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Journal search and commentary

Articles reviewed: 1. A subtype of sporadic prion disease mimicking fatal familial insomnia. 2. Prion protein conformation in a patient with sporadic fatal insomnia ☆

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Category

Insomnia, prion disease

Objectives

(a) Establish occurrence of a sporadic prion disease (sporadic fatal insomnia) with the phenotype of fatal familial insomnia.

(b) Evaluate clinical presentation, histopathology, PrP^{sc} (scrapie prion protein) and genetic characteristics of this disorder.

Study design

Case studies of patients with sporadic fatal insomnia.

Study population

Two separate and independent reports one of five patients and the other of one patient with clinical characteristics of fatal familial insomnia who did not have a family history of the disorder.

Methods

Both studies provide clinical and pathologic data on the patients which include analyses of PrP^{sc} and the prion protein gene (PRNP). The second case report of one patient includes experimental transmission of sporadic fatal insomnia to genetically engineered mice.

Results

In both studies all of the patients had clinical and pathological presentation almost identical with fatal familial insomnia. Occurrence of PrP^{sc} type 2 matched that for fatal familial insomnia except there was no marked reduction in the unglycosylated isoform. These subjects also did not show the fatal familial insomnia genetic characteristics of the mutated codon at position 178 (D178N). The patients were homozygous at codon 129 for methionine.

The second study reported that intra-cerebral transmission to mice, genetically altered to produce human

☆ First paper: Parchi P, Capellari S, Chin S, Schwarz HB, Schecter NP, Butts JD, Hudkins P, Burns DK, Powers JM, Gambetti P. A subtype of sporadic prion disease mimicking fatal familial insomnia. Neurology 1999;52:1757–1763.

Second paper: Mastrianni JA, Nixon R, Layzer R, Telling GC, Han D, DeArmond SJ, Prusiner SB. Prion protein conformation in a patient with sporadic fatal insomnia. N Engl J Med 1999;340:1630–1638.

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prion protein produced a fatal prion disease virtually identical to that seen with the same procedure for transmitting fatal familial insomnia.

Conclusion

The authors concluded that these cases demonstrate the existence of a sporadic form of the same prion disease as fatal familial insomnia and they propose the name of sporadic fatal insomnia for this form of the disease.

Comment

Characteristics of fatal familial insomnia have been described in several patients and 24 affected kindreds have been identified. The sporadic form of this disease described here has essentially the same clinical presentation. The age of onset was 36–70 years, survival duration was about 15 months to 2 years, major symptoms involved cognitive loss and motor signs in all patients and profound insomnia for five of the six patients. One patient presented initially with only a primary complaint of insomnia including a reported average sleep time of 1 h per night, but this patient was not further evaluated at that time for his insomnia. Thus, as with fatal familial insomnia, the sleep complaint may be the initial reason for seeking medical attention.

Prion diseases can be separated into three basic phenotypes: Creutzfeldt–Jakob disease (CJD) with rapidly progressive dementia, Gerstmann–Sträussler–Scheinker disease with more slowly progressive dementia and fatal insomnia with profound insomnia. Each has motor signs with ataxia but differing patterns of neuronal changes. Fatal insomnia involves atrophy of the thalamus and inferior olives. These reports indicate that like CJD the fatal insomnia disease has both a sporadic and inherited form. There have also been previous reports of a few other cases with similar clinical presentations who were not evaluated for the presence of PrP^{sc} or PRNP mutation.

The results of these studies are particularly interesting in that it appears a primary difference between familial and sporadic fatal insomnia is the ratio of the PrP^{sc} glycoforms. The PRNP mutation apparently leads to a reduction in the unglycosylated form of PrP^{sc} in the fatal familial insomnia that does not occur in the sporadic fatal insomnia.

These studies unfortunately failed to provide either detailed clinical and EEG analyses of sleep or analyses of basic circadian patterns of these six patients. Nonetheless the clinical descriptions were compelling and it seems very likely that these patients would show the same polysomnograhic results shown for fatal familial insomnia. Aside from this problem, these well documented cases fairly conclusively demonstrate a sporadic form of fatal familial insomnia which must now be considered as a rare, but important diagnosis to be excluded for a patient with severe insomnia. This is particularly relevant for sleep medicine since in at least some cases the initial presenting complaint may be only the profound insomnia.