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VIEWPOINT

JIACM 2007; 8(3): 214-6

Cancer was Never Defeated; Cancer was Only Killed

*BM Hegde**

"At a time of universal deceit - telling the truth is a revolutionary act."

- George Orwell

"They were never defeated; they were only killed", was written about the famous French Foreign Legion. The same is true of cancer today. Both the French Legion and cancer are very powerful! Thank God, we do not have today as many deaths as we used to have – when I was a medical student – due to small pox, syphilis, cholera, typhoid, and many other bacterial infectious diseases killing young people in thousands. That has, to a certain extent, pushed up the age of death today. Of course, we have more viral diseases coming up now, but on an average, the population in India and other developing countries lives a lot longer, thanks to better food and civic amenities and fall in infant mortality in many parts of the third world.

Life expectancy, not to be mistaken for life span, has gone up considerably mainly because of the fall in infant mortality. As I had written earlier on many occasions, cancer is not a disease in the conventional sense but a sort of an ageing problem with things going wrong with the normal physiological death of the body cells of which there are as many as 10^{14}. Cell death occurs even in children. It is not surprising, therefore, that if one lives longer the chance of coming up with a clinical cancer in some organ or the other is greater, although most of us have inside us every day some biological rogue cells, a potential future clinical cancer. Providentially, most – if not all – of those cells die a natural death long before they could become clinical cancers. To assist that process we need to follow a healthy lifestyle and fill our minds with universal love.

Consequently, cancer incidence has hardly gone down despite all that we claim to have done in that area. The present cancer management in modern medicine reminds one of the ways our ancestors in medicine used to brand every single disease with a red-hot iron. To cap it, the present cancer management, most of it not authenticated by scientific audits, is very expensive for an ordinary patient in the third world to afford. The vested interests do not let the indigenous drugs to have proper authentication either. To help cancer incidence go up in the third world, the common person has changed his lifestyle, apiing the western life-style, by smoking, drinking alcohol, and eating junk food with lots of salt, fat, and sugar. Acculturation into cities leads people to be obese due to sedentary lifestyles. All these add to the burden of cancer growth and incidence.

Even in the US the incidence of cancer since 1930 has not shown any remarkable decline although there seems to be a dip in the graph around 2003 or so. That might not be an absolute fall, anyway. However, the third world is in for a big surprise with incidence going up very fast. Around 40% of cancer incidence worldwide could be brought down by regular exercise, eating healthy foods and not using tobacco. More and more people in Asia are moving to the cities, have started replacing their usual cereal, fruits and vegetable based fibre diet with fatty meals, full of meat and salt. Preserved foods that were popular in the west are making a foray into Asia in a big way. Most preserved foods have very high salt content. Heavy meat and salt diet would push up cancers of the stomach and colon. The results are for all to see.

Asia-Pacific now makes up half the world's cancer deaths with nearly 4.9 million new cases a year, roughly 45% of the global total in 2002. The number might rise to 7.8 million by 2020 if nothing changes. Mainland China alone, with 1.3 billion population, accounts for one-fifth of the world cancer load with India not falling far behind. In the US, the apparent fall around 2003 is said to be due to the remarkable fall in smoking rates there. Smoking is rising in Asia with China leading the way. India would probably take over from China with our lethargy to contain smoking – both cigarette and beedi – while we are the leaders in the world for chewing tobacco with the highest incidence of oral and throat

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cancers. More than 300 million in China smoke tobacco and the estimates put at least a third of the Chinese population below 30 years at risk of dying in the near future due to lung cancer. While smoking has gone down considerably in the West, it is going up in Asia-Pacific!

"In England they had a sanatorium for breast cancer patients in the 19th century before any treatment was invented. (It was only later that William Halstead at the Johns Hopkins Medical Centre in the US developed his radical mastectomy which led to many other mutilating radical surgeries for cancer). I remember going through their statistics and remember noticing a surprising finding because all these patients had no real medical treatment except tender loving care. One-third of the patients, irrespective of the care, lived a long life and died of natural causes. I do not remember the average number of years. But definitely more than 15 to 20 years. One-third of the patients did not make it for more than 2 years. The other third lived and died of fungating cancer after various number of years. So their average survival in the sanatorium of 5 years was close to 50%. Important deduction which stands good even today is – no matter what the treatment is – in the second group cancer is so virulent that we have not made any change. First group automatically boosts the percentage number of any treatment given and boosts the ten-year survival. It is only in the last group that everybody is trying to make the difference without knowing the natural history of breast cancer. For the sake of them the other two groups are also treated similarly. Nobody has looked into this because it is not an attractive paper to read and also it must be during the later part of the 19th century before surgery was introduced for breast cancer patients. Nobody tried to develop a test to differentiate these three groups because I do not think many of those actively involved in the breast cancer are aware of this paper. We could have treated patients' selectively with better results," writes an American vascular surgeon who wanted to be a cancer surgeon during his early years of training there.

Poverty and ignorance are the leading causes of cervical cancer in the third world. Breast cancer does not lag behind lung cancer either. The western hype about pap smear screening and mammography tests have been shown to be of not much use in reducing cancer deaths by the authentic audits like the one designed by David Eddy, a former professor of cardiac surgery at Stanford, who now is their professor of health management. Alcohol, especially the country made liquor, available freely in India and other poor countries, with all kinds of added chemicals to boost the strength (methyl alcohol included), is killing people by the thousands, of cirrhosis and liver cancer. Malaysia has the highest incidence of breast cancers.

The pharma lobby is selling the idea that new vaccines against hepatitis B and Papilloma viruses would bring down death rates significantly of both liver and cervical cancers respectively. This has to be taken with a pinch of salt, as most statistics about vaccine efficacy seems to be flawed. "The statistic that is often quoted is that there are 25,000 kids infected with hepatitis B in the US. After repeatedly asking the question as to how the CDC (Centres for Disease Control) arrived at this number, Harold S Margolis, MD, Chief of the Hepatitis Branch of the CDC finally admitted that 25,000 kids is simply an estimate. They have no hard proof that there are definitely 25,000 kids with hepatitis B," wrote Lisa F Reiss. If that were the state of affairs in the US, imagine what would it be in India or Asia?

The efficacy of common vaccines may be greatly exaggerated. In a 1998 study, it was stated "investigator bias probably has overestimated the efficacy of most vaccines." "Clinicians' compliance levels in monitoring illness in vaccine recipients varied widely in trial protocols." "Less compliant investigators were far more likely to report data making vaccines appear more effective against mild-or-moderate disease. Our data suggest that observer compliance (observer bias) can significantly inflate calculated vaccine efficacy..it is likely that all recently completed efficacy trials have been affected by this type of observer bias and all vaccines have considerably less efficacy against mild disease than published data suggest" (*Pediatrics*, 1998; 102: 909-912) Now to believe that cancer incidence will be brought down by vaccination seems far fetched, at least for now.

There were researchers who found that breast cancer mortality declines with increasing sunlight intensity at 87 locations across the USA. After considering possible causal factors including diet, they conclude that "lack of exposure to UV sunlight can increase the prevalence of vitamin D deficiency [which] may place some populations at higher risk for breast cancer". *(Preventive Medicine* 19: 614-622,

1990). The same authors also did a study of sunlight and breast cancer incidence in the USSR (*Int. J Epidemiol* 1990 Dec; 19(4): 820–4) with similar results. Garland and Garland did an earlier study, 'Do sunlight and vitamin D reduce the risk of colon cancer?' (*Int. J Epidemiol* 1980; 9: 227–231) which concluded that they do. They point out in the 1990 paper that "populations at high risk for breast cancer are also at high risk for colon cancer, and those at low risk for breast cancer are typically at low risk for colon cancer".

"The history of medical attitudes to ultraviolet is interesting. In 1877 scientists discovered that sunlight had the effect of killing bacteria; research over the next thirty years showed that the UV component was responsible, and could kill-off the bacteria of tuberculosis, cholera, anthrax, and other diseases. In 1903 the Nobel prize was given to Niels Finsen for his demonstration that sunlight therapy was effective against tuberculosis, then "the captain of the armies of death". Sanatoria to treat tubercular patients by sunlight were set up, and UV therapy." Earlier studies in the US had clearly shown that breast and colon cancers were lowest in those areas with plenty of sunlight compared to others where sunlight was not as abundant.

We are back to the square one. Cancer still is an enigma. For the developing third world countries, the agenda seems to be clear from the above data. We have to concentrate on economic empowerment of our less fortunate, give them primary education, clean drinking water and decent clean food – their own native foods, proper sexual education to avoid cancer provoking infections and wage a full-scale war on alcohol, tobacco and cooking smoke with deadly carbon monoxide in it. In addition, there are many methods of treating cancer in the ancient Indian systems like *Ayurveda*, *Siddha* etc., which need to be authenticated for use without much expenditure for research. The hi-tech western cancer treatments may be reserved for those that could afford them.

The present cancer management reminds one of the way Sir Arbathnot Lane used to perform total colectomy as the cure for chronic fatigue syndromes in London for years up until the time Sir George Bernard Shaw ridiculed it in his famous *Doctors' Dilemma*. Screening for cancer is certainly not cost effective as of now for universal use, neither is it inexpensive as it is made out to be. Regular screening for cancer could be the privilege of the rich and the famous. Let us motivate our poor people to change their mode of living to avoid cancer in the end. The war on cancer reminds one of the infamous Iraq war at the moment. Whereas cancer cells could be killed by our three-pronged attack – surgery, chemotherapy and radiation – the three also destroying a sizeable chunk of normal body cells in the bargain; cancer remains to be defeated!

"If liberty means anything at all, it means the right to tell people what they do not want to hear."

– George Orwell

A DOCTOR'S PRAYER

O Vidhaatha! Bless me with such an insight, intelligence and patience
That I may listen to my patient with a smile, compassion and tolerance.

O Merciful! Guide my mind, my hands, while I examine him, not to omit...
Any sign or symptom of his illness – not even a bit!

O Creator *par excellence!* Enthuse me with such a kind and loving attitude,
That shall fill me with thoughts pure and my coffers with gold!

Grant me! Grant me!! O, the Benevolent Unseen,
May I ever serve his prime need, not my own!

– Dr. GB Jain

ORIGINAL ARTICLE

JIACM 2007; 8(3) : 217-21

High Sensitive C-Reactive Protein (hs-CRP) and its Correlation with Angiographic Severity of Coronary Artery Disease (CAD)

Tenzin Nyandak, Arun Gogna**, Sandeep Bansal***, Manorama Deb*****

Abstract

Objective: *(A) To compare the levels of hs-CRP in patients with angiographically documented acute coronary syndrome (ACS), chronic coronary artery disease (chronic CAD) and patients with normal coronary angiograms.*

(B) To compare angiographic stenosis and extent score with hs-CRP levels in patients with ACS and chronic CAD.

Method: *A total of 73 patients who were admitted with the diagnosis of ACS, chronic CAD or chest pain were included in this study. Their quantitative hs-CRP levels were measured by ELISA method. Angiography scoring was performed to measure the stenosis score and extent score. Later, the levels of hs-CRP were compared with the stenosis and extent score in angiographically documented CAD.*

Results: *There was statistically significant hs-CRP elevation in angiographically confirmed CAD subjects (P = 0.004). It was found that hs-CRP levels were much higher in acute coronary syndrome patients compared to patients with normal coronary angiograms (P = 0.003). The hs-CRP levels were found to be in direct proportion to extent score of coronary artery disease (P = 0.004). Also, angiographic stenosis score was found to be higher in patients with higher hs-CRP levels (P = 0.005).*

Conclusion: *Significant correlation was observed between the extent of coronary artery disease and hs-CRP levels. Similarly hs-CRP levels were found to be higher in patients with higher degree of angiographic stenosis. This shows that hs-CRP levels have a correlation with the disease burden in CAD patients.*

Key words: *hs-CRP, Coronary artery disease, Angiographic stenosis, Angiographic extent.*

Introduction

The predilection of Indians to CAD has been confirmed beyond doubt[1, 4]. Indian populations are more prone to develop CAD at a younger age[1-2]. By the year 2015, India will have the largest coronary artery disease burden in the world[4-5].

Less than 50% of the CAD can be ascribed to traditional risk factors and rest are unexplained[6]. CRP has emerged as the most exquisitely sensitive systemic marker of inflammation and a powerful predictive marker of future cardiovascular risk[7]. CRP's predictive power for vascular risk detection resides between 0.1 to 0.5 mg/dl – a level which is present in most of the healthy individuals without inflammation; hence a high sensitive assay is required[8].

High sensitive CRP (hs-CRP) is well standardised and it has limits of detection as low as 0.02 g/dl[9-10]. Various trials like Physician Health Study (PHS)[11] and Women's Health Study (WHS)[12] have shown that predictive values of hs-CRP are significantly higher than other traditional biochemical cardiovascular risk markers.

However, the relationship between levels of hs-CRP and the presence and extent of angiographically documented coronary artery disease have seldom been investigated, especially in the Indian context. It is possible that CRP is predictive for CHD risk either through a correlation with CAD extent (disease marker) or as an indicator of inflammation that leads to an atherothrombotic event that leads to plaque rupture (a process marker). Defining the relationship between CRP and disease markers such as CAD extent as assessed by coronary angiography will enhance our understanding of whether 'inflammation markers' such as CRP would be complementary or redundant when combined with clinical risk prediction with other risk markers[13].

This study was performed to determine whether the concentrations of hs-CRP correlate with the coronary atherosclerosis assessed by coronary angiography.

Material and methods

Patient population: This study included 73 patients

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undergoing diagnostic coronary angiography at the Cardiology Department of Safdarjung Hospital. The patients with history of coronary angiography in the recent past (< 1 month), on statins for more than one month, any systemic infection, collagen vascular disease, recent trauma and patients with documented extra-cardiac atherosclerosis were excluded from the study.

Study design: It was a cross-sectional case control study. The selected cases were those who had suffered recent Acute Coronary Syndrome (labelled as group 1) and those with Chronic CAD (labelled as group 2). Recent myocardial infarction is defined as an acute episode of infarction < 2 months from the time of the investigation. The patients who had chest pain but normal coronary angiograms were taken as control subjects (labelled as group 3).

Angiographic estimation of coronary atherosclerosis: Coronary angiography was performed by the femoral approach and included at least 4 views of the left coronary artery and 2 views of the right coronary artery.

Stenosis Score: Stenosis Score used was a modified Gensini score[14-15]. Stenosis score provides information related to the bulk of the atherosclerotic lesion and is influenced by episodic processes such as plaque rupture. Each of eight vessel segments was graded according to severity of occlusion; grade 1 for 1% to 49% occlusion in lumen diameter, 2 for 50% to 74%, 3 for 75% to 99%, and 4 for total occlusion. The score in each of the eight segments were added to give a total score out of theoretical maximum of 32. This score therefore, places emphasis on the severity of stenosis, while including some of the extent of CAD.

Extent score: Extent score used was a David R. Sullivan's[15] new angiographic score of the extent of coronary artery disease. The score indicates the proportion of the coronary arterial tree involved by angiographically detectable atheroma. The proportion of each vessel involved by atheroma, identified by luminal irregularity, was multiplied by the factor for each vessel. Left main artery, 5; left anterior descending, 20; main diagonal branch, 10; first septal perforator, 5; left circumflex artery, 20; obtuse marginal and posterolateral vessels, 10; right coronary artery, 20; and main posterior descending branch, 10. When a vessel was occluded and the distal vessel not fully visualised by collateral flow, the proportion of vessel not visualised was given the mean extent score of the remaining vessels. When the major lateral wall branch was a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the left circumflex artery a factor of 10[15]. The score for each vessel or branch were added to give a total score out of 100, that is the percentage of coronary intimal surface area involved by atheroma.

hs-CRP estimation: The CRP test was performed by using UBI MAGIWEL CRP-quantitative AD-401 kit, a solid phase enzyme linked immunosorbent assay (ELISA) as per instructions of the manufacturer (supplied with kit).

Statistical analysis

Data were analysed with SPSS for windows statistical package and are presented as mean ± SD. Univariate comparison between groups were made with nonparametric test; Kruskal-Wallis test for multigroup comparison and Mann-Whitneys test for 2-group comparison. Discrete variables were compared with chi-square test. The correlation between levels of hs-CRP and angiographic stenosis and extent was assessed by Spearman's correlation. For all results, a P value of < 0.05 was considered significant[16].

Results

Out of 73 subjects, 40 patients were in acute coronary syndrome group, 18 in chronic stable CAD and 15 patients (controls) were found to be having normal coronary angiograms.

The three groups were comparable with respect to age, sex, and other risk factors for coronary artery disease such as diabetes, hypertension, s. triglyceride, s. LDL, s. HDL levels and smoking (Table I).

Patients with ACS had the highest mean hs-CRP levels (5.60 mg/l) followed by chronic CAD patients (3.54 mg/l) and then the control group (2.28 mg/l) (Table II). It was found that there was significant difference of hs-CRP levels between group 1 and group 3, (P = 0.003), but no significant difference was observed between group 1 with 2 (P = 0.079) and group 2 with 3 (P = 0.787) (Table III), although the mean hs-CRP levels were found higher in group 2 as compared to group 3.

Table I: Baseline clinical characteristics of the study population.

	Group 1 (n = 40) No. (%)	Group 2 (n = 18) No. (%)	Group 3 (n = 15) No. (%)
Male/female	32 (80)/8 (20)	16 (88.9)/2 (11.1)	9 (60)/6 (40)
Diabetic/non-diabetic	5 (12.5)/35 (87.5)	1 (5.6)/17 (94.4)	3 (20)/12 (80)
Hypertensive/normotensive	15 (37.5)/25 (62.5)	5 (27.8)/13 (72.2)	4 (26.7)/11 (73.3)
Smoker/non-smoker	23 (57.5)/17 (42.5)	9 (50)/9 (50)	8 (53.3)/7 (46.7)
Age (mean)	53.5	54.06	50.93
S. triglyceride (mg/dl)	126.13	100.06	118.87
S. HDL (mg/dl)	43.94	43.46	44.36
S. LDL (mg/dl)	104.35	103.6	107.63

P > 0.05 in all the above variables, they are comparable.

Table II: Comparison of hs-CRP levels in ACS, chronic CAD and control population.

hs-CRP (mg/l)	Group 1	Group 2	Group 3
Mean ± SD	5.605 ± 3.70	3.544 ± 2.51	2.28 ± 2.34
Median	5.10	3.0	1.40
IQR*	8.0	3.8	2.70

Non-parametric Kruskal-Wallis test.

IQR – Inter-quartile range.*

Table III: hs-CRP correlation between groups, multiple comparison.

Group	Group	Sig. (p)
1	2	0.079
1	3	0.003
2	3	0.787

Angiographic stenosis score and extent score were compared between group 1 and 2. The mean stenosis scores were 6.15 in the acute coronary syndrome and 4.72 in chronic stable CAD. And the mean extent scores were 38.88 and 34.72 in ACS and chronic CAD groups respectively. There was no correlation in this comparison (P values > 0.05 in both the comparisons).

To see the correlation of disease burden and levels of hs-CRP, angiographic stenosis and extent scores were compared with hs-CRP levels. Spearman's correlation coefficient between hs-CRP and angiographic stenosis score was r = 0.316 (Fig. 1) and hs-CRP with angiographic extent score was r = 0.338. (Fig. 2). Statistically significant correlation exists between both angiographic stenosis and extent score with hs-CRP levels. Higher hs-CRP levels were associated with higher stenosis and extent score in CAD patients. P values were 0.005 (Fig. 1) and 0.004 respectively (Fig. 2).

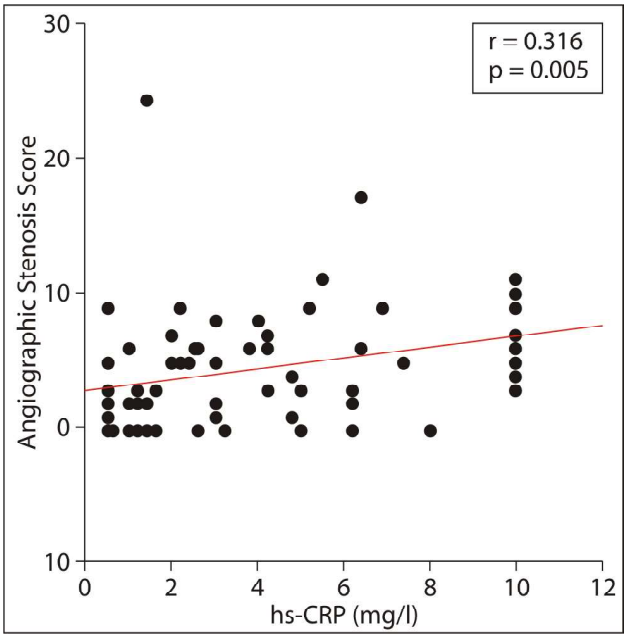

Fig. 1: *Correlation between hs-CRP level and stenosis score of coronary artery atherosclerosis.*

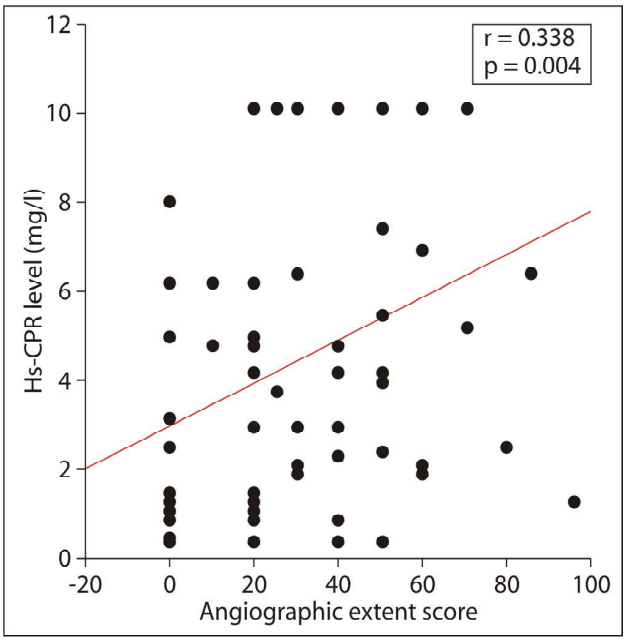

Fig. 2: *Correlation between hs-CRP level and extent score of coronary artery atherosclerosis.*

Discussion

Several population based studies have revealed that high sensitive C-reactive protein (hs-CRP) is an exquisitely sensitive systemic marker of inflammation and a powerful predictive marker of future cardiovascular risk[17-19].

These data support previous findings that CRP levels were elevated in patients with clinical CAD identified by angiography. Idrissia *et al*[16], Auer *et al*[20] and Rifai *et al*[21] had studied the levels of CRP and angiographic findings. They did not find any correlation between CRP levels and angiographic extent score. In this study, there was significant correlation observed between the extent of coronary artery disease and hs-CRP levels (Fig. 2). Also, angiographic stenosis score was found to be higher in patients with higher hs-CRP levels (Fig. 1). This shows that hs-CRP level also has correlation with the disease burden apart from being a well known indicator of presence of ACS. It therefore suggests that inflammation is not only an important trigger mechanism of acute coronary syndrome related to plaque rupture, but also a promoter of chronic atherosclerosis, as proposed that CRP might play an atherogenic role through an interaction with low density lipoproteins[20].

So far, the correlation of CRP level and angiographic score was studied in European whites and they did not find any correlation. Since in this study, subjects were Asian Indians, the correlation that we observed between hs-CRP and disease burden in CAD patients is noteworthy, which seems to be in accordance to many studies in Asian Indians where it was found that, as compared to western population, the Asian Indians have diffuse angiographic as well as premature CAD. And this is due to a genetic susceptibility, mediated through elevated levels of lipoprotein (a), which magnifies the adverse effects of lifestyle factors associated with urbanisation, affluence, and changes in diet[22-24].

Our study has certain limitations. First, it was a cross-sectional study of patients referred for coronary angiography. Such a study design cannot establish causality. It can only establish an association. Hence, any conclusion derived from such a study must be considered preliminary and hypothesis-generating rather than hypothesis-proving.

On the other hand, group 3 comprises subjects that range from absence of CAD to sub-clinical CAD. This could introduce error, but reflects clinical reality, and does not invalidate data, as coronary angiography (generally considered as a "gold standard" for invasive evaluation of the coronary arteries) has limited sensitivity for detection of sub-clinical CAD. Other diagnostic tools such as intravascular ultrasound (IVUS) could enhance diagnostic accuracy, but are not widely used in clinical practice[20]. Moreover, variability in commercial assays may limit the external validity of these data[25].

Conclusion

In conclusion, significantly higher hs-CRP levels are found in angiographically proven CAD patients with acute coronary syndrome as compared to patients with normal coronary angiography; and the levels of hs-CRP correlated well with the angiographic severity of the CAD.

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ORIGINAL ARTICLE

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Weaning Modes in Mechanical Ventilation

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Abstract

A total of one hundred patients presenting with respiratory failure and requiring mechanical ventilation were studied. Out of 100 patients, 65 were successfully weaned and 35 died. The commonest weaning mode was SIMV + PSV; used in 72.3% patients. The mean duration of weaning was shortest in acute exacerbation of bronchial asthma (2.33 days) and longest in cases of Guillian Barré syndrome (12.42 days). The percentage of total ventilator time spent on weaning varied from 43.71% in bronchial asthma to 65.85% in organo-phosphate and carbamate poisoning.

Introduction

Weaning has been defined as the process whereby mechanical ventilation is gradually withdrawn and the patient resumes spontaneous breathing. While T-piece trials remain the simplest method, several alternatives are available since 1973 when Downs *et al*[1] introduced synchronised intermittent mandatory ventilation (SIMV). The other weaning modes are pressure support ventilation (PSV), combination of SIMV and PSV, and continuous positive airway pressure (CPAP). The aims and objectives of this study were to see the weaning modes that were used, time taken for weaning, and the problems encountered. The study was conducted on 100 patients admitted to Bharati Hospital, Pune with respiratory failure and were put on mechanical ventilation. The inclusion criteria were all adult patients with respiratory failure or those developing it in the course of another illness during admission and thereby requiring mechanical ventilation. The exclusion criteria were:-

1. Patients on immediate post-operative temporary mechanical ventilation.
2. Paediatric patients presenting with respiratory failure and requiring mechanical ventilation.

Results

Out of 100 patients put on mechanical ventilation, 30% were cases of organophosphorus and carbamate poisoning (OPP), 26% of complicated pneumonia, 18% of ARDS, 10% of acute exacerbation of COPD, 7% of Guillian Barré Syndrome (GBS), 4% of cardiogenic pulmonary oedema, 3% with acute exacerbation of bronchial asthma and 2% with pleural diseases (one with haemothorax and one with pneumothorax). Table I shows the different weaning modes that were used. Table II shows the average duration of weaning, total ventilator stay and percentage of ventilator time spent in weaning in the 65 survivors. The shortest weaning period was 1 day (in two cases of bronchial asthma and one case of complicated pneumonia) and the longest was 22 days (in a case of GBS). The average duration of weaning was also the longest in GBS (12.42 days). On the whole, 75.31% of patients (49 out of 65) were weaned-off within a week; 7.69% (5 out of 65) required a weaning time of more than 2 weeks (Table III).

Discussion

As a rule, the weaning should be attempted as soon as the patient's condition has improved and allows spontaneous breathing. Conditions that must be met before initiating a weaning trial are:- resolution or improvement in the cause of respiratory failure, cessation of sedative and neuromuscular blocking drugs, normal state of consciousness, absence of sepsis or marked hypothermia, stable cardiovascular state, correction of metabolic and electrolyte disorders, adequate gas exchange, adequate respiratory pump capacity, and no anticipated surgical procedures under general anaesthesia.

Out of 65 successfully weaned patients, SIMV + PSV were the commonest mode (in 72.3%); 20% were weaned with PSV and 7.69% with T-piece.

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Table I: Weaning modes used in different conditions.

Modes	OPP and carbamate poisoning	GBS	Complicated pneumonias	ARDS/ALI	Cardiogenic pulm. oedema	Acute exacerb. of COPD	Acute exacerb. of BA	Pleural diseases	Total
Unable to wean/ failure of weaning/ Mortality	2	–	14	11	2	5	–	1	35 (35%)
SIMV+PSV	25	6	6	6	–	2	1	1	47 (47%)
SIMV	–	–	–	–	–	–	–	–	–
PSV	3	1	5	1	–	3	–	–	13 (13%)
T-piece	–	–	1	–	2	–	2	–	5 (5%)

Table II: Average duration of weaning and total average ventilator stay in different conditions.

Disease	Average duration of weaning	Total average ventilator stay (of survivors only)	% of total ventilator time spent in weaning
Organophoshorus and carbamate poisoning	Average = 6.23 days (Min = 2 d; Max = 19 d)	Average = 9.46 days	65.85%
Guillain-Barré syndrome	Average = 12.42 days (Min = 6 d; Max = 22 d)	Average = 21.05 days	59%
Complicated pneumonias	Average = 5.375 days (Min = 1 d; Max = 8 d)	Average = 7.0 days	76.78%
ARDS/ALI non-cardiogenic pulmonary oedema	Average = 4.466 days (Min = 4 d; Max = 8 d)	Average = 11.28 days	39.59%
Cardiogenic pulmonary oedema	Average = 2.50 days (Min = 2 d; Max = 3 d)	Average = 3.50 days	71.42%
Acute exacerbation of COPD	Average = 4.43 days (Min = 3 d; Max = 6 d)	Average = 7.60 days	58.28%
Acute exacerbation of bronchial asthma	Average = 2.33 days (Min = 1 d; Max = 5 d)	Average = 5.33 days	43.71%
Pleural diseases	Average = 13 days only one survivor	Average = 15 days	86.66%

Table III: Duration of weaning in different conditions.

No. of days	OPP and carbamate poisoning	GBS	Complicated pneumonias	ARDS/ALI	Cardiogenic pulm. oedema	Acute exacerb. of COPD	Acute exacerb. of BA	Pleural diseases	Total
0–3 Days	9	–	5	–	2	2	2	–	20 (30.76%)
4–7 Days	12	2	6	5	–	3	1	–	29 (44.61%)
8–14 Days	4	3	1	2	–	–	–	1	11 (16.92%)
> 2 Weeks	3	2	–	–	–	–	–	–	5 (7.69%)

The abrupt discontinuation of mechanical ventilation and resumption of spontaneous breathing through a T-tube system is the simplest and most commonly used weaning mode. Patients are usually observed for a short period (usually upto 2 hours) with T-piece to assess the tolerance of spontaneous breathing. If the trial is successful, the patient is extubated[1]. If the patient fails the trials, either of the 2 protocols may be followed. In the once daily T-piece trial, assisted control ventilation is reinstituted for 24 hours, then another trial is attempted. In the intermittent T-piece trials, assisted control ventilation is reinstituted for atleast 1 hour and the trial is repeated again or more times during the same day[1]. Brochard *et al* monitored the duration of failed weaning trial in each patient and allowed the next T-piece trial for 15 minutes less than the failed one. The patient was put back on ventilator for an hour and the duration of the next trial was increased by 15 minutes and the whole process was repeated[2]. In 5 of our patients who were weaned with T-piece, we used the intermittent T-piece trial protocol.

SIMV, the first alternative to T-tube trials, is now a frequently used mode to wean patients off the ventilator. It involves gradual reduction in the amount of support being provided by the ventilator and a progressive increase in the amount of respiratory work being performed by the patient. There is no disconnection from the ventilator; all the monitoring and alarm functions of the ventilator are retained[1]. Venus *et al* conducted a national survey in the USA, and found that SIMV was the single most frequently used weaning

technique (19.2%). It was also the primary mode of mechanical ventilatory support[3].

Pressure support ventilation is a spontaneous mode of assisted mechanical ventilation where each of the inspiratory effort is assisted by a preset level of pressure generated by the ventilator. Pressure support is reduced by steps of 2 – 4 cm of water and one or two steps per day are desirable according to the patient's tolerance. If there are no signs of intolerance at pressure support of < 8 cm of water, weaning is considered complete and extubation can be considered[2]. As the frequency and tidal volume are dependent on the patient during PSV, a specific level of back-up ventilation is not guaranteed. Combination of SIMV and PSV is available which may be beneficial for the 'difficult to wean' patients, but the time required for weaning is long with this modality[4].

Jounieax *et al* compared the 2 weaning modalities in patients with COPD requiring mechanical ventilation, i.e., SIMV and SIMV + PSV. The weaning success rates were the same in the 2 groups; with a slightly shorter (insignificantly) weaning period in the latter group[5]. Esteban *et al* in 1994, in a survey of Spanish hospitals, found that various techniques used for weaning were – T-piece trail in 24%, SIMV in 18%, PSV in 15%, SIMV + PSV in 9%, and combination of 2 or more methods in 33%. Time required for weaning using combination of SIMV and PSV was longer than the other technique[6]. In 1995, Esteban *et al*, for the Spanish Lung Failure Collaborative group, screened 546 medical-surgical ICU patients. They concluded that success of T-piece once daily was significantly greater than SIMV and PSV, with a significant difference in success between the latter two. Median time to wean was 3 days for the T-piece group and 4 and 5 days respectively for PSV and SIMV[1, 7].

Brochard *et al*, in a European multicenter trial, studied 456 medical-surgical ICU patients who were clinically ready for weaning and satisfied traditional weaning criteria. Over 3 weeks they found that PSV had the lowest weaning failure rate as compared to SIMV or T-piece (23% vs 42% and 43%) and the shortest mean duration of time to wean (5.7 days vs 9.3 days for both other modes)[2, 7].

In our study, the shortest duration of weaning was 1 day (in 2 cases of bronchial asthma and 1 of pneumonia). While the longest weaning period was 22 days in a case of GBS. The average duration of weaning was longest in patients of GBS (12.42 days). Of the 65 patients weaned, 49 (75.31%) were weaned-off within a week, and 5 (7.69%) had a weaning period of more than 2 weeks. Regarding weaning modes, the average duration of weaning was 7.21 days with SIMV + PSV, 4.38 days with PSV and 1.6 days with T-piece. So the time required for weaning with SIMV + PSV was longer than the other modes especially the T-piece trials. This is comparable with the studies mentioned above. However, we have to consider the fact that only 5 of our patients were weaned with T-piece trials, of which 2 were bronchial asthma, 2 had cardiogenic pulmonary oedema and 1 had pneumonia. These patients were relatively stable with average total ventilator time of only 3 days.

All the complications associated with intubation and mechanical ventilation per se can be reduced by reducing the time on mechanical ventilation. At the same time, premature weaning trials should be avoided. A failed trial is discomforting for the patient and may induce significant cardiopulmonary distress. Signs of weaning failure such as tachypnoea, tachycardia or bradycardia, hypotension, hypoxaemia, agitation, diaphoresis, etc., call for prompt reestablishment of ventilatory support[8].

T-piece trials, though traditional, remain a highly attractive weaning technique based on knowledge of respiratory muscle fatigue and its determinants. Over the years new and modern ventilators offer various in-built weaning modes which have reduced the inclination of the intensivists on duty to try T-piece trials. Though these modes may appear safer, the weaning time is often longer and sometimes there is a false sense of security. So the treating physician should be vigilant enough to recognise when a patient is failing a weaning trial.

Acknowledgements

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REVIEW ARTICLE

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Tumour Necrosis Factor-alpha and its Blockers – A Novel Chemotherapeutic Revolution

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Tumour necrosis factor (TNF) and lymphotoxin-α were isolated more than 10 years ago, on the basis of their ability to kill tumour cells *in vitro* and to cause haemorrhagic necrosis of transplantable tumours in mice. The complementary DNAs and genes encoding each protein were cloned immediately thereafter. Various studies have demonstrated the powerful pro-inflammatory effects of TNF and revealed its role as a central endogenous mediator of endotoxic shock. Hence, TNF has a broad spectrum of biologic activities.

The ways to block the biosynthesis or action of TNF can have important clinical applications. TNF has served as the principal end-point in most studies of endotoxin signal transduction. It is likely that drugs impairing each step of that process will soon be tested for antiinflammatory efficacy. TNF and lymphotoxin can be neutralised, and neutralisation of other members of the ligand family is being explored. Thus, new and highly specific approaches to the treatment of inflammatory disease may soon become available.

Introduction

Tumour necrosis factor-alpha (TNF-α) is a pleiotropic inflammatory cytokine. It was first isolated by Carswell *et al* in 1975 in an attempt to identify tumour necrosis factors responsible for necrosis of the sarcoma Meth A. The cytokine possesses both growth stimulating properties and growth inhibitory processes, and it appears to have self regulatory properties as well. The cytokine is produced by several types of cells, but especially by macrophages. Tracey and Cerami in 1990 suggested two beneficial functions of TNF-α which have led to its continued expression. First, the low levels of the cytokine may aid in maintaining homoeostasis by regulating the body's circadian rhythm. Furthermore, low levels of TNF-α promote the remodelling or replacement of injured and senescent tissue by stimulating fibroblast growth. Studies demonstrated the powerful pro-inflammatory effects of TNF-α and revealed its role as a central endogenous mediator of endotoxic shock. Without TNF-α, mice infected with Gram-negative bacteria experience septic shock (Janeway *et al*, 1999). Hence, TNF has a broad spectrum of biologic activities.

Systematic effects of TNF in acute vs chronic exposure.

Acute, high dose	Chronic, low dose
Shock and tissue injury	Weight loss
Catabolic hormone release	Anorexia
Vascular leakage syndrome	Protein catabolism
Adult respiratory distress disorder	Lipid depletion
Gastrointestinal necrosis	Hepatosplenomegaly
Acute renal tubular necrosis	Subendocardial inflammation
Adrenal haemorrhage Insulin resistance	Insulin resistance
Decreased muscle membrane potentials	Enhanced rate of tumor metastasis
Disseminated intravascular coagulation	Acute phase protein release
Fever	Endothelial activation

The TNF-ligand and TNF-receptor families

TNF-α is a trimeric protein encoded within the MHC. It was first identified in its 17 kd secreted form, but further research then showed that a noncleaved 27 kd precursor form also existed in transmembrane form (Perez *et al*, 1990). Stimulated macrophage produce 27 kd TNF-α which can either bind directly to TNFR-55 and TNFR-75 receptors through cell-to-cell contact or undergo cleavage and bind in its soluble form. Due to its jelly roll like structure, which it shares in common with viral coat proteins, it has been hypothesised that TNF-α and viral originated from a common ancestor cell (Jones *et al*, 1989). TNF-α shares only 36% amino acid sequence homology with TNF-B, also called lymphotoxin (LT) (Meager, 1991). Yet, the tertiary structures of the two proteins are remarkably similar and both bind to TNF receptors TNFR-55 and TNFR-75. These receptors are expressed on all somatic cells.

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Table I: Recently characterised members of the TNF-ligand and TNF-receptor families*.

Ligand	Source of ligand	Receptor	Distribution of receptors	Ability to initiate apoptosis	Cytoplasmic mediators	Mutation or knockout ligand	Phenotype receptor
TNF and lymphotoxin-α	TNF: macrophages, lymphocytes, keratinocytes, others	55-kd TNF receptor	Many cells	Yes (strong)	TRADD[14], TRAP-1[15], 55.11[16]	Both TNF and lymphotoxin α: absent lymph nodes, decreased lipopolysaccharide responses	Decreased lipopolysaccharide response; failure to contain listeria or mycobacteria infection[17,18]
	T cells	75-kd TNF receptor	Many cells	Yes	TRAP-1, TRAP-2[19]	Lymphotoxin-α: absent lymph nodes[20]	Decreased lymphocyte proliferation; decreased dermal responses to TNF; decreased TNF-induced lethality[21]
Lymphotoxin-β	T cells, others	Lymphotoxin-β receptor (TNF-receptor-related protein)	T cells, B cells, others	Yes	LAP-1 (CRAF-1)[22]	ND	ND
Fas ligand	T cells	Fas receptor	Many cells	Yes (strong)	Tyrosine phosphatase (FAP-1)[23], FADD (MORT-1)[24]	Lymphoproliferation	Lymphoproliferation
Nerve growth factor	NA	Nerve growth factor receptor	Neurons, others	No	ND	NA	Neuropathy[25]
CD40 ligand	T cells	Nerve growth factor receptor	B cells, T cells	No	CRAF-1, CAP-1[26-28]	X-linked immunodeficiency with increased IgM and decreased or absent IgG, IgA, IgE[29-31]	X-linked immunodeficiency with increased IgM and decreased or absent IgG, IgA, IgE[32]
CD27 ligand	T cells	CD27	T cells	ND	ND	ND	ND
CD30 ligand	T cells	CD30	T cells	ND	ND	ND	ND
OX-40 ligand	T cells	OX40	T cells	ND	ND	ND	ND
4-1BB ligand	T cells	4-1BB	T cells	ND	ND	ND	ND

**Other members of these two families include the CD27, CD30, OX-40, and 4-1BB ligands and receptors. TRADD denotes TNF-receptor-associated death domain, TRAP-1 TNF-receptor-associated protein 1, TRAF TNF-receptor-associated factor, LAP-1 latent membrane protein type 1-associated protein, CRAF-1 CD40-receptor-associated factor 1, ND not determined, FAP-1 Fas-associated protein, FADD (or MORT-1) Fas-associated death domain, NA NOt applicable, and CAP-1 CD40-associated protein 1.*

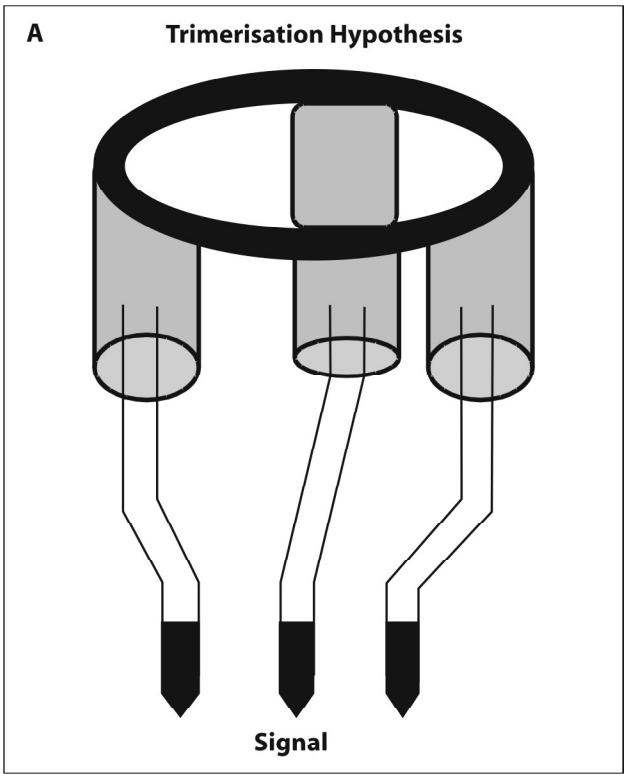
How the receptors work

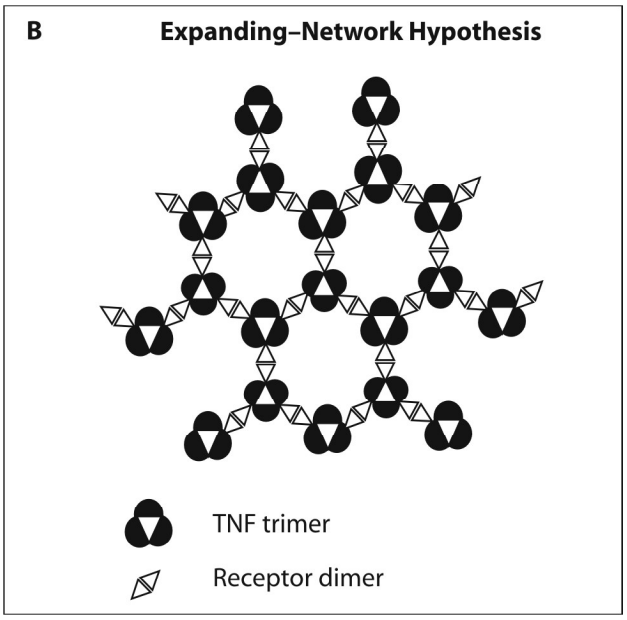
Three models of the molecular events in TNF signalling have been postulated:.

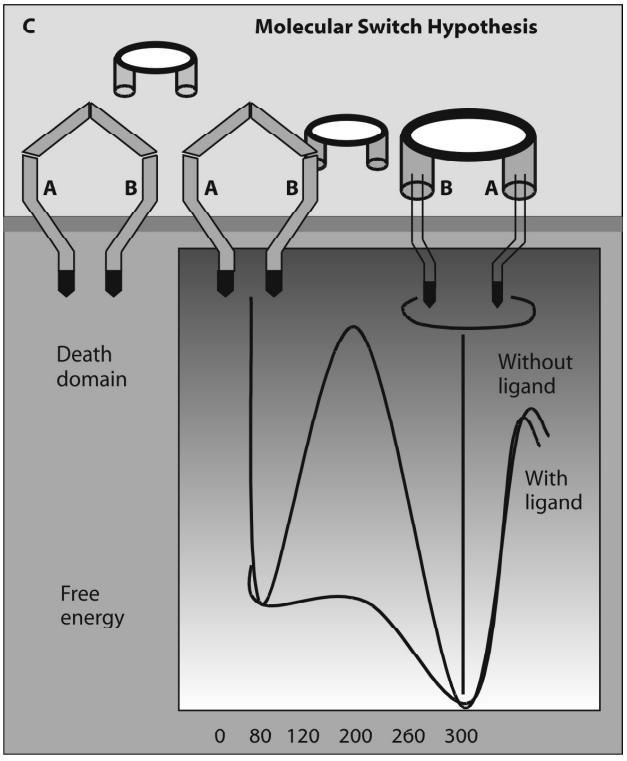
Panel A shows the trimerisation hypothesis. In this model, the juxtaposition of three receptors results from their binding of a single TNF trimer. The resultant complex generates an activating signal.

Panel B shows the expanding-network hypothesis. A growing hexagonal array of TNF trimers bound to TNF-receptor dimmer takes account of the dimeric structure of TNF receptors free of ligands and the capacity of each ligand molecule to engage three receptor subunits. "Capping" of receptors would trigger a biologic response.

Panel C shows the molecular-switch hypothesis, the most favoured model. In this model each receptor dimmer is an activatable unit. Receptor activation occurs in response to two events. First, the ligand binds to subunits B of the receptor. Second, subunit A disengages from subunits B, which permits binding of the receptor to a second available site on the ligand surface. These events cause conformational changes within the cytoplasmic domain of the receptor, leading to signal transduction. Specifically, the death domain of the 55-kd TNF receptor or Fas receptor might undergo homogimrisation. The graph shows an

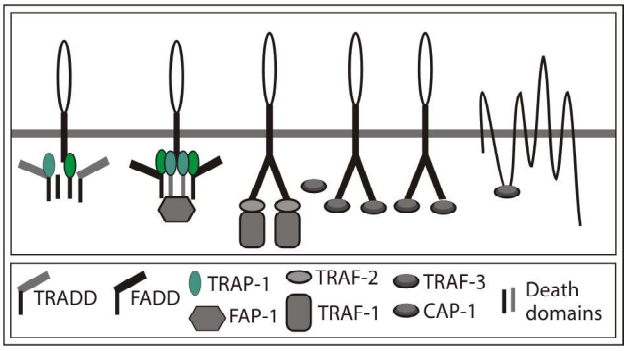






imaginary profile of the free energy associated with conformational changes between the "off" and "on" states of the receptor. It is supposed that a large activation-energy barrier prevents transition from the "off" to the "on" state in the absence of ligand and that TNF effectively catalyzes this transition therapy "throwing the switch." Moreover, as depicted here, the TNF and the receptor, may be substantially lower than the free energy of the "off" state, and this may be irreversible.

Proteins used by the TNF-receptor family for signal transduction



Proteins that bind the cytoplasmic domains of receptors for TNF, Lymphotoxin-α, Lymphotoxin-β (LT-β), CD40 ligand, Fas ligand, and Latent Membrane Protein Type 1 (LMP-1).

Lymphotoxin-α and TNF bind to the same 55-kd TNF receptors, proteins and domains (TRADD), receptor-similar structures of functions, such as TNF-receptor-associated death domain (TERADD), receptor-interacting protein (RIP), Fas-associated death domain (FADD, or MORT-1) molecules, and the death domains of the Fas and 55-kg TNF receptors, are generally protrayed by identical shapes but in different colours. Zn is used to denote proteins known to contain ring-finger and zinc-finger motifs that bind to the 75-kd TNF receptor, lymphotoxin-β receptor, and CD40-ligand receptor. TNF-receptor-associated factor type 1 (TRAF-1) lacks a zinc-finger motif but binds to TRAF-2, which has both ring-finger and zinc-finger motifs. CD40-associated protein 1 (CAP-1), which is structurally very similar to TRAF-3, is thought to be capable of replacing TRAF-3 as a binding partner for the lymphotoxin-β receptor and CD40-ligand receptor. LMP-1 is a plasma-membrane protein that spans multiple domains and is encoded by the genome of the Epstein-Barr virus. It has no homology to members of the TNF family. Not all possible combinations and interactions are shown. In addition, certain binding proteins that were not discussed in the text belong neither to the zinc-and ring-finger family nor to the death-domain family of transducers. These include TNF-receptor-associated protein 1 (TRAP-1), a heat-shock protein analogue; the 55.11 protein, proteasome regulatory subunits; and Fas-associated protein 1 (FAP-1), a protein tyrosine phosphatase that binds to the Fas receptor near its carboxy terminal and is thought to decrease the intensity of signals generated by this receptor.

Clinical implication and limitation of TNF therapy

Because of its high toxicity in animals and humans, TNF did not fulfill initial expectations for its use in the treatment of cancer. Since TNF-α plays a role in several diseases, a substantial amount of research has been conducted

concerning TNF-α therapies and anti-TNF-A therapies. Some studies involving TNFR-75 and TNFR-55 mutants have suggested that the TNFR-75 receptor plays a role in systemic toxicity, while TNFR-75 mutants will exhibit cytotoxicity but not systemic toxicity (Van Ostade *et al*, 1993).

Recombinant human tumour necrosis factor (TNF) has a selective effect on angiogenic vessels in tumours. Given that it induces vasoplegia, its clinical use has been limited to administration through isolated limb perfusion (ILP) for regionally advanced melanomas and soft tissue sarcomas of the limbs. In melanoma, the complete response (CR) rate is around 80% and the overall objective response rate greater than 90%. In soft tissue sarcomas that are inextirpable, ILP is a neoadjuvant treatment resulting in limb salvage in 80% of the cases. The mode of action of TNF-based ILP involves two distinct and successive effects on the tumour-associated vasculature: first, an increase in endothelium permeability leading to improved chemotherapy penetration within the tumour tissue; and second, a selective killing of angiogenic endothelial cells resulting in tumour vessel destruction.

Toxicities consist mainly of constitutional symptoms including fever, chills, headache, and fatigue, increasing in severity with dose escalation. The maximum tolerated dose (MTD) was 200 μg/m^2 with dose limiting toxicity being constitutional symptoms and hypotension. Constitutional symptoms (fever and chills) occur in nearly every patient at all dose levels and generally resolve within 24 to 48 hours of completion of the final infusion. Headache is observed at all dose levels. Significant decline (> 20%) in systolic and diastolic blood pressure and associated orthostatic hypotension is observed at dose levels > 100 μg/m^2 despite prehydration with 1 litre of normal saline. Haematologic changes include median decrease in both granulocyte and platelet counts of 38% and 41%, respectively (range, 16% to 85%); however, clinically significant haematologic abnormalities are rare. The recombinent TNF-alpha induced changes in lipid metabolism are manifested by median fasting triglyceride elevations above baseline (range, 16% to 89%) after five days of therapy with doses > 75 μg/m^2, associated with a median increase in very-low-density lipoprotein (VLDL) of 80%. The gastrointestinal symptoms are observed in 40% of the patients receiving doses > 100 μg/m^2.

Clinical effects of TNF and lymphotoxin blockers

The goal of treating chronic inflammatory diseases, in which slow, continuous tissue damage may occur owing to the presence of TNF, has met with greater success.

Encouraging results have emerged from the use of anti-TNF antibodies (infliximab) in the treatment of Crohn's disease.

Tumour necrosis factor alfa (TNF-alfa) is an important inflammatory mediator that plays a crucial role in rheumatoid arthritis. The monoclonal antibody (infliximab, adalimumab) and the receptor analogue (etanercept) bind to circulating TNF-α and block its interaction with membrane receptor.

Clinical and experimental evidence implicate TNF as a possible mediator of the severe immune-based pulmonary injury which can follow infection with H5N1 influenza and SARS coronavirus. Compared with the use of corticosteroids, the use of biologic TNF-inhibitors, including etanercept, has the potential to be a more specific and more effective method of ameliorating the severe alveolar damage which can occur following infection with these agents.

Other research has focused upon inhibiting the effects of TNF-α in such diseases as rheumatoid arthritis, Crohn's disease, AIDS, bacterial septic shock (caused by certain gram-negative bacteria), and bacterial toxic shock (caused by superantigens) as well as in prevention of alloreactivity and graft rejection.

One hypothetical advantage of treatment with anti-TNF-α antibodies results from its role in multiple types of inflammation. It is often difficult to determine that inflammation in burn and trauma victims is of infectious aetiology and warrants treatment with antibiotics; therefore, another treatment strategy might involve anti-TNF-α therapy (Strieter, *et al*, 1993).

The future of TNF

The molecule is one of the best-characterised gateways to apoptosis. It is essential for defense against intracellular pathogens. It is a pro-inflammatory mediator that can, when overproduced, cause shock and tissue injury. Low levels of TNF may account for the state of insulin resistance

that contributes to the development of type 2 diabetes mellitus[68-75].

The lupus-like state that follows abrogation of the function of the Fas ligand or receptor suggests that some autoimmune disorders could involve defects in the Fas- or TNF-signalling axes. The observation that the administration of TNF attenuates or prevents some autoimmune diseases in animals supports this view.

TNF may never prove useful in the treatment of widely disseminated cancer, but the insight into tumour-cell vulnerability gained through studies of TNF signal transduction may ultimately yield novel chemotherapeutic approaches.

The ways to block the biosynthesis or action of TNF could have important clinical applications. TNF has served as the principal end-point in most studies of endotoxin signal transduction. It is likely that drugs impairing each step of that process will soon be tested for anti-inflammatory efficacy. TNF and lymphotoxin-α can already be neutralised, and neutralisation of other members of the ligand family is being explored[80]. Thus, new and highly specific approaches to the treatment of inflammatory disease may soon become available.

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REVIEW ARTICLE

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Therapeutic Apheresis – A Clinical Spectrum

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Apheresis is a Greek word meaning "to separate" or "remove"[1]. Depending on the blood component being removed, it is called plasmapheresis (plasma), erythrocytopheresis (RBC), leukocytopheresis (WBC), thrombocytopheresis (platelets) stem cell apheresis or LDL apheresis (LDL). It can be performed on a normal individual or a diseased person (Table I).

Table I: Indications of apheresis

	Normal donor	Diseased individual
Erythrocytopheresis	Collection of RBC	Sickle cell anaemia, malaria, babesiosis
Leukocytopheresis	Collection of WBC	Leukemia
Thrombocytopheresis	Collection of platelets	Essential thrombocytosis
Plasmapheresis	Collection of immuno-globulin for hepatitis, etc.	Immune disorder, e.g., Myasthenia Gravis, Guillain Barré syndrome

Mechanism of action of plasmapheresis[2]

A. Removal of circulating pathologic factors like antibodies (anti-GBM disease), immune complexes (lupus nephritis), cryoglobulin (cryoglobulinaemia), myeloma protein (myeloma cast nephropathy), prothrombotic factors [haemolytic uraemic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP)].

B. Replacement of deficient plasma factor, e.g., antithrombotic or fibrinolytic factor in HUS/TTP.

C. Effect on immune system:

   1. Removal of complement products, e.g., lupus nephritis.
   2. Immune regulation, e.g., transplanted organs.
   3. Improvement in reticuloendothelial function, e.g., cryoglobulinaemia.

D. Stem cell recruitment from peripheral blood for stem cell transplant.

Techniques of apheresis

1. Centrifugation – Intermittent flow (IFC) and Continuous flow (CFC). It depends on the rate of settling of various blood components on centrifugation. In IFC, blood is removed from the body in small aliquots via a pump, processed by centrifugation, desired component removed and then returned into the body; while in CFC, large volume of blood is continuously processed and returned to the body. Table II shows the comparison between IFC and CFC[3].

2. Membrane filtration: Blood is passed over the membrane of definite pore size at the rate of 100 – 150 ml to obtain cell free plasma which can be returned to the patient body as such or again passed over another membrane of different pore size (called cascade filtration) to improve the selectivity of removal of blood component, (e.g., cryoglobulin), before returning to the patient's body. This avoids depletion of coagulation factor and decreases the requirement of replacement fluid. The procedure is complete in less than 2 hours and heparin is the anticoagulant used. The only disadvantage is that it cannot be used for collection of WBC/platelets[3,4].

Table II: Comparison of IFC and CFC.

	IFC	CFC
Advantages	1. Equipment is small and more mobile	1. Extracorporeal blood volume is small, so more suitable for children and elderly
	2. Single venipuncture site	2. Time requirement 1-3 Hrs.
Disadvantages	1. Extracorporeal blood volume larger, so more risk in children and elderly.	1. Equipment larger and less mobile.
	2. Time consumption 4 hrs as small aliquots of blood (225-375 ml) are being processed.	2. Single/double venipuncture sites

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Effective schedule of plasmapheresis (PP)

It is influenced by the volume of plasma exchanged, number of exchanges, rate of synthesis, and catabolism of pathologic components and its distribution in extravascular and intravascular compartment. IgM is removed more efficiently than IgG; as IgM is intravascular and IgG is extravascular. One plasma volume exchange (PVE) is equal to normal plasma volume of 35 – 40 ml/kg. One PVE decreases the unwanted plasma component to 30% of its initial value and second PVE decreases its concentration from 30% to 10% in the same sitting suggesting that two (PVEs) in one sitting are not more effective. Hence it is recommended to exchange 1 – 1.5 PV in one procedure[5].

Since large volume of plasma is removed during plasmapheresis, the procedure requires replacement fluid to maintain oncotic pressure and blood volume while there is no need of replacement fluid in cytopheresis where only 80 – 100 ml fluid volume is removed. The various replacement fluids available include normal saline, 5% albumin, fresh frozen plasma (FFP), and plasma protein fraction (PPF). When replacement fluid is plasma, plasmapheresis (PP) is called plasma exchange (PE), although the two terms are often used interchangeably.

Indication of therapeutic apheresis (TA)

The American Association of Blood Banks has classified the various diseases in different categories for TA on the basis of randomised controlled trials or anecdotal reports[6]. These are listed hereunder:

Category I: Diseases for which TA is standard or is a valuable first line adjunct based on well-defined randomised controlled trials or on a broad and non-controversial base of published experience.

Category II: Diseases for which TA is generally accepted but considered supportive to other definitive treatment.

Category III: Diseases in which there is suggestion of benefit but existing evidence is insufficient.

Category IV: Diseases in which controlled trials have not shown any benefit or anecdotal reports are discouraging.

Table III gives a summary of indications for therapeutic apheresis in various diseases.

Table III: Summary of various diseases according to category.

I	**For plasmapheresis**	
	A. Renal disease	**Category**
	Anti GBM RPGN	I
	Pauci-immune ANCA-mediated RPGN	II
	Haemolytic uraemic syndrome	III
	Renal transplant	
	Prevention of rejection	III
	Treatment of recurrent disease	III
	Hyperacute rejection	IV
	B. Metabolic disorders	
	Refsum disease	I
	Familial hypercholesterolaemia	II
	Acute hepatic failure	III
	Drug overdose/poisoning	III
	C. Neurologic diseases	
	AIDP	I
	CIDP	I
	Myasthenia Gravis	I
	Multiple sclerosis	
	Acute fulminant	II
	Relapsing/progressive	III
	Eaton-Lambert Syndrome	II
	Sydenhem chorea	II
	Paraneoplastic neurologic syndrome	III
	Polymyositis	III
	Stiffness syndrome	III
	Cryoglobulinaemia with peripheral neuropathy	II
	Multiple myeloma with peripheral neuropathy	III
	D. Haematologic diseases	
	TTP	I
	Post-transfusion purpura	I
	Multiple myeloma/paraproteinaemia	II
	Coagulation factor inhibitor	II
	Aplastic anaemia	II
	Red cell alloantibody with haemolytic disease of newborn	III
	Platelet isoimmunisation	III
	E. Immunologic diseases	
	Cryoglobulinaemia	II
	Raynaud phenomenon	II
	Vasculitis	III
	Autoimmune haemolytic anaemia	III
	SLE	III
	Progressive systemic sclerosis	III
II	**For cytopheresis**	
	1 Red cell exchange	
	Sickle cell disease	I
	Polycythaemia vera	II
	Secondary erythrocytosis	II
	Haemochromatosis	II
	Malaria/Babesiosis	III
	2 Leukocytopheresis – extreme leukocytosis	I
	3 Thrombocytopheresis – extreme thrombocytosis	I
	4 Lymphocytopheresis – Rheumatoid arthritis	II

Brief account of TA in various disorders

I Renal diseases

i. Anti-GBM disease (Cat. I): TPP was established as a therapeutic modality for anti-GBM disease by Lockwood *et al*. It acts by removing pathogenic anti-GBM antibodies (Ab). It is combined with short-term immunosuppressants (azathioprine + cyclophosphamide) and high dose corticosteroids for suppression of Ab synthesis[7,8]. It should be initiated early before onset of severe renal failure and/or life-threatening pulmonary haemorrhage. It is given for 2 weeks[9] and total of 4 L of plasma is exchanged. Recovery of renal function depends on the value of serum creatinine of less than 5 mg% and less than 50% of crescents on renal biopsy.

ii. Pauci-immune ANCA mediated RPGN (Cat. II): TPP is indicated in severe renal failure dialysis dependency and pulmonary haemorrhage[10]. In presence of pulmonary haemorrhage or recent renal biopsy, replacement fluid should be FFP to avoid dilutional coagulopathy.

iii. Haemolytic uraemic syndrome (Cat. III): Most of the studies of TTP in HUS found TPE of no benefit[11,12], but a few studies recommend PE of 1 – 1.5 PV until platelet counts become more than 1.5 l/cumm[13,14].

iv. Renal transplant:

- Prevention of renal transplant rejection (Cat III): TPP has been tried prior to transplantation in presensitised patients with high titres of Ab detected at one/two HLA antigens to decrease antibody levels[15].
- Recurrent disease in transplanted kidney (Cat. III): Focal segmental glomerulosclerosis (FSGS) recurs in 30% of allograft[16]. Controlled studies do not support use of TPP but a few studies have demonstrated a decrease in proteinuria and improvement in renal function when TPP is initiated early with cyclophosphamide or cyclosporine[17,18].

II Metabolic diseases

i. Refsum disease (Cat. I): TPP decreases phytanic acid levels and improves polyneuropathy, icthyosis, ataxia and cardiac dysfunction in Refsum disease[19-21].

ii. Familial hypercholesterolaemia (Cat. II): TPP is indicated in heterozygous patients inadequately controlled with maximum drug therapy. It is done every other week using 1.5 PVE[22].

LDL apheresis falls in category I because of its selective removal of LDL and lack of requirement for replacement fluid. About 2 – 5 L of plasma volume is exchanged in this procedure[23,24].

iii. Acute hepatic failure (AHF) – (Cat. III) : Several studies suggest that TPP improves bilirubin, coagulopathy, and hepatic encephalopathy in AHF[25,26], but Saibara *et al* reported that TPP decreases hepatocyte regeneration by decreasing ketones and worsens hepatic encephalopathy[27].

iv. Drug overdose: TPP is useful in removing protein bound drugs and toxins with small volume of distribution, e.g., methylparathion[28], vincristine[29], L-thyroxine[30], cisplatin[31], sodium chlorate, acetic acid, carbamazepine, theophylline, verapamil, and diltiazem.

III Neurologic diseases:

i. Acute inflammatory demyelinating poly-neuropathy (AIDP); (Cat. I): Two large randomised controlled multicentre trials in AIDP found TPP to be superior to control groups[32,33].

In TPE/Sandoglobulin GBS (Guillain Barré syndrome) trial group, TPE, intravenous immunoglobulin (IVIG), and TPE followed by IVIG were compared in a total of 383 patients of AIDP and no difference was found in the three groups[34].

TPE is initiated within 14 days of onset of neurologic symptoms[34]. 250 ml/kg of plasma is exchanged over 8 – 13 days in 5 to 6 sittings. 10% of patients treated with TPE/IVIG may relapse at a median of 6 – 21 days of treatment, relapse being

more common in patients in whom TPE is complete before the completion of active phase of the disease[35].

i. Chronic inflammatory demyelinating polyneuropathy (CIDP); (Cat. 1): TPE is most effective in demyelinating variant than axonal form[36]. 40 – 60 ml/kg of plasma is exchanged for 4 – 6 times in first 2 weeks and then 1 – 2 PE is done weekly for maximum response. Initial response to TPP may occur during first week of therapy and may plateau by the end of 4 weeks. Patients with a relapsing course may deteriorate within 2 weeks of cessation of TPP.

ii. Myasthenia Gravis (MG); (Cat. 1): No significant difference was found on comparison of TPE and IVIG in MG. But TPE combined with immunosuppression produces significant improvement as evident from studies of Dau *et al*[37] and Behan *et al*[38].

TPE is indicated in acute severe MG, post-thymectomy myasthenic crisis, preparation of patient for thymectomy, and as an adjunct to immunosuppression[39–41]. One to two litre plasma volume is exchanged on alternate days for 5 – 6 exchanges to decrease Ab titres by 85%.

Selective absorption of anti-acetylcholine receptor Ab (Anti-ACRAb) as an alternative to TPE is an effective option[42]. But it is less effective in removing non-IgG humoral factors and is ineffective in AchR Ab negative MG[43].

iv. Eaton-Lambert syndrome (Cat. II): TPP is indicated as an adjunct in patients whose neurological deficit is severe or who are unable to wait for effects of immunosuppressants or aminopyridine drugs[44]. In separate studies of Dau[45] and Newson *et al*[46], they found TPP combined with immunosuppression to be more effective than TPP alone. 1 – 1.25 PV is exchanged daily or for 5 days a week for 2 – 3 weeks until clinical and electromyographic response is obtained.

v. Multiple sclerosis (MS): Meta-analysis involving 4 randomised and 2 observational studies in chronic progressive MS involving treatment with immunosuppressants with/without TPP found a statistically significant difference in the TPP group[47].

TPP with immunosuppressants is also effective in treatment of acute exacerbation of MS not responding to intravenous corticosteroids. 1 – 1.5 PV exchanges are done on alternate days for two weeks followed by semi-weekly or weekly PVE for six weeks.

In chronic progressive MS, TPP is done for 20 weeks in combination with oral cyclophosphamide and prednisolone. IVIG after TPP has added long-term benefit, but it is not considered a standard treatment presently.

IV. Haematologic and oncologic disorders

i. TTP (Cat. I): In TTP, TPE is performed daily until platelet count becomes more than 1,50,000/cumm, serum LDH normalises, haemoglobin increases, and neurologic symptoms resolve. Then it is tapered gradually by increasing the interval between exchanges or decreasing the volume of plasma exchanged to assess the durability of response. Detection of ultra-long von Willebrand factor multimers in blood accurately predicts the subsequent recurrence of TTP[48]. A rise in platelet count and decrease in serum LDH three days after plasma exchange is a useful predictor of survival[49]. The delay in initiating TPE, presence of stupor/coma and high creatinine levels at the beginning predicts greater likelihood of treatment failure[50].

Generally, one plasma volume is exchanged and can be done twice daily in patients who do not respond or deteriorate on daily treatment or are unable to tolerate single large volume exchange.

The replacement fluid of choice in TPP is FFP as it replaces the labile inhibitor of platelet aggregation[1].

ii. Post-transfusion purpura (PTP); (Cat. I): IVIG is preferred over TPE in PTP. However, TPE is performed in bleeding patients to immediately

control haemorrhage and thrombocytopenia and who fail to respond to IVIG. Most studies report resolution in bleeding and increase in platelet count within 24 – 48 hrs after first procedure[51,52]. Usually a single procedure of TPE is curative, but 2 or 3 sessions may be required in some cases.

iii. Coagulation factor inhibitor: TPE decreases titres of inhibitors of factor VIII, V, X and thrombin[53] in patients with uncontrolled haemorrhage, preparing for surgery and render the patient responsive to porcine factor VIII in the presence of factor VIII inhibitor[54]. Some reports suggest that combined use of TPE and immunosuppression in severely affected patients with autoimmune inhibitor is quite beneficial[57].

iv. Myeloma and paraproteinaemia: Two randomised controlled trials support use of TPE over haemodialysis in removal of light chains in case of renal failure complicating multiple myeloma[56].

In hyperviscocity syndrome due to multiple myeloma or other paraproteinaemia, TPE is done daily or thrice weekly, end-points being serum creatinine, blood urea nitrogen, creatinine clearance, serum calcium, protein, and albumin.

v Sickle cell disease: Red cell exchange is indicated for infarctive crisis of stroke[57], acute chest syndrome[57], priapism[58], retinal infarct[59], hepatopathy[60], prior to surgery[61,62] when sickle haemoglobin of less than 30% is required.

vi. Malaria and babesiosis: Red cell exchange is an important adjunct in severely ill patients with high levels of parasitaemia, haemolysis, or respiratory failure, and can be combined with TPE in such severe cases[63,64].

vii. Polycythaemia vera (PCV) and secondary erythrocytosis: Erythrocytopheresis in PCV is done to maintain haematocrit (Hct) less than 60% to urgently control symptoms of hyperviscosity, haemorrhage, thrombin, or congestive heart failure[65] due to haematocrit of more than 60%.

In secondary erythrocytosis, it is done in symptomatic patients only to relieve symptoms by decreasing haematocrit to 55 – 65%. In asymptomatic patients, it has no role even if haematocrit is more than 60%.

viii. Extreme leukocytosis and thrombocytosis: Therapeutic leukapheresis and thrombocytopheresis is beneficial in patients having organ dysfunction (neurological/pulmonary) when total leukocyte count is more than 100 to 10^9/l with high percentage of blasts and promyelocytes (50 – 100x10^9/l) or platelet count is more than 1,000 x 10^9/l[66].

Therapeutic leukapheresis is also indicated in hyperviscosity syndrome in children with leukaemia[67], chronic myeloid/lymphoid leukaemia (CML/CLL)[68,69], CML during pregnancy to protect foetus from teratogenic effects of chemotherapy[70] and prevention of retinoic acid syndrome in acute promyelocytic leukaemia[71].

Complications of plasmapheresis

The incidence of adverse reactions ranges from 1.6% to 25% and severe reactions range from 0.5 – 3.1%. Mortality is mostly due to cardiorespiratory causes[72]. The different complications an listed in Table IV.

Table IV: Complications.

1. Vascular access related like phlebitis, haematoma, nerve compression.
2. Volume alteration leading to hypotension, hypertension, pulmonary oedema, vasovagal reaction.
3. Citrate related – Hypocalcaemia, tetany, arryhthmia, metabolic alkalosis.
4. Heparin – bleeding.
5. Anaphylaxis.
6. Sepsis.
7. Anaemia (Hb decreases by 20%).
8. Thrombocytopenia (decrease by 30%).
9. Hypofibrinogenaemia (decrease by 50%).
10. Haemolysis[3].
11. Cholinergic crisis in cholinesterase deficient patient[73].
12. Foamy macrophage syndrome of hydroxyl ethyl starch as replacement fluid.

Summary

Therapeutic apheresis has came a long way from a crude procedure of blood letting to a well-refined technique via use of centrifugation and membrane filtration. It has become a therapeutic modality of first choice for diseases like anti-GBM type RPGN. Refsum disease, AIDP, CIDP, MG, TTP, Posttransfusion purpura, etc. But in other diseases, its role is not well supported by the randomised controlled clinical trials despite the disease being immune mediated. Therefore, further studies are warranted in other diseases to establish the role of TPE in these disorders. Although it is associated with various complications, the incidence of severe reactions is just 0.5 – 3.1%.

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CASE REPORT

JIACM 2007; 8(3) : 240-1

Oral Tadalafil in the Management of Primary Pulmonary Hypertension

*NS Neki**

Abstract

Pulmonary arterial hypertension (PAH) is a life threatening disease with a grave prognosis. Various vasodilators like bosentan, epoprostenol, iloprost as well as sildenafil, tadalafil and vardenafil have a definite role in PAH. They are now emerging as promising therapies. Tadalafil – like sildenafil – is a selective phosphodiesterase (PDE) inhibitor with a longer duration of action. It leads to stabilisation of cyclic guanosine monophosphate (C-GMP) resulting in increase in nitric oxide (NO) at the tissue level ultimately leading to pulmonary artery vasodilatation. A case of severe pulmonary artery hypertension managed safely and effectively with tadalafil is being reported here.

Keywords: Pulmonary artery hypertension, Tadalafil.

Introduction

Pulmonary arterial hypertension (PAH) includes primary pulmonary hypertension (PPH) with no apparent cause, PAH secondary to congenital shunt lesions, connective tissue disorders, portal hypertension, drug-induced as well as HIV related PAH. It is a progressive disease that predominantly affects women in early life and is characterised by progressive dyspnoea, exertion limitation, frequent failure of right ventricle. Severe PAH, whether primary or secondary, causes management problems. Although many treatment modalities are available, there is no known cure and if untreated, results in the life expectancy of less than a year[1, 2]. The current management strategies for PPH include anticoagulants, calcium- channel blockers, epoprostenol (prostacycline), iloprost, beraprost, bosentan and sildenafil[3]. Sildenafil, a selective PDE-5 inhibitor, is a potent pulmonary vasodilator and is effective in patients of moderate to severe PH[4]. Tadalafil – like sildenafil – is a selective PDE-5 inhibitor with a longer duration of action.

Case report

A 35-year-old male presented to us with worsening exertional dyspnoea (NYHA Class III) and increasing fatigue for the last 2 years. He was non-diabetic and non-hypertensive and was unable to cycle for 100 yards. He had swelling of face and feet for the last 2 months with no history of orthopnoea, syncope, and hemoptysis. He denied history of joint pains in the past as well as in the family members. There was no history of exposure to chemicals, appetite suppressants or collagen vascular disease. On physical examination, he was moderately built, pulse-115/min, regular, BP-102/60 mmHg, JVP increased with marked a and v waves. There was no cyanosis or clubbing of fingers/toes but had marked edema on both feet. CVS examination suggested right parasternal heave and signs of tricuspid regurgitation (TR). An ejection systolic murmur in the pulmonary area and right ventricular S3 gallop was also heard. Auscultation of chest revealed occasional crepitations and rhonchi. The laboratory investigations were within normal limit including total collagen profile, liver and kidney parameters and patient was HIV negative. ECG was suggestive of sinus tachycardia, P-pulmonale, right ventricular hypertrophy with strain pattern, and right axis deviation suggestive of pulmonary hypertension. Chest X-ray showed enlargement of right heart with dilatation of main pulmonary artery. Echocardiography revealed dilatation of chambers of right heart, and main pulmonary artery. Lung functions study demonstrated mild airflow obstruction. Doppler echocardiography showed evidence of TR and PAH. The estimated systolic pulmonary artery pressure was 98 mmHg and right atrial pressure of 21 mmHg. Left ventricular systolic function was unaltered. The patient was put on digoxin, diuretics, warfarin (anticoagulant) and tadalafil in the dose of 10 mg orally once daily, which was well tolerated, gradually titrated to maintenance dose of 30 mg/day with no adverse effects. The patient showed

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progressive improvement over the next 2 months of therapy. When followed-up at 3 months, he was able to cycle 300 yards (NHYA class II) comfortably and his repeat echocardiography demonstrated a significant reduction in systolic PA pressure from previous 98 mmHg at the time of presentation to 76 mmHg after treatment.

Discussion

PPH is characterised by progressive rise of mean pulmonary artery pressure (PAP) more than 25 mmHg at rest, right ventricular failure, and death[2]. Current therapeutic options for PPH mostly include limitation of physical activity, long-term anticoagulation and vasodilators. Calcium-channel antagonists are the mainstay of treatment but only 25 – 30% of patients respond. However, the major advancement in the treatment of PPH is use of selective PDE-5 inhibitors- namely sildenafil, tadalafil, and vardenafil. Tadalafil, an analogue of sildenafil, induces smooth muscle relaxation via a nitric oxide-dependent increase in C-GMP[5]. Tadalafil has a long half-life of 36 hours with similar adverse effect profile as that of sildenafil. However, it is generally safe and well tolerated even in men with erectile dysfunction[6]. The efficacy and safety profile of tadalafil in the management of severe PAH has also been reported earlier[7].

Conclusion

Tadalafil – like sildenafil – is effective, safe, and well tolerated in the management of PAH. It is easy to administer (oral form), has low incidence of side-effects, and is much cheaper when compared to many other treatment options including continuous prostacycline infusion and heart lung transplantation which are limited by non-availability in many parts of the world, clinical difficulties, complications, and high costs[8].

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CASE REPORT

JIACM 2007; 8(3): 242-4

Recurrent Pneumonitis due to Tracheobronchial Foreign Body in an Adult

Amritpal Singh, Maninder Kaur***

Aspiration of foreign bodies into the bronchial tree is frequently seen in children but is rare in adults and usually foreign bodies are of long standing and there is lack of any history of any foreign body aspiration. Occult foreign bodies can remain undetected for months to years and often are misdiagnosed[2]. Foreign body aspiration can present in a variety of ways, ranging from no or trivial symptoms to irreversible damage to the lung which may be life-threatening. A high index of suspicion is necessary for diagnosing tracheo-bronchial foreign body[1]. We present a case of bony tracheo-bronchial foreign body diagnosed by CT and removed by bronchoscopy.

Case

A male patient, aged 50 years, presented to clinician for repeated attacks of productive cough for the last 13 years. He had received many courses of antibiotics but symptoms used to recur after some time. The personal history revealed that he liked to take his alcoholic beverage alongwith mutton. He did not give any history of foreign body aspiration. He was referred to our department for computed tomography of the chest.

His chest x-ray, which was done at some other hospital, was showing emphysematous changes in the left lung.

CT chest revealed a hyperdense lesion of size 19.2 x 17.4 x 12.2 mms in the left lower lobe bronchus at its opening. It was completely occluding it alongwith collapse of the left lower lobe. Other findings were emphysematous changes in the left upper lobe.

Virtual bronchoscopy also showed an intraluminal lesion completely occluding the left lower lobe bronchus. So a suggestion of foreign body in the left lower lobe with collapse of the left lower lobe with emphysematous changes in the rest of the left lung was given. Patient then underwent bronchoscopy whereupon, a bony foreign body was observed in the left lower bronchus with granulation tissue. It was removed and on examination it was found to be a bony piece (hemivertebra of the goat).

Discussion

Aspiration of foreign bodies into tracheo-bronchial tree is infrequently seen in adults. Foreign body aspiration in adults is more common in the setting of advanced age, underlying neurological disorder, poor dentition, alcohol consumption, and sedative use. Aspiration of organic material such as nuts, seeds, vegetable, and bone have been described in adults[1].

Tracheo-bronchial foreign body should be taken into consideration in the differential diagnosis of radiographic lesions or chronic respiratory symptoms or repeated pneumonias that are poorly explained, even in the absence of previous history of aspiration. A high index of clinical suspicion is necessary to diagnose a foreign body[1, 2]. Since computed tomography is often used to evaluate various respiratory problems in adults, it may be the first imaging modality to discover an unsuspected aspirated foreign body in the bronchial tree[4].

Chest roentgenogram has poor sensitivity in diagnosing foreign body as most of the foreign bodies in adults are not radiopaque. However, it can show secondary findings like repeated pneumonia of a particular lobe, atelectasis, compensatory emphysematous changes, and bronchiectasis. On computed tomography, endobronchial foreign bodies appear as dense structures/soft tissue lesions within the bronchial lumen. Associated findings are volume loss, hyperlucency with air trapping, and bronchiectasis in the affected lobe[4].

Now a days virtual bronchoscopy can be done by re-construction of data acquired for chest CT. Virtual broncoscopy helps in diagnosing the site of foreign body,

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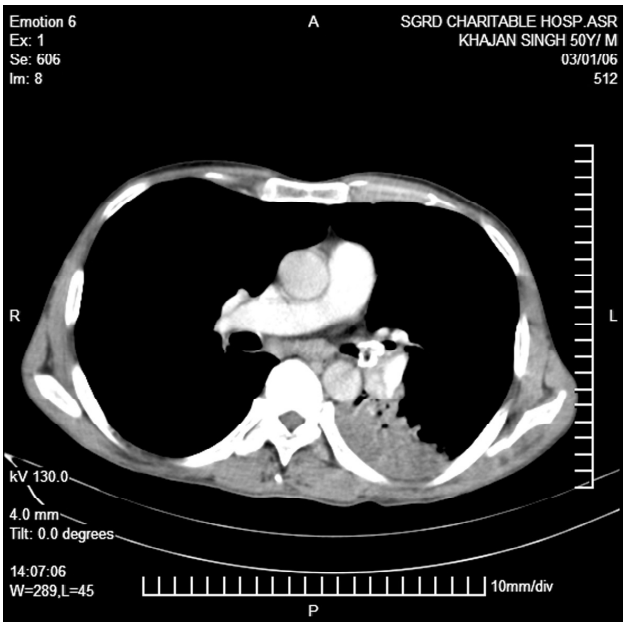

Fig. 1: *CT thorax showing a hyperdense lesion (foreign body) occluding the left lower main bronchus with collapse/consolidation of the left lower lobe.*

especially in major bronchi, with an intraluminal view of the foreign body. It also helps in better patient management as it helps in targeting the therapeutic bronchoscopy to the suspected bronchus and thus reducing the time for the procedure[6]. Broncoscopy is the gold standard for diagnosing tracheo-bronchial foreign body. Bronchoscopic findings are classified into three groups: a) foreign body in the bronchial

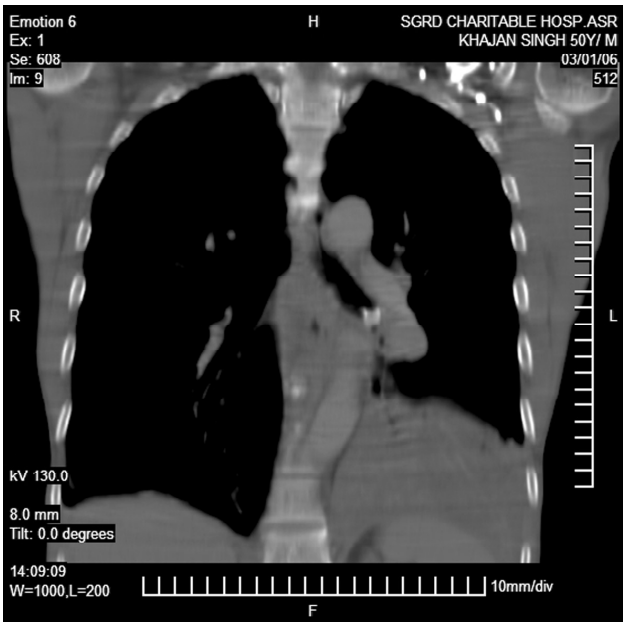

Fig. 2: *Findings of Fig. 1 in coronal CT image.*

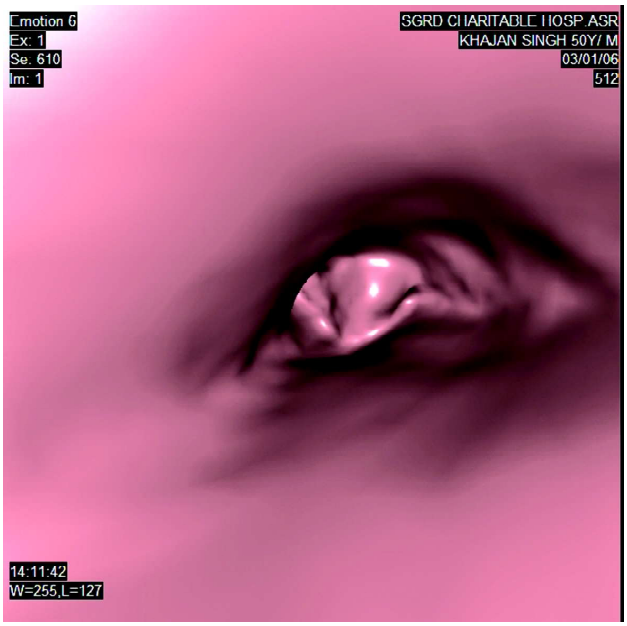

Fig. 3: *Virtual bronchoscopy image showing occlusion of the left lower lobe bronchus by the foreign body.*

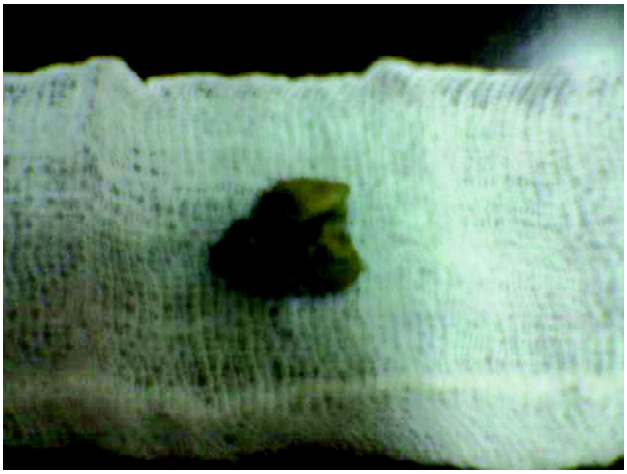

Fig. 4: *Foreign body after removal by the bronchoscope.*

tree without granulation tissue; b) foreign body in the bronchial tree with marked granulation tissue; c) foreign body embedded in the granulation tissue[3].

It is important for clinicians to maintain a high level of suspicion for diagnosing tracheo-bronchial foreign body because once diagnosed and removed, the improvement in symptoms is usually dramatic and rewarding[1, 5].

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CASE REPORT

JIAOM 2007; 8(3) : 245-6

Apert Syndrome: A Rare Presentation

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Abstract

Apert syndrome (acrocephalosyndactyly) is a rare congenital disorder characterised by craniosynostosis, mid-facial malformation and symmetrical syndactyly. We present a 7-year-old female having all the features of classical Apert syndrome.

Keywords: Apert, Syndactyly, Craniosynostosis.

Introduction

Apert syndrome (acrocephalosyndactyly) is a congenital disorder characterised primarily by craniosynostosis, mid-face hypoplasia, and syndactyly of the hands and feet with a tendency for fusion of bony structures[1]. Craniosynostosis (or craniostenosis) is defined as premature closure of the cranial sutures producing deformity of the skull. It may be primary, originating from a sutural pathology, or secondary resulting from dysgenesis of the underlying brain. It has been described in various syndromes like Apert, Crouzon, Pfeiffer and Jackson-Weiss, and is associated with specific systemic anomalies[2]. We present a 7-year-old girl with all the features of Apert syndrome.

Case report

A seven-year-old girl presented with the complaints of abnormal shape of the head, webbed fingers, and developmental delay. On examination, the baby was found to have flattened occiput with frontal prominence, abnormal contour of the head (brachycephaly), shallow orbits with bilateral proptosis, hypertelorism, depressed nasal bridge, hypoplastic maxillae, low set ears, and dental anomalies (Fig. 1). She had symmetrical syndactyly with complete fusion of all the five digits of both hands and both feet (Fig. 2). The fused fingers and toes had separate nails. There was no other apparent congenital malformation, and systemic examination revealed no other abnormality. On investigation, X-ray of the spine, abdominal ultrasonography, and echocardiography were normal. Radiographs of both hands and feet showed soft tissue syndactyly of all the digits and toes. Skull radiographs revealed fused coronal sutures, brachycephalic skull contour, elongated flat forehead with bitemporal widening, increased convolutional markings suggestive of increased intracranial pressure and hypertelorism. All findings were diagnostic of Acrocephalosyndactyly or Apert syndrome.

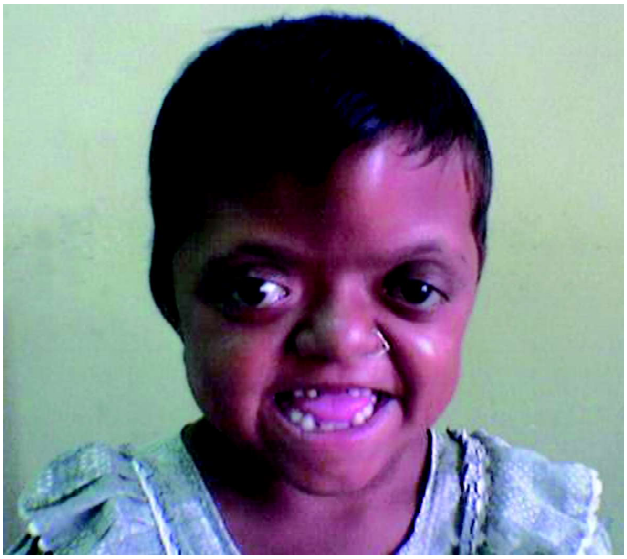

Fig. 1: *Characteristic features of Apert syndrome showing ocular hypertelorism, proptotic eyes, depressed nasal bridge, and short wide nose with bulbous tip are seen in this seven-year-old girl.*

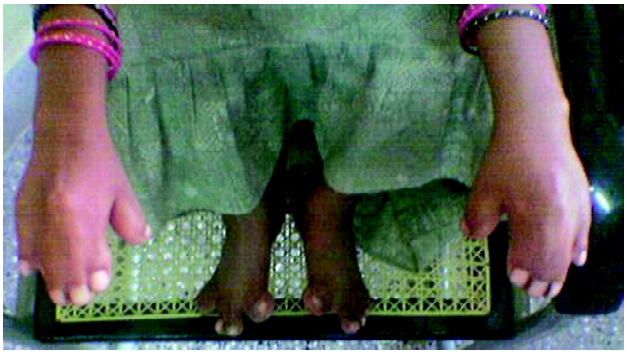

Fig. 2: *Same child with mitten appearance of the hands with syndactyly and sock-like appearance of the feet with syndactyly.*

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Discussion

Apert syndrome was first described by Eugene Apert in the year 1906. He described a triad of craniosynostosis, syndactyly, and maxillary hypoplasia. The incidence of Apert syndrome is approximately one in 50,000 births[3]. More than 98% of cases with Apert syndrome are caused by specific missense substitution mutations, involving adjacent amino acids (i.e., Ser252Trp, Ser252Phe, Pro253Arg) in the linker between the second and third extracellular immunoglobulin domains of *FGFR2*, which maps to chromosome bands 10q25 - q26. The remaining cases are due to Alu-element insertion mutations in or near exon 9 of *FGFR2*. The majority of cases are sporadic, resulting from new mutations with a paternal age effect[4]. Apert syndrome is thought to occur as a result of androgen end-organ hyper-response affecting the epiphyses and sebaceous glands. This results in early epiphyseal fusion resulting in short stature, short and fused digits, and acrocephaly[5].

In Apert syndrome, the cranial vault deformity is variable, but most often presents as a short anteroposterior dimension with craniosynostosis involving the coronal sutures resulting in a turribrachycephalic skull. The typical craniofacial appearance includes a flat, elongated forehead with bitemporal widening and occipital flattening. There is also mid-face hypoplasia accompanied by orbital proptosis, downslanting palpebral fissures and hypertelorism. High arched palate, clefts of the secondary palate, and crowding of the dental arch can also be seen. The nose is down-turned at the tip, the bridge is depressed, and the septum deviated[6]. Other central nervous system abnormalities include malformations of the corpus callosum, the limbic structures, or both, megalencephaly, gyral abnormalities, encephalocoele, pyramidal tract abnormalities, hypoplasia of cerebral white matter and heterotopic gray matter. There is also an increased incidence of delayed mental development in these children, but many of them develop normal intelligence[7]. The usual hand abnormality in Apert syndrome consists of a bony fusion of the second, third, and fourth fingers, with a single common nail. Involvement of the first or fifth digits in this bony mass is variable. There can be a similar deformity involving the foot (mitten hand and sock foot). Other skeletal abnormalities have been described in Apert syndrome. These include limited mobility at glenohumeral joint and elbow joint, multiple epiphyseal dysplasia, very short or absent neck of scapula, small capitulum, and flat radial head[8]. Commonly associated systemic features include cardiac anomalies, visual and hearing defects, cleft palate and varying degrees of acne. Acne is usually severe, extensive, and resistant to treatment. Skin, eyes, and hair may show pigmentary dilution. Other cutaneous abnormalities reported are hyperhidrosis and oculocutaneous albinism[9]. Psychological counselling should include attachment and interaction with peers. Genetic counselling is an important factor. Recurrence risk for an affected individual to have an affected offspring is 50%. Treatment involves multidisciplinary teamwork including craniofacial surgeon, neurosurgeon, pediatrician, speech pathologist, and an orthodontist. Surgical care involves early release of the coronal suture and fronto-orbital advancement and reshaping to reduce dysmorphic and unwanted skull growth changes. Craniosynostosis requires multistaged operative procedures. Surgical separation of digits (mitten-glove syndactyly) provides relatively little functional improvement.

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CASE REPORT

JIACM 2007; 8(3) : 247-9

Subacute Sclerosing Panencephalitis

Sanjeev Verma, Dinesh Srivastava***, Pushpa Yadav**, SC Sharma****

Abstract

Subacute Sclerosing Panencephalitis (SSPE) is a progressive inflammatory disease of the central nervous system with poor prognosis and high mortality. No treatment has a proven curative role. We report a case of subacute sclerosing panencephalitis.

Introduction

Subacute sclerosing panencephalitis (SSPE) is a progressive inflammatory disease of the central nervous system caused by a persistent, aberrant measles virus infection. In India, the incidence is very high (21 per million population), because of higher population of measles cases in children, more frequent subclinical measles virus infection, and perhaps, higher population of the total population below 2 years of age[1, 2]. The clinical course in SSPE is slowly progressive with death occurring within 3 years. Ten per cent of cases show either a fulminant or prolonged course of the disease[2].

Case report

A previously healthy 17-year-old female presented to the medical OPD, with history of abnormal movements of right half of the body including face (Fig. 1 and 2) with difficulty in speaking since the last 6 – 7 months. The patient gradually started getting difficulty in carrying-out routine activities, e.g., difficulty in reading and writing; her performance in school started declining, and she started to have memory lapses, particularly for recent events. On further questioning, her father revealed that she had measles in the childhood, i.e., 10 – 12 years ago. Her birth milestones were normal and she was not immunised. Family history was not significant.

On examination, she was afebrile, pulse rate – 80 beats per minute, good volume, regular. Blood pressure – 110/74 mmHg, right arm supine position. There was no pallor, cyanosis, icterus, clubbing, or lymphadenopathy.

The systemic examination of CNS: higher mental function examination revealed recent memory lapse. Cranial nerves were not affected. Muscles were of normal size with increased tone. Superficial reflexes were normal; however, deep tendon reflexes were exaggerated in both upper and lower limbs on each side There were sudden rapid jerking movements of the right half of the body. The right plantar response was extensor and the left plantar response was flexor. Sensory system was normal. Skull and spine were normal. Gait could not be tested. Fundus examination was normal bilaterally.

A clinical diagnosis of chorea was made and the following investigations were done:

Haemoglobin – 13.6 gm%, TLC – 7200/mm^3, DLC – P 70% L 30%, ESR – 02 mm/1st hour

The renal and liver function tests, serum electrolytes, blood sugar, serum calcium and phosphorus, TSH were all normal.

CSF examination was normal.

The X-ray Chest (PA View), ECG were normal.

The serum level of measles antibody titre were raised.

The MRI (Brain) was normal.

The EEG – Demonstrated higher amplitude slow and sharp waves that recurred at intervals of three seconds on a slow background, which supported the diagnosis of SSPE.

A final diagnosis of subacute sclerosing panencephalitis was made and patient was started on carbamazepine and clonazepam. The patient's condition had improved significantly at the time of discharge from the hospital.

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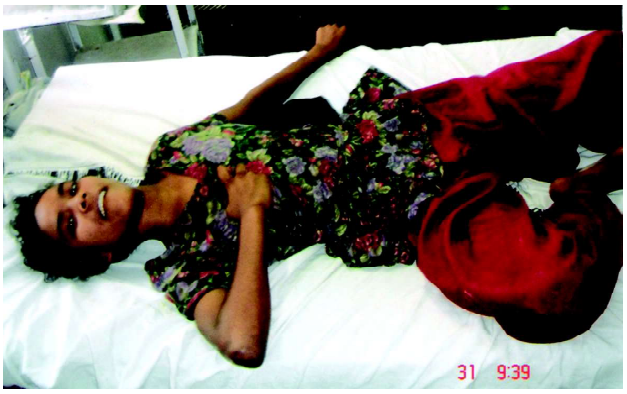

Fig. 1

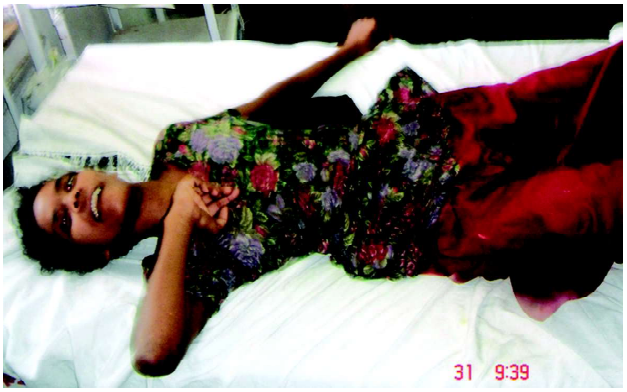

Fig. 2

Discussion

Diagnosis of SSPE requires the fulfillment of at least three of the following five criteria[3]:

i. A typical progressive subacute mental deterioration with signs of myoclonus.

ii. Characteristic EEG changes (high amplitude slow and sharp waves occurring with slow background).

iii. Elevated CSF globulin levels greater than 20% of total CSF protein.

iv. Raised titres of measles antibodies in blood and CSF, and

v. Typical histopathological findings in brain biopsy or autopsy.

The disease predominantaly affects children and adolescents (between the age group 2 – 24 year)[1, 2]. However, Bouchard *et al*, reported SSPE in higher age group male (49 years) with clinical, laboratory, and pathological findings of SSPE[4].

Gupta *et al*, reported myoclonus, cognitive disorder, and visual disturbance in a 22-year-old female patient, who had a history of measles in childhood[5].

In a series of 65 patients between the age group of 2 to 24 years, Khare *et al*, reported SSPE without any history of measles vaccination. Alexander *et al*, also reported a case of myoclonic jerks, spasticity, and dystonic posture of right upper limb with generalised seizures in a 17-year-old male who neither had measles in childhood nor was immunised against it[6].

The present case had myoclonus, cognitive disorder and loss of memory. There was history of measles infection in childhood which fulfills three out of five criteria laid down by Dyken[3]. These findings are similar to cases reported by earlier workers[5], with additional findings of memory changes[7].

Anlar *et al*, suggested CT scan and MRI head to correlate clinical and radiological changes and assess the progression of the disease[8]. Alexander *et al*, reported normal-to-slight cerebral oedema in the early stage and bilateral symmetrical or asymmetrical low density enhancing or non-enhancing lesions in grey and white matter of cerebrum in the later stages of the disease[6]. While Brismar *et al* showed multiple areas of enhancement with rapid clinical progression[9].

Contrary to the above findings, Alpay *et al* reported clinical stages of SSPE are not correlated to MR imaging and MRI remains normal in early stage of the disease and in severe disease as well[10].

Our case had a normal MRI head scan similar to the observation of Alpay *et al*[10].

Various authors (Alexander *et al*[6], Gupta[5] and Del Toro – Riera *et al*[11]) treated these patients with different combinations of medicines including intrathecal interferon, isoprinosine, ribavarin, carbamazepine, clonazepam, sodium valproate, and trihexyphenidyl; but the clinical deterioration stabilised briefly and temporarily, possibly due to the fact that virus is not eliminated with available antiviral treatment.

Our patient too stabilised symptomatically initially after over a month of treatment with carbamazepine and clonazepam.

However, these patients need further evaluation by CSF serology for follow-up to define the treatment.

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TRICLAZONE

CASE REPORT

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Megalencephalic Leukoencephalopathy with Subcortical Cyst

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Abstract

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare disease seen in India in patient mainly belonging to the Aggarwal community. It is characterised by macrocephaly and early onset white matter degeneration. A case diagnosed to have this disease is being reported.

Key words: Macrocephaly, Megalencephalic leukoencephalopathy, Subcortical cysts, White matter degeneration.

Introduction

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), is characterised by early-onset macrocephaly with mild motor developmental delay and seizures, gradual onset of ataxia, spasticity, and sometimes extrapyramidal findings, and usually late onset of mild mental deterioration. Macrocephaly is present at birth or develops during the first year of life. The gene locus for this autosomal recessive disease has been assigned to chromosome 22qtel, and a gene has been identified – presently called MLC[1, 2, 3]. It is characterised clinically by a large head and mild neurological symptoms.

Case report

A 13-year-old girl, 2nd of 3 siblings belonging to Bansal-Aggarwal community born of non-consanguinous marriage presented with large head, delayed mental and motor milestones, and unsteadiness of gait. There was no history of seizures or myoclonic jerks. Family history was negative. Examination revealed short stature, macrocrania (head circumference exceeding the 95th percentile), mild cognitive impairment, no cranial nerve deficits, bilateral pyramidal signs in the form of brisk DTRs and extensor plantar responses and ataxic gait.

MRI of Brain (T1, FLAIR, TSE, and T2W images) showed diffuse altered white matter signal intensities appearing hypointense on T1W, IR and hyperintense on FLAIR and T2W, most marked in fronto-parietal regions. In addition, small well-defined fluid attenuating lesions were noted in bilateral anterior temporal lobes (Figs.1 – 4). There was sparing of internal capsule. The MRI of lumbar spine showed transitional vertebra at lumbo-sacral junction with sacralised L5 segment.

MR spectroscopic traces showed relatively preserved and slightly lower NAA and mildly elevated choline on TE of 270 ms. Motor and sensory nerve conduction studies (CP, PT, and sural) were within normal limits. DNA sample of proband, mother and father analysed for mutation on MLC1 gene showed heterozygous for mutation in exon 2 confirming the diagnosis of MLC.

Discussion

Megalencephalic leukoencephalopathy with subcortical cysts was first described by van der Knaap *et al* in 1995[1]. MLC is a rare disease with a low carrier rate. The disease has a high incidence in populations in which consanguinity is common[2 - 4].

MLC is an autosomal recessive disorder due to mutations in MLC1 gene[5] which has its locus in chr22qtel. The physiological function of the protein is at present unknown. It is probably an integral membrane protein.

The diagnosis of MLC can be made with confidence in patients with typical clinical findings and characteristic abnormalities on cranial MRI. Macrocephaly is present at birth or, more commonly, develops within the first year of life in all patients. Early development is normal or mildly delayed. Most children achieve independence in walking. Slow deterioration of motor functions with cerebellar ataxia and mild spasticity usually starts in early childhood. The majority of the patients become wheelchair dependent in their teens. Some patients have

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extrapyramidal movement abnormalities with dystonia and athetosis, usually as a late finding. Mental decline occurs later and is much milder than motor decline. Most patients have epileptic seizures.

The typical MRI findings are present from about 6 months, maybe even before that. In typical cases, MRI findings are sufficient for the diagnosis of MLC. The MRI abnormalities that are characteristic of the disease are the discrepant severity in comparison with the clinical picture, the aspect of white matter abnormalities (diffuse homogeneous abnormality with swelling), the distribution of the abnormalities (supratentorial hemispherical white matter involvement with relative sparing of, in particular, central white matter structures), the absence of any grey matter involvement and the presence of cysts with a typical location. They are always present in the anterior temporal area and often in the frontoparietal area[8]. The MRS findings in this disorder include mild-to-moderate decreases in the NAA to choline and choline-to-creatine ratios[9].

The combination of megalencephaly and leukoencephalopathy is seen in a limited number of disorders. The characteristic swollen white matter changes, as seen on MRI, have only been reported in MLC[1, 2], Canavan's disease[3], Alexander's disease, L-2-hydroxyglutaric aciduria, and one variant of congenital muscular dystrophy.

Prenatal diagnosis is possible by analysis of DNA extracted from foetal cells obtained by amniocentesis at 16 – 18 weeks gestation, or chronic villus sampling at about 10 – 12 weeks gestation.

Megalencephalic leukoencephalopathy with subcortical cysts is the commonest form of leukodystrophy described from India. It has an autosomal recessive inheritance. The essential features include large head noted in infancy, motor disability in the form of spasticity and ataxia, and imaging evidence of extensive symmetrical white matter changes with subcortical cysts. Singhal *et al* (1991) described 18 patients with megalencephalic leukodystrophy in a specific Indian community, namely Agarwals from India[10]. The other large series was reported by Topcu *et al* from Turkey[11].

Singhal *et al* (2003) recently reported the clinical presentation in 70 patients with MLC from India[12]. There were 42 males and 28 females. The age at onset of symptoms varied from birth to 25 years. The median age at onset was 6 months. The first presenting symptom was a large head in 45 patients, developmental delay (usually delayed motor mile-stones) in 10 patients, seizures in 9 patients, and motor disability in 6 patients. Many children were able to complete schooling. Of the 46 who could go to school, 6 completed college graduation, 22 had an average school performance, and 18 were found to be below average.

So far, all attempts to treat MLC have failed. Patients have been treated with acetazolamide, but neither the clinical symptoms nor the white matter swelling improved. Supportive therapy includes the prescription of anticonvulsants if the patient has seizures. Physical therapy is important to improve motor dysfunction. Special education is required for many patients[7].

Conclusion

MLC is the most common leukodystrophy with megalencephaly observed in India and should be considered in the differential diagnosis of children with megalencephaly and leukoencephalopathy .One should suspect and carry-out genetic tests to confirm the diagnosis.

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CASE REPORT

JIAOM 2007; 8(3) : 253-5

Klüver-Bucy Syndrome – A Dreadful Post-HSE Sequelae

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Abstract

A 30-year-old, male presented with an episode of generalised tonic-clonic seizure, followed by vomiting, altered sensorium, and headache. Based on the clinical profile, neuroimaging, and CSF examination, he was diagnosed as a case of herpes simplex encephalitis. He recovered from the encephalitis after a week of therapy and later discharged. One week following discharge, he started exhibiting signs of behavioural changes with increased aggressiveness, hypersexuality, and increased oral exploratory behaviour. A diagnosis of Klüver-Bucy syndrome was made and confirmed after MRI imaging – which showed lesions in bilateral temporal region.

Key words: Klüver-Bucy syndrome, Herpes simplex encephalitis.

Introduction

In the 1930s, Klüver[1] and Bucy gave their names to an intriguing cluster of behavioural changes that were noted after bilateral removal of the anterior temporal lobes in primates. The Klüver-Bucy presentation includes:

1. "Psychic blindness," or the inability to recognise the emotional significance of objects;
2. hypersexuality, often directed indiscriminately;
3. altered emotional behaviour, particularly placidity;
4. increased oral exploratory behaviour and the ingestion of inappropriate objects (pica);
5. "hypermetamorphosis," or the tendency to react to every visual stimulus; and
6. memory deficits – retrograde amnesia.

Other researchers subsequently associated many of these behavioural changes to bilateral amygdala ablation[2], although one report exists of this syndrome occurring following unilateral anterior temporal resection.

Case report

A 30-year-old male, presented in the emergency with generalised tonic-clonic seizures followed by headache, vomiting, photophobia, and altered sensorium. He had been having fever for a week prior to this episode. A possibility of meningo-encephalitis was entertained. Laboratory investigations showed Hb: 14.5 gm%, TLC: 12,000 cells/cumm, DLC: $N_{88}L_{12}$, random BS: 70 mg/dl, and normal electrolytes. CSF revealed 15 cell/cumm (80% polymorphs and 20% lymphocytes); protein:145 mg%, glucose: 73 mg%. CSF for PCR confirmed a positive infection with Herpes Simple Virus type 2. MRI of brain (Fig. 1) showed hyperintensities involving bilateral temporal lobe and left parietal and frontal lobe, thus confirming the diagnosis of herpes simplex encephalitis. Parenteral antibiotics – namely, gentamicin and ceftriaxone – were administered, and patient showed improvement. He recovered completely from the encephalitis within a week and was later discharged. At the time of discharge he did not exhibit any behavioural changes or neurological deficits. About one week after discharge, he started showing signs of behavioural changes and cognitive decline in the form of aggressive behaviour like hitting, slapping people; and hypersexuality in the form of excessive genital fondling and exhibitionism. He was not recognising his parents and close relatives and friends, and was also unable to name common objects. There was a regression in his behaviour to that of a child. Hyperorality was noted, with instances where he was seen eating soap, toothpaste, and taking objects in his mouth and imitating as if smoking a cigarette. After a thorough neurological and psychiatric evaluation, a diagnosis of Post HSE – Klüver-Bucy syndrome was made and he was started on resperidone. After 2 months of treatment, he showed significant improvement. In the first week of January 2007, he had a prolonged episode of generalised tonic-clonic seizure. On examination, there were no focal neurological deficits. He was admitted and

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started on anti epileptic medication. Haematological and biochemical investigations were within normal limits. MRI and EEG were done which did not reveal any fresh changes. He was admitted for a week and then discharged as there was no recurrence of seizures. With every follow-up visit, he continues to show improvement in his behaviour with minimal improvement in his amnesia as he is still unable to recognise family and friends.

Case discussion

Herpes simplex encephalitis *(HSE)* is the most common cause of fatal viral encephalitis. About 90% of HSE cases are caused by herpes simplex virus type 1. It is a potentially treatable viral infection of the nervous system. Mortality in untreated cases is high (70%), hence early diagnosis is mandatory. There is a predilection for the frontal and temporal lobes of the cerebrum. Poor prognostic markers are age more than 30 years, long duration of illness, deep coma before initiation of therapy, and delay or non-use of acyclovir. It should be strongly suspected in any patient with a clinical presentation suggesting encephalitis, i.e., fever, headache, behavioural abnormality, hallucinations, seizures, and memory impairment. Demonstration of anti-herpes antibody titres in the CSF is significant but more important is the polymerase chain reaction (PCR) which involves the detection of viral DNA in the CSF and has a sensitivity of 95% and a specificity of 99% (equal to or more than brain biopsy). Early diagnosis and treatment with acyclovir is mandatory to prevent the dreadful sequelae of Klüver-Bucy syndrome – which developed in our patient. The recommended antiviral treatment for HSE is a 14-day course of acyclovir given IV, in a dose of 10 mg/kg eight-hourly. To prevent relapse and sequelae, a higher dosage and longer duration of acyclovir therapy, viz., 14 – 21 days is more appropriate. In our patient, the delay in diagnosis and non-receipt of acyclovir led to the development of this dreadful sequelae.

The first case of Klüver-Bucy Syndrome (KBS) was reported in a 22-year-old male patient with bilateral temporal damage due to herpes simplex meningoencephalitis[3]. The syndrome is characterised by psychic blindness, hypermetamorphosis, increased oral exploration, placidity, indiscriminate hypersexuality, and change in dietary habits. There have been many case reports from India where an association between KBS and other central nervous system disorders like head trauma, encephalopathy, encephalitis, subarachnoid haemorrhage, Alzheimer's disease, Pick's disease, juvenile neuronal lipofuscinosis, Huntington's disease, herpes simplex encephalitis (HSE), toxoplasmosis, hypoglycaemia, acute intermittent porphyria, tuberculous meningitis, heat stroke, adrenoleukodystrophy, shigellosis and neuroleptic medications have been described[4].

A study by Jha S *et al*[5] reported 6 patients with KBS associated with different aetiologies including neurocysticercosis and tuberculous meningitis. Possible explanation being involvement of temporal lobes by hydrocephalus in tubercular meningitis and the inflammatory reaction of the brain to the antigen liberated by the degenerating cysticercal cyst. In another study[6] he reported 12 children with features of KBS among cases of delayed mental and motor milestones, following cerebral birth anoxia consequent to hypoxic-ischaemic encephalopathy.

A case report by Pradhan *et al*[7], for the first time, described Klüver-Bucy syndrome in young children who had no environmental learning of sex. The syndrome has so far been noted only in adults after bilateral temporal lobe affection. A few of its components, especially the hypersexuality and hypermetamorphosis, are likely to manifest differently in very young children. He reported seven patients in the pre-pubertal age group, who developed KBS as post-encephalitic sequelae. The patients, 2.5 to 6-years-old, suffered from acute herpes simplex encephalitis (HSE) at 10 months to 5.5 years of age and developed KBS on regaining consciousness and ambulation. Altered emotional behaviour, changes in dietary habits, hyperorality and hypersexuality were present in all, while psychic blindness and hypermetamorphosis were noted in a few of the patients. All showed marked indifference and lack of emotional attachment towards their close relatives. Apathy and easy distractability were rare. Bulimia and strong urge to put non-food items into the mouth were common. Hypersexuality manifested as frequent holding of genitals, intermittent pelvic thrusting movements and rubbing of genitals to the bed on lying prone. Due to lack of environmental learning of sex, and also due to emotional and physical dependence on parents, the manifestations in young children showed modification over those of adults.

Intimate association of KBS with the temporal lobe damage has been widely reported. In 1939, H Klüver and PC Bucy discovered peculiar behaviour in monkeys who underwent bilateral temporal lobectomy. The monkeys became docile, hyperphagic and hypersexual and displayed visual agnosia, "psychic blindness". The complete syndrome is rarely seen in humans. Demonstration of diffuse cerebral atrophy in patients with heat stroke, and isolated symmetrical damage to the amygdalae and their cortical connections following cancer treatment has been widely confirmed by imaging and positron emission tomography (PET)[8,9].

KBS can be partially controlled with drugs like carbamazepine and medroxyprogesterone[9] acetate, which decreases sexual drive. Only few studies have been conducted on the exact incidence of KBS in HSV encephalitis. A limited study of 19 cases revealed 50% mortality with one-third of the survivors developing severe neurological deficits like KBS and Korsakoff's psychosis[10].

Conclusion

This report describes a patient with a unique constellation of limbic abnormalities that resulted in a Klüver-Bucy-like syndrome. Delay in early diagnosis and treatment of herpes simplex encephalitis led to the development of the dreadful sequelae which may be prevented with early administration of acyclovir.

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CASE REPORT

JIACM 2007; 8(3): 256-9

Panhypopituitarism

Atul Bhasin, RK Singal***

Asbtract

A 34-year-old lady married for 15 years presented with vague symptoms like pain in abdomen, fatiguability and giddiness. There was history of two foetal losses 12 years back followed by amenorrhea of 11 years duration. She had one living issue of 13 years age. On detailed evaluation she was found to have panhypopituitarism – Sheehan's syndrome, an uncommon disease. However, she conspicuously did not ever have history or presentation suggestive of apoplexy/raised intracranial tension or ICSOL. In the absence of PPH in this patient, the classical description of Sheehan's for post-partum hypopituitarism was not evident. Hence, autoimmune disease of pituitary triggered by sequestered antigens released by tissue necrosis could be considered as a cause for the delayed hypopituitarism in this case of Sheehan's syndrome. On treatment, she responded well to hormone replacement therapy.

Key words: Panhypopituitarism, Sheehan's syndrome.

Introduction

Hypopituitarism is a state of endocrinal malfunction – partial or complete – resulting from diseases of pituitary, hypothalamus, or even surrounding structures. Panhypopituitarism refers mainly to deficiency of all pituitary hormones; however, the deficiency may be limited to only one or more hormones (partial hypopituitarism). Hormones of significance in hypopituitarism are adrenocorticotrophin (ACTH), follicle stimulating hormone (FSH), luteinising hormone (LH), growth hormone (GH), prolactin (PRL), thyroid stimulating hormone (TSH), antidiuretic hormone (ADH), and oxytocin. Loss of trophic stimulus leads to reduced target hormone production by the endocrine glands.

Case report

A 34-year-old lady married for the last 15 years presented with pain in abdomen, giddiness, and generalised weakness of one week duration. There was history of early foetal loss and infant death around 12 years back. Patient had no history of PPH at the time of delivery of her lost infant and she had breast fed the child until he died at the age of one month. However, she subsequently became amenorrhoeic. There was no history of headache, nausea, vomiting, trauma, visual disturbances, bleeding disorders, cough, fever, haemoptysis, altered bowel habits, melena, haematochaezia, joint pains, and weight loss. There was no history suggestive of CAD, diabetes, hypertension, bronchial asthma, CVA, or pulmonary tuberculosis.

On examination, she was found to have tachycardia, postural hypotension (supine – 110/90; upright – 90/70 mm of Hg). She had significant pallor, facial puffiness, and oedema of feet. There was no evidence of icterus, clubbing, lymphadenopathy, petechiae, or purpura. Systemic examination was non-contributory. Routine investigations revealed severe microcytic hypochromic anaemia (Hb – 6.4 gm%). Her biochemical tests revealed a normal LFT, KFT, and serum electrolytes. Urine examination was normal. ECG showed asymmetrical T wave inversion in all the leads alongwith tachycardia. Abdominal ultrasonography was normal. Patient was given packed cell transfusion as an emergency measure in view of severe anaemia and early heart failure. Interestingly, following Inj. hydrocortisone which was given as pretransfusion medication, patient showed improvement in blood pressure but became severely hypotensive on day two of admission requiring dopamine support. ECG repeated on second day showed sinus bradycardia without any T wave changes. Hence a thyroid profile was requested, which was suggestive of secondary hypothyroidism [T3: 70 ng/dl (N: 70 – 200); T4: 3.0 mcg/dl (N 4.5 – 12.5); TSH: 0.25 uIU/ml (N 0.35 – 5.0)]. In view of secondary hypothyroidism, a suspicion of pituitary disorder was entertained and a close look at the patient revealed lack of secondary sex characters as

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well. Subsequently, her serum cortisol levels showed low value at 8 a.m. [2.3 mcg/dl (N = 5.0 – 25.0)] and 4 p.m. [2.1 mcg/dl (N = 3.0 – 13.0)]. Other hormonal profiles were also done, which revealed low normal levels of FSH [2.5 mIU/ml (N = upto 100)], LH [1.4 mIU/ml (N = upto 100)], PRL [5.1 ng/ml (N = 5 – 25)], [0.07 mcg/l (N = 0 – 7.0)] and oestradiol (E2) [10.0 pg/ml (N = 10 – 45)]. A diagnosis of panhypopituitarism was thus established. Patient was subjected to X-ray skull lateral view which showed normal sella turcica. CECT of sella revealed a small pituitary with normal attenuation with no mass lesion. A diagnosis of Sheehan's syndrome was made on the basis of: a) amenorrhoea and foetal loss, b) hypotension responsive to hydrocortisone suggestive of adrenal failure at presentation, c) hormonal profile suggestive of panhypopituitarism, d) radiological evaluation revealing normal X-ray skull with CECT showing a small pituitary.

Patient was started on replacement therapy with tab prednisolone 5 mg at morning 8 a.m. and 2.5 mg at evening 4 p.m., tab thyroxine 50 microgram increased to 100 ug after 15 days and tab duoluton-L, a combination of levonorgesterol 0.25 mg and ethinyloestradiol 0.05 mg for a 21 day cycle with 7 day tab-free period. She has responded well to the treatment and is presently normotensive and her menstrual cycle has restarted after 13 years.

Discussion

Panhypopituitarism may present as an acute onset disease with adrenal insufficiency or severe hypothyroidism versus chronic disease with signs and symptoms of pituitary mass lesion or progressive hormonal deficiency symptoms of the target organ. Sheehan's description of post-partum hypopituitarism postulates that PPH leads to necrosis of the enlarged pituitary gland of pregnancy and causes hypopituitarism. This patient, who had no evidence of PPH obviously thus does not fall in the category of Sheehan's Syndrome. Hence, she can be one falling in the "other" category of hypopituitarism where pituitary autoimmunity may be considered as the aetiology[3].

The causes of hypopituitarism are listed in Table I.

Table I: Causes of hypopituitarism.

- Pituitary tumours
  - Micro adenoma (< 10 mm)
  - Macro adenoma (> 10 mm)
- Parasellar tumour
- Suprasellar tumour
- Post-operative radiation
- Pituitary apoplexy
  - Haemorrhage into tumour
  - Post-partum (Sheehan's syndrome)
- Infiltrative disease (hypothalamic or pituitary)
- Granulomatous disease
  - Sarcoidosis
  - Eosinophilic granulomas
  - Wegner's granulomatosis
  - Lymphocytic hypophysitis
  - Haemochromatosis
  - Infection
    - Tuberculosis
    - Mycosis
- Miscellaneous
  - Empty sella syndrome
  - Trauma
  - Internal carotid artery aneurysm

Pituitary adenomas may be secretory or non-secretory in their functional physiology. They are either micro-adenomas < 10 mm, or macro adenomas > 10 mm leading to mechanical compression of normal tissue, impairing blood flow or compressing hypothalamic portal system thus disrupting the regulatory hypothalamic hormones. This possibility was not considered in this patient due to imaging suggesting contracted pituitary gland. Pituitary apoplexy was considered as a most likely cause of hypopituitarism in this patient. It may be caused due to abrupt infarction or haemorrhage in undiagnosed tumour or when predisposing factors lead to bleeding such as diabetes mellitus, bleeding disorders, radiation therapy, anticoagulants, head trauma. It may occur due to post-partum haemorrhage leading to compromised blood flow to pituitary gland (Sheehan's syndrome). Anterior pituitary is more commonly involved as posterior pituitary is relatively resistant to ischaemic changes. Sheehan's syndrome is typically due to pituitary necrosis after post-partum haemorrhage and hypovolaemia. The disease may

manifest immediately or after a delay of several years. Adrenal insufficiency, hypothyroidism, amenorrhoea and inability to breast feed are classic features. Diabetes insipidus may occur later. Many women present with history of subsequent pregnancy leading to foetal loss or infant death initially, and inability to conceive later. Other causes of hypopituitarism like lymphocytic hypophysitis also presents in similar manner after uncomplicated pregnancy and delivery, but imaging reveals enlarged pituitary. Empty sella syndrome refers to enlarged pituitary fossa resulting from arachnoid herniation through incomplete sellar diaphragm.

Classically, in pituitary apoplexy patient may present with acute severe headache, visual loss, cranial nerve palsy involving III, V, VI nerves and altered sensorium.

Corticotrophin (ACTH) deficit presents as fatigue, weakness, abdominal pain, and altered mental activity. Physical examination reveals hypotension, loss of axillary and pubic hair and absence of any pigmentation as typically seen in Addison's disease. Although normocytic, normochromic anaemia with eosinophilia, hyponatraemia are observed as in primary adrenal failure, but hyperkalaemia is typically absent in Sheehan's syndrome. Secondary hypothyroidism manifests as weight gain, constipation, and cold intolerance. Physical examination reveals bradycardia, periorbital puffiness and delayed tendon reflexes.

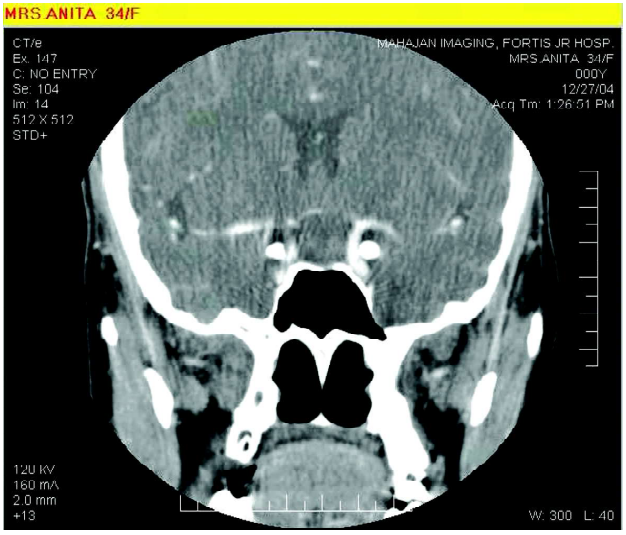

Fig. 1: *This photograph illustrates CECT of sella turica revealing small pituitary gland.*

Gonadotrophins (FSH and LH) deficit in women present with altered menstrual functions with regular anovulatory cycles or amenorrhoea with varying degrees of hot flushes, vaginal dryness, and dyspareunia. Pubic and axillary hair may be present unless associated with adrenal failure.

Growth hormone (GH) deficiency in adults leads to reduced vigour, decreased exercise tolerance, and worsening of quality of life with increased percentage of body fat.

Hyperprolactinaemia, which is commonly observed in prolactin secreting tumour or any process that interferes in transport of dopamine from hypothalamus to pituitary, is typically absent in Sheehan's syndrome.

Vasopressin deficiency of posterior pituitary leads to diabetes insipidus presenting as polyuria and polydipsia with nocturia and cold water preference. Oxytocin deficiency causes decreased milk ejection during lactation.

Endocrinal and imaging studies have special role in investigating hypopituitarism. Basal hormone level is all that is needed to confirm insufficiency, but dynamic tests are required if serum hormones levels are equivocal or to diagnose partial deficiency. As regards imaging, contrast MRI is superior to CT as optic chiasma, pituitary stalk, and cavernous sinuses – all of which may be affected by hypothalamic or pituitary mass – are better evaluated with it. High resolution CT scan with contrast in coronal sections with thin slice (1.5 mm) is an adequate alternative. Skull and sellar radiographs have little role as tumours may extend superiorly or laterally without enlarging the sella.

Management of these patients certainly includes proper hormonal replacement. Cortisol and thyroxine are required life-long as their deficiency may lead to high incidence of mortality. Gonadotrophins deficiency causing infertility and sexual dysfunction may not be a problem in particular patients. Replacement is required to reduce the incidence of decreased bone density and increased risk of osteoporosis in deficient patients. Oestrogen deficiency causes increased coronary artery disease, thus replacement being necessary to reduce the incidence of CAD. Prolactin is not known to cause any long-term

problem except deficient lactation. Adrenal insufficiency should be treated at suspicion and definitive diagnosis made post-therapy. Cortisol replacement should precede thyroxine to avoid Addisonian crisis.

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CASE REPORT

JIACM 2007; 8(3) : 260-1

Fahr's Disease

Asif Hasan, Geetika Bajpai**, Nitin Varshney***

Abstract

This is a case report of Fahr's disease or bilateral striatopallidodentate calcinosis (BSPDC) which is a neurological entity characterised clinically by chorea, dystonia, mental deterioration, seizures, and neuropsychiatric features; and pathologically by massive bilateral calcification of the basal ganglia, globus pallidus, and lateral parts of the thalamus.

Key words: Fahr's disease (FD), Choreoathetosis, Seizures, Basal ganglia.

Introduction

Fahr's disease is a rare degenerative neurological disorder characterised by the presence of abnormal calcium deposition and associated cell loss in the areas of the brain that control movement, including basal ganglia and cerebral cortex[1, 2]. The condition was first described by Fahr in 1930. According to reports in medical literature, Fahr's disease is often familial[3, 4]. It is believed to have autosomal dominant inheritance, but a few cases have been reported to have autosomal recessive inheritance and even some sporadic cases have been reported in literature[5].

Fahr's disease (FD) refers to a sporadic or familial idiopathic calcification of the basal ganglia that may lead to neurological, psychiatric, and cognitive abnormalities.

Case report

A 30-year-old, right handed female patient presented in the casualty of JN medical college hospital, with new onset generalised tonic clonic seizures. She had six episodes of seizures within four hours prior to presentation. She was treated as a case of status epilepticus as per standard protocol with phenytoin infusion. During the hospital stay, detailed examination revealed dystonia and choreoathetoid movements of upper limbs and neuropsychiatric manifestations like irrelevant speech, irritability, frequent mood changes and attentional impairment. Detailed history revealed that abnormal movements, mood fluctuations and intellectual deterioration were noticable since the last 8 months.

There was no history of fever, drug intake, exposure to toxins or any similar episodes in past. Her birth history was normal and there was nothing contributory in family history. She was married for last 8 years and had 2 live issues – 6 years and 4 years old. Her obstetric history was unremarkable.

General examination was normal except for the pallor. In central nervous system examination, the patient was conscious, oriented, but had slurred speech and an increased emotional lability. The patient had no illusions, delusions or hallucinations. Her IQ was found to be below average (60 – 70). There was no motor or sensory abnormality except for dystonia and choreoathetosis. All the other systems were normal on examination.

All the routine investigations were within normal limits except for anaemia. The assays for parathyroid hormone and serum calcium were also normal. Slit lamp and fundus examination showed no evidence of Kayser-Fleischer rings.

Radiological investigation showed normal chest and skull X-ray. The CECT head showed bilateral symmetrical calcification in the basal ganglia, globus pallidus, putamen, and thalamus (Fig1). The patient could not afford MRI study.

The patient was kept on antiepileptic (carbamazepine) and antipsychotics (haloperidol and clonotril) and her dystonia-chorea responded partially to this treatment.

Discussion

Fahr's disease or familial idiopathic basal ganglia calcification is characterised by bilateral basal ganglia calcification. The most common site of calcification is the globus pallidus and additional areas of calcification are putamen, caudate

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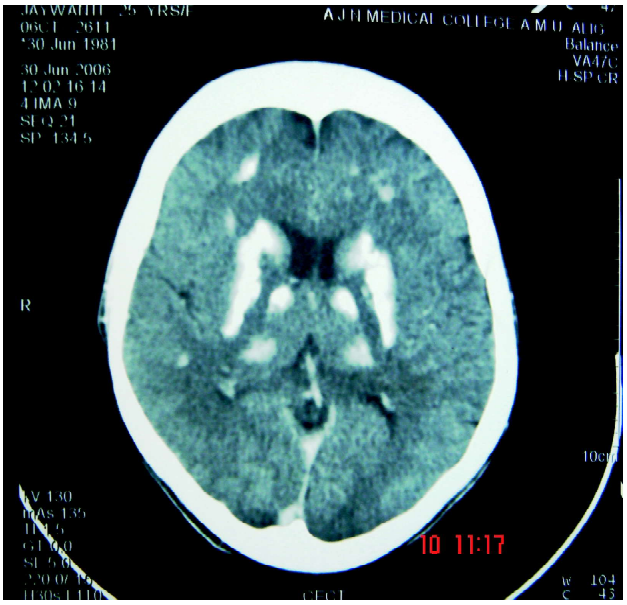

Fig. 1: *CECT head showing diffuse calcification of white matter. Bilateral symmetrical calcification is seen in the basal ganglia, globus pallidus, putamen, and thalamus.*

nucleus, internal capsule, dentate nucleus, thalamus, cerebellum, and cerebral white matter. The calcium deposits occur in the extracellular and extravascular space often surrounding the capillaries[6, 7]. It tends to be selective for small capillaries and small vessels of white matter, which is different from that in atherosclerosis. The calcification may include endothelial and stromal vascular cells as well as the interstitium. It is not clear whether the calcification in FD is a metastatic deposition, secondary to local disruption of blood brain barrier, or is due to disorder of neuronal calcium metabolism. The exact origin and pathomechanism of this disorder is still an enigma.

Typically, the age at onset of clinical symptoms is 30 to 60 years. Patients with FD mostly present with movement disorders such as Parkinsonism, chorea, tremor, dystonia, dysarthria, paresis, seizures, syncope, stroke-like events, or speech impairment. Other common neurological features are often combined with a frontal subcortical pattern of behavioural dysfunction and psychiatric symptoms such as psychosis, mood disorders, and dementia.

Radiological diagnosis could be the starting point in guiding the clinician to the possibility of Fahr's disease[8, 9].

The differential diagnosis includes Parkinson's disease, Huntington's chorea, Wilson's disease, oligodendroglioma, low-grade astrocytoma, Binswinger disease, and parathyroid disorders. All the above-mentioned differential diagnoses were effectively ruled-out in our case. Therefore, Fahr's disease or BSPDC is a diagnosis of exclusion.

There is neither a cure for Fahr's disease, nor a standard course of treatment. The prognosis is variable and hard to predict.

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CASE REPORT

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Helical CT Evaluation of Renal Mass Lesions: A Prospective Study

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Abstract

***Objective:** To study the diagnostic accuracy of helical CT in characterisation of renal mass lesions (excluding the simple renal cysts) and to study the pattern of renal mass lesions in a tertiary care institute in North India.*

***Methods:** All consecutive patients of renal mass lesions – other than simple cysts – were prospectively studied and the CT findings were compared with the final diagnosis.*

***Results:** This study included 70 patients (44 males; 26 females) in the age range of 4 to 84 years. Neoplastic lesions were observed in 39 (55.7%) cases and inflammatory lesions in 23 (32.9%). The remaining 8 patients had urinoma and complicated cyst in 3 each and renal injury in two. Renal cell carcinoma was observed in 32 cases, Wilm's tumour in 3, transitional cell carcinoma in 2, and 1 each of lymphoma and angiomyolipoma. The inflammatory renal mass lesions observed were focal pyelonephritis in 12, emphysematous pyelonephritis and renal abscess in 5 each and xanthogranulomatous pyelonephritis in 1. Helical CT was accurate in characterising 98.5% of renal mass lesions and staging 92.4% of renal cell carcinomas.*

***Conclusions:** Helical CT is highly sensitive in characterisation of renal masses. Although malignancy remains the commonest renal mass lesion, inflammatory lesions also constitute a significant proportion.*

***Key words:** Renal cell carcinoma, Inflammatory renal lesions.*

Introduction

The commonest space occupying renal lesion is a simple cyst with an incidence of 25% to 50% after the age of 50 years. Benign renal masses outnumber the malignant ones. Renal cell carcinoma is the most common tumour of the kidney comprising 3% of all malignancies found in adults[1]. The diagnosis of incidental renal carcinoma has now increased from 7 to 13% in the early 1970s to 48 – 60%[2].

In the past, surgical exploration of all space occupying renal lesions was held obligatory. Recently, sequential radiological investigations can distinguish the nature of renal masses with a diagnostic accuracy comparable to that of surgery. We studied the pattern of renal mass lesions and compared the helical CT findings with the final clinical and histological diagnosis.

Material and methods

This study was carried out at Dayanand Medical College and Hospital Ludhiana, a tertiary care centre in North India. Seventy consecutive patients of renal mass lesions (clinically suspected or incidentally detected on other imaging studies) referred for CT evaluation were included. Renal masses that adhered to the criteria of simple cyst were not included in this study. The institutional ethical and the medical university thesis evaluation committee cleared the study.

Helical CT was performed on Siemens Somatom AR Star. Oral, rectal, and intravenous contrast was given to each patient. A topogram was acquired with the patient supine in a state of suspended respiration. Initial plain scans were obtained to determine the location of the mass and pertinent vascular structures. Thereafter, 80 ml of non-ionic contrast was injected manually as a single bolus through 18-gauge catheter. Spiral CT scans with collimation of 10 mm and table speed of 15 mm per second, i.e., a pitch of 1.5 was done. Images were reconstructed at 8 mm intervals, i.e., with 20% overlap. Thinner images were reconstructed at 4 mm wherever indicated. Reconstructed images were viewed in detail. For permanent record, the relevant images of each case were recorded on 14" x 17" special laser film by Dry View Kodak camera. Axial CT images so obtained were studied in detail on soft tissue and bone window. The morphology, size, shape, enhancement pattern, character (solid or cystic), calcification if any, local or distant spread of the mass was studied. The CT staging of the malignant mass

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lesions was done according to Robson's classification[3].

The CT findings were correlated with the surgical or histological findings or the therapeutic response in the case of inflammatory lesions.

Observations

The present study included 70 patients – 44 males and 26 females – in the age range of 4 years to 84 years with a mean age of 48.5 years. More than half of the cases had neoplastic renal lesions and about 1/3rd were of inflammatory in nature. About 1/10th of the patients showed non-neoplastic and non-inflammatory renal mass lesions. The sensitivity of helical CT for accurate diagnosis of renal masses was 98.5% vs 97% of USG (Table I). One upper pole renal cell carcinoma (RCC) was misdiagnosed to be an adrenal tumour both on CT and USG. A case of RCC with perinephric haematoma was wrongly diagnosed as pyelonephritis with perinephric abscess on USG. A correct pre-operative staging of RCC was given in all cases except two. While metastasis in lung and rib was missed in one because the chest was not evaluated at the time of CT abdomen, the invasion of duodenum was missed in the second because of extensive perinephric stranding following acute haemorrhage and also the duodenum was not well distended with contrast.

Discussion

A dedicated (thin-slice) renal CT scan remains the single most important radiographic test for delineating the nature of a renal mass with a sensitivity of 94%[4, 5]; that was 98.5% in our study. Since simple renal cysts were not included in our study, the neoplastic lesions out-numbered the non-neoplastic.

The primary reason to investigate a renal mass is to exclude a malignant neoplasm. The vast majority (80 – 85%) of renal tumours are malignant adenocarcinomas[6]. A CT scan (with or without contrast), a plain chest x-ray, and, in some cases bone scan are used to stage renal cell carcinoma. Abdominal MRI rarely provides additional information. In the present study, renal cell carcinoma was the commonest neoplastic renal mass (82%) followed by Wilm's tumour (7.7%), transitional cell carcinoma (5.1%), and lymphoma and angiomyolipoma (AML) in 2.6% each. Helical CT scan was accurate in diagnosing (97.4%) and staging (92.4%) renal cell carcinoma.

Differentiating benign from malignant renal mass by radiographic or clinical means can be challenging. Angiomyolipoma is a benign clonal neoplasm that consists of varying amount of mature adipose tissue, smooth muscle, and thick-walled vessels. AML is found in 0.3% of

Table I: Characterisation of renal mass lesions.

Group	Diagnosis N (%)	USG diagnosis N (%)	CT diagnosis N (%)
Neoplastic	**39 (55.7%)**	**37 (94.9%)**	**38 (97.4%)**
• Renal cell carcinoma	32		
• Wilm's	03		
• TCC	02		
• Lymphoma	01		
• Angiomyolipoma	01		
Inflammatory	**23 (32.9%)**	**23 (100%)**	**23 (100%)**
• Focal PN	12		
• Emphysematous PN	05		
• Renal abscess	05		
• Xanthogranulomatous PN	01		
Others	**08 (11.4%)**	**08 (100%)**	**08 (100%)**
• Urinoma	03		
• Complicated cyst	03		
• Renal injury	02		

N = number of cases, TCC = transitional cell carcinoma, PN = pyelonephritis, USG = ultrasonography.

autopsies and 0.13% of population screening on ultrasonography[7]. The presence of even a small amount of fat within the renal tissue on CT (Hounsfield units ≤ 10) virtually excludes the diagnosis of RCC and is considered diagnostic of AML[7-9]. Lymphoma can have a variable appearance and on occasion may resemble renal mass[10].

When characterising a renal mass on CT, the major question to be answered is whether the mass represents a surgical or non-surgical lesion. The most important criteria used for this differentiation is the determination of enhancement. With the evolution and introduction of helical CT, it was realised that there was more variability in the Hounsfield unit reading and that 10 HU was no longer an acceptable threshold with this equipment[11]. It has been suggested that any renal mass that enhances 10 – 20 HU is indeterminate and needs further evaluation for definitive characterisation[12].

Approximately 1/3rd of renal masses in our study were inflammatory in nature and the helical CT was 100% accurate in characterising these. The confirmation of these lesions was based on aspiration cytology and culture, response to antibiotics, or post-nephrectomy renal histology. Inflammatory masses, including focal pyelonephritis and renal abscess, may mimic the appearance of a renal neoplasm. However, the correct diagnosis usually becomes apparent with an appropriate clinical history[13]. Differentiation of a cystic renal neoplasm from a sub-acute or chronic renal abscess can be difficult when the typical clinical findings are not present. Needle aspiration should be performed under these circumstances[14].

In addition, there is a group of renal mass lesions that are neither neoplastic nor inflammatory in nature. We had 3 cases each of urinoma and haemorrhage in renal cysts, and two cases of renal injury. It has been observed that a kidney that is already diseased and particularly hydronephrotic is more susceptible to injury than a healthy one[15], and CT is accurate in diagnosing retroperitoneal and intra-abdominal blunt trauma injuries[16,17].

Thus, the helical CT characterisation of renal mass lesions (other than simple renal cysts) shows a preponderance of the neoplastic lesions, with renal cell carcinoma accounting for the majority. Inflammatory mass lesions also constitute a significant proportion (33%) in developing countries. Approximately 10% of the renal mass lesions are non-neoplastic and non-inflammatory in nature. The helical CT was accurate in diagnosing (97.4%) and staging (92.4%) of renal malignancies and 100% accurate in diagnosing non-neoplastic renal mass lesions.

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CASE REPORT

JIACM 2007; 8(3) : 265-7

Thyrotoxic Periodic Paralysis

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Abstract

Thyrotoxic Periodic Paralysis (TPP) is an alarming and potentially lethal complication of hyperthyroidism characterised by muscle paralysis and hypokalaemia. This condition mainly affects patients of Asian descent. The condition is frequently overlooked and misdiagnosed on presentation. Effective control of hyperthyroidism is indicated to prevent the recurrence of paralysis. Immediate therapy with potassium supplementation and beta adrenergic blockers can prevent serious cardiopulmonary complications and hasten recovery of periodic paralysis.

Case report

A 30-year-old man presented in emergency department at around midnight with chief complaints of weakness of all four limbs.

History of fever and intravenous dextrose fluids transfusion was present. There was no history of backache, sensory loss in any limb, respiratory difficulty, involuntary movements, discolouration of urine, pain abdomen, any drug intake, heavy exercise, or trauma.

History of increased sweating and palpitations was present. On examination patient was conscious, afebrile. Vitals were stable. Pulse was around 96/min. Chest and cardiovascular examination was normal. On neurological examination higher mental functions were normal. Mild exophthalmos was present bilaterally. Rest of the cranial nerves examination was normal. Deep tendon reflexes were diminished bilaterally. Power was grade 0/V at both hip joints bilaterally and grade I/V at knee and ankle joints. Power at all joints in both upper limbs was 0/V. Tone was decreased in all four limbs. Sensory system and cerebellar examination was normal.

On investigation, serum potassium was very low (< 2 meq/l). Serum sodium, blood urea, serum creatinine, blood sugar and arterial blood gas analysis tests were normal. Thyroid functions done showed increased T3, T4, and decreased TSH. T3 was 192 mg/dl (normal 70 – 190), T4 was 17.33 mg/dl (normal 5 – 12), TSH was 0.22 mU/ml (normal 0.4 – 5.0). ECG showed prolonged QT interval.

Patient was given intravenous potassium chloride. Within few hours of giving intravenous potassium chloride, patient improved dramatically. Next day patient was moving all four limbs. Power was V/V in all four limbs and reflexes returned to normal. Patient was put on propranolol and advised to follow-up with the hospital endocrinologist for management of hyperthyroidism.

Discussion

Thyrotoxic Periodic Paralysis (TPP) is a well known complication of thyrotoxicosis in Asian population. Despite a much higher incidence of thyrotoxicosis in women, TPP predominantly affect males.

Patients are usually young adult males, 20 – 40 years of age. The attack is characterised by recurrent, transient episodes of muscle weakness that range from mild weakness to complete flaccid paralysis (Table I)[1].

Table I: Clinical features of TPP.

Features
• Adult young men
• Sporadic
• Recurrent acute paralysis with complete recovery
• Limb > trunk involvement
• Precipitated by heavy carbohydrate load, high salt diet, alcohol, exertion
• Family history of hyperthyroidism
• Clinical features of hyperthyroidism
• Hypokalaemia
• Normal acid-base balance
• Low potassium excretion rate
• Low phosphate excretion
• EMG: low amplitude compound muscle action potential with no change after epinephrine

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Proximal muscles are affected more severely than the distal muscles. Sensory function is not affected. In majority of the patients, deep tendon reflexes are markedly diminished or absent, although some patients may have brisk or normal jerks, even during paralysis[2].

Precipitating factors for an attack of TPP include trauma, infection, menses, emotion, administration of epinephrine, thyroid hormone, corticosteroids, excessive carbohydrate ingestion, alcohol, and strenuous exercise. Weakness does not occur during exercise but appears during the resting period after exercise and may be aborted by resumption of the exercise.

Periodic paralysis occurs either in a familial form with autosomal dominant inheritance, as a consequence of aldosterone-induced hypokalaemic alkalosis, potassium losing nephropathy, or in association with thyrotoxicosis. TPP has strikingly male preponderance ranging from approximately 12:1 to 20:1, compared with 3:1 in the familial variety. The age distribution is also different. The onset of familial paralysis is usually in the first two decades, whereas TPP most commonly is manifested in third and fourth decade[3].

The hallmark of TPP is hypokalaemia. Hypokalaemia occurs due to a massive shift of potassium into the cells rather than a net loss from the body. In addition to hypokalaemia, there may be hypophosphataemia and hypomagnesaemia[4].

Serum phosphorus and magnesium levels return to normal once the patient recovers from the weakness.

Electromyogram performed during spontaneous weakness typically reveals myopathic changes with reduced amplitude of compound muscle action potentials.

The pathophysiology of TPP remains unclear. Hypokalaemia is the consequence of a rapid and massive shift of potassium from the extracellular into the intracellular compartment, mainly into the muscles. This is believed to be related to increased sodium – potassium – adenosine triphosphatase (Na/K-ATPase) pump activity. There is increased number as well as activity of the Na/K-ATPase pump in patients with thyrotoxicosis: patients with TPP had significantly higher pump activity than thyrotoxic patients without TPP[5].

Apart from direct stimulation by thyroid hormones, catecholamine and insulin can also increase Na/K-ATPase activity in skeletal muscle. The enhanced beta-adrenergic response in thyrotoxicosis further increases Na/K-ATPase activity and may explain why nonselective beta-adrenergic blockers can abort or prevent paralytic attacks. Exercise releases potassium from the skeletal muscles, whereas rest promotes influx of potassium. This explains why paralytic attacks occur only during recovery from exercise and resumption of exercise can abort an attack[6].

Whether TPP patients truly have a genetic predisposition to activation of the Na/K-ATPase genes remains to be elucidated.

During periodic paralysis and marked hypokalaemia, immediate supplementation with potassium chloride (KCl) is warranted to prevent major cardiopulmonary complications. KCl is given intravenously or orally or both (Table II).

Table II: Treatment of TPP.

Treatment type
Emergency therapy
• Potassium replacement
▪ KCl 10 mEq/h iv and/or KCl 2 g every 2 h, orally
▪ Monitor serum K^+ level to avoid rebound hyperkalaemia
▪ Propranolol 3 – 4 mg/kg orally
• Prevention of recurrent attacks
▪ Avoid precipitating factor (heavy carbohydrate meals, high salt, alcohol, undue exertion until euthyroidism is achieved)
▪ Propranolol 20 – 80 mg every 8 h, orally
Determine the cause of TPP
Definitive therapy of hyperthyroidism with antithyroid drugs/thyroidectomy/radioiodine

Potassium chloride (KCl) supplementation should be given at a slow rate unless there are cardiopulmonary complications. Use of potassium supplements is not useful for prophylaxis against further paralytic attacks and should not be given to patients between attacks.

Acetazolamide and T4, which have been reported to reduce the frequency of paralytic attacks in FHPP and other forms of hypokalaemic periodic paralysis, may worsen the attacks in TPP and should be avoided[7].

To conclude, the diagnosis of TPP is often delayed because of the similarity of the paralysis with other common conditions. Early diagnosis prevents serious cardiopulmonary complications. TPP is a curable disorder that resolves when an euthyroid status is achieved.

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CASE REPORT

JIACM 2007; 8(3) : 276-7

Tubercular Osteomyelitis of Zygomatic Bones

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Abstract

***Summary:** A rare presentation of tuberculosis (TB) of maxilla/zygoma with discharging sinus over left cheek is being reported as TB of zygomatic bones is extremely rare[1].*

***Key words:** Zygoma, Tuberculosis, Osteomyelitis.*

Introduction

Tuberculosis is an infection caused by Koch's bacillus (*Mycobacterium tuberculosis*) (humanis or bovis). Most common localisation is in the lungs. Tuberculosis (TB) of large bones and vertebral column is not uncommon. It is rare in small flat bones of face, sinuses, nasopharynx, nose, and facial bones. Maxillary tuberculosis is even rarer[2, 3]. We describe a case of tubercular osteomyelitis of maxillary/ zygomatic bones and discuss its clinical features and management.

Case report

A 55-year-old male presented with swelling and discharging sinus over the left cheek since the last 6 months alongwith history of low-grade fever and cough off and on. He was a non-smoker and non-alcoholic. His medical history was not significant for previous systemic disease. Patient had no history of pulmonary tuberculosis which was confirmed by a chest skiagram. Patient developed a painful swelling over left cheek about 6 months back which had burst after 25 days, discharging yellowish pus, and leaving a sinus which persisted since then. On local examination, a sinus of size 2 x 3 cms with undermined edges with yellow discharge was present over the left cheek. The right cheek also had an inflamed, diffuse swelling. On investigation, haemogram was: Hb 9 gm%, ESR 40 mm/hr, TLC - 7,000 cells/ mm^3 with polymorphs 60% and lymphocytes 40%, Mx (Mantoux) test was 15 x 12 mm induration. X-ray chest was WNL. The Ziehl-Neelsen staining of pus smear from sinus was negative for AFB; pus culture for pyogenic organisms was sterile. ELISA for HIV was non-reactive. Pus culture of AFB showed growth of *M. tuberculosis* sensitive to all first-line antitubercular drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol). FNAC (fine needle aspiration cytology) from discharging cheek sinus was suggestive of chronic granulomatous lesion. X-ray of the para-nasal sinuses showed bony lesions with overlying soft-tissue swellings with permeative destruction in bilateral zygomatic bones. CT scan of face showed osetolytic permeative lesions in maxilla, hard palate, and zygomatic bones with overlying soft-tissue swelling (Figs. 1 and 2). The diagnosis of tuberculosis of maxilla with discharging sinus over left cheek was made and patient was treated with the standard 4 drugs antitubercular regime (rifampicin 450 mg, pyrazinamide 1500 mg, isoniazid 300 mg, and ethambutol 800 mg) for 2 months, followed by isoniazid 300 mg and rifampicin 450 mg for 4 months. It resulted in healing of the sinus and symptomatic improvement within two months. The post-treatment follow-up was uneventful.

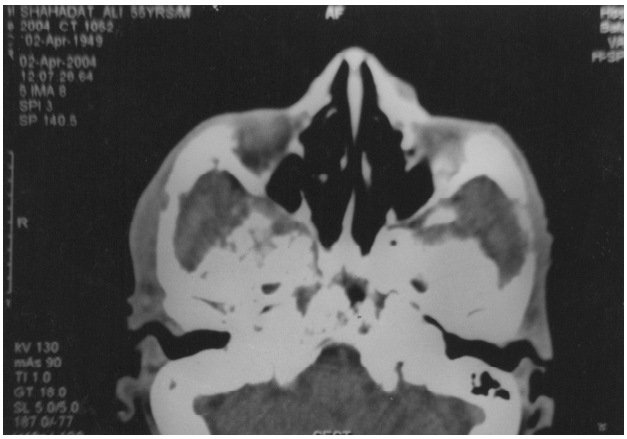

***Fig. 1:** Axial CECT of skull shows permeative destruction of bilateral maxillae, zygomatic bones, and lateral walls of both orbits and hard palate with sequestrum formation in left maxilla.*

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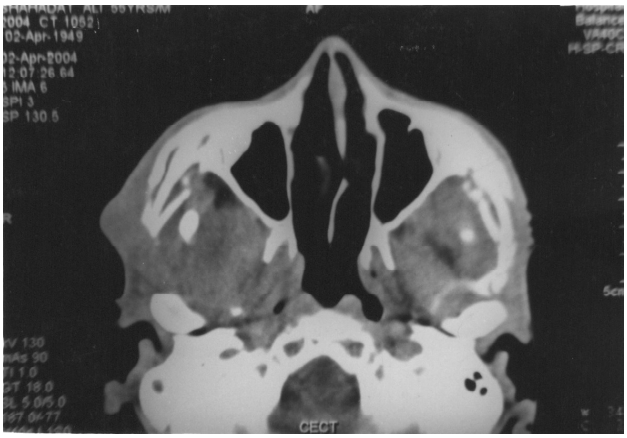

Fig. 2: *Coronal CECT of skull shows permeative destruction of bilateral maxillae, zygomatic bones, and lateral walls of both orbits and hard palate with sequestrum formation in left maxilla.*

Discussion

The primary tubercular osteomyelitis of zygomatic bone is very rare. TB affects facial bones in 1% of cases with skull involvement in 0.2 – 1.4% cases[4]. TB of facial bones is usually associated with TB elsewhere in the body, and both skeletal and pulmonary tuberculosis may occur concurrently. TB of facial bones commonly occurs after breakdown of tubercular focus elsewhere in the body when the haematogenous spread of the bacilli occurs. Most cases of tubercular involvement of maxillary sinus are secondary to pulmonary tuberculosis. Although direct spread of infection from neighbouring structures like orbit, other paranasal sinuses, face, and nasal mucosa has also been implicated, from lungs the infection spreads either by haematogenous route or lymphatics. Host immunity and the virulence of bacillus determines the further progression of the disease. It is commonly a disease of childhood and adolescence that is more common in males[5].

The localised discharging sinus or non-healing wound are the common presentation, while neuralgia and non-specific headache may also occur. The disease may go unrecognised due to its chronic nature and vague symptoms and signs.

The management of disease depends on establishing the diagnosis and adequate antitubercular treatment (ATT) and appropriate surgical intervention whenever required. Treatment is mainly conservative with antitubercular drugs. Surgery is indicated in cases of extensive destruction, presence of secondary infection, and intracranial involvement. During treatment, sometimes, radiological evidence of repair lags behind clinical evidence of improvement. The present case highlights that high index of suspicion should be kept for early diagnosis and timely treatment of the disease.

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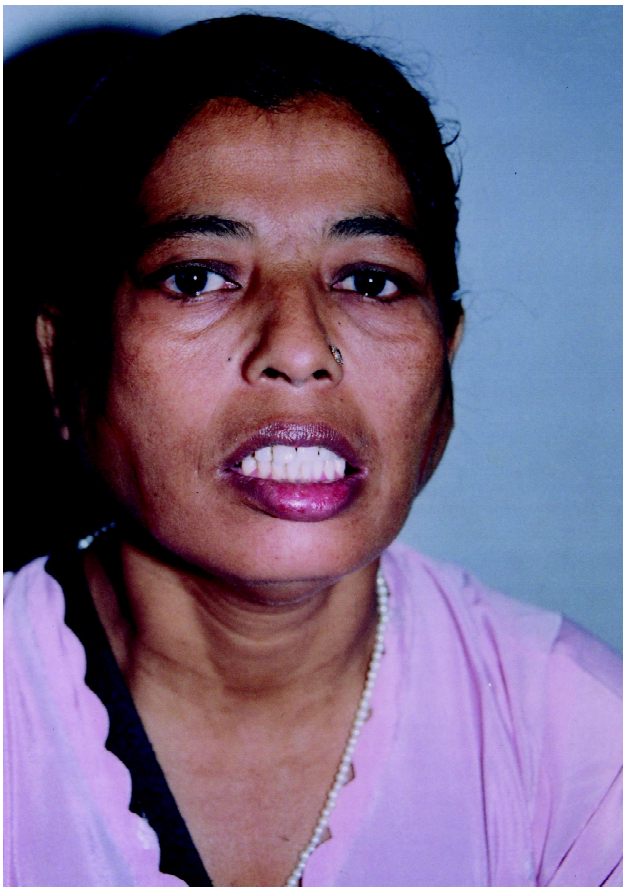
IMAGES IN CLINICAL MEDICINE

JIACM 2007; 8(3) : 278-9

Heerfordt-Waldenström Syndrome

Prashant Prakash, Pushpa Yadav**, Ajay Puri***, SC Sharma***, Dinesh Srivastava****, Sujata E Mathews******



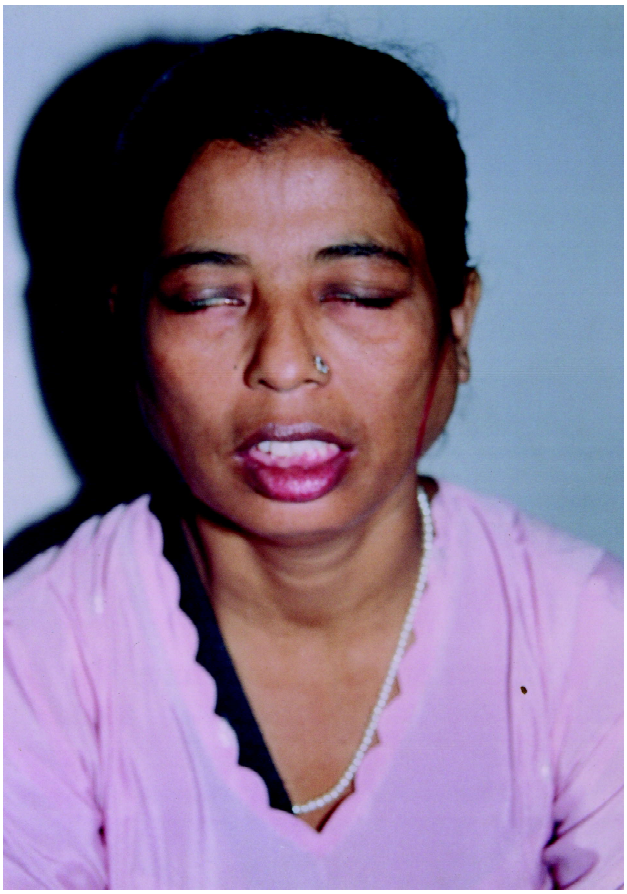


Fig. 1 and 2 : Patient's photograph showing bilateral parotid enlargement and bilateral facial palsy.

A 40-year-old woman presented with history of mild-to-moderate intermittent fever alongwith progressive bilateral swelling of face in the region of ears of three months duration. She also complained of deviation of angle of mouth to the left with inability to close her right eye since one month. There was no history of joint pains, rashes, breathlessness, chest pain, or haemoptysis. On examination, she was found to have bilateral parotid enlargement with right lower motor neuron facial palsy also (Figs. 1 and 2). Subsequently, during hospital stay she developed left lower motor neuron facial palsy also. Rest of the systemic examination was normal. Investigations revealed normal haemogram, blood sugar, and renal and hepatic functions. HIV test was negative. Serum Ca was 10 mg% and 24 hours urinary Ca was 120 mg/l. X-ray chest PA view revealed bilateral hilar enlargement. Serum ACE level was raised to 113 U/l (N - 8 - 52). Mantoux test was negative. Eye examination showed healed anterior uveitis. FNAC of the parotid gland was suggestive of chronic granulomatous pathology. The patient was thus diagnosed to be a variant of acute sarcoidosis - the Heertfordt-Waldenström syndrome. (Fever, parotid enlargement, anterior uveitis, and

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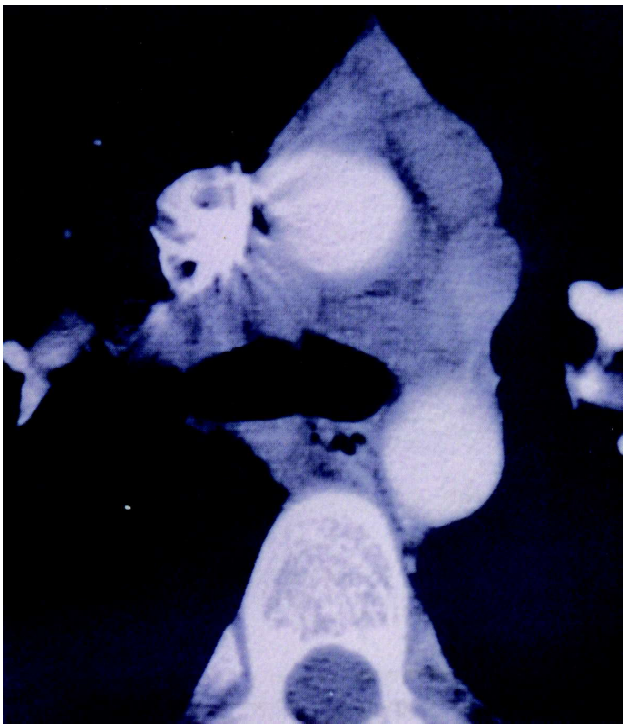

Fig. 3: *Contrast-enhanced CT scan (CECT) thorax suggestive of right paratracheal and anterior and posterior mediastinal lymphadenopathy.*

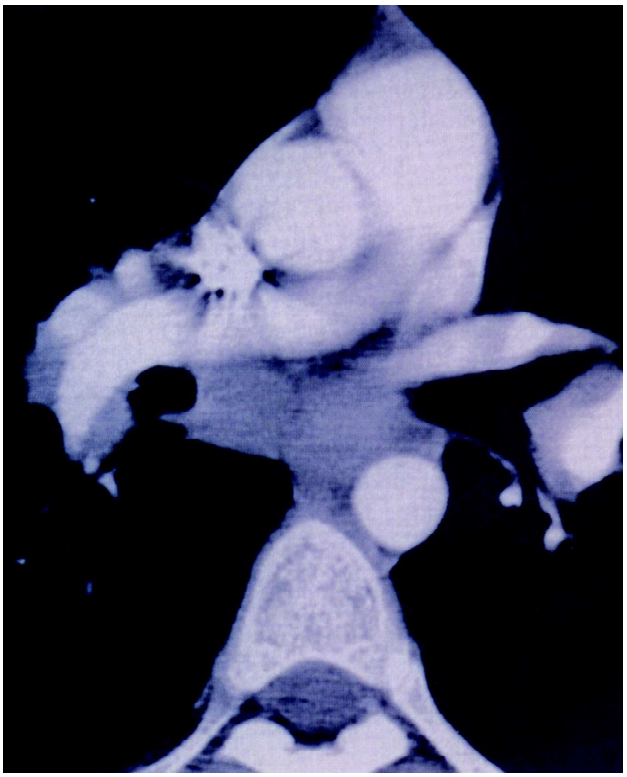

Fig. 4: *Contrast-enhanced CT scan (CECT) at a lower level of the same patient suggestive of bilar hilar lymphadenopathy.*

facial nerve palsy). Her pulmonary function test showed mild restrictive defect. CECT of chest revealed bilateral symmetrical hilar lymphadenopathy with right paratracheal and anterior and posterior mediastinal lymphadenopathy (Figs. 3 and 4). Lung parenchyma was normal.

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