Sleep Medicine Reviews 38 (2018) 70–85

Contents lists available at ScienceDirect

Sleep Medicine Reviews

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

CLINICAL REVIEW

The clinical spectrum of childhood narcolepsy

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ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form
13 April 2017
Accepted 19 April 2017
Available online 8 May 2017

Keywords:
Narcolepsy
Cataplexy
Movement disorder
Obesity
Precocious puberty
Treatment

SUMMARY

Narcolepsy type 1 is a life-long, severe, multifaceted disease often arising in childhood or adolescence. Beyond the classical symptoms (excessive daytime sleepiness, cataplexy, hallucinations, sleep paralysis and nocturnal fragmented sleep), metabolic, endocrinological, psychiatric and psychosocial aspects must be considered. Despite the increased awareness after H1N1 pandemic influenza and vaccination, narcolepsy is still misdiagnosed and unrecognized. The peculiar presentation of symptoms in narcoleptic children could in part explain the misdiagnoses. Excessive daytime sleepiness presenting as chronic drowsiness or irritability could be stigmatized as laziness or misinterpreted as behavior or inattention disorder. The persistent hypotonia and the complex hyperkinetic movements that characterize cataplexy close to the onset, could be misdiagnosed as a movement disorder or as other neurologic conditions. The consequent therapeutic delay could turn into dramatic consequences. The narcolepsy onset, indeed, is associated with abrupt weight gain and sometimes with precocious puberty that require a prompt recognition and treatment to avoid auxological and metabolic complications. Moreover, narcoleptic children could have behavioral and psychiatric disorders ranging from mood to psychotic ones that need ad hoc management. Accordingly, spreading the awareness outside the sleep specialist community is necessary in order to reduce the diagnostic delay and to obtain prompt and multidisciplinary management.

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Introduction

Excessive daytime sleepiness (EDS), with frequent lapses into sleep during daytime and cataplexy have been far back reported as the key symptoms of narcolepsy [1,2]. Sleep paralysis and hypnagogic/hypnopompic hallucinations complete the former typical disease tetrad [3], along with disrupted nocturnal sleep [4,5].

Narcolepsy is now classified within the central nervous system hypersomnias in narcolepsy type 1 (NT1), characterized by cataplexy and low level of cerebrospinal (CSF) hypocretin (hcrt)-1, and narcolepsy type 2 (NT2) with normal CSF hcrt-1 and without cataplexy [4]. An autoimmune process triggered by environmental factors is the main pathogenic hypothesis for NT1, based on the strong association with human leukocyte antigen (HLA) DQB1*0602 and other genetic features [6]. Higher markers of streptococcal infections close to disease onset and the increased incidence of NT1 following the H1N1 Pandemrix® vaccination and infection [7–10] further point to an autoimmune etiology.

NT2 seems to be less frequent compared to NT1, also, in the pediatric population [11]. Its pathogenesis is still unclear and it is still debated whether it should be considered an incomplete or prodromal form of NT1 [12,13]. The less frequent association with HLA haplotype leaves other pathogenic hypotheses open [11]. As suggested by post mortem studies, NT2 could be due to a partial loss of hypocretin neurons mirrored by normal/intermediate CSF hcrt-1 levels [14].

The dramatic picture of childhood narcolepsy was formerly reported in the early 1900, after the Spanish flu [15], but only recently it has been clarified that narcolepsy onset peaks in the pediatric age [16,17], and that the onset of the disease in children is characterized

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http://dx.doi.org/10.1016/j.smrv.2017.04.003
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Glossary of terms

ADCA-DN	autosomal dominant cerebellar ataxia with deafness and narcolepsy
ADHD	attention deficit hyperactivity disorder
BMI	body mass index
CBCL	child behavior checklist
CNS	central nervous system
CPRS-R	Conners parents rating scale revised
CSF	cerebrospinal fluid
DNMT1	DNA methyl-transferase type 1
EDS	excessive daytime sleepiness
EMA	European medicines agency
ESS	Epworth sleepiness scale
FDA	food and drug administration
GABA-b	gamma-aminobutyric acid b
GnRH	gonadotropin releasing hormone
HLA	human leukocyte antigen
HSAN 1E	hereditary sensory and autonomic neuropathy
ICSD3	international classification of sleep disorders third edition
IvIG	intravenous immunoglobulin
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
NMDA	n-methlyl-d-aspartate receptor
NPC	Niemann-Pick disease type C
NREM	non rapid eye movement
NT1	narcolepsy type 1
NT2	narcolepsy type 2
PANDAS	pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
PDSSE	pediatric daytime sleepiness scale for EDS
PSG	polysomnography
RBD	REM sleep behavior disorder
REM	rapid eye movement
ROHHADS	rapid onset obesity with hypothalamic dysfunction, hypo-ventilation, and autonomic dysregulation syndrome
SOREMPs	sleep onset REM periods
TH1	T helper 1
US	United States

by a dramatic degree of severity along with a corollary of behavioral, metabolic, endocrinological, and mood disorders [18–20]. This clinical picture gradually turns into the most typical adult form [22]. This may in part explain why the correct diagnosis is still established with years of delay [17,23,24]. Nowadays, the recognition of the "rare disease" status to narcolepsy, the introduction of new drugs especially registered for narcolepsy, the discovery of the hypocretin system and its association with narcolepsy have led to an increased interest in and awareness of narcolepsy. As a result, the shortened diagnostic delay has offered the possibility to observe children close to the disease onset and to start noticing peculiar clinical features at this stage of the disease [18,22,25,26].

Epidemiology

The prevalence of narcolepsy with cataplexy varies by ethnic group and geographic region from 0.23 per 100,000 people in Israel to 160 per 100,000 people in Japan, with an overall geographic prevalence of 30 per 100,000 people. The difference in global prevalence of narcolepsy generally reflects the different distribution of HLA-subtype DQB1*06:02 rate [6]. According to retrospective studies, the onset of narcolepsy occurs with bimodal distribution with two peaks at the age of 15 and 35 y [16,17], and until 2010 it was reported as rare before 10 y of age.

In 2000–2010 the pooled incidence of narcolepsy in children aged 5–19 y from six European countries was estimated to be 0.93 per 100.000 person-years [6] and after the mass campaign vaccine in Sweden and in Finland, a 17-fold increase in narcolepsy incidence in subjects below the age of 17-years-old was observed (raising from 0.31 to 5.3 to 100.000). An increased incidence has been observed also in unvaccinated prepubertal children following the H1N1 epidemic in China [6,27,28].

Neurological aspect

Although EDS is the core narcoleptic symptom at any age [18,22,29,30], its identification in children may be challenging.

In children, sudden, irresistible brief sleep attacks occurring in monotonous situations but also in inappropriate settings may overlap with chronic drowsiness [31,32]. Other EDS manifestations are the reoccurrence of daytime postprandial napping or the elongation of nocturnal sleep, mainly associated with the need to anticipate night sleep [33] or paradoxical irritability and motor restlessness [8,22], hence mimicking an attention deficit hyperactivity disorder (ADHD) [34,35].

Cataplexy, as well, in childhood may differ from the transient loss of antigravity muscle tone clearly evoked by strong emotions described in adult patients. In children close to disease onset, cataplexy often presents as a complex movement disorder, with mixed pattern of negative and active phenomena [18,25]. The negative component consists in a subcontinuous hypotonic condition, without a clear link to emotional stimuli and characterized by a general floppy aspect, altered gait, and in about one third of the patients by frequent and very brief (few seconds) falls to the ground [18,25], and a typical "cataplectic facies", with facial hypotonia, bilateral ptosis, mouth opening and tongue protrusion [18,25,26] (Fig. 1). These signs are further enhanced by emotional stimulation [18,25]. At the same time, hyperkinetic features involving mainly the facial district such as perioral/tongue movements, facial grimacing, eyebrow raising, but also the other body areas (stereotyped motor behaviors, and dyskinetic/dystonic movements) are evident and further enhanced by emotional stimulation proving a relation with cataplexy [18]. The latter positive component is more evident in patients with a recent streptococcal infection [18,36]. Therefore, close to disease onset, a clear link with emotions could be absent while, and according to follow-up studies, this "spontaneous" cataplexy gradually disappears turning into the picture of classical cataplexy linked with emotional stimulation [18,22,25].

Along with EDS and cataplexy, the clinical picture of narcolepsy includes multimodal hallucinations at sleep onset or offset (hypnagogic or hypnopompic, respectively), sleep paralysis, disrupted night sleep continuity, and both REM and NREM sleep related parasomnia comorbidities. The prevalence of hallucinations and sleep paralysis widely ranges from 39% [37] to more than 50% [3] and from 25% [38] to 74% [38,39] respectively. Indeed, children could have difficulties distinguishing them from dreaming or could be afraid to report these symptoms [40] (Fig. 2).

Nocturnal sleep is fragmented by frequent awakenings and oneiric activity is particularly vivid [41] (Fig. 3). Difficulties in morning awakening or irritability/aggressive behavior upon

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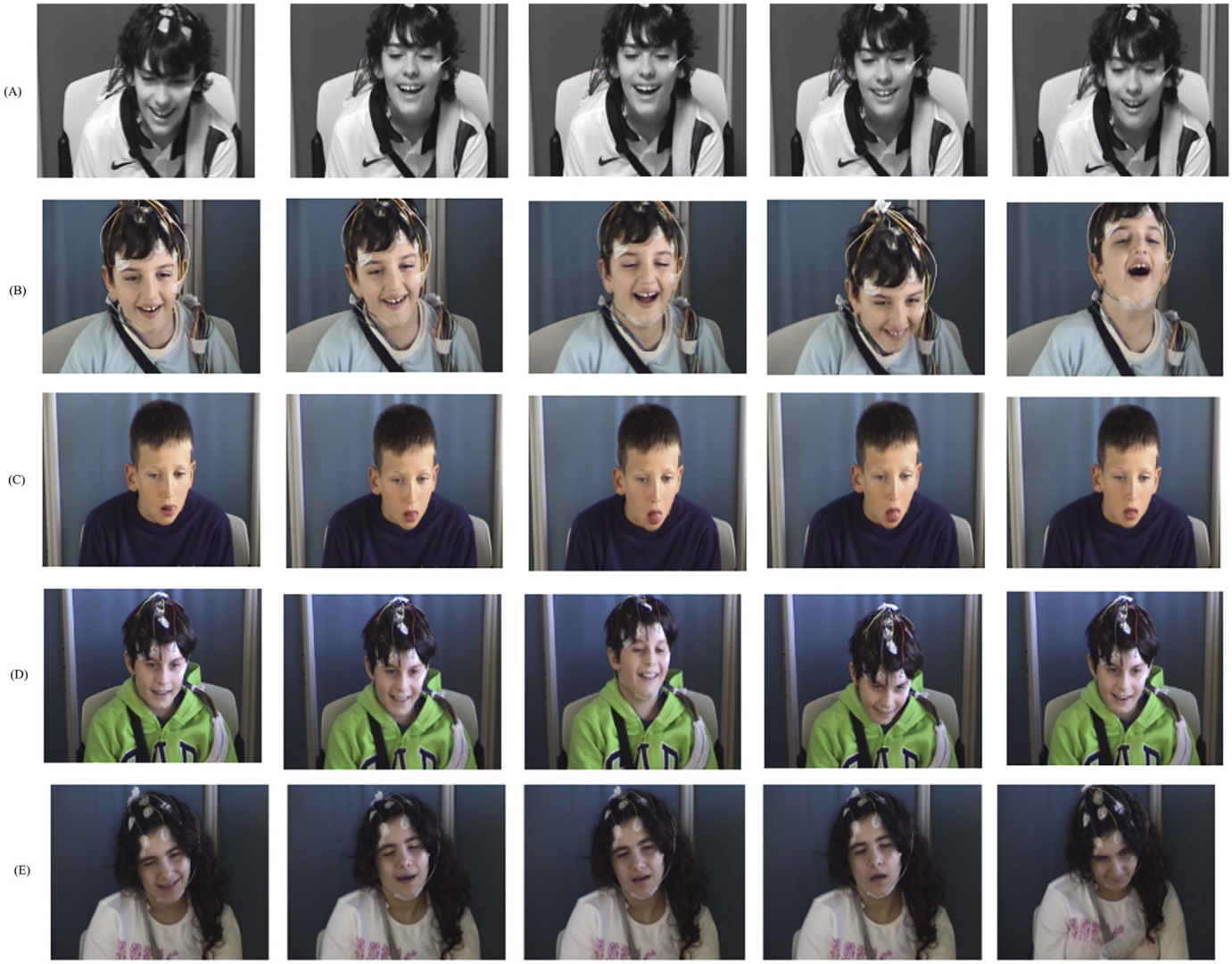

Fig. 1. Facial aspects (cataplectic facies) and complex movements of catapletic attacks close to disease onset (A) Facial weakness, onward head and trunk flexion with active shoulder raising; (B) head drop and opposing neck hyperextension viewing (when looking at something); (C) perioral movement with mouth opening and tongue protrusion; (D) bilateral ptosis with active eyebrow raising and head swaying; (E) generalized facial hypotonia with bilateral ptosis, asymmetrical facial contraction.

awakening (also from naps), especially close to narcolepsy onset, are frequently reported by parents [33,42].

REM sleep behavior disorder (RBD) is also frequent in narcoleptic patients [43,44]. In narcoleptic adult patients, significant clinical symptoms of RBD have been reported to occur in 36–71% of cases [45], and in NT1 children may also be the heralding symptom of the disease [42]. Although the few case-reports of RBD in NT1 children may give the impression of a rare phenomenon [46,42], available

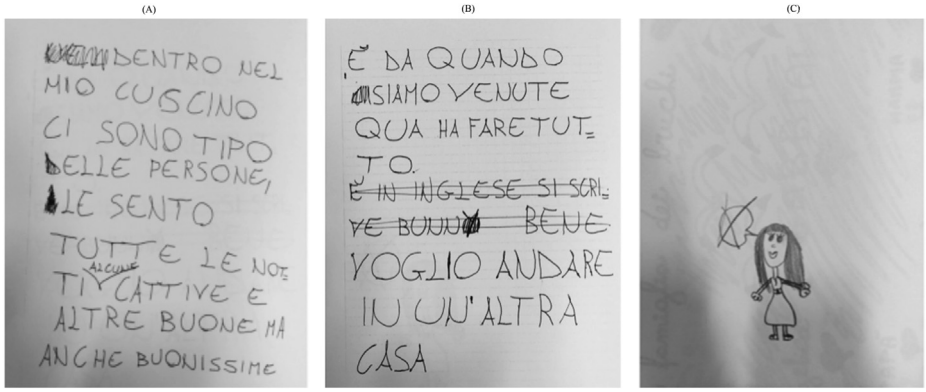

Fig. 2. Notes of a narcoleptic child: (A) «Inside my pillow there are some people, I can hear/feel them every night: some of them are bad, some good, other even very good»; (B) «it all started when we moved here… I want to move to another house». (C) Drawing of the same child showing her embarrassment when speaking of her hallucinations.

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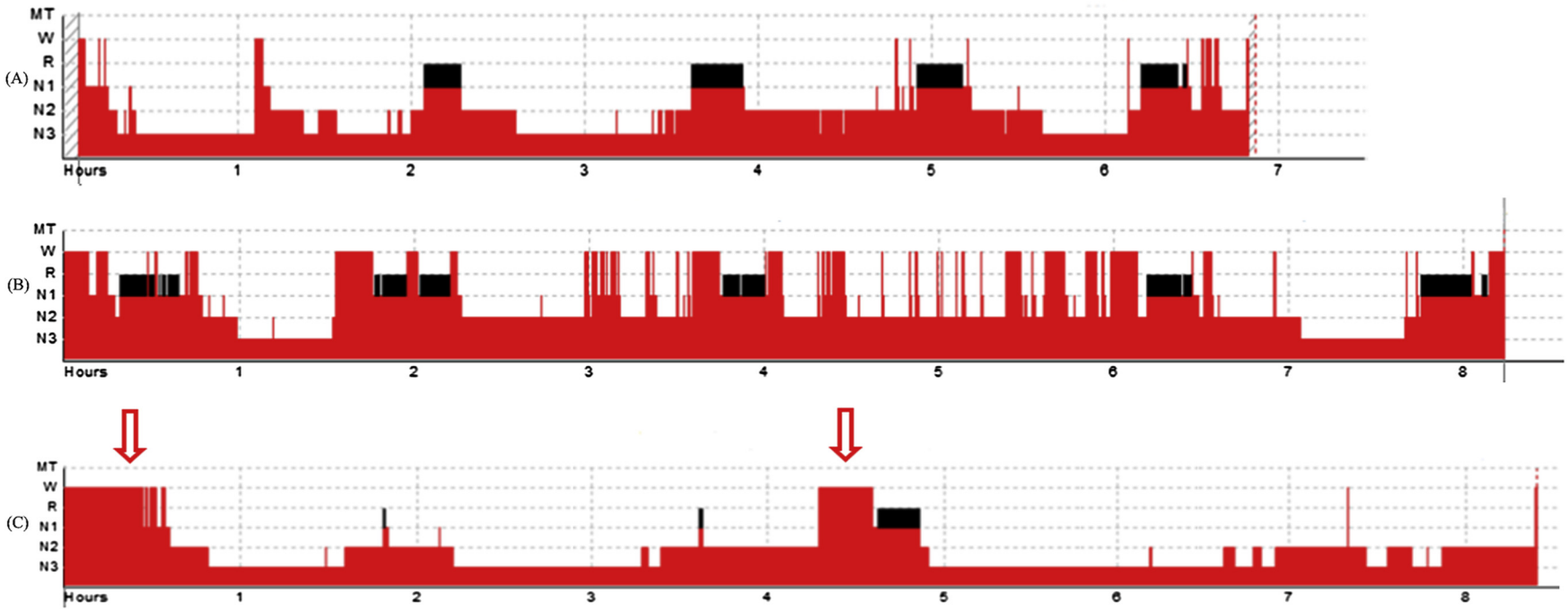

Fig. 3. Nocturnal polysomnographic recording of a healthy child (A), a drug-naive 7-year-old narcoleptic child before (B) and during (C) sodium oxybate treatment. (A) Nocturnal sleep of a healthy peer showing the regular sleep cycles. (B) Fragmented nocturnal sleep and sleep onset rapid eye movement period (SOREMP). (C) Dramatic improvement of nighttime sleep and SOREMPs disappearance after 1 mo of stable dose of sodium oxybate. The arrows indicate the drug intake.

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polysomnographic (PSG) studies reported the same frequency of RBD episodes in both NT1 children and adults (nearly 30% in the reported cohorts) [47,48].

NT1 in children: the multifaceted disease

Media campaigns on narcolepsy have significantly fostered the awareness of this disease and shortened the time gap to diagnosis. However, diagnostic delay is still an issue, likely and partly related to the masked and peculiar presentation of the classical tetrad of narcoleptic symptoms at disease onset [23].

EDS is frequently under-recognized or overlooked as important symptom by pediatricians, who are mainly trained in focusing on behavioral and attention disorders [35]. As a result, EDS is overlooked or mislabeled as laziness or inattention or misdiagnosed, when associated with irritability and hyperactivity, with other behavioral conditions such ADHD and movement disorders [49]. Yet, cataplexy is frequently mislabeled as a "functional" disorder, a motor disorder, a muscular disease or as an epileptic condition. Hallucinations and nightmares may also be mislabeled as psychological/psychiatric problems.

All these misdiagnoses are extremely harmful, causing diagnostic delay, inappropriate treatments, stigmatization, and affecting social and academic development [30], with detrimental effect on the psychosocial development of the children [31].

Noteworthy, since disease onset, NT1 impacts on metabolic and endocrinological system presenting with rapid and dramatic changes in the patient's physical aspect. Capturing these signs, namely the abrupt weight gain [19,50,51], the appearance of early signs of puberty [19,30,51,52], might give additional clues and increase the suspicion of NT1. Psychiatric comorbidities are also reported [21,53,54]. A recent study based on the Danish National patient registry confirmed that young narcoleptic patients showed more significant comorbidities compared to healthy control. The observation of these symptoms by a non-sleep specialist often occurs before the diagnosis of narcolepsy, confirming the risk to overlook narcolepsy [55]. Therefore, spreading the awareness of narcolepsy outside the restricted community of sleep specialists is mandatory. This, indeed, could reach the real opportunity to impact on diagnostic delay, as early diagnosis and appropriate management remain the main tools to achieve appropriate school learning and to prevent the development of psychosocial difficulties [17,31,56].

Once the diagnosis is suspected, it is important also to refer the patients to specialized centers for objective confirmation. Childhood NT1, indeed, is a complex disease, which requires an orchestrated interaction among different medical specialists, i.e., neurologists, endocrinologists, pediatricians and psychologists and this can be guaranteed only by a tertiary care center with expertise able to call the shots of all these different figures.

The neuropsychiatric features

Attention-deficit/hyperactivity disorder

Although narcolepsy symptoms display a clear overlap with ADHD symptoms, the presence of ADHD in narcolepsy has been poorly investigated, and the sparse findings are inconsistent. A recent cross-sectional study highlighted an over representation of ADHD symptoms in childhood NT1 patients [35] and similar results have been reported even when the presence of childhood ADHD symptoms has been retrospectively investigated in adult cases [49]. Psychostimulants are commonly used for the treatment of both ADHD and narcolepsy and therefore, these treatments could further challenge the correct diagnosis. Noteworthy, an unclear responsiveness to ADHD symptoms was evidenced in narcoleptic children, suggesting a different underlying physiopathology [17,35].

Anxiety disorder

A high level of anxiety, both general and specific, and in particular social phobia and panic attacks [54,57] were reported in children with narcolepsy, a finding that parallels the association disclosed in adults [21,58,59]. The experience of frightening hallucinations exacerbated by the childhood difficulty of discerning them from reality and the shame from unexpected sleep or cataplectic falls may represent a stressful event in a large proportion of predisposed narcolepsy subjects [59]. However, a direct role of the altered hypocretinergic transmission is also possible [60].

Mood disorder

Narcoleptic children have higher scores of internalizing problems, in particular, anxiety/depressive, withdrawal/depressed in the Child Behavior Checklist (CBCL) and worse scores in the child depression inventory and in the Conners parents rating scale-revised (CPRS-R) [56,57,61]. In a large cohort of 88 pediatric narcoleptics, high levels of depressive symptoms were reported in 25% of the patients, and girls older than 10 y appeared to be more vulnerable. Depressed children have a poor perception of their symptoms, they scored high on the subjective scale of fatigue, sleepiness and insomnia [61], and poor on the subjective perception of attention deficits [62] with a great impact on quality of life [56].

Overall, even if mood disorders are consistently reported, their primary nature is debated because of the overlap between depressive and narcoleptic symptoms, i.e., fatigue, disrupted nocturnal sleep, impaired attention, weight changes, especially if investigated only by self-reported questionnaires [21,58,59].

Intriguing mice studies revealed a specific mood modulation in pro-depressant and anti-depressant ways on the basis of the subtype of hypocretin receptors activated, although controversial results have been reported in human studies assessing hypocretin CSF levels and mood disorders [63].

Schizophrenia

Hallucinations are a common feature of both narcolepsy and schizophrenia. However, hallucinations have strong qualitative differences in narcolepsy versus schizophrenia, being mostly sleep-related vs during wakefulness and multimodal versus auditory, in the former and in the latter, respectively. Moreover, third person and commenting voices, delusions and replacement of will are typical of schizophrenia rather than of narcolepsy [40,64–66]. The co-occurrence of the two pathologies was also reported [67–69], representing a challenge for diagnosis but also for treatment, as in these cases poor responsiveness to antipsychotic treatments has been reported [70]. Insertion, broadcast and block of thought, delusions and replacement of will represent red flags that suggest the comorbidity with schizophrenia [66]. Recently, in two large European cohorts, a retrospective study reported a 1.8% frequency of comorbidity with psychosis-like schizophrenia, mainly developed within 3 y after narcolepsy onset and persistent over the life course [71]. In half of the patients, the psychotic onset followed or was worsened by psychostimulants [72].

A study investigating a large cohort reported that 9.8% of narcoleptic children developed schizophrenia after the onset of narcolepsy, but persisting even after the stopping of psychostimulants. In this cohort, a higher body mass index seemed to correlate with the development of schizophrenia [70]. However, larger epidemiological studies are needed to investigate the occurrence of schizophrenia in NT1 children.

Cognitive aspects

NT1 patients have poor performances versus controls in divided attention, vigilance [73], executive functions and decision-making

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[74,75]; an impairment of verbal comprehension and working memory was also demonstrated. The data are not homogeneous and a specific cognitive profile has not been identified [57,76]. Narcoleptic children have normal intellectual abilities and the discordant results might be linked to EDS and to the modality of administration of the tests (poor scores reported from prolonged and repetitive tasking) [77], highlighting a certain central role of sleepiness on cognitive dysfunction [78]. Indeed, the presence of psychiatric comorbidities seems to be a risk factor for poorer cognitive functioning [54].

A recent functional brain image study in young narcoleptic patients reported an alteration in brain metabolic activities: compared to controls, patients have a significant hypometabolism in different frontal lobe areas, correlating with poor neurocognitive testing results and major sleepiness [79].

Finally, few studies reported impairments on multiple domains of cognition also in NT1 children [62,47,75], but these data need to be confirmed in controlled and larger case series.

The endocrinological features

The association of obesity and childhood narcolepsy was first reported by Daniels [80]. Nowadays, weight gain, obesity, type 2 diabetes and precocious puberty are well-known features of childhood narcolepsy, being replicated in different case series [19,51,52,80–82]. The studies in children suggest that a sudden increase in weight occurs close to symptoms' onset.

Since the hypocretin system is involved not only in sleep/wake regulation, but also plays a role in modulating feeding behaviors, reward, energy homeostasis, and in hypothalamus-pituitary regulation [83], overweight/obesity could also be the final result of multiple alterations, including endocrinological abnormalities but also sleep related eating disorder [84] and other eating disorders (e.g., bulimic attacks) [85]. Indeed, overweight/obesity is a frequent, but not invariable, finding in NT1 thus not solely due to hypocretin deficiency. Interestingly, a study reported treatment with sodium oxybate to be efficacious in restoring pre-morbid BMI (body mass index) z-score level [51] (Fig. 4).

Overlap with additional autoimmune disorders?

Several autoimmune diseases may coexist in individuals and families, favoring a concept of shared autoimmunity. A recent case–control study found a higher frequency of autoimmune diseases in NT2 adults (13.2%) compared to controls (3.4%) without any increase in other autoimmune diseases in NT1 [86]. The absence of correlations between the autoimmune comorbidity and social-demographic, clinical and sleep characteristics, contrasts to what reported by a recent multicenter retrospective pediatric study [87], in which the co-presence with allergic condition was found in 48.7% of NT2 patients and in 21.1% of NT1 cases.

Secondary narcolepsy

Several acquired, developmental, and inherited diseases involving the hypothalamus can affect the hypocretin system leading to narcolepsy. Conditions like brain tumors, head trauma, diffuse axonal injury [88], lymphocytic leukemia and acute non-lymphocytic leukemia, central nervous system infections, Guillain–Barré syndrome [89,90], acute disseminated encephalomyelitis [91], multiple sclerosis, Devic's neuromyelitis optica, anti-Ma2 and anti NMDA (n-methlyl-D-aspartate receptor) encephalitis [92,93], neurosarcoidosis [94], brain irradiation [95] have all been reported as rare causal factors for secondary narcolepsy.

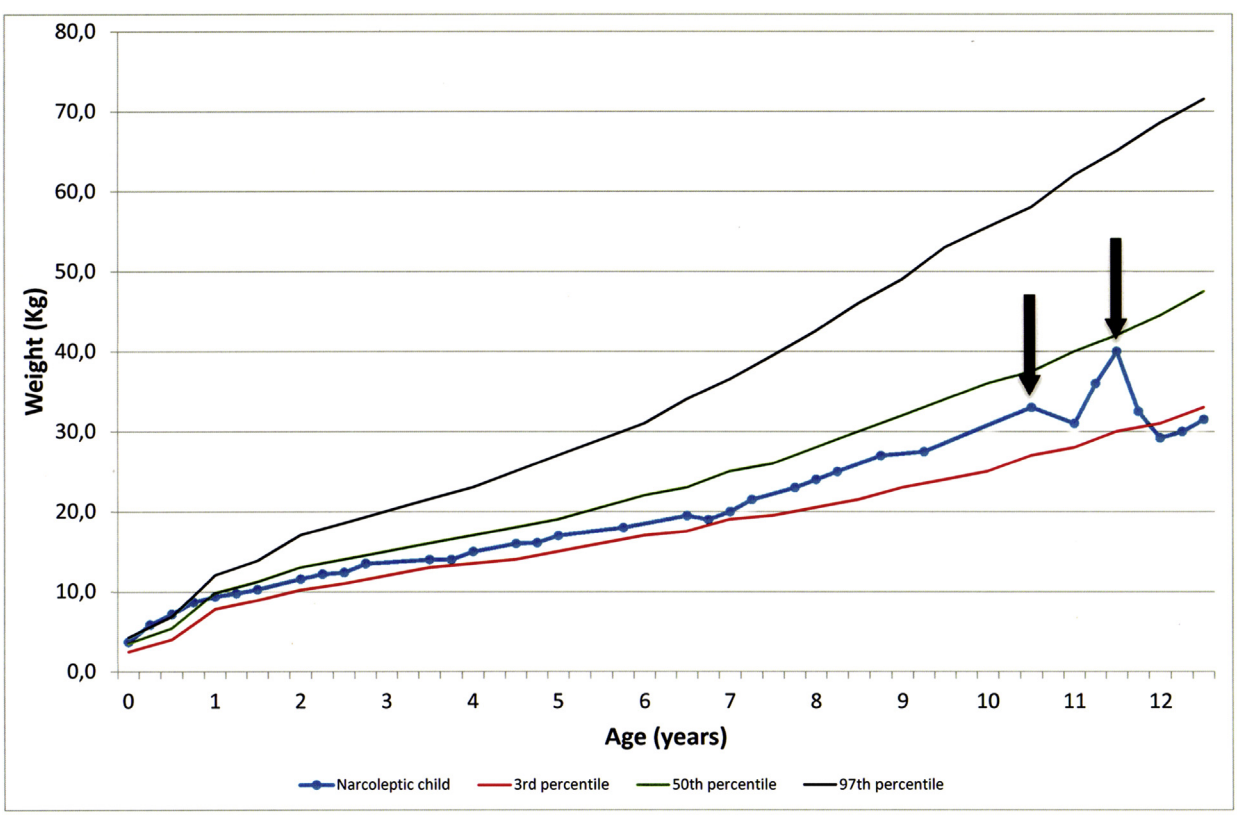

Fig. 4. Weight curve of a 12.5-year-old boy with NT1 showing a rapid 10 kg weight gain from the age of 10.5 y, corresponding to the disease onset (left arrow), and the weight loss following sodium oxybate (SO) treatment (right arrow).

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Low CSF hcrt-1 level and EDS and/or cataplexy have been also reported in rare inherited diseases.

Cataplexy, labeled as "gelastic cataplexy", is a typical sign of Niemann-Pick disease type C (NPC), although rarely described as the first neurological symptom [96], and it is found in 5–30% of NPC patients [97], along with reported low CSF hcrt-1 levels [96,98–102].

Hereditary sensory and autonomic neuropathy (HSAN1E) and autosomal dominant cerebellar ataxia with deafness and narcolepsy (ADCA-DN), linked to mutations or deletions in DNA methyltransferase type 1 (DNMT1) gene, present with narcolepsy with or without cataplexy, optic neuropathy, deafness, lower limb edema and small fiber polyneuropathy [103,104]. Although the onset has been reported mainly in adulthood, recently a novel mutation in DNMT1 gene, characterized by hereditary sensory and autonomic neuropathy, cataplexy, and cerebellar atrophy has been reported in an 8-year-old boy [105].

EDS [97,106–109], cataplexy [110–112] and also CSF hcrt-1 deficiency [97,113,114] have been reported in Prader-Willy syndrome, indicating a wide hypothalamic dysfunction

Also, inherited malformations such as holoprosoncephaly and corpus callosum agenesis may be associated with narcolepsy and cataplexy and intermediate CSF hcrt-1 [115,116]. The rapid onset of obesity with hypothalamic dysfunction, hypo-ventilation, and autonomic dysregulation syndrome (ROHHADS) is a rare pediatric disease often associated with neural crest tumors, and narcolepsy with cataplexy and undetectable CSF hcrt-1 have been reported among its features [117,118].

Finally, as regards H1N1-related narcolepsy, comparative studies with sporadic cases show a homogeneous phenotype with slight differences in clinical and polysomnographic features, greatly related to the timing of disease onset and medical referral [119]. H1N1–vaccination-related narcolepsy patients have a short diagnostic delay [120], more fragmented nocturnal sleep [119] a short sleep latency [120,121] and less periodic leg movements during sleep [122]. Interestingly, the hyperkinetic component of cataplectic attacks is more evident in non-vaccinated cases, suggesting different environmental factors, as previously shown in narcoleptic patients with a recent streptococcal infection [18].

In other inherited diseases narcolepsy and cataplexy have not been formally recognized, although key-disease symptoms may by reminiscent of NT1. Indeed, in Angelman syndrome, a maternally transmitted neurogenetic disorder, frequent smiling and laughing have been regarded as a disease hallmark. Frequently, these episodes are associated with brief loss of postural tone with a craniocaudal progression and preserved consciousness of non-epileptic nature [123].

Sleep disorders including EDS, central and obstructive sleep apnea, periodic leg movements, nocturnal and diurnal REM sleep dysregulation are frequently reported in myotonic dystrophy, where, despite the several associated conditions, EDS seems likely associated with a primary dysfunction of sleep-regulating areas of the central nervous system [124], as corroborated by the reported sleep onset REM periods (SOREMPs) (i.e., rapid eye movement sleep onset) and low CSF hcrt-1 (rarely lower than 110 pg/mL) [113,114,125,126].

Characteristic episodes of loss of muscle tone with preserved consciousness are frequently reported [127–129] also in Coffin-Lowry syndrome and Moebius syndrome, but CSF hcrt-1 measurement and data on EDS are missing [130–132].

Etiology

NT1 is caused by the destruction of over 90% of hypocretin neurons, with low or undetectable levels of CSF hcrt1 [133,134]. The selective destruction of this neuronal population supported an autoimmune hypothesis. An association with the human major histocompatibility (MHC) class II antigen DQB1*0602 was first reported in 1983 by Juji and colleagues, as more than 98% of patients with narcolepsy and cataplexy are DQB1*0602 positive [135,136]. A recent European study confirmed that this specific haplotype is the principal risk factor with an odds ratio 1:251 [136]. The presence of the DQB1*0602 haplotype is strongly associated with cataplexy and hcrt-1 CSF level under 110 pg/ml; very rare cases of HLA negative and hypocretin deficiency are reported [137].

Positive associations with smaller effect size have been established by genome-wide association studies with several immune system related loci, in Asian and European populations (polymorphism in the T cell receptor alpha chain, OX40L gene variant, cathepsin H, purinergic receptor subtype 2Y11 variant) [23,138–140].

The seasonal fluctuation of narcolepsy incidence [141], the increased concentration of antistreptococcal antibodies close to the onset [36], the rise in the incidence after the H1N1 infection and vaccination in HLA DQB1*0602 positive subjects, as well as other genetic associations with genes involved in the immune response further support the role of environmental factors as triggers in genetically predisposed individuals for an immune system dysregulation [8,142]. During the H1N1 pandemic between 2009 and 2010 season millions of persons around the world were vaccinated with adjuvanted influenza vaccine Pandemrix®, the most used vaccine in Northern European countries [27,28]. Controlled epidemiological studies conducted in several European countries comparing vaccinated and unvaccinated patients reported a four-to-13 fold increase in narcolepsy risk in children and adolescents who were vaccinated with Pandemrix® [143]. Surprisingly, only very few cases were reported for Arepanrix® used in Canada and Latin America. After the pandemic flu in China a 3.3-fold increase in narcolepsy was reported among unvaccinated children and young adults suggesting a possible association with H1N1 infection itself [10]. However, only a small fraction of infected or vaccinated individuals who carried the HLA DQB1*0602 haplotype developed narcolepsy, suggesting the presence of an underlying autoimmunity booster by environmental factors. The main hypothesis is cross-reactivity between the hypocretin epitopes and virus antigen (hemaglutinin) present in both vaccines or in the H1N1 strain, which can trigger a hypocretin specific T cell reactivity. It remains unsolved whether different processes of vaccine production and different antigenic composition could in part explain the different risk observed in association with Pandemrix® and Arepanrix® vaccinations [8]. A similar mechanism of mimicry between viral peptides and hypocretin and its receptors as a pathogenic mechanism has been recently reported in a case of narcolepsy following yellow fever and tick-borne encephalitis virus vaccination [144,145]. An association of adjuvant component and the specific viral component of Pandemrix® could be considered the trigger of narcolepsy related autoimmunity, since recent meta-analysis confirmed the safety of newly adjuvant and influenza vaccine in children under 10 y [27,146].

The acute and hypothalamus-confined process can explain the difficulty in identifying the immunological mediating mechanism. HLA class II molecules display antigenic peptides to CD4+ T cells, which might imply that narcolepsy is a T cell mediated autoimmune disease. CD4+ T cells reactive towards hypocretin epitopes were found in narcoleptic patients. A possible TH1 polarized immune response has been hypothesized on the basis of CSF cytokines/chemokines levels [147]; moreover, a recent study found increased serum cytokine with pro-inflammatory properties and especially interferon-γ being independently associated with narcolepsy close to disease onset [148]. In addition, a possible role of cytotoxic CD8+ cells as the effector branch of autoimmune destruction was hypothesized on basis of recent animal model study [149].

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Finally, a possible role of auto-antibodies response was suggested by the evidence of elevated titers of anti-tribbles homolog 2 antibodies [150–152] and increased levels of anti-ganglioside GM3 autoantibodies detected in vaccinated narcoleptic children [153].

Differential diagnosis

The peculiar narcolepsy phenotype observed in children challenges a prompt and correct diagnosis. As said, EDS can be misinterpreted as laziness, depression. Hyperactivity is also not rare in hypersomnolent children, suggesting at first a neuropsychiatric disorder. Cataplexy itself near to disease onset can mimic a spectrum of motor disorders, muscle diseases, and neuropsychiatric disorders. The loss of postural control with falls, also in the absence of clear emotional trigger, can mimic epilepsy [154,155] and when coupled with gait instability may point to cerebellar or other central nervous system involvement. The preserved consciousness and the history of episodes triggered by sudden positive emotions should be searched also in patients with spontaneous episodes as tell-tales of cataplexy. The longer duration of the episodes, precipitated by negative thoughts and associated with decreased mood, the preserved ability to communicate are suggestive of functional episodes that can also coexist with true cataplexy [156,157]. A video-polygraphy including electroencephalogram and electromyogram traces may steer toward a proper diagnosis. In children, indeed, video-polygraphic documentation of cataplectic events is quite easy, as hypotonia and hyperkinetic movements mainly involving the facial region are virtually subcontinuous and might be further enacted by emotional triggers.

The unclear emotional linking, the co-occurrence of hyperkinetic or stereotyped movements, the facial involvement, and the presence of psychiatric comorbidities might raise the suspicion of a choreic disorder, in particular Sydenham chorea and other streptococcal-related disorders. Beyond the clinical similarity, the body of evidence strongly suggests a similar autoimmune mechanism: a molecular mimicry mechanism between infection agent and neuronal antigens. The subacute onset and the cardiac involvement on the one side and the presence of obsessive-compulsive or other tic disorders, the relapsing-remitting symptoms' course on the other, respectively for Sydenham chorea and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) can help to distinguish them from narcolepsy [158].

Although the clinical features of encephalitis differ substantially from narcolepsy, the rapid onset of sleep disturbances, the abnormal movements in particular the stereotyped movements, the orofacial dyskinesias, and the occurrence of psychotic symptoms and behavioral alterations are present in both [159]. In encephalitis, the presence of decreased consciousness, severe psychosis or catatonia, frequent seizures, autonomic dysfunction, and severe cognitive impairment allow us to make the differential diagnosis [160].

Overall, NT1 diagnosis requires an instrumental confirmation encompassing the detection of peculiar neurophysiological and/or biological markers (as discussed below).

Diagnosis

A subjective EDS evaluation, albeit not specifically tailored for narcolepsy, can be made by means of severity scales such as a modified version of Epworth sleepiness scale (ESS) or pediatric daytime sleepiness scale for EDS (PDSSE) [161,162], while validated tools to address cataplexy are still lacking [163].

The objective assessment of EDS through an overnight in the polysomnography (PSG) laboratory, followed by daytime multiple sleep latencies test (MSLT) is mandatory for narcolepsy diagnosis and should document short sleep latency and SOREMPs, which are the polysomnographic narcolepsy hallmarks in both children and adults [4]. However, the validity of applying the same criteria and cut-offs to children is still a matter of debate [33,164]. Indeed, no published data defining the baseline MSLT values in children younger than 8-years-old [33,165] are currently available. Indeed, young children may be unable to follow the MSLT procedures, and sometimes deviations from the recommended protocol, such as leaving a parent in the laboratory room, may help the diagnosis. However, MSLT findings in NT1 children around 7 y of age similar to those reported in adults have been published [37,43]. In 2013 the Brighton Collaboration (Narcolepsy Working Group) developed a case definition and guidelines for data collection, analysis, and presentation for the standardized assessment of narcolepsy. Three levels of diagnostic certainty from the highest to the lowest was defined and clinical features separately from children and adults are described, pointing to the atypical features of pediatric cataplexy and indeed proposed to adopt the cut-off of <12 min for pathological sleepiness in childhood cases [19]. However, validated trials aiming to define the MSLT cut-off in children have not been conducted as yet.

In consideration of the high specificity (99%) [113,166] and sensitivity (between 88 and 94%) [113] of CSF hcrt-1 deficiency in the narcolepsy with cataplexy, the international classification of sleep disorders third edition (ICSD3) changed the terminology distinguishing NT1 (with CSF hcrt-1 deficit) and NT2 (with normal CSF hcrt-1 level), highlighting that the presence of CSF hcrt-1 concentration under 110 pg/mL beyond the EDS complaints is sufficient to establish the diagnosis of NT1, potentially substituting all neurophysiological criteria [4].

The CSF hcrt-1 assay with evidence of deficiency in NT1 did not show differences in consideration of age, ethnicity, medication, or sleep deprivation [113], therefore, despite the invasiveness and the low acceptance of the practice, it represents the best available method to achieve the maximum diagnostic certainty especially in those children with non-validated MSLT.

Despite the tight association between NT1 and the presence of HLADQB1*06:02, it has a limited value in narcolepsy diagnosis given its low specificity, but may be useful in false positive clinical and MSLT cases. However, few cases of HLA negative hypocretin-deficient NT1, with severe cataplexy and pediatric onset up to 50%, have been reported [137].

Actigraphic recording in the diagnostic work-up of NT1 have so far been limited to rule out sleep deprivation and circadian rhythm disorders prior to MSLT. However, recent data suggest its possible use as a complementary measure to support the diagnosis in both adults [167] and pediatric NT1 patients [122,168].

Actigraphy might become a promising screening tool and represent a non-invasive approach also to assess treatment outcome (Fig. 5) and prospectively track the disease course, wide-scale epidemiological studies are needed to validate this approach.

Treatment

Behavioral treatment

A good sleep hygiene including maintaining a regular sleep schedule and planned short daytime naps (15–20 min) at least two at lunchtime and during the afternoon are useful to ameliorate daytime alertness and performances, and also the memory consolidation process [169]. In addition, physical activities can also have a stimulating effect.

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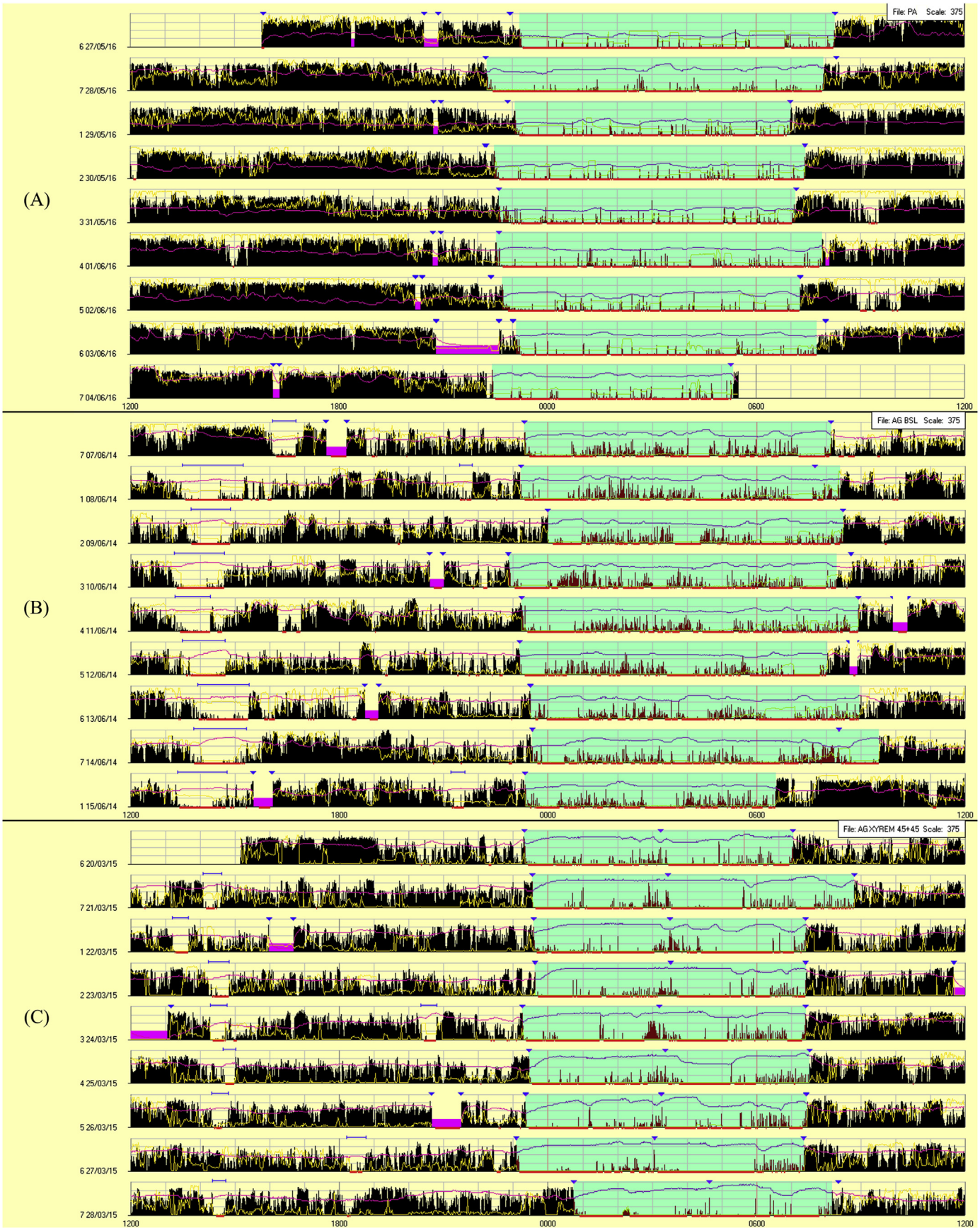

Fig. 5. Actigraphic profiles (A) of a 12-y-old healthy child showing a regular sleep timing and quality, and absence of diurnal sleep episodes (B) of drug naïve 12-year-old NT1 child depicting severe 24-hour sleep-wake disruption with sustained level of motor activity and frequent awakening through the night and daily long-lasting sleep episodes mainly during the postprandial period (C) after six months of stable dose of sodium oxybate (SO) (3.5 g + 3.5 g) showing remarkable improvement of 24-hours profile with sleep quality improvement (two awakenings corresponding to SO administration) and less frequent diurnal sleep.

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Pharmacological treatment

No pharmacological therapy is approved by Food and Drug Administration/European Medicines Agency (FDA/EMA) for narcoleptic patients under the age of 16 y. Adult medications were used off-label in the pediatric population based on empirical data in adult narcoleptics and shared among expert sleep disorders clinicians for children (Fig. 6).

Modafinil, the first approved treatment of narcolepsy, is a non-amphetamine type of wakefulness promoting agent. Its mechanism of action is unknown, reputedly it increases the alertness probably through the selective inhibition of dopamine transporters differing from the amphetamine agent for the absence of catecholaminergic effects [170]. Modafinil is very effective in reducing EDS, but it does not impact specifically on cataplexy and other symptoms [30]. Expert opinion and small case series suggest that modafinil is a safe drug also for children: the most severe side effect being headache (13.7%), irritability (6.5%), and appetite loss (2.2%), while no severe hypersensitivity reactions have been reported so far [171]. According to clinical experience, modafinil is recommended to start with an initial dosage ranging between 100 and 200 mg/d divided into two administrations during the morning hours, and gradually increase according to clinical response until a maximum dosage of 600 mg. However, dosage exceeding 400 mg/d is not commonly used.

Methylphenidate is the second line treatment. Despite the lack of randomized trials for narcolepsy treatment in childhood, it is extensively used in other pediatric conditions. It is effective in reducing sleepiness, increasing sleep onset and REM sleep latency through the inhibition of the dopamine and catecholamine reuptake. Irritability, headache, and loss of weight are the most common side effects. It is extensively used in ADHD with an initial dose of 10 mg, it is recommended that one should not exceed the maximum dosage of 60 mg/d, usually, divided into two or three administrations or provided as sustained-release preparations [172]. The same dosage is usually used also for NT1 in pediatric population.

Sodium oxybate is effective not only on EDS and cataplexy but also on the other narcoleptic features such as disrupted sleep, and obesity [173]. The active metabolite is agonist of gamma-aminobutyric acid B (GABA-B) receptor complex suppressing dopaminergic activity [29]. Its use in childhood narcolepsy is still off-label, although different retrospective studies reported its effectiveness and safety [30,163,174], further supported by ongoing trials. Sodium oxybate is well tolerated and the appearance of side effects can be frequently managed with dose adjustments: more than 60% of patients continue the therapy even after the occurrence in about 50% of the population of some side effects, in particular, enuresis at the beginning; irritability 38–39%, and weight loss, 20–25% [30]. Catathrenia and parasomnias are other possible side effects [175]. A recent study with 72 treated and untreated narcoleptic children in whom anthropometric data were collected at baseline and after 1 y of follow-up indicated a positive effect on weight loss, rather than side effects, especially, in obese/overweight children without compromising their growth [51].

The effective dose varies between 6 and 9 g usually prescribed in two doses at night, but need to be prescribed according to age and weight (Fig. 3).

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor widely used to treat cataplexy even in the pediatric population [25]. The side effects are minor: irritability and weight gain are frequently observed [30]. The initial dose is usually 37.5 mg/d often increased up to 75–150 mg/d.

Selective serotoninergic reuptake inhibitor fluoxetine is used with efficacy and safety to reduce cataplexy severity in children. Doses range from 10 to 40 mg/d [29].

Pitolisant is a wake-promoting agent recently approved by the EMA for the treatment of EDS in narcoleptic patients. It acts as selective H3 receptor inverse agonist and activates histamine neurons. It has been demonstrated that pitolisant significantly decreases EDS versus placebo in narcoleptic adults, and is also effective on cataplexy [176]. Pitolisant is well tolerated compared

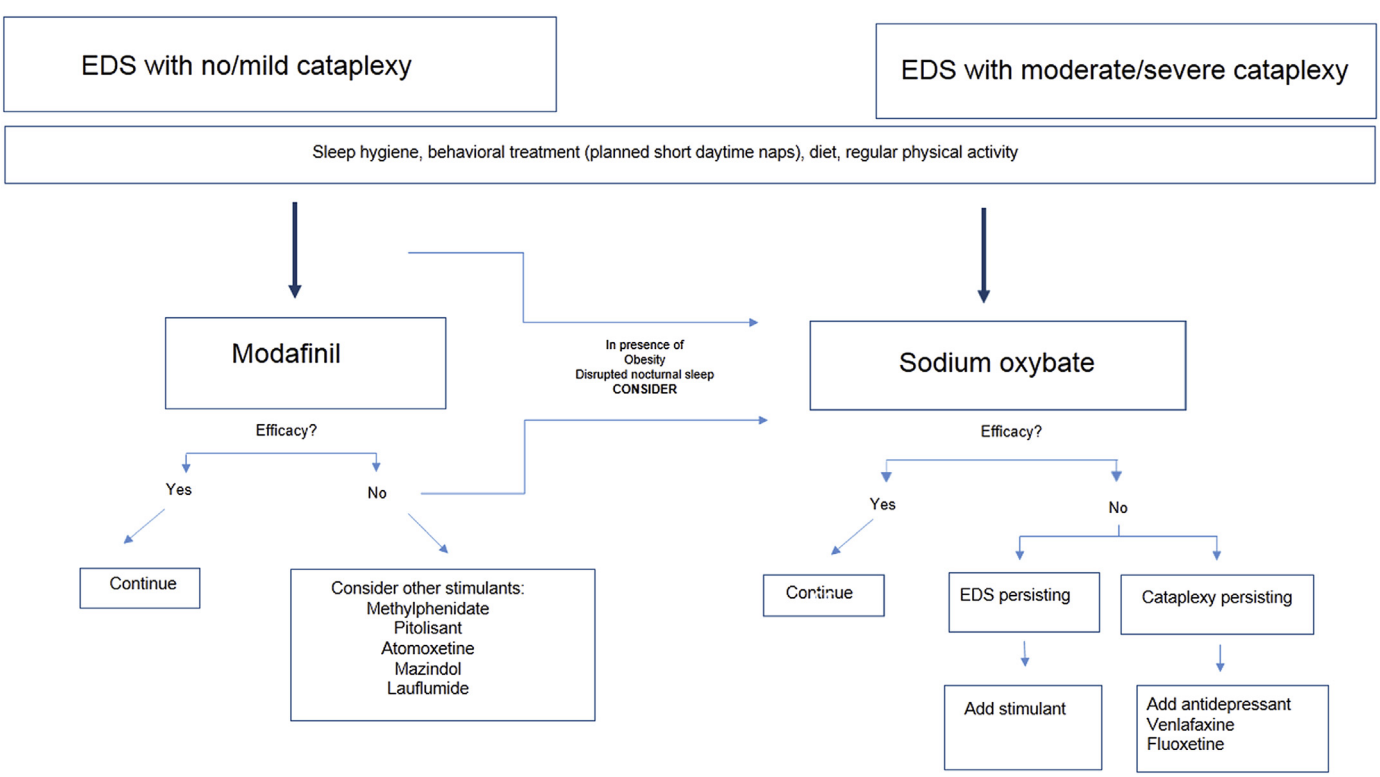

Fig. 6. Proposed therapeutic algorithm (based on expert consensus).

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with modafinil [177] and few minor adverse effects (insomnia, headache, leg pain, hot flushes, and hallucinations) especially during the first week of treatment are reported in teenage patients [178]. For adults, the therapeutic dosage usually ranges from 9 to 36 mg/d, in children few studies are available [178] but dosages up to 36 mg/have been suggested.

Atomoxetine is a selective norepinephrine reuptake inhibitor agent that increases synaptic norepinephrine and dopamine levels in the prefrontal cortex [179] and also used for the treatment of cataplexy and hypersomnia in narcoleptic patients in both adults and children. Nausea, reduced appetite, weight loss, xerostomia, urinary retention, mood disorders are the most common side effects, particular attention should be given to patients with a history of major depression due to the higher risk of suicidality [180,181]. Atomoxetine is used with efficacy in ADHD syndrome starting with a dose of 0.5 mg/kg/d and a slow titration, not exceeding the maximum dosage of 100 mg a day [172].

Other compounds

Mazindol is an imidazo-isoindol derivative and chemically a non-amphetamine, tricyclic compound [188]. Mazindol was first used to treat narcolepsy by Parkes et al. in 1975 [182]. More recently, it was shown that mazindol had a long-term, favorable benefit/risk ratio in 60% of drug-resistant hypersomniacs, including a clear benefit on cataplexy [183].

However, dedicated clinical trials with mazindol in narcolepsy patients are still lacking both in children and adults. A double-blind placebo-controlled phase II study has been promoted in the United States (US) to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release formulation of mazindol in adults with ADHD. Based on the future results of this study, the product could be developed for patients presenting with NT1 or NT2 and/or idiopathic hypersomnia.

Immunomodulatory treatment

A number of immunomodulatory therapies, including corticosteroids, intravenous immunoglobulin (IvIG) and plasmapheresis, have been evaluated in narcolepsy [184–186].

The rationale for using immunotherapy (IvIG) in narcolepsy was that the treatment could target and prevent the assumed underlying autoimmune destruction of hypocretin neurons and was of particular interest, especially when administered close to disease onset. The first published case of IvIG administration was reported in a 10-year-old child, very close to disease-onset and showed beneficial effects on the amount and severity of cataplexy but no improvement was observed in EDS [187]. The following published reports on the use of IvIG in patients with narcolepsy have been uncontrolled case studies involving very small numbers of patients. The results of these studies have been contradictory, although with limited evidence that early intervention shortly after disease onset may be more effective than later intervention. Moreover, very few of these studies were based on objective measures such as polysomnography followed by MSLT or maintenance of wakefulness test (MWT), CSF hcrt-1 assessment prior to and after IvIG administration [188–192].

More recently, a study conducted in a group of 24 NT1 children receiving IvIG versus 32 NT1 children on standard care alone, showed that in patients with high-baseline symptoms, IvIG-treatment lead to improvement of symptoms more rapidly when compared to those on standard treatment [193].

However, these studies were unblinded, non-randomized, or based on a small number of patients and are too weak to permit valuable conclusions on the potential curative effect of IvIG in the treatment of narcolepsy. Given the importance of emerging therapies in the field of narcolepsy, well conducted, randomized controlled trials should be strongly encouraged in the near future.

Comorbidities treatment

Precocious puberty

The indications to start treatment may be auxological, psychological or behavioral, or a combination of them, and every case must be individually evaluated by a pediatric endocrinologist. An observation period of 6–12 mo to define the progression rate is required. The agonist analogues of gonadotropin releasing hormone (GnRH), particularly the depot preparation, are the first line treatment. The major objectives of the treatment are preventing menarche, stopping the development of secondary sex characteristics, slowing the height velocity and bone maturation, moreover, safeguarding an appropriate psychological development, ameliorating the height potential to achieve the target height range, avoiding abnormal body proportion, and preserving normal bone density. Triptorelin and leuprolein are the most widely used. To achieve a complete pituitary-gonadal suppression the recommended dosage of triptorelin is 75–100 mg/kg body weight/4 wk and a dose of 90/mg/kg body weight for leuprolin. In Europe the recommended starting dose is 3.75 mg for body weight >20 kg and 1.875 mg for a body weight <20 kg [194]. Once started, the effects of therapy must be evaluated by a follow-up every 6 mo. Generally, GnRH analogues are well tolerated, but in up to 10% of patients the formation of sterile abscesses and allergic reaction to the injection site have been reported. Complete reversibility of suppression of the hypothalamic-pituitary-gonadal axis after GnRH analogues therapy has been demonstrated. Data are conflicting on the long-term risk of polycystic ovary; fertility seems not to be compromised. An increase and subsequent decrease of fat mass at the start of the treatment has been reported, but GnRH analogues do not appear to have a negative impact on BMI [195].

Obesity

General recommendations regarding a well-balanced intake of nutrients, avoiding large amounts of carbohydrates, are usually suggested in order to reduce weight gain. In severe cases, a nutrition consultation might be needed. Among children, sport activities and hobbies are greatly recommended.

Finally, stimulants and sodium oxybate might help in reducing weight, the latter with an effect that is more evident in obese children [51].

Behavioral and psychological difficulties

As stressed above, a prompt diagnosis and treatment is pivotal in order to prevent psychosocial difficulties (like poor social interaction, school difficulties), and mood disorders (anxiety, depression, psychotic symptoms). Particularly, in order to prevent embarrassment, it might also be important to inform schoolteachers and schoolmates about the disease and about its related needs (scheduled naps, or at times, school assistance and extra time for school exams). In severe cases, a psychological support might be required (Table1).

Cognitive and behavioral treatment however has been poorly investigated with regard to narcolepsy, and there are no systematic studies on the best approach, but just general recommendations [196]. In children, particularly, cognitive therapy might be useful to identify and modify the dysfunctional behavior that negatively affects daily life, emotions, especially in their self-esteem and in their interaction with school teachers/mates and friends. A

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Table 1
Differential diagnosis.

Narcoleptic mimics	Confounding overlapping features	Clinical clues	Objective features	
			Laboratory/neuroimaging	Neurophysiology
Neuromuscular diseases	Hypotonia Hyporeflexia	Additional neurological findings (weakness, worsening with exercise, etc)	Elevated CPK, aldolase, LDH, altered muscle imaging/histology	Altered EMG pattern
Epileptic attacks	Head drops Axial drops Falls Negative/positive myoclonus	Loss of consciousness, rapid onset, post critical confusion, tongue biting, incontinence	Increased CPK after generalized episodes Discrete metabolic abnormalities related to different etiologies Neuroimaging abnormalities	Critical epileptic EEG discharges, Inter-ictal EEG epileptic abnormalities
Cerebellar ataxias	Unstable gait, slurred speech, hypotonia and hyporeflexia	Persistent condition (although fluctuating), lack of emotional triggers, additional neurological findings (e.g., nystagmus, appendicular ataxia) frequent involvement of other CNS structures	Different biochemical/genetic abnormalities according to different underlying diseases Neuroimaging abnormalities	
Choreic disorders	Diskynesia with prominent facial involvement and psychiatric comorbidities, recent streptococcal infection, and/or elevated streptococcal antibodies titer	Presence of piano-playing choreiform movements, systemic involvement	Evidence of recurrent streptococcal infections coupled with clinical worsening Different biochemical and genetic findings may occur in different choreic conditions	Active bursts on EMG leads (vs hypotonia in NT1)
Encephalitis	Acute onset of sleep disturbance, abnormal movements (orofacial dyskinesias, stereotyped movements), psychiatric/behavioral changes	Impaired consciousness, severe psychosis or catatonia, frequent seizures, autonomic dysfunction, and severe cognitive impairment	Serological autoimmune/paraneoplastic markers Altered CSF findings (e.g., altered brain blood barrier)	EEG abnormalities (e.g., potential occurrence of epileptic activity)
ADHD	Hyperactivity, lack of attention, decreased school performances, fidgeting	Lack of pathological EDS		

CPK, creatine phosphokinase; LDH, lactic dehydrogenase; EMG, electromyography; EEG, electroencephalogram; CNS, central nervous system; NT1, narcolepsy type 1; CSF, cerebrospinal fluid; ADHD, attention-deficit/hyperactive disorder; EDS, excessive daytime sleepiness.

neuropsychiatric assessment with a proper pharmacological approach might be needed in case of a dual diagnosis [79].

Conclusions

Pediatric NT1 is a complex disease, encompassing neurological, endocrinological and less often psychiatric symptoms and consequently requiring an orchestrated cooperation among different specialists. Recent reports highlight the peculiar features of NT1 in children close to the disease onset, which overall shows a more severe degree of symptoms. However, very little is currently known and further studies are required, trying to better characterize this condition. A prompt diagnosis, indeed, is important in order to prevent educational and social difficulties. On that regard, consensual data on the diagnostic value of neurophysiological procedures are missing, as MSLT has not been validated yet in children and not all patients would allow a lumbar puncture. A behavioral and cognitive approach is important, but a standardized protocol is not available yet. Finally, modafinil and sodium oxybate are currently used as first line treatments, empirically showing good efficacy, but studies to assess the efficacy and safety in children are not available and therefore well-timely needed in order to obtain the approval from the FDA and the EMA.

Practice points

1. NT1 is caused by the destruction of over 90%of hypocretin neurons, with low or undetectable levels of CSF hcrt1.
2. The clinical hallmark of NT1 is cataplexy, which distinguishes NT1 from NT2.
3. The key symptoms of NT1, i.e., EDS, cataplexy, sleep paralysis and hypnagogic/hypnopompic hallucinations and disrupted nocturnal sleep, may have peculiar features in children
4. Cataplexy may be subcontinuous at disease onset, lacking the typical emotional triggers, and may be associated with dyskinesia involving mainly the facial region.
5. A sudden increase in weight may occur close to symptom onset, along with additional endocrinological dysfunction, i.e., obesity, type 2 diabetes and precocious puberty.
6. Misdiagnoses at disease onset are frequent: cataplexy in children may be mislabeled with a neuromuscular disorder, if the hypotonic component is prominent, or with a movement disorder (chorea) if diskinesia prevails; EDS with ADHD and hallucination/nightmares with a psychiatric condition.
7. NT2 may be a transient condition. Repeated MSLTs are often required to confirm the diagnosis.
8. Diagnosis requires a PSG followed by daytime MSLT documenting short sleep latency and sleep onset REM periods (SOREMPs), but cut-offs have not been validated in patients younger than 8 y.
9. Behavioral treatment is recommended (i.e., scheduled nap).
10. Pharmacological approaches are given as “off-label”. Modafinil and sodium oxybate are the first line options.

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Research agenda

1. To evaluate and validate the best sensitive and specific neurophysiological markers in NT1 children.
2. To better understand the natural history of NT1 and especially NT2.
3. To understand the biological dysfunction associated with NT2.
4. To prove the autoimmune dysfunction in children with NT1 that may lead to therapeutic or even preventive intervention with the right classes of immune modulators.
5. Further studies are needed aiming to obtain the authorization from the Food and Drugs Administration/European Medicine Agency for the use of registered drugs in NT1 children.
6. To develop new tools to assess treatment efficacy in children

Conflict of interest

EP, EA, FP have no conflict of interest; ML has received consultant honoraria from UCB pharma, Jazz pharmaceuticals and Bioprojet; YD has received funds for speaking, board engagement, and travel to conferences from UCB pharma, Jazz pharmaceuticals, Theranexus, Flamel, and Bioprojet; GP has received consultant honoraria from UCB pharma, Jazz pharmaceuticals and Bioprojet.

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