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## The autoimmune hypothesis of narcolepsy and its unexplored clinical features

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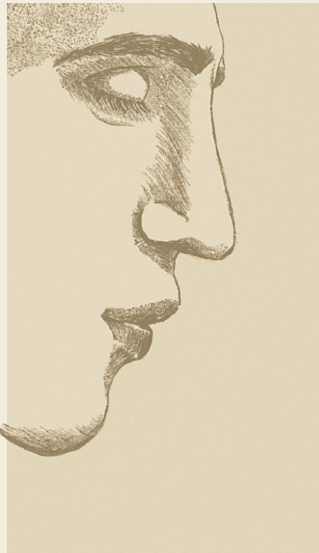
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# Chapter 1

## **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 (NT1) 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 (Thannickal et al., 2000, Peyron et al., 2000). The hypocretin-1 concentration in the cerebrospinal fluid (CSF) serves as a biomarker for the presence or absence of these hypocretin-producing neurons (Nishino et al., 2000b). Therefore, this measurement is part of the diagnostic criteria for NT1 and can be performed as an alternative to the frequently used polysomnography with multiple sleep latency test when there is a clinical suspicion of NT1.

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 (Kubota et al., 2003, Kanbayashi et al., 2002). 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.

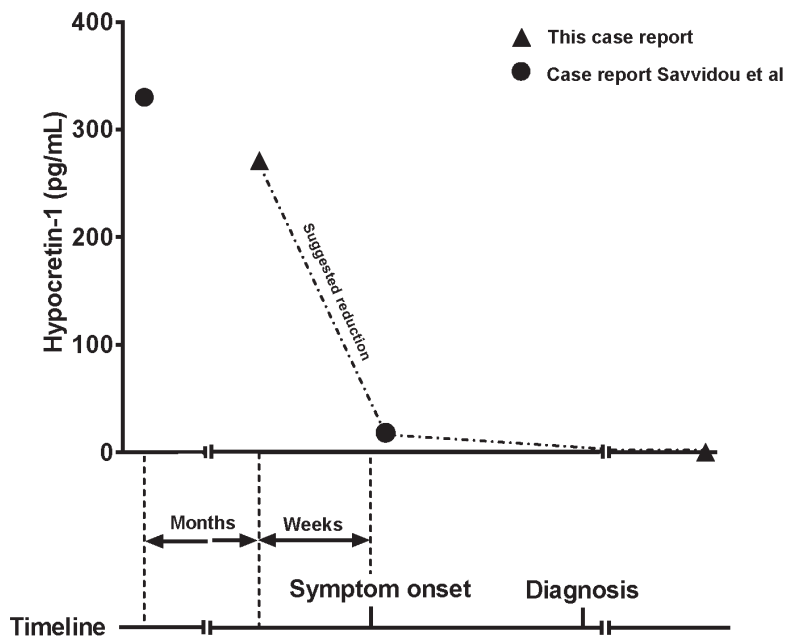
## Report of case

In May 2017, we diagnosed a 17-year old Dutch girl with NT1 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 kilograms 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 NT1: a polysomnography with a sleep onset REM period (SOREMP) was followed by a mean sleep latency on MSLT of 2.9 minutes with SOREMPs in 3 out of 5 naps.



**Figure 1.1.** 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 (Savvidou et al., 2013, Kanbayashi et al., 2002, Kubota et al., 2003). Hypocretin-1 concentration was in the normal range only weeks before symptom onset.

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

assay has a detection limit of 50 pg/mL and an intra-assay variability of <5%. To adjust for inter-assay variability to previously reported values, Stanford reference CSF samples were included in the assay (Ripley et al., 2001).

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 NT1. Hypocretin-1 measurements in both CSF samples of this patient were repeated in duplicate in one assay, to rule out inter-assay 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 NT1 (Postiglione et al., 2018). Interestingly, the first NT1 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 (Kubota et al., 2003, Kanbayashi et al., 2002). Another case report also shows both a hypocretin-1 measurement prior to and several months after symptom onset (Savvidou et al., 2013). 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 NT1, but also subacute, as in this case. The latter course of symptom onset is described particularly in pediatric (Postiglione et al., 2018) and post-H1N1 influenza narcolepsy cases (Sarkanen et al., 2016). 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 NT1 symptom onset (such as *Streptococcus pyogenes* (Ambati et al., 2015)) 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 autoimmune 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 autoimmune reaction resulting in the onset of NT1 can be swift and closely linked to symptom onset (Figure 1.1). Thereby, it stresses the importance of performing experiments on the autoimmune hypothesis of NT1 shortly after symptom onset. Additionally, this case highlights the importance of focusing future research on the final common pathophysiological pathway of NT1 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.



