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LONG-TERM IMPROVEMENT AFTER COMBINED IMMUNOMODULATION IN EARLY POST-H1N1 VACCINATION NARCOLEPSY

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We previously described the possible clinical effects of early monotherapeutic IV-immunomodulation (IVIg) treatment in sporadic[1] but not in post-H1N1 vaccination narcolepsy type 1 (NT1).[2] We report here an early post-H1N1 vaccination NT1 case treated with combined immunomodulation of IVIg and methylprednisolone, and a comparable sporadic NT1 case.

Case report. In late 2009, a 2.5-year-old boy (child 1) was H1N1 vaccinated with H1N1 pandemic influenza vaccine (Pandemrix; GlaxoSmithKline, London, United Kingdom). He had a history of asthma/allergies and sleep talking/sleepwalking. Medio August 2013, he developed severe sleepiness, took 2–4 naps/day, and experienced episodes of sleep paralysis. We examined him primo September 2013 when the baseline Epworth Sleepiness Scale (ESS) score was 14/24 and multiple sleep latency test (MSLT) showed a mean sleep latency of 5 minutes with sleep onset REMs (SOREMs) in 4/4 nap opportunities. CSF hypocretin-1 levels were low (77 pg/mL; normal values ≥200 pg/mL).

In late September 2013, cataplexy (tongue protrusion, facial muscles hypotonia, and head drop) triggered by laughter/emotional stress emerged and rapidly escalated to several partial/fulminant attacks/day. In the beginning of October 2013, having obtained informed consent, we initiated treatment of IVIg 1 g/kg/day for 2 consecutive days, followed by methylprednisolone 20 mg/kg/day for 4 days, administered 3 times at monthly intervals (T1, T2, and T3). During T1, T2, and T3 methylprednisolone treatment days, cataplexy completely disappeared: he did activities such as watching cartoons and making jokes, without muscle weakness. However, cataplexy gradually reappeared 1–2 weeks after treatment. Likewise, the ESS score normalized from 14/24 to 3/24 during T1 methylprednisolone treatment, from 8/24 to 2/24 during T2 IVIg and methylprednisolone, and from 14–16/24 to 7/24 after T3. After T3, hypnagogic hallucinations emerged, but no microsleeps were reported; he took only 1 daily nap. The CSF hypocretin-1 levels had dropped to undetectable levels (<40 pg/mL). From October 2014 to January 2015, his status was 3–4 naps/day, cataplexy and hypnagogic hallucinations several times/week. Follow-up MSLT mean sleep latencies in January 2014 and June 2015 were normal (11.5 minutes and 12.5 minutes, respectively).

In late March 2015, another, otherwise healthy, 6-year-old boy (child 2) developed 2–4 sleep attacks/day. His nocturnal sleep was disrupted by awakenings, nightmares, and dream enactment, and cataplexy (tongue protrusions and unsteady gait) became apparent in May 2015. Primo July 2015, the ESS score was 17/24, and he presented extensive spontaneous cataplexy, additionally exacerbated by joy/excitement. MSLT mean sleep latency was 2.1 minutes with SOREMs in 4/5 naps. CSF hypocretin-1 levels were <40 pg/mL. A similar treatment regime as for child 1 was initiated. During T1 methylprednisolone treatment, the ESS score dropped transiently to 11/24, and the frequency of cataplexy decreased from 8 to 6 attacks/day. After T1, the ESS score returned to 16/24, and cataplexy gradually decreased to 3 attacks/day, remaining at that frequency until follow-up. Medio October, the follow-up ESS score was 16/24, and MSLT mean sleep latency was 6 minutes with SOREMs in 4/4 naps. He still had disrupted night sleep, and cataplexy had increased to 5–7 attacks/day. The CSF hypocretin-1 levels were unchanged (table).

Discussion. The present post-H1N1–vaccinated NT1 case treated early after disease onset with combined IVIg and methylprednisolone is notable for several reasons. First, the transient abrupt clinical improvement during the methylprednisolone infusion, a drug thought mainly to target cellular immune mechanisms, supports the recent indications of antigen presentation to T cells as central factors in narcolepsy pathophysiology.[3] Second, although his CSF hypocretin-1 levels subsequently dropped to undetectable levels, there was long-term clinical improvement, as the objective sleep latencies were normal, cataplexy frequency was reduced, and he

Table Demographic, clinical, and paraclinical data

	Child 1			Child 2	
Sex/age	Male/6 y 6 mo			Male/6 y 2 mo	
Ethnicity	White			White	
H1N1 vaccinated (Pandemrix)	Autumn 2009			No	
Weight gain (yes-no)	No			Yes, 5 kg	
Onset EDS (month/year)	Mid August 2013			Late March 2015	
Onset cataplexy (month/year)	Late September 2013			May 2015	
		Follow-up			
Immunomodulation period	**Baseline October 2013**	**January 2014**	**June 2015**	**Baseline July 2015**	**Follow-up October 2015**
ESS (score/24)	14/24	7/24	12/24	17/24	16/24
Cataplexy (episodes per day)	Multiple	**6**	**1**	3	5–7
Hypnagogic hallucinations (yes-no)	No	Yes	No	No	No
Sleep paralysis (yes-no)	Yes	No	No	No	No
Disturbed night sleep (yes-no)	Yes	Yes	Yes	Yes	Yes
Dream enactment (yes-no)	Yes	Yes	Yes (but less)	Yes	Unknown[a]
Medication (yes-no)	No	No	No	No	No
PSG total sleep time (minutes)	603	674	600	560	NA[b]
PSG sleep latency, min	6	1	12.1	1.9	NA[b]
PSG SOREM (yes-no)	Yes	No	No	No	NA[b]
MSLT MSL, min	5.0	**11.5**	**12.5**	2.1	6.0
MSLT SOREMs (number/naps)	4/4	3/4	5/5	4/5	4/4
CSF hypocretin-1 concentration (pg/mL; low <150 pg/mL)[c]	77	<40	Not measured	<40	<40

Abbreviations: EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; MSL = mean sleep latency; MSLT = multiple sleep latency test; NA = not available; PSG = polysomnography; SOREM = sleep onset REM.

[a] A precise description of dream enactment symptoms was not specified at the time of follow-up examination.

[b] Because of technical reasons, data from PSG were lost, but the parent who coslept reported that he fell asleep after 5–10 minutes and slept from 19:55 to 06:40.

[c] Baseline and follow-up hypocretin-1 measurements were analyzed in the same radioimmunoassay (Phoenix) kit to avoid interassay variability.

managed school without medication at 18 months of follow-up.

Apart from a single very early NT1 case, previous monoimmunotherapy and a single combined immunomodulation attempt in sporadic NT1 produced mild/moderate subjective, but not objective improvements.[1] Based on the strong HLA-DQB1*0602 association,[4] possible antigen presentation to T cells,[3] and additional immunogenic polymorphisms,[5] narcolepsy is strongly believed to be an autoimmune disease. In animal models as well as in a human case,[6] hypocretin deficiency occurs around the time of clinical disease onset. Although it is not known exactly what the potential immunomodulation therapeutic window is, early chronical combined immunomodulation (including steroids) in genetic narcoleptic dogs resulted in long-term milder disease. The direct pharmacologic effect on narcoleptic symptoms (for example direct anticataplectic effect) was not observed in these dogs, so combined immunomodulation was the probable cause of improvement.[7] As child 1, but not child 2, improved clinically and initially had a low but still detectable CSF hypocretin-1 level, we speculate that early (enough) combined humoral and cellular immunomodulation can result in long-term disease improvement in human narcolepsy.

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