Recent Italian FFI Cases

Maurizio Pocchiari, Anna Ladogana, Rosella Petraroli, Franco Cardone, Marco D'Alessandro

National Registry of Creutzfeldt-Jakob disease, Istituto Superiore di Sanità, Rome, Italy.

In 1993, the Istituto Superiore di Sanità (Rome, Italy), within an EU project, instituted the Italian National Registry of Creutzfeldt-Jakob disease (CJD) and related disorders: Gerstmann-Sträussler-Scheinker syndrome (GSS) and Fatal Familial Insomnia (FFI). The method of case ascertainment was through direct notification mainly from neurologists and neuropathologists. Cases were classified according to European diagnostic criteria (9). Genetic analysis for the screening of mutations and polymorphism at codon 129 of PRNP were always performed when the blood of patients was available and their relatives gave informed consent. In autopsied cases, the clinical diagnosis was confirmed by neuropathology, or Western blot identification of the proteinase resistant disease-specific amyloid PrP, or both. The genetic test was done even in patients whose familial history did not reveal the presence of CJD or other dementing illnesses.

In this 5 year-period we screened 229 cases which were referred to the Registry as suspected CJD. One-hundred-fifty-one patients fulfilled the criteria for CJD, GSS, or FFI, and 38 of them carried a point mutation of the PRNP gene; the estimate incidence of the genetic form over the sporadic form (about 25%) was therefore higher than previously reported (10). Among them we identified 2 cases of GSS (carrying the P102L mutation), 6 cases of FFI (D178N coupled with methionine at codon 129 of the mutated allele), and 30 cases of familial CJD (carrying either the E200K or the V210I mutations). Interestingly, we found no cases of familial CJD linked to the D178N mutation coupled with valine at codon 129. Four of the 6 FFI cases belonged to known kindreds (cases 3 and 4, family FFI-1 (7); cases 5 and 6, family FFI-2 (6)), one belonged to a new Italian kindred (unpublished data), and the other one had an apparently negative family history (Table 1).

The mean age at onset was 51.7 ± 4.2 years (mean ± SD) and it was not influenced by the polymorphism at codon 129 of the non-mutated allele. On the contrary, the duration of the disease was shorter in methionine homozygous patients (10, 11 and 8 months, respectively) compared with heterozygous ones (23, 17 and 20 months, respectively), confirming previous observation that the presence of methionine at position 129 of the non-mutated allele modifies the severity of FFI (2, 3).

Clinical characteristics of these patients (Table 1) do not substantially differ from those previously described. The disease presented with early sleep disturbances in 4 patients (3 cases were methionine homozygous at codon 129), but all patients showed a severe insomnia during the disease. Vegetative signs were only reported in 3 patients, but we cannot rule out the possibility that referring physicians did not report us these clinical manifestations. None of the patients presented with early mental deterioration and only 3 of them developed a clear dementia during the course of illness; another patient showed only minimal cognitive impairment. All patients developed at least two of the following clinical signs during the clinical course: myoclonus, pyramidal , or cerebellar signs. Visual disturbances were recorded in half of the patients and in two of them they were early clinical features.

As previously reported, EEG activity was always abnormally slow, but it never presented the typical periodic pattern observed in classical CJD (5). Protein 14-3-3 was not present in the 3 available CSF samples, confirming our previously unpublished data (in 3 further FFI samples kindly provided by Dr. Cortelli) that CSF analysis is of no help in the diagnosis of FFI, while it is generally positive in other familial forms of CJD or GSS and in sporadic CJD (4, 11, and personal data).

Clinical diagnosis of FFI is relatively simple when the patient has a family history of neurological disorders and presents with sleep disturbances, vegetative signs and a combination of focal neurological signs. However, the early appearance of sleep disturbances, often referred as severe insomnia, are also present in sporadic or familial CJD (1, 8). In these years of surveillance, neurologists have referred to the National Registry of CJD 9 cases whose the presenting symptom was sleep disturbance. Five of them did not present any known point or insert mutation of PRNP; four of them were sporadic CJD while in the fifth one neuropathological examination revealed cerebral metastasis without any spongiform changes. A sixth patient carried the V210I mutation of PrP. For the 3 remaining patients, blood samples were not available for genetic analysis; however, all of them had a negative family history for neurological disorders and were older than 70 years at onset

Corresponding author:
M. Pocchiari, National Registry of Creutzfeldt-Jakob disease, Laboratory of Virology, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy; Tel.: +39-6-49903203; Fax +39-6-49903012; E-mail: pocchia@virus1.net.iss.it

Patients	1	2	3	4	5	6
Year of referral	1994	1995	1996	1996	1997	1997
Family history	-	+	+	+	+	+
Sex	M	F	F	M	M	M
Age at onset (years)	53	54	49	45	52	57
Duration (months)	10	11	21	17	8	20
Clinical features at onset						
Sleep disturbances	+	+	+	-	+	-
Dysautonomia	+	-	-	-	-	-
Psychiatric disturbances	+	+	-	-	-	-
Ataxia	-	-	-	+	-	-
Oculomotor disturbances	-	-	-	+	-	+
Cognitive impairment	-	-	-	-	-	-
Clinical signs during the course of disease						
Sleep disturbances	+	+	+	+	+	+
Dysautonomia	+	+	-	-	-	+
Cognitive impairment	+	+	-	+	-	-
Myoclonus	+	+	+	-	+	-
Pyramidal	+	+	-	+	+	+
Extrapyramidal	-	+	-	-	-	-
Visual	+	-	-	+	-	+
Cerebellar	+	-	+	+	+	+
Diagnostic tests						
Periodic EEG activity	-	-	-	-	-	-
Codon 129 polymorphism	m/m	m/m	m/v	m/v	m/m	m/v
14-3-3 brain protein	ND	ND	ND	-	-	-
Post-mortem confirmed	+	+	+	+	+	ND

ND, not done; - absent; + present.

Table 1. Clinical features and diagnostic tests of FFI cases

of disease, an age relatively uncommon for FFI (2). One of them had also a typical periodic EEG and histological examination of the brain showed diffuse spongiosis in the cortical and subcortical areas without any particular involvement of the thalamic nuclei. Thus, a correct diagnosis may be sometime difficult especially when the family history is not initially correctly investigated (case 2 was referred with a negative family history for neurological disease) or is absent (as in case 1). Genetic analysis for the screening of D178N mutation and the polymorphism at codon 129 of the PRNP gene should therefore routinely be done in all patients where there is a clinical suspicion of FFI.

Acknowledgements

We thank Ms Alessandra Garozzo for editorial assistance. This work was partially supported by the National Registry of Creutzfeldt-Jakob Disease of the Italian Ministry of Health - Istituto Superiore di Sanità.

References

1. Chapman J, Arlazoroff A, Goldfarb LG, Cervenakova L, Neufeld MY, Werber E, Herbert M, Brown P, Gajdusek DC, Korczyn AD (1996) Fatal insomnia in a case of familial Creutzfeldt-Jakob disease with the codon 200Lys mutation. *Neurology* 46: 758-761
2. Gambetti P, Parchi P, Petersen RB, Chen SG, Lugaresi E (1995) Fatal familial insomnia and familial Creutzfeldt-Jakob disease: Clinical, pathological and molecular features. *Brain Pathol* 5:43-51
3. Goldfarb LG, Petersen RB, Tabaton M, Brown P, LeBlanc AC, Montagna P, Cortelli P, Julien J, Vital C, Pendelbury WW, Haltia M, Wills PR, Hauw JJ, McKeever PE, Monari L, Schrank B, Swergold GD, Autilio-Gambetti L, Gajdusek DC, Lugaresi E, Gambetti P (1992) Fatal familial insomnia and familial Creutzfeldt-Jakob disease: Disease phenotype determined by a DNA polymorphism. *Science* 258: 806-808.
4. Hsich G, Kinney K, Gibbs CJ, Jr, Lee KH, Harrington MG (1996) The 14-3-3 brain protein in cerebrospinal fluid as a marker for transmissible spongiform encephalopathies. *N Engl J Med* 335: 924-930
5. Manetto V, Medori R, Cortelli P, Montagna P, Tinuper P, Baruzzi A, Rancurel G, Hauw JJ, Vanderhaeghen JJ, Mailleux P, Bugiani O, Tagliavini F, Bouras C, Rizzuto N, Lugaresi E, Gambetti P (1992) Fatal Familial Insomnia: Clinical and pathologic study of five new cases. *Neurology* 42: 312-319

6. Medori R, Montagna P, Tritschler HJ, LeBlanc AC, Cortelli P, Tinuper P, Lugaresi E, Gambetti P (1992) Fatal familial insomnia: a second kindred with mutation of prion protein gene at codon 178. *Neurology* 42: 669-670.

7. Medori R, Tritschler HS, LeBlanc AC, Villare F, Manetto V, Chen HY, Xue R, Leal S, Montagna P, Cortelli P, Tinuper P, Avoni P, Mochi M, Baruzzi A, Hauw JJ, Ott J, Lugaresi E, Autilio-Gambetti L, Gambetti P (1992) Fatal Familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl J Med* 326: 444-449

8. Terzano MG, Parrino L, Pietrini V, Mancia D, Spaggiari MC, Rossi G, Tagliavini F (1995) Precocious loss of physiological sleep in a case of Creutzfeldt-Jakob disease: A serial polygraphic study. *Sleep* 18: 849-858

9. Will RG (1996) Surveillance of prion diseases in humans. In: *Prion Diseases*, Baker HF, Ridley RM (eds.), Chapter 7, pp. 119-137, Humana Press: Totowa, NJ, USA.

10. Will RG, Alperovitch A, Poser S, Pocchiari M, Hofman A, Mitrova E, de Silva R, D'Alessandro M, Brander JP, Zerr I, van Duijn C (1998) Descriptive epidemiology of Creutzfeldt-Jakob disease in six European countries 1993-1995. *Ann Neurol* (in press)

11. Zerr I, Bodemer M, Weber T (1997) The 14-3-3 brain protein and transmissible spongiform encephalopathy. *N Engl J Med* 336: 874