SHORT REPORT

# Hypocretin (orexin) deficiency predicts severe objective excessive daytime sleepiness in narcolepsy with cataplexy

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Cerebrospinal fluid (CSF) hypocretin-1 deficiency is associated with definite (''clear cut'') cataplexy in patients with narcolepsy. The relationship between CSF hypocretin-1 levels and other narcoleptic symptoms (including excessive daytime sleepiness, EDS) is not properly understood.

In a consecutive series of 18 subjects with narcolepsy and definite cataplexy, patients with undetectable CSF hypocretin-1 (n = 12) were found to have significantly lower mean sleep latencies (p = 0.045) and a higher frequency of sleep onset REM periods (SOREMPs, p = 0.025) on multiple sleep latency test than patients (n = 6) with detectable levels. Conversely, Epworth sleepiness scale scores, the frequency of hallucinations/sleep paralysis, and the frequency and severity of cataplexy were similar in both groups.

These results suggest that hypocretin deficiency identifies a homogenous group of patients with narcolepsy characterised by the presence of definite cataplexy, severe EDS, and frequent SOREMPs.

Hypocretin deficiency in cerebrospinal fluid (CSF) is associated with narcolepsy with definite (''true'', ''clear cut'') cataplexy. Up to 11% of patients with definite narcolepsy-cataplexy, however, have normal CSF hypocretin-1 levels,[1] while some patients with narcolepsy without (definite) cataplexy with low or undetectable CSF hypocretin-1 levels also exist.[1–4]

Conversely, the association between CSF hypocretin-1 levels and other narcoleptic symptoms, including excessive daytime sleepiness (EDS), remains poorly understood. The aim of this study was to assess the relationship between CSF hypocretin-1 levels and clinical, polysomnographic/multiple sleep latency test (MSLT) findings in patients with narcolepsy with definite cataplexy.

## METHODS

We studied 18 Caucasian patients (11 women and seven men, mean age 36 years, range 18–64) with narcolepsy and definite cataplexy. Cataplexy was considered to be definite according to the following previously suggested criteria: (i) loss of muscle tone with a visible effect or involving other muscle groups in addition to leg muscles; (ii) cataplexy occurring more than once a month; (iii) duration of cataplexy (often or always) <10 min; and (iv) cataplexy (often or always) associated with a normal state of consciousness.[4–7] The diagnosis of narcolepsy was made by an experienced clinician (CBas) according to standard criteria.[5 6]

Epworth Sleepiness Scale (ESS), Ullanlinna Narcolepsy Scale (UNS), Swiss narcolepsy scale (SNS), and Sleep Propensity in Active Situations (SPAS) scores were obtained and calculated. UNS scores >14, SNS scores <0, and SPAS scores >7 are suggestive of narcolepsy.[4] The frequency of cataplexy was graded as follows: 1, more than one attack per month but less than one per week; 2, more than one attack per week but less than one per day; and 3, more than one attack per day. The severity of cataplexy was graded as follows: 1, mild (partial, only one body region involved); 2, moderate (generalised, without falls); and 3, severe (generalised, with falls). A clinical/neurological examination (n = 18), a standardised sleep history (n = 18), polysomnography (n = 16), MSLT (n = 17), and HLA typing (n = 17) were available for most patients. Tests were conducted and scored according to standard criteria. In all patients, pharmacological treatments were discontinued 7–14 days before hospital admission. Two patients with a familial form of narcolepsy have been previously described.[8]

Crude lumbar CSF from all patients was used for determination of hypocretin-1 by radioimmunoassay with a detection limit of approximately 60 pg/ml and an intra-assay variability of 4%. Normal values (>320 pg/ml) were ascertained by determination of CSF hypocretin-1 levels in a control group of 20 healthy subjects without signs of sleep-wake or other neurological disorders.

We also systematically reviewed the literature. We identified 64 patients with narcolepsy-cataplexy for whom detailed CSF hypocretin-1 levels and sleep latencies on MSLT were reported.[3 9 10] The ESS score was also reported in one of these studies.[3]

Because of the large interassay variability of the radioimmunoassay and the still unknown pathophysiological significance of low or intermediate CSF hypocretin-1 levels, we decided to group patients into those with and without detectable CSF hypocretin-1 levels (detectable hypocretin: DH; undetectable hypocretin: UH).

Statistical analyses were performed using Student's *t* test, the Mann-Whitney U test, and the Pearson correlation test.

## RESULTS

CSF hypocretin-1 levels were undetectable in 12 patients, low (<320 pg/ml) in three patients (range 68–118), and normal in three patients (range 527–546). Two of the latter three patients had a familial form of narcolepsy.[8] The mean ESS score was 16.1 (standard deviation (SD) 3.6) and mean sleep latency (MSL) was 2.0 min (SD 1.7). UNS and SNS scores suggestive of narcolepsy were found in 13 of 14 (93%) and 10 of 13 (77%) patients, respectively. Typical MSLT findings were found in 14 of 17 (82%) patients (MSL <5 min and ≥2 sleep onset REM periods (SOREMPs)). The HLA haplotype DQB1*0602 was present in 15 of 17 (88%) patients. We observed one 38 year old female patient with narcolepsy-cataplexy, undetectable CSF hypocretin-1 levels, an MSL of

**Abbreviations:** CSF, cerebrospinal fluid; DH, detectable hypocretin; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MSL, mean sleep latency; MSLT, multiple sleep latency test; PSG, polysomnography; SNS, Swiss narcolepsy scale; SOREMP, sleep onset REM period; SPAS, Sleep Propensity in Active Situations; UH, undetectable hypocretin; UNS, Ullanlinna Narcolepsy Scale

**Table 1** Comparison of patients with narcolepsy and definite cataplexy with and without detectable CSF hypocretin-1 levels

| | CSF hypocretin-1 undetectable | CSF hypocretin-1 detectable |
|---|---|---|
| n | 12 | 6 |
| Age | 37.3±16.4 | 34.3±8.6 |
| Males | 4/12 | 3/6 |
| ESS score | 16.5±3.8 | 15.2±3.1 |
| SPAS score | 10.0±3.5 | 9.1±1.9 |
| UNS score | 23.9±5.9 | 20.4±6.0 |
| SNS score | −35.5±28.5 | −5.0±23.0 |
| Severity of cataplexy (see text) | 1: n=4, 2: n=4, 3: n=4 | 1: n=3, 2: n=2, 3: n=1 |
| Frequency of cataplexy | 1: n=4, 2: n=3, 3: n=5 | 1: n=1, 2: n=4, 3: n=1 |
| Sleep paralysis | 6/12 | 4/6 |
| Hallucinations | 6/12 | 4/6 |
| HLA DQB1*0602 positive | 10/11 | 5/6 |
| Sleep latency on PSG | 3.3±2.9 | 7.3±5.2 |
| Sleep efficiency on PSG (%) | 91±8 | 94±8 |
| ⩾2 SOREMPs on MSLT | 11/11 | 3/6 |
| MSL on MSLT | 1.4±0.8 min | 3.5±1.9 min |
| MSL on MSLT <5 min | 11/11 | 4/6 |

ESS, Epworth Sleepiness Scale; MSL, mean sleep latency; SNS, Swiss narcolepsy scale; SOREMPs, sleep onset REM periods; SPAS, Sleep Propensity during Active Situations (see text); UNS, Ullanlinna Narcolepsy Scale.

0.6 min, and 4/4 SOREMPs on MSLT, who was HLA DQB1*0602 negative. Hypothalamic lesions were not detected in cerebral MRI scans of this patient.

The frequency and severity of cataplexy, the frequency of hallucinations and sleep paralysis, and the mean ESS, SPAS, UNS, and SNS scores were similar in DH and UH patients. MSLs were significantly shorter in UH patients (mean 1.4 min (SD 0.8)) than in DH patients (mean 3.5 min (SD 1.9); $p = 0.045$). The frequency of SOREMPs on MSLT and polysomnography (PSG) was higher in UH than in DH patients ($p = 0.025$ and $p = 0.012$, respectively). These and other results in DH and UH patients are summarised in table 1.

There were no significant differences between patients with normal ($n = 3$) and with low ($n = 3$) CSF hypocretin-1 levels when demographics, questionnaires, and PSG or MSLT results were compared.

In a review of the literature, MSLs were significantly shorter in 56 UH patients (mean 2.6 min) than in 25 DH patients (mean 4.2 min, $p = 0.005$; table 2). Conversely, the mean ESS scores were similar (UH: $n = 22$, mean 18.5; and DH: $n = 15$, mean 17.2; $p = 0.36$).

## DISCUSSION

The aim of this single centre study was to describe the impact of hypocretin deficiency on the clinical and polysomnographic/MSLT characteristics of patients with narcolepsy and definite cataplexy. We found a significant association between undetectable CSF hypocretin-1 levels and both low MSLs and a high frequency of SOREMPs during MSLT, but not with other narcolepsy symptoms such as severity or frequency of cataplectic attacks, subjective sleepiness (as assessed by the ESS), and frequency of hallucinations/sleep paralysis. The main finding of shorter MSL in UH patients when compared to DH patients was confirmed in our meta-analysis.

A tendency towards shorter MSLs in patients with lower hypocretin levels has been suggested before: Mignot *et al* reported a higher frequency of typical MSLT findings (MSL ⩽5 min and ⩾2 SOREMPs) in patients with low hypocretin levels as compared to those with normal levels (78% *v* 48%).[2] This comparison was, however, performed in patients with narcolepsy with and without cataplexy. In addition, clinical and polysomnographic/MSLT data were obtained from different centres and most patients were receiving pharmacological treatment, which modifies MSLT results. More recently, our group reported significantly lower ($p = 0.045$) MSLs in narcoleptic patients with hypocretin-1 deficiency as compared to patients without definite cataplexy, in whom, however, hypocretin-1 levels were not available.[4]

The absence of a relationship between CSF hypocretin-1 levels and the severity and frequency of cataplexy and the frequency of sleep paralysis and hallucinations may, obviously, be due to the size of our study (type II error) or the type of assessment chosen in our analysis. It should be stressed, however, that in contrast to previous analyses, we included in this study only patients with definite (''clear cut'') cataplexy. In fact, narcolepsy without definitive cataplexy and narcolepsy without cataplexy are usually (but not always) associated with normal CSF hypocretin-1 levels.[1] The absence of a (significant) link between CSF hypocretin-1 levels and the frequency of hallucinations and sleep paralysis confirms the fact that these symptoms are not specific, being relatively frequent also in other sleep disorders and in the general population and, as a consequence, not necessarily reflective of increased REM sleep pressure.[11 12] A further explanation for the absence of an association between the severity and frequency of cataplexy, hallucinations, and sleep paralysis and hypocretin levels in CSF could reflect differences in the development of these symptoms in individual patients with narcolepsy.[11]

Based on our findings and on previous studies, we suggest that undetectable CSF hypocretin-1 levels identify an homogenous subgroup of patients with narcolepsy characterised by (i) the presence of definite cataplexy, (ii) severe, objective EDS, and (iii) a high frequency of SOREMs.

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**Table 2** Review of published patients with narcolepsy-cataplexy for whom detailed CSF hypocretin-1 levels were available

| | CSF hypocretin-1 undetectable | | CSF hypocretin-1 detectable | | |
|---|---|---|---|---|---|
| | n | Mean MSL | n | Mean MSL | p |
| Baumann *et al* (this study) | 11 | 1.4 | 6 | 3.5 | 0.045 |
| Kanbayashi *et al*[9] | 7 | 2.2 | 4 | 4.1 | 0.13 |
| Dauvilliers *et al*[3]* | 10 | 2.8 | 9 | 5.0 | 0.14 |
| Nishino *et al*[10] | 28 | 3.0 | 6 | 3.9 | 0.45 |
| Total | 56 | 2.6 | 25 | 4.2 | 0.005 |

*Seven patients in the current study have already been described by Dauvilliers *et al*[3]; these patients were excluded from the series of Dauvilliers *et al* for this analysis.
MSL, mean sleep latency on MSLT (in minutes).

Competing interests: none declared

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