Kleine-Levin syndrome: Functional imaging correlates of hypersomnia and behavioral symptoms
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Kleine-Levin syndrome (KLS) is a disorder characterized by recurrent episodes of hypersomnia associated with perception, cognitive, and behavioral disturbances, such as hyperphagia and hypersexuality. Episodes are separated by intervals of normal alertness, cognition, and behavior. Primary KLS predominantly affects adolescent males, with a prevalence of 2–10 per million, although this is probably underestimated. KLS diagnosis does not rely on any reliable biological marker, while its pathophysiology remains elusive. It was suggested that KLS could result from viral or postinfectious autoimmune encephalitis with a primary involvement of the hypothalamus because of the important role of this structure in regulating sleep and behavior.

We report 2 young right-handed patients, fulfilling the International Classification of Sleep Disorders–II criteria for KLS, both examined by 18F-fluorodeoxyglucose (18F-FDG) PET scan during a symptomatic and an asymptomatic period.

**Case reports.** The first subject was a 17-year-old boy who was admitted for an episode of hypersomnia; he slept more than 20 hours per day with intense dreaming and hypnagogic hallucinations. When awake, he reported “dream-like” perceptions, compulsive eating, and memory disturbances. The episode was the fourth in 2 years; the previous ones lasted between 5 and 7 days. He was thoroughly investigated to exclude other potential diagnoses. A brain 18F-FDG-PET scan was performed during this symptomatic period, free of medication, and repeated 3 months later, when the patient was asymptomatic.

The second subject was an 18-year-old woman, first examined following the end of her fourth episode of recurrent hypersomnia, lasting for 10 days. During the episode, sleep duration was increased and, when awake, she reported heavy fatigue, a feeling of unreality, and blurred memories. She also ate large amounts of food with preference for sweets. Extensive laboratory and imaging tests were normal. A brain 18F-FDG-PET scan was performed 3 weeks after the end of this episode, when she fully recovered from this episode. The PET scan was repeated 6 months later, on the occasion of a new episode, after lithium therapy was started.

During the PET scan procedures, quiet wakefulness was monitored through EEG recordings by an on-site EEG-trained physician for 20 minutes following 18F-FDG injection. Both patients provided informed consent. Brain PET processing and analyses were managed using SPM8. Images of the 2 patients were averaged, subtracted between symptomatic and asymptomatic periods, normalized with PET images performed during the asymptomatic period, and convoluted to automated anatomical labeling gray-matter mask, using a threshold of 5% for significant metabolic increase/decrease.

Significant increases and decreases in brain glucose metabolism determined during the symptomatic period are illustrated in the figure, which shows average changes found in both patients. Overall, during their symptomatic episode, patients exhibited a significant metabolic decrease in the hypothalamus, the orbitofrontal and frontal parasagittal areas, and the bilateral posterior regions, while metabolic increase was observed in the anterior caudate nuclei, the cingulate, and the premotor cortex.

**Discussion.** Considering the pathophysiology of KLS, the hypothalamic hypometabolism may implicate sleep regulation, control of food intake, and sexual behavior. The decreased orbitofrontal and anterior parasagittal brain metabolism may correlate with motivational and behavioral symptoms (such as apathy, disinhibition, inappropriate conduct, abnormal eating patterns), while the decreased metabolism in posterior areas might reflect altered perception (delusions, hallucinations, dream-like experiences). Increased caudate, cingulate, and premotor metabolism could result from recruitment of compensatory mechanisms. Enhanced activity surrounding the primarily affected regions represents a well-known compensatory mechanism following focal brain injury, or an adaptive response to neural disorganization of diffuse brain damage.

In previous functional neuroimaging studies using SPECT, thalamic hypoperfusion was the most consistent finding during the symptomatic...
period. Other reported abnormalities include hypothalamus, basal ganglia, frontal, and temporal hypoperfusion. Recently, one patient with KLS was evaluated with FDG-PET, showing decreased glucose metabolism in the thalamus, hypothalamus, and basal ganglia while symptomatic. The fact that in our study we did not find significant metabolic changes in the thalamus could be due to the limited number of patients, the averaging of our subjects (enhancing common metabolic alterations), and the variability of KLS clinical presentation. In addition, previous observations showed that abnormalities found during the symptomatic period may not disappear after recovering from paroxysmal symptoms. This seems related to the number of attacks and the duration of the disease; our patients were young and had a limited number of remitting attacks.

Our findings appear concordant with the symptoms reported by our patients and suggest that KLS is associated with specific and widespread organic brain abnormalities. Given the limited number of patients, further studies are necessary to confirm our findings.

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Author contributions: Dr. Haba-Rubio collected the data, conducted the study, and drafted the initial manuscript. Dr. Prior participated in the design of the study, collected the data, reviewed the text for important intellectual content, and drafted the figure. Dr. Guedj carried out statistical analyses, drafted the figure, and reviewed the text for important intellectual content. Dr. Tafti collected the data and reviewed the text for important intellectual content. Dr. Heinzer collected the data and reviewed the text for important intellectual content.
DROPPED HEAD SYNDROME: REPORT OF THREE CASES DURING TREATMENT WITH A MEK INHIBITOR

The MAPK (mitogen-activated protein kinase) kinase (MEK1/2) signal transduction cascade plays a central role in the regulation of many cellular processes. Selumetinib (AZD6244, ARRY-142886), a selective non-ATP competitive small-molecule inhibitor of MEK1/2,1 has been used in clinical trials for various solid tumors. The most common adverse effects include dermatitis acneiform, diarrhea, nausea, and peripheral edema,2 with the most common being dermatologic side effects, possibly related to the inhibitory effect of selumetinib on MEK1/2, a component of epidermal growth factor receptor (EGFR) pathway.3 We describe 3 patients treated with selumetinib as part of an institutional review board–approved uveal melanoma monotherapy clinical trial (NCT01143402) who developed dropped head syndrome.

Case reports. Case 1. A 71-year-old woman with choroidal melanoma metastatic to the lung and breast was started on selumetinib (75 mg twice daily) in September 2010. In October she experienced pain and stiffness in the neck and shoulders, followed by neck extensor weakness. On examination, the neck extensor strength was 2/5. Creatine phosphokinase (CPK) was 402 units/L (normal range 38–174 units/L) and erythrocyte sedimentation rate (ESR) was 55 mm/hour (normal 0–20 mm/hour). EMG demonstrated mild axonal sensorimotor polyneuropathy and myopathic changes in the left biceps and cervical paraspinus muscles. MRI of the cervical spine showed disk bulging at C4/5 and C5/6 without abnormal signal changes or enhancement in the neck muscles. 18F-fluorodeoxyglucose PET (FDG-PET) scan was significant for intense uptake in the posterior neck muscles (figure, A and B). Selumetinib was discontinued with full recovery of neck extensor strength and normalization of the CPK approximately 1 month later.

Case 2. A 76-year-old woman with uveal melanoma arising from the ciliary body with liver metastases was started on selumetinib in April 2011. One month later, she developed pain in the right occipital and posterior neck after a fall. The pain ultimately resolved; however, she then developed neck extensor weakness a few days later. On examination, strength of the sternocleidomastoid and trapezius muscles were 4+/5, neck extensors 3–5/5, and neck flexors 4/5. EMG showed myopathic units in cervical paraspinous muscles. MRI of the cervical spine only demonstrated moderate degenerative spondylosis. PET scan was significant for intense uptake in the muscles of the shoulder girdle and posterior neck (figure, C and D). Serum CPK was 335 units/L and the ESR was 38 mm/hour. The patient was initiated on prednisone 60 mg for 1 week and subsequently tapered off while selumetinib was continued. Despite the steroid, neck weakness persisted and later resolved after stopping selumetinib.

Case 3. A 73-year-old man with uveal melanoma with lung metastases was initiated on selumetinib in August 2011. Within weeks he developed neck soreness extending to both shoulders, followed by difficulty lifting his head. On examination, neck extensors were 4–5/5 with easy fatigability. The sternocleidomastoid and trapezius muscles were 5–5/5 bilaterally, with other muscles intact. CPK was 857 units/L (figure, E). Selumetinib was stopped and a muscle biopsy of the right trapezius was performed 10 days later, showing abnormal fiber size variation and rare myofibers with regenerative changes. There was no evidence of inflammation, denervation, metastasis, or mitochondrial abnormalities. The neck
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