J. Sleep Res. (2002) 11, 357–358

Letter to the Editor

Effect of the prion 129 polymorphism on nocturnal sleep and insomnia complaints: a population-based study

In June 1999, Huber *et al.* published in this journal an extensive study in prion protein deficient mice entitled 'Prion protein: a role in the sleep regulation?' (Huber *et al.* 1999). The interest for prion protein in the sleep field was gathered by the discover that fatal familial insomnia (FFI) segregate with a mutation in the codon 178 of prion protein gene (Medori *et al.* 1992).

The role of the prion protein (PrP) in the pathogenesis of animal and human transmissible spongiform encephalopaties (TSE) is well established. The FFI is the only known human TSE to affect sleep and it is a very severe disease. Its symptomatology is characterized for motor disturbances, loss of circadian rhythmicity and several neurovegetative symptoms as increased perspiration and salivation, tachycardia, systemic hypertension and fever but mainly for a gradual sleep loss, leading to death.

Most classically, a mutation at codon 178 (e.g. Asp178Asn) is present in FFI as well as CJD but a *cis* polymorphism in codon 129 determines familial FFI versus CJD phenotypes. A valine residue at the codon 129 (129V) segregates with CJD and a methionine in the same position (129M) lead to FFI (Goldfarb *et al.* 1992). Interestingly, the 129 polymorphism, without the mutation at the codon 178 is very common in the general population and does not cause any prion disease, the 129M allele frequency range from 0.62 to 0.68.

Whereas much has been learned regarding the role of abnormal prions in the generation of these TSEs, little is known regarding the normal role of the wild type protein. Genetics studies in the sleep field have identified important genes regulating sleep and circadian rhythms and FFI is a potential model for genetics studies of insomnia (Taheri and Mignot 2002).

Thus in the present study we explored if the 129V/M polymorphism influences sleep in the general population, with special emphasis on items related to insomnia complaints and sleep disruption.

A population based random sample of 884 middle-aged men and woman enrolled in an epidemiological study of natural history of sleep disorders was used in this analysis (Young *et al.* 1993). All subjects had undergone blood draw as part of an overnight sleep protocol and were asked to complete a 4-item insomnia questionnaire. Mean age ± SD was 50.0 ± 7.9 years. 489 subjects (55.3%) were males.

We genotype the 129 V/M polymorphism in the population sample using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) as described in Goldfarb *et al.* (1992). Subjects were categorized in three groups on the basis of their prion genotype (129M/M, 129M/V and 129 V/V). Linear and logistic regression were used to assess differences between groups for polysomnographic parameters and the insomnia questionnaire responses, respectively. Analysis were adjusted for the potential confounding factors such as age, sex, ethnic heritage, body mass index (BMI) and apnoea–hypoapnoea index (AHI). *P*-values <0.05 were considered to indicate statistical significance. The SAS statistical package was used for all analysis.

Overall allele frequencies for 129M was 0.66 in this mostly Caucasian (90%) sample. Genotype distributions for 129M, 129M/V and 129V were 406/884, 370/884 and 108/884, respectively. These distributions did not deviate from expected Hardy–Weinberg frequencies.

Nocturnal polysomnography (Table 1) and insomnia questions did not differ consistently across genotypes. Only two comparisons led to borderline significant differences. In one, 129V negative subjects reported waking up more at night and having more difficulties getting back to sleep [Odds ratio, 95% CI: 0.72 (0.64, 1.01, $P = 0.05$)]. However, 129V positive and negative subjects did not differ with respect to the other three insomnia questions. Furthermore, during the nocturnal

Table 1 Polysomnographic measures of nocturnal sleep for the three genotypes

Sleep parameters	*129VV (n = 108)*	*129MV (n = 370)*	*129MM (n = 406)*
Stage 1 (%)	9.4 ± 0.6	9.0 ± 0.3	9.4 ± 0.3
Stage 2 (%)	**59.5 ± 1.0**	**60.4 ± 0.6**	**60.1 ± 0.6**
Stage 3/4 (%)	12.1 ± 0.9	12.4 ± 0.5	12.0 ± 0.5
REM sleep (%)	18.6 ± 0.6	18.1 ± 0.4	18.4 ± 0.4
Sleep onset latency (min)	9.5 ± 1.3	12.1 ± 0.8	12.2 ± 0.8
Wake after sleep onset (min)	54.0 ± 3.6	57.2 ± 2.1	51.6 ± 2.1

Data are mean ± SE adjusted for age, sex, heritage, AHI and BMI.
n = number of subjects.
REM, rapid eye movement.

Correspondence: Mario Pedrazzoli, Universidade Federal de São Paulo, Departamento de Psicobiologia, Rua Napolea 925, São Paulo, SP, Brazil, CEP: 04024002. Tel.: 55 11 55390155; fax: 5 11 55725092; e-mail: pedrazzo@psicobio.epm.br

polysomnography, 129V positive subjects had more time awake after sleep onset (56.6 ± 1.5, $n = 478$ vs. 51.9 ± 2.0 min, $n = 408$; $P = 0.05$, adjusted for age, sex, heritage, AHI and BMI).

The results obtained in the present study show that the PrP 129 polymorphism has no effect on insomnia symptoms or nocturnal sleep in the general population. Most importantly, we could not corroborate the preliminary finding of Plazzi *et al.* (2001) suggesting that 129 PrP polymorphism affect sleep in healthy subjects.

No striking differences in insomnia or nocturnal sleep were reported. Discrepant results were obtained using subjective (questionnaire) and objective (polysomnography) data. In one case, 129V positive subjects reported less insomnia symptoms (subjectively) yet during nocturnal sleep recordings, these subjects had more wake after sleep onset. Discrepancies between objective and subjective measures of insomnia are not uncommon, indicating great difficulties in measuring insomnia objectively.

Further studies extending on the mice knockout work (Huber *et al.* 1999), looking more specifically at the role of the 129 polymorphism, may be needed to further our understanding of the role of the prion protein in sleep regulation.

ACKNOWLEDGEMENTS

Dr Mario Pedrazzoli thanks FAPESP for the fellowship. This work was supported by NIH grants NS33797 and HL59601 to Dr Emmanuel Mignot.

REFERENCES

Goldfarb, L. G., Petersen, R. B., Tabaton, M., Brown, P., LeBlanc, A. C., Montagna, P., Cortelli, P., Julien, J., Vital, C., Pendelbury, W. W. et al. Fatal familial insomnia and familial Creutzfeldt–Jakob disease: disease phenotype determined by a DNA polymorphism. *Science*, 1992, 258: 806–808.

Huber, R., Deboer, T. and Tobler, I. Prion protein: a role in sleep regulation? *J. Sleep Res.*, 1999, 8 (Suppl. 1): 30–36.

Medori, R., Tritschler, H. J., LeBlanc, A., Villare, F., Manetto, V., Chen, H. Y., Xue, R., Leal, S., Montagna, P., Cortelli, P. *et al.* Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl. J. Med.*, 1992, 13: 444–449.

Plazzi, G., Reelke, M., Montagna, P., Nobili, L., Cortelli, P., Avoni, P., Tinuper, P., Gambeti, P., Lugarezi, E. and Ferrilo, F. The 129 codon polymorphism of the prion protein gene influences sleep. *Neurology*, 2001, 56 (Suppl. 3): A9.

Taheri, S. and Mignot, E. The genetics of sleep disorders. *Lancet Neurol.*, 2002, 1: 242–250.

Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S. and Badr, S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl. J. Med.*, 1993, 328: 1230–1235.

Mario Pedrazzoli[1], Lin Ling[2], Theresa B. Young[3], Laurel Finn[3], Sergio Tufik[1] and Emmanuel Mignot[2]
[1]*Department of Psychobiology/Sleep Institute, Universidade Federal de São Paulo, São Paulo, Brazil,*
[2]*Department of Psychiatry and Behavioral Sciences, Center for Narcolepsy, Stanford University School of Medicine, Stanford University, Palo Alto, CA, USA and*
[3]*Department of Population Health Sciences, University of Wisconsin Medical School, Madison, WI, USA*