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Does the Clinical Phenotype of Fatal Familial Insomnia Depend on *PRNP* codon 129 Methionine-Valine Polymorphism?

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CASE REPORTS

Fatal familial insomnia (FFI) is a rare, hereditary prion-protein disease. Methionine-valine polymorphism at codon 129 of the prion-protein gene (*PRNP*) determines the phenotype in other hereditary prion-protein diseases, but association with the clinical phenotype in FFI remains uncertain.

Early clinical findings in FFI comprise disturbances of the sleep-wake cycle and mild neuropsychiatric changes which typically emerge during middle to late adulthood. Here we describe an unusually early onset and rapid progression of FFI associated with dorsal midbrain involvement in a female patient with *PRNP* mutation at codon 178 and homozygote methionine polymorphism at codon 129. Early dorsal midbrain involvement became apparent by total loss of REM sleep and isolated bilateral trochlear nerve palsy.

Early onset and rapid progression disease type associated with dorsal midbrain involvement may indicate a different spatiotemporal distribution of the neurodegenerative process in FFI patients with *PRNP* mutation and codon 129 methionine homozygosity compared to methionine-valine heterozygosity.

Keywords: Fatal familiar insomnia, methionine-valine polymorphism, trochlear palsy, thalamic degeneration, sleep regulation

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Fatal familial insomnia (FFI) is a rare, autosomal-dominant inherited prion-protein (PrP) disease, which has been documented in 27 pedigrees worldwide. It is attributable to a *PRNP* missense-mutation at codon 178 and methionine-valine polymorphism at codon 129 on chromosome 20. FFI is always fatal and affects both sexes equally. Mean age at onset of disease is around 50 years, while the duration of the disease varies from 8 to 72 months. Early clinical features in FFI combine subtle disturbances of the sleep-wake cycle, sleep abnormalities such as loss of sleep spindles plus mild neuropsychiatric changes.[1]

PRNP codon 129 polymorphism determines clinical phenotype in other hereditary prion diseases such as familial Creutzfeldt-Jakob disease (fCJD) by modifying PrP conformation and protein-protein interaction. Genetic analysis for *PRNP* codon 129 polymorphism, however, were only carried out in less than the half of the published FFI cases.[1] Therefore it remains uncertain to which degree *PRNP* codon 129 polymorphism influences the clinical phenotype of FFI.

To contribute to elucidating the influence of methionine-valine polymorphism on clinical phenotype, we report a case with unusual early onset and rapid progression of FFI associated with early dorsal midbrain involvement in a patient with *PRNP* missense-mutation at codon 178 and homozygote methionine polymorphism at codon 129, indicating a different clinical phenotype in FFI patients with *PRNP* mutation and codon 129 methionine homozygosity compared to methionine-valine heterozygosity.

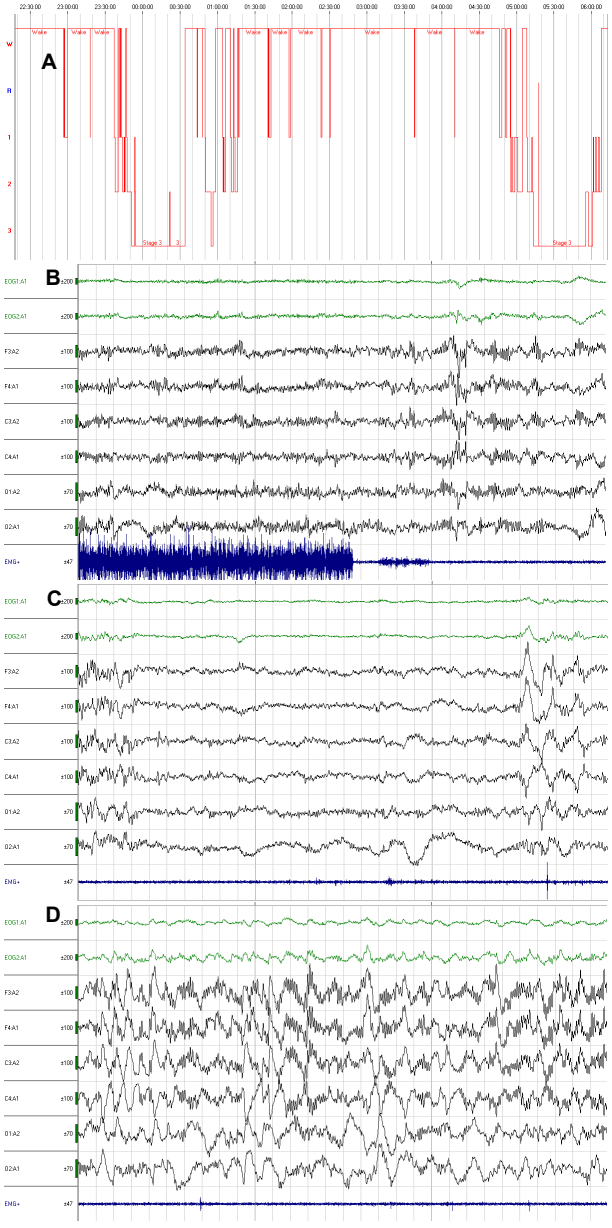
REPORT OF CASE

A 23-year-old female, presented with double vision emerging when looking down and to the left and right. Neuroophthalmological examination showed superior oblique motility deficits on both sides indicative of bilateral trochlear nerve palsy. Apart from that neurological and neuropsychological examination was normal. Neurological work-up excluded neuromuscular, inflammatory, metabolic, or vascular disturbances. MRI scan of the brain was normal.

The patient´s history revealed that the maternal grandfather and his brother died from suspected prion disease. Genetic analysis confirmed *PRNP* mutation at codon 178 and homozygote methionine polymorphism at codon 129 in our patient.

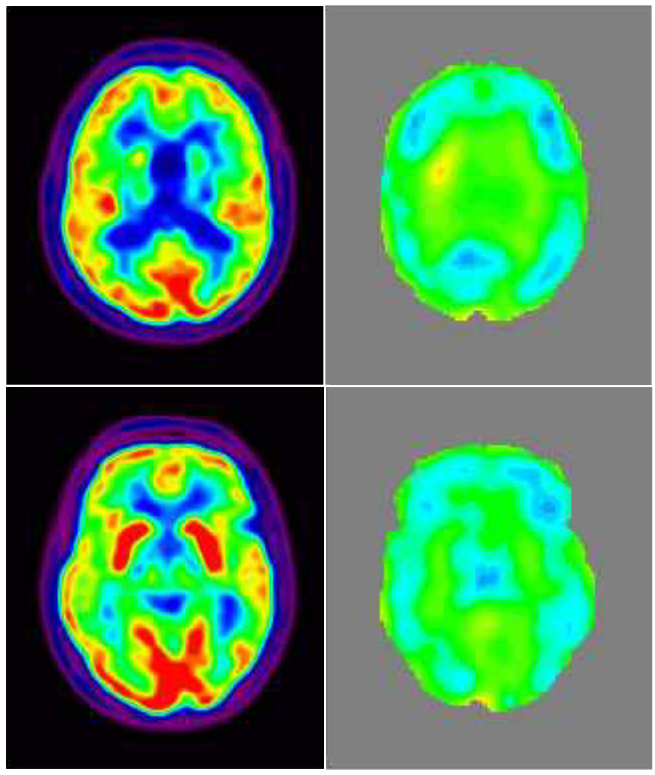
Polysomnographically, cyclic sleep organisation was replaced by rapid alternations between wakefulness and sleep stage NREM 1/2 interrupted delta sleep (**Figure 1**). REM sleep and sleep spindles were not detectable at all (**Figure 1**). Within 3 months, the patient developed the typical FFI features, including pronounced disturbances in sleep-wake cycle, cognitive decline, autonomic hyperactivity, and extrapyramidal motor symptoms. ^{18}F-FDG-PET revealed now bilateral thalamic and frontoparietal accentuated cortical hypometabolism (**Figure 2**) accompanied by frontoparietal cortical atrophy on the corresponding CT. Cerebrospinal fluid analysis was normal including normal levels of 14-3-3 protein. The patient died 5 months later due to respiratory failure. Autopsy was not performed.

Figure 1—Overnight sleep profile **(A)** and representative polysomnographic 30-sec epochs including wake-sleep transition **(B)**, NREM 2 **(C)** and delta sleep **(D)**



Sleep profile: Absence of cyclic sleep organization replaced by rapid alternations between wakefulness and sleep stage NREM 1/2 interrupted by preserved episodes of delta sleep. Wake-sleep transition: Initial awake EEG patterns characterized by symmetrical diffuse alpha activity replaced by low voltage mixed frequency theta activity in the second half of the epoch. NREM 2: Low voltage theta and superimposed alpha activity followed by a series of K-complexes. Sleep-spindles are not detectable. Delta Sleep: Diffuse polymorphic delta activity superimposed by alpha activity.

Figure 2—^{18}F-FDG-PET of the brain



Reduced bilateral thalamic metabolism and widespread cortical hypometabolism with frontoparietal and left-hemispheric accentuation.

DISCUSSION

Bilateral trochlear nerve palsy and loss of REM sleep are unusual early findings in FFI, highly indicative for dorsal midbrain involvement. Together with early onset and rapid disease progression, this indicates a distinct FFI phenotype in patients with *PRNP* codon 129 homozygote methionine polymorphism.

Trochlear nuclei are located in the tegmental midbrain, and only dorsal midbrain lesions can affect trochlear nerves bilaterally.[2] REM sleep generating areas such as pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei are closely located to the trochlear nuclei. Lesions of the PPT and LDT nuclei reduce or even eliminate REM sleep without affecting NREM sleep in animal studies.[3,4]

Early neurodegenerative manifestation in FFI seems to be predominantly restricted to the thalamus and adjacent regions.[1] Loss of sleep spindles, indicative for thalamic involvement, was also present early in our patient. Presence of bilateral trochlear palsy combined with loss of REM sleep indicates concomitant affection of dorsal midbrain structures. Histopathological changes have also been described for dorsal midbrain structures in FFI, particularly in patients with short disease duration.[1] However, neuropathological midbrain involvement has not yet been linked to *PRNP* codon 129 polymorphism.[1]

In addition to midbrain manifestation, early onset and rapid disease progression were prominent features in our patient. In fCJD *PRNP* codon 129, polymorphism determines age of onset and progression of disease.[5] An association between *PRNP* codon 129 methionine homozygosity and short disease duration could also be demonstrated in FFI.[1]

FFI primarily manifest in middle to late adulthood. However, several FFI cases with onset of disease in early adulthood have recently been reported.[6] Together with our findings, this

indicates an association between early disease onset and *PRNP* codon 129 methionine homozygosity.

In agreement with previous studies detection of 14-3-3 protein in CSF, which is highly predictive in the diagnosis of other prion diseases, was negative in our patient. In fCJD, 14-3-3 protein levels depend on *PRNP* codon 129 polymorphism.[7] Such a linkage between 14-3-3 protein levels and *PRNP* codon 129 polymorphism has, however, not been systematically addressed in FFI.[7]

Taken together, our case supports the assumption of a distinct clinical phenotype in patients with *PRNP* codon 129 methionine homozygosity. Since FFI is a diagnostic challenge, clinicians should be aware of unusual clinical features and FFI needs to be considered in young patients with unclear neuropsychiatric symptoms.

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