Serial Positron Emission Tomographic Findings in an Atypical Presentation of Fatal Familial Insomnia

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**Background:** Genetic analyses of fatal familial insomnia, a prion disease, disclose a broader range of symptoms than previously described. Although insomnia and dysautonomia have been described as hallmarks of the disease, there is substantial variability in clinical presentation.

**Objective:** To evaluate serial fluorodeoxyglucose positron emission tomographic and electroencephalographic findings in atypical fatal familial insomnia without clinical insomnia.

**Patient:** A 63-year-old man who had a history of gait ataxia developed rapidly progressive dementia with mild dysautonomic features. Genetic investigation confirmed diagnosis of fatal familial insomnia (D178N mutation of the prion protein gene and Val/Met polymorphism on position 129 of the mutated allele) with typical neuropathologic findings.

**Results:** Clinical signs were not specific. An electroencephalogram showed scanty triphasic-like elements and general slowing. We found thalamic hypometabolism in positron emission tomographic scans to be present in a very early stage with progressive deterioration, and patchy cortical alterations showing progression over 6 months.

**Conclusions:** In the absence of clear clinical signs, an electroencephalogram was of major diagnostic value, although its specificity in fatal familial insomnia is under debate. Selective thalamic hypometabolism seems to be an early marker in fatal familial insomnia, while cortical changes vary with clinical presentation and stage.

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**PRION DISEASES are unique because they may present as inherited, sporadic, and infectious disorders. Fatal familial insomnia (FFI), a condition whose clinical and pathologic features were first described by Lugaresi et al., is a disorder arising from a mutation at codon 178 of the prion protein (PRPN) gene, cosegregating with the methionine polymorphism at codon 129 of the mutated allele.** Two main clinical subtypes are described with either a short or a prolonged clinical course depending on whether a homozygote Met/Met or a heterozygote Met/Val polymorphism is found at codon 129. Disturbances of wake-sleep cycle, dysautonomia, and motor signs (eg, ataxia) have been reported as typical diagnostic findings. The neuropathologic hallmarks are thalamic degeneration, particularly with selective involvement of the anterior ventral and mediodorsal thalamic nuclei, as well as inferior olivary and cerebellar changes and some spongiform change of the cerebral cortex. However, genetic analyses disclose at present a wide range of symptoms in contrast to the uniform genetic mutation. Previous reports about positron emission tomographic (PET) findings suggest thalamic hypometabolism to be a stable finding in FFI, while cortical hypometabolism seems to be more variable, particularly over time, although only very few patients have been characterized using PET methods. We report the case history and provide serial PET scanning data of a patient with FFI who had rapidly progressive dementia, dysautonomic features, and electroencephalographic abnormalities, but an absence of clinical insomnia.

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**REPORT OF CASE**

A 63-year-old man was admitted to the hospital with a 6-month history of mild dizziness, alternating gait ataxia, erectile dysfunction, and fluctuating diplopia (especially while watching television). Neurological examination could not elucidate any reproducible sign, apart from slight ataxia in the left lower limb with characteristic heel-
shin ataxia, with slightly irregular side-to-side errors when placing his heel on the opposite knee and moving down his shin. However, ataxia disappeared completely when the patient was asked to count simultaneously. His wife described him as being more forgetful, slightly buoyant, and less reliable than usual. Intensive clinical, radiological (including brain magnetic resonance imaging and a fluorodeoxyglucose F 18 labeled–positron emission tomographic scans and electroencephalographic recordings) were obtained twice: first early after presentation (top row), then 6 months later (second row). For the positron emission tomographic scans (resting state), subtraction images have been performed to assess absolute reduction of glucose uptake in brain regions. The positron emission tomographic scans show axial sections at the level of the thalamus and paramedian sagittal sections. Note that relative thalamic hypometabolism is present at both time points and somewhat progresses over time, while cortical changes (including cerebellum) are heterogeneous in their spatial distribution and show even stronger metabolic reductions in some areas.

Three months later the disease had rapidly progressed. The patient was wheelchair bound, mildly demented, and developed a slurring staccato speech. The lack of insight into his progressing disease was obvious; he mistook names and lost orientation. Eye pursuit movements became saccadic, voluntary movements dysmetric, and gait increasingly ataxic. Apart from repeated abundant sweating, adjusted hypertension (while receiving propranolol hydrochloride therapy), and an increased heart rate at rest (average, 70-80 beats/min), no dysautonomic features were noted. The sleep pattern appeared to be normal. Neuropsychological testing revealed impairment of short-term memory, decline of intellectual abilities, and reduced concentration and attention. The progressive dementia prompted further specific investigations for metabolic and genetic causes. Additional cerebrospinal fluid markers were normal (protein 14-3-3 negative, tau, and S100 protein levels were within the normal range); investigation for rare metabolic diseases were unremarkable (particularly β-galactosidase, β-hexosaminidase, and arylsulphatase A); and extensive genetic testing (including testing for CAG repeats for Huntington disease, apolipoprotein E 3, spinocerebellar ataxias 1, 2, 3, 6, and 8) did not disclose the cause of the disease. At this point, an electroencephalogram showed scant triphasiclike elements (along with general slowing), giving a further hint toward possible prion disease. Follow-up PET imaging revealed patchy hypometabolism in the frontal cortex, thalamus, brainstem, and cerebellum. With further progression of disease, the patient became less able to be aroused and ultimately died of pneumonia 3 months later.

Neuropsychological testing included Mini-Mental State Examination, tests of the Wechsler Adult Intelligence Scale, as well as tests from a standard German testing battery (Nürnberger Altersinventar). On admission, the Mini-Mental State Examination score was 26 of 30 and only subtle cognitive slowing was noticed (eg, on the Trail Making Test). Six months later, the Mini-Mental State Examination score fell to 21 and decline of concentration and executive tasks became apparent with pronounced impairment on the Wechsler Adult Intelligence Scale performance tests (visuospatial skills like "picture arrangement" or "picture completion") and slight deficits on "digit span" and "similarity" subtests. By the last examination (the Mini-Mental State Examination score was 16), the patient was severely impaired on most Wechsler Adult Intelligence Scale subtests.

Genetic investigations revealed a D17SN mutation of the prion protein with a Val/Met polymorphism on position 129 and Met on the mutated allele, thus making the diagnosis of FFI, and more specifically indicating the slowly progressive subtype of FFI.5

Postmortem macroscopic examination of the brain solely showed ventricular enlargement and minor cerebellar atrophy. Histologic study revealed severe neuronal loss and astrogliosis in the thalamus (particularly mediodorsal, centromedian, and reticular nuclei), with spongiform change mainly in ventrolateral nuclei, as well as marked gliosis in the inferior olivary nucleus (without spongiform change) and the dentate nucleus of the cerebellum (Figure 2B-C). The cerebral cortex showed only minor alterations: some mild to moderate spongiform change and astrogliosis were seen in a few cortical regions, mainly the anterior cingulate cortex and upper layers of the superior parietal cortex (Figure 2C), and to a minor extent in the entorhinal cortex. We applied the paraffin-embedded tissue blot technique8 to detect scrapie prion protein, showing stronger reactivity in medial thalamic nuclei (Figure 2D).

**COMMENT**

This case not only illustrates the clinical variability in FFI but also gives hints to the correlation of metabolic abnormalities and symptoms in this disease. Rare causes of dementia impose diagnostic difficulties, particularly if symptoms tacitly assumed to be essential are missing.
Beside rapid progression of disease, the clinically most useful hint in this case was in fact the electroencephalogram, which showed an abnormality frequently seen in other prion diseases (though not typically in FFI).

Although Lugaresi et al introduced FFI as an “insomnia and dysautonomia” characterized by specific thalamic degeneration, the latter symptom is sometimes given less consideration, although it forms a core feature of the disease. In the present case, the only symptoms that might have indicated dysautonomia were profound sweating on several occasions, erectile dysfunction, and to a minor extent, mild hypertension and slightly increased heart rate. The absence of clinical insomnia illustrates the importance of polysomnography for differential diagnosis of dementia, since this, indeed, might have been a valuable diagnostic tool. The diagnostic significance of this investigation goes beyond FFI, possibly including other forms of dementia. The close relation of insomnia and dysautonomia in FFI is, however, interesting because it might give clues to the role of medio-dorsal thalamic nuclei in these functions. Indeed, severe thalamic hypometabolism was demonstrated on the PET scans of this patient, with further progression on repeated PET scans (Figure 1).

Although in this case PET was not a major diagnostic clue, it reveals some interesting aspects. First, it confirms marked thalamic hypometabolism postulated in earlier studies, which was present on the first scan, showing further progression after 6 months (Figure 1, center row). As the first time point was early in the disease, it might be assumed that relatively selective metabolic impairment in the thalamus is an early feature of FFI. Still, the patient was lacking certain symptoms (insomnia and prominent dysautonomia) expected with such a degree of hypometabolism. Second, our patient demonstrated widespread patchy reductions in cortical glucose uptake. Indeed, these had been estimated to be more significant on the first scan. Cortical hypometabolism has been demonstrated in previous studies, but the relation to the stage of disease has remained unclear. In our case, prominent reductions were present in the orbitofrontal cortex, caudate, and cerebellum. Not surprisingly, these locations show a close functional relation to the symptoms, ie, changes of mood, ataxia, and cognitive impairment. Frontal hypometabolism corresponded to the clinical observation that our patient presented initially as being rather cheerful with a change of personality and with fairly subtle cognitive deficits. The limited resolution of PET,

Figure 2. Neuropathologic findings. Postmortem histologic examinations (A through C: hematoxylin-eosin, bars indicate 25 µm) indicates gliosis and nerve cell loss in the medial thalamus (A) and inferior olive (B). While most of the cortical regions were spared, a few patches with mild to moderate spongiform change were found in the anterior cingulate and superior parietal lobe (C, upper cortical layers of section through superior parietal lobule). Deposits of scrapie prion protein were found in the thalamus, particularly in the medial nuclei (D, showing a coronal section through the thalamus at the level of the centromedian nuclei; medial thalamus is on the left of the image).
however, did not allow a more detailed correlation of cortical alterations to those in the thalamic subnuclei. Interestingly, anterior cingulate hypometabolism was less uniform than assumed. While most of this cortical region was hypometabolic already in the first scan, single areas in the rostral part were relatively hypermetabolic (Figure 1, sagittal sections). Nevertheless, this finding is in line with assumptions from previous studies, implicating this brain region together with the thalamus to show most prominent changes. Also, cerebellar alterations were quite remarkable and showed substantial progression in at least some regions. Finally, the subtraction images demonstrate progression of metabolic impairment in the thalamus, but also in the occipitoparietal and orbitofrontal cortices, cerebellum, and caudate, while cingulate metabolism further declined mostly in the rostral parts. This supports the view that cortical hypometabolism might be related to stage of disease and is thus much more variable than thalamic changes, which are at the core of FFI.

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