious health care problem associated with increased hospitalisation and poor prognosis as well as poor quality of life. Its associated mortality is much more than that of most cancers. Coronary artery disease (CAD) and hypertension are the most commonly associated conditions. The disease is characterised by many abnormalities including impaired vascular tone, left ventricular dysfunction, and skeletal muscle changes leading to breathlessness and fatigue. Neurohormonal and cytokine activation lead to imbalance between catabolism and anabolism further leading to symptomatology and pathophysiology of CHF. Cardiac cachexia has been identified as an independent prognostic factor in CHF. In addition to neurohormonal alteration, many pathophysiological changes occurring in the form of chronic anaemia and enhanced immune activation have been the target for therapeutic intervention with variable success. The excess of catabolic hormones and deficiency of anabolic hormones has been well identified but until recently restoration of this anabolic hormone balance has been relatively ignored as a potential therapy. So testosterone has been postulated as an immune-modulating therapeutic modality with promising result although there are some conflicting reports to support this.

Key words: Chronic heart failure; testosterone; cachexia.

Introduction

Chronic heart failure (CHF) is a major health problem throughout the world causing increased mortality and morbidity as well as high hospitalization rate and poor prognosis[1]. Patients with CHF have a poor quality of life, decreased life expectancy, and reduced functional capacity[2]. In the past decade, the prognosis of CHF has significantly improved due to widespread use of medical therapies including ACE inhibitors, ARBs, beta-blockers, aldosterone receptor antagonists, and vasodilators, etc[3]. However, the only therapy which provides long-term survival is cardiac transplantation but it has its own limitations of nonavailability of donors and recipient suitability. Hence there is a need for therapies which alleviate the suffering associated with CHF with an aim to reduce the mortality. Now testosterone therapy has been proposed as a useful adjunctive therapeutic modality for men with CHF although there are conflicting reports of their beneficial effect[4,5]. CHF is characterised by left ventricular dysfunction, impaired vascular tone, and skeletal muscle abnormalities occurring as a result of neuroendocrine and cytokine activation. The neuroendocrine activation produces an imbalance between the anabolism and catabolism responsible for symptomatology of CHF, reduced muscle bulk and function, exercise intolerance, and occurrence of cardiac cachexa[5,6]. Anabolic deficiency is an important component of the anabolic/catabolic imbalance characterised by impairment of growth hormone /insulin like growth factor -1 axis [7,8,9,10,11]. The anabolic impairment is a multifaceted phenomenon and is related to abnormalities in at least 3 key anabolic endocrine axes namely gonadal, adrenal and somatotropic. Various mediators are involved in the pathogenesis of wasting process (cardiac cachexia) and these are tumour necrosis factor (TNF), secretion of neurohormones and peptides including growth hormone, ghrelin, cortisol, adrenaline, noradrenaline and insulin and a relative deficiency of micronutrients as well as macronutrients[9,11]. Testosterone therapy has been proposed as a useful add on treatment for men with CHF[12,13]. In this article, an attempt has been made to review the role of testosterone in the management of chronic heart failure in men and to know the cardiovascular, neurohormonal actions, and cytokine activation of testosterone.

Gonadal function in men with CHF

As age advances, there occurs a progressive fall in the secretion of anabolic hormones including testosterone, responsible for the chronicity of the disease[14]. The rate of decline is about 1% per year after the age of 30 years and this fall becomes much more in the presence of co-morbid conditions and drugs like steroids. Regarding the role of neuroendocrine system in CHF, the renin-angiotensin aldosterone (RAA) axis is mainly affected and is associated with disturbance in other endocrinal gland secretions. Some studies have reported deficiencies of testosterone, DHEA-S[5,11,15], IGF-1[8,16] while other workers have not found such deficiencies in their study[16,17]. It is presumed that reduced DHEA secretion in CHF may be due to insulin resistance and hyperinsulinaemia[18]. Insulin is a physiological inhibitor of DHEA secretion in healthy

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subjects[19]. Malkin *et al*[13] in their study demonstrated beneficial effects in patients of CHF with testosterone therapy. It has been postulated that these deficiencies potentially exacerbate the catabolic imbalance and adversely affect the disease progression[20,21].

Jankowska *et al*[22] studied the prevalence and prognostic consequence of deficiencies in circulating total testosterone (TT) and free testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), and insulin like growth factor-1 (IGF-1) in men with chronic heart failure(CHF). It was found that there were marked deficiencies of TT, FT, DHEAS and IGF-1; DHEAS had positive correlation with left ventricular ejection fraction and inverse correlation with N terminal pro-brain natriuretic peptide. They concluded in their study that deficiency of each of the anabolic hormones is an independent marker of poor prognosis, while men with CHF having multiple hormone deficiencies carry a poor prognosis. The androgen levels in elderly males with CHF were found to be markedly low and the level of FT had inverse relation with heart failure as shown in Chinese study[23]. In another Chinese study, the levels of TT and FT were found to be low in elderly subjects with systolic CHF and had a positive correlation to disease activity, but they were not independent predictors for mortality[24]. DHEAS and FT were found to be inversely associated with NYHA class ($p < 0.01$ for both) in a study by Guder *et al*[25].

Effects on cardiovascular function

Some studies[26,27] have reported that men with ischaemic heart disease have low androgen levels while men with proven coronary atheroma have low testosterone levels as compared to healthy controls. In animals, castration promotes atherosclerosis while androgen therapy retards it[28]. Androgen levels have been found to be low in hypertensive men[26]. DHEAS deficiency is an independent risk factor of ischaemic heart disease[29] and a predictor of all cause and cardiovascular mortality in males[30]. In rats, androgen therapy has been shown to improve coronary blood flow, increase myocardial oxygen consumption, thus causing improvement in cardiac function[31,32,33].

Effect of immune mediators on heart failure (cytokine activation)

Recently, immune mediators have been shown to play an important role in the pathogenesis and prognosis of CHF. The cytokine hypothesis is based on the known actions of many cytokines[34] which mediate many of the pathophysiological processes of heart failure. Serum levels of proinflammatory cytokines like tumour necrosis factor (TNF)[35] and interleukin-6 (IL-6)[36] are increased in CHF and are independent predictors of mortality. Moreover, TNF-α markedly stimulates the secretion of matrix metalloproteinase (MMP) thus responsible for ventricular remodelling[37]. Effect of testosterone therapy on ventricular remodelling in CHF, occurs on account of reduction in the myocardial hydroxyproline contents. This beneficial effect is mediated by suppressing TNF-α or by down-regulation of MMP-9 directly [38,39]. TNF is produced mainly by macrophages but also by the myocardium in CHF. It impairs synthesis and protein catabolism of skeletal muscle, and reduces testosterone production. It leads to endothelial dysfunction and thus nitric oxide (NO) production by endothelium is reduced[40]. Anti-TNF therapy may improve cardiac function[41] in CHF. In men, androgen levels have inverse correlation with plasma cytokine levels and gonadotropin therapy suppresses high levels in hypogonadal men[42].

Skeletal muscle and strength

The cardinal feature of CHF is fatigue and poor exercise tolerance which may be out of proportion to the degree of left ventricular dysfunction. In CHF, there occurs loss of skeletal muscle mass, reduced muscle strength, alteration of muscles fibre type and mitochondrial structure. This leads to reduction in the enzymes of Kreb's cycle and oxidative chain[43]. These deleterious effects are corrected by testosterone therapy which improves vasodilation, increases protein synthesis, and inhibits the catabolic effect of glucocorticoids[12]. In healthy men, androgens produce skeletal muscle hypertrophy, increased muscle bulk and strength[44]. Few studies have shown improvement in leg strength and grip and increase in lean body mass with testosterone therapy in elderly men[45].

Conclusion

Testosterone receptors are present in endothelial cells, vascular smooth muscle cells, and cardiomyocytes. Testosterone therapy causes vasodilation in the vascular arterial wall and induces protein synthesis and hypertrophy in the cardiomyocytes[10]. In this review, some studies have shown worse prognosis with low levels of testosterone therapy. This indicates that androgen deficiency aggravates CHF symptoms and accelerates disease progression. Cardic cachexia is directly related to the prognosis of heart failure. The neuroendorine and cytokine activation is associated with the pathophysiology and symptomology of CHF. Testosterone therapy in the form of gels, ointment, bioadhesive buccal tablets, depot injections has shown some positive benefits but at the same time it carries some adverse effects. Large randomised controlled trials are still needed to know the long-term safety and efficacy of testosterone in CHF.

References

1. Cleland JG, Khand A, Clark A. The heart failure epidemic: exactly how big is it? *Eur Heart J* 2001; 22: 623-6.
2. Nieminen MS, Bohm M, Cowie MR *et al*. ESC Committee for Practice Guideline (CPG). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 384-416.
3. Levy D, Kenchaiah S, Larson MG *et al*. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; 347: 1397-402.
4. Shapiro J, Christiano J, Frishman WH. Testosterone and other anabolic steroids as cardiovascular drug. *Am J Ther* 1999; 6: 167-74.
5. Pugh PJ , English KM , Jones TH *et al*. Testosterone: a natural tonic for the failing heart. *QJ Med* 2000; 93: 689-94.
6. Anker SD, Chua TP, Ponikowski P *et al*. Hormonal changes and catabolic/ anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* 1997; 96: 526-34.
7. Packer M, Lee WH, Kessler PD *et al*. Role of neurohormonal mechanisms in determining survival in patients with severe chronic heart failure. *Circulation* 1987; 75: IV 80-IV92.
8. Anker SD, Volterrani M, Pflaum CD *et al*. Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. *J Am Coll Cardiol* 2001; 38: 443-52.
9. Niebauer J, Pflaum CD, Clark AL *et al*. Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. *J Am Coll Cardiol* 1998; 32: 393-97.
10. Dalla Libera L, Ravara B, Volterrani M *et al*. Beneficial effects of GH/IGF-1 on skeletal muscle atrophy and function in experimental heart failure. *Am J Physiol Cell Physiol* 2004; 286: C138 -C144.
11. Sacca L. Heart failure as a multiple hormone deficiency syndrome. *Circ Heart Fail* 2009; 2: 151-6.
12. Anker SD, Clark AL, Kemp M *et al*. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. *J Am Coll Cardiol* 1997; 30: 997-1001.
13. Malkin CJ, Pugh PJ, West JN *et al*. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006; 27: 57-64. First published on August 10, 2005, doi: 10. 10973/eur heart j/ehi 443.
14. Matsumoto AM. Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol A Biol Sci Med Sci* 2002; 57: M76-99.
15. Moriyama Y, Yasue H, Yoshimura M *et al*. The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. *J Clin Endocrinol Metab* 2000; 85: 1834 -40.
16. Kontoleon PE, Anastasiou-Nana MI, Papapetrou PD *et al*. Hormonal profile in patients with congestive heart failure. *Int J Cardiol* 2003; 87: 179-83.
17. Al-Obaidi MK, Hon JKF, Stubbs PJ *et al*. Plasma insulin-like growth factor-1 elevated in mild-to moderate but not severe heart failure. *Am Heart J* 2001; 142: E10.
18. Swan JW, Anker SD, Walton C *et al*. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. *J Am Coll Cardiol* 1997; 30: 527-32.
19. Nestler JE. Regulation of human dehydroepiandrosterone metabolism by insulin. *Ann NY Acad Sci* 1995; 774: 73-81.
20. Rauchhaus M, Doehner W, Anker SD. Heart failure therapy: testosterone replacement and its implications. *Eur Heart J* 2006; 27: 10-12.
21. Pugh PJ, Jones RD, Jones TH. Heart failure as an inflammatory condition: potential role for androgens as immune modulators. *Eur J Heart Fail* 2002; 4: 673-80.
22. Ewa A. Jankowska, Bartosz Biel, Jacek Majda *et al*. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation* 2006; 114: 1829-37.
23. Chen Q, Li XY, Li JY *et al*. A comparative survey of sex hormone levels between elderly men with chronic heart failure and normal elderly subjects. Zhonghua Xin, Xue Guan Bing ZA Zhi 2005; 33: 505-8.
24. Wu HY, Wang XF, Wang JH, Li JY. Testosterone level and mortality in elderly men with systolic chronic heart failure. *Asian J Androl* 2011; 13: 759-63.
25. Guder G, Frantz S, Bauersachs J *et al*. Low circulating androgens and mortality risk in heart failure. *Heart* 2010; 96: 504-9.
26. English KM, Steeds R, Jones TH *et al*. Testosterone and coronary heart disease: is there any link? *QJ Med* 1997; 90: 787-91.
27. English KM, Mandour O, Steeds RP. Men with coronary artery disease have lower levels of androgen than men with norma coronary angiograms. *Eur Heart J* 2000; 21: 890-4.I
28. Alexandersen P, Haarb J, Byrjalsen I *et al*. Natural androgens inhibit male atherosclerosis. A study in castrated cholesterol fed rabbits. *Circ Res* 1999; 84: 813-9.
29. Feldman HA, Johannes CB, Araujo AB *et al*. Low dehydroepiandrosterone and ischemic heart disease in middle aged men: prospective results from the Massachusetts Male Aging Study. *Am J Epidemiol* 2001; 153: 79-89.
30. Barrett-Conner E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulphtate, mortality and cardiovascular disease. *N Engl J Med* 1986; 315: 1519-24.
31. Scheuer J, Malhotra A, Schaible TF *et al*. Effects of gonadectomy and hormonal replacement on rat hearts. *Circ Res* 1987; 61: 12-9.
32. Costarella CE, Stallone JN, Rutecki GW *et al*. Testosterone causes direct relaxation of rat aorta. *J Pharmacol Exp Ther* 1996; 277: 34-9.
33. Honda H, Unemoto T, Kogo H. Different mechanisms for testosterone induced relaxation of aorta between normotensive and spontaneously hypertensive rats. *Hypertension* 1999; 34: 1232-6.
34. Seta Y, Shan K, Bozkurt B *et al*. Basic mechanisms in heart failure: The cytokine hypothesis. *J Card Fail* 1996; 2: 243-9.
35. Ceconi C, Boraso A, Mele D *et al*. TNF alpha in patients with congestive heart failure. *Basic Res Cardiol* 2004; 99: 12-7.
36. Tsutomoto T, Hisanaga T, Wada A *et al*. Interleukin-6 spill over in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998; 31: 391-8.
37. Ducharme A, Frantz S, Aikawa M *et al*. Targeted deletion of matrix metallo proteinase-9 attenuates, left ventricular enlargement and collagen accumulation after experimental myocardial infarction. *J Clin Inves* 2000; 106: 55-62.
38. Miyamoto H, Altuwaijri S, Cai Y *et al*. Inhibition of the Akt, cyclooxygenase-2, and matrix metallo proteinase-9 pathways in combination with androgen deprivation therapy: potential therapeutic approaches for prostate cancer. *Mol Carcinogen* 2005; 44: 1-10.
39. Zhang YZ, Xing XW, He B *et al*. Effects of testosterone on cytokines and left ventricular remodelling following heart failure. Cell Physiol Biochem 2007; 20: 847-52.
40. Yoschzumi M, Perella MA, Burnett JCJ *et al*. Tumour necrosis factor down regulates endothelial nitric oxide synthase mRNA by shortening its half life. *Cir Res* 1993; 73: 205-9.
41. Deswal A, Bozkurt B, Seta Y *et al*. Safety and efficacy of soluble P75 tumour necrosis factor receptor ((Enbrel, etanercept) in patients with advanced heart failure. *Circulation* 1999: 99: 3224-6.
42. Yesilova Z, Ozata M, Kocar IH *et al*. The effects of gonadotropin treatment on the immunological features of male patients with idiopathic hypogonadotropic hypogonadism. *J Clin Endocroniol Metab* 2000; 85: 66-70.
43. Drexler H, Riede U, Munzel T *et al*. Alterations of skeletal muscle in chronic heart failure. *Circulation* 1992; 85: 1751-9.
44. Bhasin S, Storer TW, Berman N *et al*. The effects of supra physiological doses of testosterone on muscle size and strength in normal men. *New Engl J Med* 1996; 335: 1-7.
45. Urban RJ, Bodenburg YH, Gilkison C *et al*. Testosterone administration to older men increases skeletal muscle strength and protein synthesis. *Am J Physiol* 1995; 269: E 820-6.

CASE REPORT

JIACM 2014; 15(2): 137-8

Tuberculosis of rib with cold abscess

*SJ Keny**

Abstract

Tuberculosis of rib is a rare condition and is often missed till osseous destruction of the rib is seen on chest radiograph or a cold abscess is formed in the chest wall. Such a case is reported here in view of its rarity.

Key words: Osseous destruction, chest wall mass, haematogenous dissemination.

Introduction

Any bone in the body can be a site for tuberculosis. However, tuberculosis of rib is an extremely rare condition. Tuberculosis of rib must be distinguished from other types of inflammatory bone lesions of the ribs and from benign and malignant tumours. The cold abscesses must be distinguished from cysts and tumours of chest wall and from somewhat more common types of cold abscesses in this area secondary to tuberculosis of thoracic spine[1]. A case report of tuberculosis of rib with cold abscess in the chest wall is presented hereinunder.

Case report

A 37-year-old female non-smoker presented with a one-month history of pain and swelling over the left side of the chest. Pain was insidious in onset, localised and non-radiating, and aggravated on movement and coughing. There was history of low-grade fever and loss of weight over one month. She had no past history of tuberculosis or contact with a case of tuberculosis. On general examination, patient was afebrile with no pallor, clubbing, and lymphadenopathy. She had pulse rate of 72/min, respiratory rate of 20/min, and blood pressure of 120/80 mm of Hg in the right upper arm. On examination of her respiratory system, a soft non-tender fluctuant non-pulsatile swelling was palpable on the left side of the chest in mid-axillary line, measuring about 10 x 10 cms in size. Local temperature over the swelling was not raised and there was no cough impulse. There were no other significant findings and other systems were normal. Investigations showed her haemoglobin to be 11 gm%, total leucocyte count 7,500/cmm, neutrophils 72%, lymphocytes18%, and eosinophils 10%. Her blood sugar level and liver function tests were normal and she was not immunocompromised. Her chest radiograph showed evidence of osseous destruction of the left 7th rib in its lateral aspect with associated soft-tissue swelling over the chest wall (Figure 1). Chest ultrasonography showed evidence of a hypoechoeic lesion in the lateral aspect of chest wall showing thick internal echoes measuring 8.5 x 4.5 cms. There was no evidence of pleural effusion. Fine needle aspiration of this swelling was done. Smear of the aspirate showed lymphocytes, lymphoblasts, and histiocytes. The picture was reported as suggestive of cold abscess due to tuberculosis. She was started on antituberculous treatment with category one DOTS, i.e., 2HREZ+4HR thrice weekly which she tolerated well. Her chest swelling subsided gradually and she showed signs of improvement over the course of treatment.

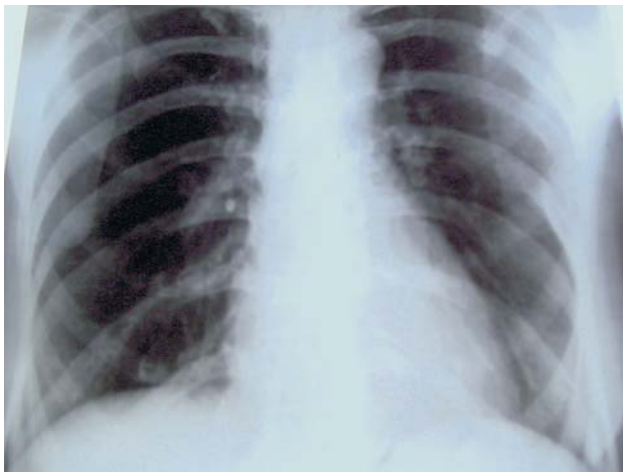

Fig. 1: *X-ray chest showing evidence of osseous destruction of the left 7th rib in its lateral aspect with associated soft-tissue swelling over the chest wall.*

Discussion

As mentioned earlier, tuberculosis of the rib is a rare condition. It has an insidious onset and less than 50% of patients have active pulmonary disease[2]. Destruction of bone in tuberculosis results from pressure necrosis by granulation tissue and also by the direct action of invading organisms[3]. Mechanism of rib tuberculosis includes:- (1)

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haematogenuous dissemination associated with activation of a dormant tuberculous focus (most common); (2) direct extension from a lymphadenitis of chest wall, and (3) direct extension from lungs[4]. Presenting symptoms of rib tuberculosis are a painful or non-tender chest wall mass or chest pain. The mass can be cystic or doughy. The location of the mass is not classic since any part of the rib can be involved[2]. Diagnosis of rib tuberculosis may be difficult and is based on bacteriologic or histologic confirmation – as is true in all tuberculosis cases[5]. This patient presented with tuberculosis of rib with chest wall swelling without any pleuro-pulmonary involvement. She probably had rib involvement due to isolated haematogenuous dissemination from a dormant tuberculous focus which might have got activated due to some impairement of immunity. However, her serological assay for HIV was negative. The diagnosis was made on the basis of aspiration cytology of the swelling which showed signs of cold abscess due to tuberculosis. She responded well to antituberculous chemotherapy.

Acknowledgement

I wish to thank Dr V. N. Jindal, Dean, Goa Medical College, for permitting me to publish this case.

Referneces

1. Johnson MP, Rothstein E. Tuberculosis of the rib. *JBJS* 1952; 34: 878-82.
2. Asnis DS, Niegowska A. Tuberculosis of the rib. *Clin Infect Dis* 1997; 24: 1018-9.
3. Singh SK, GuptaV, Ahmed Z *et al*. Tuberculous osteomyelitis of rib-a case report. *Respiratory Medicine CME* 2009; 2: 128-9.
4. De U. Tuberculosis of eleventh rib masquerading as renal colic. *Journal of Chinese Clinical Medicine* 2010; 51: 242-3.
5. Kuzucu A, Soysal O, Gunen H. The role of surgery in chest wall tuberculosis. *Interact Cardiovasc Thoracic Surg* 2004; 3: 99-103.

CASE REPORT

JIACM 2014; 15(2): 139-40

Recurrent severe anaemia in a setting of auto-immune haemolysis

M Manjula, BC Mithra*, Veda P***, R Ravikumar**, Manjunath*****

Abstract

Auto-immune haemolytic anaemia (AIHA) is an acquired type of haemolytic anaemia caused by autoantibodies directed against the red cells. We hereby report a case of chronic severe anaemia which was caused by immune haemolysis. Treatment with prednisolone resulted in significant improvement of the haematological parameters. AIHA should be kept in mind while evaluating chronic anaemia.

Introduction

Auto-immune haemolytic anaemia (AIHA) is the clinical condition caused by autoantibodies, which bind to the red cell surface resulting in extravascular haemolysis. RBC destruction is mediated via the complement system or the reticuloendothelial system. Macrophages recognise F_c receptor of Ig and/or C_{3b} and phagocytise a portion of the red cell membrane, each time it passes through the spleen. The recurrent loss of cell membrane results in shortening of the red cell life span, and chronic anaemia.

AIHA are classified into warm AIHA, cold AIHA, mixed type and drug induced type. Warm antibody type accounts for 70% of all AIHA. It is of Ig G type and usually does not fix the complement. AIHA can be a primary disorder (50%) or secondary to lymphoproliferative diseases, other systemic autoimmune diseases, viral infections, immune deficiency states, etc. Direct Coombs' test which detects Ig and/or complement bound to the surface of the red cell is the diagnostic test for AIHA.

Case report

A 28-years-old female patient presented with complaints of weakness, breathlessness on exertion, and palpitations of 15 days duration. She was previously admitted elsewhere on several occasions (within past 3 - 4 months) with similar complaints, and had recieved multiple blood transfusions. As the patient was from a low socio-economic status, and peripheral smear had shown microcytic hypochromic picture, she was treated as iron deficiency anaemia (traditional approach). There was no history of blood loss or bleeding diathesis, no history of fever, joint pain or rash, no history of recent drug intake.

On clinical examination, the patient was moderately built and nourished, with severe pallor and mild icterus. There was post-polio residual paralysis of the left lower limb. There was no clubbing, lymphadenopathy or oedema. Pulse was 110/min, regular. BP was 110/70 mm Hg. Cardiovascular and respiratory system examination revealed no significant abnormality. Per abdomen examination revealed mild splenomegaly (2 cm below the left costal margin) but no hepatomegaly.

Investigations revealed Hb% of 3.3 g/dl, total corrected leukocyte count = 8,200/cumm, platelet count = 180,000/cumm, ESR = 80 mm/1st hr, reticulocyte count was 39.5 % (Figure 2), reticulocyte production index of 5.4 (RI above 3 is suggestive of haemolytic anaemia). Hematocrit -19.4%, mean corpuscular volume - 127.6 fL (↑), mean corpuscular haemoglobin = 36.2 pg, Mean corpuscular haemoglobin concentration- 28.4 g/dl, red cell distribution width (RDW-CV) was 26% (↑). Peripheral smear showed numerous spherocytes, nucleated RBCs (200 nRBC/100WBC) and polychromasia (Figures 1 & 3) indicating a haemolytic process. Serum bilirubin = 2.5 (direct = 0.6), CPK = 411 U/l, lactate dehydrogenase (LDH) = 2,775 U/l (NR up to 400 U/l). Serum Haptoglobin was below 6.63 (30-200 mg/dl). All these findings pointed towards haemolytic anaemia.

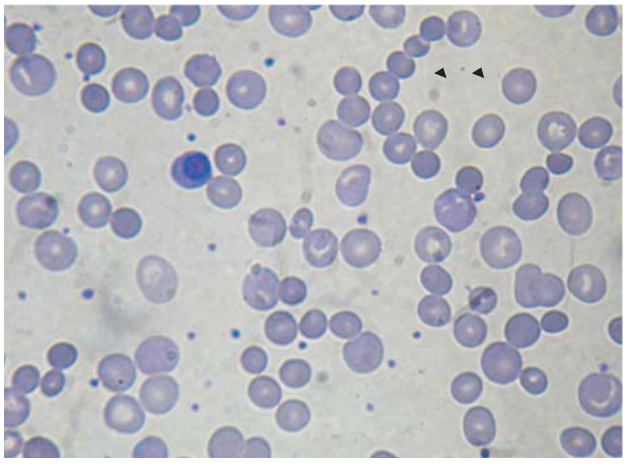

Fig. 1: *Peripheral smear showing spherocytes, one normoblast, and polychromasia.*

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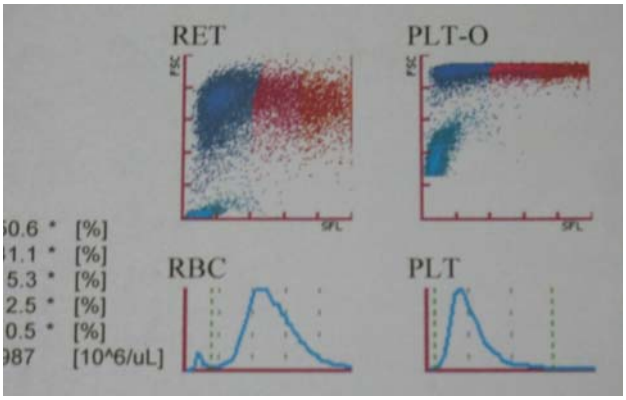

Fig. 2: *Haemogram showing marked reticulocytosis.*

Fig. 3: *Positive direct Coombs' test.*

Hb quantification using HPLC (high performance liquid chromatography) was normal. Serum G6PD activity was normal. Anti-nuclear antibody was negative. Direct Coombs' test (using gel card) was positive (4+) at both 37° C and at room temperature. Indirect Coombs' test was negative. Based on these findings, a diagnosis of warm antibody type immune haemolytic anaemia was made.

Blood urea was 23 mg/dl, creatinine was 0.7 mg/dl, ultrasonography of abdomen was normal, HIV and HBsAg were negative, VDRL was non-reactive. IgG levels were 1540 mg/dl (NR 700 - 1600 mg/dl). IgM levels were 169 mg/dl (40 - 230 mg/dl). C_3 levels were 129 mg/dl (90 - 180 mg/dl). Ebstein Barr virus VCA (viral capsid antigen) and EBNA (nuclear antigen) was negative. TORCH screening (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes simplex virus) was negative. A diagnosis of warm antibody type auto-immune haemolytic anaemia (AIHA), probably of idiopathic type, was made and the patient was started on steroid therapy. She was transfused with three units of blood.

After 1 week, repeat haemoglobin was 11 gm%. Peripheral smear showed reduction in the number of normoblasts (6 - 8 nucleated RBC /100 WBC). Repeat reticulocyte count was 18%. Serum LDH level at the end of one week was 593 U/l reflecting decrease in haemolytic activity.

Discussion

The course of warm antibody AIHA varies with age. In children, AIHA is usually a self-limiting disease, arising 1 - 3 weeks after a viral infection, and disappearing within 1 - 3 months. In adults, the disease may have a variable manifestation. Severe AIHA can be a medical emergency. Red cell transfusion poses a special problem as the transfused cells are rapidly destroyed, but can be life-saving because in the meantime steroids can exert their effect. This unique situation requires good liaison and understanding between the clinical unit and the serology lab. Thus it is very important to diagnose this condition and treat accordingly. Untreated, chronic auto immune haemolysis progresses to severe anaemia and associated complications. No association between past poliomyelitis and auto-immune haemolytic anaemia was found. Hence we report this case to emphasise the need to completely evaluate a patient, as it has several therapeutic implications.

References

1. Cotran, Ramzi S *et al*. Robbins and Cotran Pathologic basis of diseases. St. Louis, *Mo: Elsevier Saunders* 2005; pp: 637.
2. Kumar P, Clark M. Clinical Medicine (6th Ed) Elsevier Saunders 2005; pp: 437.
3. Bottiger LE, Werterholm B. Acquired haemolytic anaemia-Incidence and Etiology. *Acta Med Scand* 193(3): 223-6.
4. Nowak-Wegrzyn A, King KE, Shirey RS *et al*. Fatal warm auto immune haemolytic anaemia. *J Pediatr Hematol Oncol* 2001; 23(4): 250-2.
5. Morqensztern D, Kharfan-Dabaja MA *et al*. Warm antibody auto immune haemolytic anaemia developing after TTP. *Acta Haematol* 2002; 108(3): 154-6.
6. Garratty G, Petz LD. Approaches to selecting blood for transfusion to patients with auto immune haemolytic anaemia. *Transfusion* 2002; 42: 1390.
7. Gupta S, Szeiszen A, Nakhl F *et al*. Severe refractory auto immune haemolytic anaemia with both warm and cold auto antibodies. *J Med Case reports* 2011; 5: 156.

"They know enough who know how to learn."

– Henry Brooks Adams: The Education of Henry Adams.

CASE REPORT

JIACM 2014; 15(2): 141-2

Salmonella typhi causing hip arthritis with dislocation

V Gupta, A Priyadarshi** , N Mehra*** , TP Yadav****, V Dewan******

Abstract

Salmonella typhi is endemic in several parts of India causing enteric fever. Salmonella typhi septic arthritis in children without risk factors like sickle cell anaemia, systemic lupus erythematosis, immunodeficiency, or trauma to joint, etc., is uncommon. Here we report a child with Salmonella typhi septic arthritis who developed dislocation hip while on treatment. Clinical presentation and management of the same has been discussed.

Key words: Salmonella typhi, arthritis, dislocation hip.

Introduction

Salmonella causes two clinical syndromes in humans: a gastroenteritis that is usually self-limited, and enteric fever that is a relatively severe systemic illness classically caused by *S. typhi*[1]. Enteric fever can presents with various extraintestinal complications like encephalopathy, meningitis, Guillain-Barré syndrome, myocarditis, congestive heart failure, pneumonia, empyema, osteomyelitis, hepatitis, psoas abscess, cutaneous vasculitis, and haemophagocytosis syndrome, etc[1]. Though the non typhus salmonella are a common cause of septic arthritis in children[2], salmonella typhi causing septic arthritis with hip dislocation has been infrequently reported. Here we report a child with enteric fever with no risk factors, complicating as septic arthritis of hip and knee joint along with dislocation of hip.

Case report

A 3½-year-female child was admitted with complaints of fever for 5 weeks, pain and swelling in the left hip and knee joint for the last 4 weeks, yellowish discoloration of eyes for 15 days. There was no history of loose motions, rash, vomiting, dysuria, or urtheral discharge. On examination, the vitals were stable, pallor and icterus were present, left leg was kept abducted, flexed, and externally rotated at the hip with flexion at the knee joint. Both joints (left hip and knee) were swollen, tender, warm to touch, with restriction of movements. Systemic examination revealed hepatomegaly of 3 cm and splenomegaly of 1 cm. The other general physical and systemic examination was normal. Patient was managed provisionally with diagnosis of septic arthritis with IV ceftriaxone, vancomycin, and above knee traction with ½ kg wt. Hip joint aspiration grew *Salmonella typhi*, sensitive to genatmicin, ciprofloxacin, amikacin, ceftriaxone, ofloxacin, piperacillin-tazobactum, and resistant to chloramphenicol, nalidixic acid, cotrimoxazole, and ampicillin. Knee joint could not be tapped because of minimal effusion. Haemogram revealed Hb 7.4 gm/dl, TLC 10,300/mm^3 (P60%, L40%), platelet count of 150,000/mm^3. LFTs were deranged (total bilirubin 6.6 mg/dl, direct 4.6 mg/dl, SGOT 154 IU/L, SGPT 85 IU/L). All other biochemical tests were within normal range. Widal test was positive with 'O' and 'H' titre of 1/480. IgM antibody for hepatitis A and Hepatitis E virus were negative and HIV serology was non reactive. PT, aPTT, and chest X-ray were normal. Mantoux skin test did not show any induration. Sickling test and ANA were negative. Blood culture was sterile.

Antibiotics were changed to ceftriaxone and ofloxacin after the culture report. Despite 10 days of hospital stay, the fever persisted along with pain and tenderness at both the joints. By the 15th day of admission, pain and swelling at the left hip joint increased with exacerbation of signs and symptoms. X- ray hip joint showed osteomyelitic changes of left femoral head with dislocation from the acetabular cavity as shown in Figure 1A. Immediate arthrotomy and drainage of hip was done along with reduction of hip joint. Inflammatory granulation tissue and pus were sent for histopathological and culture-sensitivity examination. K wire fixation was done to prevent re-dislocation, and hip spica was applied to stabilise the joint (Figure 1B. Antibiotics were changed to ofloxacin and azithromycin. Later, synovial biopsy revealed ulcerations with chronic inflammatory granulation tissue. Pus culture re-grew *Salmonella typhi* with the same sensitivity pattern as mentioned above. Gradually, the patient became afebrile, with decrease in pain and tenderness over a

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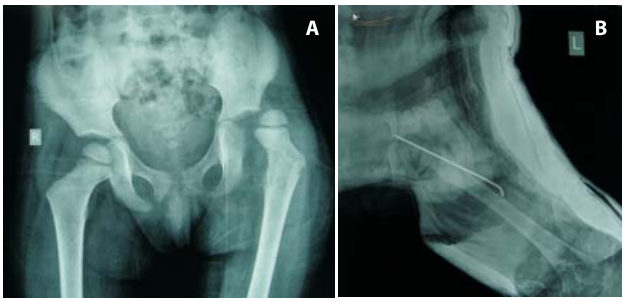

***Fig. 1**: A) Displacement of left femur head with sclerotic area at the upper end of femur suggestive of osteomyelitis. B) Left femoral head fixed with K wire with hip spica.*

period of few days. Icterus gradually disappeared and there was regression of spleen and liver. Parentral antibiotics were given for a total duration of 4 weeks. Hip spica was removed after 6 weeks. Repeat USG hip joint showed minimal effusion with complete resolution of knee joint. Serum bilirubin and liver enzymes normalised by the end of 4 weeks.

Discussion

Septic arthritis is an important osteoarticular infection in children[3]. There are three ways by which the joint gets invaded by the bacteria. These are: Percutaneous route, haematogenous seeding from a distal site of infection, or contiguous metaphyseal osteomyelitis decompressing into the joint capsule[4]. Organisms commonly responsible for septic arthritis are *Staphylococcus aureus*, *Haemophilus influenzae* type b, streptococci, salmonella, *Kingella kingae*, and Moraxella[2,4-6].

Salmonella that causes septic arthritis is almost invariably a non-typhoidal species and that too in patients with risk factors like sickle cell anaemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery, malnutrition, anaemia, and repetitive minor trauma to the joint[1,2,7]. Septic arthritis in a previously healthy child is an extremely rare complication of *S. typhi* infection[8] which has been reported very infrequently from India[9,10]. Although any skeletal site can become infected, Salmonella infections of the bone typically involve the long bones resulting in arthritis of hip, knee, ankle, and shoulder[3,11]. The synovium is a particular metastatic focus of Salmonella infection resulting in septic arthritis[12]. Septic arthritis usually presents with fever, joint pain, local warmth, swelling, and limitation of motion in all ranges[5,6] as in our case. *Salmonella typhi* arthritis complicating osteomyelitis and pathological fracture have been reported[13] but dislocation hip was an unusual complication, as was seen in our case. In our patient, repeat X-ray of hip done 7 weeks after the onset of illness showed features of osteomyelitis in the left femoral head. Whether the osteomyelitis occurred first and then spread to the joint or both hip joint and head of femur were simultaneously seeded by the bacteria is debatable.

Salmonella typhi arthritis requires prolonged antibiotic treatment of more than 4 weeks[11,14]. Antibiotic selection should be guided by culture-sensitivity report, though quinolones and third-generation cephalosporins, especially ceftriaxone, have been most commonly used[11]. Abscess formation, osteomyelitis, sequestrum of necrotic bone, and failure to respond to IV antibiotic therapy are indications for surgical intervention[14].

This case report describes the unusual complication of salmonella arthritis with hip dislocation. Though *Staphylococus aureous* remains the most common cause of septic arthritis in children, a high index of suspicion should be kept towards the possibilities of salmonella arthtritis in endemic regions. Early diagnosis, treatment with appropriate systemic antibiotics, along with surgical intervention – as and when required – plays a pivotal role in successful treatment, thus preventing long-term joint damage.

References

1. Bhutta ZA. Salmonella. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. 18th ed. Saunders publication, Elsvier 2007; 1182-91.
2. Faseela T S, Malli C S, Balakrishna AK *et al*. Salmonella Typhi Septic Arthritis Of The Hip - A Case Report. *Journal of Clinical and Diagnostic Research* 2010; 4: 2308-10.
3. Papapetropoulou M, Leontsini F, Ierodiakonou M. Salmonella enteritidis septic arthritis of the hip: A case report. *Pediatr Infect Dis J* 2009; 4: 305-7.
4. Yang WC, Huang YC, Tsai MH *et al*. Salmonella Septic Arthritis Involving Multiple Joints in a Girl with Acute Lymphoblastic Leukemia at Diagnosis. *Pediatr Neonatol* 2009; 50: 33-35
5. Wang CL, Wang SM, Yang YJ *et al*. Septic arthritis in children: relationship of causative pathogens, complications, and outcome. *J Microbiol Immunol Infect* 2003; 36: 41-6.
6. Timsit S, Pannier S, Glorion C ***et al***. Acute osteomyelitis and septic arthritis in children: one year experience. *Arch Pediatr* 2005; 12: 16-22.
7. Lavy CB, Lavy VR, Anderson I. Salmonella septic arthritis in Zambian children. *Trop Doct* 1995; 25: 163-6.
8. Chiu S, Chiu CH, Lin TY *et al*. Septic arthritis of the hip caused by Salmonella typhi. *Ann Trop Pediatr* 2001; 21: 88-90.
9. Agnihotri N, Dhingra MS, Gautam V *et al*. Salmonella tyhpi septic arthritis of hip- A case report. *Jpn J Infect Dis* 2005; 58: 29-30.
10. Fule RP, Chidgupkar J. Salmonella typhi septic arthritis of elbow – a case report. *Indian J Med Sci* 1994; 48: 161-2.
11. Ulug M, Celen MK, Geyik MF *et al*. Sacroiliitis caused by Salmonella typhi. *J Infect Dev Ctries* 2009; 3: 564-8.
12. Chen JY, Luo SF, Wu YJ *et al*. Salmonella septic arthritis in systemic lupus erythematosus and other systemic diseases. *Clin Rheumatol* 1998; 17: 282-7.
13. Tóth F, Szabó G, Abed R *et al*. Multifocal simultaneous Salmonella typhi osteomyelitis in an immunocompetent adult. *Scand J Infect Dis* 2002; 34: 770-2.
14. Zimmerman B, Mikolich DJ, Lally EV. Septic sacroiliitis. *Semin Arthritis Rheum* 1996; 26: 592-604.

CASE REPORT

JIACM 2014; 15(2): 143

Thoracic insufficiency syndrome with cor pulmonale in an adult

Sourya Acharya, Amit Gupta**, Dinesh Sing**, SN Mahajan****

The case

A 45-year-old housewife, presented with gradual onset dysnoea on exertion over 3 months and oedema of feet since 15 days. Her general examination revealed a pulse of 102/min, RR 24/min (abdomino-thoracic), BP 134/80 mm of Hg, JVP 12 cms, with prominent 'a' waves and bilateral pitting oedema of feet. CVS examination was normal. RS examination revealed bilateral diminished chest wall movement of 3 cms. Trachea was central. Auscultation revealed bilateral diminished air entry, vescicular breath sounds bilaterally, and few scattered fine crepts. Per abdominal examination revealed hepatomegaly.

Investigations showed normal TLC, DLC, kidney function and liver function tests. Chest X-ray showed bilateral severe rib crowding and thoracic scoliosis (Figure 1) without any evidence of pulmonary or pleural pathology. PFT revealed severe restriction (FEV_1 = 53% of predicted, FVC 32% of predicted). HRCT of thorax revealed fusion of vertebral bodies and posterior neural arch elements of vertebral bodies with anterior wedging of vertebrae representing congenital fusion (Figure 2). 2D echo/Doppler showed pulmonary hypertension (pulmonary artery systolic pressure of 58 mm of Hg with moderate TR). A diagnosis of thoracic insufficiency syndrome (TIS) with cor pulmonale was made and she was treated with diuretics, and sildenafil 25 mg. Her symptoms improved within a week and she was referred to a higher centre.

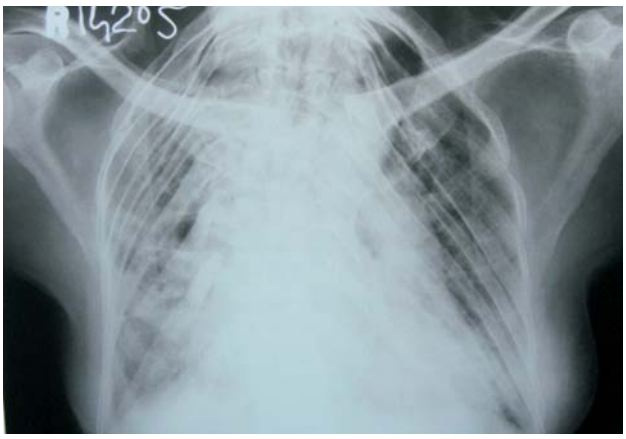

Fig. 1: *Showing bilateral severe rib crowding and thoracic scoliosis.*

Discussion

Spondylothoracic dysplasia or thoracic insufficiency syndrome (TIS) has been defined as the inability of the thorax to support normal respiration or lung growth. TIS is associated with severe malformations of the chest, spine, or ribs that result in small thoracic volumes and inadequate lung development which leads to thoracic stiffness and lack of compliance. But, ironically, if it is survived in infancy and early childhood then the presentation can be late in life[1,2]. Normally the spine and ribs act together as a dynamic biomechanical structure, which can only work efficiently at respiration within certain parameters. When a significant deformity of the thoracic cage exists, it changes the dynamics of this system, and can interfere with normal respiration and lung development. Usually it presents with severely compromised respiratory function in the growing child, is typically associated with failure to thrive, as well as the need for frequent hospitalisations associated with respiratory infections[3]. Clinical tolerance of the restrictive lung disease in this disorder is impressive, but no clear reason has yet been identified for the clinical pulmonary health in the face of severe restrictive lung disease. Patients who survive infancy show no progression of congenital anomalies and can have a good quality of life[4,5].

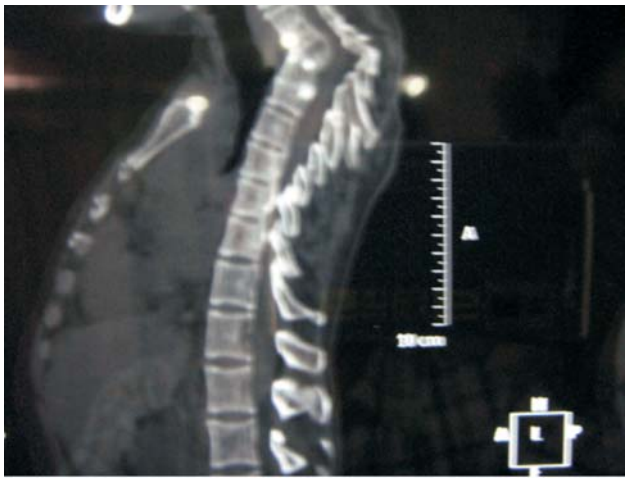

Fig. 2: *HRCT of thorax revealing fusion of vertebral bodies and posterior neural arch elements of vertebral bodues with anterior wedging of vertebrae representing congenital fusion.*

References

1. Dimeglio A. Growth of the spine before age 5 years. *J Pediatr Orthop Part B* 1993; 1: 102-7.
2. Damsin JP, Cazeau C, Carlioz H. Scoliosis and fused ribs. A case report. *Spine* 1997; 22: 1030-2.
3. Hull D, Barnes ND. Children with small chests. *Arch Dis Child* 1974; 47: 12-9.
4. Day GA *et al*. Pulmonary functions in congenital scoliosis. *Spine* 1994; 19: 1027-31.
5. Day GA, Upadhyay SS, Ho EK *et al*. Pulmonary functions in congenital scoliosis. *Spine* 1994; 19: 1027-31.

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CASE REPORT

JIACM 2014; 15(2): 144-6

An unusual case of digital gangrene

*SA Kanitkar****, M Kalyan***, AL Kakrani*****, AN Gaikwad****, R Agarwal**, B Bhimavarapu**

Abstract

Gangrene of the digits is a very rare manifestation of Wegener's granulomatosis. We report the case of a 20-year-old boy presenting with fever and right index digital gangrene. The gangrene progressed to the right fifth toe with rapid lividity. Together with renal and pulmonal symptoms, Wegener's was suspected, the diagnosis being confirmed by kidney biopsy and positive c-ANCAs. Therapy with cyclophosphamide and corticosteroids resulted in autoamputation of the affected digits with clinical improvement. Comparing the five worldwide reported cases presenting with digital gangrene, there is a concordance in the occurrence of an extremely high disease activity together with glomerulonephritis.

Key words: Wegener's granulomatosis, c-ANCA.

Introduction

Wegener's granulomatosis (WG) is an immunologically mediated uncommon multi-system disorder, first described by Friedrich Wegener in 1936. However, detailed description of WG is given by Godman and Churg[1]. In January 2011, the Board of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that the name Wegener's granulomatosis be changed to Granulomatosis with polyangiitis (Wegener's), abbreviated as GPA[2]. WG is a primary systemic vasculitis affecting small-sized blood vessels and capillaries. It is typically characterised by granulomatous inflammation of the upper and lower respiratory tract and necrotising vasculitis in multiple organs, in particular the kidneys. In 1990, the American College of Rheumatology (ACR) proposed the following four specific criteria for the classification of WG: (1) Oral ulcers or nasal discharge; (2) The presence of nodules, fixed infiltrates, or cavities on a chest radiograph; (3) Abnormal urinary sediment (red blood cell casts or more than five red blood cells per high power field); (4) Granulomatous inflammation on biopsy. For the diagnosis of WG, a minimum of two criteria should be fulfilled from the above-mentioned (ACR 1990) criteria[3].

Case report

A 20-year-old male patient presented with fever and a bluish discoloration of his right index finger (Figure 1) since 20 days. There was no history of cough, haemoptysis, or Raynaud's phenomena at the time of admission. He was a non-smoker with no significant past history. On day 3, the patient had severe pain in his right leg with bluish discoloration of the right fifth toe (Figure 2). On day 8, he developed purpura and ulcers on lower limbs, haemoptysis, haematuria, and right-sided scrotal pain. On general physical examination, this patient was moderately built and nourished, conscious and

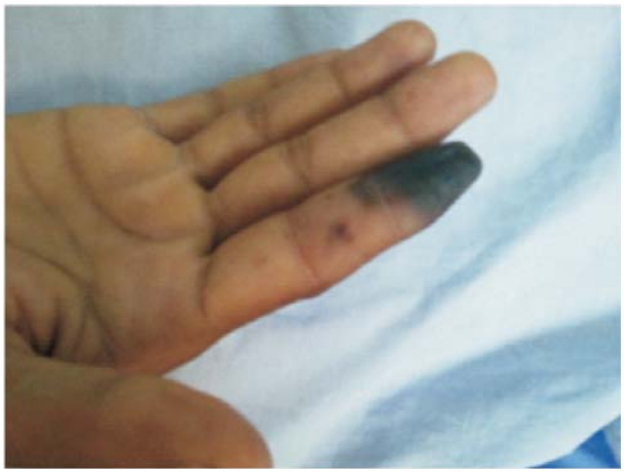

Fig. 1: *Bluish discolouration of right index finger.*

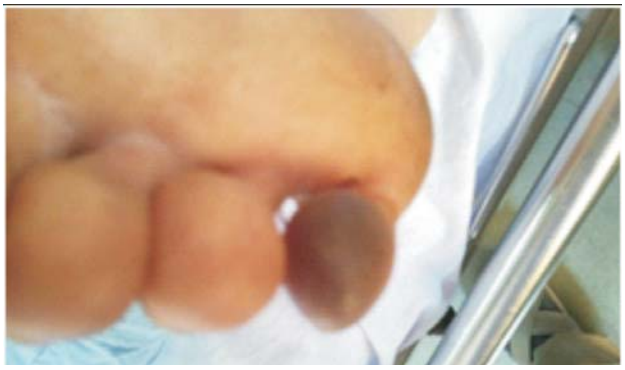

Fig. 2: *Bluish discolouration of right fifth toe.*

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cooperative. Mild pallor was present. Jaundice, cyanosis, clubbing, and lymphadenopathy were absent. Pulse was 120/min, regular, no radio-radial or radio-femoral delay, feeble right radial pulse on right upper limb, feeble dorsalis pedis and posterior tibialis artery pulsations on right lower limb. BP was 130/90 mmHg in the right upper limb. Respiratory rate was 20/min. Splinter haemorrhages (Figure 3) were present in the nail beds in both hands. Dry gangrenous changes were seen in the right index finger extending up to the proximal phalanx and in right fifth toe. There were no subcutaneous nodules. Respiratory system revealed crepitations in the right mammary and infra-mammary areas. CVS, abdominal, and CNS examinations were unremarkable. Fundoscopy was normal. Investigations revealed Hb – 8.8 gm/dl, TLC – 10,000/mm^3, platelets – 550,000/mm^3, ESR - 52 mm. RFT revealed s. creatinine - 1.5 mg/dl, s. urea – 75 mg/dl. LFT, serum proteins, and electrolytes were normal. Urine routine examination showed 16 - 18 RBCs and granular casts. 24-hour urinary proteins were normal. Chest X-ray revealed bilateral nodular lesions in both upper zones. ECG was normal. 2D echocardiography and trans-oesophageal echocardiography was normal. Blood and urine cultures were negative. Arterial Doppler of right upper limb showed no colour flow in digital arteries of index finger – suggestive of complete obstruction. Arterial Doppler of right lower limb showed complete obstruction of right peripheral arteries and dampened flow proximal to obstruction with presence of collaterals. USG abdomen was normal. USG scrotum showed right-sided epididymo-orchitis. c-ANCA was strongly positive. p-ANCA, ANA, RA factor, CRP, anti-thrombin 3 activity, Factor V Leiden, APLA, serum homocysteine were negative. HRCT thorax revealed small, well-defined soft-tissue density nodular lesions of 5 - 10 mm in the periphery of both upper lobes and multiple irregular small tissue nodular lesions in the peripheral portions of the right upper and lower lobes. Renal biopsy (Figure 4) and skin biopsy revealed crescentic glomerulonephritis and necrotising vasculitis respectively.

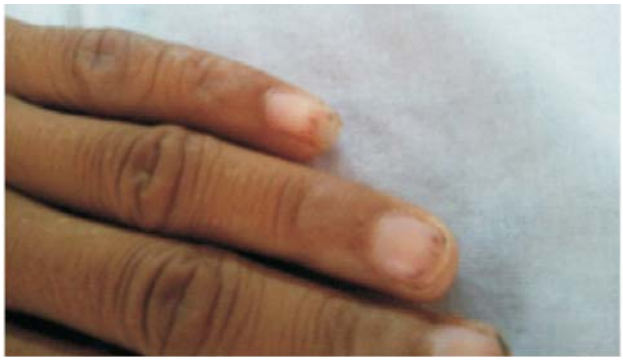


Fig. 3: *Splinter haemorrhages in nail beds.*

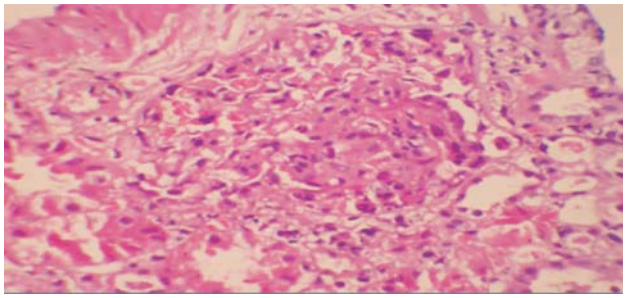


Fig. 4: *Renal biopsy showing crescentic glomerulonephritis.*

From the above positive findings, a diagnosis of Wegener's granulomatosis was made. The patient was put on pulses of cyclophosphamide and steroids which led to auto-amputation of the affected right index finger and right fifth toe with clinical improvement.

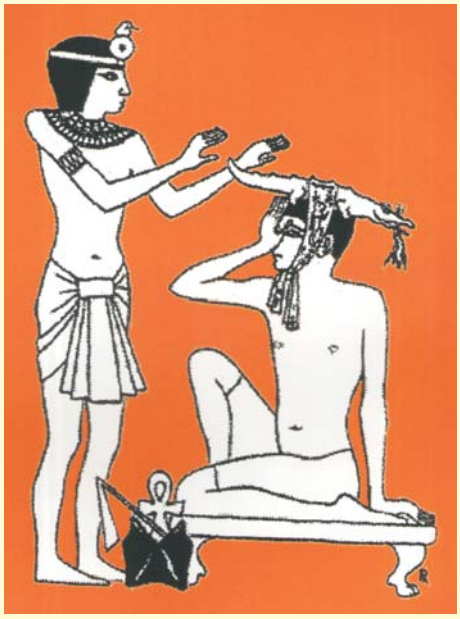
Discussion

The common manifestations of the disease include the classic triad of upper airway, lung, and kidney in 87%, 69%, and 48% of the patients, respectively. The less common manifestations involve the skin, central nervous system, eye and orbit, heart, breast, salivary gland, gastrointestinal tract, spleen, and male and female urogenital tracts; each of these accounts for less than 15% in all cases and below 5% for most of the patients. The manifestations of WG in many of the uncommon anatomical sites of involvement may be distinctive or atypical; and therefore, the histopathological diagnosis must be correlated with clinical and laboratory test findings[4]. The disease is highly associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA) directed against proteinase 3 (PR3) or myeloperoxidase (MPO). Cutaneous manifestations occur in up to 40 - 50% of WG patients. However, it is less common as a presenting feature with a frequency of only 1% to 13%[5, 6]. Skin findings include palpable and non-palpable purpura, papules, subcutaneous nodules, ulcers, digital necrosis, splinter haemorrhages, and vesiculobullous lesions[7]. Different treatment protocols were given including prednisolone, prednisolone and cyclophosphamide (CYC), azathioprine (AZT). Glucocorticoids combined with CYC or methotrexate (MTX) are the only two regimens that have thus far been shown to induce remission of active WG affecting a major organ. Patients with alveolar haemorrhage, rapidly progressive glomerulonephritis, central nervous system disease, or other manifestations that are immediately life-

threatening should initially be treated with CYC and glucocorticoids. Once remission has been induced, consideration can be given to stopping CYC and beginning AZA or MTX treatment to maintain remission. Good prognosis with long-term remissions has been reported with combination therapy[8]. The case reported here responded with steroid and cyclophosphamide therapy.

References

1. Carol S, Donald C, Indraneel B *et al*. Oral manifestations of Wegener's granulomatosis: -A report of three cases and a literature review. *J Am Dent Assoc* 2007; 138 Suppl 3: 338-48.
2. Falk RJ, Gross WL, Guillevin L *et al*. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. *Arthritis Rheum* 2011; 63: 863.
3. Rosa MR-F, Enrique Z-L, Consuelo C-C, Jorge B-A. Wegener's granulomatosis: Description of a case with oral manifestation. *Med Oral Pathol Oral Cir Bucal* 2010; 15 Suppl 4: 601-4.
4. Lie JT. Wegener's granulomatosis: histological documentation common and uncommon manifestation in 216 patients. *Vasa* 1997; 26(4): 261-70.
5. Hoffman G, Kerr G, Leavitt X *et al*. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-98.
6. Frances C, Du L, Piette J *et al*. Wegener's granulomatosis: Dermatological manifestations in 75 cases with clinicopathologic correlation. *Arch Dermatol* 1994; 130: 861-7.
7. Comfere NI, Macaron NC, Gibson LE. Cutaneous manifestations in Wegener's granulomatosis: a clinicopathologic study of 17 patients and correlation to antineutrophil cytoplasmic antibody status. *J Cutan Pathol* 2007; 34: 739-47.
8. Carol AL. Wegener's granulomatosis: current and upcoming therapies. *Arthritis Res Ther* 2003; 5:180-91.



Migraine treatment in Ancient Egypt

Records indicate that Egyptians used leech therapy over 3,500 years ago. Leeches are seen in the hieroglyphics painted on the walls of ancient Egyptian temples. Leech therapy was used to treat a wide range of conditions -- from migraines to haemorrhoids. Leeches were used for the purpose of secreting their saliva into the skull through trephining -- making small holes in the skull. The saliva was thought to contain medicinal properties. Bloodletting -- purposefully cutting the human body to release blood -- is an ancient ritual, associated with both healing and sacrifice. Bloodletting was a regular form of medical treatment. It began with the Egyptians, then continued with the Greeeks and Romans, the Arabs and Asians, and spread through Europe during the Middle Ages and the Renaissance. It reached its peak in Europe in the 19th century but subsequently declined.

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

CASE REPORT

JIACM 2014; 15(2): 147-9

Restrictive cardiomyopathy an enigma: Role of tissue Doppler imaging

Mridul Chaturvedi, Pranav A Oza**, Anjana Pandey***, Prem Mohan Jha*****

Abstract

Hypothyroidism is quite prevalent in our country. Diastolic dysfunction is a well known cardiac condition associated with hypothyroidism. Diastolic dysfunction of grade 1 and grade 2 are frequently reported but a diastolic dysfunction of grade 3 and grade 4 (restrictive pattern) are rarely seen. Here we report a case of subclinical hypothyroidism with grade 4 (irreversible restrictive pattern) diastolic function and discuss the role of tissue Doppler imaging in diagnosis of restrictive versus constrictive physiology.

Key words: Hypothyroidism, diastolic dysfunction, tissue Doppler imaging.

Introduction

Hypothyroidism is associated with varied cardiac manifestations like pericardial effusion, cardiomyopathy, and impaired cardiac relaxation (diastolic dysfunction)[1].

Mild diastolic dysfunction is quite common with subclinical hypothyroidism, but severe diastolic dysfunction grade 3 and grade 4 restrictive pattern is relatively uncommon. Overall prevalence of restrictive pattern of diastolic dysfunction is around 10% as reported by various studies[2].

Restrictive cardiomyopathy in itself is quite uncommon in subclinical hypothyroidism. With the advent of tissue Doppler imaging it is easy to differentiate between restrictive and constrictive physiology instead of cumbersome procedures like cath studies and CT chest.

On tissue Doppler imaging, early systolic velocity E′ > 8 cm/sec has 89% sensitivity and 100% specificity for diagnosis of constrictive pericarditis[3] and low E′ velocity with other manifestations of restrictive cardiomyopathy is strongly suggestive of restrictive cardiomyopathy. Newer data reveal that the addition of systolic contraction velocity (*S*2), obtained by TDI provides incremental value to the *E*2 velocity measurement. An *S*2 value of 6 cm/s or more increases the sensitivity of an *E*2 of 8 cm/s or more from 70 to 88%[4].

We have reported a case of restrictive cardiomyopathy without any obvious aetiology associated with subclinical hypothyroidism.

Case report

A 57-year-old male, a known case of subclinical hypothyroidism since 1 year, presented with complaints of breathlessness on exertion since 3 months; and pedal oedema, decreased urine output, and right hypochondrial pain since 15 days. History of orthopnoea was present and there is no history of fever, cough with expectoration, haemoptysis, chest pain, abdominal distension, cachexia, weight gain, anasarca, radiation exposure in the past.

On physical examination, pallor and peripheral oedema were present, JVP was raised, and neck veins were engorged. On respiratory examination: bilateral basal crepitations were present; on cardiac examination; a pansystolic soft blowing murmur was heard at the mitral area, grade 3/6 with no appreciable radiation. On abdominal examination, soft tender hepatomegaly was present approximately one finger breadth below the costal margin, with no evidence of ascites. On central nervous system examination, motor and sensory and cerebellar functions were intact, no evidence of autonomic neuropathy was present, and all cranial nerves were intact.

Biochemical investigations were as follows: Hb = 9.4 gm/dl, TLC = 9,800 (N_{80}, L_{16}, E_2, M_2), TSH = 9 mIU/l, AST = 70 U/l, ALT = 120 U/l. Serum iron = 70 µg/dl, serum ferritin = 160 µg/l, TIBC = 360.

ECG showed a heart rate of 80/min, rhythm is regular. Chest X-ray showed cardiomegaly with cardiothoracic ratio > 0.55, lung fields appeared congested with prominent pulmonary artery.

Echocardiography revealed the following:

- **On 2D examination** – Apical four chamber view showed biatrial dilatation with concentric left ventricular hypertrophy (IVSd = 19mm, IVSs = 21mm) (Figure 1), dilatation of IVC appox. 2.6 cm with < 50% respiratory variation (Figure 5).
- **Doppler study showed** – Moderate tricuspid regurgitation, RVSP = 70 mm Hg, severe pulmonary

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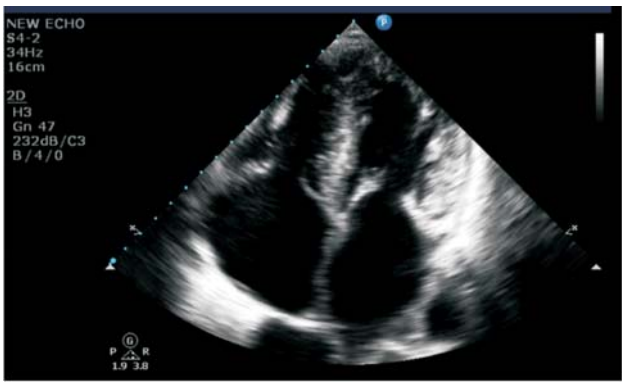

Fig. 1: *Apical four chamber view showing bi-atrial enlargement and concentric LVH.*

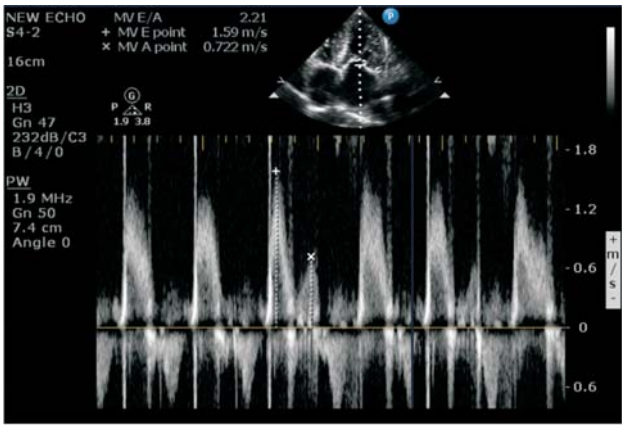

Fig. 2: *Mitral valve inflow velocity on pulsed wave doppler showing type 4 diastolic dysfunction.*

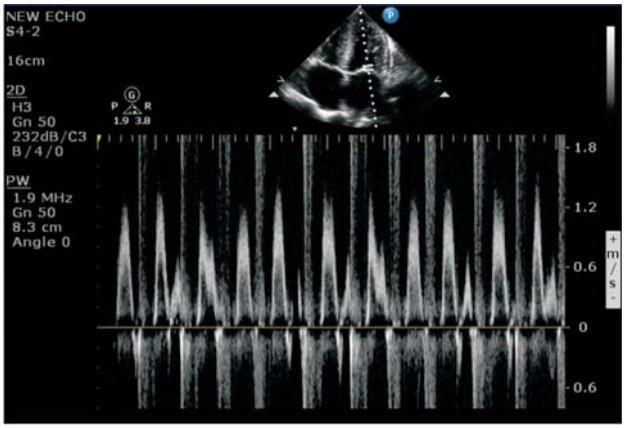

Fig. 3: *Mitral valve inflow velocity on pulsed wave Doppler showing <25% variation.*

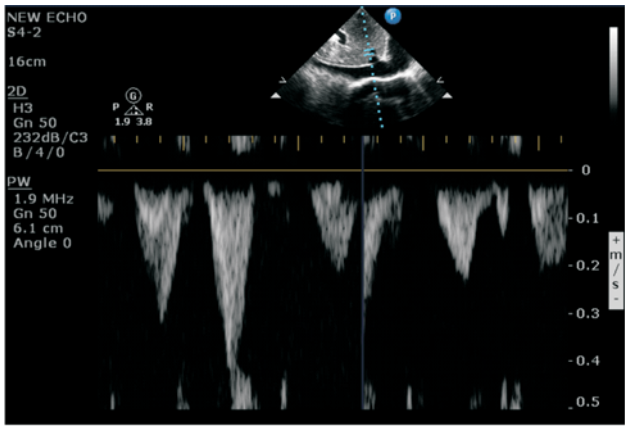

Fig. 4: *Pulsed wave Doppler at hepatic vein showing systolic velocity less then diastolic velocity.*

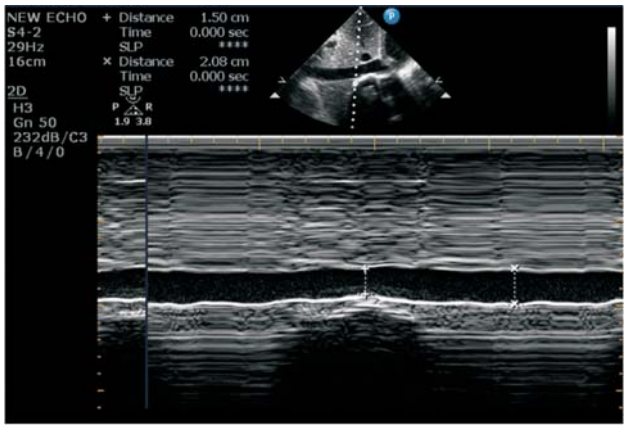

Fig. 5: *M- mode across IVC showing dilatation of IVC with <50% respiratory variation.*

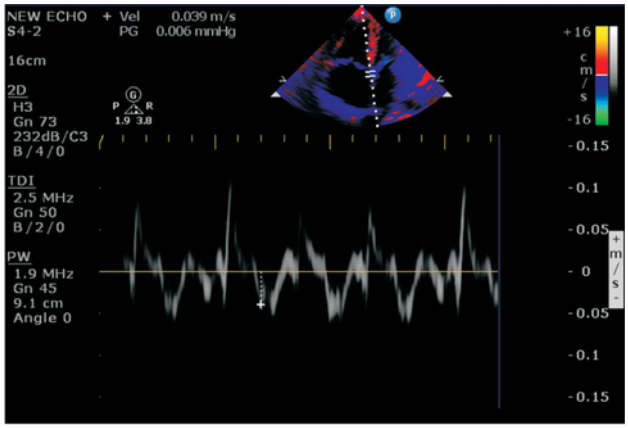

Fig. 6: *Tissue Doppler imaging at medial mitral annulus showing early systolic velocity E'=3.9cm/sec.*

hypertension, moderate mitral regurgitation, mild aortic regurgitation, grade 4 diastolic dysfunction restrictive pattern (E = 159cm/sec, A = 72.2 cm/ sec, E/A = 2.21); no reversal of velocity seen with Valsalva manoeuvre (Figure 2); mitral valve inflow velocity variation on pulsed wave Doppler < 25% (Figure 3); and on tissue Doppler imaging early diastolic velocity E' = 3.9 cm/sec (Figure 6) and hepatic vein flow shows systolic velocity less than diastolic velocity (Figure 4).

Discussion

Probable cases of restrictive cardiomyopathy in the Indian subcontinent are basically limited to Kerala region and have presented as subendocardial fibrosis with predominant biventricular as well as right or left ventricular failure with prominent mitral regurgitation as well as tricuspid regurgitation[5]. There is no definite major literature available in our country regarding the sporadic cases of restrictive cardiomyopathy. In Western literature, major causes of restrictive cardiomyopathy are senile, idiopathic, various infiltrative disorders like amyloidosis, sarcoidosis, and various storage diseases like haemochromatosis[6].

Association of hypothyroidism with restrictive cardiomyopathy is quite uncommon however severe left ventricular diastolic dysfunction is very well reported with hypothyroidism which may clinically present as restrictive cardiomyopathy. Other cardiac manifestations of hypothyroidism are pericardial effusion and dilated cardiomyopathy.

With the advent of tissue Doppler and other advancements of echocardiography, it is easy to make a diagnosis of sporadic cases of restrictive cardiomyopathy without the use of cumbersome investigations like cath studies, CT chest, or MRI which is not affordable by the poor unfortunate patients who come to the government hospitals; and these sophisticated investigations are available in very few sophisticated tertiary centres in our country.

In our case, we suspect the patient as having restrictive cardiomyopathy as the 2D- echocardiography and Doppler study showed:

1. Bi-atrial enlargement with left ventricular hypertrophy.
2. Mitral valve inflow velocity on pulsed wave Doppler showing type 4 diastolic dysfunction.
3. Mitral valve inflow velocity on pulsed wave Doppler showing < 25% variation.
4. Pulsed wave Doppler at hepatic vein showing systolic velocity less then diastolic velocity.
5. M-mode across IVC showing dilatation of IVC with < 50% respiratory variation.
6. Tissue Doppler imaging at medial mitral annulus showing early systolic velocity E′ = 3.9cm/sec.

On tissue Doppler imaging, various findings that help to distinguish between constrictive pericarditis and restrictive cardiomyopathy are as follows:-

Constrictive pericarditis[7]:

- Mitral septal annulus velocity is decreased < 7cm/sec.
- E′ varies with respiration, with E′ higher in expiration than with inspiration.

Restrictive cardiomyopathy[8]:

- From the septal mitral annulus.
- Decreased systolic velocity - S′ < 5cm/sec.
- Decreased early diastolic velocity - E′ < 7cm/sec.

However, even after a lot of advancement in the field of tissue Doppler imaging, a definitive diagnosis of constrictive pericarditis or restrictive cardiomyopathy requires further confirmation by costlier and more invasive procedures like cath studies and MRI or CT scan which are not universally available.

Thus, till further advancements are made in the field of tissue Doppler imaging and better diagnostic criteria of TDI are available to differentiate between constrictive and restrictive physiology, diagnosis of constrictive pericarditis and restrictive cardiomyopathy by echocardiography will remain an enigma.

References

1. Williams GH, Lily LS, Seely EW. The heart in endocrine and nutritional disorders. in : Heart disease a textbook of cardiovascular medicine, Braunwald. 5th Ed. W. B. Saunders company. 1997; 61: 1885-913.
2. Subclinical Thyroid Dysfunction, Cardiac Function, and the Risk of Heart Failure, *J Am Coll Cardiol* 2008; 52(14): 1152-9. doi:10.1016/j.jacc.2008.07.009
3. Ha JW, Ommen SR, Tajik AJ *et al*. Differentiation of constrictive pericarditis from restrictive cardiomyopathy using mitral annular velocity by tissue Doppler echocardiography. *Am J Cardiol* 2004; 94: 316-9.
4. Choi EY, Ha JW, Kim JM *et al*. Incremental value of combining systolic mitral annular velocity and time difference between mitral inflow and diastolic mitral annular velocity to early diastolic annular velocity for differentiating constrictive pericarditis from restrictive cardiomyopathy. *J Am Soc Echocardiogr* 2007; 20: 738-43.
5. Seth S, Thatai D, Sharma S *et al*. Clinico-pathological evaluation of restrictive cardiomyopathy (endomyocardial fibrosis and idiopathic restrictive cardiomyopathy) in India. *Eur J Heart Fail* 2004; 6 (6): 723-9. doi:10.1016/j.ejheart.2003.11.009
6. Kushwaha SS, Fallon JT, Fuster V. Restrictive Cardiomyopathy. *N Engl J Med* 1997; 336: 267-76.
7. Jae K Oh, Steward JB, Tajik AJ. The echo manual. 3rd ed. Lippincott williams and wilkins. 2011; 17: 298-9.
8. Jae K Oh, Steward JB, Tajik AJ. The echo manual. 3rd ed. Lippincott williams and wilkins. 2011; 15: 269.

CASE REPORT

JIACM 2014; 15(2): 150-2

Rasmussen's encephalitis in an adult

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Abstract

A 30-year-old male presented with complaints of multiple partial seizures involving the right half of the body, epilepsia partialis continua, progressive right-sided hemiparesis, loss of speech and progressive personality changes. MRI brain revealed disease process confined to the left cerebral hemisphere in the form of hyperintensity in left cerebral hemisphere on T2W and FLAIR sequences involving both gray and white matter suggesting early stage (stage 2) of Rasmussen's encephalitis. The seizures responded poorly to treatment and combination of 3 antiepileptics plus corticosteroid was used to reduce seizure frequency.

Key words: Rasmussen's encephalitis, partial seizures, epilepsia partialis continua, hemiparesis.

Introduction

Rasmussen's encephalitis (RE) is a rare, chronic immune-mediated disease of children that usually affects one hemisphere of the brain. It is characterised by frequent partial motor seizures, which are treatment resistant[1]. Rasmussen and his team described focal seizures due to "chronic encephalitis" in 1958[2]. Twenty years later Rasmussen reported 27 cases, most of them having a syndrome which we now term as Rasmussen syndrome or Rasmussen encephalitis (RE). This syndrome occurs primarily in young children – 5 to 10 years being the most common age group and most common clinical features being intractable seizures, often with *epilepsia partialis continua*; a slowly progressive hemiparesis, hemianopia, progressive mental retardation and progressive cortical atrophy[3]. Initially, the underlying aetiology of this condition was thought to be a viral infection[2]; however, later extensive histopathological studies on RE brains proved T-cell mediated cyototoxic damage as the main underlying mechanism[4]. Multiple antiepileptics are usually not able to control the seizures well. Corticosteroids and immunoglobins can be used. Once the neurological deficit stabilises, hemispherectomy might be helpful in controlling the seizures. As mentioned above, RE primarily occurs in children, adults being very rarely affected. Here we report a case of RE in an adult.

Case presentation

A 30-year-old male, right-handed, labourer by occupation, presented with complaints of abnormal movements involving the right half of his body 3 to 4 times a day since the last 4 months. These abnormal movements occurred as sudden onset jerky movements of the right upper and lower limb along with twitching of the face. These abnormal movements subsided in a few minutes and there was no loss of consciousness at the time of these movements. The patient was given antiepileptic drugs for abnormal movements by various physicians but they failed to subside. There was also complaint of progressive weakness of right half of the body since the last 3 months – initially in the form of clumsiness in holding objects and walking, but at the time of presentation the weakness was so profound that the patient was not able to walk unsupported. The patient's attendants also complained that he had lost the ability to speak since the last 2 months. There was also history of change of personality since the last 2 months. On the day of presentation, there was complaint of continuous abnormal movements of right half of the body without any pause for the last 1 day (suggesting *epilepsia partialis continua*). After admission to our hospital, the seizures were controlled with difficulty, and phenytoin, phenobarbitone, and carbamazepine were used in combination for control of seizures.

Neurological examination revealed motor aphasia, right-sided upper motor neuron type facial weakness; all other cranial nerves were normal and there was weakness of right upper and lower limb – power being 2/5 at all joints in the right upper and lower limb; there was increased tone in the form of clasp knife spasticity in the right upper and lower limb. On the right side biceps, triceps, knee and ankle jerk were brisk and plantar was extensor. Power, tone, and reflexes were normal and plantar was flexor on the left side.

Electroencephalography (EEG) was done which revealed left hemispherical slowing and temporo-parietal spike discharges. All other routine investigations were within normal limits. MRI brain showed evidence of unilateral

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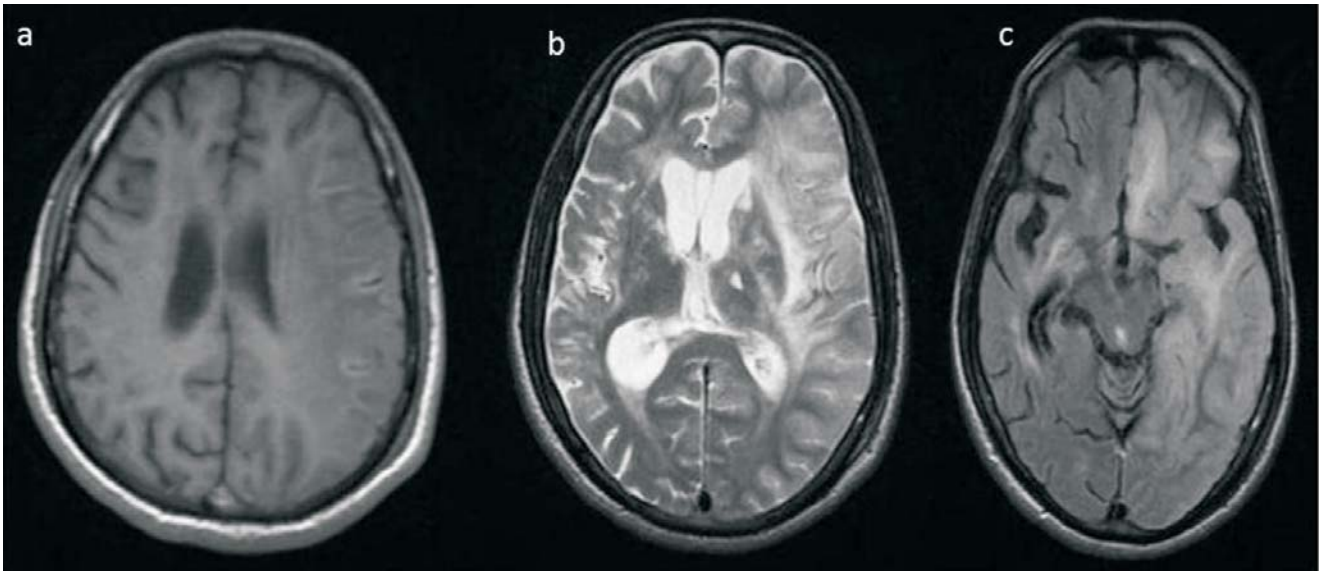

Fig. 1: *Axial MRI* ***(a)*** *T1-weighted;* ***(b)*** *T2-weighted; and* ***(c)*** *Fluid-attenuated inversion-recovery (FLAIR) images show diffuse hyperintensity in the left cerebral hemisphere on T2W and FLAIR sequences involving both gray and white matter with diffuse cortical thickening and effaced left lateral ventricle (c).*

involvement of brain in the form of diffuse hyperintensity in the left cerebral hemisphere on T2W and FLAIR sequences involving both gray and white matter. There was diffuse cortical thickening and diffusion restriction with no significant enhancement on post-contrast studies. Also, there was evidence of minimal mass effect in the form of effacement of ipsilateral lateral ventricle and minimal midline shift towards the right side. On correlating with the clinical history of the patient, these findings were suggestive of an early stage (stage 2) of Rasmussen encephalitis.

As the clinical features, EEG features were very suggestive of a diagnosis of Rasmussen encephalitis and the MRI findings were also suggestive of early stage of RE. Rasmussen encephalitis was kept as diagnosis of this patient and he was started on intravenous methylpredinisolone. The combination of phenytoin, phenobarbitone, and carbamazepine was used for controlling seizures, and the patient responded to this treatment in the form of reduced seizure frequency, although the neurological deficits persisted without any further progression.

Discussion

Rasmusssen encephalitis is a rare, chronic inflammatory disease that usually affects one hemisphere of the brain[1]. This syndrome occurs primarily in younger children (very rare in adults) and is characterised by intractable seizures, often with *epilepsia partialis continua*; a slowly progressive hemiparesis, hemianopia, progressive mental retardation and progressive cortical atrophy[3]. Our patient had intractable partial seizures and *epilepsia partialis continua* as well as progressive hemiparesis, mental deterioration, and motor aphasia, thus matching the classical clinical features as described for Rasmussen encephalitis[3]. Reports from developing countries show 84.2% of patients with RE have hemiparesis and 73.6% of patients with RE have eplepsia partialis continua[6]. Our patient was having both of these common clinical features.

MRI has been shown to demonstrate the progression of RE and may suggest the diagnosis in the early stages, often before the appearance of neurological deficits[5]. There are four recognised stages of RE based on T2 weighted MRI criteria[7]. These are swelling with hyperintense signal (stage 1); normal volume with hyperintense signal (stage 2); atrophy with hyperintense signal (stage 3); and progressive atrophy and normal signal (stage 4)[6]. Thus, according to this staging our patient was in stage 2 as his MRI showed hyperintensity on T2 weighted MRI with normal volume. We can expect to get unilateral atrophy in our patient on follow-up MRI.

A combination of antiepileptic drugs may not be able to control epileptic seizures and progressive neurodeficit. Immune modulators like immunoglobulins and corticosteroids have been proved to be beneficial[1,8]. We observed reduction in seizure frequency and some clinical improvement after treatment with corticosteroids and combination of antiepileptics. Unfortunately, immunoglobulins are not available at our centre. Better results are obtained in RE patients who undergo either of the two options of surgical resection, namely focal cortical resection and functional hemispherectomy[9]. Despite the controversy surrounding the introduction of functional

hemispherectomy, it is still the only curative treatment for RE[9,10]. The use of positron emission tomography (PET) has been advocated for the pre-surgical evaluation of RE patients to ascertain whether or not they could benefit from surgery[11]. Early diagnosis of RE is crucial for selecting patients for aggressive medical therapy or major surgical interventions[12].

References

1. Bien CG, Granata T, Antozzi C *et al*. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005; 128, 454-71.
2. Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. *Neurology* 1958; 8: 435-45.
3. Rasmussen T. Further observations on the syndrome of chronic encephalitis and epilepsy. *Appl Neurophysiol* 1978; 41: 1-12.
4. Bauer J, Bien CG and Lassmann H. Rasmussen's encephalitis:a role for autoimmune cytotoxic T lymphocytes. *Curr Opin Neurol* 2002; 15: 197-200.
5. Chiapparini L, Granata T, Farina L *et al*. Diagnostic imaging in 13 cases of Rasmussen's encephalitis: can early MRI suggest the diagnosis? *Neuroradiology* 2003; 45(3): 171-83.
6. Ramesha KN, Rajesh B, Ashalatha R *et al*. Rasmussen's encephalitis: experience from a developing country based on a group of medically and surgically treated patients. *Seizure* 2009; 18(8): 567-72.
7. Osborne AG, Blaser SI, Salzman KL *et al*. Rasmussen encephalitis. Diagnostic imaging Brain. Ed 1, Amirsys Inc, Utah, 2005; pp. I: 8: 42-5.
8. Granata T, Fusco L, Gobbi G *et al*. Experience with immunomodulatory treatments in Rasmussen's encephalitis, *Neurology* 2003; 61: 1807-10.
9. Muto A, Oguni H, Takahashi Y *et al*. Nationwide survey (incidence, clinical course, prognosis) of Rasmussen's encephalitis. *Brain Dev* 2009; Nov 24. [Epub ahead of print].
10. Marras CE, Granata T, Franzini A *et al*. Hemispherotomy and functional hemispherectomy: indications and outcome. *Epilepsy Res* 2010; 89(1): 104-12.
11. Shetty-Alva N, Novotny EJ, Shetty T *et al*. Positron emission tomography in Rasmussen's encephalitis. *Pediatr Neurol* 2007; 36(2): 112-4.
12. Chiapparini L, Granata T, Farina L *et al*. Diagnostic imaging in 13 cases of Rasmussen's encephalitis: can early MRI suggest the diagnosis? *Neuroradiology* 2003; 45(3): 171-83.

CASE REPORT

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Tuberous sclerosis presenting as chorea

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Abstract

Tuberous sclerosis is an autosomal dominant genetic disorder. It is also known as Bourneville's disease and is characterised by the triad of mental retardation, seizures, and facial angiofibromas. Small benign tumours develop in the brain as well as in visceral organs like kidneys and liver. Neurological manifestations of the disorder are due to involvement of brain. Our case presented with facial angiofibromas and with chorea (neurological symptom) without any family history of tuberous sclerosis. MRI examination revealed tuberous changes in the brain. On considering all these findings, our patient was diagnosed as a case of tuberous sclerosis (facial angiofibromas, tuberous changes in brain, and chorea). As such, chorea is a rare presenting feature of tuberous sclerosis; so we present this case as a case of academic interest.

Introduction

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a rare, multi-system genetic disease that causes non-malignant tumours to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. Tuberous sclerosis has an approximate incidence of one in ten thousand to fifty thousand. The clinical triad of papular facial naevi, seizures, and mental retardation is found in less then half the patients. Thus the radiological hallmarks of this neurocutaneous syndrome are universally accepted as sufficient for diagnosis[1]. A combination of symptoms may include seizures, developmental delay, behavioural problems, skin abnormalities, lung and kidney disease. TSC is caused by a mutation of either of two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin respectively. These proteins act as tumour growth suppressors, agents that regulate cell proliferation and differentiation[2]. The name, composed of the Latin "tuber" (swelling) and the Greek "skleros" (hard), is due to the pathological finding of thick, firm, and pale gyri, called "tubers", in the brains of patients as seen on postmortem. In 1880, Désiré-Magloire Bourneville was the first to describe these tubers; and these cortical manifestations are still known by the eponym Bourneville's disease. The physical manifestations of tuberous sclerosis are due to the formation of hamartia (malformed tissue such as the cortical tubers), hamartomas (benign growths such as facial angiofibromas and subependymal nodules) and, very rarely, cancerous hamartoblastomas.

Case report

A 32-year old female presented in our out-patient department with choreiform movements for the last 8 months. On examination, the patient was having facial angiofibromas (Figure 1) and involuntary movements (chorea). Considering all investigations, the patient was diagnosed as a case of tuberous sclerosis. MRI confirmed the diagnosis as it showed a typical picture of tuberous sclerosis. The patient was neither mentally retarted nor having any learning difficulties. There was no family history of this disease. There was no history of aggressive behaviour or self-injurious behaviour in the patient. Patient was put on drugs for chorea.

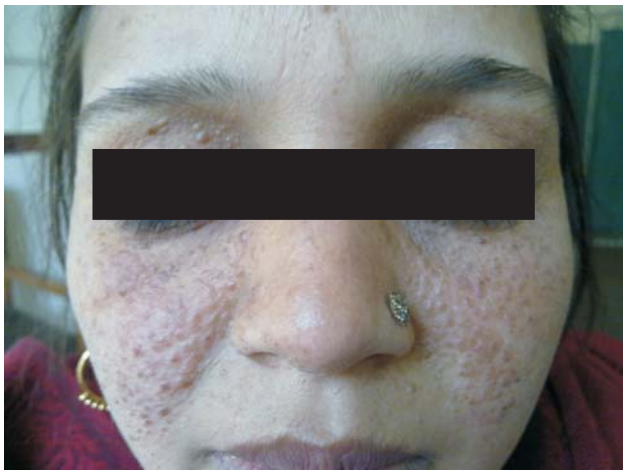

Fig. 1: *Showing facial angiofibroma.*

Discussion

Tuberous sclerosis is a genetic disorder with an autosomal dominant pattern of inheritance, and penetrance is variable[3]. Two-thirds of TSC cases result

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from sporadic genetic mutations, not inheritance, but their offspring may inherit it from them. Current genetic tests have difficulty locating the mutation in approximately 20% of individuals diagnosed with the disease. So far it has been mapped to two genetic loci, TSC1 and TSC2. Tuberous sclerosis, the second commonest neurocutaneous synrome, is characterised by a constellation of major and minor features. Major features include facial angiofibromas, non-traumatic ungula or peri-ungual fibromas, hypomelanotic macules, shagreen patch, retinal hamartomas, cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, cardiac rhabdomyoma, lymphangio-myomatosis, and renal angiomyolipoma. Minor features include dental enamel pits, hamartomatous rectal polyps, bone cysts, gingival fibromas, non-renal hamartomas, retinal achromic patch, confetti skin lesions, renal cysts, and cerebral cortical dysplasia.

Common sites for these tumours include the kidneys, lungs, and the heart[4]. Incidence of rhabdomyomas of the heart is up to 50% of children with tuberous sclerosis which may cause congestive heart failure, conduction abnormalities, refractory arrhythmias[5]. Renal lesions are angiomyolipoma and polycystic disease which results in haematuria, pain, and rarely renal failure. Angiomyolipomas of lungs (only 1%) result in generalised cystic or fibrous pulmonary changes. Various neurological symptoms are seizures, developmental delay, and behavioural problems. Incidence of learning difficulties is in about 50% to 60% of people with TSC[6], and reported incidence of autism is between 25% and 60% of affected individuals, with an even higher proportion showing features of a broader pervasive developmental disorder[7]. Reported incidence of self-injurious behaviour is about 10% of people with TSC[8]. Other conditions, such as ADHD, aggression, behavioural outbursts, and OCD can also occur. Lower IQ is associated with diffuse brain involvement. The most common neurological manifestations of tuberous sclerosis include mental retardation, which can be severe and incapacitating, and seizures[9].

Nodular tumours, fibromas, and papillomas have been found on the tongue and palate in 11% of patients with tuberous sclerosis which result in difficult intubation[10]. Tuberous sclerosis patients can present with retinal hamartomas (in 75% cases) along with mulberry lesions of retina, and rarely with chorea (as in our case).The occurrence of chorea can be due to disrupted neural migration resulting in an aberrant cellular interaction and synaptic transmission in the basal ganglia and their connection in general, and caudate nucleus in particular[11,12].

The prognosis for the patient with tuberous sclerosis depends on the severity of symptoms. Although individuals with more severe symptoms may have serious disabilities, the life expectancy is not significantly decreased given appropriate medical care[13].

Conclusion

Tuberous sclerosis patients present with a triad of papular facial naevi, seizures, and mental retardation. Rarely, tuberous sclerosis patients can present with haematuria due to angiomyolipomas of kidneys as in our case, as both kidneys were involved with angiomyolipomas, significantly big enough to cause haematuria. Chorea can be an unusual presentation of tuberous sclerosis and its occurrence can be attributed to the neuronal migration disorder associated with tuberous sclerosis.

References

1. Braffman BH, Bilaniuk CT, Zimmerman RA. MR of central nervous system neoplasia of the phakomatoses. *Sem Roentgenol* 1990; 25: 198-217.
2. Tuberous Sclerosis Fact Sheet. NINDS. 2006-04-11. Retrieved 2007-01-09.
3. Northrup H, Au K (5 December 2005). Tuberous Sclerosis Complex. GeneReviews. Retrieved 2007-09-02.
4. Behrman, in Nelson's Textbook of Pediatrics, 17th ed., 2004, Ch. 589 Neurocutaneous Syndromes, Philadelphia PA, WB Saunders, pp. 1705-9.
5. Cope JT, Lindsey JH, Kron IL. Cardiac tumors. C.C.L. Pediatric cardiac surgery, 3rd ed, 2003, St. Louis: Mosby, pp 689-701.
6. Ridler K *et al*. Neuroanatomical Correlates of Memory Deficits in Tuberous Sclerosis Complex, Cerebral Cortex 2007; 17(2): 261-71.
7. Harrison JE, Bolton, PF, Annotation: Tuberous sclerosis, *Journal of Child Psychology and Psychiatry* 1997; 38: pp 603-14.
8. Staley BA, Montenegro MA, Major P *et al*. Self-injurious behavior and tuberous sclerosis complex: frequency and possible associations in a population of 257 patients. *Epilepsy Behav* 13 (4): 650.
9. Curatolo P, Verdecchia M, Bombardieri R, Tuberous Sclerosis complex: A review of neurological aspects. *Eur J Paediatr Neurol* 2002; 6: pp 15-23.
10. Gomez MR, ed. Tuberous Sclerosis, 2nd Ed., New York, Raven Press, 1988, pp. 139-48.
11. Shah PA, Hussan I, Bardi HG *et al*. Tuberous Sclerosis With Chorea 2009; 11: 200-1.
12. Evans BK, Jankovie J. Tuberous Sclerosis and Chorea. *Ann Neurol* 1983; 13: 106-7.
13. Shepherd C, Gomez M, Lie J *et al*. Causes of death in patients with tuberous sclerosis. *Mayo Clin Proc* 1991; 66 (8): 792-6.

CASE REPORT

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Gynaecomastia: Case report and a brief overview

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Abstract

Gynaecomastia, defined as a benign proliferation of male breast glandular tissue, is usually caused by increased oestrogen activity, decreased testosterone activity, or the use of numerous medications. Although a fairly common presentation in the primary care setting and mostly of benign aetiology, it can cause patients' considerable anxiety. The initial step is to rule out pseudogynaecomastia by careful history taking and physical examination. A stepwise approach that includes imaging and laboratory testing to exclude neoplasms and endocrinopathies may facilitate cost-effective diagnosis. If results of all studies are normal, idiopathic gynaecomastia is diagnosed. The evidence in this area is mainly of observational nature.We report a case of a 22-yrs-old male who presented to our clinic with enlargement of both breasts – gradually increasing in size – since the last 3 yrs. Hormonal profile showed marked hyperoestrogenaemia and a slightly decreased testosterone level.Other investigations were normal. Biopsy findings revealed benign proliferating glandular tissue referred to as gynaecomastia. In presenting this case we tried to observe any difference in the clinical presentations other than those mentioned in literature, and highlight the need for diagnostic work-up and treatment in such cases. Proper patient education, reassurance, and periodic follow-up are all that is needed in such cases.

Key words: Gynaecomastia, neoplasm, diagnostic work-up.

Introduction

Gynaecomastia is defined as a benign proliferation of male breast glandular tissue[1]. Asymptomatic gynaecomastia is very common and has a trimodal age distribution, occurring in neonatal, pubertal, and elderly males. The prevalence of asymptomatic gynaecomastia is 60% to 90% in neonates, 50% to 60% in adolescents, and up to 70% in men aged 50 to 69 years[2-5]. Prevalence of symptomatic gynaecomastia is markedly lower. A screening for gynaecomastia in 214 hospitalised adult men aged 27 to 92 years revealed that 65% had gynaecomastia, defined in this study as nodule size greater than 2 cm; however, none of them were symptomatic[3]. Variation in reported prevalence across studies is attributed to variations in the size of the palpable breast tissue used to define gynaecomastia and to population characteristics such as age and setting of treatment (primary care vs referral clinics). The evaluation and management perspectives presented in this article do not pertain to physiologic, neonatal, and adolescent cases but rather to symptomatic adults who are concerned and seek evaluation and treatment.

Although breast cancer is rare in men, those with gynaecomastia often become anxious and seek medical attention, making this presentation fairly common in primary care settings. Diagnostic evaluation of these cases can be costly and involves laboratory and radiographic testing; therefore, a diagnostic algorithm that facilitates step-by-step evaluation may be cost-effective and reduces the associated patient anxiety. This article describes the pathophysiology, and common mechanisms and causes of benign gynaecomastia and introduces a diagnostic algorithm to facilitate evaluation and management of symptomatic cases that present in a primary care settings.

Case report

A 22-years-old male presented to our clinic with enlargement of both breasts gradually increasing in size since the last 3 years (Figure 1). He also complained of discharge from both breasts occasionally. Family history, past medical history, surgical history, drug history was unrevealing. Secondary sexual characteristics were

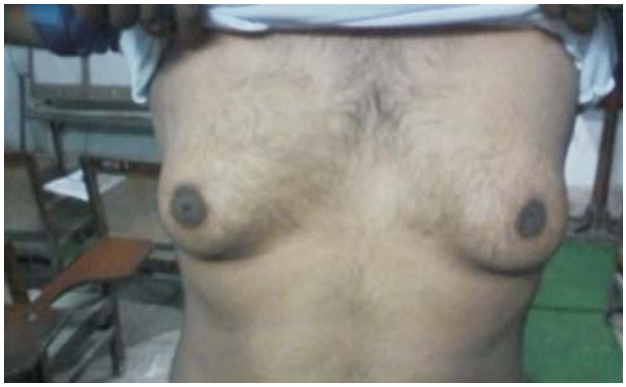

Fig. 1: *Showing enlarged breasts in our patient.*

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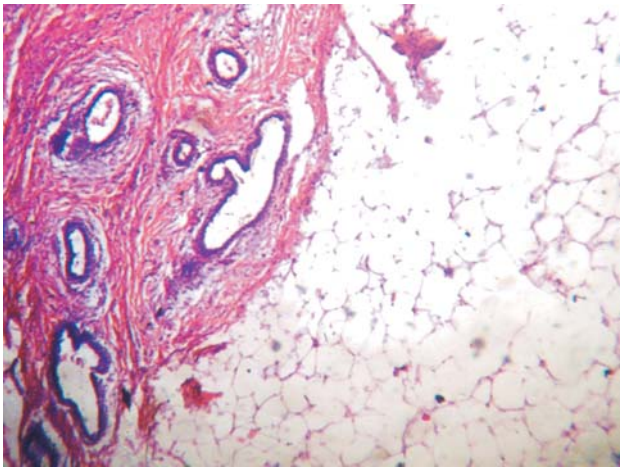

Fig. 2: *Biopsy slide of histological section showing terminal ducts lined by multi-layered epithelium with small papillary tufts (H&E 40X) consistent with gynaecomastia.*

normal. On clinical examination, a 12 cm^2-sized mass was found in both breasts with regular borders, firm in texture and free from underlying breast tissue and skin. Nipple retraction was present on right breast and no lymph node enlargement was found. Thyroid function tests, lipid profile, renal function tests, liver function tests, chest X-ray were all within normal limits. High-resolution scrotal biopsy to rule-out testicular malignancy did not reveal any abnormality. Similarly, CECT abdomen was also normal, which was performed to look for any adrenal pathology. Hormonal profile showed an oestrogen-testosterone imbalance revealing oestrogen excess. Hormonal profile was: Testosterone - 3.0 ng/ml (Normal range: 4 - 10 ng/ml), Oestradiol - 57.2 pg/ml (Normal range: 10 - 39 pg/ml), HCG-2 miu/ml (Normal range: < 3 miu/ml), Prolactin - 21.2 ng/ml (Normal range: 0 - 20 ng/ml), FSH - 2.8 miu/ml (Normal range: 1 - 12 miu/ml), LH - 3.4 miu/ml (Normal range: 2 - 12 miu/ml). Tamoxifen 10 mg BD dose was given as a treatment to combat this hormonal imbalance, and biopsy was taken to rule-out malignancy and identifying gynaecomastia or adipose tissue as a cause of breast enlargement. Biopsy findings revealed benign proliferating glandular tissue referred to as gynaecomastia as a cause of breast enlargement (Figure 2). Patient was advised to remain in continuous follow-up and treatment and reassured that surgery would be considered if the pharmacological measures fail.

Discussion

The imbalance between oestrogen actions relative to androgen action at the breast tissue level appears to be the main aetiology of gynaecomastia[6]. Elevated serum oestrogen levels may be a result of oestrogen-secreting neoplasms or their precursors, e.g., Leydig or Sertoli cell tumours, human chorionic gonadotropin (hCG)–producing tumours, and adrenocortical tumours, but more commonly are caused by increased extragonadal conversion of androgens to oestrogens by tissue aromatase (as occurs in obesity). Levels of free serum testosterone are decreased in patients with gonadal failure, which can be primary (Klinefelter syndrome, mumps orchitis, castration) or secondary (hypothalamic and pituitary disease). Androgen resistance syndromes due to impaired activity of enzymes involved in the biosynthesis of testosterone can also be associated with gynaecomastia[7]. The balance between free testosterone and oestrogen is also affected by serum levels of sex hormone-binding globulin, which is the proposed mechanism of gynaecomastia in certain conditions, such as hyperthyroidism, chronic liver disease, and the use of some medications such as spironolactone[1]. Receptors of androgens can also have genetic defects or become blocked by certain medications (e.g., bicalutamide, used in the treatment of prostate cancer), and the receptors of oestrogens can be activated by certain medications or environmental exposures[1]. Of note, patients with pubertal gynaecomastia have normal levels of serum oestradiol, testosterone, and dehydroepiandrosterone sulfate and a normal oestrogen-testosterone ratio. However, free testosterone levels in these patients are lower than those of controls without gynaecomastia[8].

Careful history taking and physical examination often reveal that patients actually are presenting with pseudogynaecomastia, which means accumulation of subareolar fat without real proliferation of glandular tissue. Examination of these patients reveals diffuse breast enlargement without a subareolar palpable nodule. These patients do not need additional work-up and only require reassurance. Gynaecomastia is usually bilateral[3,9], but patients may present with asymmetrical or unilateral findings. Palpation usually demonstrates a tender, firm, mobile, disc-like mound of tissues[1,4] that is not as hard as breast cancer and is located centrally under the nipple-areolar complex. When palpable masses are unilateral, hard, fixed, peripheral to the nipple, and associated with nipple discharge, skin changes, or lymphadenopathy, breast cancer should be suspected and a thorough evaluation is recommended. Anthropometric measurements (e.g., body mass index) may also be helpful because obesity can be associated with increased peripheral conversion of androgens to oestrogens and is associated with a higher prevalence of gynaecomastia[3,10]. The presence of varicocoeles has also been strongly associated with gynaecomastia[9]. A family history of gynaecomastia has been elicited in 58% of patients with persistent pubertal gynaecomastia. History may also reveal a clear and temporal association with a causative

drug and obviate the need for extensive and costly evaluation. If the association with a drug is unclear, then evaluation is recommended. It has also been associated with the use of alcohol and illicit drugs, such as marijuana, heroin, methadone, and amphetamines[4]. Several herbal supplements, particularly those containing phyto-oestrogen, may also cause gynaecomastia[12]. In one case series, history and physical examination detected a predisposing medical condition or causative medication in 83% cases of gynaecomastia[13]. All breast cancer cases in that series presented with a dominant mass on clinical examination or other signs suggestive of malignancy. After initial history and examination exclude pseudogynaecomastia and other obvious explanatory conditions, mammography can differentiate true gynaecomastia from a mass that requires tissue sampling to exclude malignancy. Mammography was found to be fairly accurate in distinguishing between malignant and benign male breast diseases and can substantially reduce the need for biopsies. The sensitivity and specificity of mammography for benign and malignant breast conditions exceed 90%; however, the positive predictive value for malignant conditions is low (55%) because of the low prevalence of malignancy in patients presenting with gynaecomastia[14]. Imaging of the scrotum is only recommended if palpable masses are present.

Laboratory investigations are pursued in cases of true gynaecomastia without clear explanation. Liver, kidney, and thyroid function tests exclude the respective medical conditions. Hormonal testing measures the levels of total and bioavailable testosterone, oestradiol, prolactin, luteinising hormone, and hCG, and its findings can direct toward pituitary, gonadal, and extragonadal endocrinopathies and neoplasms as seen in the stepwise algorithm depicted in Figure 3. If all tests are unrevealing, idiopathic gynaecomastia is diagnosed. The differential diagnosis of a palpable breast mass in a male patient includes pseudogynaecomastia, gynaecomastia, breast cancer, and numerous other benign conditions. A review of all mammographic findings in men for a period of 5 years in literature revealed a 1% rate of malignancy. Most cases were due to benign causes; of these, gynaecomastia represented 62%, with other causes including lipomas, dermoid cysts, sebaceous cysts, lymphoplasmacytic inflammation, ductal ectasia, haematomas, and fat necrosis[13]. In contrast, the differential diagnosis of gynaecomastia *per se*, as demonstrated in a series of young adult patients with gynaecomastia aged 19 through 29 years, includes idiopathic gynaecomastia (58%), hypogonadism (25%), hyperprolactinaemia (9%), chronic liver disease (4%), and drug-induced gynaecomastia (4%)[10]. The frequency distribution of these aetiologies is imprecise because of the small number of cases reported in the literature and may vary widely across publications and practice settings. Overall, gynaecomastia is a benign condition and is usually self-limited. Over time, fibrotic tissue replaces symptomatic proliferation of glandular tissue and tenderness resolves. If the appropriate work-up does not reveal considerable underlying pathology, reassurance and periodic follow-up are recommended. Although evidence is lacking to support a recommendation for follow-up intervals, 6 months seems reasonable. Causative medications should be withdrawn or the underlying causative medical conditions (e.g., hyperthyroidism) should be addressed. Most cases of pubertal gynaecomastia usually resolve in less than a year[8]. If gynaecomastia persists and is associated with pain or psychological distress and if the patient wishes to pursue treatment, pharmacological and surgical options are available. Pharmacotherapy is likely beneficial if implemented early before fibrous tissue replaces glandular tissue, whereas surgery can be performed at any time.

Several pharmacological agents have been used to manipulate the hormonal imbalances thought to cause gynaecomastia. However, the studies that evaluated their efficacy were in general small and uncontrolled, making inference challenging. Oestrogen receptor modifiers appear to be fairly safe and beneficial. Alagaratnam[15] treated 61 Chinese men with tamoxifen for a median of 2 months with 36-months of follow-up, demonstrating an 84% rate of complete regression of breast swelling. Lawrence *et al*[16] used a 3- to 9-month course of oestrogen receptor modifiers (tamoxifen or raloxifene) to treat 38 consecutive patients with persistent pubertal gynaecomastia and demonstrated a mean reduction in breast nodule diameter of 2.1 cm with no serious adverse effects. Similar results were reported in another case series of 37 patients who used tamoxifen; reductions in pain and nodule size were seen in all patients without long-term adverse effects[17]. Dihydrotestosterone, danazol, clomiphene, and aromatase inhibitors such as testolactone and anastrozole may also have benefit but are less commonly studied and used[4]. Overall, the use of all these drugs is supported by a very low quality of evidence, and the uncertainty about the balance of their benefits and harms should be highlighted to candidate patients. Surgery is the criterion standard treatment for gynaecomastia. The most commonly used technique is subcutaneous mastectomy that involves the direct resection of the glandular tissue using a periareolar or transareolar approach with or without associated liposuction. Liposuction alone may be sufficient if breast enlargement is purely due to excess fatty tissue without substantial glandular hypertrophy[18]. Skin resection is needed for more advanced cases. In general, surgical

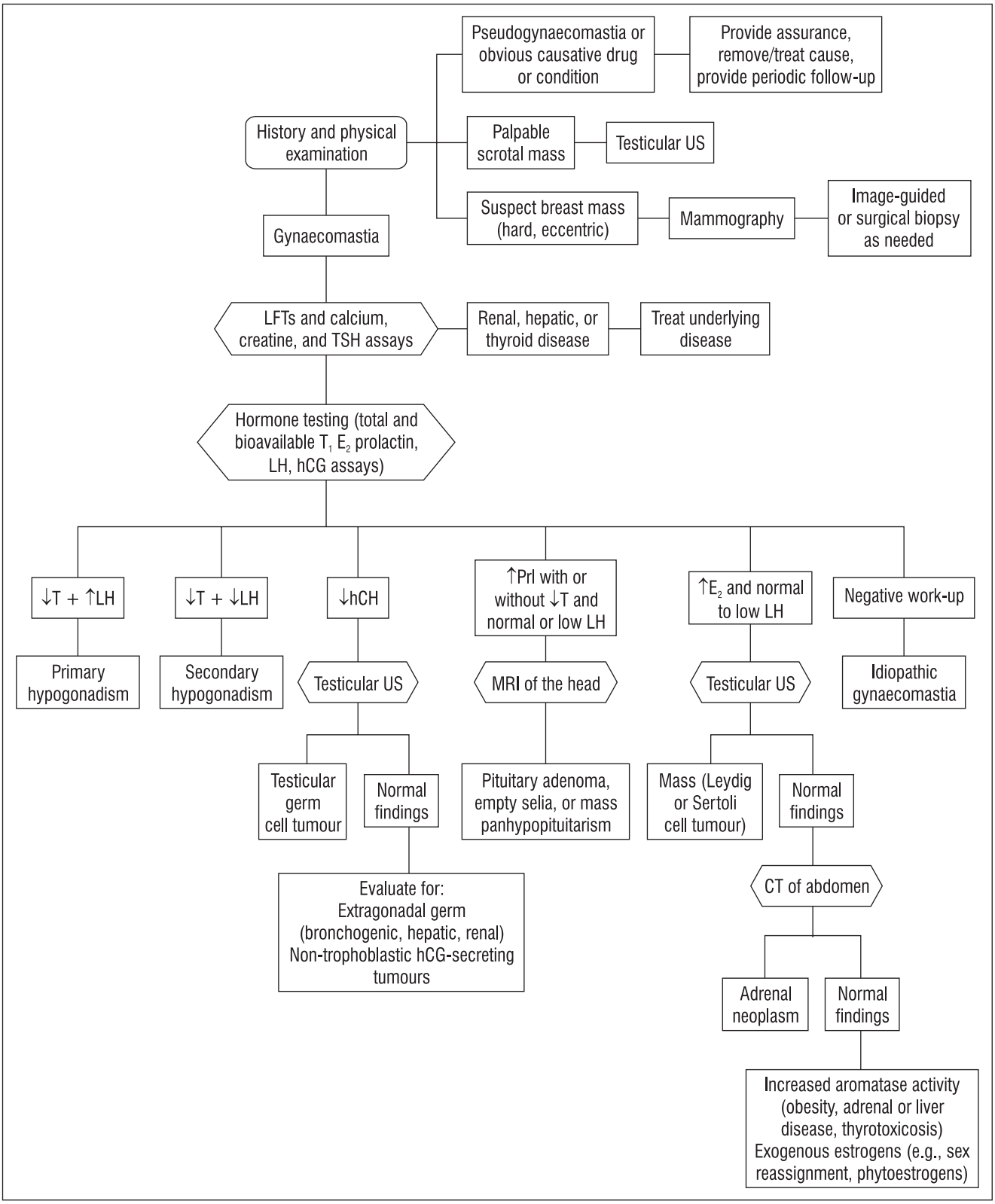

Fig. 3: *Showing diagnostic approach to a case of gynaecomastia. Diagnostic algorithm for gynaecomastia. CT = computed tomography; E_2 = oestradiol; hCG = human chorionic gonadotropin; LFT = liver function test; LH = luteinising hormone; Prl = prolactin; T = testosterone; TSH = thyroid-stimulating hormone; US = ultrasonography.*

treatment produces good cosmesis and is well tolerated. Newer, less invasive techniques that require minimal surgical incision have recently emerged and may offer faster recovery and lower rates of local complications[18-20]. Histologic analysis is recommended in true gynaecomastia corrections because unexpected histologic findings such as spindle-cell haemangioendothelioma and papilloma may occur in 3% of cases[21].

Patients with gynaecomastia have a favourable prognosis. These patients present with 2 main concerns: ruling-out breast cancer and cosmetic correction. The first concern is adequately addressed by following the appropriate diagnostic evaluation. Breast cancer is rare in males, representing less than 1% of all cases of breast cancer; only 1% of mammograms in men reveal breast cancer.[13] Therefore, the decision to treat and the choice of treatment should be based on the degree to which this condition has affected the quality of life and mental health of patients and on their desire for cosmetic correction. The body of research supporting the diagnostic approach and treatment strategies for gynaecomastia consists of expert opinion, case series, and observational studies; hence, the evidence is considered to be of low to very low quality. By acknowledging this low quality of evidence when discussing testing and treatment options with patients, physicians allow room in the process of decision making for consideration of other factors, such as resources, availability of services, and patients' values and preferences[22].

Conclusion

Though gynaecomastia is a benign condition, the possibility of underlying malignancy must be excluded. Family history, age, drug history, clinical manifestations, and diagnostic modalities remain crucial in differentiation and treatment. By presenting this case of gynaecomastia we aim towards increasing awareness of such a clinical entity and also highlight the work-up and treatment as and when needed.

References

1. Braunstein GD. Gynaecomastia. *N Engl J Med* 2007; 357(12):1229-37.
2. Georgiadis E, Papandreou L, Evangelopoulou C *et al*. Incidence of gynaecomastia in 954 young males and its relationship to somatometric parameters. *Ann Hum Biol* 1994; 21(6): 579-87.
3. Niewoehner CB, Nuttal FQ. Gynaecomastia in a hospitalized male population. *Am J Med* 1984; 77(4): 633-8.
4. Nordt CA, DiVasta AD. Gynaecomastia in adolescents. *Curr Opin Pediatr* 2008; 20(4): 375-82.
5. McKiernan JF, Hull D. Breast development in the newborn. *Arch Dis Child* 1981; 56(7): 525-9.
6. Braunstein GD. Aromatase and gynaecomastia. *Endocr Relat Cancer* 1999; 6(2): 315-24.
7. Mathur R, Braunstein GD. Gynaecomastia: pathomechanisms and treatment strategies. *Horm Res* 1997; 48(3): 95-102.
8. Biro FM, Lucky AW, Huster GA *et al*. Hormonal studies and physical maturation in adolescent gynaecomastia. *J Pediatr* 1990; 116(3): 450-5.
9. Kumanov P, Deepinder F, Robeva R *et al*. Relationship of adolescent gynaecomastia with varicocele and somatometric parameters: a cross-sectional study in 6200 healthy boys. *J Adolesc Health* 2007; 41(2): 126-31.
10. Ersöz H, Onde ME, Terekeci H *et al*. Causes of gynaecomastia in young adult males and factors associated with idiopathic gynaecomastia. *Int J Androl* 2002; 25(5): 312-6.
11. Braunstein GD. Gynaecomastia. *N Engl J Med* 1993; 328(7): 490-5.
12. Braunstein GD. Environmental gynaecomastia [editorial]. *Endocr Pract* 2008; 14(4): 409-10.
13. Hines SL, Tan WW, Yasrebi M *et al*. The role of mammography in male patients with breast symptoms. *Mayo Clin Proc* 2007; 82(3): 297-300.
14. Evans GF, Anthony T, Turnage RH *et al*. The diagnostic accuracy of mammography in the evaluation of male breast disease [published correction appears in Am J Surg. 2001;181(6):579]. *Am J Surg* 2001; 181: 96-100.
15. Alagaratnam TT. Idiopathic gynaecomastia treated with tamoxifen: a preliminary report. *Clin Ther* 1987; 9(5): 483-7.
16. Lawrence SE, Faught KA, Vethamuthu J *et al*. Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynaecomastia. *J Pediatr* 2004; 145(1): 71-6.
17. Derman O, Kanbur NO, Kutluk T. Tamoxifen treatment for pubertal gynaecomastia. *Int J Adolesc Med Health* 2003; 15(4): 359-63.
18. Courtiss EH. Gynaecomastia: analysis of 159 patients and current recommendations for treatment. *Plast Reconstr Surg* 1987; 79(5): 740-53.
19. Prado AC, Castillo PF. Minimal surgical access to treat gynaecomastia with the use of a power-assisted arthroscopic-endoscopic cartilage shaver. *Plast Reconstr Surg* 2005; 115(3): 939-42.
20. Zhu J, Huang J. Surgical management of gynaecomastia under endoscope. *J Laparoendosc Adv Surg Techniq A* 2008; 18(3): 433-7.
21. Handschin AE, Bietry D, Hüsler R *et al*. Surgical management of gynaecomastia – a 10-year analysis. *World J Surg* 2008; 32(1):8-44.
22. Swiglo BA, Murad MH, Schünemann HJ *et al*. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 2008; 93(3): 666-73. Epub 2008 Jan 2.

"Science without conscience is the death of the soul."

– Francois Rabelais.

CASE REPORT

JIACM 2014; 15(2): 160-1

Central retinal artery occlusion: A rare complication of viperine snake bite

Geetha C Rajappa, Sangamesh Asuti**, CN Gupta***, U Sudhir*****

Abstract

Snake bite is endemic in some parts of India with its associated complications affecting various organ systems. Venomous snake bites may result in either neurologic or haemostatic dysfunction. Ocular effects following snake bite are rare. Viper envenomation is known to cause subconjunctival haemorrhage, hyphema, retinal and vitreous haemorrhage. In this paper, we present a case of central retinal artery occlusion following snake bite.

Key words: Viper envenomation, ocular effect, vision loss.

Introduction

Snake bite is endemic in some parts of India with its associated complications affecting various organ systems. Venomous snake bites may result in either neurologic or haemostatic dysfunction[1,2]. Ocular complications following snake bite are uncommon.

Case report

A farmer aged 60-years, hailing from Bangalore rural region was bitten by a snake over the right index finger while working in his farm. The snake killed by the bystanders was identified as a saw-scaled viper. The patient presented to our hospital 24 hours later with swelling and pain in the right hand. He was admitted to our Medical Intensive Care Unit for further management. On examination, his pulse rate was 104 beats/min, blood pressure was 140/100 mmHg, and respiratory rate of 20 cycles/min. Local examination revealed fang marks over the right index finger with swelling and tenderness of whole right hand. There was no bleeding from the bite site. Pupils were bilateral equal and reactive to light. Fundoscopy revealed bilateral grade-II hypertensive retinopathy. Higher mental functions and cranial nerves examination showed no abnormality. There were no signs and symptoms of systemic envenomation. But blood investigation revealed a deranged coagulation profile with prothrombin time being > 2 minutes, aPTT 51.6 sec. and INR of 2; haemoglobin – 16.9 gm/dl; total leukocyte count – 26,980 with neutrophil predominance, platelet count of 400,000/cumm, with normal LFT and deranged RFT (serum creatinine – 1.6 mg/dl). Chest X-ray and ECG were within normal limits. USG abdomen showed bilateral grade-III nephropathy. But patient had no past history of hypertension or diabetes mellitus. Patient was started on anti-snake venom (ASV), antibiotics (piperacillin-tazobactum and metronidazole). Emergency fasciotomy was done for right hand cellulitis under fresh frozen plasma (FFP) coverage.

On the next day, the patient complained of diminished vision in his left eye. Fundus examination revealed features suggestive of central retinal artery occlusion (CRAO) (Figure 1) and tonometry showed increased intra-ocular pressure (IOP). He was treated with acetazolamide (both oral and topical eye drops) along with regular ocular massaging. In due course, the patient developed haematuria and progressively decreasing urine output and rising serum creatinine (2.8 mg/dl) with arterial blood gas (ABG) showing metabolic acidosis. The patient required haemodialysis. Further, haemoglobin and platelet counts also dropped with persistently deranged coagulation profile for which the patient received

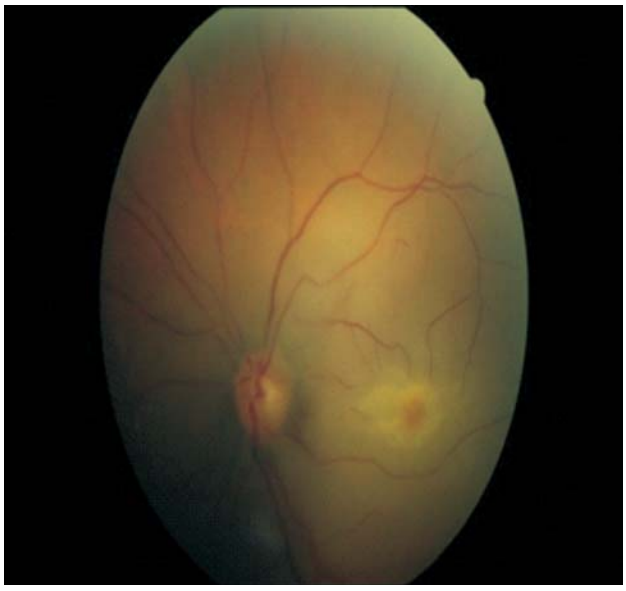

Fig. 1: *Fundoscopy showing central retinal artery occlusion.*

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necessary corrections with blood products as and when needed.

The fasciotomy wound was managed with regular dressing, but gangrenous changes developed in the right index finger, with the line of demarcation gradually becoming prominent. Digital amputation was planned for the same. There was no improvement in the vision of the left eye but IOP returned to normal. On the 6th day of admission, our patient developed haemoptysis and respiratory distress with decreasing oxygen saturation requiring intubation and mechanical ventilation. Chest X-ray showed features suggestive of alveolar haemorrhage. Subsequently, the patient developed hypotension requiring ionotropic support. Despite resuscitative and supportive measures, the patient continued to deteriorate and expired on the 10th day.

Discussion

Snake venom is an intricate mixture of enzymes and proteins which is either neurotoxic or haematotoxic[1,2]. Viperine venom is made of components mainly affecting the haemostatic mechanisms that have contradictory effects. Venom consists of enzymes that cause hyperfibrinogenaemia, hypoprothrombinaemia, thrombocytopenia, fibrinolysis; and also comprise of potent proteases acting as activators of coagulation factors X and V, thereby promoting coagulation[3]. The net result is usually consumption coagulopathy leading to disseminated intravascular coagulation with ischaemic sequelae to major organs[4]. Certain viperine venoms may have a direct effect on the vascular endothelium provoking intense vascular spasm or cause thrombosis secondary to toxic vasculitis[5].

Ocular manifestations following snake bite are not commonly reported in literature. Neurologic disturbance occurring as ophthalmoplegia is the commonest ocular manifestation[6]. Direct venom inoculation can lead to penetrating injury which may cause keratomalacia, uveitis and globe necrosis leading to visual loss[1]. Viper envenomation is known to cause subconjunctival haemorrahage, hyphema, retinal and vitreous haemorrhage[7]. Other rare ophthalmic complications of snake bite include ptosis, central retinal artery occlusion, optic neuritis, optic atrophy, cortical blindness, and macular infarction. Anti-snake venom has been reported to cause uveitis and retinal necrosis[8]. Visual prognosis may remain poor despite treatment for CRAO. Bhalla *et al* have reported a similar case of CRAO following viper bite with slight improvement in vision and unchanged fundus picture on follow-up. Our patient developed central retinal artery occlusion following viper bite possibly due to direct effect of toxins on the retinal artery endothelium or due to haematotoxic effect with formation of microthrombi.

In conclusion, our patient had unilateral central retinal artery occlusion following snake bite. Although it is uncommon, it can result in vision loss despite treatment and overall prognosis of the patient depends on the involvement of other organ systems.

Conflict of interest: None to declare.

References

1. Singh J, Singh P, Singh R *et al*. Macular infarction following viperine snake bite. *Arch Ophthalmol* 2007; 125(10): 1430-1.
2. Tungpakorn N. Unusual visual loss after snakebite. *J Venom Anim Toxins incl Trop Dis* 2010; 16(3): 519-23.
3. Siigur J, Aaspollu A, Tonismagi K *et al*. Proteases from *Vipera lebetina* venom affecting coagulation and fibrinolysis. *Haemostasis* 2001; 31(3-6): 123-32.
4. Schwartzman RJ, Hill JB. Neurologic complications of disseminated intravascular coagulation. *Neurology* 1982; 32(8): 791-7.
5. Murthy JM, Kishore LT, Naidu KS. Cerebral infarction after envenomation by viper. *J Comput Assist Tomogr* 1997; 21(1): 35-7.
6. Bhalla A, Jain AP, Banait S *et al*. Central retinal artery occlusion: an unusual complication of snakebite. *J Venom Anim Toxins incl Trop Dis* 2004; 10(3): 311-4.
7. Nayak SG, Satish R, Nityanandam S *et al*. Uveitis following anti-snake venom therapy. *J Venom Anim Toxins incl Trop Dis* 2007; 13(1): 130-4.

"An education that confines itself to impart in knowledge is no education."

– Aurobindo Ghosh.

PICTORIAL CME

JIACM 2014; 15(2): 162-3

Aortic dissection in a young female with Marfan's syndrome

Santa Subhra Chatterjee, Kallol Sengupta*, Prabuddha Mukhopadhyay**, Dipanjan Bandyopadhyay****

Aortic dissection is defined as separation of the layers within the aortic walls. Tears in the intimal layer result in propagation of dissection (proximally or distally) secondary to blood entering the intima-media space.

We report a 33-year-old lady, a known case of Marfan's syndrome presenting to us with severe retrosternal chest pain with haemodynamic compromise. On examination, she was diaphoretic and hypotensive. BP in right arm was 100/60, and in left arm it was 60/40. Her left radial pulse was impalpable. Chest and cardiac auscultation was unremarkable. ECG showed sinus tachycardia. CXR showed widened mediastinum. Echocardiography showed dissecting aortic aneurysm extending up to the right CCA; dissecting flap seen extending up to the arch of aorta; dilated aortic root; sinotubular junction 4.62 cm and proximal ascending aorta 6.95 cm; mild AR.

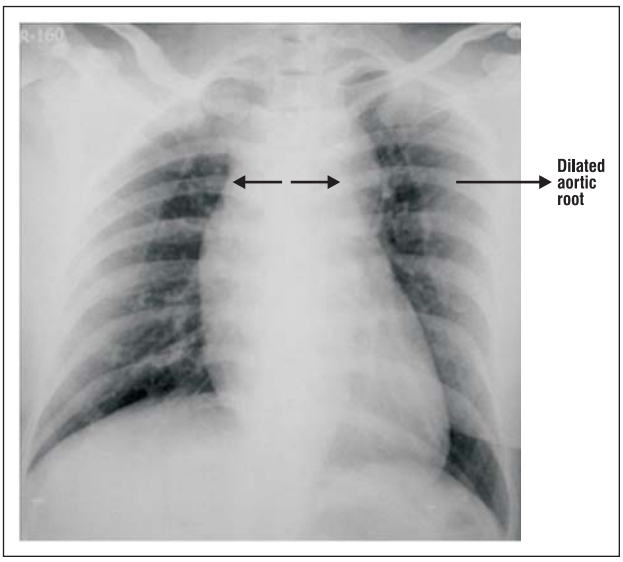

Fig. 1: *Chest X-ray showing widened superior mediastinum.*

With a provisional diagnosis of aortic dissection, a CT angiography was ordered. CT angiography revealed extensive dissection of aorta starting from ascending aorta, extending through thoracic and abdominal aorta up to bilateral common iliac arteries and beyond. Right brachiocephalic artery, left common carotid artery, coeliac trunk, and left renal arteries were also involved. She underwent prosthetic graft for Elephant Trunk repair and survived the episode.

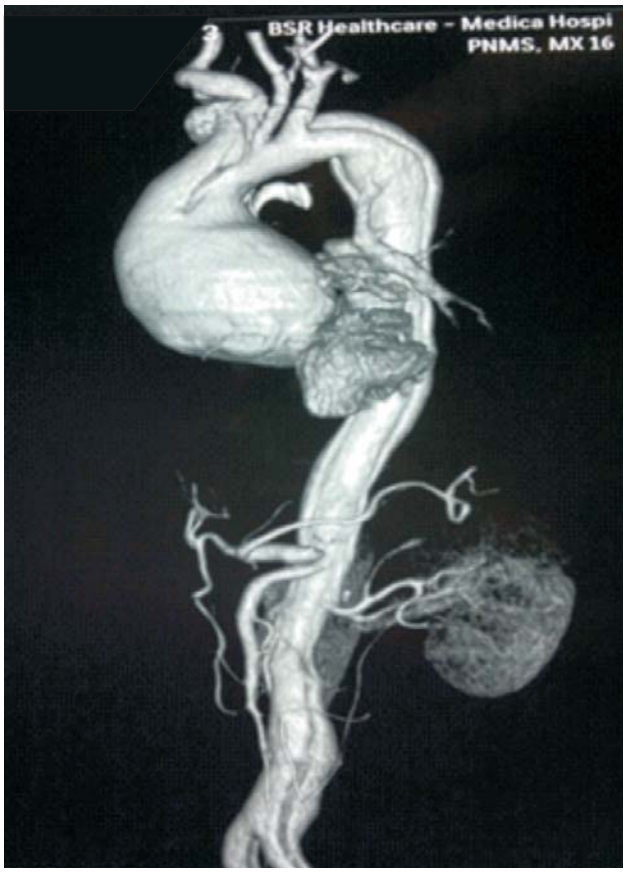

Fig. 2: *CT angio showing dissection of aorta starting from ascending aorta and extending through thoracic and abdominal aorta upto bilateral common iliac artery.*

The most common site of initiation of aortic dissection is the ascending aorta (50%) followed by aortic regions in the vicinity of ligamentum arteriosum. The Stanford classification is divided into 2 groups – A and B, depending on whether the ascending aorta is involved[1]:-

- **A** – Involves the ascending aorta and/or aortic arch, and possibly the descending aorta[2].
- **B** – Involves the descending aorta or the arch (distal to right brachiocephalic artery origin), without

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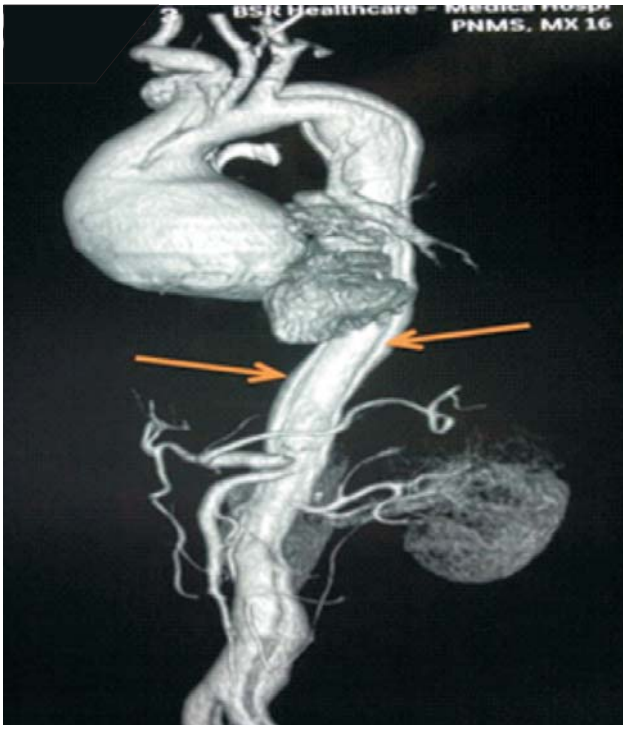

Fig. 3: *CT angio delineating dissection of thoracic and abdominal aorta.*

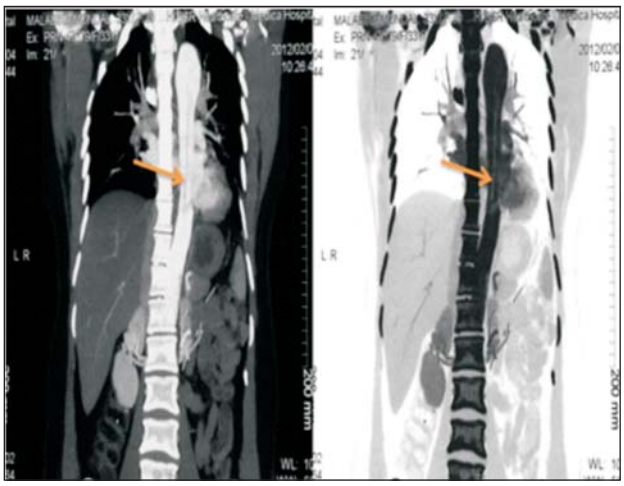

Fig. 4: *Coronal image showing dissection.*

involvement of the ascending aorta[3].

About 96% of individuals with aortic dissection present with severe pain that had a sudden onset. It may be described as tearing in nature, or stabbing, or sharp in character. Marfan's syndrome is noted in 5 - 9% of individuals who suffer from aortic dissection. In this subset, there is an increased incidence in young individuals. Individuals with Marfan syndrome tend to have aneurysms of the aorta and are more prone to proximal dissections of the aorta.

References

1. Daily PO, Trueblood HW, Stinson EB *et al*. Management of acute aortic dissections. *Ann Thorac Surg 1970;* 10 (3): 237-47.
2. Masafumi S, Saiho H, Hironori K. Antero-Lateral Thoracotomy with Partial Sternotomy for Retrograde DeBakey III Type Closing Aortic Dissection. *Japanese Journal of Cardiovascular Surgery* 2006; 35 (1): 21-4.
3. DeBakey ME, Henly WS, Cooley DA *et al*. Surgical management of dissecting aneurysms of the aorta. *J Thorac Cardiovasc Surg* 1965; 49: 130-49.

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