Wilson's Disease

Sir,

I read with interest the review article 'Wilson's Disease' by Singh et al that appeared in J Assoc Physicians India.1

However, in this context I would like to draw your attention to the fact that the clinical presentation of Wilson's disease in India does not always follow the pattern as is usually seen in the Western world. Wadia et al2 first drew attention in this regard and observed that generalized osteoporosis, rickets, or even renal rickets without any involvement of the liver or the central nervous system could be the striking manifestations, at least in eight out of 23 patients. The authors suggested that these unusual features could be indicative of the modification of one gene or even of the involvement of multiple alleles. Dastur et al3 felt that this variation in clinical manifestations could be attributable to the modification of a suppressor gene and interestingly, serum copper oxidase level was found uniformly low in their study.

Maghani et al,4 in a follow-up study similarly observed a low serum copper oxidase level in those patients of Wilson's disease, whose predominant feature was osseomuscular involvement and they suggested that this phenotypic expression possibly indicated relatively benign nature of the illness as evidenced by the late onset, slow progression of the disease and absence of neurological signs as is usually observed in our country. Some other features like, generalized aminoaciduria, cysteinuria, calcuria and phosphaturia were also found by these workers in a relatively high proportion of the cases and thus Fanconi's syndrome could be an associated feature in our patients. Arjundas et al5 from Chennai too, documented renal rickets and osteomalatic myopathy, presenting as proximal muscle weakness in a number of cases. These differences in the clinical features have often been attributed to mutations in the 13q 14.3 gene and more than hundred of such mutations in Chinese, Spanish, Greek, Polish and other population have been identified with some changes in the phenotypic expression.6

The point of interest is that the presentation as proximal muscle weakness in a young subject, particularly males, in India may masquerade as myopathy. I had this experience myself some time ago, when a young male, admitted with the suspicion of Duchenne muscular dystrophy, was found to exhibit dystonia in one hand and florid Kayser-Fleisher rings in the cornea were detected thereafter. One more experienced neurologist from Kolkata too, narrated his experience to me in his younger days he admitted a case with the same provisional diagnosis and how in a few days, a bout of hematemesis and cirrhosis of the liver clinched the issue. Since then, I have personally formulated a dictum; in any suspected case of Duchenne muscular dystrophy it would be wise to look for the Kayser-Fleisher rings and then to seek the opinion of an ophthalmologist to comment on the same by slit-lamp examination, lest we miss Wilson's disease, a potentially treatable condition. After all, none is happier than the neurologist to know that his diagnosis of Duchenne muscular dystrophy did not come true!

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REFERENCES


Reply from the Author

Sir,

We thank Dr. KB Bhattacharya for interest shown in our review article entitled "Wilson's Disease".1

Dr. Bhattacharya has drawn attention to different pattern of clinical presentation of Wilson's Disease in India, which he believes is different from that seen in the Western world. He has cited an article by Wadia et al wherein it is believed eight out of 23 patients had generalized osteoporosis, rickets / renal rickets without involvement of central nervous system.2 Having gone through this article in depth, I found that Dr. Wadia and colleagues described four families of Wilson's Disease, of which only six patients were personally examined. All the cases had hepatic and/or neurological examination. There was not a single case who did not have neurological or hepatic involvement and showed presence of osteoporosis or rickets. Indeed, in this article, the authors do not mention about osteoporosis and rickets in any of the cases reported.2 However, Dastur et al.3 have reported 20 cases of Wilson's disease. Whereas, in the Table (Table no. 1 in the article) the authors mention rickets/renal rickets in three cases without neurological or hepatic involvement, in the text they report "six patients had no clear neurological or hepatic signs or symptoms of the disease but had bones or joints charges..."
and muscular weakness and wasting". I presume in the other three cases neurological involvement may have been mild. Dastur et al very rightly believed that genetic involvement is not very simple as is apparent from different modes of presentation, variable severity and age of onset. In 1994 Petrukhin et al described the gene responsible for Wilson's disease and named it WND gene. They proposed genetic heterogeneity as the responsible cause of clinical heterogeneity. It is now known that there are several different types of missense and non-sense mutations in ATP7B gene. It is known that nonsense mutations give rise to severe disease with childhood onset hepatic dysfunction, whereas, missense mutations lead to milder disease with childhood onset hepatic dysfunction, whereas, missense mutations lead to milder disease with later age of onset. Indeed, all organ systems are involved in Wilson's disease and this is mentioned in our review article as well, which needed to be cut short for editorial and space constraint. In our previous review of clinical and radiological features of Wilson's disease we did not come across any patient with musculoskeletal involvement with the exclusion of hepatic and neurological involvement. In the published literature we did not find evidence of Fanconi's syndrome, musculoskeletal involvement, rickets with the exclusion of hepatic and neurological involvement in any cases except those described by of Dastur et al (Manghani et al followed up these very cases). The article published by Dr. Arjun Das is not easily available for review. In the older literature ceruloplasmin was referred to as serum copper oxidase and that is the reason articles published in 1960s and 70s mention serum copper oxidase instead of ceruloplasmin. We in our review used the term ceruloplasmin as it is now called. Dr. Bhattacharya also cites a case he had seen in his earlier days with suspicion of Duchenne muscular dystrophy but who also had neurological involvement (dystonia) and Kayser-Fleisher ring. I believe, if it is a case of Wilson's disease, a thorough clinical examination will certainly betray involvement of nervous system or liver or presence of Kayser Fleisher ring even in the presence of muscular weakness as was seen in the patient mentioned by Dr. Bhattacharya. My dictum is to examine each case thoroughly clinically first to make a clinical diagnosis, and not to miss any treatable condition.

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Received : 14.6.2003

REFERENCES

Cardiac Involvement in Wilson’s Disease - An Electrocardiographic Observation

Sir,

The article “Cardiac involvement in Wilson’s disease - An electrocardiographic observation” J Assoc Physicians India; vol 52: 294-296 is the new kind study about Wilson’s disease regarding cardiac aspect of Wilson’s disease; probably it is first Indian Study, from a well organized group of our country and naturally raises the many queries. In the above study, does cardiac involvement depend upon the clinical subtype of Wilson’s disease like hepatic presentation, neurological, renal and hematological, is there any variation of ECG changes among the patients who have predominant neurological or predominant hepatological involvement. There is also another interesting point, that in Wilson’s disease copper accumulates in tissue including myocardium, various arrhythmias, autonomic dysfunction, cardiomyopathy have been reported (Kuan P. Cardiac Wilson disease. Chest 1987; 91 : 579-583).

Here this study shows that sinus bradycardia and sinus tachycardia and sinus tachycardia occur 12% and 16% respectively, but whether it is due to autonomic dysfunction or cardiomyopathy is not clearly amplified. The patients in this study who have sinus bradycardia or tachycardia does have another feature of cardiomyopathy, not clearly described. So it is not clear whether these findings are due to sclerodegenerative process resulting from cardiomyopathy or related to dysautonomia. Table 2 shows that patients with abnormal ECG have serum and hepatic copper (µgm/dl) 51.34 ± 25.43 in respect to patient without abnormal ECG who have serum copper 58.58 ± 26.04 but is there any correlation between serum copper level with specific type of different ECG changes and duration of illness or age of the patients. Similarly whether serum ceruloplasmin level or liver copper associated with specific type of ECG abnormality also not clearly demonstrated. As all patients of this study were on copper chelating agent, and the mean serum copper was 56.37 ± 25.81, so is there any variation on ECG finding between the patients who are not on copper chelating agent is also not clearly cited here.

The patients who have ECG changes, among them is there any correlation between several ECG changes with different CT/MRI brain changes. Whether ECG changes reverse with the clinical amelioration of disease with treatment; we have to focus regarding this aspect. The clinical significant of
cardiac involvement in Wilson's disease still a enigma, but we hope in coming future they will provide the answer. Is there any relationship of the type of the mutation of WD gene or any relation to satellite marker of WD and this electrocardiographic changes are interrelated or not have been focused.

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Received : 12.5.2004

**Reply from the Author**

We appreciate the interest of Mitra and Ganguly and their remarks on our article “Cardiac involvement in Wilson’s disease - an electrocardiographic observation”.1

This was a cross-sectional study focusing exclusively on ECG changes in Wilson’s disease (WD) from a cohort followed at neurosecience center. All these patients had illness dominated by neurological symptoms at the time of evaluation and therefore analysis based on sub-types of presentation (hepatic, neurological, etc.) of WD and ECG changes was not performed. None of these patients had features of cardiomyopathy, however they were not evaluated by echocardiography. In earlier studies, dysautonomia in WD had been demonstrated2,3 and hence autonomic dysfunction was speculated as the cause of tachycardia and bradycardia. We did not expect and observe any significant difference (p=0.53) in serum ceruloplasmin levels among patients with or without ECG changes. Hepatic copper estimation and genetic study were not carried out. All patients were on regular treatment with depckering agents and hence effect of therapy could not be inferred.

We agree with Mitra and Ganguly that future prospective and longitudinal study should address these issues in hithero under-recognized but important aspect of Wilson’s disease.

**AB Taly**

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Received : 7.6.2004

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**Low Cost Anti-retroviral Options: Chloroquine Based ARV Regimen Combined with Hydroxyurea and Lamivudine: A New Economical Triple Therapy**

Sir,

Though the cost of triple drug therapy for the treatment of symptomatic HIV disease has drastically come down it is still out of reach for the majority of Indian population. Hence there is an ever-increasing need for feasible and cost effective regimens. Various international studies have found that both chloroquine and hydroxyurea have in vivo and in-vitro1-2 effects on HIV. They can be used in combination with nucleoside inhibitors like ddl, AZT.1,2,5 As studied by Boelaert JR et al7 there is in vitro additive anti-HIV-1 activity of chloroquine, in combination with Hydroxyurea + Zidovudine supporting the idea that this triple regimen should be studied in clinical trials. Similarly the combination of chloroquine, hydroxyurea, & didanosine has also been studied7 With this background we conducted a prospective open-label pilot study to evaluate the safety, tolerability and efficacy of the combination of chloroquine, hydroxyurea and lamivudine.

We studied anti-retroviral naïve patients with viral load >50,000 copies/ml, CD4 count >350 cells/mm³ and no OIs. The regimen consisted of Chloroquine (250 mg bid), Hydroxyurea (500 mg bid) and Lamivudine (150 mg bid) for 6 months and beyond.

Twenty eligible patients were recruited and two were withdrawn due to non-compliance, 18 completed the study protocol (median age 27, baseline VL 56,643 copies/ml). The median VL reduction was significant (p<0.001) and the median rise in CD4 count was 78 cells/mm³. At week 24, 10 patients had undetectable VL. The VL reduction was again significant (p<0.001) and the rise in CD4 count was 174 cell/mm³ (p<0.001). The treatment was well tolerated and there were three adverse events.

The combination of Chloroquine, Hydroxyurea and Lamivudine is safe and well tolerated. The significant reduction in VL may be of value in patients is an interesting observation. The relatively low cost makes this new triple combination an attractive regimen in resource-limited settings. This is just a pilot study. We plan to do a prospective randomised double blind study to support our findings.

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1. Boelaert JR, Sperber K, Piette J. The additive in vitro anti-HIV-1 activity of nucleoside inhibitors like ddl, AZT.1,2,5 As studied by Boelaert JR et al7 there is in vitro additive anti-HIV-1 activity of chloroquine, in combination with Hydroxyurea + Zidovudine supporting the idea that this triple regimen should be studied in clinical trials. Similarly the combination of chloroquine, hydroxyurea, & didanosine has also been studied7 With this background we conducted a prospective open-label pilot study to evaluate the safety, tolerability and efficacy of the combination of chloroquine, hydroxyurea and lamivudine.

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**Announcement**

**Training in Diabetes Foot Care**

Project funded by the World Diabetes Foundation (WDF)

**Academic Support by:**
- Consultative section on the diabetic foot- International Diabetes Federation (IDF)
- International Working Group on the Diabetic Foot (IWGDF)
- Diabetic Foot Society of India (DFSI)
- Muhimbili University and College of Health Sciences (MUCHS), Dar es Salaam, Tanzania

**Project Committee:** Sharad Pendsey, India; Karel Bakker, The Netherlands; Ali Foster, U.K.; Zulfiqarali Gulam-Abbas, Tanzania; Vijay Vishwanathan, India

**Excellent opportunity for practicing doctors, with a special interest in Diabetes !**

**Project at a glance:** 100 doctors with their paramedics (one doctor with one paramedical staff), to be trained in practical diabetic foot care management.

1. Basic Course: 2 days at four centers in India (Kolkata, New-Dehli, Mumbai & Chennai). Each center will have 25 doctors & 25 paramedics. The course is likely to be held between September/October 2004.

2. Advanced Course: 2 days (after 1 year) for the same participants is mandatory

**Faculty: Experts in the field of Diabetic Foot Care**

Selected participants will be provided with excellent educational material along with diagnostic/therapeutic instrument kits. Travel to nearest venue, lodging & boarding, access to training and resource materials are covered by a grant from WDF Certificate of participation on completion of the advanced course.

Preference to postgraduates, coming from private/public/corporate/govt. medical institutions.

Opportunity to start Preventive Diabetes Foot Care Clinic.

Selection committee’s decision will be binding on all applicants.

**The last date of receipt of application is 30th June 2004.**

**Write for application form to**

Dr. Sharad Pendsey
Project-Incharge, Diabetes Clinic & Research Center
“Shreeniwas”, Opp.Dhantoli Park, Nagpur 440 012 (India)