Child Neurology: A Case Series of Heterogeneous Neuropsychiatric Symptoms and Outcome in Very Early-Onset Narcolepsy Type 1

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Abstract

Narcolepsy type 1 is a central disorder of hypersomnia characterized by excessive daytime sleepiness, cataplexy (i.e., sudden loss of muscle tone during wakefulness triggered by emotions), and REM sleep-related manifestations that can present with a peculiar phenotype when arising at a pediatric age. Several features of childhood-onset narcolepsy type 1 are also common in neuropsychiatric conditions; discrete neuropsychiatric comorbidity has also been demonstrated. Here, we report on 3 children with very early narcolepsy type 1. All 3 patients had psychiatric features at the time of symptom onset coupled with peculiar motor disturbances. The course of narcolepsy symptoms also paralleled neuropsychiatric symptoms, suggesting a possible intrinsic link between sleep and psychological features. Multidisciplinary management is mandatory for pediatric narcolepsy type 1 since prompt disease management addressing neuropsychiatric symptoms could lead to better clinical outcomes and quality of life.
Narcolepsy type 1 (NT1) is a central disorder of hypersomnolence characterized by excessive daytime sleepiness (EDS), cataplexy (i.e., sudden loss of muscle tone triggered by emotions), and additional rapid eye movement (REM) sleep-related manifestations (sleep paralysis, hypnagogic/hypnopompic hallucinations, disrupted nocturnal sleep, and REM sleep behavior disorders). NT1 is linked to cerebrospinal hypocretin-1 (CSF hcr-1) deficiency, reflecting the loss of hypothalamic neurons that produce hypocretin, likely because of an autoimmune process. NT1 typically arises during adolescence and young adulthood with age-specific features. Childhood NT1 has a peculiar phenotype with EDS manifesting as increased sleep need or hyperactivity with behavioral changes and cataplexy as a complex movement disorder including a gait disorder or a persistent hypotonia typically involving the face (cataplectic facies) intermingled with hyperkinetic features. In addition, early endocrinologic and neuropsychiatric features can manifest. The peculiar clinical presentation and nonneurologic features may contribute to diagnostic delay and frequent misdiagnosis at the first referral. Here, we report on 3 NT1 children diagnosed at a very early age (<5 years) who displayed different clinical outcomes at follow-up.

Case Reports

Patients were referred to the Bologna Center for Narcolepsy for a second opinion, undergoing a diagnostic workup including neurologic evaluation, actigraphy, in-laboratory cataplexy video documentation, continuous 48-hour video-polysomnography (PSG), multiple sleep latency test (MSLT), brain MRI with contrast, serum testing for human leukocyte antigen (HLA) DQB1*06:02 haplotype, lumbar puncture for CSF analysis (including cytochemical and immunoblot examination, search for autoantibodies responsible for autoimmune encephalitis, virologic examination, and hcr-1 assay), and endocrinologic evaluation.

Case 1

A 2-year and 9-month-old boy with speech delay was admitted for an acute-onset gait disorder, recurrent falls to the ground, generalized hypotonia, and remarkable sleepiness. To evaluate for a suspected encephalopathy, he underwent brain MRI, EEG, toxicologic analysis, and blood and CSF examination with normal findings. Prolonged daytime (3–4 hours) and nighttime (13 hours) sleep episodes, along with remarkable motor activity during sleep, led to our referral 3 weeks after symptom onset. He presented with EDS, irritability, generalized hypotonia, and recurrent episodes of transient muscular atonia involving the face, limbs and trunk, also leading to falls, apparently triggered by eating and physical tasks (Video 1, Segments 1–3). He also showed intense motor and verbal activities and multiple awakenings during nocturnal sleep (Video 1, Segments 4 and 8). Sleep studies, low CSF hcr-1, and DQB1*06:02 positivity led to NT1 diagnosis (Table 1). IV immunoglobulin (IVIG) treatment did not modify his symptomatology, and at 6 month follow-up, he showed a subcontinuous cataplectic state with diffuse hypotonia, wide-based gait, and hyperkinetic movements involving the face (Video 1, Segments 5–7). His speech was dramatically compromised (language limited to few words), and he presented with irritability, temper tantrums, motor restlessness, and 9-kg weight gain leading to obesity (BMI 23.1; Z-score 4.1). At 3 years and 5 months of age, treatment with sodium oxybate (SO) up to 2.5 g was started but immediately withdrawn by his parents because of difficulties in administration. At 7 years and 2 months of age, he presented with remarkable sleepiness, subcontinuous cataplexy, severe sociocommunicative difficulties, selective interests, rigidity/resistance to change, and motor stereotypes, consistent with a diagnosis of autism spectrum disorder (Video 1, Segment 9). BMI was 37 kg/m² (Z-score 3.1). We gradually titrated SO up to 8 g. At his last follow-up after 5 months of therapy with SO at 7 years and 7 months of age, he showed remarkable improvement in nocturnal sleep, EDS, and cataplexy with weight loss (BMI 33.6 kg/m²; Z-score 2.9). Moreover, he showed a significant improvement in autistic symptoms with reduced aggressiveness.

Case 2

A 4-year and 10-month-old boy presented with involuntary movements of the face, trunk, and limbs 1 month after a flu-like syndrome. Choreiform movements, hypotonia, dysmetria, and a wide-based gait led us to suspect cerebellitis (Video 2, Segment 1). Brain MRI was normal with the exception of a cystic pineal gland. EEG, toxicologic analysis, and blood and CSF analyses were also unremarkable. We observed the patient 2 months after symptom onset with EDS, nocturnal sleep disruption (motor restlessness and screaming) (Video 3, Segment 5), and severe cataplexy. Indeed, the boy showed cataplectic facies (Video 2, Segment 4), with episodes of sudden atonia in facial muscles, ptosis, and mouth opening, elicited by positive emotional stimuli like watching cartoons. His examination was also notable for choreiform-like movements in his limbs and trunk (Video 2, Segments 2 and 3). A moderate weight gain was reported (BMI 17.8 kg/m²; Z-score 1.5). Sleep studies, low CSF hcr-1, and DQB1*06:02 positivity led to NT1 diagnosis (Table 1). IVIG treatment did not significantly improve the clinical picture. At 6 months of follow-up (5 years and 4 months of age), he presented with spontaneous EDS amelioration, and pitolisant was started up to 18 mg/d with further improvement of subjective sleepiness. Cataplexy was markedly reduced together with his movement disorder. One year after symptom onset (5 years and 10 months of age), SO (up to 5 g/d) was added on with significant improvement in nocturnal sleep efficiency and daytime sleepiness (Figure 1).

At last follow-up (10 years and 1 month of age), sleepiness and cataplexy were not entirely controlled by pharmacologic (pitolisant 18 mg/d and SO 5 g/d) and behavioral (scheduled nap and regular sport activity) therapy. Of note, he developed a mild mood disorder with social isolation, sadness, and irritability.

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Case 3
A 3-year and 8-month-old girl with an unremarkable history became frankly somnolent after a flu-like episode needing prolonged naps (3 hours) both at school and at home. Her parents reported difficulties falling asleep at night when she often experienced frightening visual hallucinations, awakenings, sleep talking, and limb movements.

Over the course of 2 weeks, she presented with a droopy face and spontaneous mouth openings, tongue protrusions,
eyelid closures, and laughter-related falls. She developed irritability and increased appetite, leading to a weight gain of 8 kg in 2 months (BMI 20.5 kg/m²; Z-score 2.6). A psychiatric disorder was alleged because brain MRI, EEG, and blood and CSF analyses were unremarkable. Sleep studies, low CSF hcrth1, and DQB1*06:02 positivity led to NT1 diagnosis 2 months after symptom onset (Table 1). Early signs of secondary sexual development (breasts and pubic hair) were noted (Tanner stage 2), and hormonal examination indicated a central precocious puberty treated with GnRH agonist therapy. She was initially treated with modafinil 100 mg without benefit. IVIG therapy was then added without significant clinical benefit. At 5 years and 2 months of age, SO was added on up to 8 g, resulting in improved EDS, cataplexy, and weight control.

Video 3 shows the progressive improvement of cataplexy during follow-up at 5 years and 2 months of age (Segment 1) and 6 years and 9 months of age (Segment 2). At the last follow-up (15 years and 2 months of age), narcolepsy symptoms were well controlled.

Discussion
This case series describes 3 patients with early-onset NT1 coupled with different neuropsychiatric features and prominent motor disturbances (cataplectic facies associated with gait disturbance in patient 1 and hyperkinetic movements in patient 2).

Narcolepsy is a rare chronic condition, and disease burden is worsened by diagnostic delay, emphasizing the need to recognize the unusual clinical and neuropsychiatric symptoms associated with NT1. Indeed, all patients in our case series met the diagnostic criteria for NT1 and presented with some peculiar behavioral and motor manifestations that have been included as red flags for early NT1 recognition by a recent consensus.

Patient 1 showed the worst clinical course, with inadequate therapy response leading to a severe limitation in daily activities. Patient 2 had mild residual symptoms and mood disturbances at long-term follow-up. Patient 3, despite precocious puberty and an initial eating disorder, did not report any residual neuropsychiatric symptoms and showed an excellent response to pharmacologic therapy.

Neuropsychiatric symptoms in these patients co-occurred with sleep disturbances and followed different clinical trajectories significantly affecting disease burden and outcome. These trajectories may be influenced by the severity of the initial psychiatric symptoms; however, it is possible to speculate that greater control over narcolepsy symptoms may also lead to better neuropsychiatric outcomes. Childhood NT1 shares phenologic aspects with common neuropsychiatric symptoms such as irritability, hyperactivity, emotional dysregulation, aggressive behavior, impulsiveness, and poor attention. Furthermore, the neuropsychiatric comorbidity that has been demonstrated in NT1 children includes attention deficit hyperactivity disorder (ADHD) (29%), mood disorder...
(20%), anxiety disorder (10%), oppositional defiant disorder (ODD) (7%), pervasive developmental disorder not otherwise specified (3%), and eating disorders (3%). Despite few reports, the prevalence of autism among patients with narcolepsy is unknown. As demonstrated by case 1, there is a complex interplay between narcolepsy-related symptoms that can augment autistic traits and be exacerbated by neuropsychiatric symptoms. It is currently unknown whether hypocretin deficiency and NT1 symptoms affecting very young patients may lead to a neuropsychiatric disorder or be intrinsically part of an underlying neurodevelopmental disorder. Our cases showed different clinical outcomes, pointing to a complex relationship between genetic predisposition, neuropsychiatric symptoms, and hypocretin deficiency. Overall, a multidisciplinary approach is mandatory to address neuropsychiatric and neuropsychiatric symptoms and improve overall quality of life for pediatric patients with NT1.

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**Appendix**

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**References**
9. Lecendreux M, Berthier J, Corny J, Bourdon O, Dussieux C, Delcaux C. Intravenous immunoglobulin therapy in pediatric narcolepsy: a nonrandomized,

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