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The spectrum of REM sleep-related episodes in children with type 1 narcolepsy

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Type 1 narcolepsy is a central hypersomnia due to the loss of hypocretin-producing neurons and characterized by cataplexy, excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations and disturbed nocturnal sleep. In children, close to the disease onset, type 1 narcolepsy has peculiar clinical features with severe cataplexy and a complex admixture of movement disorders occurring while awake. Motor dyscontrol during sleep has never been systematically investigated. Suspecting that abnormal motor control might affect also sleep, we systematically analysed motor events recorded by means of video polysomnography in 40 children with type 1 narcolepsy (20 females; mean age 11.8 ± 2.6 years) and compared these data with those recorded in 22 age- and sex-matched healthy controls. Motor events were classified as elementary movements, if brief and non-purposeful and complex behaviours, if simulating purposeful behaviours. Complex behaviours occurring during REM sleep were further classified as 'classically-defined' and 'pantomime-like' REM sleep behaviour disorder episodes, based on their duration and on their pattern (i.e. brief and vivid-energetic in the first case, longer and with subcontinuous gesturing mimicking daily life activity in the second case). Elementary movements emerging either from non-REM or REM sleep were present in both groups, even if those emerging from REM sleep were more numerous in the group of patients. Conversely, complex behaviours could be detected only in children with type 1 narcolepsy and were observed in 13 patients, with six having 'classically-defined' REM sleep behaviour disorder episodes and seven having 'pantomime-like' REM sleep behaviour disorder episodes. Complex behaviours during REM sleep tended to recur in a stereotyped fashion for several times during the night, up to be almost continuous. Patients displaying a more severe motor dyscontrol during REM sleep had also more severe motor disorder during daytime (i.e. status cataplecticus) and more complaints of disrupted nocturnal sleep and of excessive daytime sleepiness. The neurophysiological hallmark of this severe motor dyscontrol during REM sleep was a decreased atonia index. The present study reports for the first time the occurrence of a severe and peculiar motor disorder during REM sleep in paediatric type 1 narcolepsy and confirms the presence of a severe motor dyscontrol in these patients, emerging not only from wakefulness (i.e. status cataplecticus), but also from sleep (i.e. complex behaviours during REM sleep). This is probably related to the acute imbalance of the hypocretinergic system, which physiologically acts by promoting movements during wakefulness and suppressing them during sleep.

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Abbreviations: MSLT = multiple sleep latency test; N1/2/3 = stages 1, 2 and 3 of non-REM sleep; NREM = non-REM; NT1 = type 1 narcolepsy; PLM = periodic limb movements; PSG = polysomnography; RBD = REM sleep behaviour disorder; REM = rapid eye movement

Introduction

Type 1 narcolepsy (NT1) is a central disorder of hypersomnolence (ICSD third ed.), characterized by loss of boundaries between sleep and wake, with frequent state transitions and intrusions of REM sleep into the other ongoing states of being (Broughton *et al.*, 1986; Dauvilliers et al., 2007*a*; Diniz Behn *et al.*, 2010), due to a deficiency of hypothalamic hypocretin 1 (orexin) signalling (de Lecea *et al.*, 1998; Sakurai *et al.*, 1998), of a likely autoimmune aetiology (Partinen *et al.*, 2014). It is a lifelong disorder, arising in childhood (Nevsimalova, 2009; Aran *et al.*, 2010; Luca *et al.*, 2013; Thorpy and Kriger, 2014) and early adulthood (Dauvilliers *et al.*, 2001). The diagnostic delay is of many years after the onset of symptoms (Ohayon *et al.*, 2005; Luca *et al.*, 2013; Thorpy and Kriger, 2014). Consequently, phenotypic features at presentation may be missing, even if at this stage peculiar typical features have been recently described (Plazzi *et al.*, 2011; Pizza *et al.*, 2013), suggesting that NT1 close to disease onset is a 'shimmering' condition.

Clinically, cataplexy is considered to be the most specific sign of the NT1 pentad, along with sleep attacks, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nocturnal sleep (ICSD third ed.), the latter being as much a prominent feature as daytime symptoms. Mitchell and Dement (1968) reported this feature as prominent and even preceding the other symptoms. Nowadays, neurophysiological investigation of sleep in narcolepsy has grown (Mukai *et al.*, 2003; Dauvilliers *et al.*, 2007*b*; Ferri *et al.*, 2008*a*, 2009; Roth *et al.*, 2013; Sorensen *et al.*, 2013; Jensen *et al*, 2014; Christensen *et al.*, 2015; Pizza *et al.*, 2015), but so far it has mainly focused on sleep dynamics, omitting the phenomenological descriptions of movement disorders occurring during sleep.

REM sleep behaviour disorder (RBD) is reported to occur in NT1 (ICSD third ed.) with a frequency ranging between 7% and 63% in different cohorts (Schenck and Mahowald, 1992; Mayer *et al.*, 1993; Nightingale *et al.*, 2005; Knudsen *et al.*, 2010). Nevertheless, RBD features in NT1 are poorly characterized because the very few video polysomnography (PSG) studies available have been conducted mainly in adult patients and in non-controlled cohorts (Schenck and Mahowald, 1992; Mayer *et al.*, 1993; Cipolli *et al.*, 2011; Franceschini *et al.*, 2011; Frauscher *et al.*, 2011). The RBD pattern of NT1 may share similarities (Oudiette *et al.*, 2012), but has generally been reported to be calmer if compared to that of idiopathic RBD or of RBD within a neurodegenerative condition (Iranzo *et al*, 2009; Cipolli *et al.*, 2011; Franceschini *et al.*, 2011). Its occurrence seems to be sporadic (Mayer *et al.*, 1993; Nightingale *et al.*, 2005; Cipolli *et al.*, 2011; Frauscher *et al.*, 2011; Oudiette *et al.*, 2012). An association with history of parasomnia (Schenck and Mahowald, 1992; Mayer *et al.*, 1993), DQB1*06:02 positivity (Mayer *et al.*, 1993; Mattarozzi *et al.*, 2007), orexin levels (Knudsen *et al*, 2010), cataplexy (Nightingale *et al.*, 2005), and REM sleep without atonia (Knudsen *et al.*, 2010; Cipolli *et al.*, 2011) has been reported.

In narcolepsy, states of boundary instability is a neurophysiological hallmark and RBD and cataplexy are both expressions of this state dissociation (Antelmi *et al.*, 2016) and both have been related to low orexin levels (Knudsen *et al.*, 2010). This breakdown of states of boundary has been reported to be more severe in children, as shown by the presence of the so-called 'cataplectic face' and subcontinuous positive and negative motor phenomena during daytime (Serra *et al.*, 2008; Plazzi *et al.*, 2011). Night-time motor behaviour in children, however, has received little attention, and there are only a few case reports of RBD in NT1 children, hence leading to the belief that it is a rare phenomenon (Turner and Allen, 1990; Sheldon and Jacobsen, 1998; Nevsimalova *et al.*, 2007; Bonakis *et al.*, 2008; Lloyd *et al.*, 2012). In two PSG studies, the prevalence of RBD episodes in NT1 children was similar to that of adults (nearly 30% of the cohort) (Nevsimalova *et al.*, 2011, 2013); however, the diagnosis was mainly based on history taking and scoring of REM sleep without atonia, while the phenomenological description of the events is missing.

In this study, we have systematically analysed the video and PSG charts of night-time sleep and multiple sleep latency test (MSLT) in drug-naïve children with NT1, aiming to analytically characterize the clinical and neurophysiological features of motor events occurring during sleep, based on an event-to-event observation. Video-PSG indeed represents the gold standard for the characterization of sleep events, and especially sleep-related behaviours and movement disorders.

Materials and methods

Subjects were consecutive drug-naïve children attending the Clinic for Narcolepsy of the Department of Biomedical and Neuromotor Sciences of the University of Bologna, who received a final diagnosis of NT1, according to the current international diagnostic criteria (ICSD, third ed.). All patients underwent complete clinical and neurological examination, subjective sleepiness assessment with the adapted version of the Epworth Sleepiness Scale (Melendres *et al.*, 2004),

conventional brain MRI, 48-h continuous PSG recording followed by a standard five-nap MSLT (Littner *et al.*, 2005), human leukocyte antigen (HLA) typing and, whenever possible ($n = 37/40$), lumbar puncture for cerebrospinal hypocretin-1 level assay. The 48-h PSG was performed with concomitant PSG-synchronized infrared video and included conventional EEG, bilateral electrooculogram, submentalis and anterior tibialis EMG, respiratory parameters, and ECG (AASM, 2007).

The key advantage of this approach is that movements can be recorded continuously over the complete recording period, analysed offline in high temporal resolution, and directly correlated to PSG signals. PSG signals were sampled at 256 Hz and stored on hard disk in European data format for further analysis. Two consecutive night PSGs were also recorded in 22 age- and sex-matched healthy subjects, who served as healthy controls.

The study was approved by the local Institutional Review Board and written informed consent was obtained from parents and assent from patients.

Data classification and sleep macrostructure analysis

Sleep stages were scored according to the American Academy of Sleep Medicine (AASM, 2007) criteria by a registered and expert technician (S.V.).

The following conventional sleep data were analysed from nocturnal recordings: sleep latency from lights off, REM sleep latency, total sleep time, sleep period, wakefulness after sleep onset, sleep efficiency; and absolute time spans and percentages of total sleep time spent in N1, N2, N3 and REM sleep. For the sleep onset period, absolute latencies from lights off to the occurrence of the first epoch of all sleep stages were calculated to identify sleep onset in REM sleep period (SOREMP) (i.e. REM sleep occurring within 15 min from the sleep onset) and the sequential occurrence of sleep stages up to the first REM sleep episode.

Chin muscle atonia during REM sleep was evaluated by means of the REM atonia index, using the validated automatic analysis implemented in Hypnolab v. 1.2 (Ferri *et al.*, 2008*a*, *b*, *c*). This index can vary from 0 (absence of mini-epochs with $amp \leqslant 1$), which means complete absence of EMG atonia, to 1 (all mini-epochs with $amp \leqslant 1$), which means stable EMG atonia. The periodic limb movements (PLM) index was computed automatically with the same software, and double-checked manually according to standard criteria (AASM, 2007). MSLT recordings were scored and interpreted (mean sleep latency, number of SOREMP) as recommended (Littner *et al.*, 2005).

As a potential marker of sleep instability, we also calculated sleep transitional indexes, which measure the frequency of transitions between different states of being in different combinations [i.e. wakefulness, non-REM sleep stage 1 (NREM) and REM sleep]. The following transitional indexes were computed: (i) transition index between wakefulness and sleep (tW-Si); (ii) transition index between wakefulness, NREM and REM sleep (tW-NR-Ri); and (iii) transition index between wakefulness, N1, NREM sleep (N2 and N3), and REM sleep (tN1-NR-Ri), as previously detailed (Pizza *et al.*, 2015).

Movements analysis

Time synchronized video-MSLT and video-PSG recordings of the second night were first reviewed by a single sleep expert (E.A.), blinded to the clinical condition of the subject. Marked events were then reviewed by a second scorer (M.F.), blinded as well to the clinical diagnosis. The mean interscorer agreement was 0.91 ($P = 0.001$). Finally, episodes with divergent or doubtful scoring were reviewed by the senior author (G.P.), to reach a final consensus on the classification of every event.

For each movement, we evaluated duration, pattern, body part involved, and type of movements. Brief (< 150 ms) myoclonic movements and comfort movements were not taken into account. Movements were then classified as elementary or complex, based on their pattern. Elementary movements identified (i) small, brief (< 5 s) or apparently non-purposeful movements, which would have not been noticed by the parents; and (ii) stereotypies—referring to automatism-like events (e.g. smacking, fumbling, pelvic movements, and smiling). Complex behaviours identified, instead, more scenic behaviours with a purposeful component, seemingly expressive of a subject's mentation and an 'acting-out' of a dream. When occurring during REM sleep, and configuring by definition RBD (ICSD, third ed.), they were further subclassified into (i) 'pantomime-like' events—when characterized by subcontinuous (throughout the whole duration of the REM cycle) and calm gesturing mimicking daily life activities, performed in a stereotyped fashion; and (ii) 'classically-defined' events—when characterized by brief (seconds to minutes) and more vivid, vigorous or violent motion. Violent movements were defined as forceful and vehement movements in which the patient can potentially hurt or injure himself and/or the bed partner (e.g. kicking or punching). Vocalizations (talking, crying, laughing, yelling, and swearing) were also analysed if associated with a movement.

Statistical analysis

Continuous and categorical data were explored by means of mean ± standard deviation (SD) and frequency. Comparisons between groups (NT1 versus healthy controls and between subgroups of patients, i.e. NT1 with and without complex behaviours during REM sleep) were performed using non-parametric approaches including the Mann-Whitney U-test and the chi-square tests, as appropriate. A P-value < 0.05 was considered to be statistically significant.

Results

Population

The study sample included 40 NT1 children, 20 females (50%) (mean age: 11.8 ± 2.6) and 22 age- and sex-matched healthy controls, 15 females (68.2%) (mean age 13 ± 4.5). Clinical data and results of investigations in NT1 patients are reported in Table 1.

Nocturnal sleep macrostructure and stage transition features

The PSG data of the second nocturnal recording in each group are reported in Table 2. As expected, NT1 patients had a significantly shorter sleep latency and REM sleep latency, increased wakefulness after sleep onset, and decreased N1 and N2 percentage. Yet they had a significantly increased PLM index and decreased REM atonia index, when compared to healthy controls. State transition analysis showed a significant increase of all sleep transitional indices in NT1 patients versus healthy controls.

Table 1 Clinical and demographic data in patients

n	40
Females *n* (%)	20 (50)
Age at evaluation (years ± SD)	11.8 ± 2.6
Disease duration (years ± SD)	2.1 ± 1.4
Age at onset (years ± SD)	9.6 ± 2.3
Adapted ESS (mean values ± SD)	14.6 ± 3.7
Positive family history for sleep disorders, %	15
Positive personal history for impaired nocturnal sleep, %	16
Sleep paralysis, %	35
Hypnagogic hallucinations, %	43
Impaired nocturnal sleep, %	43
Status cataplecticus, %	35
HLA positivity, %	100
Orexin levels (*n* = 37/40) values (pg/ml) ± SD	18.3 ± 26.6

ESS = Epworth Sleepiness Scale.

Classifications of movements

Comparison between patients with NT1 and healthy controls

In NT1 patients and healthy controls, video analysis detected the presence of elementary movements in both NREM (97.5 versus 100% of NT1 and healthy controls, respectively) and REM sleep (90 versus 86.4% of NT1 and healthy controls, respectively). The index evaluating simple movements per hour of total sleep time and of NREM sleep did not differ between the two groups, while the index of simple movements per hour of REM sleep was significantly increased in the patients group ($P = 0.004$) (Table 3). Indeed, during REM sleep, they tended to occur more frequently in NT1 children when compared to healthy controls ($P = 0.001$); NT1 patients had frequently more than seven episodes per night, while healthy controls never presented with more than six episodes per night (Table 3).

Elementary movements during NREM stages consisted of simple and brief (< 5 s) movements like rubbing the nose, the face or pelvic movements. The same pattern was observed during REM sleep, but in NT1 children, along with the above reported features, additional patterns of proactive movements, mainly recurrent, were observed, such as episodes of chewing (seven patients), smiling (six patients), mumbling (five patients), facial grimaces (three patients), and raising one arm (two patients).

Complex behaviours during NREM sleep were detected in a single NT1 patient (a 9-year-old boy), who presented with six different episodes of confusional arousals, during

Table 2 Neurophysiological data in patients and controls

	NT1 (*n* = 40)	Healthy controls (*n* = 22)	*P*-value
Nocturnal PSG			
SL (min ± SD)	3.7 ± 4.9	16.9 ± 16.1	< 0.001
REM sleep latency (min ± SD)	46.6 ± 72.7	83.7 ± 39.7	< 0.001
TST (min ± SD)	451.8 ± 50.8	447.2 ± 55.1	ns
WASO (min ± SD)	52.9 ± 45.5	15.9 ± 10.2	< 0.001
Sleep efficiency (% ± SD)	88.5 ± 8.5	91.2 ± 9.7	ns
N1 (% ± SD)	10.6 ± 5.5	5.7 ± 2.9	< 0.001
N2 (% ± SD)	39.1 ± 10.1	48.1 ± 7.5	0.001
N3 (% ± SD)	26.6 ± 11.2	24.1 ± 7.6	ns
REM (% ± SD)	23.5 ± 6.3	22.1 ± 5.6	ns
PLM index (mean values ± SD)	7.5 ± 7.9	2.4 ± 5.8	0.003
Atonia index (mean values ± SD)	0.7 ± 0.2	0.9 ± 0.1	< 0.001
Stage transitions			
tWSi (mean values ± SD)	7.9 ± 3.3	3.5 ± 1.7	< 0.001
tWNRRi (mean values ± SD)	11 ± 3.1	5.8 ± 1.9	< 0.001
tWN1NRRi (mean values ± SD)	15.4 ± 0.2	8.6 ± 2.7	< 0.001
MSLT			
Sleep latency (min ± SD)	4.2 ± 3.9	-	-
SOREMP (*n* ± SD)	4.3 ± 0.9	-	-

MSLT = multiple sleep latency test; SOREMP = sleep onset in REM sleep period; TST = total sleep time; tW-Si = transition index between wakefulness and sleep; tW-NR-Ri = transition index between wakefulness, NREM and REM sleep; tN1-NR-Ri = transition index between wakefulness, N1, N2, N3 and REM sleep; WASO = wakefulness after sleep onset; ns = non-significant.

Table 3 Elementary and complex events during sleep in patients and controls

	NT1 (*n* = 40)	Healthy controls (*n* = 22)	*P*-value
Nocturnal PSG			
Simple gesturing in NREM (%)	97.5	100	ns
Index of simple gesturing per hour of NREM sleep	1.1 ± 1	1.3 ± 0.9	ns
Numbers of events (%)			ns
0	2.5	-	
1–6	77.5	59	
7–14	12.5	31.8	
>14	7.5	9.1	
Simple gesturing in REM (%)	90	86.4	ns
Index of simple gesturing per hour of REM sleep	4.8 ± 4.1	1.6 ± 1.3	0.004
Numbers of events (%)			0.001
0	12.5	13.6	
1–6	40	86.4	
7–14	27.5	-	
>14	20	-	
Index of simple gesturing per hour of sleep	1.92 ± 1.40	1.35 ± 0.78	ns
Complex gesturing in NREM (%)	1	0	ns
Complex gesturing in REM (%)	32.5	0	0.003
Numbers of events (%)			
0	70		
1	7.5		
>1	22.5		
Duration (%)			
Seconds–minutes	66.6		
Subcontinuous	33.3		
MSLT			
Simple gesturing in NREM (%)	40		
Numbers of events (%)			
0	60		
1–6	40		
Simple gesturing in REM (%)	70		
Numbers of events (%)			
0	25		
1–6	50		
7–14	10		
>14	5		
Complex gesturing in NREM (%)	0		
Complex gesturing in REM (%)	17.5		
Numbers of episodes (%)			
0	82.5		
1–6	2.5		
7–16	15		
Duration of the episodes (%)			
Few seconds	28.6		
>10 s	71.4		

ns = non-significant.

which he raised his head, looked around and, at times, could move his right or left arm.

Finally, complex behaviours during REM sleep were detected only in NT1 children (Table 3) (32.5% of the NT1 patients versus none of the healthy controls, $P = 0.003$).

Video features of complex behaviours during REM sleep

Thirteen NT1 children presented with complex behaviours during REM sleep. i.e. RBD (ICSD, third ed.) (Supplementary Table 1). Of these patients, seven showed brief (up to 2 min) 'classically-defined' RBD episodes, acting energetically as if they were enacting their dream (e.g. gesturing vividly and energetically, or raising the head and the arms and then trying to grab something or to throw something). In all patients, the episodes recurred two, up to three times during the night, through different REM cycles. In six patients longer and 'pantomime-like' RBD episodes were detected, characterized by slow, calm and repetitive gesturing articulated in quasi-purposeful dream-like behaviours, i.e. the patients could manipulate their pyjamas, perform movements as if they were searching for or handling non-existent objects (Supplementary Videos 1 and 2). These behaviours occurred whenever the patients entered a REM cycle, either with a waxing and waning course, i.e. they ended spontaneously after a while (usually after 10 to 20 s) and then recurred after few seconds to minutes in the same REM cycle, or occurring subcontinuously for several minutes (Fig. 1). Both 'classically-defined' and 'pantomime-like' RBD events occurred similarly in the first or second half of the night and were grossly stereotyped throughout the night in each individual.

Overall, complex behaviours mainly involved the limbs (arms more than legs) and the face. Of note, during these behaviours, patients frequently briefly opened their eyes (6/13 patients) (Supplementary Table 1).

Seven patients also showed complex behaviours in REM sleep recorded during MSLT (Supplementary Video 1), all of them also had these behaviours during night-time, with similar features (intraindividual stereotypic pattern). Only one patient showed a pattern of violent RBD with energetic and ample movements during MSLT (he moved his arms, then raised the trunk and the head, he had a fearful expression and presented episodes of intermittent 'head-extension' due to the occurrence of cataplexy while dreaming) (Supplementary Video 3). These episodes recurred during each nap and the patient had five grossly stereotyped motor behaviours in total during the whole MSLT.

During episodes emerging from MSLT, a dream content report was available in five out of seven patients. Three of these patients denied being asleep and two reported a dream content not completely matching with the 'acting-out' performed.

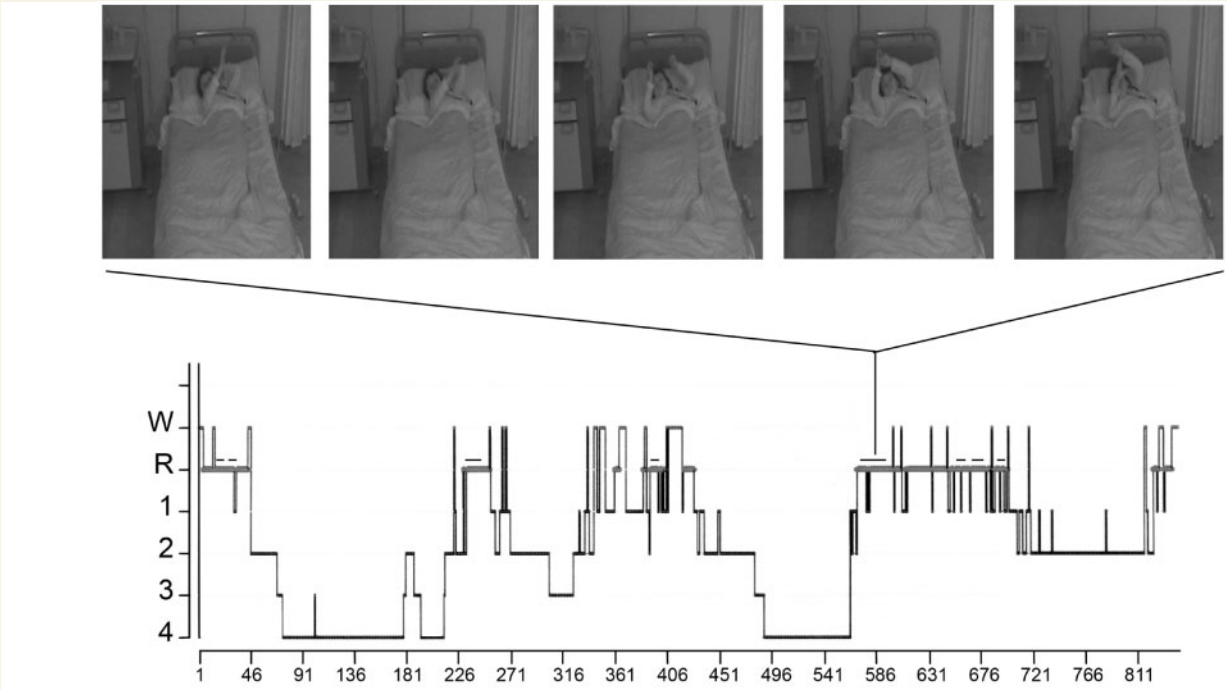

Figure 1 Hypnogram of nocturnal polysomnography in an 8-year-old patient with subcontinuous complex episodes (pantomime-like) during REM sleep. W = wakefulness; R = REM stage; 1 = stage 1 of NREM sleep; 2 = stage 2 of NREM sleep; 3 = stage 3 of NREM sleep. Lines above the hypnogram indicate the occurrence of the complex behaviours. Photograms above the hypnogram show an example of the subcontinuous movements. Numbers below the *x*-axis indicate number of the 30 s sleep epochs.

Comparison between NT1 with and without complex behaviours

Patients with complex behaviours had a significantly decreased REM atonia index when compared with those without complex behaviours (Table 4), with increased values at the scale evaluating daytime sleepiness and increased subjective complaints of impaired nocturnal sleep at the history taking (Table 5). Yet, they exhibited more frequently a cataplectic face/status cataplecticus when compared with those without (Table 5). All the other clinical and neurophysiological descriptors did not differ significantly between the two groups.

Supplementary Fig. 1 shows an example of the PSG and MSLT charts in a patient with complex behaviours during REM sleep. The neurophysiological background was that of a dissociated REM stage, as REMs could be detected on the electrooculogram channels; however, there was an increased phasic/tonic activity over the EMG channel of the submentalis muscle and the EEG showed low amplitude and mixed frequencies, including bursts of alpha activity and of theta waves.

Discussion

This is the first study that has systematically analysed video-PSG/MSLT recordings in a controlled cohort of children affected by NT1 and matched healthy controls, to characterize motor behaviours during sleep.

NT1 patients versus healthy controls

Our data confirm that children with NT1, when compared to healthy control subjects, have impaired nocturnal sleep with shorter sleep latency and REM sleep latency, increased infra-sleep awakenings and increased light sleep. Yet, they show a marked instability of state boundary, as shown by the presence of significantly increased sleep transitional indices. Instability of sleep dynamics has recently been reported in adults affected with NT1 (Roth *et al.*, 2013; Sorensen *et al.*, 2013; Pizza *et al.*, 2015), but never analysed in a cohort of children.

Analysing motor episodes occurring during NREM sleep, we show that both NT1 and healthy control subjects present with the same probability of displaying elementary movements, while complex behaviours suggesting NREM parasomnias, except for a single NT1 patient, are not frequent. On the contrary, both groups have elementary movements occurring during REM sleep, but their number and index per hour of REM sleep are greater in the NT1 patients.

Complex behaviours in REM sleep are instead detectable only in NT1 patients (32.5% of the patients).

Regarding the pattern of RBD episodes, only one patient had a violent and energetic behaviour, raising up the head

and the trunk and moving the arms energetically. In the remaining patients, behaviours were mainly quiet and non-violent and ranged from 'classically-defined' RBD episodes, i.e. episodic and briefer energetic 'acting-out' of a dream (seven patients) (Arnulf, 2012), to almost continuous/subcontinuous 'pantomime-like' activities (six patients). These latter episodes usually consisted of calm, repetitive, and slow gesturing, resembling purposeful behaviours or reminiscent of lively interactions with the environment and/or persons. A calm pattern of RBD has been reported frequently in RBD due to narcolepsy (Cipolli *et al.*, 2011; Franceschini *et al.*, 2011), and, even if rarely, in idiopathic RBD or in RBD due to neurodegeneration (Oudiette *et al.*, 2009, 2012). However, in NT1 children these episodes share some similarities with what has been described in patients with 'status dissociatus' (Antelmi *et al.*, 2016) because, similar to this condition, behaviours not only are quiet and slow in quality, mimicking simple daily-life activities, such as dressing or manipulating fictitious objects, but are also subcontinuous in duration and repeated in a stereotyped fashion, as if the patients were performing behaviours in an almost continuous 'loop'. Moreover, the patients may engage motor activities with eyes open and, when questioned, may deny being asleep (Antelmi *et al.*, 2016).

The neurophysiological correlate is a dissociated REM stage, with increased phasic and tonic chin EMG activity, a mixture of slow and rapid eye movements, and mixed frequencies over the EEG channels (including bursts of theta waves and alpha activity).

Overall, RBD episodes as already reported (Cipolli *et al.*, 2011; Franceschini *et al.*, 2011) are not restricted to REM sleep of the latter part of the night, but occur throughout the night and even during REM sleep at MSLT. In the current study, we did not perform a direct comparison with PSG recordings of adults affected with NT1; however, contrary to what has been previously reported about RBD occurrence in NT1 adult cohorts (Mayer *et al.*, 1993; Dauvilliers *et al.*, 2007*c*; Cipolli *et al.*, 2011), episodes appeared to occur more than once per night. Previous studies in NT1 adults indeed mainly failed to capture episodes during PSG studies (Mayer *et al.*, 1993; Dauvilliers *et al.*, 2007*c*; Cipolli *et al.*, 2011; Nevsimalova *et al.*, 2013),

Table 4 Neurophysiological data in patients with and without complex behaviour during REM sleep

	NT1 with CB in REM sleep (n = 13)	NT1 without CB in REM sleep (n = 27)	P-value
Nocturnal PSG			
SL (min ± SD)	3.1 ± 5.4	4.03 ± 4.70	ns
REM sleep latency (min ± SD)	45.4 ± 66.4	47.07 ± 76.50	ns
TST (min ± SD)	460.1 ± 54.2	447.80 ± 49.70	ns
WASO (min ± SD)	43.4 ± 50.4	57.39 ± 43.14	ns
Sleep efficiency (% ± SD)	90.5 ± 8.8	87.54 ± 8.28	ns
N1 (% ± SD)	10.2 ± 5.0	10.7 ± 5.7	ns
N2 (% ± SD)	36.7 ± 9.5	40.3 ± 10.4	ns
N3 (% ± SD)	29.4 ± 13.4	25.2 ± 10	ns
REM (% ± SD)	23.7 ± 6.2	23.6 ± 6.4	ns
PLMs index (mean values ± SD)	5.2 ± 6.8	8.6 ± 8.3	ns
Atonia index (mean values ± SD)	0.6 ± 0.2	0.7 ± 0.1	0.003
Stage transitions			
tWSi (mean values ± SD)	7.9 ± 3.4	7.9 ± 3.4	ns
tWNRRi (mean values ± SD)	10.8 ± 2.9	11.4 ± 3.6	ns
tWN1NRRi (mean values ± SD)	15.1 ± 3.2	15.9 ± 4.4	ns
MSLT			
Sleep latency (min ± SD)	3.6 ± 2.5	4.5 ± 4.5	ns
SOREMP (n ± SD)	4.5 ± 0.9	4.3 ± 0.9	ns

CB = complex behaviours; ns = non-significant; PLM = periodic limbs movements; SOREMP = sleep onset in REM sleep period; tW-Si = transition index between wakefulness and sleep; tW-NR-Ri = transition index between wakefulness, NREM and REM sleep; tN1-NR-Ri = transition index between wakefulness, N1, N2, N3 and REM sleep.

Table 5 Clinical and demographic data in patients with and without complex behaviours during REM

	NT1 with CB in REM sleep (n = 13)	NT1 without CB in REM sleep (n = 27)	P-value
Age at evaluation (years ± SD)	11.2 ± 2.2	12.1 ± 2.4	ns
Disease duration (years ± SD)	2.1 ± 1.6	2.2 ± 1.4	ns
Age at onset (years ± SD)	9.1 ± 2	9.9 ± 2.4	ns
Positive family history for sleep disorders (%)	15.4	14.8	ns
Sleep paralysis (%)	30.8	37	ns
Hypnagogic hallucinations (%)	46.2	40.7	ns
Impaired nocturnal sleep (%)	92.3	18.5	<0.0001
Cataplectic face/status cataplecticus (%)	84.6	11.1	<0.0001
Adapted ESS (mean values ± SD)	16.2 ± 3.9	13.9 ± 3.4	0.048
Orexin levels (pg/ml; mean values ± SD)	13.7 ± 23.2 (n = 13/13)	21.8 ± 28.8 (n = 24/27)	ns

CB = complex behaviours; ESS = Epworth Sleepiness Scale; ns = non-significant.

speculating that RBD in NT1 is different from idiopathic RBD or RBD due to synucleinopathies (Iranzo *et al*, 2009; Oudiette *et al*., 2012), hence mirroring the levels of the higher atonia index (Dauvilliers *et al*., 2007*c*; Ferri *et al*., 2008*a*). In children, however, the picture seems to be quite different. It is known that all types of body movements during sleep (Fukumoto *et al*., 1981), along with the number of phasic muscle twitches during REM sleep (Liefting *et al*., 1994) are higher in infants and decrease with age, in agreement with the REM atonia index, found to be decreased in preschool age and preadolescent age when compared to young adulthood (Ferri *et al*., 2012*a*). In NT1 children, the derangement of the hypocretinergic network (Chase, 2013; Hu *et al*., 2015), might further enhance this physiological bent for night-time movements, as detailed below.

We did not systematically assess the mental content of these behaviours; however, the sub-cohort of patients that were questioned about their dream content at the end of the MSLT naps either denied being asleep or reported content not always congruous with the movements. This may be related to the marked instability of sleep dynamic with an increase in time spent in 'ambiguous-intermediate sleep-covert REM' (Lairy *et al*., 1967; Mitchell and Dement, 1968; Schwartz *et al*., 1968; Cadilhac *et al*., 1973; Passouant *et al*., 1973; Montplaisir 1975). Mental activity resulting from intermediate sleep has been reported to be less hallucinatory and bizarre when compared to that of full-blown REM sleep (Nielsen *et al*., 2000), thus reflecting the twilight neurophysiological state, with admixture of mentation in between REM and NREM mentation. Some denied being asleep, indicating that self-reflective awareness, as already suggested (Terzaghi *et al*., 2009; Mazza *et al*., 2014), might be impaired, and corroborating the idea of a dissociated state of mind too (Antelmi *et al*., 2016). We must acknowledge, however, that dissertations on that matter may only be speculative here, as the dream recall is available only for a small portion of patients and patients have not been questioned after forced awakenings from REM sleep (Valli *et al*., 2015).

The PLM index was significantly higher in NT1 children, when compared to healthy controls. This feature has long been reported in NT1 adults (Dauvilliers *et al*., 2007*b*), but less investigated in children (Vendrame *et al*., 2008; Jambhekar *et al*., 2011; Ferri *et al*., 2012*b*) and confirms that motor dyscontrol is not restricted to REM sleep.

Finally, even if NREM parasomnia is reported to be frequent in narcoleptic children (Mayer *et al*., 1993; Frauscher *et al*., 2011), we could document this disorder only in a single NT1 patient. This might be related to the fact that NREM parasomnias are not an every-night phenomenon and therefore they may be more difficult to capture during a single night recording (Kotagal, 2009).

NT1 patients with and without complex behaviours during REM sleep

When comparing NT1 patients with and without complex behaviours during REM sleep, the strongest neurophysiological marker able to discriminate between the two groups was the REM atonia index, which was significantly decreased in those having a complex behaviour during REM sleep.

REM sleep without atonia has been previously reported in adults to correlate (Knudsen *et al*., 2010) or not (Schenck and Mahowald, 1992) with abnormal motor activity during night-time. On the other side, REM sleep without atonia has been reported to correlate with lower orexin levels (Knudsen *et al*., 2010). In our children, even if orexin levels tended to be lower in patients with complex behaviours when compared to those without, the difference did not reach statistical significance. Therefore, it seems that other factors, over and above the loss of orexin, may play a role in the impaired motor pattern during REM. However, the result may also be related to the fact that orexin levels are very low in all the patients and therefore there might be a floor effect.

NT1 children with complex behaviours in REM sleep had also significantly increased cataplectic face/status cataplecticus during daytime, implying the presence of a 24-h motor dyscontrol. This could be related to the knock-out of the hypocretinergic system orchestrating motor control during wakefulness and sleep (Chase, 2013; Hu *et al*., 2015), by promoting motor neuron discharges during wakefulness while reducing motor activity during REM (Yamuy *et al*., 2010). Indeed, the acute derangement of this network occurring in a brain much more prone to plastic changes may reputedly render differently from what we see in adults and in the stable chronic course of the disease. In this view, complex behaviours observed during REM sleep might represent the sleep-related facet of the state dissociation emerging from wakefulness (i.e. cataplectic face-status cataplecticus).

Sleep transitional indexes even confirming to be increased in children with NT1 did not distinguish between the two groups (i.e. patients with and without motor dyscontol during sleep). This may be due to the fact that abnormal sleep dynamics are even subtler, as episodes emerge from a disassociated REM (lack of atonia, increased phasic activity, increased alpha activity and bursts of theta waves). Presence of indeterminate, unstable or ambiguous sleep indeed has been reported as far back as a neurophysiological tell-tale of narcolepsy (Lairy *et al*., 1967; Mitchell and Dement, 1968; Schwartz *et al*., 1968; Cadilhac *et al*., 1973; Passouant *et al*., 1973; Montplaisir, 1975) and lately elegantly corroborated by Diniz Behn *et al*. (2010), showing the sleep instability in a murine model of narcolepsy by means of a state space analysis of the EEG signals.

Therefore, the standard 30-s scoring may miss some aspects of this polygraphic dissociation.

It is important also to point out that children with complex behaviours during REM sleep, despite a comparable sleep stage architecture, have more subjective complaints of excessive daytime sleepiness and impaired nocturnal sleep. This further suggests that current standard scorings cannot capture the complex dynamics of abnormal sleep in dissociated states of being (Antelmi *et al.*, 2016), but also points to the importance of treating these behaviours to face the patient complaints.

Conclusion

Our study points to a relatively severe motor dyscontrol during sleep in children with NT1, probably more severe than that reported to date in NT1 adults. This motor instability may emerge from wakefulness, with the already described 'status cataplecticus' but also from sleep, with complex motor behaviours occurring in REM sleep. The marked motor instability might be related to the acute derangement of the hypocretinergic system. The decreased REM atonia index seems to be the neurophysiological marker of the increased motor and behavioural activity during REM sleep. Motor instability occurring during sleep significantly affects subjective complaints of impaired nocturnal sleep and of excessive daytime sleepiness in our cohort. It remains to assess whether acting on nocturnal sleep with drugs able to stabilize sleep in NT1 patients (e.g. sodium oxybate) may, in turn, decrease the abnormal motor activity and result in improvement of daytime subjective complaints.

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Conflicts of interest

G.P. participated in advisory board of UCB pharma, Jazz pharmaceuticals and Bioproject.

Supplementary material

Supplementary material is available at *Brain* online.

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