FATAL FAMILIAL INSOMNIA: A HUMAN MODEL OF PRION DISEASE

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Drowsiness has been reported to occur in goats, cats, minks and hamsters with prion encephalopathies. Instrumental evaluation of sleep-wake abnormalities in these prion affected animals, however, has never been reported.

Very recently Tobler et al. documented that mice devoid of prion protein manifest impaired sleep-wake and other circadian rhythms. A clinical picture characterized by disordered sleep and impaired circadian activities has been described in Fatal Familial Insomnia. FFI is an autosomal dominant prion disease presenting with loss of sleep, sympathetic hyperactivity and progressive attenuation of autonomic and endocrine circadian oscillations. These cardinal features of the disease are associated with selective thalamic degeneration. Therefore experimental and clinical data suggest that the prion protein plays a major role in physiological mechanisms regulating the rest-activity cycles of living organisms. FFI represents a human model to study the anatomic and molecular basis of sleep-wake and other circadian rhythms.

FFI patients appear apathetic and drowsy: neuropsychological tests demonstrate a progressive impairment of attention and vigilance. Behaviorally, these patients appear to be in an ongoing transition between sleep and wakefulness. 24h polygraphic recordings demonstrate a progressive inability to generate physiological EEG sleep patterns.

Sleep spindles, EEG activities of thalamic origin, which characterize physiological sleep onset and the shift from NREM to REM sleep and vice versa, disappear very early in the course of the disease and only brief episodes of REM sleep or delta sleep emerge, directly and abnormally, from wakefulness.

In other words, in FFI patients the disappearance of spindling activity impairs the onset and maintenance of sleep. 24 h sleep time is radically shortened and any cyclic organization of sleep is lacking. Disappearance of sleep is associated with sympathetic hyperactivity with tachycardia, tachypnea, hypertension, hyperthermia, sweating, impotence and constipation.

24 h recordings demonstrate that body temperature, and heart and breathing rates are abnormally high and that circadian oscillations are severely reduced. Blood pressure also increases, showing ever more reduced circadian oscillations with the progression of the disease. 24 h determinations of hormonal secretion document an abnormal pattern; cortisol, prolactin, catecholamines display increased concentrations; ACTH and GH lack physiological peaks of secretion. In addition, the amplitude of circadian oscillations of all
hormones is reduced. Nocturnal melatonin increase, physiologically associated with darkness (and not with sleep), is greatly reduced from the early stages of the disease and disappears in the advanced stages. PET scans reveal that the thalamus is the only or the most severely affected cerebral region.

The medio-dorsal and antero-ventral thalamic nuclei are invariably and severely affected (with a neuronal loss of over 70%). Other thalamic nuclei (pulvinar, central-median and others) are less consistently and less severely involved. The pathology of the cerebral cortex is very mild in short-lasting cases, more pronounced in long duration cases. The lesions are more severe in some limbic and paralimbic cortical regions (i.e., the rostral part of the cingulate gyrus, orbital and entorhinal cortex). Therefore FFI can be defined as a preferential thalamic degeneration prevalently involving the dorso-median and anteroventral nuclei (i.e., the visceral or limbic portion of the thalamus). The DM nucleus is closely connected with the prefrontal cortex on the one side and the anterior hypothalamus and basal forebrain on the other. The AV nucleus is strictly connected with the rostral part of the cingulate gyrus on the one hand and the posterior hypothalamus and midbrain on the other. The anterior hypothalamus and the basal forebrain contain sleep-inducing structures, whereas the posterior hypothalamus and the midbrain incorporate activating neuronal structures which trigger wakefulness. Atrophy of the DM and AV nuclei of the thalamus could therefore disturb both the circuits activating wakefulness and those promoting sleep.

The hypersomnolent-insomniac condition characteristic of FFI and also typical of paramedian thalamic strokes could be due to the impairment of two different neuronal circuits controlling vigilance level and sleep respectively.

According to Moruzzi and many others, sleep is an instinctive behaviour which is triggered by a low level of vigilance (sub-wakefulness or drowsiness). Recalling this, it becomes clear that the two neuronal circuits, one regulating vigilance and the other inducing sleep, are different.

Sleep onset is marked by the appearance of characteristic bioelectric activities (the sleep spindles) which originate in the thalamus and from there irradiate to the prefrontal cerebral cortex and other neuronal brain structures.

Some experimental studies have demonstrated that atrophy of the DM nuclei prevents spindling spreading to the prefrontal cortex. This could be why patients with FFI have difficulty initiating and maintaining sleep despite being in a condition of persistent somnolence. In other words, degeneration of the limbic portion of the thalamus, disturbing both the circuits controlling wakefulness and those which induce sleep leads to hypersomnolence associated with the inability to sleep: the typical behaviour pattern of FFI patients. Loss of sleep is associated with persistent sympathetic hyperactivation and progressive attenuation of autonomic and endocrine circadian oscillations. A tentative explanation for this complex autonomic and endocrine impairment is the following: atrophy of DM and AV thalamic nuclei (i.e.: the limbic portion of the thalamus) interrupts the most important cortical control over the hypothalamus. The impaired hypothalamic regulation of body homeostasis results in an activated autonomic and endocrine pattern stemming from this functional imbalance.

The progressive attenuation of circadian and endocrine oscillations is an expression of ever increasing prevalence of activating system: if a pendulum swinging between two extremes tilts its axis towards one end, the greater the shift, the more limited its oscillations will be. FFI anatomoclinical findings demonstrate that the selective degeneration of the limbic thalamus impairs sleep and wakefulness and, more generally, endocrine and autonomic homeostasis. This is probably due to the fact that the hypothalamus is released from major cortico-limbic control.

The symptoms encountered in FFI are in some way similar to those observed in mice devoid of prion protein. This suggests that the anatomic damage caused by the protease resistant prion protein disturbs the same circuits in which the physiological prion protein...