FFI Cases from the United Kingdom

Robert G. Will[1], Malcolm J Campbell[2], Timothy H Moss[2], Jeanne E. Bell[1], James W. Ironside[1]

[1] CJD Surveillance Unit, Western General Hospital, Edinburgh
[2] Department of Neurosciences, Frenchay Healthcare Trust, Frenchay Hospital, Bristol, U.K.

National surveillance of Creutzfeldt Jakob disease (CJD) was instituted in the United Kingdom in 1990 and case identification has relied on the referral of suspect cases of CJD, mainly from neurologists (3). Since 1990 analysis of the prion protein gene has been carried out in a proportion of cases referred in life, provided permission for genetic analysis has been obtained from the relatives of the patient (5). In the course of this systematic survey, two cases of fatal familial insomnia (FFI) have been identified, although it is of note that both patients were notified to the Unit as suspect CJD.

Case Reports

Case 1. The initial symptoms in this 61 year-old female patient included insomnia, exhaustion and drenching night sweats. The insomnia was persistent and unresponsive to treatment with benzodiazepines and the patient lost two stones in weight over a period of months. Five months after the onset of symptoms she developed involuntary twitching movements of the limbs, dysarthria, and a month later she developed diplopia and ataxia. Within a few weeks she then developed delusions and became progressively confused and disorientated. On admission to hospital eight months after the onset of symptoms, she was disorientated, confused, ataxic and had a left ptosis. Following admission she developed myoclonus, nystagamus and primitive reflexes and rapidly deteriorated to a state of mutism. The patient died a month later with a total duration of illness of ten months.

Normal investigations included cerebrospinal fluid examination and a CT brain scan. Serial electroencephalograms (EEGs) showed excessive slow wave activity, but periodic triphasic complexes were not seen. The clinical diagnosis was possible CJD. Analysis of the open reading frame of the prion protein gene showed aspartate to asparagine mutation at codon 178. The genotype at codon 129 of the PrP gene was homozygous for methionine.

Neuropathological examination showed marked neuronal loss and gliosis in the thalamus (particularly the anterior ventral and dorsomedial nuclei) and the paraventricular nucleus of hypothalamus. No evidence of spongiform change was noted in the cerebral cortex, corpus striatum, thalamus, hypothalamus, brain stem or cerebellum. The cerebral cortex and hippocampus exhibited age-related changes, with no evidence of Alzheimer's disease. The putamen and globus pallidus showed patchy neuronal loss with astrocytosis, but no spongiform change. The cerebellum showed a variable loss of Purkinje cells and granular neurones, with occasional folia appearing midly atrophic. Neuronal loss and astrocytosis was also noted in the dentate nucleus of the cerebellum and more markedly in the inferior olivary nucleus of the medulla. The pontine nuclei also showed evidence of neuronal loss and astrocytosis and the inferior and middle cerebellar peduncles were atrophic. Immunocytochemistry for PrP showed a weak positive reaction in the thalamus, with a synaptic pattern of accumulation in the main thalamic nuclei, particularly in the dorsomedial nucleus. PrP staining in other brain regions was negative. The distribution of immunoreactive PrP in the brain correlated with results of Western blot examinations (1); this case was transmitted experimentally to transgenic mice (2).

The patient was classified as a case of FFI on the basis of the genetic analysis and neuropathological findings. Detailed investigation of the family history in the case was not possible, but the patient's father was said to have died of Parkinson's disease at the age of 67 years.

Case 2. At the age of 38 this female patient developed insomnia, restlessness and anxiety. After six months she became progressively forgetful and confused and a month later ataxic. She was admitted to hospital for investigation eleven months after the initial symptoms and was emaciated and agitated with occasional verbalisation of words and phrases. There were primitive reflexes and upper motor neurone signs in the form of hyperflexia, extensive plantar responses, and paratonic rigidity of the limbs. Myoclonus was not described, but the patient did exhibit choreiform involuntary movements of the limbs. The patient died fourteen months after the onset of clinical symptoms.

Normal investigations included cerebrospinal fluid examination and MRI brain scan. A CT brain scan was reported to show early cortical atrophy. Serial EEGs showed diffuse slow wave activity, but there were no

Corresponding author:
Dr R.G. Will, CJD Surveillance Unit, Western General Hospital Edinburgh EH4 2XU UK; Tel. : +44 131 332 2117; Fax : +44 131 343 1404

periodic complexes. Left frontal brain biopsy showed no evidence of spongiform encephalopathy.

Post-mortem was carried out and histological examination revealed bilateral and symmetrical gliotic degeneration of the thalamus, mammillary bodies, caudate nuclei, putamen and inferior olivary nuclei. The most severely affected areas within the thalamus were the anterior ventral and dorsomedial nuclei. No evidence of spongiform change was noted in the thalamus, cerebral cortex or hippocampus. Spongiform change with gliosis was identified in the anterior corpus striatum on the left. The cerebellar cortex showed only mild loss of Purkinje cells with no evidence of astrocytosis in the dentate nucleus and no spongiform change. PrP immunocytochemistry showed a negative reaction in all areas of the cerebrum: hippocampus, corpus, striatum, thalamus, hypothalamus, brain stem and cerebellum.

Analysis of the PrP gene showed a mutation at codon 178 and a methionine homozygous genotype at codon 129 of the PrP gene.

This case was classified as FFI on the basis of the genetic and neuropathological findings. There is only limited information on the pedigree. The patient's mother was alive and well at the time of the death of the index case. The patient's father is said to have died prematurely of a stroke in his fifties.

Both these cases fulfill genetic and neuropathological criteria for the diagnosis of FFI. One case was classified clinically as suffering from CJD and the diagnosis of FFI only became apparent when the results of genetic analysis became available some time after death and after the seminal publication by the Bologna group describing the genetic basis of FFI (4). Although not fulfilling formal criteria for the diagnosis of possible CJD, the clinical diagnosis of CJD was suspected in the second case because of the rapidly evolving clinical course associated with involuntary limb movements. Both cases were referred to the Surveillance Unit as suspect CJD, although in retrospect the prominent early insomnia might have raised the possibility of a diagnosis of FFI.

Analysis of the clinical presentation of these cases suggests that in the later stages of FFI some patients may exhibit a clinical phenotype similar to CJD. It is inevitable that a surveillance programme aimed at identifying the CJD phenotype will selectively identify cases of familial CJD with this type of clinical presentation. In the UK study the clinical features of genetic cases of CJD are virtually indistinguishable as a group from the non-genetic cases underlining the selective identification of familial cases with CJD phenotype.

Two cases of FFI have been identified out of a total of 369 cases of all forms of definite and probable CJD in the UK since May 1990. Only a proportion of these cases have undergone genetic analysis and the two FFI cases have been identified out of a total of 170 cases with genetic analysis available and represent two out of 26 cases in which PrP mutations have been identified. Although neuropathological information is available in a high proportion of all suspect CJD cases in the UK, potentially leading to the identification of FFI cases not recognised clinically, there is the possibility that cases of FFI are missed by CJD surveillance procedures. It is pertinent to note that in neither of these two cases of FFI was a family history of a similar condition immediately prominent or forthcoming. Early insomnia occurs in a significant proportion of cases of classical CJD, but the frequency of insomnia is similar to age and sex matched hospital controls. In the second UK case the diagnosis of FFI was suspected prior to the availability of genetic analysis because of the characteristics of the insomnia which was persistent and severe and was associated with other autonomic features. The dissemination of information on the clinical characteristics of FFI and in particular the classical FFI phenotype may allow improved identification of this rare disease.

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