

NEUROLOGICAL DISORDERS

Post Tick-Borne Encephalitis Virus Vaccination Narcolepsy with Cataplexy

Hildegard Hidalgo, MD^{1,*}; Ulf Kallweit, MD^{1,2,*}; Johannes Mathis, MD²; Claudio L. Bassetti, MD²¹Neurocenter Rhine-Lahn, Clinic Katzenelnbogen, Katzenelnbogen, Germany; ²Department of Neurology, Bern University Hospital, and University of Bern, Switzerland; *co-first authors

Study Objectives: Narcolepsy with cataplexy (NC) is a chronic neurological disorder thought to result from an altered immune response based on a genetic predisposition coupled with environmental factors. Pandemrix vaccination has been reported to increase the risk of narcolepsy. We aimed at identifying other vaccines associated with the onset of narcolepsy.

Methods: Case series and retrospective database study.

Results: We identified four cases of NC following a tick-borne encephalitis (TBE) vaccination with FSME Immun. Additional four cases could be detected in the database of the Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines in Germany.

Conclusions: Our findings implicate TBE vaccination as a potential additional environmental factor for the development of NC and add additional evidence for an immunological mechanism in the pathogenesis of the disease.

Keywords: narcolepsy, cataplexy, hypocretin, tick-borne encephalitis virus vaccination, granzyme, dendritic cells

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Significance

Here we describe for the first time tick born vaccination as potential triggering factor of narcolepsy-cataplexy.

INTRODUCTION

Narcolepsy with cataplexy (NC) is a chronic neurological sleep-wake disorder with a prevalence of 25–50 per 100,000. Symptom onset typically peaks during the second decade of life.

The etiology of NC is still incompletely understood, but increasing evidence underlines that NC may be an immune-mediated disorder affecting genetically predisposed individuals after exposure to environmental factors.¹ This immune process eventually results in a selective loss of hypocretin (HCRT) cells in the posterior hypothalamus. Correspondingly, cerebrospinal fluid (CSF) hypocretin-1 (hcrt-1) levels are low or below detection limit in ~95% of NC patients. The strong association (> 98%) of NC with the HLA DQB1*0602 haplotype underlines the importance of the DQB1 locus for both genetic risk and protection in the development of NC.²

Different environmental factors have been suggested to be associated with the onset of NC. In early reports on the etiology of NC,³ associations with various infections have been reported at the onset of NC. Elevated anti-Streptococcal antibodies have been observed near disease onset, suggesting that streptococcal infections may act as a trigger for NC.⁴ Further, H1N1 virus infection in 2010 led to a major increase of NC incidence in China.⁵ The increase of NC incidence after H1N1 vaccination with Pandemrix in several European countries since 2009, particularly in children and young adults, was a key event and pointed to the vaccination as a possible environmental trigger for disease onset.⁶ Initially, the AS03 adjuvant in Pandemrix was supposed to be the pivotal trigger for post H1N1 NC.⁷ However, the AS03 adjuvant has also been used in Arepanrix, another H1N1 vaccine, without any increase of NC rate.⁸ A higher amount of polymeric H1N1 virus nucleoprotein (NP) for Pandemrix, probably due to different purification process was detected in Pandemrix when compared to Arepanrix and may have led to higher levels of IgG-antibodies in children with predisposed susceptibility for developing

post-H1N1-NC.⁸ There are no reports on other vaccines associated with the onset of NC.

Here we report four cases of NC onset shortly after tick-borne encephalitis (TBE) vaccine in Germany and Switzerland.

CASE REPORTS

For further data please see Table 1.

General

Clinical, neurological, and psychiatric examinations as well as brain MRI and EEG studies were without pathological findings in all cases. CSF examinations for measuring hypocretin levels were declined by patient 1 and 4.

Patient 1

A 13-year-old boy together with his heterozygotic twin brother and his 15-year-old sister, received on 11 April 2013 the second booster injection against TBE with FSME Immun 0.5 mL (Baxter Germany). This injection followed primary immunizations in 2004 and 2005 with FSME junior Baxter 0.25 mL and a first booster with Encepur Kinder in 2009.

In June 2013 he developed excessive daytime sleepiness (EDS) followed by the onset of cataplexy a few weeks later. He presented a weight gain of 10 kg in 6 months. He was diagnosed for narcolepsy with cataplexy on 20 November 2013 by clinical symptoms and Multiple Sleep Latency Test (MSLT). Laboratory data were unremarkable except an eosinophilia of 6.4% (normal range < 5.5%). Medical history revealed a history of frequent upper airway infections until the age of 2 years in contrast to his twin brother. Subsequently, he complained of disrupted night sleep and hypnagogic hallucinations and described increased perspiration at nighttime and further worsening of cataplexy. In March 2014, Epworth Sleepiness Scale (ESS) score was 20/24 points and Ullanlinna narcolepsy scale 13; laboratory findings revealed a vitamin D deficiency (7.4 ng/mL); ASL titer was negative. There was no family history of narcolepsy or

Table 1—Demographic, clinical, sleep laboratory (PSG, MSLT), laboratory (HLA, hypocretin) and vaccine data of four NC patients suffering from NC after TBE vaccination.

	Case 1	Case 2	Case 3	Case 4
Demographic data				
Age (years) at last vaccination	13	12	21	32
Gender	m	f	m	m
Vaccine data				
Vaccine 1	26-Apr-2004*	29-Jun-2011*	11-Mar-2009**	12-Jul-2013**
Vaccine 2	24-May-2004*	28-Jul-2011*	25-Mar-2009**	26-Jul-2013**
Vaccine 3	14-Apr-2005*	1-Aug-2012*		
Vaccine 4	2-Apr-2009 ^x			
Vaccine 5	11.04.2013**			
Name of vaccine administered	Baxter Immun *0.25 / **0.5 ^x Encepur Kinder	Baxter Immun *0.25	Baxter Immun **0.5	Baxter Immun **0.5
Clinical symptoms				
Onset excessive daytime sleepiness	Jun-2013	Jul-2011	Apr-2009	Aug-2013
Onset cataplexy	Aug-2013	8-Aug-2011	Summer 2009	Sep-2013
Sleep disruption	Autumn 2013	2014	2009/10	Autumn 2013
Weight gain (kg)	10	no		no
Questionnaires				
Epworth Sleepiness Scale	20	24	22	17
Ullanlinna Narcolepsy Scale	13	19		19
Polysomnography data				
Date of polysomnography	21-Nov-2013	17-Oct-2011	15-Jul-2014	9-Aug-2014
Total sleep time (min)	415	484	387	354
Sleep efficiency (%)	94	94	98	87
Sleep latency (min)	18.2	4	1.5	1.5
REM latency (min)	12.0	5.3	3	5.0
Multiple Sleep Latency Test data				
Date of Multiple Sleep Latency Test	22-Nov-2013	18-Oct-2011	16-Jul-2014	11-Aug-2014
Sleep latency (min)	5.5	3.1	0.5	0.45
REM latency (min)	5.3	4.5	3.8	1
Number SOREM Periods	2/5	2/5	3/5	3/5
Laboratory				
HLA DQB1*0602	positive	positive	positive	positive
CSF Hcrt-1 (pg/mL)		< 20	25	
Vitamin D µg/L (reference value > 20)	7.4	13.9		15.1

MLST, Multiple Sleep Latency Test; NC, narcolepsy with cataplexy; PSG, polysomnography; TBE, tick-borne encephalitis.

daytime sleepiness. His HLA-DQB1*0602 positive siblings did not present any symptoms of narcolepsy.

Patient 2

A previously healthy 13-year-old girl with an unremarkable personal and family history of neurological or sleep disorders presented with EDS one month after her first TBE vaccine with FSME-Immun 0.25 junior (Baxter) in June 2011. Ten days after the second administration of FSME-Immun 0.25 junior, the first cataplexy occurred in July of 2011. She was diagnosed for NC in October 2011. She is HLA DQB1*0602 positive, and CSF hcr-1 was below detection limit. Another booster immunization of FSME-Immun 0.25 junior was administered in 2012, but did not lead to any change of symptoms.

Patient 3

A 21-year-old healthy male without family history of NC or other neurologic disorders presented in 2009, one month after

TBE-vaccinations on 11 March 2009 and 25 March 2009 with FSME Immun (Baxter)—according to a rapid immunization pattern—with EDS, rapidly followed by sleep paralysis, hypnagogic hallucinations, cataplexy, nightmares, and REM sleep behaviour disorder (RBD). Diagnosis of NC was made in July 2014. He is HLA DQB1 0602 positive; CSF hcr-1 was 25 pg/mL.

Patient 4

A 32-year-old male reporting an increased sleep need since infancy and a family history of a “sleepy grandfather” presented with EDS and cataplexy of increasing number and severity a few (approximately 2) weeks after receiving TBE-vaccinations with FSME Immun adult (Baxter) on 12 July 2013 and 26 July 2013 following a rapid immunization schedule. Night sleep was disrupted with the patient spending often more than 3 hours awake. He is HLA DQB1 0602 positive. Diagnosis of NC was established in November 2014 based upon clinical symptoms and MSLT.

DISCUSSION

TBE vaccine is a recommended prophylaxis for pathogenic flavivirus tick-borne encephalitis virus infections in endemic regions of Germany, Switzerland, and Austria same as in other European countries and northern Asia.⁹ Vaccination coverage in endemic regions is rated at 31–37% (grade schoolers: 33–44%) and 15% (12%) in non-risk regions for Germany and 34% for Switzerland, respectively.^{10,11} Vaccine is offered in Europe in two preparations: Encepur (Novartis) and FSME Immun (Baxter). Encepur Kinder is approved for children from 1–11 years (FSME Immun Junior: 1–15 years) and Encepur Erwachsene for adolescents and adults \geq 12 years (FSME Immun Erwachsene: 16–60 years). Of such immunizations, FSME Immun has been prescribed in 60.6% (children: 64.12%) vs. Encepur in 39.4% (35.88%) of cases (data for Germany, mean from period 2011–2015).¹⁰ Key differences between vaccines are the presence of human albumin: only in FSME Immun, and in the strain and dose of utilized viruses (1.5 μ g Karlsruhe 23 virus strain vs 2.4 μ g Neudörfel strain). Both preparations contain formaldehyde inactivated antigens adsorbed to a similar dose of aluminium hydroxide (0.35 mg vs 0.3–0.4 mg). Preparations for children of both vaccines contain half of adult doses and are recommended for children under 12 or 16 years in FSME Immun, respectively.^{12,13}

Conventional schedules for both preparations in Germany and Switzerland involve two injections with a 4-week interval between injections and a booster after one year, which is to be repeated after 3 years. The rapid schedule suggests application on day 0, 14, and 300.^{12,13} No information is available on the rate of conventional vs. rapid immunisations.

In addition to our 3 German cases, the serious adverse events (SAE) database of the Paul-Ehrlich-Institut-Federal Institute for Vaccines and Biomedicines in Germany, documents additional 4 cases of narcolepsy following FSME Immun vaccination.¹⁴ No case of narcolepsy following Encepur vaccine has been described so far. Due to data protection laws, no additional information on these cases is available.

Common features of all our cases is the use of Baxter FSME Immun vaccine and in three patients the deviation of the classic immunization schedule, including one patient receiving double of dose the recommended dose for his age (case 1), and two the accelerated schedule (cases 3, 4).

The time interval between vaccinations and onset of first symptoms is between one and six weeks (cases 2–4) and approximately 11 weeks in case 1 and hence similar to cases with post H1N1 vaccination NC.¹⁵ Our patients rapidly evolved a full-blown phenotype of narcolepsy, which also has been described frequently in post H1N1 NC.¹⁶

There is no known congruence of ingredients between Pandemrix and TBE vaccines. Aluminium hydroxide (AH) is a frequently used adjuvant in many vaccines. There are no reports of NC after vaccination with other vaccines using AH. Human albumin (HA) in FSME Immun is used as a component to reduce TNF- α , IL-1 β , IL-6, and IL-8 induced side effects.¹⁷ HA can potentially cause allergic reactions. In very rare cases, TBE vaccines were associated with the induction of autoimmune diseases such as Guillain Barré Syndrome or multiple sclerosis.¹⁸

No case of narcolepsy following TBE virus infection has previously been described.

A special feature of FSME Immun is that it has been found to suppress expression of granzyme B (GrB) by human plasmacytoid dendritic cells (pDC).¹⁹ Although the mechanism of this suppression is still unclear, this finding is not observed in other vaccines. Granzymes are serine proteases expressed by several types of immune cells and seem to have immunomodulatory functions such as suppression of T cell expansion at the site of an infection. Granzymes also potentially suppress autoreactive T cells. Extracellular soluble granzymes are elevated in the circulation of patients with autoimmune diseases.²⁰ The role of granzymes in the development of narcolepsy, however, remains speculative.

This case series is to our knowledge the first report of a potential association between TBE vaccination and NC. Due to coverage of TBE vaccination in only 15% to 30% of the population and the low incidence of narcolepsy, a limited number of NC cases associated with the vaccine can be expected among those presenting with new onset “sporadic” narcolepsy. However, it remains striking that the only reported cases of NC occurred following FSME Immun and not Encepur, even though both vaccines were used quite similarly.

Although there are no common features with the influenza vaccine Pandemrix, which has been shown to induce antibodies to influenza nucleoprotein that cross-react with hypocretin receptor 2,²¹ it is possible that a specific, not yet defined, component in the TBE FSME Immun vaccine may trigger in predisposed individuals, a cross-reactive immune response that may lead to NC. We hypothesize that a stronger immune reaction was induced in our patients by either deviation of dosage or rapid immunization. If true, it may also be possible that rather than specific vaccine ingredients, NC may be triggered in a bystander fashion as a consequence of an enhanced immune response. Collectively, our data adds additional evidence of potential immunological mechanisms in the pathophysiology of NC and calls for further evaluation of alternative cellular immune response mechanisms, possibly involving, e.g., DC and GrB.

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Address correspondence to: Dr. Ulf Kallweit, Department of Neurology, Inselspital, Bern University Hospital, Freiburgstrasse 18, 3010 Bern, Switzerland ; Tel: +41 (0)31 632 3066; Fax: +41 (0)31 632 9679; Email: ulf.kallweit@insel.ch

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