pii: jc-00406-15 http://dx.doi.org/10.5664/jcsm.5604

JCSM
Journal of Clinical Sleep Medicine

CASE REPORTS

Cataplexy with Normal Sleep Studies and Normal CSF Hypocretin: An Explanation?

Panagis Drakatos, MD[1]; Guy Leschziner, PhD, FRCP[1,2]

[1]Sleep Disorders Centre, Guy's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]King's College London, UK

Patients with narcolepsy usually develop excessive daytime sleepiness (EDS) before or coincide with the occurrence of cataplexy, with the latter most commonly associated with low cerebrospinal fluid (CSF) hypocretin-1 levels. Cataplexy preceding the development of other features of narcolepsy is a rare phenomenon. We describe a case of isolated cataplexy in the context of two non-diagnostic multiple sleep latency tests and normal CSF-hypocretin-1 levels (217 pg/mL) who gradually developed EDS and low CSF-hypocretin-1 (< 110 pg/mL).

Keywords: cataplexy, narcolepsy, orexin, hypocretin

Citation: Drakatos P, Leschziner G. Cataplexy with normal sleep studies and normal csf hypocretin: an explanation? *J Clin Sleep Med* 2016;12(3):449–450.

INTRODUCTION

The pathogenesis of human narcolepsy remains uncertain, but the clinical expression of the disorder is likely to depend upon interplay between one or more genetic factors and environmental triggers.[1] Excessive daytime sleepiness (EDS) is considered one of the cardinal symptoms of narcolepsy, and the presence of cataplexy alongside a mean sleep latency (MSL) ≤ 8 min and ≥ 2 sleep-onset REM periods (SOREMPs) on multiple sleep latency testing (MSLT) and nocturnal polysomnography (NPSG), or low cerebrospinal fluid hypocretin-1 (CSF-hcrt-1) categorizes it as type 1 (NT1).[1] EDS typically precedes or coincides with the development of cataplexy, although onset of cataplexy prior to other manifestations of narcolepsy is rare but well recognized.[2]

REPORT OF CASE

A 39-year-old man presented with an 18-month history of progressively worsening episodes of loss of muscle tone affecting his arms, his back, and the upper part of his legs, triggered by humor or laughter, with preserved full consciousness. The frequency of the events was one per month. He described features of REM sleep behavior disorder, restless leg syndrome (RLS), and a longstanding history of sleepwalking. He was experiencing tiredness, with an Epworth Sleepiness Scale (ESS) score of 10/24, and he denied hypnagogic hallucinations or sleep paralysis. Physical examination was normal and his past medical history was unremarkable except for hemorrhoids. He was on no regular medication.

MRI of the brain, and cervical and thoracic spine was normal. HLA typing showed HLA DQB1*0602 haplotype. NPSG, performed as per current recommendations,[3] revealed delayed REM onset, mild obstructive sleep apnea (OSA), significantly elevated arousal index, reduced sleep efficiency, and borderline elevated periodic limb movement index (PLMI). His 2-week sleep diary showed an average of 7 h of sleep prior to his MSLT.[4] The MSLT revealed MSL of 13.5 min and no SOREMPs (**Table 1**). A lumbar puncture revealed normal CSF constituents and the CSF-hcrt-1was normal at 217 pg/mL (Neuroimmunology Laboratory, University of Oxford). His serum ferritin was low at 7 mcg/L.

Weight loss and a mandibular advancement device were recommended to the patient for his mild OSA, he was treated with ferrous sulphate and pregabalin for his RLS and mildly elevated PLMI, and with an anti-cataplectic agent (venlafaxine sustained release 75 mg in the morning), for his presumed isolated cataplexy. His episodes of loss of muscle tone were completely abolished by the venlafaxine. The patient underwent treatment of bleeding hemorrhoids.

However, despite weight loss and treatment of his RLS symptoms, he began to experience increasing EDS. Two years after the initial investigations, he reported an ESS of 16/24. Repeat polysomnography did not show overt sleep pathology. His MSLT demonstrated a MSL = 9.3 min with no SOREMPs, although he remained on venlafaxine during this study. However, a repeat CSF examination showed decreased CSF-hcrt-1 of < 110 pg/mL (**Table 1**).

The patient was diagnosed with NT1, and modafinil was initiated alongside venlafaxine, to good effect.

DISCUSSION

We describe a patient who presented with isolated cataplexy in the absence of a diagnostic MSLT/NPSG, and with normal CSF-hcrt-1. Even after the onset of subjective EDS, repeat

Table 1—Results of the polysomnographies, multiple sleep latency tests (MSLT) and CSF-hcrt-1.

	Course of Studies	
	First	Second*
Polysomnography		
Sleep onset (min)	16.0	15.9
AHI (events/h)	14.0	2.4
PLMI (events/h)	16.0	1.7
Sleep efficiency (%)	70.8	93.0
Arousal index (events/h)	43.0	14.2
REM latency (min)	145.0	136.0
MSLT		
MSL (min)	13.5	9.3
SOREMPs (n)	0.0	0.0
CSF-hcrt-1 (pg/mL)	217.0	< 110.0

*Studies performed 2 years later. Patient on pregabalin 225 mg and venlafaxine 75 SR.

MSLT/NPSG remained nondiagnostic, and only after re-examining the CSF after a 2-year interval was the CSF-hcrt-1 level found to be low.

This case illustrates a number of important issues. Although typically EDS tends to precede or coincide with the occurrence of cataplexy, in rare cases cataplexy may precede other features of narcolepsy by several years.[2] The time course of the development of CSF-hcrt-1 deficiency in these patients remains unclear, but almost all patients with NT1 show a decreased CSF-hcrt-1 and positivity in HLA DQB1*0602.[5,6] In this case however, the patient with subsequently confirmed NT1 on the basis of CSF findings would not have met the International Classification of Sleep Disorders, Third Edition diagnostic criteria based upon either MSLT result or on the first CSF examination.[1]

This phenomenon of absolute CSF deficiency developing significantly after the onset of cataplexy may explain some of those patients with obvious cataplexy in whom CSF-hcrt-1 is "normal." This points to a relative change in CSF-hypocretin levels as underlying the development of cataplexy, or that significant loss of hypocretin-producing neurons resulting in clinical manifestations occurs prior to a fall in CSF-hypocretin levels.[7]

Clinicians should be aware of this phenomenon, and it is important to realize that, as with the MSLT, the CSF hypocretin level remains another data-point upon which to base the diagnosis of NT1, but is not a gold standard.

ABBREVIATIONS

CPAP, continuous positive airway pressure
CSF, cerebrospinal fluid
EDS, excessive daytime sleepiness
ESS, epworth sleepiness scale
hcrt-1, hypocretin-1
MSL, mean sleep latency
MSLT, multiple sleep latency test
NPSG, nocturnal polysomnography
NT1, narcolepsy type 1
OSA, obstructive sleep apnea
PLMI, periodic limb movement index
RLS, restless leg syndrome
SOREMPs, sleep-onset REM periods

REFERENCES

1. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.
2. Sturzenegger C, Bassetti CL. The clinical spectrum of narcolepsy with cataplexy: a reappraisal. J Sleep Res 2004;13:395–406.
3. Berry RB, Gamaldo C, Harding S, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Version 2.0.2. www.aasmnet.org. Darien, IL: American Academy of Sleep Medicine, 2013.
4. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519–24.
5. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553–62.
6. Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. Sleep 1997;20:1012–20.
7. Gerashchenko D, Murillo-Rodriguez E, Lin L, et al. Relationship between CSF hypocretin levels and hypocretin neuronal loss. Exp Neurol 2003;184:1010–6.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2015
Submitted in final revised form October, 2015
Accepted for publication October, 2015
Address correspondence to: Guy Leschziner, Dept of Neurology, Guy's Hospital, Great Maze Pond, London, SE1, 9RT, United Kingdom; Tel.:+442071884100; Fax: +442071880939; Email: Guy.leschziner@gstt.nhs.uk

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Leschziner has received honoraria from UCB Pharma and Somnomed as an advisory board member. Dr. Drakatos reports no financial conflicts of interest. The study was conducted at Guy's Hospital Sleep Disorders Centre, London, United Kingdom. There was no off-label or investigational use.