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ORIGINAL COMMUNICATION

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No persistent effect of intravenous immunoglobulins in patients with narcolepsy with cataplexy

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Abstract We report on four patients with narcolepsy with cataplexy (NC), who were treated with high-dose intravenous immunoglobulins (IVIg). Although in some patients transient effects were seen of both objective (multiple sleep latency test and maintenance of wakefulness test) and subjective symptoms (Epworth Sleepiness Scale and frequency of cataplexy), these effects lasted at the most for a few weeks and did not persist. Our report challenges the recent observations of a favorable and persistent effect of IVIg in NC patients.

Key words narcolepsy · cataplexy · intravenous immunoglobulins · excessive daytime sleepiness

Introduction

The etiology of the selective loss of hypocretin (orexin) neurons in the posterolateral hypothalamus in sporadic narcolepsy with cataplexy (NC) is not known. Because of the tight association of narcolepsy with certain human leukocyte antigen (HLA) alleles, an autoimmune mechanism is considered [1, 2]. Two groups recently reported on hypocretin-deficient NC patients, who experienced a significant and sustained reduction of frequency and severity of cataplexy after administration of high-dose intravenous immunoglobulins (IVIg), in particular when treated early after disease onset [3, 4, 8]. These findings seemed to corroborate the autoimmune hypothesis and suggested that early IVIg treatment in NC might favorably modify the course of disease.

In this report we describe four hypocretin-deficient NC patients without or with uncertain benefit from IVIg therapy.

Case 1

This 43-year-old woman noticed in summer 2004 the gradual appearance of daytime sleepiness with daily irresistible and restorative naps. In December 2004 she experienced the first cataplectic attacks involving the head and both lower limbs, triggered by strong emotions (mainly laughter), and occurring up to several times per day. Her night-time sleep was increasingly disturbed by frequent awakenings, and dreams became more vivid and realistic. She also had rare episodes of (hypnagogic) hallucinations and sleep paralysis. Epworth Sleepiness Scale (ESS) was 19/24, Ullanlinna Narcolepsy Score (UNS) 16/44, and Swiss Narcolepsy Scale (SNS) 36 [7, 10]. Clinical examination was unremarkable. Magnetic resonance imaging (MRI) scan of the brain showed few, nonspecific, small (< 1 cm) hyperintense signal alterations of the subcortical/white matter without gadolinium enhancement. Cerebrospinal fluid (CSF) examination revealed normal glucose and protein content, 5 mononuclear cells/µl, and no oligoclonal bands. CSF hypocretin-1 was undetectable (< 40 pg/ml). HLA typing was positive for DQB1*0602, DQA1*01, DRB1*15 and DRB5*. Polysomnography (PSG), multiple

sleep latency tests (MSLT; showing 4 sleep onset REM periods [SOREMP] in 5 tests) and maintenance of wakefulness tests (MWT; showing 2/4 SOREMPs) were consistent with narcolepsy (Fig. 1).

Methylprednisolone 1000 mg/d was administered intravenously for 3 consecutive days and then orally tapered over 8 days. During the first 3 weeks after steroid treatment the patient reported a mild (10–20 % better as estimated by the patient) but only transient reduction of EDS and cataplexy. This prompted a trial with IVIg at a dose of 1 g/kg/day over 2 days, repeated three times at 5-week intervals (latency from cataplexy onset: 4 months). After the first two IVIg infusions, the patient reported a gradual improvement of EDS (decrease of ESS from 15–19/24 at baseline to 11/24 after the second IVIg trial) and a mild reduction of frequency of self-reported cataplexy (measured by a cataplexy diary). However, after the third IVIg infusion, cataplexy and severity of EDS (ESS = 17/24) returned to pre-treatment levels. No effects were noted on hallucinations, sleep paralysis and MSLT/MWT results during and after IVIg (Fig. 2).

Case 2

This 59-year-old woman developed EDS and cataplectic attacks after a flu-like infection in 1987. She had 3–4 short irresistible and restorative naps per day, her cataplectic attacks affected mainly the head and neck, triggered by laughter, but also by negative emotions, occurring up to 1–3 times/day. Acoustic (hypnagogic) hallucinations occurred once a month, and a few years later she also developed rare episodes of sleep paralysis. Most drugs, including modafinil, methylphenidate, dexamphetamine and mazindol, were not tolerated. Fluoxetine had a moderate effect on cataplexy.

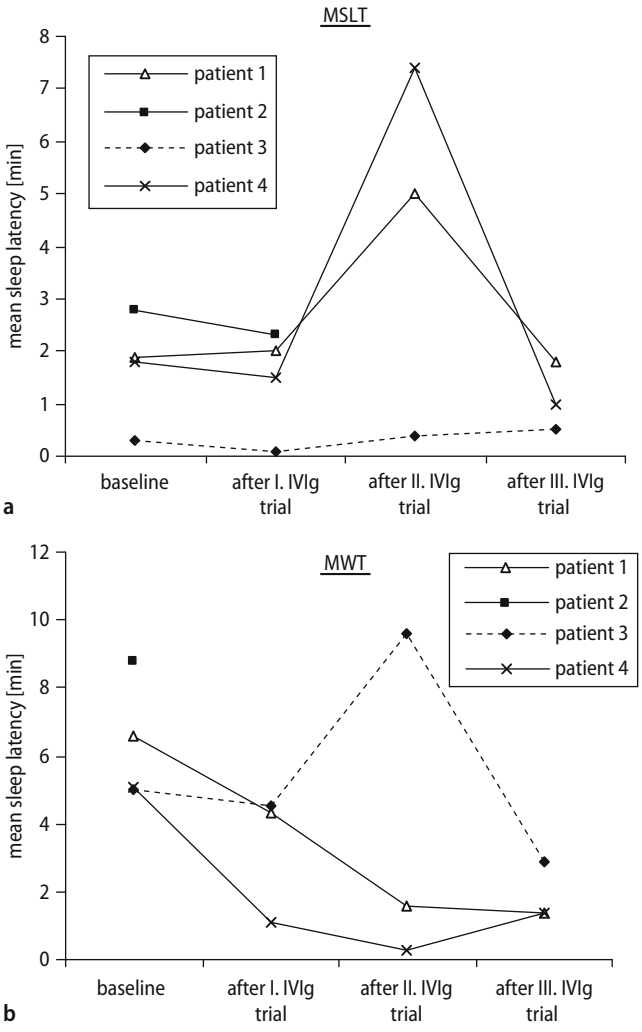

Fig. 1 **a** Multiple sleep latency test (MSLT) and **b** the maintenance of wakefulness test (MWT) at baseline and their response to IVIg treatment

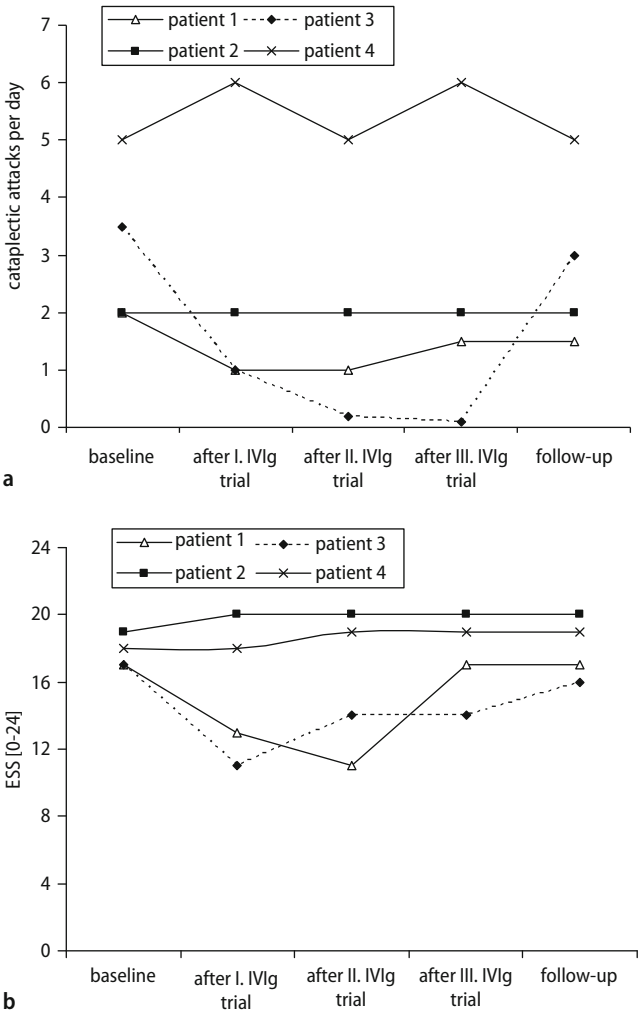

Fig. 2 **a** Frequency of self-reported cataplectic attacks and **b** Epworth Sleepiness Scale (ESS, measuring subjective sleepiness) at baseline and after each administration of intravenous immunoglobulins

In August 2003 a common variable immunodeficiency syndrome (deficiency of IgG subclasses II and IV, [9]) was diagnosed and a treatment with IVIg infusions of 20 g every 3 weeks was started.

In September 2004 we first saw the patient. ESS was 20/24, UNS 30/44, and SNS –66. Clinical examination and brain MRI were unremarkable. Routine CSF examinations were normal. CSF hypocretin-1 was undetectable. HLA-typing was positive for DQB1*0602, DQA1*01, DRB1*15 and DRB5*. Sleep-wake tests (PSG, MSLT with 2/4 SOREMPs, MWT without SOREMPs) were typical for narcolepsy (Fig. 1).

Considering the failure of all previous medications and the diagnosis of a common-variable immunodeficiency syndrome, additional treatment with high-dose IVIg infusions was started (latency from narcolepsy onset: 17 years). Because of allergic reactions the usual dose (2 g/kg) was distributed over 5 days (and not as usual over 2 days). No effects were noted on EDS, cataplexy, hallucinations, sleep paralysis, and MSLT/MWT results during and after IVIg (which was stopped after the second administration because of recrudescence of allergy) (Fig. 1).

Case 3

This 41-year-old man developed EDS with irresistible naps within a few days in August 2004 while mastering an unusually stressful family situation. In the following months he experienced few generalized and several partial clear-cut cataplectic attacks per day which were triggered by laughing and other positive emotions, as well as occasional sleep paralysis and hypnagogic and hypnopompic hallucinations. Night-time sleep became more fragmentary and his dreams intense and threatening. ESS was 22/24, UNS 29/44, and SNS –95. Clinical examination and brain MRI were unremarkable. Sleep-wake tests were typical for narcolepsy, including 4/4 SOREMPs in MSLT and 3/4 SOREMPs in MWT (Fig. 1). Repeated CSF examination showed a mild pleocytosis (4–10 mononuclear cells/μl), without oligoclonal bands. CSF hypocretin-1 was undetectable. HLA-typing was positive for DQB1*0602, DQA1*01, DRB1*15 and DRB5*. Extensive serologic and immunologic tests were negative.

The combination of modafinil 100–200 mg b.i.d. with venlafaxine 75 mg completely controlled cataplectic attacks, hallucinations and sleep paralysis and significantly improved EDS (the ESS went from 22 to 15). He was able to return to work in full time position for 2.5 years. In association with an increased psychosocial stress (divorce) and weight gain his narcoleptic symptoms exacerbated and became disabled despite several modifications of his medical therapy. This prompted treatment with IVIg infusions at a dose of 1 g/kg/day over 2 days, repeated three times at 5-week intervals (latency disease onset: 4 years).

The patient reported a significant reduction in number and severity of cataplectic attacks from 3–4/d at baseline to 1–2/week after the second and 0–1/week after the third IVIg infusion. The overall improvement of cataplexy was estimated to be around 80–90 %. However, during the short hospitalizations on occasion of the IVIg trials, the persistent occurrence of daily cataplectic attacks could be witnessed by several of us (POV, RK, CLB). There was also a strong improvement of subjective EDS, which the patient reported to recognize already within the first hour of the first IVIg infusion (reduction of ESS from 15–19/24 at baseline to 11/24 after the first IVIg). Objective parameters (MSLT, MWT), however, remained unchanged. In the following weeks, the patient experienced also a progressive reappearance of narcoleptic symptoms. Eight weeks after the last IVIg trial severity of EDS, cataplexy and sleep paralysis and hallucinations were comparable to pre-treatment levels.

Case 4

In June 2006 this 52-year-old woman developed EDS with irresistible need of 2–3 restorative naps/day and severe cataplectic attacks with falls, triggered by both positive and negative emotions, and occurring up to ten times per day. She did not notice any change of her night-time sleep, but her dreams became more intensive. She has never experienced any hypnagogic hallucinations or sleep paralysis. ESS was 17/24, UNS 39/44, and SNS –92. Clinical examination and brain MRI were unremarkable. Routine CSF examination was normal. CSF hypocretin-1 was undetectable. HLA-typing was positive for DQB1*0602, DQA1*01, DRB1*15 and DRB5*. Sleep-wake tests were typical for narcolepsy, including 2/4 SOREMPs in MSLT tests and 3/4 SOREMPs in MWT (Fig. 1).

Treatment with modafinil 50 mg/d and fluoxetine 20 mg/d was started, leading only to a mild improvement of both subjective EDS and cataplexy. Treatment with modafinil and fluoxetine was gradually tapered, and after a drug-free period of 3 weeks a trial with IVIg was started at a dose of 1 g/kg/day over 2 days, repeated three times at 5-week intervals (latency from cataplexy onset: 11 months). No effects were noted on EDS, cataplexy, and MSLT/MWT results during and after IVIg treatment.

Discussion

We report the absence of persistent improvements of narcoleptic symptoms in four patients treated with IVIg infusions. Although transient effects were seen concern-

ing MSLT in patients 1 and 4, MWT in patient 3, cataplectic attacks in patient 3, and ESS in patients 1 and 3, these effects lasted at the most for a few weeks and did not persist. This observation is in contrast with the recent reports by Dauvilliers, Lecendreux, and collegues, on five narcolepsy patients [3, 4, 8] in whom a sustained reduction in number and severity of cataplexy and a moderate effect on EDS (in all five patients) were achieved. The lack of a significant and persistent effect of intravenous steroids given early after onset of symptoms in one of our four patients also confirms the report of Mignot [6].

Four factors may account for the lack of significant effects of IVIg in our patients. First, only two of our patients were treated early after onset of cataplexy (four and eleven months, respectively, after the first appearance of cataplectic attacks). However, one patient described by Dauvilliers et al. was treated with IVIg with a delay of 9 years from disease onset, but reported improvement on both cataplexy and EDS with persistence of efficacy after 22 months without any anticataplectic or stimulant treatment. Second, in all of our patients CSF hypocretin-1 was already undetectable, suggesting that (presumed) autoimmune destruction of hypocretin neurons was already complete when IVIg therapy was started. However, all patients reported by Dauvilliers et al. had also undetectable CSF hypocretin-levels before IVIg treatment was started. Third, the treatment protocol was not identical in each patient, with patient 1 receiving corticosteroids and patient 2 receiving IVIg in lower dosages prior to the three IVIg trials. Fourth, our patients were older at disease onset (39, 40, 41 and 51 years) than those reported by Dauvilliers et al. (10, 12, 21 and 43 years). Both the efficacy of IVIg and the susceptibility to placebo effects may significantly depend on the patient's age at disease onset.

The discrepancy between lack of objective improvement (of EDS) and strong subjective improvement (of both cataplexy and EDS) in patient 1 and 3 suggest that a placebo effect might explain, at least in some cases, the improvement of narcoleptic symptoms (and particularly cataplexy) after IVIg. Indeed, a similar observation was recently reported in a narcoleptic patient who underwent a double-blind placebo-controlled administration of IVIg [5]. The authors could not find a difference between placebo and IVIg treatment. Furthermore, a recent trial with sodium oxybate has proven the existence of a placebo effect on cataplexy [11].

Our report challenges the first, very optimistic observations on the favorable effects of IVIg in patients with narcolepsy with cataplexy [3, 4, 8], without proving the absence of any effect of IVIg (particularly on cataplexy). Only a randomized, double-blind and placebo-controlled study with narcolepsy patients with both early and late disease onset could determine the "true" value of IVIg in the treatment of narcolepsy and the ideal interval after onset of symptoms for this expensive and possibly harmful therapeutic intervention.

Conflict of interest The authors declare no conflict of interest.

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