The Kleine-Levin Syndrome: A Paramedian Thalamic Dysfunction?

Comment on Huang YS; Guilleminault C; Kao PF et al. SPECT Findings in the Kleine-Levin Syndrome. SLEEP 2005;28(8):955-960

Michel Billiard, MD

School of Medicine, Gui de Chauliac Hospital, Montpellier Cedex, France

KLEINE-LEVIN SYNDROME STANDS AS A WELL DEFINED, ALTHOUGH RARE, SYNDROME INCLUDING RECURRENT EPISODES OF HYPERSOMNIA, BEHAVIORAL disturbances such as binge eating, hypersexuality, irritability, and cognitive abnormalities such as feelings of unreality, confusion and hallucinations, of one to two weeks’ duration, separated by asymptomatic periods of one to several months’ duration. In regard to these clinical features laboratory tests are rather uninformative and etiopathogenesis is still unknown.

Routine blood tests are normal. Hormonal levels as well as 24-hour secretory patterns are, with a few exceptions, normal. Plasma and CSF bacterial and viral serologies are normal. A twofold decrease in hypocretin-1 level during the hypersomniac episode as compared to the asymptomatic period has been reported in a single patient. CT scan and MRI are usually normal. The typical EEG pattern is one of general slowing of the background activity frequently associated with bursts of bisynchronous, generalized, moderate to high voltage 5 to 7 Hz waves. 24-hour continuous polysomnography prolonged over 24 hours typically demonstrates prolonged total sleep time, up to 16-18 hours in some reports. The most contributive investigations up to now include: a few neuropathological examinations in favor of localized encephalitis of viral origin, in different locations however; a significant increase of HLA-DQB1*0201 allele frequency; and reports of SPECT studies in single patients documenting hypoperfusion in different parts of the brain, not in the thalami.

As for etiopathogenesis an hypothalamic dysfunction has often been suggested mainly based on the combination of clinical features; in a one patient study showing increased values for TSH and PRL, and decreased values for GH and cortisol, an abnormality of hypothalamic dopaminergic tone has been proposed. More recently an autoimmune disorder has been put forward based on the recurrence of episodes, frequent flu-like illness or infection of the upper airway immediately before the onset of the first episode, young age at onset, and data suggesting an association with HLA.

The present report of brain imaging SPECT in 5 subjects affected with the Kleine-Levin syndrome, documenting a more than 30% diminished perfusion of both thalami during a symptomatic period in comparison with an asymptomatic period in all cases, plus an hypoperfusion in the basal ganglia and various cortical sites in a majority of cases, can be considered as a breakthrough in the rather uneventful history of the syndrome.

Based on previous experience the authors have attempted a comparison between their current findings in Kleine-Levin syndrome patients and previous findings in a 23 and a 28 years old black men diagnosed with paramedian thalamic lesions. These subjects were brought to an emergency room with miotic pupils and in a stuporous condition. Both subjects were strongly suspected for previous use of crack. There was no evidence of focused signs or any other neurological abnormalities on examination, but CT scan and MRI showed the presence of isolated bilateral paramedian thalamic lesions. Most interestingly the patients were reported, after the first 15 days, to present an excessive sleepiness status and intermittent abnormal behaviors such as abusive language, aggressivity, increase of sex drive with nurses and short term amnesia, reminiscent of those behavior abnormalities found in the Kleine-Levin syndrome. The first EEG recordings performed 24 and 48 hours after admission showed a pattern of drowsiness characterized by a mixture of low-amplitude, irregular diffuse theta and alpha range frequencies, a complete absence of sleep spindles, K complexes and other well-formed sleep patterns. A polysomnography performed in the 28 year old subject 10 days after the event showed a total sleep time of 257 min and a regular NREM-REM cycle succession. Sleep architecture was obviously abnormal, with 24% of total sleep time scored as stage 1, 64% as stage 2, with very few spindles, 7% as stages 3 and 4, and 5% as REM sleep. Three years later the same patient was unable to work at a permanent job and he was reported to lie down and close his eyes in a sleep-like behavior when left alone. Polysomnography showed a total sleep time of 263 min with a sleep latency of 109 min, stage 2 was recognizable in spite of rare spindles, stages 3 and 4 took up 6% of the total sleep time and REM sleep 12%. To sum up the patient was representative of patients with paramedian thalamic lesion with disturbance of both wakefulness (insufficient arousal or dearousal) and night sleep (decreased sleep spindles and reduced NREM sleep stages 3 and 4 percentage).

By which type of ischemic lesions can the state of reduced alertness and impaired sleep of these patients be explained. There are quite a number of clinical and neuropathological studies performed in subjects with bilateral paramedian thalamic infarction. These studies generally agree on the involvement of thalamic nuclei (mainly intralaminar nuclei) with widespread projection to the cerebral cortex as well as other dorsal thalamic nuclei (mainly the mediodorsal nuclei) with projections to the frontal and circular cortices. These nuclei transfer over the cortex the activating impulses arising in brain stem cholinergic and glutamatergic neurons and thus maintain a high excitability of the cerebral cortex. Their lesion is likely to produce deafferentation
of the cerebral cortex, tendency to sleep or hypersomnia, depending on the extent of cellular loss.

Can an analogy be drawn between these ischemic lesions and the thalamic hypoperfusion disclosed by SPECT studies? First, due to limited resolution, SPECT studies do not disclose a hypoperfusion of specific nuclei, but a global hypoperfusion of the thalamic nuclei. Second the type of polysomnographic abnormalities described in the Kleine-Levin syndrome does not mimic those of paramedian thalamic nuclei infarction: there is no report of decreased sleep spindles or stages 3 and 4 disappearance, but rather REM sleep abnormalities such as reduced REM latency, sleep onset REM periods or REM sleep repeatedly interrupted by awakenings and gross body movements. Finally it is rather puzzling that the current SPECT study showed homogeneous findings centered on the thalami in 5 subjects, while none of the other published SPECT studies document hypoperfusion of the thalami.

In conclusion the emphasis put on the thalamus in the article by Huang et al. provides a new pathophysiological orientation of definite interest. However additional SPECT studies and PET studies are certainly warranted, before claiming an involvement of the thalamus in the Kleine-Levin syndrome.

REFERENCES
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