Authors' reply

Dear Sir,

We thank the authors for showing interest in our article Netto *et al*., 2011[1] and appreciate their critical view about the manuscript. We are pleased to provide our responses to the queries raised by the authors.

- The study population is drawn from the weekly Wilson's disease (WD) clinic and in-patient services of the Department of Neurology. The authors have not mentioned the standardization procedure used for defining the cases. Also, there is a mention about magnetic resonance imaging (MRI) evaluation done on the selected patients in the abstract but the radiological data is not presented in the text.

  Response: The study population was indeed recruited from the outpatient and inpatient services. The diagnosis of WD is based on clinical features, presence of corneal Kayser–Fleischer ring (slit lamp), low serum ceruloplasmin, and total copper.

MRI of brain is carried out routinely to support the diagnosis and assists in prognosis Sinha *et al*., 2006.[2] All the 25 patients underwent MRI study; and in 24 patients, it was carried out within a month of the polysomnographic (PSG) study. Brain MRI was abnormal in all patients except one (whose MRI became normal after de-coppering). Cerebral atrophy was diffuse and was best evaluated on T1-weighted multiplanar images. In six patients, cerebellar and brainstem atrophy was significant and disproportionate to cerebral atrophy. The MR signal abnormalities were noted in midbrain - 18 (72%); putamen - 17 (68%); thalami and globus pallidus each in 13 (52%); pons - 10 (40%); white matter - 7 (28.0%); cerebellum - 4 (16%); caudate - 3 (12%); and middle cerebellar peduncle - 2 (8%). The pathognomonic "face of giant panda" sign and "central pontine myelinosis-like" changes were observed in 11 and 8 patients, respectively. Three patients had T1 pallidal hyperintensity. The medulla was not involved in any of the patients. White matter signal changes were diffuse and symmetrical in seven patients and had a frontal preference. There was no neuro-anatomical correlation between sleep parameters and any of the MRI abnormalities Netto *et al*., 2010.[3]

- The sample was recruited prospectively over a 2 year period. During this period, only 25 cases were deemed eligible for selection. No information is gleaned on the number of subjects deemed ineligible or those who were not consenting. Did the authors attempt a comparison between these groups if information is available? This would have implications on the external validity of the findings.

  Response: It was carried out prospectively over 2 years. This tertiary care center has a registry of over 500 patients of WD. A weekly WD clinic provides focused care to about 20-25 patients. It was non-consecutive sampling of patients which primarily depended on the willingness to participate for the study and availability of the investigator (Netto Archana). Comparison of patients who did not consent was not carried out.
- The study sample is inherently heterogeneous with regard to age range (14-62 years) and duration of illness (2-312 months). In a study such as this, it would have been better to use a more homogenous sample. It is conceivable that factors like age, obesity, duration, etc., will have a bearing on sleep parameters studied and therefore will be potential confounders. The authors have not mentioned about the possible effect of these confounders although they have acknowledged sample heterogeneity briefly in their discussion.

  Response: We have mentioned that the cohort was small and heterogeneous. The mean body mass index of patient group was 18.62 (14.1-24.9) and that of control group was 19.2 (16.2-24.6). The other confounding factors mentioned in the letter namely age and duration of illness have been analyzed and mentioned in the article.
- The authors have not given the distribution of patients who are drug naive and on de-coppering treatment. The study has found that patients with longer duration of illness and those on de-coppering treatment had significantly lesser daytime somnolence. However on scrutiny, the number of patients with abnormal Epworth sleepiness scale (ESS) in de-coppered patients was 19 and in drug naive cases, it was 3. This is confusing to us. The authors have not mentioned the corresponding percentages and the *P* value for statistical significance.

  Response: Twenty patients were on de-coppering treatment (penicillamine = 12; zinc = 20) while five were drug naive. Subgroup analysis of the patients revealed that individuals with longer duration of illness (abnormal ESS: <8 years - 3; >8 years - 0; $P = 0.05$) and on de-coppering treatment (abnormal ESS: drug naive - 3/5; on treatment - 19/20; $P = 0.03$) had significantly lesser excessive daytime somnolence.
- We also notice a flaw in the selection of control group. They were essentially staff of the institute or healthy relatives of in-patients who were admitted for other disorders. No mention is made of their medication status if any. The sleep quality of these relatives who were attending to the patients in the ward will naturally be affected compared with their home settings and therefore cause distortion in interpretation of findings. This may explain the high prevalence of sleep abnormalities noted in control group in the study. Lack of age and gender matching is also noticed between cases and controls. This is at variance with previous comparable studies.[2,3] It is also possible that the case population being drawn from a specialty clinic in a tertiary hospital, the catchment area will be wider and this further affects the comparability between cases and controls. All these factors point to an unmatched control group.

  Response: The flaw in selection of control group is acknowledged in the article. None among the control group were on any type of medication.
- The study concludes that a significant proportion of patients with WD suffer from sleep abnormalities. It is a

moot point whether the sleep symptomatology noted were independent of depression or not. Various studies across cultures put the estimates of co-morbidity between WD and depression at 20-30%.[4] If the former were the case, it would mean that distortions in sleep duration and architecture are inherent to WD and not just an epiphenomenon of depression.

Response: None had depression. But we do agree that presence of co-morbid state might alter sleep architecture Portala *et al*., 2002.[4] The sample size was too small to carry out a logistic regression.

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