Hypocretin Deficiency Develops During Onset of Human Narcolepsy with Cataplexy

Andri Savvidou, MD; Sline Knudsen, MD, PhD; Mia Olsson-Engman, MD; Steen Gammeltoft, MD; Poul Jennum, MD; Lars Palm, MD, PhD

1Paediatric Department, Blekinge Hospital, Karlskrona, Sweden; 2Danish Center for Sleep Medicine, University of Copenhagen, Glostrup Hospital, Denmark; 3Department of Clinical Biochemistry, University of Copenhagen, Glostrup Hospital, Denmark; 4Section for Paediatric Neurology, Department of Paediatrics, Skåne University Hospital, Malmö, Sweden

INTRODUCTION

Narcolepsy with cataplexy is associated with the almost complete loss of hypothalamic neurons, which produce the sleep-wake regulating neuropeptides, the hypocretins.1,2 The time point of the neuron loss has remained unknown, but as the narcoleptic phenotype is not congenital, it is generally believed to occur just before disease onset, although this has never been demonstrated definitively. We hereby report that hypocretin deficiency is indeed acquired in relation to disease onset in human narcolepsy.

In December 2010 we diagnosed a 10-year-old Swedish (Caucasian) boy with narcolepsy with cataplexy at the Paediatric Department, Blekinge Hospital, Sweden. He had previously been healthy, except for CSF confirmed neuroborreliosis (Lyme disease) in June 2009, from which he had fully recovered after antibiotic treatment.

As part of the general H1N1-vaccination programme in Sweden, he had also been vaccinated with Pandemrix on 2 November 2009 and 1 February 2010. Mid-February 2010, approximately 15 days after the second Pandemrix vaccination, he developed extreme daytime sleepiness and sleep attacks during meals, while reading and in school. In September 2010, the first typical cataplectic attacks (head-dropping, knee-buckling, and occasional general atonia with falls triggered by laughter) appeared and gradually worsened. His night sleep became disrupted by awakenings, nightmares and hypnagogic/hypnopompic hallucinations, but he had no sleep paralysis. Moreover, he gained 12 kg between disease onset and the time of examination.

The general and neurological examination, brain MRI and routine blood parameters gave normal results. HLA-typing revealed DQB1*0602-positivity. The sleep investigations supported the narcolepsy diagnosis: a normal polysomnogram and an MSLT mean sleep latency of 5.2 min (reference values Palm et al.) with sleep onset REM periods (SOREMPS) in 4/5 naps.

Fortunately, CSF obtained following the episode of neuroborreliosis in July 2009 had been saved (frozen), which enabled comparison between pre-narcolepsy onset CSF hypocretin-1 levels and a second CSF sample obtained after the narcolepsy onset on 23 March 2011 (measurement techniques as for Knudsen et al.).4 To minimize measurement variability and exclude sample mix-up, samples were analyzed within the same assay kit and results subsequently confirmed in another assay kit. Moreover, confirmation of patient identity and tube labelling is a standard procedure before sample collection.

CSF levels of protein, glucose, IGG-index, and OCB were normal in both CSF samples. As expected, the amount of CSF leucocytes was increased (28 × 10⁶) in the pre-narcolepsy onset sample and normal in the second sample.

The CSF hcrt-1 level was normal (318 pg/mL; 341 pg/mL) before narcolepsy onset but dropped to severe hypocretin deficiency (10 pg/mL; 22 pg/mL) after disease onset.

DISCUSSION

Here we confirm for the first time that hypocretin deficiency develops in parallel to disease onset in human narcolepsy with cataplexy.

It is well known that hypocretin deficiency may present soon after disease onset in narcoleptic patients.3 However, although these patients are generally reported to be healthy before disease onset, it has never previously been demonstrated their hypocretin system was originally intact. The present finding supports the predominant theory, which, based on animal models, proposes a direct causal and temporal relation between loss of hypocretin-producing neurons and the emergence of the narcoleptic phenotype.5

Submitted for publication February, 2012
Submitted in final revised form May, 2012
Accepted for publication July, 2012
Address correspondence to: Sline Knudsen, MD, Danish Center for Sleep Medicine, University of Copenhagen, Glostrup Hospital, Nordre Ringvej 57, DK-2600 Glostrup, Denmark; Tel: +4543232512; Fax +4543233923; E-mail: stine.knudsen@dadlnet.dk

SLEEP, Vol. 36, No. 1, 2013
Most probably, an autoimmune reaction causes the hypocretin neuron loss. This theory is mainly based on the very strong association between narcolepsy and HLA type DQB1*0602 and a genetic association with polymorphisms in the T-cell receptor alpha gene.\textsuperscript{7}

The narcolepsy disease onset can be abrupt within a few days but the symptoms can also appear gradually as in the present narcolepsy case. Although post-H1N1 narcolepsy has been described as particularly severe and abrupt, our case must nevertheless be considered to be post-H1N1, as he developed the symptoms only 15 days after the second H1N1 vaccination, in concordance with the increased numbers of narcolepsy cases after the H1N1 vaccinations.\textsuperscript{8-10} Other environmental triggers such as \textit{Streptococcus pyogenes} infection (increased ASO titers) has also been associated with onset of both sporadic\textsuperscript{11} and post-H1N1 narcolepsy,\textsuperscript{9} however ASO titers were unfortunately not available in the present case.

The proven fall of CSF hypocretin-1 after the vaccination in our case supports the idea of an autoimmune reaction induced by the H1N1 virus strand used or/and the adjuvant components of the vaccine. However, the increased frequency of narcolepsy after active H1N1 disease and the seasonal variation of new cases\textsuperscript{10} imply an active role of the H1N1 virus in the process.

Post-H1N1 narcolepsy shares the core symptoms, the HLA-predisposition and the hypocretin deficiency with sporadic narcolepsy,\textsuperscript{8-10} which could suggest that the pathogenetic mechanism is identical, including the causal and temporal relationship between development of hypocretin deficiency and disease onset.

**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

**REFERENCES**