FATAL FAMILIAL INSOMNIA

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INTRODUCTION

Fatal familial insomnia (FFI) is a rapidly progressive autosomal dominant disease, and may be the third most common inherited prion disease.[1,2] Its duration is from about 7–36 months, with an onset of between ages 35 and 61 years. There are two groups, one with a short duration (9·1+1·1 months) and one with a prolonged duration (30·8+21·3 months).[3] Apart from the examples of inherited disease a number of sporadic cases have been reported,[4] and animal experiments have shown that it shares transmissibility with other prion diseases.[5]

SYMPTOMS AND SIGNS

The condition presents with a progressive loss of the ability to sleep, associated with dysautonomia and endocrine and motor disturbances.[6] The autonomic ones include hyperhidrosis, hyperthermia, tachycardia and hypertension; respiratory problems have also been reported that may be related to brainstem lesions.[7] Overall motor activity is markedly increased, and this energy expenditure can contribute to progressive exhaustion and death.[8] Neurological abnormalities comprise diplopia, ataxia, dysarthria, pyramidal tract signs, abnormalities of muscle tone and myoclonus. Complex hallucinations and dreams are common.[9] Cortisol levels may be high with normal adrenocorticotrophic hormone (ACTH) levels suggesting hypercortisolism, while melatonin and somatotropin levels gradually decline.[3] Polysomnographic recordings can confirm a markedly reduced total sleep time, and gross electroencephalographic disorganisation of sleep patterns including a virtual absence of typical rapid-eye-movement (REM) periods and deeper non-REM phases characterised by K-complexes, spindles and slow waves.[10]

Fatal familial insomnia has been reported in many countries in Europe and around the world.[11] For example, Padovani *et al*.[12] have reported a family in Italy. The propositus showed disorders of behaviour, sleep, cognition and motor function, associated with thalamic and olivary atrophy, and with spongiosis confined to the parahippocampal gyrus. However, the protease-resistant prion protein was widely distributed in the brain. It was considered that the duration of the disease determined the histopathology and the distribution of this protein, rather than codon 129 polymorphism. Almer *et al*.[13] studied five patients in an Austrian family, suffering from this condition. Severe loss of weight was an early symptom, and four of the patients developed insomnia and autonomic dysfunction. Analysis of the prion protein gene revealed the codon 178 point mutation and methionine homozygosity at position 129. Autopsies in four of the patients confirmed thalamic and olivary degeneration, as well as cortical and brain stem lesions. In another report, in a 12-generation kindred from Germany, the difficulties of diagnosis are stressed due to the variability of the clinical and pathological findings.[14]

THE PATHOLOGY OF FFI

Typical findings include marked atrophy of the anteroventral and mediodorsal thalamic nuclei, and varying degrees of cerebral and cerebellar cortical gliosis, as well as olivary atrophy.[15] Spongiosis of the cortex can also be present.[7] In contrast to other prion diseases pavalbumin-positive neurons, which are a subset of GABAergic interneurons, are well preserved or only moderately reduced, especially in the temporal cortex and adjacent hippocampus.[16] The differences from other prion diseases on light microscopy are not found on electron microscopy, the ultrastructural picture being much the same, including the presence of tubulovesicular structures.[17]

The lesions in the thalamus may well be related to the disturbances of sleep and endocrine functions in this condition, as the role of the thalamus in controlling sleep and sleep-related behavioural and metabolic changes, and of growth hormone, prolactin, and melatonin regulation, has been reported.[18,19] The role of thalamic lesions in causing insomnia is supported by the finding of a variety of Creutzfeldt-Jakob disease (CJD) in which the thalamus is particularly affected and in whom intractable insomnia is a prominent feature.[20] The lesions in the thalamus consist of selective atrophy of the anteroventral and mediodorsal nuclei that constitute the limbic part of the thalamus, interconnecting limbic and paralimbic regions of the cortex and other subcortical structures in the limbic system, including the hypothalamus. The connections of the mediodorsal nuclei are of particular importance. The hypothalamus released from cortico-limbic control is shifted to a prevalence of activating, as opposed to deactivating, functions such as loss of sleep, sympathetic hyperactivity and the attendant attenuation of autonomic circadian and endocrine oscillations. This confirms that the limbic thalamus has an important role, through controlling autonomic responses, in regulating the body's homeostasis.[19,21]

Neuronal loss is certainly a predominant feature in FFI, and Dorandeu *et al.*[22] have shown that this loss may occur through an apoptotic process.

Wanschitz *et al.*[23] studied the serotonergic system in eight patients with FFI, and found no total neuronal loss in median raphe nuclei but a substantial increase of tyrosine hydroxylase positive (TH+) neurons compared with controls. This may result in an enhanced role for serotonin and explain some of the symptoms of the condition. For example, the disturbance of the sleep–wake cycle and some of the exaggerated cardiovascular responses. However, Correlli *et al.*[24] advised against contributing too many of the symptoms to this finding as there may be a number of other reasons. Klöppel *et al.*[25] have also demonstrated a significantly reduced availability of serotonin transporters in the thalamus-hypothalamus region in affected patients.

THE GENETICS OF FFI

This condition is a transmissible spongiform encephalopathy linked to a point mutation at codon 178 of the prion protein gene located on the short arm of chromosome 20,[26] which results in an aspartic acid to asparigine substitution. In FFI the mutation is coupled with the methionine codon at position 129 of the mutant allele in a cis relation (on the same chromosome pair),[27] to the 178 codon mutation, whereas in CJD the coupling is with the valine codon at position 129.[8, 12] Some studies have shown that the genotype-phenotype correlation is not as tight for the aspartic acid to asparigine mutation at codon 178 as had been supposed,[27] and that the phenotypic expression may be influenced by multiple factors.[28] For example, a subtype of sporadic prion disease has been described which mimics closely the characteristics of FFI but lacks the mutation at codon 178 of the prion protein gene.[29] Patients with short duration of the disease have been found to be homozygous (methionine/methionine) at codon 129, whereas those with a long duration were heterozygous (methionine/valine) at this codon.[30] It has also been shown that the homozygotes had more prominent dreams, insomnia and dysautonomia at the onset, and histopathological changes are more restricted to the thalamus, whereas the heterozygotes showed an onset with ataxia, dysarthria, earlier sphincter loss and grand mal seizures, and more extensive cortical involvement.[9, 31]

THE DIAGNOSIS OF FFI

As FFI cannot be distinguished readily from sporadic CJD on clinical grounds, and an appropriate family history of neurodegenerative disease is not always available, it may be essential to perform molecular genetic investigations of the prion protein gene.[9]

The findings on the electroencephalogram (EEG) and magnetic resonance imaging are non-specific, although positron emission tomography may be helpful.[32] Bär *et al.*[33] and Cortelli *et al.*[34] have confirmed that the results of the latter were compatible with progressive thalamic hypometabolism, and that this was a stable finding, present in the early stages of the disease; while cortical hypometabolism varied with the clinical presentation and the stage of the disease.

However, there seems to be no doubt that the prion protein gene plays a part in regulating sleep in both normal subjects and in those with this disease. In FFI there is a progressive reduction in total sleep time, early disappearance of sleep spindles, loss of slow wave sleep and disintegration of sleep cycle organisation.[35] It has also been found that the relevant mutation at codon 178 in FFI does not induce any sleep spindling or slow wave activity alteration before the clinical onset, or differences in the sleep EEG composition between carriers and non-carriers of the codon 178 FFI mutation.[36]

Apart from differentiating FFI from other prion diseases, especially Gerstmann-Sträussler-Scheinker disease,[37] it may be necessary to exclude other degenerative disorders by appropriate investigations. For example, Morvan's syndrome of myokymia, muscle pain, excessive sweating, and disordered sleep, which can show almost identical biochemical findings but not antibodies to voltage-gated K+ channels.[38]

THE TREATMENT OF FFI

The giving of sedatives and hypnotics such as benzodiazepines and barbiturates may well be of limited value, but treatment with gammahydroxybutyrate may be of some help.[11] If a significant disturbance of serotonin function is confirmed there may be a role for treatment with serotonin antagonists in the treatment of FFI.[24]

CONCLUSIONS

Fatal familial insomnia is certainly an unusual and uncommon disease, but it does help to shed new light on prion diseases in general and on sleep disorders in particular. Its study emphasises the role of the thalamus in controlling sleep and in causing dreams. The hope for the future is that the ongoing research into prion diseases will result in more effective prevention and treatment.

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