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(ESTD.1980)

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Editorial

Epidemic of Intracerebral Hemorrhage

* B.N. Mohapatra, * C.B.K. Mohanty

Stroke is defined by WHO as the clinical syndrome of rapid onset of focal (or global as subarachnoid haemorrhage) cerebral deficit lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one. It is the 3rd commonest cause of mortality and leading cause of major adult disability.[1] There is lack of population based data about the prevalence of stroke in developing countries including India. In a recent study at a tertiary care hospital of Orissa, 13.9% of all admissions to medical ward was due to stroke making it a major cause of serious illness in the society. (Personal Communication, Parija B.L.).

There are are 3 pathological types of stroke : ischemic stroke, primary intracerebral haemorrhage (ICH) and subarachnoid haemorrhage[2]. Spontaenous ICH is a serious disease despite progressing medical knowledge. ICH appears suddenly without warning, unlike ischaemic stroke that often preceeded by a transient ischaemic attack. Outcome is determined by the initial severity of bleeding. Mortality and morbidity of ICH is high.[3] Only 31% are functionally independent at 3 months. Only 38% of the cases survive the 1st year.[4] In the published report in this journal the mortality among the ICH cases was 70% in 1st month.[5] There is a great controversy regarding relative prevalence of ICH in western countries and in tropics.[11] In North America and European population 15% of the stroke is due to ICH and 80% are due to ischaemic stroke.[6,2] In an earlier study from India the incidence of haemorrhagic stroke varies from 5-7 to 37.9%.[7] Later on ICH was reported to be 28% of the stroke.[8] However, in the published study 64.32% cases of stroke were due to ICH which is more than 4 times higher than non-tropics and more than twice the incidence that has been reported from India in 1990.[2,5,8] ICH in this geographical area is like an epidemic. Hence there is a great need of finding out the cause of ICH. Like the reports from the other parts of the world and India increasing age and male sex are risk factors for ICH.[3,5,8] Whether propensity of male gender to ICH is due to gender difference or due to other associated habits like alcoholism is not known.[3,5,8]

Hypertension is the commonest risk factor for ICH. The published report has found 47% of cases of ICH with hypertensions which is nearly same as at other western countries.[3,5] Hypertension increases 4 times the risk of ICH.[4]

Like in western countries, diabetes mellitus and smoking are not significant risk factors for ICH even in India. In the published

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report only 9.3% had diabetes mellitus and 10.3% had history of smoking.[3,5]

In western countries alcoholism has been associated with increase in ICH and being considered as an important risk factor.[3] However from India including the published study from Orissa only few cases were associated with alcoholism.

Hypercholesterolemia and its relations to ICH is controversial. There is trend, to be a lower risk of ICH with higher cholesterol level.[3] From India 77% of ICH had normal cholesterol value (< 200 mg/dL) and 79% cases had LDL (< 130 mg/dL).[5] This supports the view that hypercholesterolemia is not a risk factor for ICH.

Unlike ischaemic stroke ICH is not related to diabetes mellitus, hypercholesterolemia and current smoking which denotes that atherosclerosis is not the prevailing pathophysiologic mechanism of ICH.[3]

Hypertension is characterised by proliferations of arteriolar smooth muscles followed by apoptotic smooth muscle cell death and collagen deposition. Collagen has no contractile capability, and brittle, hence unable to stand to breakage due to high blood pressure resulting in ICH.[9]

Among the nonhypertensive cases with ICH cerebral amyloid angiopathy appears to be the important cause.[6] Amyloid depositions in the tunica media causes brittle arterioles with poor contractility resulting in ICH. Presently the hypertensive angiopathy and amyloid angiopathy can be detected by gradient echo MRI before the development of ICH by the presence of micro-bleeding and white matter changes, where aggressive blood pressure control and avoidance of anti-coagulant therapy may help in preventing ICH.[10] However the facility for the test is not available and affordable to most populations. Therefore early detections and treatment of hypertension remain the most important method for preventing ICH.

Since arteriolar bleeding is slower than arterial bleeding several hours exist where interventions may be useful.

Medical therapy for ICH is controversial, even though guidelines for blood pressure, intracranial pressure, blood glucose and seizure management exist.[6]

Upto 40% of hematoma grows in 1st hour and associated with early clinical deterioration. Two randomized clinical trial of recombinant factor VIIa resulted in limiting hematoma growth and improved outcome.[4] Surgical trials have shown no benefit over conservative medical therapy.[4]

ICH is the commonest type of stroke in tropics whose epidemic will rise further as life expectancy will rise, the cause of which is not known. There is a great need of research to find out the cause of high prevalence of ICH in tropics and effective preventive measures and ideal treatment protocol for better outcome.

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ANNOUNCEMENT

The 26th Annual Conference of the Association of Physicians of India, Orissa State Branch is going to be held on 11th & 12th November, 2006 at SCB Medical College, Cuttack. His excellency The Governor of Orissa Sj. Rameshwar Thakur is going to inaugurate the function. Physicians of Orissa are requested to contact Dr. S.N. Das, the Organising Secretary of the Conference / Hon. Secretary, API Orissa State Branch, Cuttack.

API, Orissa State Branch

Original Article

Epidemiology and clinical profile of HIV infection in a tertiary care hospital of western Orissa

*P.K. Mohanty, *D.K. Patel, **P.K. Padhi, ***P.N. Sahu

ABSTRACT

HIV infection is a major public health problem in India with almost all states affected by it. However, this epidemic is extremely dynamic, and growing with great variations in infection level and character between different provinces, districts and between rural and urban areas. We studied the epidemiology, clinical profile and outcome of 28 cases of HIV infection. The mean age at presentation was 32.9 years and male to female ratio was 3:1. The mode of transmission in all the cases were heterosexual, the commonest source being commercial sex workers (71%). Fever was the commonest presentation (78.5%) followed by generalized weakness (75%) and weight loss (71%). The commonest opportunistic infection was tuberculosis (57%) with majority having pulmonary involvement followed by oropharyngeal candidiasis (40%) and lobar pneumonia (14%). In majority cases (60%) CD4+ T cell count was less than 200/cmm, which indicated advanced stage of disease. Only 35 percent could be initiated with highly active antiretroviral therapy (HAART). However, followup of these cases were poor as majority of them did not turn up regularly.

Key words: HIV infection, epidemiology, clinical profile, Western Orissa.

INTRODUCTION

HIV infection is a global epidemic and virtually no country remains unaffected by this problem[1]. By the end of year 2005, 38.6 million people were estimated to be living with HIV / AIDS world wide[2]. In the same year, 4.1 million new HIV infections were recorded and there were 2.8 million deaths[2]. About half of the cases were accounted for by young people aged 15 to 24 years[2]. The epidemic remains extremely dynamic, growing and changing in character[1].

HIV infection is also major public health problem in Indian subcontinent. By the end of year 2005, 5.7 million Indians were estimated to be living with HIV / AIDS[2]. Adult HIV prevalence in India is reported to be 0.9%[2]. However, there is great variations in infection levels between different provinces, states or districts and between rural and urban areas. In India, 92% of all nationally reported AIDS cases are found in 10 of the 38 states and union territories; the greatest numbers were from Maharastra and Gujarat in the west; Tamilnadu, Andhrapradesh and Karnataka in south; and Manipur and West Bengal in north-east[3]. According to UNAIDS / WHO, between 2,70,000 and 6,80,000 Indians died of AIDS in 2005 [2]. Current prevalence of HIV infection in state of Orissa is 0.25% and total number of AIDS cases reported in 31st Aug. 2006 was 641[3,4].

The clinical course and nature of opportunistic infections in HIV / AIDS varies from patient to patient and from country to country[5]. Although Pneumocystis carinii pneumonia (PCP) is the commonest opportunistic infection in Western countries, tuberculosis is the most common infection in India[6,7]. Other common opportunistic infections in India are oropharyngeal candidiasis,

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staphylococcal skin infections, cryptococcal meningitis and cryptosporidial diarrhoea etc.[5,6,7,8]

Till date, there is no completely safe and effective treatment modality for HIV / AIDS. Also, no effective vaccine is yet available. The problem is further compounded by the emergence of resistance to antiretroviral drugs and associated adverse drug reactions.

In view of the above facts, it is pertinent to study epidemiology and clinical profile of HIV infection in different regions of the country. V.S.S. Medical College Hospital, Burla is a tertiary care multi-disciplinary hospital of Western Orissa. There is no study so far from this institution. Therefore the present study was taken up.

PATIENTS AND METHODS

The present study was conducted in department of Medicine, V.S.S. Medical College Hospital, Burla over a period of 2 years from July 2004 to July 2006. Adult cases (≥15 yrs) attending to out patient department or admitted to the department of medicine with clinical features suggestive of HIV infection were referred to local voluntary counseling and testing center (VCTC) of National AIDS Control Organization (NACO) located at Department of microbiology V.S.S. Medical College, Burla for counseling, testing and establishment of diagnosis. HIV infection was diagnosed when serum is found reactive for HIV antibodies on all the three tests namely ELISA / Simple / rapid assay. Western blot test was done wherever indicated to confirm the diagnosis in case of indeterminate antibody tests. Cases were studied for various manifestations and opportunistic infections. CD4+ T cell count was done to assess the stage of HIV infection and institution of anti retroviral therapy (ART). Associated complications and infections were treated. The cases were followed up at regular intervals. Informed consent was taken in all cases.

RESULTS

Of the 28 cases of HIV infection, majority 11 cases (39.5%) were in 20-29 yrs age group; 32 percent were 30-39 years, 21.5 percent 40 - 44 years and 7 percent were above 50 years of age at presentation. The mean age at presentation was 32.9 years. Seventy five percent of cases were male and rest were female. The mode of transmission in all cases in the present study was heterosexual. Commercial sex workers were the commonest source of infection (Figure 1).

The male HIV cases in the present study were mainly truck drivers (18%), farmers and business men (18% each) by occupation; all the female cases were housewives.

Three cases (10.7%) of HIV infection in the present series were asymptomatic and detected on screening. The commonest presentation was fever (78.5%) followed by generalized weakness (75%), weight loss (71.4%) and chronic diarrhoea (32%); generalized lymphadenopathy was found in 18 percent of cases (Figure 2).

The commonest opportunistic infection was tuberculosis in our study population found in 57 percent of cases (Table - 1). Of them 56.25 percent had pulmonary tuberculosis where as the rest were having extrapulmonary tuberculosis; the commonest form being tubercular meningitis (Table - 2).

Intracranial infection was a common problem amongst these cases and CT scan of brain done in 6 of these cases revealed various pathology like meningitis, cerebellar ring enhancing lesion and tuberculoma etc. (16.6 % each) (Table - 3).

CD4+ T cell count was done in 23 cases. Sixty one percent of cases had CD4 count < 200 cells / cmm ; in 26 percent of cases the count was 200-350 cells / cmm

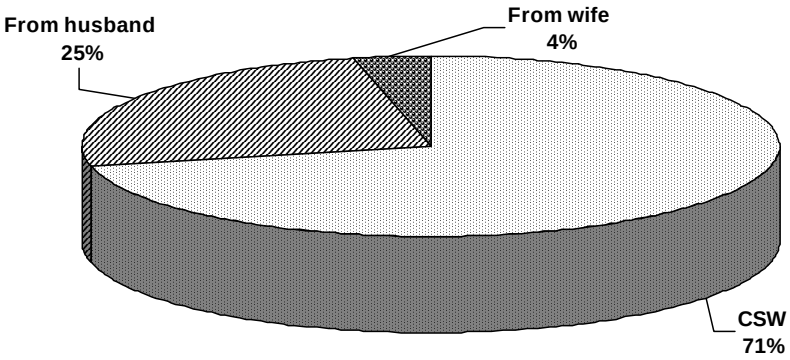

Figure - 1: Mode of transmission and distribution in 28 cases of HIV / AIDS

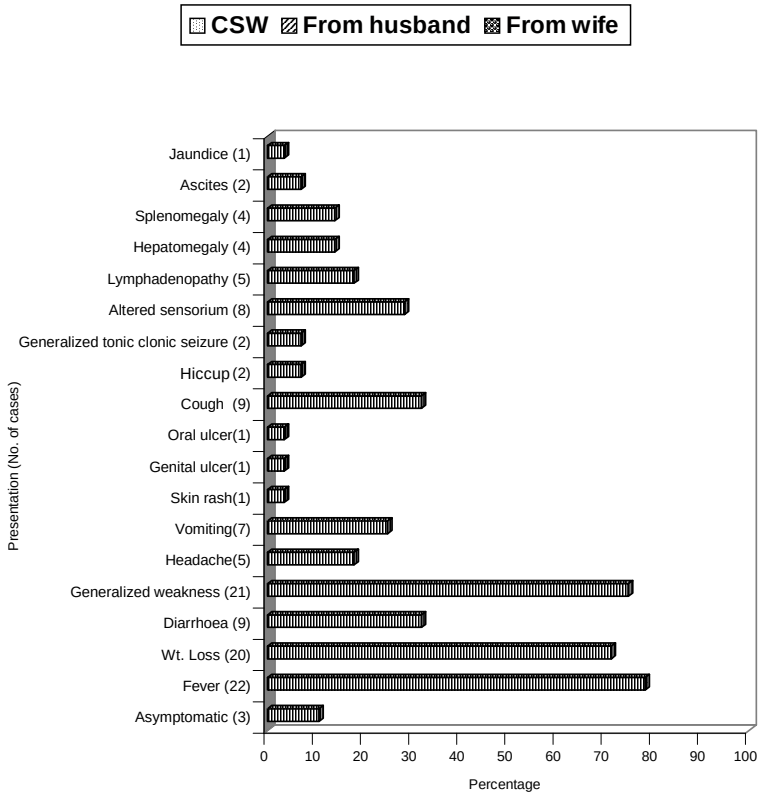

Figure 2: Clinical Presentation in 28 cases of HIV / AIDS.

Table – 1
OPPORTUNISTIC INFECTION IN CASES OF HIV / AIDS (N = 28)

Presentation	No. of cases	Percentage
Oral candidiasis	6	22
Esophageal candidiasis	5	18
Pulmonary tuberculosis	9	32
Extra pulmonary tuberculosis	7	25
Lobar pneumonia	4	14
Cerebral abscess	1	3.5
Recurrent furunculosis	2	7
Sinusitis	1	3.5
Scabies	1	3.5

Table – 2
DISTRIBUTION OF VARIOUS FORMS OF TUBERCULOSIS IN CASES HIV / AIDS IN (N = 16)

Types	No. of cases	Percentage
Pulmonary Tuberculosis	9	56.25
Tuberculous meningitis	3	18.75
Tuberculous adenitis	1	6.25
Tuberculous peritonitis	1	6.25
Tuberculous pleural effusion	1	6.25
Multiple tuberculoma	1	6.25

Table – 3
FINDINGS ON CT SCAN OF BRAIN IN 6 CASES OF HIV / AIDS

Feature	No. of cases	Percentage
Meningitis	1	16.66
Cerebellar ring enhancing lesion with hydrocephalus	1	16.66
Tuberculous meningitis with hydrocephalus	1	16.66
Cerebral abscess	1	16.66
Multiple tuberculoma	1	16.66
Basal ganglia infarction	1	16.66

Table – 4
DURATION OF ILLNESS BEFORE DETECTION OF HIV INFECTION IN SYMPTOMATIC CASES OF HIV / AIDS (N = 25)

Duration	No. of cases	Percentage
< 30 days	3	12
1 – 6 month	13	52
6 month – 1 yrs	7	28
1 – 2 yr	1	4
2 – 3 yr	1	4

where as in 13 percent of cases it was 350-500 cell /cmm.

Three cases (10.71%) in the present series were asymptomatic and did not receive antiretroviral therapy (ART). Unfortunately 53.57 percent cases could not be given ART because of different reasons although it was indicated in them. Only 35.7 percent cases could be treated with highly active anti retroviral therapy (HAART). Follow up of these cases was also very poor as majority of them (53.5%) were lost to follow up.

Majority of the patients (52%) were symptomatic for 1 to 6 months before detection of the HIV infection whereas in one case (4%) patient remained symptomatic for a duration of 3 years before HIV infection could be detected. (Table-4).

Examination of spouse and children of the index cases was largely unsuccessful. In 13 cases (52%) the spouse was positive for HIV infection; in the rest of the cases the status of infection in other family members could not be ascertained.

DISCUSSION:

The prevalence of HIV infection amongst the study population was 0.29 percent. The prevalence of HIV infection as per the data collected during screening of women attending antenatal clinic was reported to be 0.25 percent in Orissa[4]. The mean age at presentation was 32.9 years in the present study which is similar to that of George J. et al[7]. Male to female ratio was 3:1 similar to that of Kumarasamy N et al[6] and Sircar AR et al.[10]

The lone mode of transmission in this study was heterosexual unlike that reported by others[6,7,10]. While majority of males acquired infection from commercial sex workers (CSWs), all female cases acquired it from their husbands. We did not find any case of HIV infection acquired through injection drug use, blood / blood products transfusion or needle stick injury. Male patients with HIV infection were from occupations like truck drivers, businessmen and farmers.

Fever was the commonest clinical presentation (78.5%) followed by generalized weakness (75%), weight loss (71.4%), cough (32%) and chronic diarrhoea (32%). Various other less common presentations were skin rash, oral ulcer, genital ulcer, hiccup, headache, vomiting and seizures. The common physical findings were altered sensorium (28.5%), generalized lymphadenopathy (18%), hepatosplenomegaly (14%) and ascites (7%). George J. et al reported fever in 98.3 percent, weight loss in 85 percent and cough in 36.7 percent of cases[7]. Severity five percent of patients in present study had severe weakness as an important presentation not reported by others.

The commonest opportunistic infection seen was tuberculosis (57%), oropharyngeal candidiasis (40%) and lobar pneumonia (14%). Recurrent furunculosis was found in 7 percent of cases. The different forms of opportunitistic mycobacterial infections in the present study were pulmonary tuberculosis (56%), tuberculous meningitis (19%); tuberculous adenitis, peritonitis, pleural effusion and tuberculoma found in 6.25 percent each. Kumarasamy N. et al reported an incidence of pulmonary tuberculosis in 49 percent of their cases[6]. Agarwal SK et al in a study of eighty cases of HIV infection reported the incidence of tuberculosis in 33.75 percent cases of which two third had pulmonary tuberculosis and one third had extrapulmonary tuberculosis, which is much less compared to our observation[11]. Of the six cases of HIV infection presenting with CNS manifestations in the present study CT scan of brain revealed tuberculous meningitis with hydrocephalus, solitary cerebellar ring enhancing lesion with hydrocephalus, cerebral abscess, multiple tuberculomas, basal ganglia infarction and meningitis in one case each.

Majority of the cases in present series (60%) had CD4+ T cell count <200 /cmm indicating an advanced stage of disease at presentation.

The mean duration of illness before the detection of HIV infection was 6.9 months. This highlights the fact that the treating physicians were unsuspecting which lead to delayed initiation of antiretroviral therapy in these patients.

Antiretroviral therapy (ART) could not be initiated in majority of cases (54%) because of various reasons like social stigma, unaffordability, fear and anxiety of isolation and ignorance. Only 35 percent (10 cases) received highly active antiretroviral therapy (HAART). Of these 10 cases only 3 (11%) are on regular follow up. The three asymptomatic cases are also on regular follow up. This indicates that only 22 percent of cases with HIV infection are having proper follow up and regular ART.

CONCLUSION

Of late HIV infection has made its presence felt in western Orissa. This may represent only the tip of the iceberg in view of existing social stigma and poor level of awareness among health care professionals. This has led to delayed diagnosis and advanced stage at presentation of disease. Due to various reasons only small number of patients are on regular follow up and treatment. This necessitates measures to increase awareness of this dreaded problem amongst health care professionals, to educate the community in general and provide an adequate support system.

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Original Article

Risk Stratification of Intracerebral Hemorrhage with Special Reference to Lipid Profile

*B.L. Parija, **P.K. Routray, **A.N. Sahu,
**S. Singh, **S. Giri, **P. Patro, ***P. Jena, ****G.Ray

ABSTRACT

During the study period of two years (Sept. 2004 - Sept. 2006) a total of 300 cases of Intracerebral hemorrhage (ICH) admitted to Medicine ward of S.C.B. Medical College, Cuttack were selected randomly. Incidence of Cerebrovascular accident(CVA) was 13.9% and incidence of hemorrhage among CVA patients was 64.52%. Commonest age group affected was 60-69 yrs, with Male : Female ratio 1.56 : 1. Hypertension was found to be the commonest risk factor (142 cases / 47.3%). Focal Neurological deficit was found in 249(83%) cases. ICH was Putaminal in 95 (31.6%) cases, Lobar in 51 (17%) cases, Thalamic in 63 (21%) cases, Cerebellar in 15 (3%) cases, Multiple in 11 (2.9%) cases, Midbrain 3(1%) cases, Caudate 4(1.1%). Parietal lobal involvment was seen in 80% of cases of all lobar hemorrhage. On follow up for 6 months, 8 cases were in grade 5 Glasgow outcome scale and 9,10,6,17 cases were found in grade 4, 3, 2,1 respectively. Volume of supratentorial hemorrhage correlates directly with prognosis ($p< 0.001$). Amongst site, lobar hemorrhage had good prognosis and pontine hemorrhage had worst prognosis. 70% mortality occured within 1st month. 77% of patients had total cholesterol level < 200 mg/dl and 79% of patients had LDL cholestrerol < 130 mg/dl. ($p < 0.001$).

INTRODUCTION :

The Cerebrovascular accident(CVA) is the third commonest cause of morbidity and mortality (after CAD and all cancers taken together) in developed countries and probably second commonest cause in developing countries.[1] Among all strokes, intracerebral hemorrhage(ICH) forms a major bulk which has worse prognosis in terms of economical burden over the society in comparision to infarction. Until now, limited attempts have been made to search systematically for the risk factor profiles associated with ICH patients. Studies conducted previously to evaluate risk factors for stroke focused mainly on ischaemic stroke or a combination of ICH and SAH rather than spontaneous ICH as a separate entity. There has also been need for studying the lipid profile as an independent risk factor of ICH as there are recent studies which correlated hypocholesterolemia with ICH but this has to be confirmed in larger studies.

The present study "**RISK STRATIFICATION OF INTRACEREBRAL HEMORRHAGE WITH SPECIAL REFERENCE TO LIPID PROFILE".** is an attempt to understand the risk factors, clinical presentation, sites involved, prognosis according to site and size of ICH and hypocholesterolemia as a newer emerging risk factor.

PATIENTS & METHODS

This study was carried out at the Department of Medicine S.C.B. Medical College Cuttack. from Sept. 2004 to Sept. 2006.Our study design included 300 patients of ICH proved by CT scan. Meticulous history taking, clinical examination and laboratory investigation

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were carried out in all patients. Randomly 50 patients were followed up for 6 months to study their pattern of progression. Their neurological improvement were assesed according to Glasgow outcome scale and their neurological improvement were compared to their site and volume of hemorrhage. Serum lipid profile such as Serum total cholesterol, LDL cholesterol and triglyceride was done in all patients and they were correlated with ICH.

RESULTS :

The present study comprised of 300 patients. Total number of patients admitted to Department of Medicine, S.C.B. Medical College, Cuttack in one year was 17131 amongst which 2382 (39.9%) were CVA patients. Out of 2382 CVA patients incidence of Intracerebral hemorrhage was 1537 (64.52%).

The base line clinical and laboratory features are summarized in following tables.

TABLE - 1
SEX & AGE DISTRIBUTION

Age in yrs	Male	Female	Total
20-29	3	2	5
30-39	4	6	10
40-49	25	12	37
50-59	38	23	61
60-69	61	38	99
> 70	52	36	88
TOTAL	**183 (61%)**	**117 (39%)**	**300**

Maximum patients were found in the age group of 60-69 years. Males were more affected than females with male -female ratio of 1.56:1.

TABLE - 2
RISK FACTORS OF ICH

RISK FACTORS	TOTAL NO. OF PATIENTS	PERCENTAGE(%)
Hypertension	142	47.3
DM	28	9.3
CAD	21	7
Renal disease	17	5.6
Alcohol	27	9
Smoking	31	10.3
Drugs	24	8
H/O TIA	22	7.3
H/O Infarction	9	3
H/O Hemorrhage	25	8.3
Total	**300**	**100**

Hypertension remains the most common associated risk factor with 47.3% of patients having histroy of hypertension or ECG evidence of LVH. Other common risk factors associated were smoking (10.3%), diabetes mellitus (9.3%), alcohol (9%). Patients had history of prior hemorrhage in 8.3% of cases.

TABLE - 3
COMMON CLINICAL PRESENTATION

Symptoms & Signs	Cases	Percentage(%)
Headache	166	55.3
Reeling of head	54	18
Convulsion	36	12
Hypoaesthesia	48	16
Cerebellar signs	8	2.6
Focal neurological deficit	249	83

Headache was one of the most common premonitory symptoms while other frequently occuring symptoms were reeling of head, convulsion, cerebellar signs. Most common sign was focal neurological deficit in the form of hemiplegia (83%).

TABLE - 4
ATYPICAL CLINICAL PRESENTATION

Symptoms	No. of cases	Percentage(%)
Headache	12	4
Reeling of head	11	3.6
Convulsion	7	2.3
Vomiting	9	3
Visual	3	1
Altered behaviour	9	3
Total	**51**	**17**

17% of patients had symptoms other than focal neurological deficit like reeling of head, visual symptoms, altered behaviour etc.

TABLE - 5
SITE OF HEMORRHAGE

SITE	NO. OF CASES	PERCENTAGE (%)
Putamen	95	31.6
Lobar	51	17
Pontine	27	9
Thalamus	63	21
Cerebellar	15	3
Multiple	11	2.9
Midbrain	3	1
Caudate	4	1.1
Large area (massive)	31	10
TOTAL	**300**	**100**

The most common site of ICH was putamen (31.6%). Multiple sites of hemorrhage was found in 2.9% of cases while midbrain was the least common site of hemorrhage.

Sites of ICH in decreasing order of frequency: Putamen > Thalamus > Lobar > Pontine > Cerebellar > Caudate > Midbrain.

TABLE - 6
LIPID PROFILE IN ASSOCIATION WITH ICH TOTAL CHOLESTEROL

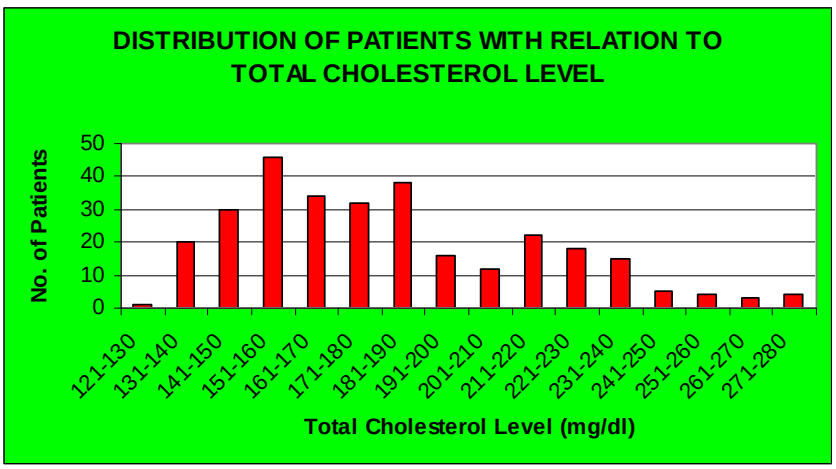
Serum level (mg/dl)	No. of cases	Percentage %
<200	230	77%
≥200	70	23%
TOTAL	**300**	**100%**

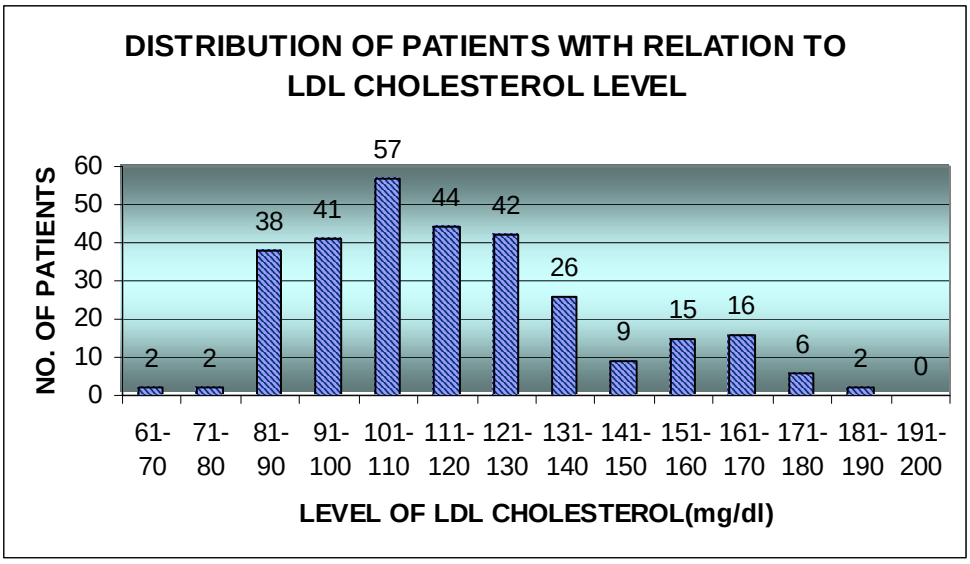
TABLE - 7
LIPID PROFILE IN ASSOCIATION WITH ICH LDL CHOLESTEROL

Serum level (mg/dl)	No. of cases	Percentage %
≤ 130	237	79%
>130	63	21%
Total 300	**100%**	

TABLE - 8
LIPID PROFILE IN ASSOCIATION WITH ICH TRIGLYCERIDE

Serum level (mg/dl)	No. of cases	Percentage %
< 160	239	79.6%
≥160	61	20.4%
TOTAL	**300**	**100%**





DISCUSSION

In the present study, incidence is calculated from the no. of patients admitted to Medicine Department. Of 17131 patients admitted in one year, 2382 patients were diagnosed as CVA clinically and subsequently proved by CT scan. It amounts to 13.9% of all admitted patients in Medicine ward. In other studies, the incidence in the U.K. is approximately 2/1000/year.[1] So the incidence depicted in this study appears to be higher than western studies. This can be attributed to two reasons. First, our study is based on hospital admission and S.C.B. Medical College and Hospital is a tertiary care referral centre. Secondly, illiteracy and poor socioeconomic status leading to poor health care and poorly controlled hypertension.

In our study, the incidence of hemorrhage among patients of CVA is around 64.52%, with 1537 of 2382 CVA patients having CT scan evidence of intracerebral hemorrhage, which is much higher than other studies. ***National Institute of Neurological and Communicative Disease and Stroke (NINCDS)*** data bank had reported the incidence of intracerebral hemorrhage to be 10.7%. Similar figures were obtained in community or population studies from Denmark (10.4%), Holland (9%), Oxfordshire England (10%).[1] The incidence of hemorrhagic stroke in India varies from 5-7 to 37.9% of CVA admitted to hospital ***(Jain et al, 1985)*** and 28.3% ***(Dhamija et al, 1990)*** and this discrepancy in figure of incidence of hemorrhage can be due to the size of the study as all previous Indian studies have taken less than 100 subjects and there have been no large South Asian studies to verify the incidence.[2-3] There must be some added unrecognised risk factors for ICH in the developing countries. The possible factors may be poor socioeconomic status, poor health check-up, smoking, pollution, poor nutritional status etc.

The present study agreed with the previous studies in context of age. The incidence of ICH increases with age, with maximum patients in 60-69 years age group in our study. ***Dhamija et al (1990)*** reported 38% of cases are >60 years age group while only 18 patients were below 40 years. In the

present study only 15 patients are below 40 years and 2/3 rd (62.3%) of all cases are above 60 years. ***I.S. Gambhir et al*** also reported 65% of all patients to be between 5th and 6th decade.[3]

Study by ***Dhamija et al, 1990*** has reported male : female ratio of 1.5:1. Our study also found similar ratio of 1.56 : 1 between males and females. ***Gambhir et al, 1993*** had also shown male preponderance (2.3:1), same as our observation.[3]

In the present study, hypertension was found in 142 (47%) patients of intracerebral hemorrhage. The association of hypertension is more strong in higher age groups. 58 patients were found to be hypertensive in the age group 40-60 years while around 81 patients are found in age group > 60years. Similar association was reported by ***Brott and colleagues*** *(45%)*,***Schutz and associates*** *(59%), and* ***Dhamija et al****(78.7%).*[3,4,5]

The present study showed association of Diabetes in 9% cases, smoking in 10% cases and CAD in 7% cases.

In the present study alcohol ingestion is found in only 9% of cases. The series reported by ***Donahue and associates*** and ***Juvela and colleagues*** also documented an increased risk of ICH in relation to alcohol ingestion.[6] The poor association of ICH with alcohol may be due to low incidence of alcoholics in our country and patients being in altered sensorium, the attendants fail to give or lie about alcoholic history.

The present study found ICH in only 3 patients taking OCP and rest 21 patients were either taking aspirin, clopidogrel, statins or combination of these drugs. ***SALT (Swedish Aspirin Low-dose Trial)*** secondary stroke prevention trial had documented a significantly higher frequency of hemorrhagic stroke in the group assigned to aspirin (75 mg / day).

The present study of 300 patients have found history of TIA in 22(7%) patients and history of prior attack of hemorrhage in 8% of patients. Similar results are shown by ***Dhamija et al (1990)*** which reported history of hemorrhage in 5% of cases and history of TIA in 3% of cases.[3]

In the present study focal neurological deficit is found in 83% of cases while 17% of patients had symptoms other than focal neurological deficit like headache (4%), reeling of head (3.6%), convulsion (2.3%), vomiting (3%), visual symptoms (1%), altered behaviour (3%).

On admission 88(29.3%) cases were comatose while 129 (43%) cases were stuporous and 64 (21%) cases confused. 19 (6.3%) cases were admitted with GCS-15. The study by ***Dhamija et al*** showed that coma is present at admission in 30% of cases.

On follow up of cases for 7 days during hospital stay 54.7% of patients are found to be in confused state with Glasgow coma scale (11-14) while 8.3% of patients continue to be in comatose state, 26.8% of patients in stuporous state and 10.2% of patients were having normal GCS of 15.

Putaminal hemorrhage is the commonest site (31.6%) in the present study followed by thalamic hemorrhage. Midbrain is the least common site (1%). Massive hemorrhage is found in 31 (10%) cases. Multiple hemorrhages are found in 11(2.9%) cases. Similar results are reported in study by ***Dhamija et al*** with putaminal hemorrhage constituting 32% of cases, followed by lobar. 22 (28%) cases, thalamic 17 (21%) and pontine 11 (14%) cases. In the present study putamen is followed by thalamic 63 (21%), lobar 51 (17%), pontine 27 (9%), cerebellar

15 (3%), caudate 4 (1%) and midbrain 3 (1%) cases.

The present study also showed parietal lobe involvement in 80% of cases and frontal in 13.7% of cases and occipital lobe in 6.3% of cases. Similar results were shown by ***Kase C.S. et al*** study which reported parietal lobe involvement in 72% of cases.[7]

On follow up of 50 patients for 6 months, 8 cases were in Grade 5 Glasgow outcome scale and 9,10,6,17 cases were found in Grade 4, 3, 2, 1 Glasgow outcome scale respectively. To summarize the follow up of 50 patients, 8 (16%) patients returned to the level of everyday participation and physical functioning of community-matched persons who have not had stroke. 9 cases (18%) were independent in their daily routine lives while 10 cases (20%) of patients were conscious but needed help for their daily routine lives. 6 cases (12%) after 6 months continued to stay at persistent vegetative state while there were 17 (34%) mortality in 6 months.

Study by ***Bruce H Dobkins et al*** showed that 25% of patients returned to normal activity and maximum gains are by 3 to 4 months after stroke which observation is very much similar to our observation.[8]

In the study, volume of supratentorial cerebral hemorrhage directly correlates with prognosis with mean volume of 3.13cm^3 in patients of Grade 5 glasgow coma scale and mean volume in Grade 4, 3, 2, 1 are 10.6cm^3, 16.2cm^3, 22.1cm^3 and 29.2cm^3 respectively. Using ***Student's 't' test***, t= 4.9, p <0.001. So there is significant association of volume with prognosis of supratentorial hemorrhage. Similar results were shown by ***Kase C.S. et al*** study which reported more number of mortality in cerebral hemorrhage of size >40cm^3 when compared to 20cm^3 or 20-40cm^3.[7]

Of follow up cases, 50% of Grade 5 Glasgow outcome scale are of lobar hemorrhage while putamen constitutes 25% and caudate and cerebellar each constitute 12.5% of Grade 5 Glasgow outcome scale. Pontine hemorrhages on follow up stay in Grade 1 or Grade 2 Glasgow outcome scale. So lobar hemorrhage has better prognosis than other sites and pontine hemorrhage has worst prognosis. There is no such predilection for any grades in putaminal or thalamic hemorrhage. Similar results were obtained by ***Kase C.S. et al*** study which showed that prognosis in lobar hematoma is usually better than other forms of intracerebral hemorrhages. ***Dhamija et al*** study showed that 26% of mortality occurred in lobar hemorrhages and 34% of mortality in pontine hemorrhages.[3,7]

33 cases (11%) died within 7 days of admission while there are 34% deaths after discharge on follow up for 6 months. 70% of mortality occurred in 1st month while 41% of mortality occurred within first 7 days after discharge. In ***NOMASS*** study the adjusted 30 day case - fatality rate was 33% which is much less than our study. The explanation for this discrepancy may be due to poor control of hypertension and poor nursing care as the patients are less educated and of poor economic status.

In the present study 230 (77%) cases of intracerebral hemorrhage are found to have total cholesterol less than 200 with median value of 174 mg/dl. 25th quartile is 156 mg/dl and 75th quartile is 208 mg/dl.Using **Z test** for proportion, **Z** is 15, p value <0.001.

Similarly LDL cholesterol ≤130mg/dl is found in 237 cases (79%) and median falls at 116mg/dl. 25th quartile is 98mg/dl and 75th quartile is 127 mg/dl. Using **Z test** for

proportion, **Z** is 17 which is equivalent to $p<0.001$.

So the above observations suggest that hypocholesterolemia is significantly associated with intracerebral hemorrhage. Same findings are shown by ***Alan Z Segal (1999)***. Study by ***Daniel Woo et al (2004)*** concluded that hypercholesterolemia is associated with a lower risk of intracerebral hemorrhage. ***Tirshwell D. et al (2004)*** published a study showing lower level of total cholesterol in association with an increased risk of all hemorrhagic stroke.[9,10]

In our study there are 79.6% patients who had triglyceride level less than 160 and only 20.4% patients with triglyceride level ≥160. Using **'Z'** test for proportion it is derived that there is significant association between low triglyceride level and intracerebral hemorrhage.

CONCLUSION

In the present study it is concluded that hypertension is the commonest risk factor associated with ICH. Predictors of death and prognosis after hemorrhage include volume of hemorrhage and site of hemorrhage. Maximum case fatality rate is in first months. There is significant association between hypocholestrolemia and ICH and it can be considered as an occult risk factor in growing incidence of ICH among CVA patients.

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Original Article

Evaluation of Homocysteine Levels in Coronary Atherosclerotic Heart Disease in Coastal Orissa

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ABSTRACT

Coronary artery disease (CAD) is one of the most important cause of mortality and morbidity world wide. Asian Indians at home or settled around the world have the highest incidence. CAD among Indians occurs at a earlier age, is severe, extensive and has a malignant course. A number of patients lack the conventional risk factors and this has led to search of new and novel risk factors like elevated homocysteine levels (tHcy).**Aims and objectives**: To study the tHcy levels in patients of Angina pectoris. Unstable angina and Acute myocardial Infarction in hospital setting. To study tHcy levels in age and sex matched controls and find out the significance if any. To study tHcy levels after administration of B vitamins over 6 weeks**. Patients and Methods**: 40 patients with proved CAD, were studied. Controls were also taken for clinical, biochemical and cardiological evaluation. 46 healthy volunteers or non CAD patients were taken as controls and tHcy levels were established in both the groups. **Observations**: In the age group of < 45 yrs with CAD mean tHcy levels were21.2 ± 7.42 µmol/l against 10.58± 3.09 µmol/l in controls (p <0.001) and in age group > 46 yrs with CAD mean tHcy levels were 20.48 ± 6.47 µmol/l against 13.62 ± 4.47 µmol/l in controls(p<0.001) Correlation was strong with multivessel disease. CAD patients without conventional risk factors when matched with controls had significantly raised tHcy levels. There was significant reduction of tHcy level after treatment with B vitamins. **Conclusion:** Observation in the study group strongly supports the role of increased tHcy levels as an independent and multiplicative risk factor for CAD. Raised tHcy levels can be therapeutically intervened in the hope of ameliorating or arresting the process of atherosclerosis and its complications.

Coronary artery disease (CAD) is looming large as a new epidemic. It has become one of the most important cause of mortality and morbidity around the world. In the US there are 1.1 Million AMIs per year with 30% mortality. Asian Indians settled around the world have the highest rates of CAD. To compound the problem further, CAD among Indians tend to occur earlier in life, is more severe and extensive and follows a malignant course.[1,2] By the end of 2010 CAD in India is projected to affect 100 million people.

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Some CAD patients lack the traditional risk factors. In this context new potential risk factors are on the search and a few have been identified, like elevated total homocysteine levels (tHcy), fibrinogen, lipoprotein (a) etc. Elevated tHcy is now recognised as an independent and modifiable risk factor for CAD.[3,4,5] Concentration of tHcy are determined by an interplay of hereditary and environmental factors.

The present study was done in the P.G Department of Medicine, S.C.B. Medical College, Cuttack with the following aims:

1. To evaluate the level of Homocysteine in patients hospitalised with stable angina (SA), Unstable Angina (UA) or AMI.

2. To evaluate the level of Homocysteine in age and sex matched controls.

3. To compare various traditional risk factors and the homocysteine levels in cases and controls.

4. To evaluate the Homocysteine levels after administration of homocysteine lowering B-Vitamins.

PATIENTS AND METHODS

This prospective and cross sectional study was done in 40 hospitalised cases

1. Presenting with typical complaints of SA, UA or AMI together with ECG evidence of CAD with Echocardiography and Angiocardiographic confirmation.

2. Patients presenting with atypical or no chest pain but with positive TMT, ECHO, Angiographic evidence of CAD were also included in the Study.

Age and sex matched healthy volunteers or patients with other diseases but without evidence of CAD were taken as controls.

Patients with diseases which can adversely affect the outcome of study like CRF, Hypothyroidism CVA or patients on methotrexate, Phenytoin and biguanides were excluded from the study.

Study Period: Aug 2004 to Aug 2006.

A detailed history, general examination and cardiovascular examination were done. Investigations including FBS, RFTs, LFTs and a thyroid profile was done. Lipid profile and tHcy levels were done in all cases. ECG, Echocardiography was done in all cases. Stress Test and Coronary Angiography were done in selected cases.

OBSERVATIONS

Total 40 cases were studied, (28 males and 12 females) and 45 controls. Majority of cases (57.5%) were from urban areas. Maximum number of cases and controls belonged to age group of 45-54years. Mean age of presentation was 50 years in cases. Male to female ratio was 2.3:1 in cases and 1.42:1 in controls.

AMI was the commonest type of CAD (65% cases), followed by stable Angina (17.5%) and UA (17.5%).

Among the case group dyslipidemia was the commonest conventional risk factor 21 cases (52.5%), Hypertension in 12 cases (30%). (Picture-1)

Mean Homocysteine level in cases was 20.43 ± 6.57µmol/l. and 12.3 ± 4.16 µmol/l in controls. (Table-1)

High tHcy level (>18µmol/l) was seen in 23 cases (57.5%) and 5 (10.86%) controls. (p <0.001) (Table-2)

Table-1
SERUM HOMOCYSTEINE LEVELS IN CASES AND CONTROL
Mean homocysteine levels (µmol/L) in cases and control with SD

Age group	Case group	Control group	t value	p value
Young age <45 (n = 15)	21.2 ± 7.42	10.58 ± 3.09	5.23	<0.001
Old age >45 (n = 25)	20.48 ± 6.47	13.62 ± 4.47	4.39	<0.001
All ages	20.43 ± 6.57	12.3 ± 4.16	5.64	<0.001

Table-2
EVALUATION OF HIGH HOMOCYSTEINE (> 18µmol/L) IN DIFFERENT AGE GROUPS

Age group	Case group (n= 40)	Control group (n = 46)
Younger age <45 yrs (n=15)	9 (60%)	1 (5%)
Older age >45 yrs (n =25)	14 (56%)	4 (15.38%)
All ages	23 (57.5%)	5 (10.86%)

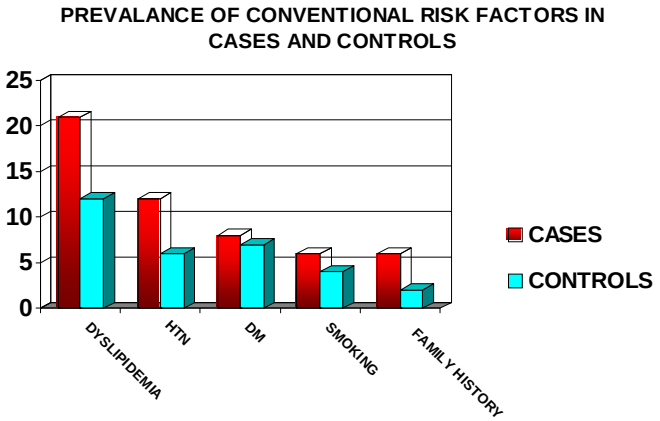
Table-3
PREVALANCE OF HIGH HOMOCYSTEINE (> 18µmol/L) WITH CORONARY LEISIONS BY ANGIOGRAPHY

Parameter	SVD			DVD			TVD		
	M (n=2)	F (n=1)	T (n=3)	M (n=3)	F (n=1)	T (n=4)	M (n=6)	F (n=2)	T (n=8)
tHcy >18 mol/L	1 50%	0 0%	1 33%	3 100%	0 0%	3 75%	5 83%	2 100%	7 87.5%

Table-4
LEVEL OF HOMOCYSTEINE AFTER TREATMENT

Before Treatment	After Treatment	t value	p value
26.77 ± 4.81	16.18 ± 2.68	6.08	<0.001

Picture-I



There was no statistically significant difference in the tHcy level among males and females.

Serum Total Cholesterol, TG, LDLc and VLDLc were higher in cases compared to controls.But HDL cholesterol was lower compared to controls.

Coronary Angiography was done in 15 cases, Tripple Vessel Disease (TVD) in 8 (53%), Double Vessel Disease (DVD) in 4 (27%) and Single Vessel Disease (SVD) in 3 (20%) cases.

Raised tHcy were observed in 7 (87.5%) cases of TVD;3 (75%) cases of DVD and 1 (33.3%) 1 case of SVD. This proves a proportional correlation of increased total Homocysteine level to increasing severity of CAD. (Table-3)

Serum tHcy levels were higher in cases with conventional risk factors except smoking and positive family history. CAD patients without conventional risk factors when matched with controls had significantly high tHcy levels thus confirming the role of increased tHcy as an independent risk factor for CAD.

After treatment with Homocysteine lowering vitamins, there is a significant (p value < 0.001) reduction of tHcy levels after 6 weeks of therapy. (Table-4)

CONCLUSION

Observation of study group strongly supports the role of raised tHcy level as an independent & multiplicative risk factor in CAD.

Indian, particularly Oriya diet contains a plethora of B-VITAMINS. Despite this dietary adequacy the significantly raised values of tHcy in Oriya people can be explained by the INDIAN DIETARY PARADOX. Prolonged heating and frying destroys Folic Acid and the predominantly vegetarian diet lacks adequate Vit. B_{12}. What ever the causative mechanism, raised tHcy levels can be therapeutically intervened in hope of ameliorating the process of atherosclerosis and associated complications.

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EHLERS DANLOS SYNDROME

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Eighteen years Female Patient presented with easy bruisability, hypermobility of joints leading to difficulty in walking. On examination the joints were hypermobile, muscle flabby, soft and thin skin, hyperlaxity of the skin, so that skin was stretchable over the forehead, nose and scalp. The final diagnosis was “Ehlers Danlos Syndrome” (EDS).

EDS refers to a group of inherited, clinically variable & genetically heterogeneous connective tissue disorder. It is characterised by skin fragility and hyperextensibility, joint laxity & hypermobility. 11 types of EDS are described basing on the extent of skin, joints, other tissue involvement & genetic inheritance. Type I & II account for 80% of cases. Type IV patients are predisposed to sudden death from rupture of large blood vessels and other hollow organs. Type V is inherited as an x-linked trait. Type VI is characterised by ocular fragility & keratoconus. Type VIII is associated with prominent periodontal changes. The diagnosis of EDS is based on clinical criteria. There is no specific therapy.

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COLOUR

FAMILIAL HYPERLIPIDEMIA

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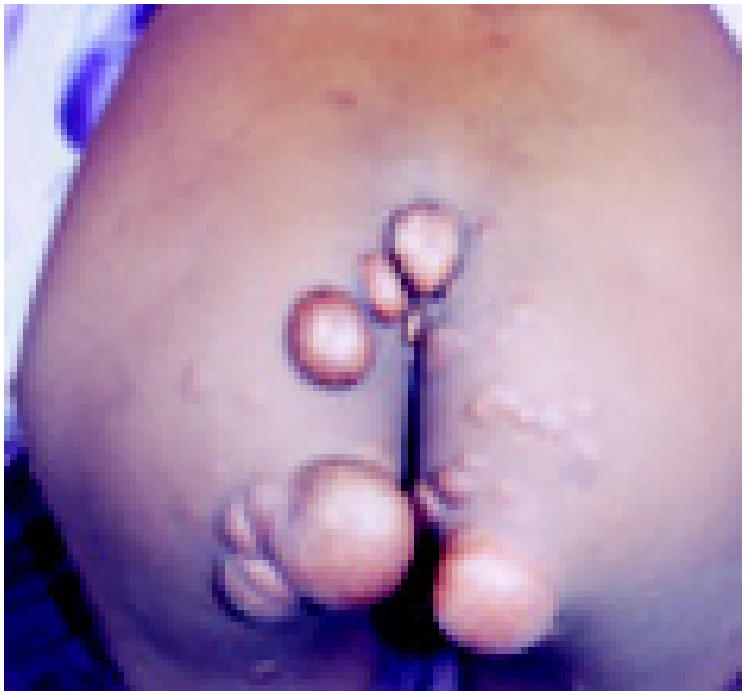

Twelve years female patient presented with nodular soft tissue swellings over perianal and buttock region. The swellings were small & large. She had also swellings on the dorsal surface of hand. The swellings are known as 'Xanthomas'. Her brother also suffers from similar condition. On investigation, Serum Cholesterol was 680 mg/l & Serum Triglyceride was - 320mg/I. Final diagnosis of "familial Hyperlipidemia" was made. She was managed with hypolipidemic drugs, exercise and fat restriction.

Hyperlipidemias are among the commonest metabolic diseases seen in clinical practice. They are important because they may lead to a number of sequelae including coronary heart disease, peripheral vascular disease, dermatological manifestations (xanthelasmata, xanthomata), pancreatitis, rarely ocular & neurological anomalies. Such xanthomas are usually seen in Type I, IIa, III & V hyperlipoproteinemia (Frederickson classification).

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COLOUR

Review Article

Hypertension - Treatment Guidelines

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The ultimate Public Health Goal of anti-hypertension therapy is the reduction of cardiovascular & renal morbidity and mortality. The standard treatment guideline recommends drugs which are affordable, tolerable and matches to the situation. However, the decision of the clinician remains final in any particular case.

Procedure of BP measurement and classification :

Mean of 2 or more properly measured seated BP readings on each of two or more office visits using appropriate size cuff.

	Systolic (mm of Hg)	**Diastolic (mm of Hg)**
Normal BP	< 120	< 80
Prehypertension	120-139	80-89
Stage-I	140-159	90-99
Stage-II	> 160	> 100

Other Cardiovascular risk factors in association with hypertension :

Cigarette smoking, Obesity (BMI > 30), Physical inactivity, Dyslipidaemia. Diabetes Mellitus, family history and ethnic groups are to be taken care of.

Look for target organ damage :

Heart - LVH, angina, prior myocardial infarction, prior coronary revascularisation, heart failure.

Brain - Stroke or TIA.

Kidney - Chronic renal disease.

Peripheral arterial disease & retinopathy.

Try to find out the identifiable causes of hypertension.

Drug induced, Chronic kidney disease, primary aldosteronism, Renovascular disease, Chronic steroid therapy, Cushing's syndrome, pheochromocytoma, coarctation of aorta, Thyroid or parathyroid diseases and sleep apnoea syndrome.

Do a careful physical examination :

Measurement of BP, BMI, Exam. of optic fundi, carotid, abdominal or femoral bruit, palpation of thyroid gland, thorough examination of heart & lungs. Examination of abdomen for kidney enlargement, lower limb for peripheral pulses & oedema.

Laboratory tests and minimum diagnostic procedures to be done :

Hematocrit, urine analyhsis, blood glucose, serum potassium, calcium & creatinine, lipid profile and ECG.

Treatment :

The expected BP goal is 140/90 mmHg. In patients with diabetes, renal disease and hypertension the BP goal is less than 130/80 mmHg.

The Algorithm for treatment of hypertension is as follows :

Optimize dosage or add additional drugs until goal BP is achieved.

Life Style modifcation for prevention of high BP and management of those with hypertension :

Adaptation of healthy life style by all individuals is critical for prevention of high BP and an indispensible part of the management of hypertension. Major life style modifications decreases BP, enhances anti-hypertensive drug efficacy and decreases cardiovascular risk. They include -

1. Weight reduction.
2. Eating food rich in Calcium, Potassium with reduced total fat and saturated fat.

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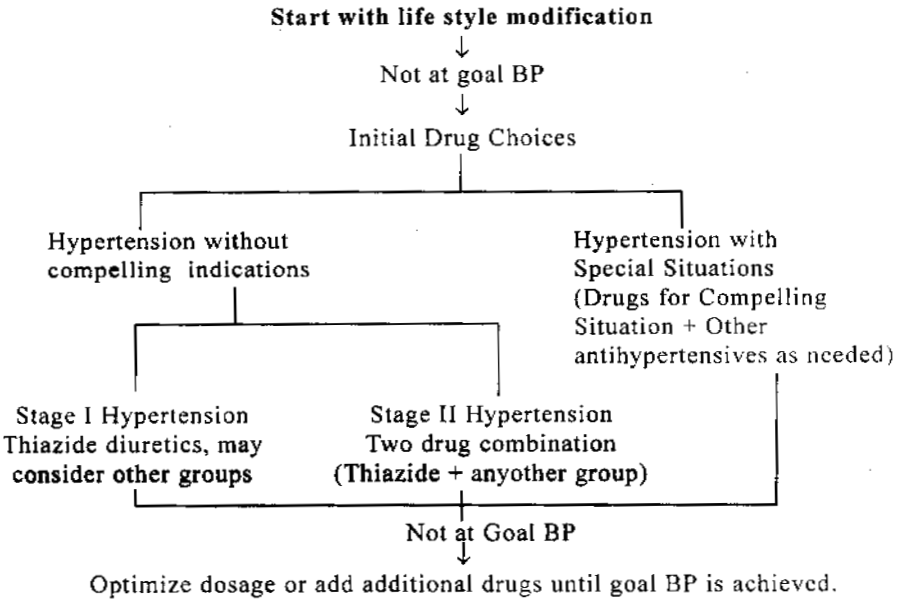

3. Dietary Sodium restriction (6 Gm of Sod Chloride / day).
4. Physical activity - Brisk Walking, Swimming, and Jogging.
5. Moderation of alcohol consumption.
6. Stop Smoking.

PHARMACOTHERAPY

Failure to achieve the goal by life style modifcation necessitates for initiation of pharmacotherapy. Classes of drugs used are outlined in the following table.

Commonly used antihypertensives :

		Dose (Mg/day)	**Frequency**
Thiazide Diuretics	Hydrochlorothiazide	12.5-50	1
	Indapamide	1.25-2.5	1
	Metolazene	0.5-1	1
Loop Diuretic	Furosemide	20-80	2
Potassium Sparing	Amiloride	5-10	1-2
Diuretic	Triamterene	50-100	1
β Blockers	Atenolol	25-100	1
	Bisoprolol	25-10	1
	Metoprolol	50-100	1-2
	Timolol	20-40	2
	Pindolol	10-40	2
Combined α & β Blocker	carvedilol	12.5-50	2
	labetolol	200-800	2
ACE inhibitors	Benazepril	10-40	1 - 2
	Enalapril	2.5 - 40	1 - 2
	Lisinopril	10 - 40	1 - 2
	Perindopril	4 - 8	1 - 2
	Ramipril	2.5 - 20	1
	Trandolapril	1 - 4	1

Angiotensin II Antagonist (ArB)			
	Candesartan	8 - 32	1
	Irbesartan	150 - 30	1
	Losartan	25 - 100	1 - 2
	Telmisartan	20 - 80	1
	Valsartan	80 - 320	1
Calcium Channel Blocker			
	Verapamil	80 - 320	2
	Amlodipine	2.5 - 10	1
	Felodipine	2.5 - 20	1
	Nifedipine (long acting)	30 - 60	1
α_1 Blocker	Prazosin	2 - 20	2 - 3
	Terazosin	1 - 20	1 - 2
Centrally acting drug	Clonidine	0.1 - 0.8	2
	Methyldopa	250 - 1000	2
	Reserpine	(0.05 - 0.25)	1
Direct Vasodilator	Hydralazine	25 - 100	2
	Minoxidil	2.5 - 80	1 - 2

Principles of Pharmacotherapy:

1. Start with Thiazide Diuretic alone or in combination with one of other classes (ACE inhibitors, ARBS, Beta blockers, CCBS).
2. Add a 2nd drug of another group if single drug fails to achieve BP goal.
3. When BP is more than 20/1 0 mm Hg above goal consider initiating therapy with 2 drugs.
4. Isolated systolic hypertension to be treated alike.

Fixed drug combination have been recommended for use in hypertension:

Such Combination are:

1. ACE Inhibitors + CCBS
2. ACE inhibitors + Diuretics
3. ARB + Diuretics.
4. Beta blockers + Diuretics
5. Beta blockers + CCBS
6. Centrally acting drugs + Diuretics.

***Anti hypertensive drug therapy recommended for use in special situations (Compelling indications)* :**

(A) Patients with IHD.

- Stable Angina - β blocker, long acting CCBS.
- Unstable Angina & Myocardial infarction - β blockers + ACE inhibitors
- Post myocardial infarction - ACE inhibitors, β blockers. aldosterone antagonist

(B) Patients with heart Failure:

Asymptomatic Ventricular dysfunction - ACEI, β blockers.

Symptomatic Ventricular dysfunction - ACEI, β blockers, ARBS, Aldosterone antagonist.

(C) Diabetics with hypertension:

Combination of 2 or more drugs usually required. Thiazide diuretic β blockers, ACEI, ARBS and CCBS are beneficial.

Diabetic nephropathy - ACEI or ARB or Combination favourably affects the prognosis.

(D) Pregnancy:

Methyldopa, β blockers and CCBS are to be used. ACEI & ARBs contraindicated.

(E) Women & Hypertension:

Oral contraceptives increase BP. Hypertension not a contraindication for HRT.

(F) Hypertensive emergencies like encephalopathy, myocardial infarction, unstable angina, pulmonary oedema, eclampsia, stroke, life threatening arterial bleeding, aortic dissection require hospitalisation & parenteral drug therapy. Contraindication & unfavourable sideffects of differnet drugs are to be kept in mind and drugs to be changed as &when required. Resistant hypertension is the failure to achieve goal BP, who are adhereing to fulldoses of an appropriate 3 drug regimen, requires multi disciplinary consultation. Public health measures like diet & excercise are to be emphasized by the treating physician.

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Update Article

Antimalarials in Falciparum Malaria - WHO Guidelines

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INTRODUCTION

Malaria is one of the most serious public health problems in India and it is an important cause of death, an illness in children and adults in tropical countries. Mortality in malaria, currently estimated at over a million people per year, has risen in recent years, probably due to increasing resistance to antimalarial medicines. The affordable and widely available antimalarial chloroquine that was in the past a mainstay of malaria control is now ineffective in most falciparum endemic areas, and resistance to sulfadoxine-pyrimethamine is increasing rapidly. The discovery and development of the artimisinin derivatives in China, and their evaluation in South-East Asia and other regions have provided a new class of highly effective antimalarials, and have already transformed the chemotherapy of malaria in South East Asia.[1]

Resistance to antimalarial medicines : [2,3,4]

Resistance to antimalarials has been documented for P. falciparum, P. vivax and recently, P. malariae. In P. falciparum, resistance has been observed to almost all currently used antimalarials (amodiaquine, chloroquine, mefloquine, quinine and sulfadoxine-pyrimethamine) except for artemisinin and its derivatives. P. vivax has developed resistance rapidly to sulfadoxine-pyrimethamine in many areas. Chloroquine resistance in P. vivax is confined largely to Indonesia, East Timor, Papue, New Guinea and other parts of Oceania. P. vivax remains sensitive to chloroquine in South-East Asia, the Indian subcontinent, the Korean peninsula, the Middle East, north-east Africa, and most of South and Central America.

Widespread and indiscriminate use of antimalarials places a strong selective pressure on malarial parasites to develop high level of resistance. Resistance can be prevented or its onset slowed considerably by combining antimalarials with different mechanisms of action and ensuring very high cure rates through full adherence to current dose regimens.

These treatment guidelines are based on a review of current evidence and are developed in accordance with WHO's standard methodology. Antimalarials for which there is adequate evidence of efficacy and safety now, and which are unlikely to be affected by resistance in the near future, are recommended. [1]

TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction. In acute falciparum malaria there is a continuum from mild to severe malaria.

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Treatment objectives

The objective of treating uncomplicated malaria is :

- to cure the infection which means eradication from the body of the infection that caused the illness. This will help prevent progression to severe disease and prevent additional morbidity associated with treatment failure.
- to reduce transmission of the infection to others, i.e. to reduce the infectious reservoir.
- to prevent the emergence and spread of resistance to antimalarials.

Antimalarial combination therapy

Combinations of antimalarials are now recommended by WHO for the treatment of falciparum malaria in order to improve therapeutic efficacy and to delay the development of resistance to the individual components of the combination. Antimalarial combination therapy is the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite.

Artemisinin – based combination therapy (ACT) are the recommended treatments for uncomplicated falciparum malaria. This is because artemisinin and its derivates (artesunate, artemether, artemotil, dihydroartemisinin) produce rapid clearance of parasitaemia and rapid resolution of symptoms.[5] They reduce parasite numbers by a factor of approximately 10,000 in each asexual cycle, which is more than other current antimalarials (which reduce parasite numbers 100-1000 fold per cycle). Artemisinin and its derivatives are eliminated rapidly. When given in combination with rapidly eliminated compounds (tetracycline, clindamycin) a 7 day course of treatment is required, but when given in combination with slowly eliminated antimalarials (lumefantrine, amodiaquine, mefloquine) shorter courses of treatment i.e. 3 days are effective.

In 3 day ACT regimens the artemisinin compound is present in the body during only two asexual parasite life-cycles (each lasting 2 days, except for P. malariae infections). This exposure to 3 days of artemisinin treatment reduces the number of parasites in the body by a factor of approximately one hundred million ($10^4 \times 10^4 = 10^8$). However complete clearance of the parasites is dependant on the partner medicine being effective and persisting at parasiticidal concentrations until all the infecting parasites have been killed. Thus the partner compounds need to be relatively slowly eliminated. As a result of this each of the drug is “protected” from resistance by the partner medicine.

The artemisinin compounds are active against all four species of malaria parasites that infects humans and are generally well tolerated. The only significant adverse effect to emerge from extensive clinical trials has been rare type-1 hypersensitivity reactions (manifested initially by urticaria).

These drugs also have the advantage of reducing gametocyte carriage and thus transmissibility of malaria, which contributes to malaria control in areas of low endemicity.

The following ACTs are currenly recommended :

Artemether-lumefantrine, Artesunate+ amodiaquine, Artesunate + mefloquine, Artesunate + sulfadoxine - pyrimethamine.

The artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.

Artemether-Lumefantrine (AL) [6,7,8,9]

This is currently available as co-formulated tablets containing 20mg of artemether and 120mg of lumefantrine. The total recommended treatment is a 6 dose regimen of AL twice a day for 3 days, with the 2nd dose on the first day given any time between 8hrs & 12 hrs after the first dose. The advantage of this combination is that lumefantrine is not available as a monotherapy and has never been used by itself for the treatment of malaria. Lumefantrine absorption is enhanced by co-administration with fat. Therefore this ACT should be taken with milk or fat-containing food.

Artesunate + Amodiaquine [9]

This is currently available as scored tablets containing 50mg of artesunate and 153mg base of amodiaquine, respectively. The total recommended treatment is 4mg/kg bw of artesunate and 10mg base / kg bw of amodiaquine given once a day for 3 days. This combination is sufficiently efficacious only where 28 day cure rates with amodiaquine monotherapy exceed 80%. Resistance is likely to worsen with continued availability of chloroquine and amodiaquine monotherapies.

Artesunate + Mefloquine

This is currently available as separate scored tablets containing 50mg of artesunate and 250mg base of mefloquine, respectively. The total recommended treatment is 4mg/kg bw of artesunate given once a day for 3 days and 25mg base / kg bw of mefloquine usually split over 2 or 3 days. To reduce the acute vomiting and optimize absorption of mefloquine the 25mg/kg dose is usually split and given either as 15mg/kg (usually on the 2nd day) followed by 10mg/kg one day later, or as 8.3mg/kg per day for 3 days. Mefloquine is associated with an increased incidence of nausea, vomiting dizziness, dysphoria and sleep disturbance in clinical trials, but in general it has been well tolerated in this ACT.

Artesunate + Sulfadoxine – Pyrimethamine

This is currently available as separate scored tablets containing 50mg of artesunate and tablets containing 500mg of sulfadoxine and 25mg of pyrimethamine. The total recommended treatment is 4mg/kg bw of artesunate given once a day for 3 days and a single administration of sulfadoxine pyrimethamine (25/1.25mg base/kg bw) on day 1.

Important Aspects of Clinical Management

- Partial treatment should not be given even when patients are considered to be semi-immune or the diagnosis is uncertain. If malaria is suspected and the decision to treat is made, then a full effective treatment is required whether or not the diagnosis is confirmed by a test.
- The artemisinins and partner medicines of ACTs should not be available as monotherapies in order to avoid chances of development of drug resistance.
- Patients with high parasitaemias are at an increased risk of treatment failure and of developing severe malaria and an increased risk of dying, although the relationship between parasite counts and prognosis varies at different levels of malaria endemicity. Hyperparasitemic patients with no other signs of severe disease should be treated with oral artimisinin derivatives under the following conditions:
  a. Patients must be monitored closely for the first 48hrs after the start of treatment.

b. If the patient does not retain oral medication, parenteral treatment should be given without delay.

Non immune patients with parasitemia of >20% should receive parenteral antimalarial treatment.

- Symptomatic treatment of fever is indicated. Paracetamol and ibuprofens are the preferred options.

Management of Treatment Failures

Recurrence of falciparum malaria can be the result of a reinfection, or a recrudescence (i.e. failure), which is difficult to distinguish in an individual patient. If fever and parasitaemia fail to resolve or recur within 2 weeks of treatment then this is considered a failure of treatment.

Wherever possible treatment failure must be confirmed parasitologically-preferably by blood slide examination (as HRP2 based tests may remain positive for weeks after the initial infection even without recrudescence). This should be treated with second-line antimalarial treatments as recommended below, in order of preference:

1. Alternative ACT known to be effective in the region.
2. Artesunate (2mg/kg once a day) + Tetracycline (4mg/kg four times of day) or (doxycycline (3.5mg/kg once a day) or clindamycin (10mg/kg twice a day). Any of these combinations to be given for 7 days
3. Quinine (10mg salt/kg three times a day) + Tetracycline (4mg/kg four times of day) or (doxycycline (3.5mg/kg once a day) or clindamycin (10mg/kg twice a day). Any of these combinations to be given for 7 days

The alternative ACT has the advantage of simplicity, and where available co-formulation to improve adherence. The 7 day quinine regimens are not well tolerated and adherence is likely to be poor if treatment is not observed.

Recurrence of fever and parasitaemia more than 2 weeks after treatment, which could result either from recrudescence or new infections, can be retreated with the first line ACT. However, reuse of mefloquine within 28 days of first treatment is associated with an increased risk of neuropsychiatric sequelae, and in this particular case, second line treatment should be given.

Treatment of Specific Populations and Situations

Pregnancy :

The antimalarials considered safe in the first trimester of pregnancy are quinine, chloroquine, proguanil, pyrimethamine and sulfadoxine-pyrimethamine. Of these quinine remains the most effective and can be used in all trimesters of pregnancy. But artemisinin derivatives should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy, due to the disadvantages of quinine i.e. long course of treatment and the increased risk of hypoglycemia in the second and third trimesters. The recommended treatment is :

First trimester – Quinine + clindamycine given for 7 days, or ACT should be used if it's the only effective treatment available.

Second and third trimesters – Artesunate + clindamycin given for 7 days or quinine + clindamycin given for 7 days.

Inadvertent exposure to antimalarials in early pregnancy is not an indication for termination of pregnancy.

Lactation :

Lactating women should receive standard antimalarial treatment (including ACTs) except for tetracyclines which should be withheld during lactation.

HIV Infected Patients :

Patients with HIV infection who develop malaria should receive standard antimalarial treatment regimens as recommended. Treatment or intermittent preventive treatment with sulfadoxine – pyrimethamine should not be given to HIV patients receiving cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis as there is probably an increased risk of sulfa related adverse effects and the development of drug resistance to SP (due to their similar antimalarial action)

TREATMENT OF SEVERE FALCIPARUM MALARIA

There has been no change in the earlier definition of severe falciparum malaria, which consists of vital organ dysfunction.

Treatment objectives :

- The primary objective of antimalarial treatment in severe falciparum malaria is to prevent death, and in pregnancy, to save the life of the mother.
- Secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities.

The mortality of untreated severe malaria is thought is approach 100%. With antimalarial treatment, the mortality falls to 15-20% overall. Death from severe malaria often occurs within hours of admission to hospital or clinic, and so it is essential that therapeutic concentrations of antimalarials are achieved as soon as possible. Though detailed definitions of severe malaria are available, in practice, any patient whom the attending physician or health care worker suspects of having severe malaria should be treated as such initially. The risks of undertreating severe malaria considerably exceed those of giving parenteral treatment to a patient who does not need it.

Specific Antimalarial Treatment :

Two classes of drugs are currently available for the parenteral treatment in severe malaria : the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Parenteral chloroquine is no longer recommended because of widespread resistance.

Quinine : [10,11]

Quinine treatment for severe malaria was established before modern trial methods were developed. Pharmacokinetic studies suggest that a 20mg salt/kg bw loading dose results in effective blood levels of quinine being reached by the end of a 4 hr infusion or within 4 hr of i.m. administration. If a loading dose is not given, therapeutic concentration may not be reached in the first 12 hrs of treatment. After the first day of treatment, the total daily maintenance dose of quinine is 30mg salt / kg (usually divided into three equal administrations at 8hr intervals). The preferred route of administration is rate-controlled i.v. infusion (not exceeding 5mg salt/kg/hr), but if this connot be given safely then i.m injection to the anterior thigh is a satisfactory alternative. After 48hrs of treatment, if there is no clinically improvement or in acute renal failure or hepatic dysfunction, the maintenance dose should be reduced by one-third to avoid accumulation. Dose adjustments are not required if patients are receiving dialysis.

Artemisinin Derivatives :

The artemisinin derivatives that have been used for the treatment of severe malaria include artesunate, artemether, artemisinin (rectal) and artemotil. The pharmacokinetics properties of artesunate is superior to others as it is water soluble and can be given either by intravenous or intramuscular injection. Ranomised trials camparing artesunate and quinine from South East Asia show clear evidence of benefit with artesunate. [12,13,14] In the largest multicentre randomized trial comparing artesunate and quinine from South East Asia, where 1461 patients were enrolled, mortality was reduced by 34.7% in the artesunate group, compared to the quinine group.[13] So artesunate 2.4mg/kg i.v. or i.m. at time 0, 12hr, 24hr, then once a day is the recommended choice in low transmission area and outside malaria endemic areas. Dose of Artemether is 3.2mg/kg i.m. on admission, then 1.6mg/kg i.m. per day.

The only recent change is the higher maintenance dose of parenteral artesunate recommended (2.4mg/kg), which is based on pharmacokinetic and pharmacodynamic studies and by extrapolation from studies with oral artesunate. Dose adjustments of artemisinin derivatives are not required in vital organ dysfunction.

Follow – on treatment :

Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with the same medicines orally to complete a full 7 days of treatment. In non-pregnant adults, doxycycline is added to either quinine, artesunate or artemether and should also be given for 7 days. Doxyclycline is preferred because it can be given once daily and does not accumulate in renal failure. Clindamycin may be substituted in pregnant women and children as doxyclycline is contraindicated. Mefloquine should be avoided if the patient presented initially with impaired consciousness because of the increased incidence of neuropsychiatric complications associated with it following cerebral malaria.

Severe malaria in pregnancy :

Pregnant women, particularly in the second and third trimester of pregnancy are more likely to develop severe malaria than other adults, often complicated by pulmonary oedema and hypoglycaemia. Parenteral antimalarials should be given in full doses without delay. Artesunate is the first and artemether the second option in the second and third trimesters. As quinine is associated with recurrent hypoglycemia, it is better avoided. In the first trimester as the risk of hyperglycaemia associated with quinine is lower, and the uncertainities over the safety of artemisinin derivatives are greater, both artesunate and quinine may be considered as options.

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MANUSCRIPT SUBMISSION

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Editor, OPJ

Current Concept

Current Perspectives on Statins

* Trinath Kumar Mishra

INTRODUCTION

An epidemic of coronary artery disease (CAD) looms large in the horizon of India. There has been striking increase in CAD prevalence in India. A meta-analysis has shown that CAD prevalence in urban population increased from 4% in the 1960s to 9% in the 1990s and in rural subjects the prevalence increased from 2% in the 1970s to 4% in 1990s.[1] The high rate of CAD is accompanied by a paradoxically low prevalence of conventional risk factors such as hypertension, cigarette smoking and hypercholesterole-mia.[2] The mean total cholesterol in CAD patients is 200 mg/dl in urban and 169 mg/dl in rural subjects.[3]

Given the relatively normal serum cholesterol levels in Indian CAD patients relative to the western counterparts, the role of lipid lowering agents like statins appears debatable on face value. However, several trials conducted over last decades in western countries involved normal people as well as CAD patients with normal serum cholesterol levels and have found beneficial results.[4-6] So the principle may well be, 'lower the better' so far serum cholesterol and low-density lipoprotein (LDL) - cholesterol values are concerned. In this connection reports of various trials have been analysed to have a look and to discuss the role of statins in Indian subject.

AFCAPS / TexCAPS TRIAL

In this primary prevention trial among 6605 males and females, lovastatin was compared with placebo in individuals Without clinically evident atherosclerotic cardiovascular disease with average cholesterol lev-els (mean base-line total serum cholesterol, 221 mg/dl) and below average high-density lipoprotein (HDL) - cholesterol levels (mean base-line level of 36 mg/dl for men and 40 mg/dl for women). The mean follow-up period was 5.27 years. The primary end point analysis was the incidence of first acute major coronary events defined as fatal or non-fatal myocardial infarction (MI), unstable angina or sudden cardiac death. The inclusion of unstable angina was a unique feature of the study. The secondary objectives were to investigate whether long-term treatment with lovastatin, compared with placebo would decrease cardiovascular morbidity and mortality across the spectrum of clinical events which included fatal or non-fatal revascularisation procedures, fatal or non-fatal cardiovascular mortality and CAD mortality besides the 2 primary end points. The tertiary objective was to investigate the safety of the drug.

Treatment with lovastatin resulted in 37% reduction in the risk of first acute major coronary events. The difference between the 2 treatment groups appeared as early as first year. Risk reduction with lovastatin across the spectrum of cardiovascular events was further confirmed by 33% risk reduction in the need for revascularisation and 25% risk reduction in both total cardiovascular and total coronary events. The benefit was demonstrated across all tertiles of LDL-cholesterol. The trial concluded that lovastatin at a dose of 20-40 mg/day reduced the risk of first acute major coronary event in men and women with average total cholesterol and below average HDL- cholesterol levels. The study also provided reassuring data about long-term safety of the statin.

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WOSCOPS Primary Prevention Study

This was another primary prevention study carried out in males with moderately elevated cholesterol levels (mean base-line total cholesterol 272 mg/dl).[7] A total of 6595 men, 45-64 years of age, were randomised to pravastatin 40 mg/day or placebo. The mean follow-up period was 4.9 years. The primary end point was the combined incidence of non-fatal MI or death from CAD. Pravastatin therapy resulted in significant improvements in the lipid profile. Total cholesterol and LDL - cholesterol were decreased by 2096 and 2696 respectively. Triglycerides were decreased by 2096 and HDL cholesterol was increased by 596.

The study demonstrated a 31% risk reduction of CAD death or non-fatal MI in individuals given pravastatin. A subgroup analysis compared event rates between patients with the same LDL-cholesterol levels in the placebo group and pravastatin group and found a lower event rate in the later group. This finding suggests that at least some beneficial effects of statins may be independent of their LDL-cholesterol lowering properties.[8]

Cholesterol and Recurrent Events (CARE) Trial

This secondary prevention trial evaluated MI survivors having average base-line cholesterol level (mean total cholesterol, 209 mg/dl). The study enrolled 4 159 patients, 21-75 years of age, who were randomised to pravastatin 40 mg daily or placebo for 5.7 years. Cholestryramine (8-16g daily) was added to the designated therapy if the LDL-cholesterol levels remained at 175 mg/dl or more after intensified dietary therapy in both groups. The primary end point was non-fatal MI and death from CAD. The trial was designed with an 80% power to detect 20% reduction in the number of recurrent primary end point events with pravastatin. The frequency of primary end point was 10.2% in the pravastatin group and 13.2% in the placebo group, a 24% reduction in risk. There were 26% and 23% reduction in coronary artery by-pass grafting (CABG) and angioplasty respectively in the group receiving pravastatin. The study concluded that benefit of cholesterol lowering therapy extends to majority of patients with CAD, despite having average cholesterol levels. However, the trial could not demonstrate any significant reduction in total mortality.

Lipid Study

Like CARE study, the LIPID study was a secondary prevention trial that evaluated pravastatin in 9014 patients over a period of 6.1 years.[9] The study enrolled patients with broad range of cholesterol levels (165--271 mg/dl). All the individuals had suffered from acute MI or unstable angina between 3-36 months before randomisation. The study population was randomised to pravastatin 40 mg/day or placebo. The relative risk reduction by pravastatin in deaths from CAD was reduced by 24% compared with the placebo.

The LIPID trial provided extremely strong evidence that pravastatin therapy in secondary prevention is clinically beneficial across a broad range of base-line cholesterol values and is associated with a reduction in total and cardiac mortality without any increase in death due to violent behaviour, suicides or accidents.

4S Trial

In this large scale, double blind, placebo controlled trial, simvastatin therapy was evaluated in the patients with earlier MI or angina or both.[10] The mean base-line cholesterol level was 261 mg/dl. In the 5.4 years long trial, 4444 people were recruited and randomised to receive either placebo or 20 mg of simvastatin daily with the allowance of dose titration in an attempt to reduce the serum cholesterol to 116-200 mg/dl. The primary end point was the impact of the drug on total mortality though number of secondary end points were also determined such as coronary deaths, acute and resuscitated cardiac arrest.

In the simvastatin group, total cholesterol was reduced by 28%, LDL-cholesterol by 38% and triglyc-eride by 15%. HDL-cholesterol was increased by 8%. The study demonstrated a significant 34% risk reduction of non-fatal coronary event. This landmark trial demonstrated clearly that statin therapy would reduce mortality in a secondary prevention trial.

MRC / BHF Heart Protection Study

All the trials described so far have proved that statins reduce coronary mortality and morbidity in certain high risk patients. These studies suggested that reduction in LDL-cholesterol by about 40 mg/dl and maintained for 5 years produced a reduction in non-fatal MI and coronary death to about 25%.

The Heart Protection Study (HPS) recruited people hitherto not studied 20536 individuals without diagnosed CAD who have diabetes or non-coronary occlusive arterial disease and they were included besides those having diagnosed CAD. Importantly, many with below average LDL-cholesterol concentration (33.1% had LDL cholesterol below 116 mg/dl) were part of the study group. Interestingly, anyone in whom statin therapy was considered by their own doctor to be clearly indicated was not taken up for the study.

The individuals were randomised to receive 40 mg simvastatin daily or matching placebo. The average period of follow-up was 5 years. In the 2 x 2 factorial design, the study also evaluated role of anti-oxidant vitamins (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily). During the study period, participants and their general practitioners were advised of results emerging from their trials, and encour-aged to use a non-study statin if they considered that it has become indicated.

The primary comparisons were of the effects of allocation to simvastatin of deaths from all cause, from CAD, and from all other causes. Secondary comparisons were of the effects (i) on specific non-coronary causes of death (ii) on major coronary events (defined as non-fatal MI or death from CAD), and on major vascular events (defined as major coronary events, strokes of any type), and coronary or non-coronary revascularisation and (iii) on non-fatal or fatal strokes of any type. The trial demonstrated that all cause mortality was significantly reduced due to a highly significant 18% proportional reduction in the coronary death rate. There were also highly significant reductions of about one quarter in the first event rate for non-fatal MI or coronary death. The benefit of simvastatin therapy was evident even among individuals with LDL-cholesterol below 116 mg/dl. In this later group, risk reduction in rate of major vascular events was 17.6% in Simvastatin-allocated versus 22% in placebo group which was statistically highly significant.

The study concluded that, among the many types of high risk individuals studied, 5 years of simvastatin would prevent 70-100 people per 1000 from suffering at least one of the major vascular events.

The HPS trial is another landmark trial which has established the incontrovertible role of statin in high risk individuals in preventing major coronary events. This beneficial role, of statin was demonstrated irrespective of the base-line serum cholesterol, thus suggesting that there is no threshold value of serum cholesterol below which risk reduction of coronary events cannot be demonstrated. This is in contrast to earlier studies like WOSCOPS which indicated that such a threshold value might exist:

So, where do we go from here? While earlier trials concluded that clinical benefits of statins were entirely explained by their effect on serum cholesterol, there are many additional effects of statins which go beyond lipid lowering. These potential mechanisms include (i) endothelial normalisation, (ii) anti-inflammatory effects, (iii) depletion and physicochemical stability of lipid core, (iv) strengthening of fibrous cap, (v) inhibition of platelet thrombus formation and deposits and

(vi) reduction of thrombogenic response.[8] Of these, effect of statins on endothelial function has received considerable attention in recent years. A beneficial effect on endothelial function helps explain some of the substantial clinical benefits observed in the several trials with stains.

SUMMARY

As the epidemic of coronary artery disease rages on round the globe, research is always on to find suitable drugs to reverse the trend. While aspirin, beta-blockers and ACE inhibitors have been shown to reduce coronary mortality and morbidity, statins are rapidly coming to fore as another important cog in the wheel of primary and secondary prevention of coronary artery disease. Newer trial like Heart Protection Study suggests benefit of statin for high risk individuals, irrespective of initial serum cholesterol concentrations. This may be of great relevance in the Indian context taking into consideration the vast majority of coronary artery disease patients having normal to mildly elevated serum cholesterol in contrast to their western counterparts.

CONCLUSION

- An epidemic of CAD is raging round the world. India is no exception.
- Dyslipidemia is one of the most potent risk factors for CAD.
- Normal values of serum cholesterol found in western people may be too high for Indian subjects.
- Current Trend is to reduce the serum cholesterol level to lowest level possible.
- Statin, a HMG CO A reductase inhibitor is safe as well as effective.

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Current Concept

What is New in Stroke ?

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INTRODUCTION : Cerebro Vascular Accident or stroke, one of the commonest medical emergency in day to day practice of medicine. Gone are the days when physicians were left with supportive care only only with wait and watch policy. Latest developments in the understanding of pathophysiology, use of ^{133}XE to measure cerebral perfusion to novel techniques of laser-speckle-flowmetry has lead to development of new therapeutics and investigational modalities. Let's have a quick reveiew of such new developments in stroke.

Developments in the field of Pathophysiology & Genetics

Recently it has been shown that infection/ inflammation and immune reactions have fundamental role in etiology and pathophysiology of stroke. There is functional interrelation between conventional vascular risk factors, infection/inflammation and genetic predisposition in stroke pathogenesis[1]. Several traditional vascular risk factors are associated with proinflammatory alterations including leukocyte activation and predispose the cerebral vasculature to thrombogenesis on inflammatory stimulation. Accumulation of inflammatory cells mainly monocytes/ macrophages within the vascular wall starts early during atherogenesis. Later on, their activation can lead to plaque rupture and thrombus formation & increasing stroke risk. Inflammatory markers (eg: leukocytes, fibrinogen, CRP) are independent predictors of ischemic stroke. Chronic infections (eg: C. pneumoniae, H. pylori) were found to increase the risk of stroke, however, study results are at variance[1]. Acute and exacerbating chronic infections may act by activating coagulation and chronic infections and may contribute to atherogenesis. Macko et al showed that circulating antithrombotic "Activated protein-C" (APC) was decreased in stroke subjects and those with an antecedent infection/ inflammation had the lowest concentrations of APC. Stroke patients with recent infection/ inflammation had elevated levels of C_4b-binding protein, which binds the anticoagulant protein S, and a distinctively lower ratio of active tissue plasminogen activator to plasminogen activator inhibitor[1]. Ameriso et al found increased D-dimer levels in stroke patients with infection. Following stroke there is delayed expansion of proinflammatory $CD3^+$ $CD4^+$ $CD28^-$ lymphocytes. Increase in median percentage of circulating $CD4^+$ $CD28^-$ T cell lymphocytes were associated with stroke recurrence and poor out come[3]. In carotid atherosclerotic plaques clonal expression of T cells has been seen. The role of Herpes virus, adeno virus, HIV etc. has been speculated to support the clonal expansion of T cells. Few studies predicted the risk of ischemic stroke on the basis of increased leukocyte count, possibly as a result of inflammation. Neutrophilic leukocytosis lasting about one week predicts elevated risk of recurrent stroke. This has been strengthened

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by the finding of reduced risk of haemorrhagic transformation after neutrophil depletion using neutrophil depletion antibodies[2]. Polymorphism of the P-selectin Glycoprotein ligand-1 associated with lower capacity of neutrophils to bind activated platelets were linked to a reduced risk of cerebral ischemia. Polymorphisms in the gene of cathepsin-G & platelet-Activating Factor were associated with increased stroke risk.

Polymorphism in the $EAAT_2$ Gene (Glutamate transporter) leads to increased glutamate concentration in brain and ischemic Injury[3]. Methylenetetrahydrofolate reductase 677 C→T polymorphism is associated with hyperhomocystinemia and risk of stroke[3]. Polymorphisms within the "Phosphodiesterase 4D gene" (PDE4D) on 5q12 are associated with Ischemic stroke[3]. FLAP protein (Five lipoxygenase activating protein) is necessary for syntheis of leukotriens and inflammatory leukocyte mediators. Nine genetic variants in FLAP-Gene (Alox5AP) have been associated with increased stroke risk[3]. Altered expression of Apoptosis-related genes, increased Rho-kinase activity & Atrial-natriuretic-polypeptied gene polymorphisms are associated with ischemic stroke[3].

CADASIL (Cerebral autosomal dominant arteriopathy and subcortical ischemic leukoencephalopathy) is caused by stereotyped mutations within exons 3,4,5,6 of the Notch-3 gene resulting in recurrent stroke & dementia with deposition of Notch-3 in arterial smoooth muscle. Studies shows that Notch-3 is dispensable for normal development and inhibition of its production could be a potential treatment. Regulatory elements between -13 & -1.5 kb of Notch-3 inhibits its transcription[3]. Mutations in Krit1 and malcaverin leads to perturbation of β1-integrin mediated endothelial cell angiogenesis leading to cerebral cavernous malformation[3]. G-protein B_3 (GNBB) 825T allele is an independent risk factor for non-cardio embolic ischemic stroke as it infers protection against atrial fibrillation[2]. Promotor variants in the eNOS gene are associated with early-onset-ischemic stroke[2]. BAD, a protein of pro-apoptotic bcl-2family expression has important role in cell survival and death. BAD pathway plays an important role in neuronal cell death after cerebral ischemic. Leukoaraiosis, has been shown to predispose to intracerebral haemorrhage and anticoagulant associated recurrent haemorrhages. The subtype of ischemic stroke most strongly predicted by leukoariosis is lacunar infarct. Studies have shown that matrix metalloproteinases are elevated after stroke. Higher levels of MMP-9(> 140 ng/ml) is associated with haemorrhagic transformation and thrombolysis failure following rt-PA administration leading to hemorrhagic infarct[5,6].

Linkage analysis have shown that new loci 5q22q31, 7q11, 14q22, 19q13 are associated with Intracranial aneurysms[3]. ACE 1 Allele, TAFI homozygotes and fibrinogen allele genes were associated with decreased recanalisation rates following rt-PA infusion.

β1-Adrenergic receptor polymorphism moderates the risk of cardiac injury after SAH. This is due to excessive release of catecholamines from myocardial sympathetic nerves[3]. Left insular stroke is associated with neurogenic stunned myocardium & ischemic preconditioning phenomenon.

Developments in Neuroimaging

There has been spectacular development in the field of stroke as far as neuroimaging is concerned. Latest guidelines and recommendations of stroke council of the American Heart Association has solved many diagnostic problems[7].

Xenon enhanced computerised tomography (XeCT) can be used to acquire

quantitative data, especially absolute values of cerebral blood flow and may be helpful in determining the risks & benefits of revascularisation of the acute stroke patient, including post-thrombo-lysis hemorrhage (Grade A). XeCT perfusion imaging with an acetazolamide challenge test can be used to define a group of patients with chronic ischemia who are at significant risk for infarction (Grade A).

Single photon Emission CT (SPECT) studies can be used to determine the relative risks of haemorrhage following thrombolysis in acute stroke patients, whatever the time after onset of symptoms (GradeA).

Perfusion-weighted (PW) and Diffusion-weighted (DW) MRI can image not only cerebral perfusion but also status of the cerebral tissue and patency of the vasculature. PW1 and DW1 has been recommended as techniques capable of demonstrating severly ischemic tissue. The techniques are probably useful at differentiating between reversible and irreversible ischemic tissue (Grade B).

It has been postulated that HARM (Hyperintense Acute reperfusion-marker-Gadolinium enhancement of intrasulcal space) on Flair-MRI is associated with reperfusion and haemorrhagic transformation. Echoplaner gradient-Echo MRI is more effective for detection of thromboembolic occlusion of of MCA-territory than CT[2]. High resolution gradient Echo. T_2 -weighted images can identify site of acute occlusion in all major cerebral arteries[3]. PET using penumbral marker ^{18}F-Misonidazole (^{18}FM180) shows the evidence of existence of ischemic penumbra in white matter. Laser specle-flowmetry is more effective than laser-doppler flowmetry to image different arterial territories bilaterally and simultaneously and to differentially assess flow changes in the cerebral vasculature[2]. Line scan diffusion MRI probably the most relible technique to diagnose spinal cord infarction in the acute setting.

Developments in the field of Management

Till now intravenous rt-PA within 3 hours of onset of ischemic stroke is the only GradeA recommendation of the American stroke council in the thrombolytic category[8]. Intra arterial thrombolysis alone or in combination with I.V. thrombolysis holds great promise, but the use of these approaches is preferable in the settings of randomized clinical trials. Extension of the window period of I.V. thrombolysis beyond 3 hours is now the field of interest. Combined systemic thrombolysis with half dose of rt-PA and Abciximab, IV thrombolysis within 3 to 6 hours using multimodal MRI selection protocol, IA thrombolysis following full dose of IV rt-PA low dose Argatroban (direct thrombin inhibitor) with IV rt-PA, rt-PA with VELCADE (proteasome inhibitor), preactivation of rt-PA, with plasminogen, IV rt-PA with Eptifibatide, early treatment using Abciximab alone etc. have shown promising results but still in experimental stage[3]. Microbubbles administration, induces further acceleration of ultrsound enhanced thrombolysis in patients treated with IV rt-PA[3].

Thrombin-Activable-Fibrinolysis-inhibitor (TAFI) is a newly identified endogenous fibrinolysis inhibitor. It is a factor for resistance to rt-PA. After blocking several residues from fibrin, plaminogen binding sites are eliminated and fibrinolysis is inhibited consuming plasma TAFI levels. So low TAFI levels predict rt-PA induced recanalization resistance[2]. Circadian fluctuations of endogenous Fibrinolysis plays a role in the success of thrombolytic therapy. Recanalisation said to be more frequent in the afternoon whereas most reocclusions occur in the morning hours.[2] Gender differences also has some role in thrombolysis. Women

recanalise more frequently than men after IVrt-PA.[3] Newer thrombolytic drugs like Teneckteplase, Desmoteplase are under evaluation now.[3]

Hyperbaric oxygen along with Edavarone, NXY-059 - a nitrogen based free radical trapping agent[9], Glycogen-synthase kinase 3β inhibitor,[2] MMP inhibitors BB94[2], STAZN (Stilbazulenyl nitrone) have proved to be effective in Acute Ischemic Stroke (AIS).

Peroxisome proliferator-activated receptor-γ agonist (PPAR-γ) e.g. rosiglitazone reduces infarct volume with functional recovery in AIS.[3] Erythropoietin enhances proliferation, differentiation, and mobilisation of Endothelial progenitor cells leading to repair of injured vascular endothelium & angiogenesis.[3]

Statins ameliorate cerebral vasospasm, maintain cerebral autoregulation and reduce the incidence of ischemic deficits after aneurysmal SAH. They also reduces cerebral infarction in AIS via inhibiting NADPH oxidase derived superoxide.[3] Studies show that Magnesium Sulfate reverses cerebral vasospasm and reduces delayed cerebral ischemia in aneurysmal SAH.[3]

Use of Recombinant Hb-polymers, bone marrow stromal cells, Neural stem cells, Endothelial progenitor cells, Granulocyte colony stimulating factors in AIS are in experimental stage now, though the results are encouraging.[3] Local surface cooling with a cooling helmet suppresses the brain swelling in AIS.[3] Novel peptides like Ependymin, Human Albumin etc. has neuroprotective role.

For the first time, solid evidence is emerging on the management of strokes due to Intracerebral hemorrhage. Recombinant factor 'VIIa' is found to be effective when given in early hours. It significantly reduces hematoma growth, disability, mortality and improves global functional outcome at 90 days. It is associated with a small increase in the risk of acute thrombo embolic events which is not statistically significant.[11]

Preventive Strategies :

American stroke council has recommended Aspirin, Combination of Aspirin with extended release dipyridamole or clopidogrel for secondary prevention of ischaemic stroke.[8] Recent reports have shown clopidogrel & aspirin unresponsiveness in AIS patients.[3]

Ximelagatron, a novel oral direct thrombin inhibitor under investigation (SPORTIF TRIAL) as an alternative anticoagulant to warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation.[3] Argatroban, a direct thrombin inhibitor is also under trial.[3]

Recent studies have suggested that drugs that increase angiotensin 2 (AT_2) formation including thiazides, CCBs & ARBs, may be more effective in stroke prevention than AT_2 suppressive drugs such as ACEIs and β-blockers. LIFE trial showed that Losartan, reduces the rate of stroke by 25%.[2]

PLAATO (Percutaneous Left atrial appendage Transcatheter occlusion) is used to seal left atrial appendage to eliminate the source of thromboembolism and should be preserved for patients if they have a contraindication against warfarin therapy.[3] A permanent arterial Filtration diversion device (the Diverter) is an upcomming modality to prevent the embolic phenomenon.[2]

Physical activity improves neovascularisation in the postischemic brain.[3]

Neurochemical Study :

In AMI, biomarkers are an integral part of the diagnosis & management. Studies are in process to establish the relevance of such biomarkers in diagnosis and management of stroke.

One study found that the neural biomarkers were high among stroke patients compared to controls e.g. CRP, D-Dimer, MMP-9, Brain-natriuretic-polypeptide, Neuron-specific enolase & caspase-3 except for lower levels of secretagogin. Best specificity was for caspase-3 (78%) & sensitivity for D-dimer(81%). Combinations (i.e. Caspase 3+ D-dimer + MMP-9) gained specificity (92.8%)[3]. Elevated levels of specific phenotypes of circulating Endothelial membrane-microparticles (ECMP) in peripheral blood of stroke patients were associated with stroke severity[3]. Increased levels of H-CRP & IL-6 were associated with silent brain infarction & raised IL18 was associated with increased carotid Intimal median thickness.[3]

CONCLUSION

Research in the field of stroke is fast advancing. Advancement in the field of Genetics, Understanding of pathophysiology radiodiagnosis, and detection of serial biomarkers have brought a new hope for successful management of stroke patients.

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Case Report

Symmetric Peripheral Gangrene in a Case of Falciparum Malaria - A Rare Presentation

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ABSTRACT

Symmetric peripheral gangrene (SPG) is a rare clinical presentation in case of falciparum malaria. Few cases have been so far reported from India and abroad. Here we report such a case from this hospital and discuss the pathophysiology and management.

KEY WORDS

Symmetric peripheral gangrene (SPG), Falciparum malaria, Disseminated intravascular coagulation (DIC)

INTRODUCTION

SPG is an uncommon clinical condition characterized by sudden onset of symmetric dry gangrene of acral distribution without any evidence of vasculitis or arterial obstruction. This has been described in conditions like infections most commonly bacterial (meningococcal, streptococcal, Pneumococcal, *E.coli* septicaemia) and viral (varicella and viral gastroenteritis), low output states like myocardial infarction, shock, CCF or use of drugs like vasopressin and ergot and other conditions like polymyalgia rheumatica,cryoglobinaemia. In all these conditions DIC has been the basic pathogenesis (90%)[9].

The incidence of DIC and SPG in cases of falciparum malaria has rarely been reported as one of its multiple complication[1].

CASE REPORT

A 15 years boy from Raigarh (C.G.) admitted to this hospital in last week of December 2005 with history of fever associated with chill and rigor (20 days), sudden blackening of distal parts of fingers, toes of all limbs , tip of nose and lateral part of pinna of both ears (15 days) and altered sensorium for 3 days. He was treated at the local hospital with I/V fluid, antibiotic and decadron , without any improvement.

There was no history of joint pain, trauma, sore throat, spontaneous bleeding, thromboembolic episode or any relevant disease like SCD, HTN, DM. He was a student in a residential school without habit of smoking or alcohol. There was no relevant family history.

On examination the patient was stuporous with Temperature 100^0F , pulse – 100/min , regular low volume and all the peripheral pulsations well felt without brachiofemoral delay. BP was 110/70 mm of Hg (both U/L), with moderate pallor and features of dehydration. There was no icterus , clubbing, lymphadenopathy or thyromegaly. Cardiovascular and Respiratory system revealed no abnormality. There was no hepatosplenomegaly. Neurological examination revealed mild neck rigidity with diminished DTJ and plantar was flexor. Examination of skin and digits showed blackening of tip of nose

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(Fig.1), both ear pinna on lateral aspects (Fig 2) and distal parts of toes and fingers of all limbs (dry gangrene) (Fig 3 & 4). There was clear line of demarcation between the healthy and affected parts.

Investigation on the day of admission showed

Hb: 6.2 gm%, DC : N - 48, E-2, L-48, M-2, B-0, TLC: 9800/mm^3 TPC: 60,000/mm^3 RBS : 116mg% B. Urea : 96mg% Serum Creatinine : 1.5mg%

Blood smear : Showed P.falciparum rings and gametocytes

LFT : Serum Bilirubin : Total 0.78mg% Direct 0.26mg% SGOT: 39U/L SGPT : 36U/L

Alkaline phosphatase: 50U/L

Electrolytes: Serum Na+-138meq/L

Serum K+ - 3.6meq/L

Serum Ca++ - 8.5 mg/dl

Prothrombin time (PT) – 16 second (control 12.5) Activated partial thromboplastin time (aPTT) 29.5 seconds (control – 28)

Fibrinogen : 187mg/dl (N : 250-450mg/dl)

The patient was treated with injection Artesunate, injection Ceftriaxone 2gm I/V

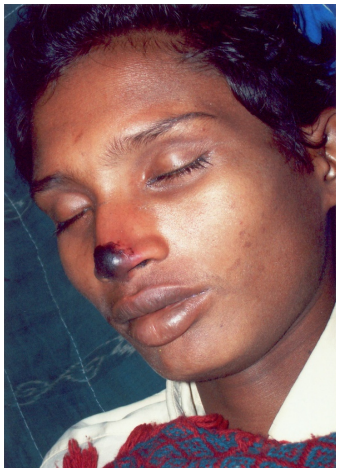

Figure 1

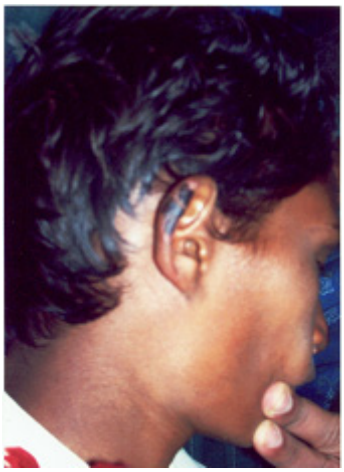

Figure 2

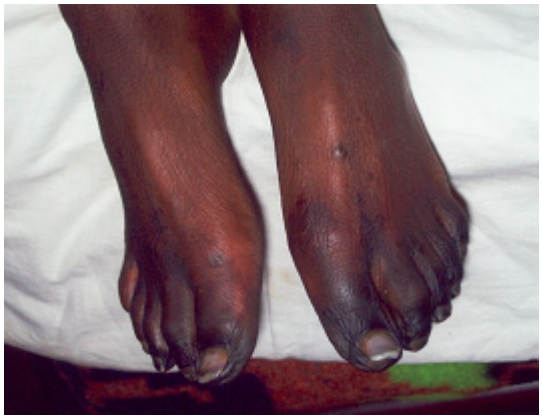

Figure 3

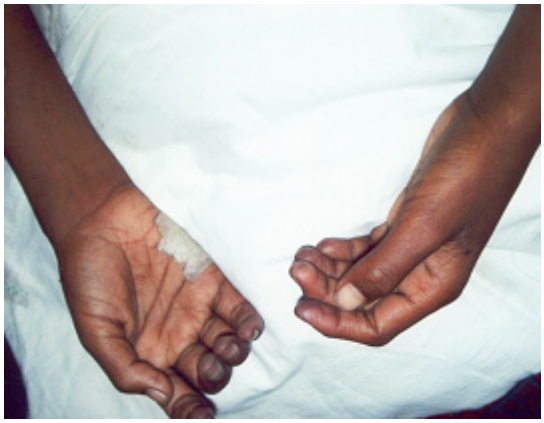

Figure 4

BID,injection Omnacortil, Injection Ranitidine 8 hourly, I/V fluid and tablet Cilostazol 100mg BID with care of the skin , bladder, bowel and maintaining nutrition. He was stabilised on 2nd day and gained consciousness and there was clinical improvement. Two units of whole blood transfusion given.

On further investigation urine analysis was normal and haemoglobin electrophoresis was AA (to exclude SCD – common in this belt). USG of abdomen and pelvis was normal. Test for antinuclear factor, LE cell, Rheumatoid factor, VDRL were negative, Test for cryoglobulin was normal. Coagulation profile, Antineutrophil cytoplasmic antibodies, Antinuclear antibodies, anti double stranded DNA, complement –3 , complement – 4 were normal. Serum uric acid was 3.9 mg/dl.

Echocardiography did not reveal any thrombi or vegetation. The Doppler study of the vessels demonstrated normal flow pattern upto digital arteries in all four limbs.

Biopsy of an affected area of the skin showed thrombi in dermal capillaries without any evidence of vasculitis.

Blood could not be tested for fibrin degradation products (FDPs). However evidence of DIC was seen in skin biopsy.

Gradually the patient improved. Full anti-malarial course was given and antibiotic was given for 7 days. Zilast was continued and omnacortil was gradually tapered. Slowly the gangrenous parts improved and patient was discharged on 12th day. No surgical intervention was required.

DISCUSSION

SPG has been reported in various medical conditions including falciparum malaria[1, 7, 4, 2, 6,12]. Our patient had no clinical or laboratory evidence of other causes like sepsis, vasospastic condition, ergot or other drugs. There was no evidence of vasculitis, cryoglobulinaemia, polycythemia or thrombocythaemia. The common pathogenic mechanisms of SPG is DIC[9]. All the cases reported had evidence of DIC.

Reduced fibrinogen level, thrombocytopenia, prolonged PT, prolonged aPTT and histopathological evidence of microvascular thrombi indicate the presence of DIC in this patient[1].

Alteration of coagulation and fibrinolytic system in falciparum malaria is well recognized[5]. A functionally active but controlled coagulatory state exists in falciparum malaria even in uncomplicated cases[5]. Elevation of FDPs reflecting the ongoing fibrinolysis have been documented[11]. Heavy parasitaemia triggering the coagulation pathway[10], alteration in the lipid distribution across the surface membrane of the parasitized erythrocytes activating the intrinsic coagulation cascade[8] and activation of complement system[5] have been postulated as possible mechanism for DIC in falciparum malaria. Sequestration of the parasitised erythrocytes in the microcirculation by molecular interactions with endothelial receptors, mainly intracellular adhesion molecule[10] – 1(ICAM – 1) may occur. Rosetting of the healthy erythrocytes around parasitised red cells may occur and these multicellular aggregates further exacerbate the vascular obstruction caused by sequestration[3].

DIC is encountered in less than 10% of patients with cerebral malaria[3] and manifest as spontaneous bleeding from gum and GIT. But in a review of 71 cases of SPG and DIC significant bleeding complications were not recorded[9].

Our patient who had no other cause of peripheral gangrene made satisfactory

recovery on specific antimalarial therapy supporting the observation that falciparum malaria was the triggering mechanism for the DIC and subsequent SPG.

CONCLUSION

In conclusion we report that falciparum malaria may present as peripheral dry gangrene and this possibility though uncommon must be taken into consideration while encountering patients in endemic areas.

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