Vaccine 31 (2013) 994–1007

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Narcolepsy as an adverse event following immunization: Case definition and guidelines for data collection, analysis and presentation

Francesca Poli[a,2], Sebastiaan Overeem[b,*,2], Gert Jan Lammers[c,2], Giuseppe Plazzi[a,2], Michel Lecendreux[d,2], Claudio L. Bassetti[e,1,2], Yves Dauvilliers[f,1,2], Daniel Keene[g,1,2], Ramin Khatami[h,1,2], Yulin Li[i,j,1,2], Geert Mayer[k,1,2], Hanna Nohynek[l,1,2], Barbara Pahud[m,1,2], Teresa Paiva[n,1,2], Markku Partinen[o,1,2], Thomas E. Scammell[p,1,2], Tom Shimabukuro[q,1,2], Miriam Sturkenboom[r,1,2], Kristy van Dinther[s,1,2], Max Wiznitzer[t,1,2], Jan Bonhoeffer[i,j,2]

[a] *IRCCS Istituto delle ScienzeNeurologiche di Bologna, Bologna, Italy*
[b] *Department of Neurology, Donders Institute for Neuroscience, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, Netherlands*
[c] *Leiden University Medical Center, Leiden, Netherlands*
[d] *Robert Debré Hospital, Paris VII University, Paris, France*
[e] *Neurology Department, University Hospital, Bern, Switzerland*
[f] *Montpellier University Hospital Center, Montpellier, France*
[g] *Health Canada, Ottawa, Canada*
[h] *Klinik Barmelweid, Barmelweid, Switzerland*
[i] *University Children Hospital, Basel, Switzerland*
[j] *Brighton Collaboration Foundation, Basel, Switzerland*
[k] *Hephata Clinic, Schwalmstadt-Treysa, Germany*
[l] *National Institute for Health and Welfare, Helsinki, Finland*
[m] *Children's Mercy Hospital and Clinics, Kansas City, MO, USA*
[n] *Sleep Medicine Center – CENC, Medical Faculty of Lisbon, Portugal*
[o] *University of Helsinki, Helsinki, Finland*
[p] *Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA*
[q] *Centers for Disease Control and Prevention, Atlanta, USA*
[r] *Erasmus Medical Centre, Rotterdam, Netherlands*
[s] *CSL Biotherapies, Parkville, Australia*
[t] *Rainbow Babies & Children's Hospital, Cleveland, USA*

ARTICLE INFO

Article history:
Available online 16 December 2012

Keywords:
Cataplexy
Hypocretin
Classification
Sleep
Autoimmunity
H1N1
Children

Abbreviations: AASM, American Academy of Sleep Medicine; AEFI, adverse event following immunization; CSF, cerebrospinal fluid; HLA, human leukocyte antigen; ICSD-2, international classification of sleep disorders, second edition; MSLT, multiple sleep latency test; PSG, polysomnography; REM, rapid eye movement; SL, sleep latency; SOREMP, sleep onset rapid eye movement period; VAESCO, Vaccine Adverse Event Surveillance and Communication Project.

* Corresponding author. Tel.: +31 24 3615202; fax: +31 24 3617018.
E-mail addresses: contact@brightoncollaboration.org, S.Overeem@neuro.umcn.nl (S. Overeem).

[1] Co-authors are listed following alphabetic sequence of the last names.

[2] On behalf of the Brighton Collaboration Narcolepsy Working Group, an initiative of the Brighton Collaboration and the European Narcolepsy Network; see Appendix A.

0264-410X/$ – see front matter
http://dx.doi.org/10.1016/j.vaccine.2012.12.014

1. Preamble

1.1. The need for developing a case definition for narcolepsy as an adverse event following immunization (AEFI)

1.1.1. General introduction

Narcolepsy is a sleep disorder primarily characterized by excessive daytime sleepiness and cataplexy – episodes of muscle weakness brought on by emotions [1]. Additional symptoms may comprise hypnagogic hallucinations (vivid dream-like experiences occurring during the transition between wakefulness and sleep), sleep paralysis (episodes of inability to move during the onset of sleep or upon awakening, lasting for a few seconds or minutes), fragmented nocturnal sleep, as well as impaired ability for sustained attention and non-sleep symptoms such as obesity, anxiety, cognitive and emotional disturbances, and behavioral problems and precocious puberty in children [2–7]. Excessive daytime sleepiness can occur in other disorders [8], but most patients suffering from narcolepsy experience their unwanted sleep episodes as short and refreshing [3,4]. Cataplexy consists of brief episodes of muscle weakness without altered consciousness, usually triggered by emotions. Cataplexy constitutes a virtually pathognomonic symptom for narcolepsy [1], although it must be separated from a specific feeling of muscle weakness with emotions in normal subjects [4]. Cataplexy may rarely occur in some other disorders which are easily distinguished from narcolepsy, such as Niemann-Pick type C, Coffin-Lowry syndrome, and Norrie Disease [10–19]. Given its specificity, determining of cataplexy is of paramount importance, although an objective test is not available [9] as of yet.

1.1.2. Diagnosis of narcolepsy

Formally, the diagnosis of narcolepsy can be made on clinical grounds [1]. However, particularly when cataplexy is absent, the diagnosis must be supported by additional polysomnographic testing and/or by the measurement of the neuropeptide hypocretin-1 (also called orexin A) in the cerebrospinal fluid (CSF) obtained by lumbar puncture [1]. A very low or undetectable hypocretin-1 level (<110 pg/ml) is the most specific finding in narcolepsy in general. For narcolepsy with cataplexy it also is highly sensitive: more than 90% of unambiguous cases are hypocretin deficient, making this neuropeptide a valuable diagnostic biomarker [20,21]. For narcolepsy without cataplexy it is much less sensitive, with up to 20% of cases hypocretin-1 deficient [21–24]. Intermediate levels of CSF hypocretin-1 (between 110 and 200 pg/ml) may not always suggest a diagnosis of narcolepsy, as they may also be observed in other neurologic conditions, tumors, infections, acute traumatic brain injury, and syndromic/genetic cases [25–36]. Importantly however, these conditions are unlikely to lead to diagnostic confusion, since they have substantially different symptoms compared to narcolepsy. CSF hypocretin-1 measurement is the most precise diagnostic tool available in narcolepsy with cataplexy [1,21,37], and will be incorporated in the upcoming 3rd edition of the International Classification of Sleep Disorders (ICSD) as preferential and not only alternative criterion [1].

The main polysomnographic test is the Multiple Sleep Latency Test (MSLT), typically showing a short mean sleep latency (SL, $\leq$8 min) and $\geq$2 Sleep Onset Rapid Eye Movement Periods (SOREMPs) [1]. With such cut-offs, the MSLT sensitivity is 94.5% but the specificity is only 73.3% [38,39].

1.1.3. Demographics and diagnostic rate

Narcolepsy with cataplexy has an estimated prevalence of 2–5/10,000 [40] and an average incidence of 7.4 per million person-years [41]. More than 50% of cases appear to have disease onset before 18 years of age [42]. Onset as late as 70 years of age is rare but has been described [4,43]. Bimodal peaks have been reported, with one around 15 years of age (range 10–19 years) and the other around 35 years [44]. Onset of the disease can be insidious (over years) or acute (within weeks or even days). Acute onset is most often reported in children, especially for narcolepsy with cataplexy associated with a large BMI increase close to the onset of narcoleptic symptoms. Cataplexy develops in 5–8% of patients as an initial symptom but usually either together with excessive daytime sleepiness or within on average 6 years after the onset of sleepiness [4,45–47]. Significant sex differences are not observed, although a slight male predominance was reported, while females showed a slightly earlier manifestation of symptoms in one German study [47]. As with many other rare diseases, narcolepsy is often overlooked or misdiagnosed, leading to an estimated mean diagnostic delay of 8 years, ranging from a few weeks to 60 years after the onset of clinical symptoms [48]. The delay between excessive daytime sleepiness and cataplexy onset may contribute to diagnostic delay [47]. In clinical practice, recognition of childhood cases is increasing, perhaps because of better awareness of the disease in the general population and in medical community [5,48–51]. Recognition of the disease in children is particularly challenging, since a wide range of daytime sleep requirements is often considered normal, cataplexy in children presents with atypical features [51], and there is a lack of objective pediatric diagnostic criteria [1].

1.1.4. Pathophysiology

Sporadic narcolepsy with cataplexy is associated with a loss of hypocretin-producing neurons in the hypothalamus (which is not always the case in secondary or familial forms of narcolepsy) as demonstrated in post-mortem studies on sporadic cases [52–54], but the exact pathological mechanism still remains to be elucidated. Abnormalities in genes coding for hypocretin peptides or their receptors could only be identified in a single patient with a point mutation in the prepro-hypocretin gene [53]. An autoimmune etiology is hypothesized on the basis of a strong association with the Human Leukocyte Antigen (HLA) DQB1*06:02, with 85–98% of patients carrying this allele [55]. So far studies have not identified hypocretin neuron specific antibodies [56–60]. More recently, the hypothesis of an autoimmune etiology was supported by association with a polymorphism in the T cell receptor alpha locus, involved in the HLA-peptide presentation, and with a polymorphism of the T cell and natural killer P2RY11 receptor, involved in the regulation of immune-cell survival [61,62]. Moreover, patients with recent onset narcolepsy showed elevated anti-streptolysin-O titers, suggesting recent streptococcal infections [63], and increased titers of antibodies against Tribbles homolog 2, an intracellular and membrane protein enriched in hypocretin neurons, were detected in a small but significant proportion of recent onset narcolepsy patients [64]. The relation between these findings and hypocretin cell loss has yet to be explained.

In contrast to narcolepsy with cataplexy, narcolepsy without cataplexy is probably not a single disease. Only some individuals in this heterogeneous group will develop cataplexy later, but most will not [65–68]. For this latter group there is evidence that narcolepsy without cataplexy may be caused by a partial localized loss of hypocretin cells when compared to narcolepsy with cataplexy, which may explain why hypocretin-1 levels are normal/intermediate rather than undetectable [20,37,67–71]. A pathophysiological mechanism similar to narcolepsy with cataplexy is presumed in these patients. However, there is also evidence that a clinical picture resembling narcolepsy without cataplexy can occur with behaviorally induced insufficient sleep, sleep related breathing disorders, periodic limb movement disease, or environmental sleep disorder [1,72–75]. The differential diagnosis should consider these conditions, which can however be co-morbid with