The Austrian FFI Cases

Herbert Budka[1], Gabriele Almer[2], Johannes A. Hainfellner[1], Thomas Brücke[2], Kurt Jellinger[3]

[1] Institute of Neurology and [2]Clinic of Neurology, University of Vienna
[3] Department of Neurology, Lainz Hospital, Vienna, Austria

In 1996, we identified fatal familial insomnia (FFI) in a new Austrian family (1-3); a detailed report is in preparation. FFI was first suspected in a male of 25 years according to the clinical course; the pathognomonic FFI prion protein (PrP) genotype was identified on DNA extracted from leukocytes. Retrospectively, other three affected family members were found: the propositus' mother (age 58), his grand-aunt (age 20) and the latter's mother (age 60). A brother of the first patient died at age 37 only recently and is under further investigation. These 5 patients have died after disease of 13, 8, 10, 18 and 4 months, respectively. The clinical course was relatively uniform, including prominent weight loss and dysarthria in all patients, impairment of sleep, memory loss, perioral myoclonus, diplopia, gait ataxia, vegetative dysfunction and impaired vigilance in 4, apathy and fatigue in 2, tremor, vertigo, confusion and hallucinations in one patient each. Insomnia was not observed in one patient.

All 4 patients examined had the same PRNP genotype of D178N and M129M (molecular genetic data by courtesy of Drs. O. Windl and H. A. Kretzschmar, Institute of Neuropathology, University of Göttingen, Germany).

Autopsy material was available in 4 affected members; the clinical report only is available from the 60 year-old patient. Neuropathology was remarkably uniform, with prominent degeneration of thalamus and inferior olives. Two brains showed additional olivary pseudohypertrophy. Spongiform change was observed in only one area of one brain. Immunocytochemistry for PrP on numerous tissue blocks revealed mild deposits in the cerebellar molecular layer of one brain only; the brain of the recently deceased patient is under further investigation. Western blotting of one brain showed only trace amounts of PrPres (preliminary data by courtesy of Drs. K. Sidle, A. Hill and J. Collinge, Imperial College at St. Mary's, London, UK).

From data on this family, we conclude that (1) brain pathology in FFI dissociates prominently from PrP deposition; with regard to the unresolved pathogenetic role of PrPres; these data support a loss of function model rather than neurotoxicity; and (2) there is considerable variability of manifestation age and disease duration in this FFI family, in spite of constant homozygous methioninePRNP genotype at codon 129.

Corresponding author:
Herbert Budka, M.D., Institute of Neurology, University of Vienna, AKH 4J, P0B48, A-1097 Wien, Austria; Tel.: +431 40400-5501; -5573; Fax :+43 - 1 - 40400-5511; -5573; E-mail: h.budka@akh-wien.ac.at

Acknowledgement

This study is part of the EU Concerted Action on Human Transmissible Spongiform Encephalopathies (Project leader: H. Budka).

References

1. Almer G, Hainfellner JA, Budka H, Brücke T (1997) Clinical, pathological and molecular features of the first Austrian family with fatal familial insomnia (abstr). *Europ J Neurol* 4 Suppl 1: S1
2. Budka H, Hainfellner JA, Almer G, Brücke T, Windl O, Kretzschmar HA, Hill A, Collinge J (1997) A new Austrian family with fatal familial insomnia: brain pathology without detectable PrPres (abstr). *Brain Pathol* 7: 1267
3. Hainfellner JA, Almer G, Brücke T, Jellinger K, Kleinert R, Bayer G, Windl O, Kretzschmar HA, Hill A, Collinge J, Budka H (1997) Fatal familial insomnia in a new Austrian family: dissociation of brain pathology from PrP deposition (abstr). *Clin Neuropathol* 16: 261