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## Brief Communication

# Preliminary results on CSF biomarkers for hypothalamic dysfunction in Kleine–Levin syndrome



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## ABSTRACT

**Objective:** To measure CSF biomarkers of hypothalamic dysfunction in patients with typical Kleine–Levin syndrome (KLS) during symptomatic and asymptomatic periods.

**Patients/methods:** Two patients with typical KLS were admitted during symptomatic and asymptomatic periods to a research Sleep Disorders Center. Cerebrospinalfluid (CSF) hypocretin-1, histamine (HA), and its major metabolite *tele*-methylhistamine (t-MHA) levels were measured in two KLS patients in and out of episode.

**Results:** CSF biomarkers of hypothalamic dysfunction measured in two KLS patients in and out of episode revealed low hypocretin levels (within the narcolepsy–cataplexy range) during a hypersomnia episode in the more severe patient, and a 42% decrease (although within normal range) in the second patient. CSF HA and t-MHA measurements in and out of episode revealed a two-fold in-episode decrease in HA in the more severe patient, with no significant change for the second patient, nor for t-MHA levels.

**Conclusion:** We reported reversible changes in CSF hypothalamic biomarkers in a typical patient with KLS that reinforces the hypothesis that in some patients KLS episodes may be caused by recurrent functional alterations of the hypothalamus.

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## 1. Introduction

Kleine–Levin Syndrome (KLS) is a rare disease characterized by recurrent episodes of hypersomnia associated with behavioral disturbances, cognitive abnormalities, hyperphagia, and hypersexuality [1,2]. Although clinical diagnostic criteria have been defined, reliable biomarkers have not. Whereas the underlying pathophysiology remains unclear, studies have suggested recurrent primary hypothalamic dysfunction mediated by immune mechanisms [2,3]. Hypocretin and histamine neurons in the lateral and posterior hypothalamus play critical roles in wakefulness maintenance, feeding behavior, and neuroendocrine and autonomic function [4]. A few CSF hypocretin-1 measurements in and out of KLS episodes have been reported in the literature [5–7]. We report on measurements of three CSF hypothalamic biomarkers: hypocretin-1, histamine (HA), and its major metabolite *tele*-methylhistamine (t-MHA) in two patients with typical KLS during symptomatic and asymptomatic periods.

## 2. Case reports

A 13-year-old boy was admitted to our sleep clinic for having five recurrent severe hypersomnolence episodes (>20 h of sleep per day) with a mean episode duration of 8.2 days. Megaphagia (with high preference for sugar and fat food), internet pornography consumption, and feelings of derealization were noted during episodes, with no cataplexy, sleep paralysis, or hypnagogic hallucinations. Symptoms occurred regularly at 4–6 weeks intervals during episodes without any symptoms in between. No triggering factors were found, and toxicology screening was negative for psychotropic drugs. Diagnosis of typical KLS was made according to the criteria in the ICSD-3 [1]. The patient was drug-free at the time of evaluation, and has never been treated for KLS. A 24-h polysomnography (PSG) during the third day of the fifth episode revealed 15 h sleep duration with high-amplitude posterior slow waves when awake and a slower alpha frequency. Three months later, PSG revealed normal sleep time (6.5 h), normal EEG spectrum, and multiple sleep latency test results of 18.6 min. The 18F-FDG PET scan revealed bilateral temporo-occipital hypometabolism and frontal hypermetabolism during symptomatic episodes compared with asymptomatic periods as previously described [2,3]. Lumbar punctures were performed during a severe symptomatic episode (4 days after onset of fifth episode) and an asymptomatic period (3 months later). CSF

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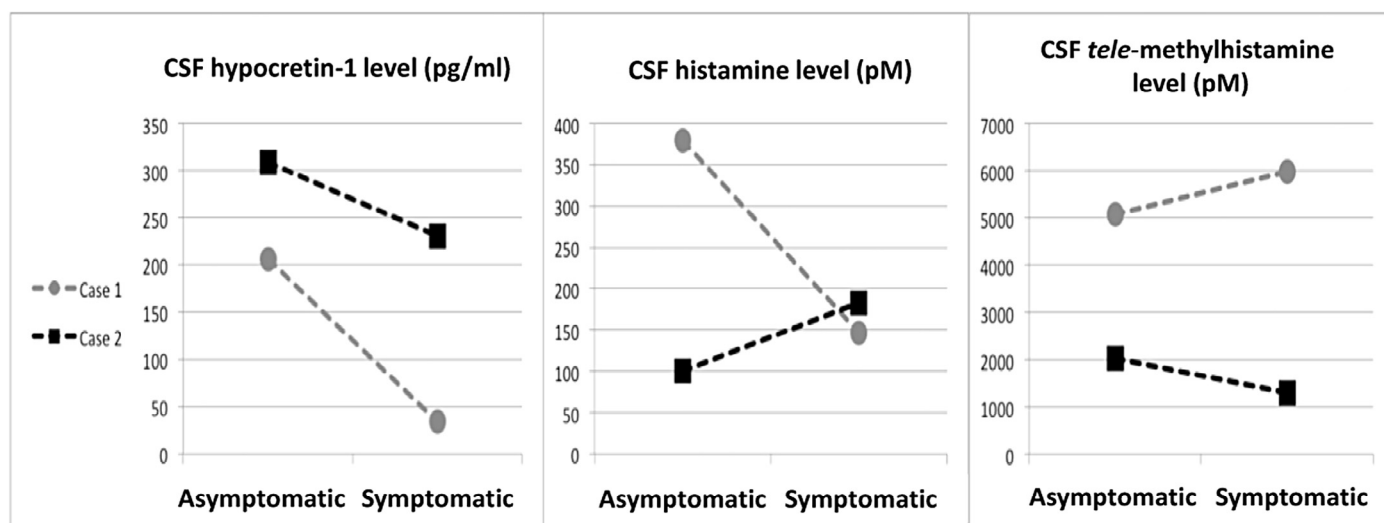


Fig. 1. CSF hypocretin-1, histamine, and telemethyl-histamine levels in two patients with Kleine-Levin syndrome.

hypocretin-1, HA, and t-MHA measured within the same kit revealed 33.95 pg/ml, 146.94, and 5975.29 pmol/l respectively in episode and 206 pg/ml, 378.54, and 5068.6 pmol/l out of episode (Fig. 1). HLA-DQB1\*06:02 was negative.

A 16-year-old boy presented a typical history of KLS [1], with four recurrent episodes of prolonged hypersomnia (>20 h), derealization, and hypersexuality, usually triggered by cannabis intake or febrile illness. Physical and neurological examinations were normal in between episode. A 24-h PSG during the fourth day of the second episode (in drug-free condition) showed a total sleep time of 12.6 h. Lumbar punctures were performed in symptomatic episode (3 days after onset of the second episode) and in asymptomatic period (3 months later). CSF hypocretin-1, HA, and t-MHA measured within the same kit revealed 230 pg/ml, 182.25, and 1288.81 pmol/l respectively during a symptomatic episode; and 308 pg/ml, 100.19, and 2021.47 pmol/l out of episode (Fig. 1). HLA-DQB1\*06:02 was positive.

All lumbar punctures were performed between 5 and 7 p.m. and stored immediately at  $-80^{\circ}\text{C}$  until use. CSF protein, IgG, and leukocyte levels were normal in both cases, in and out of episode. Blood contamination was checked visually, and no CSF samples abnormal coloring was found. Both subjects and parents gave their written informed consent to participate in the study, which was approved by the Montpellier University Hospital's ethics committee.

### 3. Discussion

CSF biomarkers of hypothalamic dysfunction (Hypocretin-1, HA, and t-MHA) measured in two KLS patients in and out of episode revealed low hypocretin levels (within the narcolepsy-cataplexy range) during a hypersomnia episode in the more severe patient, and a 42% decrease (although within normal range) in the second patient. CSF hypocretin-1 might be temporarily decreased during KLS hypersomnia episodes, in line with findings [5–7]. CSF HA and t-MHA measurements in and out of episode revealed a two-fold in-episode decrease in HA in the more severe patient, with no significant change for the second patient, nor for t-MHA levels. Even variable and still controversial, the latter findings were in agreement with normal values reported in other central hypersomnias and neurological controls [8].

Our findings suggest that episodic hypothalamic dysfunction and state-dependent variations in hypocretin levels might occur in KLS, concurring with some functional neuroimaging findings

[2,3,9,10]. Intermittent alteration of the diencephalic system may vary in degree between patients and between episodes, depending on the phenotype and its severity. The more severe patient had CSF hypocretin-1 levels in the narcolepsy-cataplexy range during a symptomatic episode only. CSF hypocretin-1 is therefore a potential candidate biomarker for some patients affected with KLS in the acute phase. The absence of associated cataplexy during episodes for this patient may relate to the absence of HLA DQB1\*06:02. However, it is unknown whether hypocretin deficiency is functionally significant to explain classical KLS symptoms. Hypothetically, symptomatic episodes could be triggered in not yet defined genetically-predisposed subjects by environmental factors that produce blood-brain barrier lesions, leading to the release of acute inflammatory substances (cytokines) to the lateral and posterior hypothalamus areas, thus inhibiting hypocretin neuron activity [11], and possibly also histamine neurons, with decrease in CSF HA level in the more severe patient.

**In conclusion**, evidence of reversible changes in CSF hypothalamic biomarkers in a typical patient with KLS reinforces the hypothesis that KLS episodes may be caused in some patients by recurrent functional alterations of the hypothalamus. Further longitudinal studies including a larger number of patients are needed to more accurately determine the diagnostic value of measuring CSF hypocretin-1 in KLS patients during acute periods and to assess relationships between abnormal behavior, potential dysautonomia, functional neuroimaging, and CSF hypothalamic biomarkers in and out of symptomatic episodes.

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### Conflict of interest

Y. Dauvilliers has received funds for speaking and board engagements with UCB pharma Jazz and Bioprojet. R. Lopez, L. Barateau and S. Chenini had no disclosure.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2014.07.022>.

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