SLEEPJ, 2019, 1–2

doi: 10.1093/sleep/zsz009
Advance Access Publication Date: 21 January 2019
Letter to the Editor

LETTER TO THE EDITOR

The development of hypocretin deficiency in narcolepsy type 1 can be swift and closely linked to symptom onset: clues from a singular case

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Introduction

Narcolepsy type 1 is associated with a selective and irreversible loss of >90% of neurons in the lateral hypothalamus that produce the sleep-wake regulating neuropeptides hypocretin-1 and -2 [1, 2]. The hypocretin-1 concentration in the cerebrospinal fluid (CSF) serves as a biomarker for the presence or absence of these hypocretin-producing neurons [3]. Therefore, this measurement is part of the diagnostic criteria for narcolepsy type 1 and can be performed as an alternative to the frequently used polysomnography with multiple sleep latency test when there is a clinical suspicion of narcolepsy type 1.

Several case reports show that shortly after narcoleptic symptoms arise the hypocretin-producing neuronal loss is severe enough to lead to very low or undetectable CSF hypocretin-1 concentrations [4, 5]. However, there is hardly any information about how long it may take before the critical number of cells is lost or how long it takes before severe hypocretin-1 deficiency leads to clinical symptoms. We describe a case that may shed (more) light on this lack of knowledge.

Report of Case

In May 2017, we diagnosed a 17-year-old Dutch girl with narcolepsy type 1 at the outpatient clinic of the Sleep-Wake Centre SEIN in Heemstede, the Netherlands. She had previously been healthy except for a hospital admission in September 2016 because of high fever, and a suspicion of a viral meningitis. Because of this suspicion, a lumbar puncture was performed. Analysis of the CSF showed a normal cell count and normal protein and glucose levels, excluding a viral meningitis. According to the hospital routine procedures, excess CSF was stored for later use, if necessary. Eventually, the fever was attributed to a PCR-confirmed enteroviral gastroenteritis. Since there were no respiratory or dermatologic symptoms, the clinical suspicion of an infection with *Streptococcus pyogenes* was low and further diagnostic testing was not performed.

Within weeks after her dismissal from the hospital in September 2016 she developed severe excessive daytime sleepiness. In December 2016, typical cataplectic attacks (knee-buckling and later general atonia with falls triggered by laughter and being angry) started to occur. These attacks lasted several seconds, and up to several minutes when the trigger remained present. She also experienced hypnagogic hallucinations, disrupted nocturnal sleep, sleep paralysis and gained 7 kg in several months.

When she visited our institution in March 2017, she had high scores on both the Epworth Sleepiness Scale (ESS; 19/24) and the Fatigue Severity Scale (FSS; 6/7). HLA-typing showed HLA-DQB1*06:02 positivity. Sleep investigation results were also supportive for the diagnosis of narcolepsy type 1: a polysomnography with a sleep onset REM period (SOREMP) was followed by a mean sleep latency on MSLT of 2.9 min with SOREMPs in three out of five naps.

We were allowed to use the previously stored CSF for hypocretin-1 measurement. A hypocretin-1 concentration

Submitted: 9 October, 2018; **Revised:** 13 November, 2018

of 271 pg/mL was detected. Hypocretin-1 concentrations were measured in duplicate with a iodine-125 hypocretin-1 radioimmunoassay (Phoenix Pharmaceuticals, Mountain View, CA). This assay has a detection limit of 50 pg/mL and an intraassay variability of <5%. To adjust for interassay variability to previously reported values, Stanford reference CSF samples were included in the assay [6].

Because of this finding, a second lumbar puncture was performed in March 2018, after informed consent, that showed an undetectable hypocretin-1 level in the CSF, which confirmed the diagnosis of narcolepsy type 1. Hypocretin-1 measurements in both CSF samples of this patient were repeated in duplicate in one assay, to rule out interassay variability as an explanation for the observed difference between both samples. In line with the earlier measurements, hypocretin-1 levels before and after symptom onset were 272 and 0 pg/mL, respectively.

Discussion

The disease phenotype and sleep laboratory findings in this patient are characteristic of sporadic pediatric narcolepsy type 1 [7]. Interestingly, the first narcolepsy symptoms arose shortly after a normal hypocretin-1 level was measured in the CSF of this patient. This adds to the knowledge from previous case reports that hypocretin-1 deficiency could already be measured within weeks after symptom onset [4, 5]. Another case report also shows both a hypocretin-1 measurement before and several months after symptom onset [8]. Since the first measurement was more than a year before symptom onset, it remained largely unclear how long it took for the hypocretin-producing neurons to disappear in that case. The short interval between hypocretin-1 measurement and symptom onset in this case suggests that the decrease in hypocretin-1 concentration from normal to undetectable levels may be a process lasting only a few weeks or even less.

The onset of symptoms can be gradually in narcolepsy type 1, but also subacute, as in this case. The latter course of symptom onset is described particularly in pediatric [7] and post-H1N1 influenza narcolepsy cases [9]. This pediatric patient was not vaccinated in the 2009 H1N1 vaccination campaign. There was also no indication that other environmental triggers presumed to be linked to narcolepsy symptom onset (such as *S. pyogenes* [10]) were present in this patient. However, the enteroviral infection that led to the patient's admission to a hospital for several days might constitute an environmental trigger, that has not been described previously. This case thereby supports the theorem that multiple different environmental triggers are able to cause the presumed auto-immune reaction ultimately leading to the destruction of hypocretin-producing neurons to occur in genetically predisposed individuals.

This case combined with earlier reports suggests that the presumed auto-immune reaction resulting in the onset of narcolepsy type 1 can be swift and closely linked to symptom onset (Figure 1). Thereby, it stresses the importance of performing experiments on the auto-immune hypothesis of narcolepsy type 1 shortly after symptom onset. Additionally, this case highlights the importance of focusing future research on the final common pathophysiological pathway of narcolepsy type 1 to be able to identify individuals at-risk for developing the disease, rather than addressing the diversity of environmental triggers, of which we might only have identified the top of the iceberg.

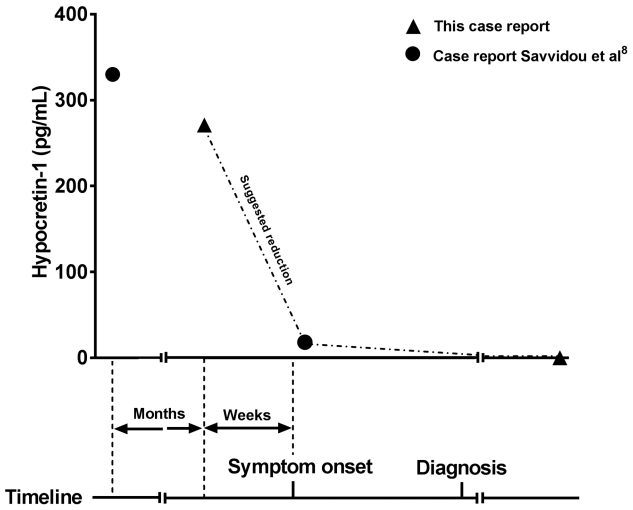

Figure 1. This figure visualizes the suggested steep and swift decrease in cerebrospinal fluid hypocretin-1 concentrations that is closely linked to symptom onset, based on this case report combined with previous reports [4, 5, 8]. Hypocretin-1 concentration was in the normal range only weeks before symptom onset.

Conflict of interest statement. M.S.S., G.J.L., and R.F. report no financial or non-financial disclosures relevant in this context.

References

1. Thannickal TC, *et al*. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;**27**(3):469–474.
2. Peyron C, *et al*. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med*. 2000;**6**(9):991–997.
3. Nishino S, *et al*. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet*. 2000;**355**(9197):39–40.
4. Kubota H, *et al*. Decreased cerebrospinal fluid hypocretin-1 levels near the onset of narcolepsy in 2 prepubertal children. *Sleep*. 2003;**26**(5):555–557.
5. Kanbayashi T, *et al*. CSF hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. *J Sleep Res*. 2002;**11**(1):91–93.
6. Ripley B, *et al*. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. *Neurology*. 2001;**57**(12):2253–2258.
7. Postiglione E, *et al*. The clinical spectrum of childhood narcolepsy. *Sleep Med Rev*. 2018;**38**:70–85.
8. Savvidou A, *et al*. Hypocretin deficiency develops during onset of human narcolepsy with cataplexy. *Sleep*. 2013;**36**(1):147–148.
9. Sarkanen T, *et al*. Clinical course of H1N1-vaccine-related narcolepsy. *Sleep Med*. 2016;**19**:17–22.
10. Ambati A, *et al*. Increased β-haemolytic group A streptococcal M6 serotype and streptodornase B-specific cellular immune responses in Swedish narcolepsy cases. *J Intern Med*. 2015;**278**(3):264–276.