Serum Cholesterol in Cirrhosis of Liver

Sir,

A male (34 years) who consumed more than 80 grams of alcohol per day for more than 10 years was admitted in a hospital in Mumbai in 1994 with deep jaundice, ascites, fever and drowsiness. He was diagnosed as alcoholic hepatitis with cirrhosis of liver. His serum total (direct) bilirubin was 53.8 (37.8) mg/dl. He recovered from hepatic coma within two weeks. He was re-admitted in 1995 with hematemesis due to grade III esophageal variceal bleed and was treated with sclerotherapy followed by band ligation in 1997. He was administered propranolol (10 mg bid) and isosorbide mononitrate (10 mg bid) to lower portal venous pressure and reduce chance of rebleeding.

In 1998 he presented with fever and ascites and was diagnosed as spontaneous bacterial peritonitis (SBP). He recovered with ofloxacin (400 mg bid) for 7 days. He kept reasonably well with salt restriction till October 2003 when he again presented with ascites and fever. His bilirubin was 32 (18) mg/dl, prothrombin time (PT) 26 seconds (control 12 seconds), partial thromboplastin time (PTT) more than 100 seconds (control 32 seconds). Ascitic fluid showed cell count of 10,300/ml (polymorphs - 98 %), total protein (albumin) of 0.5 (0.3) gm/dl, indicative of SBP. He was treated with ofloxacin (400 mg bid for 7 days). On discharge there was no ascites on ultrasonography of abdomen and bilirubin was 21.2 (12) mg/dl. In January 2004, he died of variceal bleeding and hepatic coma.

Hemoglobin 7.1 gm/dl, MCV - 100, white cell count 5470/ml, platelet 74,400/ml, ESR 1 mm (wintrobe) and 5 mm (westergreen), creatinine 0.8 mg/dl. Liver function tests and serum cholesterol are shown in Table 1. HBsAg, Anti - HCV, Anti - HEV were negative. CT scan and MRI abdomen were suggestive of cirrhosis of liver with no suspicion of hepatoma. Isotope liver spleen scan with sulphur colloid showed an enlarged (16.2 cms) hot spleen with colloid shift to marrow and hepatic perfusion index = 0.81 (normal 0.4). Apolipoprotein A1 was <30 (96 -176 mg/dl) mg/dl and apolipoprotein B was 43 (43 - 128 mg./dl) mg/dl.

The patient was suffering from Child C cirrhosis with low albumin (2.3 gm/dl), prolonged PT (26/12) and PTT (> 100/32) and very low total cholesterol (< 10 mg/dl) from 26.09.2003 to January 2004. Low cholesterol in Child C cirrhosis is due to reduction of cholesteryl ester. High serum cholesterol with intra and extra hepatic cholestasis is due to an increase in free cholesterol. The progressive decrease in serum cholesterol has a prognostic significance; patients with serum cholesterol less than 100 mg/dl have a high mortality risk during 2 years follow up.[1] In cirrhosis apolipoprotein A (apo-A1) levels were decreased with excellent correlation with liver function tests.[2] Apo A1 not only indicates severity of cirrhosis of liver but also predicts liver function after liver transplantation.[2] Apolipoprotein A1 and B deficiency suggests advanced cirrhosis of liver while isolated apolipoprotein B deficiency suggest etiology of cirrhosis.[3]

Our patient showed a persistently low total cholesterol value of < 10 mg/dl (lowest ever recorded in literature) for four months, while had significantly low values for about 10 years.

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Table 1 : Liver function tests and serum cholesterol

Date	Total.(Direct) Bilirubin mg/dl	SGOT U/L	SGPT U/L	PT Secs	SAP * U/L	Albumin gm/dl	Total Cholesterol mg/dl
30/6/94	53.8 (37.8)	70	17	19	123	3.3	79
8/11/95	4.3 (1.9)	76	42	—	169	2.9	146
18/7/96	4.1(1.9)	114	55	—	121	3.0	141
9/7/97	2.4 (1.4)	46	30	—	153	2.5	103
26/2/99	1.4 (0.5)	57	49	—	156	3.0	118
3/8/2000	3.4 (1.5)	93	68	—	171	2.7	88
6/9/2000	3.5 (1.7)	115	78	21.5	177	2.4	72
16/1/2001	2.8 (1.4)	80	71	18.3	207	2.8	84
16/5/2002	3.0(1.5)	84	55	24	243	2.7	80
26/9/2003	18.5(11.2)	124	73	26.2	217	2.1	< 10

* SAP = Serum Alkaline Phosphatase.

Dandy-Walker's Variant Adulthood Presentation

Sir,

Dandy and Kenneth Daniel Blackfan in 1914 described a 13 months child with the combination of hydrocephalus, cysts in the posterior fossa of the skull, and hypoplasia of the vermis of the cerebellum.[1] Classical Dandy Walker malformation consists of a triad of complete or partial agenesis of vermis, cystic dilatation of 4th ventricle of brain, enlarged posterior fossa with upward displacement of lateral sinuses tentorium and torcula. Dandy Walker variant consists of variable dysplasia of the vermis without enlargement of posterior fossa.[2] We describe here a case of adulthood presentation of Dandy-Walker's Variant.

A 25 years female presented to Medicine Department with a history of disturbance of gait of two years duration. She denied history of any drug intake, fever or trauma. There was uneventful birth history and childhood except delayed achievement of milestones. Her family history was non-significant. Her general physical examination was non-contributory. On central nervous system examination her higher mental functions were normal and speech and memory were intact. She had truncal ataxia and walked with the legs widely separated. She also had symmetrical nystagmus along with ataxia. But other cerebellar signs such as dysmetria, intention tremor, dysdiadochokinesia, abnormal rebound, nose-finger-nose, heel-knee-shin, scanning speech were absent. She had normal power in all four limbs. The tone and deep tendon reflexes in all four limbs were normal and planters were bilaterally flexor. Sensory system was normal. Her bladder and bowel were intact. Cardiovascular system, respiratory system and abdomen were essentially normal.

Investigations showed Hb of 9 gm% and biochemical parameters were in normal range. Chest X-ray and echocardiography showed no cardiac abnormality. Ultrasonography for abdomen was normal. Fundoscopic examination showed normal optic disc. Electroencephalography was normal. Spiral CT head showed partial agenesis of cerebellar vermis, dilatation of the fourth ventricle having communication with cisterna magna. There was no other cerebral or cerebellar anomaly (Fig. 1). Considering the history, clinical examination, investigation and spiral CT findings, there was no second thought in making a diagnosis of Dandy-Walker variant with atypical adult onset presentation.

The Dandy-Walker syndrome is a malformation of the brain that involves the maldevelopment of the cerebellum, associated with a cystic enlargement of this area, and frequently hydrocephalus. This malformation occurs in approximately one in 25,000 babies. It accounts for approximately 1-4% of cases of hydrocephalus and is seen more frequently in females than in males. Its aetiology is uncertain. In some rare cases, the disease is a dominant or recessive inheritable trait. The usual clinical presentation is early in life with hydrocephalus and a prominent occiput.

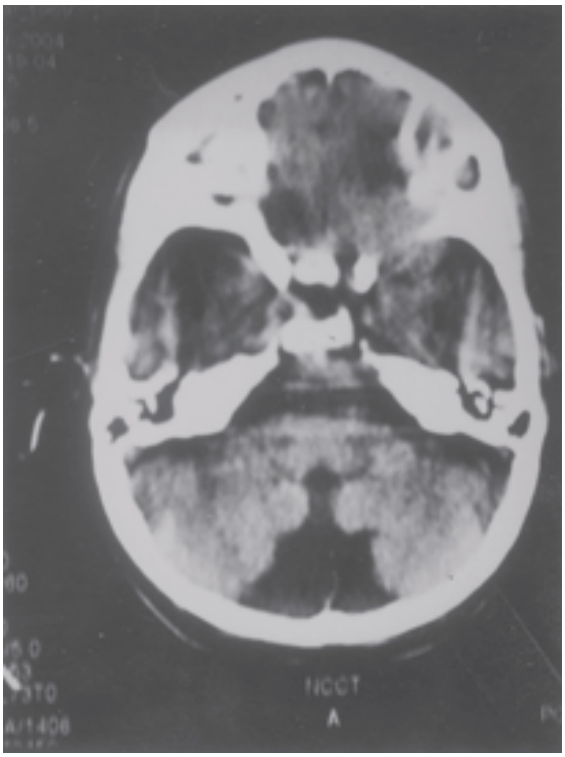

Fig. 1 : Spiral CT scan showing partial agenesis of cerebellar vermis and dilatation of IVth ventricle, communicating with cisterna magna.

The majority of patients are usually diagnosed within the first year of life. There is progressive enlargement of the head, congested veins in the scalp, bulging of anterior fontanelle and separated cranial sutures. Delay in intellectual development is a common feature of the Dandy-Walker malformations. In adults, cerebellar signs tend not to be prominent. But cranial nerve palsies, nystagmus and truncal ataxia have been described. The commonest associated CNS anomaly is ventriculomegaly and commonest non-CNS anomalies are structural heart defects. In general, the outcome is worst if there are associated abnormalities and best for isolated Dandy-Walker variant.[3]

Radiological diagnosis is relatively straight forward for Dandy-Walker malformation. Prenatal ultrasonography diagnosis can be made at 18 weeks of gestation. CT scan is single most useful diagnostic procedure. The Dandy-Walker malformation is surgically treatable. The available treatment requires that a shunt from the interior of the brain or cyst is inserted to allow the continuous drainage of the blocked non-flowing CSF. The primary malformation of the brain, however, cannot be corrected, and these patients continue to have problems with motor coordination and balance as well as with learning to walk. If a chromosomal abnormality is identified and associated with other anomalies, appropriate genetic counselling should be given. If there are no associated abnormalities and the chromosomes are normal, the recurrence risk is 1 to 5 percent.[3]

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Thrombocytopenia and TNF-α Levels in Malaria

Sir,

The original article by Jadhav *et al*[1] in the Aug. 2004 issue of JAPI, on correlation of type and severity of malaria to thrombocytopenia was critically appraised by a studied editorial on malaria hematopathy, in the same issue.[2] In past, attempts to correlate the type and severity of malaria, to the clinical and laboratory features have faced major challenges.[3,4]

In our research study in patients with malaria (n=20), we had carried out intense profiling of parasitic, haematological, biochemical and immunological markers associated with malaria. We too observed thrombocytopenia in 15 patients (75%) - 51.7 ± 22.3 x 10^3/mm^3 (M ± SD). However, there was no correlation observed with severity vis-a-vis with the type of the malarial parasite. However, with therapeutic response there was a significant increase in the platelet count in 12 patients to 175.9 ± 99.5 x 10^3/mm^3 (M ± SD; $p < 0.001$) in seven days. Despite occasional literature reports of bleeding with marked thrombocytopenia[5] we, like Jadhav *et al*, did not find any evident bleeding.

The pathogenesis of underlying thrombocytopenia in malaria is not well understood. Pro-inflammatory cytokines like TNF-α, IL-6 and IFN-γ have been reported to play an important role for diverse features of malaria, including thrombocytopenia.[6,7] In our study, we had assayed TNF-α by ELISA, basal and on day 1, 3 and 7 of treatment. Table 1 shows TNF-α data in patients (n=8) with platelet counts less than 75 x 10^3 basaly. There was a significant increase in platelet count on the day 7 ($p < 0.01$). However, decrease in TNF-α did not show statistical significance (due to a wide range and some outliers) but definite directionality of an in the platelet count was seen in all the patients. TNF-α has been recently reported to induce thrombocytopenia and platelet fragmentation both in vivo and vitro experiments.[8] The observations in our study need to be followed up in a large study, possibly involving platelet function tests, aggregation etc. with concurrent assay of pro-inflammatory and anti-inflammatory cytokines.

CS Godse*, AB Vaidya, PS Tathed+, RA Vaidya*****

Table 1 : Platelet count and TNF-α levels in malaria patients basal (0'D) and on 7th day of treatment

ID	Platelet count n x 10^3/mm^3		TNF-α pg/ml	
	0'D	7'D	0'D	7'D
1	25	172	15.6	18
6	29	148	310	5.2
11	51	159	52	20
12	39	77	470	20
14	22	156	330	5.4
15	45	75	46	10
16	57	91	50	11
21	68	140	13.5	7.2
22	49	41	145	42
Mean ± SD	42.8 ± 14.9	117 ± 45.5#	159.1 ± 158.7	15.4 ± 11.3@

#P < 0.01 @ NS compared to basal values

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Cost Effective Treatment of Acute, Uncomplicated *Plasmodium falciparum* Malaria

Sir,

We read with interest the article "a cost effective analysis of three anti-malarial treatments for acute, un-complicated *Plasmodium falciparum* malaria in Mumbai, India" published in September issue of JAPI (page 877-879) by Gogtay *et al*. Paul Russell wrote in 1946 "but all the evidence we possess would seem to indicate not that poverty is responsible for

malaria but malaria maintains poverty". This view is today widely shared by international organizations and governments. Same is true for this article.We appreciate the contribution by authors which probably is first of it's kind in the country and could serve as a base line information for policy-makers in the areas of high grade chloroquine resistance in the era of resurgent malaria in the country.We would like to give our comments, which will further widen the relevance of the article:-

1. Authors have attempted to address the problem of "when it is appropriate to switch to a more expensive but more effective anti-malarial". In this respect we fully agree with the formula given by Philips & Philips which is easily applicable to almost all areas of India where falciparum malaria is a problem.
2. As authors have quoted "the limitation of our study are that it is post hoc based on retrospective clinical trials data that did not originally incorporate an economic component and obtained in a tertiary referral center where the patients seen are on an average more serious". Why un-complicated patients of *P. falciparum* hospitalized at a referral center to increase the cost of treatment. Whether in anticipation of complications, and if so why chloroquine was used and not quinine/mefloquine/ artimisinine compounds were used?
3. As per study mefloquine is a better drug with no resistance, but it has the potential to increase neuro-psychiatric sequel so it may not be a suitable alternative. Simultaneously it is evident from the present study that coartemether has 4.6 percent RI though not yet marketed in India so it may not be a promising drug to the trust of time, which also supports World Health Organization warning against indiscriminate use of artimisinine compounds.
4. Furthermore the authors have said "the major issue to be addressed in economic analysis in malaria is the growing tension between expensive drugs that work and cheap drugs that are rapidly losing efficacy" and they have attempted to address this issue in this paper. While in our country people are using newer and expensive drugs without knowing the strain of parasite when a patient presents with high grade fever without complications in remote areas and by the time patient reaches at referral / higher level neither the peripheral blood film will be informative nor the patient has any details of treatment given by quack or a health worker which poses a practical problem regarding cost, complications and drug resistance to newer anti-malarials.

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Reply from the Author

Sir,

We thank Shubakaran and Jakhar R for their insightful comments on our paper on "A cost effectiveness analysis of three anti-malarial treatments for acute, uncomplicated *Plasmodium falciparum* malaria in Mumbai, India[1] and would like to respond to their comments. 1. The reason why paients with uncomplicated falciparum malaria were admitted and not treated on an outpatient basis was because they were all subjects in clinical trials where hospitalization was a pre requisite for safety and efficacy evaluation. 2. Chloroquine and not quinine was used as the comparator because it was the drug of first choice for falciparum malaria at the time of conduct of these trials in 1996-98. 3. The resistance of 4.6% seen in coartemether was of the RI type, a relatively mild type of resistance picked up during the course of follow up. while the drug is not yet marketed in India, it may be premature to comment on its anticipated efficacy, given the fact that the patients treated with it during the course of the trial were seen in a tertiary referral center and on an average more serious than patients seen in primary care. 4. Finally we agree that all antimalarials and particularly artemisinin derivatives need to be used judiciously. Efforts also need tobe made at all levels to improve diagnostic facilities, which still represents a major problem in the country.

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Received : 24.11.2003; Accepted : 24.2.2004

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Epidemic of Leptospirosis : An ICU Experience

Sir,

The article by Chawla *et al*[1] should be of interest to clinicians dealing with leptospirosis in the Indian population. The prognosis can be broadly guessed and the outcome be explained to relatives on the basis of data cited.

Our experience on 115 documented cases managed in south India (central Kerala) also was more or less on par with the observation made by Chawla *et al*. Pulmonary involvement was observed in 54 of whom chest skiagram showed variable pattern in 46 patients (85.1%). Ventilation support was offered to 43 patients who presented with features of Adult Respiratory Distress Syndrome (ARDS). Of them 33 patients

died following multiorgan dysfunction (76.7%).

Patients developing multiorgan dysfunction presenting as encephalopathy, coagulopathy, ARDS and/or refractory hypotension had an unfavourable outcome. A distinct group (44.3%) with only hepatic and renal involvement of insidious onset had full recovery.

Therefore, there are two distinct clinical syndromes for leptospirosis - one with isolated involvement of liver, and/or kidney offering better prognosis and the other, with early pulmonary involvement and stormy onset, often associated with multi system disease.[2] Early recognition and timely management without waiting for microbiological confirmation form the essence of the management.

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Reply from the Author

Sir,

We sincerely thank VP Gopinathan for the keen interest and valuable comments regarding the article.

Previously leptospirosis was described as having two classical forms of presentation-less severe anicteric form and icteric form associated with higher incidence of complications and mortality. Also manifestations of pulmonary involvement were thought to be appearing late in the course of clinical illness and often pre-terminal.[1] But anicteric cases with severe and frequently fatal hemoptysis have been reported from China and early pulmonary haemorrhages are described in patients without jaundice or renal failure in study from Nicaragua[2] consistent with findings of VP Gopinathan.[3] These reports will help clinicians in early identification of patients at high risk of mortality. However, bacteraemia, secondary to pneumonia, indwelling catheters, blood transfusion may complicate the course of otherwise recovering patients[4] and isolated hepatic and renal involvement may not necessarily augur favourable outcome in such patients if clinicians are not adequately vigilant in prompt detection and treatment of such secondary infections.

ARDS and alveolar haemorrhages[5] are two of the most fatal conditions in not only leptospirosis but in other tropical infections like malaria, dengue and tuberculosis as well. Other forms of pulmonary oedema secondary to myocarditis, renal failure and over hydration must be differentiated from ARDS. Earlier reports painted a gloomy picture of outcome in these patients but with the use of mechanical ventilation applying lung protective strategies based on the use of low tidal volumes, scenario is now changing for the better.

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