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 hypersomnolence characterized by excessive daytime sleepiness, cataplexy (i.e., sudden loss of muscle tone during wakefulness triggered by emotions), and rapid eye movement 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 three children with very early narcolepsy type 1. All three patients had psychiatric features at 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.

**Keywords:** narcolepsy, cataplexy, movement disorder, autism, neuropsychiatric symptoms

**Introduction**

Narcolepsy type 1 (NT1) is a central disorder of hypersomnia 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 disorder). NT1 is linked to cerebrospinal hypocretin-1 (CSF hcr1) deficiency, reflecting the loss of hypothalamic neurons that produce hypocretin, likely due to 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 endocrinological and neuropsychiatric features can manifest. The peculiar clinical presentation and non-neurological features may contribute to diagnostic delay and frequent misdiagnosis at first referral.

Here we report on three 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 neurological evaluation, actigraphy, in-laboratory cataplexy video documentation, continuous 48hr video-polysomnography (PSG), multiple sleep latency test (MSLT), brain MRI with
contrast, serum testing for Human Leucocyte Antigen (HLA) DQB1*06:02 haplotype, lumbar puncture for CSF analysis (including cytochemical and immunoblot examination, search for autoantibodies responsible for autoimmune encephalitis, virological examination, hcr-t-1 assay\textsuperscript{8}), and endocrinological evaluation.

Case 1
A two-year and nine-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, toxicological 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 three 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 1-2-3). 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-t-1, and DQB1*06:02 positivity led to NT1 diagnosis (Table 1). Intravenous immunoglobulin (IVIG) treatment did not modify his symptomatology\textsuperscript{9}, and at six-month follow-up he showed a sub-continuous cataplectic state with diffuse hypotonia, wide-based gait, and hyperkinetic movements involving the face (Video 1, Segments 5-6-7). 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 three years and five months of age, treatment with sodium oxybate (SO) up to 2.5 grams was started but immediately withdrawn by his parents due to difficulties in administration. At seven years and two months of age, he presented with remarkable sleepiness, sub-continuous cataplexy, severe socio-communicative difficulties, selective interests, rigidity/resistance to change, and motor stereotypies, consistent with a diagnosis of autism spectrum disorder (Video 1, Segment 9). BMI was 37 (Z-score 3.1). We gradually titrated SO up to 8 grams. At his last follow-up after five months of therapy with SO at seven years and seven months of age, he showed remarkable improvement in nocturnal sleep, EDS, and cataplexy with weight loss (BMI 33.6; Z-score 2.9). Moreover, he showed a significant improvement in autistic symptoms with reduced aggressiveness.
Case 2

A four-year and ten-month-old boy presented with involuntary movements of the face, trunk and limbs one 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, toxicological analysis, and blood and CSF analysis were also unremarkable. We observed the patient two 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 exam 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; Z-score 1.5). Sleep studies, low CSF hcrt1, and DQB1*06:02 positivity led to NT1 diagnosis (Table 1). IVIG treatment did not significantly improve the clinical picture. At six months of follow-up (five years and four months of age), he presented with spontaneous EDS amelioration, and pitolisant was started up to 18 mg/day with further improvement of subjective sleepiness. Cataplexy was markedly reduced together with his movement disorder. One year after symptom onset (five years and ten months of age) SO (up to 5 g/day) was added-on with significant improvement in nocturnal sleep efficiency and daytime sleepiness (Figure 1).

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

Case 3

A three-year and eight-month-old girl with an unremarkable history became frankly somnolent after a flu-like episode needing prolonged naps (three 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 two weeks, she presented with a droopy face and spontaneous mouth openings, tongue protrusions, eyelids closures, and laughter-related falls. She developed irritability and increased appetite,
leading to a weight gain of 8 kg in two months (BMI 20.5; Z-score 2.6). A psychiatric disorder was alleged since brain MRI, EEG, and blood and CSF analysis were unremarkable. Sleep studies, low CSF hcr1, and DQB1*06:02 positivity led to NT1 diagnosis two 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 five years and two 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 five years and two months of age (Segment 1) and six years and nine months of age (Segment 2). At the last follow-up (fifteen years and two months of age), narcolepsy symptoms were well-controlled.

Discussion

This case series describes three 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 pharmacological therapy.

Neuropsychiatric symptoms in these patients co-occurred with sleep disturbances and followed different clinical trajectories significantly impacting 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 phenomenological 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%)\textsuperscript{3,12}. Despite few reports, the prevalence of autism among patients with narcolepsy is unknown\textsuperscript{13}. 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\textsuperscript{14}.

Our cases showed different clinical outcomes, pointing to a possible complex relationship between genetic predisposition, neuropsychiatric symptoms, and hypocretin deficiency. Overall, a multidisciplinary approach is mandatory to address neurological and neuropsychiatric symptoms and improve overall quality of life for NT1 pediatric patients.
References


Table 1

Laboratory results, HLA characterization, brain MRI, anthropometric measures, endocrinological and psychiatric aspects. MRI: magnetic resonance imaging; ASO anti-streptolysin-O; hcr-1: hypocretin-1; HLA: Human Leukocyte Antigen; BMI: body mass index. (I): first evaluation; (II): second evaluation. EDS: excessive daytime sleepiness; DNS: disrupted nocturnal sleep; HH hypnagogic hallucinations; SP: sleep paralysis; PSG: polysomnography; MSLT: multiple sleep latency test; REM: rapid eye movement; SOREMP: sleep onset REM periods.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
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<td>Movement Disorder</td>
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<td>Mild Depressive Feelings</td>
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Figure 1:

Actigraphic recordings (segments) from Case 2 referred to long-lasting monitoring. Each panel shows a window of five days. Black bars symbolize movement detected by wrist actigraphy; absence of black bars indicates supposed sleeping periods. Horizontal lines represent consecutive 24-h periods with clock hours indicated on the x-axis. Sky-blue highlight = nocturnal sleep period. Yellow highlight = diurnal sleep episodes. Fuchsia highlight = periods of device removal.

Before the diagnosis (panel A), actigraphy depicts the 24-hour profile typical of NT1 children. At three and six month follow-up, actigraphy shows progressive and spontaneous reduction of daytime sleep time coupled with a decrease of nocturnal motor activity intensity (panel B and C). At nine month follow-up (panel D-stable treatment with pitolisant 18mg/day), actigraphy documented a further reduction of diurnal sleep episodes coupled with improvement of subjective sleepiness and cataplexy. At twelve month follow-up, SO was added-on and actigraphy (panel E) documented a significant improvement in nocturnal sleep efficiency and a shortening of nighttime sleep duration, paralleled by a decrease in afternoon nap frequency.
Video Legends

Video 1 (Patient #1)

Segment 1: Age 2y9m (video recorded by parents); diffuse hypotonia, ataxic gait with tendency to fall.

Segment 2: Age 2y9m (video recorded by parents); cataplectic attack triggered by eating with eye ptosis, mouth opening, and atonia requiring the child to lie down to avoid falls.

Segment 3: Age 2y10 m (synchronized video-polygraphic recording during first hospitalization); cataplectic attacks with sudden loss of tone in neck and trunk muscles triggered by watching cartoons. Hypotonic facies with eye ptosis and mouth opening.

Segment 4: Age 2y10m (nocturnal polysomnography at first hospitalization); motor activity involving both upper limbs during REM sleep (RBD).

Segment 5: Age 3y3m (recording during neuropsychiatric evaluation); sub-continuous cataplectic state: diffuse hypotonia, wide-base gait, cataplectic facies with frequent involuntary hyperkinetic movements of the mouth and tongue.

Segment 6: Age 3y5m (recording during second hospitalization); wide-base gait, obesity, irritability.

Segment 7: Age 3y5m (recording during second hospitalization); Diffuse hypotonia. Masked facies with frequent involuntary jaw opening and tongue protrusion. Truncal movements and stereotypies.

Segment 8: Age 3y5m (nocturnal polysomnography at second hospitalization); an episode of nightmare arising from NREM sleep.

Segment 9: Age 7y2m (recording during neuropsychiatric evaluation); Sub-continuous cataplexy. Impaired language. Motor stereotypes and repetitive behaviors.

Video 2 (Patient #2, Age 5y, recording during first hospitalization)

Segment 1: Wide-based gait, choreiform-like movements of limbs and trunk.

Segment 2: Brief episodes of sudden loss of tone in facial and limb muscles while watching cartoons.

Segment 3: Diffuse hypotonia, cataplectic attacks with head nodding, eye ptosis and mouth opening triggered by laughter.

Segment 4: Cataplectic hypotonic facies with eye ptosis and facial grimacing.
Segment 5: An episode of parasomnia during PSG registration arising from NREM sleep.

Video 3 (Patient #3)

Segment 1: Age 5y2m. Diffuse hypotonia with trunk swinging and tendency to fall. Masked facies with frequent involuntary mouth opening and tongue protrusion. Cataplectic attacks with mouth opening and eyelid closure triggered by laughter. Obesity and breast development.

Segment 2: Age 6y9m (on pharmacological treatment). Normal facies, no cataplectic attacks, weight reduction.
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