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Original Article

Agrypnia Excitata

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ABSTRACT

The concept of Agrypnia excitata (AE) was originally proposed as a concept deriving from the clinical and anatomo-pathological observations obtained in three different diseases, Fatal familial insomnia (FFI), Delirium tremens (DT), and Morvan syndrome (MS). *Agrypnia* refers to a condition of severely reduced or absent sleep due to organic disorders. *Excitata* refers to the association of agrypnia with generalized motor and autonomic hyperactivation. AE is a syndrome that has been claimed to relate to a dysfunction in the thalamo-limbic circuits that govern sleep–wake cycles and autonomic activities.

1. Introduction

Fatal familial insomnia (FFI) is an autosomal dominant disease clinically characterized by loss of sleep associated with autonomic and motor overactivity, and pathologically by selective thalamic degeneration [1]. From the outset we attributed the main clinical features of FFI to the intralimbic disconnection caused by atrophy of the "visceral" thalamus (anterior and medio-dorsal thalamic nuclei) [1].

Later we observed that Morvan Syndrome (MS), an autoimmune limbic encephalopathy, and Delirium Tremens (DT), the well-known alcohol withdrawal syndrome, share the main clinical and polysomnographic (PSG) features of FFI [2,3].

We hypothesized that the syndrome, which we named agrypnia excitata (AE) and was characterized by a loss of sleep associated with generalized motor and autonomic hyperactivation, is due to an anatomic (FFI) or functional (MS, DT) interruption of the thalamolimbic circuits regulating the sleep–wake cycle and body homeostasis [4,5].

2. Clinical features and pathophysiology of FFI, MS and DT

2.1. Fatal insomnia (FI)

Fatal familial insomnia (FFI) is a hereditary autosomal dominant disease caused by a missense mutation at codon 178 of the prion protein gene (PRPN) co-segregating with methionine at Methionine (M) – Valine (V) polymorphic codon 129 in the mutated allele. More than 50 affected families have been identified to date all over the world and in every ethnic group. Non-genetic cases (Sporadic Fatal Insomnia, SFI) are extremely rare (just ten cases have been described).

FFI patients homozygous at codon 129 (codifying M also in the non-mutated allele at codon 129 of PRPN) have a more rapid evolution (9–10 months as a mean) than FFI heterozygous patients (codifying V at position 129 of the non-mutated allele) who have a two to threefold longer disease duration. The short-evolution cases (M-M patients homozygous at codon 129) present the most typical features of the disease. We shall refer to these cases in describing the hallmarks of the syndrome.

2.1.1. Symptoms and signs

Although patients often fail to report it, one of the earliest features of the disease is a difficulty falling asleep, early awakening, and an inability to take their usual naps. At the same time, they appear apathetic and drowsy and this condition progressively worsens over the passing days and weeks. Patients become increasingly taciturn and appear indifferent to their surroundings and even their fate. They seldom complain of drowsiness, but this becomes apparent from an increasingly expressionless face, lowered eyelids, and the head tending to fall forwards (Table 1). These signs are subsequently accompanied by episodes of profuse perspiration, lacrimation, and salivation. Pulse rate quickens and arterial pressure increases. Mild fever, transient diplopia, urgency, and impotence in males are commonly encountered in the full-blown disease stage.

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Table 1
Clinical features of fatal insomnia.

CLINICAL FEATURES OF FATAL INSOMNIA		Age at onset (yrs)	Disease duration (mean; mths)	Symptoms/Signs
FFI	Short evolution	51 ± 7	9 ± 1	•Difficulty falling asleep •Apathy •Drowsiness •Oneiric stupor •Sympathetic overactivity •Spontaneous and evoked myoclonic jerks
FFI	Long evolution	51 ± 8	31 ± 21	
SFI		50 ± 11	19 ± 5	

Automatic gestural movements mimicking daily-life activities, like dressing, combing the hair, washing, and manipulating a non-existent object are consistently present and may appear in the earliest stages of the disease.

Patients often link these gestures to an oneiric scene: if questioned they say "I was dreaming of getting dressed, combing my hair, adjusting the sails on my boat…".

As the disease progresses gait becomes unsteady and worsens, resulting in ataxia–abasia. Speech becomes slurred, increasingly feeble, and incomprehensible. In the full-blown stage, evoked and spontaneous myoclonic jerks are present, while diffuse prolonged muscle spasms may appear in the terminal stages. Patients progressively lose weight and die from sudden cardiorespiratory failure or ensuing infections.

2.1.2. Laboratory findings

2.1.2.1. Neuropsychological examination. Serial neuropsychological examinations documented an early progressive impairment of attention and vigilance, whereas intellectual function remains substantially intact until the advanced stages of disease. The neuropsychological picture resembles a disturbance of consciousness (confusional state) rather than true dementia [6].

2.1.2.2. Autonomic, hormonal, and motor activities examination. Cardiovascular background and stimulated sympathetic activities along with norepinephrine (NE) secretion are higher than normal and increase with advancing disease stages. By contrast, parasympathetic functions are consistently preserved. Sympathetic skin response was abolished in four FFI patients we tested [7]. Muscle sympathetic nerve activity (MSNA) during resting wakefulness was abnormally high in an FFI patient recently examined [8].

Serial 24 h monitoring of autonomic and hormonal functions performed in several FFI patients documents that heart and breathing rates, body core temperature and arterial pressure are consistently over the normal limits during both the day and night, and that plasma concentrations of adrenaline and cortisol, and especially NE, measured in hourly blood samples, are invariably elevated, whereas melatonin (MLT) secretion is reduced and most of all lacks the physiological nocturnal peak [9–11] (Fig. 1a, b).

CSF analysis disclosed an increase in 5-HT metabolism in the three FFI cases we examined [12]. An enhanced serotoninergic neurotransmission in FFI was confirmed on brain tissue obtained at autopsy [13]. Actigraphic wrist recordings, continuously performed for weeks or even months, showed an increased motor activity, namely the absence of prolonged pauses (Fig. 1c). The 24-h energy expenditure measured in a respiration chamber was 60% above the physiological level in one FFI patient [14].

2.1.2.3. EEG and polygraphic findings. Routine EEG tracings are usually normal, although EEG signs of drowsiness (diffuse alpha rhythm or increased alpha activity on eye opening) are invariably present. Prolonged diurnal polygraphic recordings highlight short REM episodes lasting less than 30–40", recurring, often in clusters lasting several minutes, and alternating with episodes of sub-wakefulness (stage 1, light stupor) (Fig. 2a,b; Fig. 3a).

Serial 24 h polygraphic recordings repeated throughout the disease course show a progressive reduction and disappearance of spindles, *K* complexes, and delta sleep activities. Spindles and *K* complexes could not be evoked by pharmacological means, such as intravenous administration of high dosages of barbiturates or benzodiazepines (Fig. 2c). By contrast, short isolated or clustered REM sleep episodes recur day and night until the most advanced disease stages. Hence a state of sub-wakefulness, polygraphically characterized by stage 1 with interspersed short REM sleep episodes, becomes the dominant diurnal and nocturnal EEG and behavioural pattern (Fig. 2a). Clustered REM sleep episodes frequently coincide with gestures mimicking daily-life activities.

2.1.2.4. In vivo (neuroimaging) and post-mortem brain examination.

2.1.2.4.1. Neuroimaging. CT and MRI scans are unremarkable except for a mild cerebral and cerebellar atrophy in the most advanced disease stages.

Serial PET (18 FDG-PET) scans invariably show a thalamic hypometabolism from the early stages of the disease [15]. Impaired thalamic metabolism may appear several months before disease onset in FFI mutation carriers [16]. Although hypometabolism is invariably more pronounced in the thalamus, it extends to the mesial areas of the frontal lobe as the disease progresses, affecting the entire cortex and basal ganglia in the most advanced disease stages of long evolution cases. The metabolic impairment prevails in the mesial areas of the frontal lobe in both short and long evolution cases.

2.1.2.4.2. Pathology. Bilateral symmetric thalamic degeneration is the most consistent finding in all FFI cases: the thalamic structures invariably and most severely affected are the mesial part of the mediodorsal (MD) nuclei, and the anterior nuclei, namely the anteroventral (AV) nuclei. Neuronal loss in the MD and AV thalamic nuclei is up to 80%, often reaching 95–100% in the most affected parts (AV nucleus and mesial part of the MD) [17]. Other thalamic nuclei are less consistently and less severely affected.

According to Gambetti (personal communication), the extent of neuronal loss in the thalamic reticular nucleus – TRN- (a wide thin structure) is difficult if not impossible to determine even with morphometric analysis. However, Schulman [18], in an ante-litteram case of FFI, and Macchi et al. [19] in two other cases of FFI in which the thalamic nuclei were studied by morphometric analysis, documented that the TRN was one of the most damaged thalamic structures. The *inferior olives* are severely affected in almost all FFI patients. Mild spongiform degeneration confined to the mesial-orbito-frontal cortex and anterior cingulate gyrus is a common finding in short evolution cases, whereas spongiform degeneration spreads to the neocortex in long evolution cases (Fig. 4).

Interestingly, the cortical involvement is most prominent in the cortico-limbic regions (anterior cingulate gyrus and mesial orbito-frontal cortex) regardless of disease duration [17,20]. Therefore FFI can be deemed a limbic or prevalently limbic (thalamolimbic) encephalopathy.

2.1.2.5. Genetics and molecular biology.

2.1.2.5.1. Genetics. As previously mentioned, FFI is an autosomal dominant disease linked to a missense mutation at codon 178 of the PRNP [21]. The same mutation at codon 178 causes a familial variant of Creutzfeldt–Jakob Disease (fCJD^{178}) characterized by a rapid dementia associated with widespread cortical spongiform degeneration [22]. The different phenotypes of FFI and fCJD^{178} are determined by different genotypes at Methionine-Valine polymorphic codon 129 of the PRNP. The FFI phenotype co-segregates