



## A distinct psychotic phenotype in pediatric narcolepsy type 1: a case-control study

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### ABSTRACT

**Introduction:** To determine whether pediatric patients with narcolepsy type 1 (NT1) who develop psychotic symptoms exhibit a distinct clinical and sleep-related phenotype compared with those with NT1 without psychosis.

**Methods:** We report on clinical and polysomnographic features of nine consecutive pediatric patients observed at our center between 2014 and 2025, who developed psychotic symptoms either at NT1 onset or within one year from NT1 diagnosis, and on a control group of 96 consecutive NT1 patients without evidence of psychotic symptoms.

**Results:** Final psychiatric diagnoses included very-early-onset schizophrenia, psychosis not otherwise specified, psychotic depression, obsessive-compulsive disorders, or autism spectrum disorder with psychotic features. Compared to control NT1 patients, NT1 cases with psychosis showed much higher rates of psychiatric family history (OR = 36, 55.6% vs. 2.2%,  $p < 0.01$ ), lower cerebrospinal fluid hypocretin-1 levels ( $4.9 \pm 9.0$  pg/mL vs.  $18.9 \pm 24.2$  pg/mL,  $p = 0.02$ ) and the following polysomnographic features: shorter nocturnal total sleep time ( $430.8 \pm 86.5$  min vs.  $503.7 \pm 76.8$  min,  $p = 0.03$ ), lower nocturnal sleep efficiency ( $75.6 \pm 15.6\%$  vs.  $89.5 \pm 7.6\%$ ,  $p = 0.02$ ), and higher rate of daytime naps ( $3.7 \pm 1.8$  vs  $2.6 \pm 1.7$ ,  $p = 0.04$ ). Sleep-wake transition metrics indicated increased nocturnal sleep fragmentation, namely higher transition indices between wakefulness and sleep and between wakefulness NREM and REM sleep, respectively.

**Conclusions:** Our findings suggest the presence of a pediatric NT1-psychotic phenotype characterized by more severe hypocretin deficiency and pronounced daytime and nighttime sleep disruption, suggesting that these features may reflect the interaction between hypocretin deficiency and broader neuro-developmental vulnerabilities. Early recognition of this phenotype may guide toward tailored treatment strategies and inform about prognosis in this complex disorder.

### 1. Introduction

Narcolepsy type 1 (NT1) is a chronic central disorder of hypersomnolence characterized by excessive daytime sleepiness (EDS), cataplexy,

sleep-related hallucinations, sleep paralysis, and disturbed nocturnal sleep [1]. NT1 is pathophysiologically linked to the loss of hypothalamic neurons that produce hypocretin, also called orexin, a neuropeptide essential for regulating wakefulness, arousal, and REM sleep. The above

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neural loss is believed to result from autoimmune processes triggered by environmental factors in genetically predisposed individuals, particularly those carrying the HLA-DQB1\*06:02 allele [2].

The onset of NT1 generally occurs at two peaks of age, with over half of the cases manifesting before the age of 18. When the onset of NT1 occurs in childhood, presentation may also include generalized weakness rather than classic cataplexy, avoidance behavior, hyperactivity, complex wake and sleep movement disorders, and cataplectic facies [3–5]. In addition to the classic pentad, pediatric NT1 has been increasingly associated with metabolic and endocrine disturbances, particularly rapid weight gain, obesity, and early puberty, and also cognitive and behavioral impairments, suggesting a broader hypothalamic and systemic involvement beyond sleep regulation [6,7].

Comorbid psychiatric symptoms, such as depression and anxiety, are frequent in both children and adults with NT1 compared to the general population [8,9]. Specifically, in children with NT1, neuropsychiatric comorbidity may include attention deficit hyperactivity disorder, mood disorder, anxiety disorder, oppositional defiant disorder, and pervasive developmental disorder [10]. Emotional and social difficulties, including depression, are commonly reported in these patients [11,12].

Dual cases of NT1 and psychosis have been described in adults and adolescents, although a clear association between psychotic disorders and NT1 has not been demonstrated so far [13–15]. Prevalence of schizophrenia was reported more frequently in early-onset NT1 [15].

These reports describe patients with vivid hallucinations, altered behavior, and delusional thinking, in whom distinguishing between NT1-related phenomena and true psychotic disorders proved clinically challenging. Whether psychotic disorders are purely incidental remains unsolved. The use of stimulant medications or oxybate, commonly prescribed in NT1, can further complicate the clinical picture. While sodium oxybate is not generally considered psychotogenic, rare cases of psychotic or dissociative symptoms have been reported, particularly during treatment initiation or dose escalation, especially in vulnerable individuals [16,17]. Although rarely, stimulant-induced psychosis has been described in pediatric and adult populations, particularly at high doses or with prolonged use, raising concerns about potential iatrogenic contributions to psychiatric symptoms [18,19].

The characteristics of patients with psychosis associated with NT1 during childhood remain poorly explored [15]. Specifically, in childhood and adolescence, psychosis associated with NT1 has been reported to present with distinctive features compared with pediatric patients with NT1 without psychotic symptoms. According to previous reports, psychotic symptoms typically emerge approximately 2.5 years after NT1 onset, often during early puberty, and are characterized by prominent visual hallucinations, higher rates of major depression, and greater severity at presentation, frequently requiring hospitalization. These cases are also marked by poor response to antipsychotic treatment, increased body mass index at NT1 onset, and a higher frequency of the DQB1\*06:02 haplotype [15].

In our clinical practice, we have noticed a small cohort of children and adolescents with NT1 who developed severe and persistent psychotic symptoms, notably auditory hallucinations, not explained by the hypnagogic hallucinations typical of narcolepsy.

Thus, we aimed to describe clinical and neurophysiological features of these patients and compare them with matched individuals with NT1 but without psychotic symptoms. We hypothesized that these patients with NT1 and psychosis have a distinct phenotype, which should be recognized to help understanding, identifying, and managing a complex comorbidity in pediatric age.

Accordingly, this study was conceived as an exploratory, hypothesis-generating investigation aimed at characterizing whether pediatric patients with NT1 and psychosis exhibit a distinct clinical and neurophysiological phenotype compared with NT1 patients without psychotic symptoms.

## 2. Methods

### 2.1. Ethics committee and patients' consent

This study was approved by the Independent Ethics Committee of Area Vasta Emilia Centro (CE-AVEC) (protocol number: 17,009).

Parents/legal tutors of all participants signed a written informed consent.

### 2.2. Participants

We analyzed clinical data from pediatric patients diagnosed with NT1 before the age of 18 at the Narcolepsy Center of the IRCCS Institute of Neurological Sciences of Bologna, from January 2014 to January 2025.

Recruited patients had comprehensive medical documentation and regular follow-up visits for at least two years at the Narcolepsy Center after the initial diagnostic hospitalization. Patients who developed clinically significant psychotic symptoms at NT1 onset or during the early course of the disease, defined as the first years following diagnosis in developmental age, were included in the psychosis + NT1 group.

All of them had undergone standardized neuropsychiatric or psychodiagnostic evaluations and received systematic follow-up assessments every 3, 6, or 12 months, depending on clinical needs. Board-certified child and adolescent psychiatrists ascertained the presence of psychotic symptoms diagnosed through clinical interviews, long-term observation, and documentation of ongoing symptoms beyond sleep-related phenomena, in line with DSM-5 criteria. From the same time span, consecutive age- and sex-matched patients with a diagnosis of pediatric NT1 and without any psychotic symptoms at the diagnosis and in the first year of follow-up were selected (control-NT1 group), matched for age and sex with patients with NT1+psychosis group.

Information regarding ongoing pharmacological treatments (including stimulants, antidepressants, and antipsychotics) were collected when available from clinical records.

### 2.3. Diagnostic evaluation for narcolepsy

The diagnostic work-up included clinical evaluation by board-certified neurologists specialized in sleep medicine with systematic assessment of anthropometric measures, clinical features of central disorders of hypersomnolence with a structured interview and the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), and physical neurological examination [20].

According to the standardized protocol of the Narcolepsy Center, all participants were hospitalized in a room, accompanied by a parent/legal tutor, and underwent two days of continuous video-polysomnographic (PSG) recording with an ambulatory device, in unrestricted conditions. As previously detailed, continuous PSG recording consists of two nighttime recordings (night1-PSG and night2-PSG), with lights-off scheduled according to each patient's usual habit, and daytime recording (day1-PSG and day2-PSG) in which the patients have the opportunity to sleep or do usual activities (e.g., playing, reading, watching TV, doing homework) as they please [21,22].

Night2-PSG, invariably terminated at 7:30 a.m., was followed by an attended multiple sleep latency test (MSLT).

When specific consent was given, HLA-DQB1\*06:02 typing and lumbar puncture for cerebrospinal fluid (CSF) hypocretin-1 measurement were performed.

CSF hypocretin-1 concentrations were measured by direct radioimmunoassay (RIA) using a commercial kit (Phoenix Pharmaceuticals, Belmont, CA, USA). Quantification was performed at the Stanford Center for Narcolepsy according to the Stanford reference standard; values < 110 pg/mL were considered diagnostic of hypocretin deficiency.

Based on the findings of this protocol, NT1 diagnosis was established

according to the criteria of the International Classification of Sleep Disorders (ICSD) version in use at the time of evaluation—either the third edition (ICSD-3) or its text revision (ICSD-3-TR) [23].

## 2.4. Psychiatric assessment

Psychiatric comorbidities were evaluated through thorough clinical assessments conducted either at our facility or by board-certified child and adolescent psychiatry specialists from collaborating institutions. All diagnoses were made in accordance with DSM-5 or ICD-10 criteria, based on ongoing clinical interviews with the child and their caregivers, direct observation of the child's behavior, and a review of detailed clinical records. This was a single-center study. At our center, psychiatric assessments were conducted during the initial diagnostic hospitalization and throughout follow-up visits and included a careful reconstruction of the developmental and emotional history, an evaluation of current psychological functioning, and ongoing monitoring of behavioral symptoms over time.

Psychotic symptoms were considered present when children exhibited persistent hallucinations, delusional beliefs, or marked disorganization in thought or behavior that occurred outside of sleep-wake transitions and significantly impaired their social or academic functioning. Attention was also given to differentiating narcolepsy-related hallucinations, which typically occur at sleep onset or upon awakening, from true psychotic phenomena, based on their temporal relationship to sleep, content, and associated behavioral context. In addition to their temporal dissociation from sleep-wake transitions, psychotic symptoms were required to show persistence over time and to be associated with clear functional impairment, to be distinguished from the vivid but typically brief hypnagogic/hypnopompic hallucinations characteristic of NT1. Only children who met full diagnostic criteria for a psychiatric disorder with psychotic features were included in the NT1+psychosis group.

Grouping patients into the NT1+psychosis subgroup was based on the presence of persistent psychotic symptoms rather than diagnostic homogeneity, reflecting the clinical reality that psychotic features in this population span multiple nosological categories.

## 2.5. Family history assessment

First-degree family histories of psychiatric and neurological disorders were systematically collected for all participants through clinical interviews with patients and caregivers, as well as review of available medical records. The presence of psychiatric disorders, including mood disorders, psychotic disorders, anxiety disorders, and neurodevelopmental disorders such as autism spectrum disorder and attention deficit/hyperactivity disorder, and neurological conditions was specifically investigated in biological parents and siblings. Data collection covered both officially diagnosed conditions and clinically suspected cases reported by caregivers. When available, the age of onset and the disorder's course were also documented.

## 2.6. Polysomnographic data

Continuous ambulatory PSG recording was conducted according to the standards of the American Academy of Sleep Medicine (AASM). The PSG setup included electroencephalogram (EEG), bilateral electrooculogram (EOG), electromyogram (EMG) of the submental and tibialis anterior muscles, electrocardiogram (ECG), airflow measurement (nasal pressure transducer and thermistor), thoracoabdominal effort belts, pulse oximetry, and body position sensors. Sleep stages were scored by trained technicians following AASM criteria. For this project, we analyzed data from night1-PSG, which was completely unrestricted. The following variables were extracted: nocturnal sleep latency (n-SL), rapid eye movement (REM) sleep latency (n-REML), total sleep time (n-TST), time in bed (n-TIB), sleep efficiency (SE), percentage of TST spent in N1,

N2, N3, and REM sleep (N1%, N2%, N3%, R%), and wake after sleep onset (WASO). The number of transitions between sleep stages and wakefulness was computed, and indices of transitions per hour of time TIB were calculated as measures of sleep fragmentation. Namely, as previously published, the following transition indices were considered: index of bidirectional transitions between wakefulness and any sleep stage (tW-S-index); index of unidirectional transitions from N2-N3-REM stages to N1 or wakefulness (W/N1-index); index of bidirectional transitions between wakefulness, NREM, and REM sleep (tW-NR-R-index); index of bidirectional transitions between NREM and REM sleep (tNR-R-index) [24,25].

From day 2-PSG (day 1-PSG not analyzed as starting time depends on admission of the patient), the number of spontaneous naps (d-NAP), total sleep time during the naps (d-TST), and the number of sleep-onset REM periods during the naps (d-SOREMPs) were collected.

The mean SL (mSL) and number of SOREMPs from the MSLT were also collected.

## 2.7. Statistical analysis

For the analysis, the cohort was divided into two groups: psychosis + NT1, including patients who developed psychotic comorbidities, and NT1-nonpsychotic, consisting of those without such comorbidities.

The descriptive statistics were reported as medians with means and standard deviation (SD) for continuous variables and as numbers (n) and percentages (%) for categorical variables. Comparisons between the psychosis + NT1 and NT1-non psychotic groups were performed using the Mann-Whitney *U* test for continuous variables and the Chi-square test for categorical variables.

A value of  $p < 0.05$  was considered significant. All statistical analysis was performed using SPSS Statistics version 26 (IBM).

## 3. Results

One-hundred-five patients (57.9% male) were recruited. The study sample included 9 children with psychiatric comorbidities and 96 children without psychiatric comorbidities.

### 3.1. Characteristics of patients with NT1 and psychosis

Diagnoses included very early-onset schizophrenia ( $n = 2$ ), schizophrenia ( $n = 2$ ), psychosis not otherwise specified ( $n = 2$ ), obsessive-compulsive disorder with psychotic features.

( $n = 1$ ), autism spectrum disorder with psychotic features ( $n = 1$ ), and psychotic depression ( $n = 1$ ).

Although the diagnoses were heterogeneous, all patients shared the presence of psychotic symptoms.

Tables 1a and 1b and 1b summarize the clinical trajectory of each patient. Table 1a focuses on the temporal sequence of NT1 onset, neurophysiological diagnosis, treatment initiation, and emergence of psychiatric symptoms, while Table 1b reports psychiatric comorbidities, clinical features, and treatments. Full narrative descriptions of the nine clinical cases are provided in the Supplementary Material (Supplementary Text 1).

Social withdrawal was documented as a premorbid psychiatric symptom in 62.5% of patients with psychosis + NT1. In addition, qualitative review of clinical records revealed other recurrent premorbid features, including cognitive rigidity, obsessive traits, irritability, and atypical behavioral patterns, which were not systematically quantifiable but consistently reported across several cases.

In six patients, psychiatric symptoms emerged within a few months after initiating NT1 treatment; in the remaining three, they manifested between one and three years following NT1 onset. All patients in the NT1+psychosis group (9/9, 100%) received sodium oxybate at some point during follow-up, compared with 76/96 (79%) in the Control-NT1 group; this difference was not statistically significant ( $p = 0.20$ ).

**Table 1a**  
Temporal clinical trajectory of NT1 and onset of psychotic symptoms.

| Case ID | Prodromal psychiatric symptoms at NT1 onset        | Family history of psychiatric disorders                                              | Characteristics of psychiatric symptoms                                                                                        | Psychiatric diagnosis                                                        | Pharmacological treatment for psychiatric disorder                            | Pharmacological treatment for NT1                                                                                                                                                                                      |
|---------|----------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Case 1  | Social withdrawal and anxiety symptoms             | Positive for depressive disorders                                                    | Visual hallucinations of cartoons and animals, delusions, stereotypies, and disorganized behavior                              | Very early onset schizophrenia                                               | Several drug regimens with Risperidone, Aripiprazole and Olanzapine           | First treatment with Modafinil interrupted for psychomotor agitation. Second treatment with Sodium Oxybate interrupted for hallucinations and delusions                                                                |
| Case 2  | Social withdrawal and emotional dysregulation      | Negative                                                                             | Visual hallucinations of cartoons, aggressive behaviors, delusions, disorganized behavior and obsessive behaviors towards food | Very early onset schizophrenia                                               | Several drug regimens with Risperidone, Aripiprazole, Promazine and Clozapine | First treatment with Modafinil interrupted for psychomotor agitation. Second treatment with Sodium Oxybate interrupted for aggressive behaviors, visual hallucinations, and delusions. Third treatment with Pitolisant |
| Case 3  | Social withdrawal and irritability                 | Positive for attention deficit hyperactivity disorder and specific learning disorder | Obsessive behaviors, rituals, and suspiciousness                                                                               | Autism spectrum disorder and intellectual disability with psychotic symptoms | Sertraline                                                                    | First treatment with Sodium Oxybate                                                                                                                                                                                    |
| Case 4  | Social withdrawal                                  | Positive for autism spectrum disorder                                                | Suspiciousness and delusions                                                                                                   | Schizophrenia                                                                | Several drug regimens with Sertraline, Aripiprazole                           | First treatment with Sodium Oxybate interrupted for positive symptoms                                                                                                                                                  |
| Case 5  | None                                               | Positive for Specific Learning Disorder                                              | Obsessive behaviors towards sleep, rituals, aggressivity and delusions                                                         | Obsessive compulsive disorder with psychotic symptoms                        | Sertraline                                                                    | First treatment with Sodium Oxybate interrupted for aggressivity and delusions. Second treatment with Pitolisant                                                                                                       |
| Case 6  | Social withdrawal and irritability                 | Negative                                                                             | Low mood, aggressivity and paranoid delusions                                                                                  | Psychotic depression                                                         | Several drug regimens with Aripiprazole, Risperidone and Quetiapine           | First treatment with Sodium Oxybate interrupted for hallucinations. Second treatment with Pitolisant                                                                                                                   |
| Case 7  | None                                               | Positive for Panic Disorder                                                          | Visual hallucinations of children and animals                                                                                  | Psychosis not otherwise specified                                            | -                                                                             | First treatment with Sodium Oxybate. Second treatment with Pitolisant                                                                                                                                                  |
| Case 8  | None                                               | Negative                                                                             | Kinesthetic and auditory hallucinations, delusions                                                                             | Schizophrenia with predominant negative symptoms                             | Several drug regimens with Risperidone, Aripiprazole and Haloperidol          | First treatment with Sodium Oxybate interrupted for hallucinations. Second treatment with Modafinil                                                                                                                    |
| Case 9  | Social withdrawal, anxiety, and behavioral changes | Negative                                                                             | Delusions of persecution, auditory hallucinations, social withdrawal, mutism, disorganized behavior                            | Psychosis not otherwise specified                                            | Haloperidol, Aripiprazole, Olanzapine                                         | First treatment with Sodium Oxybate                                                                                                                                                                                    |

**Table 1b**  
Psychiatric symptomatology, diagnoses, and treatments in the NT1-psychosis.

| Case ID | Age at NT1 onset | Age at NT1 diagnosis (with PSG/MSLT) | Age at treatment start for NT1 | Time of psychotic symptom onset            | Ongoing NT1 medication at psychosis onset | Temporal relation to NT1 treatment        |
|---------|------------------|--------------------------------------|--------------------------------|--------------------------------------------|-------------------------------------------|-------------------------------------------|
| Case 1  | 9                | 15                                   | 10                             | Within months after NT1 diagnosis behavior | Modafinil                                 | Emerges after treatment initiation        |
| Case 2  | 7                | 9                                    | 10                             | At NT1 onset                               | Sodium Oxybate                            | Present before treatment                  |
| Case 3  | 3                | 3                                    | 3                              | 1 year after NT1 diagnosis                 | Pitolisant                                | Persisted after treatment discontinuation |
|         |                  |                                      |                                |                                            | Sodium Oxybate                            |                                           |
| Case 4  | 10               | 10                                   | 10                             | Within months after treatment initiation   | Venlafaxine                               | Worsened after treatment                  |
| Case 5  | 11               | 13                                   | 11                             | 1–3 years after NT1 onset                  | Sodium Oxybate                            | Emerges during follow-up                  |
| Case 6  | 5                | 11                                   | 11                             | At NT1 onset                               | Pitolisant                                | Independent of treatment                  |
| Case 7  | 7                | 13                                   | 7                              | Within months after NT1 diagnosis          | Sodium Oxybate                            | Persisted despite treatment withdrawal    |
| Case 8  | 15               | 17                                   | 15                             | 2 years after NT1 onset                    | Pitolisant                                | No temporal improvement after withdrawal  |
| Case 9  | 11               | 16                                   | 14                             | Within first year after NT1 diagnosis      | Sodium Oxybate                            | Not clearly medication-related            |
|         |                  |                                      |                                |                                            | Modafinil                                 |                                           |
|         |                  |                                      |                                |                                            | None                                      |                                           |

In all cases, psychotic symptoms were characterized by persistent hallucinations and/or delusional beliefs that were not restricted to sleep–wake transitions and required psychiatric intervention.

### 3.2. Comparisons of clinical variables

Patients with and without psychosis did not differ in sex, age at onset of symptoms of NT1, and age at diagnosis. A positive family history of

psychiatric disorders was significantly more frequent among patients with psychosis (55.6 vs. 2.2%,  $p < 0.01$ ). CSF hypocretin-1 levels were significantly lower in the psychotic phenotype group, while no significant differences emerged in body mass index, frequency of HLA-DQB1\*06:02 presence, or ESS-CHAD scores. Regarding cataplexy, the frequency of daily episodes ( $\geq 1$  per day) did not differ between patients with and without psychosis (67% vs. 46%,  $p = 0.50$ ).

The frequency of hypnagogic/hypnopompic hallucinations (55.5% vs. 44.2%,  $p = 0.46$ ) and sleep paralysis (11% vs. 32.6%,  $p = 0.27$ ) did not differ significantly between groups.

Table 2 summarizes comparisons of demographic and clinical characteristics.

### 3.3. Comparisons of neurophysiological features

Table 3 presents nighttime and daytime PSG and MSLT parameters. Compared to patients without psychosis, children with psychosis had significantly decreased n-TST and SE, and an increased number of d-Naps. In the group with psychosis, there was a trend toward longer n-REML ( $p = 0.08$ ), lower N2% ( $p = 0.07$ ), longer n-TST ( $p = 0.09$ ), and fewer MSLT SOREMPs ( $p = 0.08$ ), although they did not reach statistical significance.

Patients with psychosis exhibited significantly higher tW-Si and tW-NR-Ri, indicating a more marked nocturnal sleep fragmentation. No significant differences were found for tNR-Ri and W/N1-index.

**Table 2**

Demographic and clinical characteristics of the groups.

|                                                       | NT1+psychosis (n = 9) | Control- NT1 (n = 96) | P-value |
|-------------------------------------------------------|-----------------------|-----------------------|---------|
| <b>Sex, (male), n (%)</b>                             | 5 (55.5)              | 58 (60.4)             | 0.27    |
| <b>BMI, (kg/m<sup>2</sup>), Mean (SD)</b>             | 24.15 (3.26)          | 23.37 (5.20)          | 0.39    |
| <b>Narcolepsy duration (years), Mean (SD)</b>         | 2.89 (2.44)           | 1.98 (2.14)           | 0.35    |
| <b>Age at diagnosis (years), Mean (SD)</b>            | 10 (4.1)              | 10.95 (2.78)          | 0.45    |
| <b>Age the onset of narcolepsy (years), Mean (SD)</b> | 9.1 (3.5)             | 9 (2.52)              | 0.92    |
| <b>ESS-CHAD, (total score) Mean (SD)</b>              | 14.88 (2.64)          | 14.36 (3.72)          | 0.81    |
| <b>CSF Hypocretin (pg/mL), Mean (SD)</b>              | 4.95 (9)              | 18.89 (24.17)         | 0.02    |
| <b>HLA-DQB1*06:02, n (%)</b>                          | 9 (100)               | 89 (94.7)             | 1.00    |
| <b>Positive psychiatric family history, n (%)</b>     | 5 (55.6)              | 2 (2.2)               | < 0.01  |
| <b>Frequency of cataplexy, n (%)</b>                  |                       |                       |         |
| ≥ 1 day                                               | 6 (67)                | 44 (46)               | 0.50    |
| 1/week - 1/day                                        | 2 (22)                | 42 (44)               |         |
| 1/month - 1/week                                      | 1 (11)                | 8 (9)                 |         |
| 1/year - 1/month                                      | 0                     | 1 (1)                 |         |
| <b>Cataplexy duration, n (%)</b>                      |                       |                       |         |
| 2min - 10min                                          | 2 (22)                | 8 (9)                 | 0.65    |
| 10s - 2min                                            | 0                     | 20 (20)               |         |
| < 10s                                                 | 7 (78)                | 69 (71)               |         |
| <b>Emotional triggers of cataplexy, n (%)</b>         |                       |                       |         |
| Angry                                                 | 5 (55.5)              | 42 (43.5)             | 0.53    |
| Laughter                                              | 7 (78)                | 91 (95)               | 0.10    |
| While telling a joke                                  | 8 (89)                | 70 (73)               | 0.38    |
| Sudden surprise                                       | 1 (11)                | 14 (15)               | 0.77    |
| Unexpected encounter                                  | 1 (11)                | 10 (10.5)             | 0.96    |
| <b>Body distribution of cataplexy, n (%)</b>          |                       |                       |         |
| Generalized weakness                                  | 8 (89)                | 61 (64)               | 0.21    |
| Partial weakness of the face/jaw                      | 9 (100)               | 84 (87)               | 0.36    |
| Partial weakness of the neck                          | 8 (89)                | 76 (79)               | 0.72    |
| Partial weakness of the knees                         | 7 (78)                | 76 (79)               | 0.68    |
| Partial weakness of the arms/hands                    | 4 (44)                | 66 (69)               | 0.10    |
| <b>Hypnagogic/hypnopompic hallucinations, n (%)</b>   | 5 (55.5)              | 42 (44.2)             | 0.46    |
| <b>Sleep paralysis, n (%)</b>                         | 1 (11)                | 31 (32.6)             | 0.27    |

BMI = Body Mass Index; ESS-CHAD = Epworth Severity Scale for Children and Adolescents; CSF = Cerebrospinal fluid.

**Table 3**

Comparison of nighttime, sleep-wake instability, and daytime sleep parameters between NT1+psychosis and control- NT1.

|                                          | NT1+psychosis (n = 9) | Control- NT1 (n = 96) | P-value |
|------------------------------------------|-----------------------|-----------------------|---------|
| <b>NIGHTTIME, Mean (SD)</b>              |                       |                       |         |
| n-TST (min)                              | 430.83 (86.48)        | 503.71 (76.79)        | 0.03    |
| n-SL (min)                               | 6 (6.13)              | 3.84 (3.64)           | 0.25    |
| SE (%)                                   | 75.6 (15.62)          | 89.47 (7.60)          | 0.02    |
| WASO (min)                               | 110.2 (78.5)          | 59.42 (48.89)         | 0.10    |
| N1%(% of TST)                            | 15.06 (12.37)         | 10.54 (5.19)          | 0.30    |
| N2%(% of TST)                            | 27.59 (16.09)         | 38.48 (7.32)          | 0.07    |
| N3%(% of TST)                            | 32.76 (14.66)         | 27.25 (9.20)          | 0.29    |
| REM%(% of TST)                           | 18.1 (9.16)           | 23.78 (6.50)          | 0.10    |
| n-REML (min)                             | 8.1 (17.4)            | 24.45 (52.34)         | 0.08    |
| <b>Sleep-wake transitions, Mean (SD)</b> |                       |                       |         |
| tW-S-index (n/hour of TIB)               | 11.57 (5.33)          | 6.41 (3.08)           | < 0.01  |
| tNR-R-index (n/hour of TIB)              | 2.88 (1.81)           | 3.05 (1.10)           | 0.48    |
| W/N1-index (n/hour of TIB)               | 5.10 (1.78)           | 4.61 (1.38)           | 0.48    |
| tW-NR-R-index (n/hour of TIB)            | 27.11 (10.04)         | 17.11 (6.33)          | < 0.01  |
| <b>DAYTIME, Mean (SD)</b>                |                       |                       |         |
| d-Nap (n)                                | 3.68 (1.82)           | 2.64 (1.68)           | 0.04    |
| d-SOREMP (n)                             | 2.11 (1.90)           | 2.88 (1.46)           | 0.26    |
| d-TST (min)                              | 181.4 (85.9)          | 126.17 (72.42)        | 0.09    |
| <b>MSLT</b>                              |                       |                       |         |
| MSLT mSL (min)                           | 3.57 (4.17)           | 3.25 (2.59)           | 0.73    |
| MSLT SOREMPs (n)                         | 2.11 (1.90)           | 4.32 (0.92)           | 0.08    |

d = daytime = daytime; n = nocturnal; MSLT = multiple sleep latency test; N1, N2, and N3 = non-rapid eye movements sleep stage 1, 2, and 3; NT1 = narcolepsy type 1; REML = rapid eye movements sleep latency; SE = sleep efficiency; sEDS = subjective excessive daytime sleepiness; SL = sleep latency; SOREMP = sleep-onset rapid eye movement period; TST = total sleep time; TIB = time in bed; WASO = wake after sleep onset; tW-S-index = sleep-wakefulness transition index; tNR-R-index = NREM-REM sleep transition index; W/N1-index = N2/N3/R transitions to wakefulness/N1; tW-NR-R-index = wakefulness-NREM-REM sleep transition index.

## 4. Discussion

We report on a peculiar NT1+psychotic phenotype in pediatric patients: in this subgroup, the psychiatric presentations, though diverse in diagnosis, share core psychotic features close to disease onset and biological underpinnings. Although the psychiatric diagnoses within the NT1+psychotic group were heterogeneous, all patients shared the presence of persistent psychotic symptoms temporally close to narcolepsy onset. This common temporal pattern justifies examining this subgroup as a distinct clinical phenotype. At the same time, grouping schizophrenia, psychotic depression, obsessive-compulsive disorder with psychotic features, and autism spectrum disorder with psychosis inevitably introduces clinical and neurobiological heterogeneity. Therefore, the identified phenotype should be interpreted as hypothesis-generating and as a clinically meaningful pattern within the NT1 spectrum, rather than representing a distinct diagnostic entity.

Given the exploratory design and multiple comparisons, statistical findings and p-values should be interpreted with caution.

We could summarize the main features of this specific NT1-psychotic phenotype as follows: a) first-degree family history of mood/psychotic disorders; b) premorbid social withdrawal, cognitive rigidity, obsessive traits; c) rapid emergence of persistent hallucinations or delusions not clearly linked to sleep-wake transitions; d) marked nocturnal fragmentation/reduced SE despite typical NT1 management; e) increased daytime napping despite stable therapy.

The emergence of psychotic symptoms in NT1 raises critical clinical questions and suggests a possible link with hypocretin/orexin dysfunction affecting emotional and arousal regulation.

Interestingly, there were no significant differences in the age at NT1 onset or the time to first hospitalization between the NT1+psychotic and

NT1-nonpsychotic groups. This supports the idea that the core clinical phenotype of NT1 remains consistent, with psychotic features adding complexity rather than signifying a completely different presentation. The matching approach used in our study may have further reduced the impact of developmental differences on these comparisons.

Patients with NT1+psychotic phenotype were significantly more likely to have a positive family history of psychiatric disorders, particularly mood or psychotic conditions. This finding aligns with evidence that first-degree relatives of individuals with schizophrenia or bipolar disorder are at increased risk for psychopathology, suggesting a heritable vulnerability [26,27]. Indeed, in the context of childhood NT1, familial history may indicate an underlying vulnerability that interacts with hypocretin/orexin deficiency during neurodevelopment, rather than reflecting a more severe hypocretin breakdown. Further, larger genetic studies should test the hypothesis that NT1 may interact with a complex genetic background, favoring different psychiatric comorbidities.

Notably, CSF hypocretin-1 levels were significantly lower in the NT1-psychotic phenotype group compared to controls; however, measurements in this low range are subject to greater assay-related variability, and both group means fall far below the diagnostic threshold for hypocretin deficiency (<110 pg/mL), indicating that both groups were severely and comparably hypocretin-deficient in absolute clinical terms. The magnitude of this numerical difference should therefore be interpreted with caution and requires replication using standardized assay protocols with larger sample sizes. Given the widespread projections of hypocretinergic neurons to key dopaminergic regions, such as the ventral tegmental area (VTA), prefrontal cortex (PFC), and nucleus accumbens, hypocretin deficiency may impact dopaminergic tone and contribute to the development of psychotic symptoms, as suggested in models of schizophrenia [28–30]. Dopaminergic dysregulation, a hallmark of schizophrenia, may also play a role in the pathophysiology of narcolepsy, particularly in patients with psychiatric comorbidities. Importantly, hypocretin deficiency is neither specific to psychotic outcomes nor sufficient, on its own, to explain the broad spectrum of psychiatric comorbidities observed in NT1. Although ADHD, anxiety, and mood disorders are common in pediatric NT1, these conditions are more likely related to chronic sleep–wake instability, disease burden, and psychosocial and neurodevelopmental factors rather than to hypocretin deficiency per se.

In this framework, hypocretin-related alterations in arousal regulation may represent a permissive background condition. Psychosis may emerge only in a subset of patients in whom this background interacts with additional modifiers, including strong familial liability for psychotic or mood disorders, early neurodevelopmental deviations, and critical periods of brain maturation. In the absence of these converging factors, the same disease context may instead manifest as more common non-psychotic psychiatric comorbidities. Within this vulnerability framework, it can be hypothesized that hypocretinergic dysfunction may partly contribute to altered meso-cortical connectivity in NT1, particularly when interacting with developmental and genetic risk factors [31].

Neuroimaging studies further support this interpretation. Functional magnetic resonance imaging (fMRI) documented widespread alterations in intrinsic brain activity in NT1, involving thalamic, striatal, cingulate, insular, occipital, and somatosensory regions, pointing to disrupted large-scale networks that subserve arousal regulation, sensory integration, and emotional processing [32]. Similar evidence in early-onset psychosis shows widespread dysconnectivity involving prefrontal, cingulate, and temporal nodes of the default mode and salience networks, consistent with disrupted large-scale integration mechanisms that normally support salience allocation and cognitive-emotional regulation [33]. Moreover, recent pediatric fMRI data show that even basic affective–motor reactions such as spontaneous laughter recruit an abnormal cortico–subcortical profile in NT1, characterized by over-activation of the motor–premotor cortex, thalamus, and particularly the

subthalamic nucleus/zona incerta (STN/ZI), a region absent in controls and thought to reflect compensatory engagement of arousal-regulation circuits in the context of hypocretin deficiency [34].

Overall, these findings strengthen the hypothesis that the NT1+psychotic phenotype emerges from the interaction between hypocretinergic dysfunction, which affects dopaminergic and arousal-regulating pathways, and the large-scale network vulnerabilities documented by functional imaging, compounded by the developmental susceptibility of fronto-striatal circuits and the chronic instability of arousal-state transitions.

Moreover, evidence from amphetamine-induced psychosis can lead to persistent alterations in dopamine transporter availability, even in individuals without prior psychiatric disorders [31,35–38]. Furthermore, sleep–wake instability, quantified through tW-S-index and tW-NR-R-index, was significantly more elevated in the NT1+psychosis. These findings indicate a more severe phenotype, likely shaped by the additive impact of hypocretin loss and sleep–wake fragmentation on neural systems regulating arousal and cognition [24]. However, although TST and SE were statistically reduced in the psychosis group, their absolute differences were relatively small. These nocturnal variations should therefore be interpreted with caution, as modest PSG changes in pediatric populations may reflect contextual or clinical factors not fully controlled for in this study.

These patterns suggest that psychotic symptoms in NT1 may not reflect isolated comorbidities but rather manifestations of a latent vulnerability driven by hypocretinergic dysfunction and unstable state transitions. This framework, supported by our qualitative case review, highlights the neurodevelopmental complexity of this phenotype, which seems to arise from the interaction between early circuit-level changes and sleep–wake dysregulation. It is also important to acknowledge that several clinical factors, such as medication exposure at the time of PSG, duration of NT1 before psychosis onset, comorbid sleep disorders, and psychosocial stressors, may influence sleep–wake measures and psychiatric expression. These variables were not systematically controlled for in our study and may partly contribute to the observed sleep differences.

Beyond these PSG findings, across the nine clinical cases, recurring developmental trajectories were revealed, often characterized by a gradual progression from prodromal symptoms, such as social withdrawal, obsessive thinking, irritability, and altered sensory-perceptual experiences, to overt psychosis. In several cases, the boundary between hypnagogic hallucinations and psychotic phenomena became increasingly blurred, particularly in the context of severe sleep fragmentation and arousal instability.

Early obsessive-compulsive traits and rigid cognitive styles were frequent antecedents, suggesting dysfunction within fronto-striatal circuits involved in emotional regulation and cognitive flexibility. Additional features, such as autistic traits and cognitive regression, were also observed, pointing to broader developmental deviations beyond the sleep–wake domain.

Given that most cases developed psychotic symptoms temporally associated with sodium oxybate, medication exposure is discussed primarily in relation to oxybate, with stimulant use considered within the broader literature. Regarding medication exposure, when temporal information was available, psychotic symptoms either preceded initiation of wake-promoting agents or persisted after discontinuation. Notably, all patients in the NT1+psychosis group received sodium oxybate at some point during follow-up, and in most cases, treatment was discontinued because of the emergence or worsening of psychotic symptoms. However, sodium oxybate use was also highly prevalent in the Control-NT1 group (76/96, 79%), with no statistically significant difference between groups, suggesting that this high exposure likely reflects a local prescribing practice for NT1 management at our center rather than a specific pharmacological trigger for psychosis.

However, symptoms persisted and did not systematically remit after oxybate discontinuation. Although stimulant-induced psychosis is a

recognized phenomenon in NT1, the limited and heterogeneous exposure to stimulants in our case series does not allow firm conclusions regarding their causal role; when used, psychotic symptoms either preceded treatment initiation or persisted after discontinuation [15,38]. These observations indicate that iatrogenic effects alone cannot fully explain the clinical picture. Instead, the coexistence of vivid hypnagogic hallucinations, arousal instability, and behavioral disorganization in NT1 complicates distinguishing it from primary psychotic disorders. While dopaminergic stimulants are often discussed as potential contributors to psychotic worsening, our findings and the clinical courses of several cases suggest they are unlikely to be the primary cause in this group [39].

Similarly, selective serotonin reuptake inhibitors (SSRIs) have also been debated as possible triggers of psychotic symptoms, particularly in vulnerable youth, although evidence remains inconsistent and causal links are not firmly established [40].

In most patients, psychotic symptoms either appeared before wake-promoting agents/antidepressants use or continued despite dose reduction or stopping, suggesting that wake-promoting agents might only amplify an already unstable arousal–emotional system rather than directly cause psychosis.

Overall, medication effects in NT1 should be interpreted within a broader vulnerability–stress framework: pharmacological agents may modulate symptom severity or timing, but the emergence of persistent psychotic phenomena appears more tightly linked to the interaction between hypocretin deficiency, neurodevelopmental susceptibilities, and profound instability in arousal regulation.

Taken together, these clinical patterns resonate with what some authors have tentatively described as “narcoleptic psychosis”, not as a distinct diagnostic entity, but as a conceptual space that captures the blurred boundaries between NT1-related arousal instability, vivid dream–wake phenomena, and true psychotic symptoms [41–43].

Seen through this lens, our findings support the idea that persistent psychotic manifestations in NT1 emerge from the interaction between intrinsic neurobiological vulnerabilities and external modulators (including medications), rather than from pharmacological effects alone.

Importantly, these patients represent diagnostically and therapeutically challenging cases. The convergence of sleep-related hallucinations, behavioral disorganization, and emotional dysregulation can easily blur the boundaries between narcoleptic features and emerging psychosis, particularly in developmental age. This ambiguity may lead to delays in appropriate recognition, misdiagnoses with primary psychotic disorders, or misattributions to medication side effects.

Moreover, standard treatment protocols for NT1 might be inadequate or even unsuitable for this subgroup. For instance, while stimulant use, despite being vital for controlling excessive daytime sleepiness, may worsen underlying vulnerabilities, antipsychotic medications could unintentionally suppress cataplexy or REM-related phenomena, thereby obscuring the true clinical presentation. The absence of clear diagnostic criteria or management guidelines for psychiatric symptoms in NT1 increases the uncertainty and may lead to fragmented care.

Early recognition of atypical psychiatric profiles in NT1, especially those with psychotic features, is essential to enhance diagnostic accuracy and tailor personalized management strategies [9,44,45].

This investigation has several limitations. Its retrospective design may have introduced selection bias. Psychiatric diagnoses were based on clinical records rather than standardized, structured assessments, which may have led to misclassification. Given the exploratory nature of the study and the limited sample size of the NT1-psychotic group, we did not apply formal corrections for multiple comparisons; therefore, p-values should be interpreted with caution and the results considered hypothesis-generating. Medication exposure at the time of PSG (including stimulants, antidepressants, and antipsychotics), psychiatric treatments, disease duration before psychosis onset, comorbid sleep disorders, and psychosocial stressors were not systematically

documented and thus could not be included as covariates. In addition, detailed cataplexy severity, BMI-adjusted interpretations, and standardized measures of pubertal stage or medication washout protocols were unavailable for several participants. These unmeasured variables may have contributed to some of the observed differences in sleep architecture.

Together with the small sample size and the diagnostic heterogeneity of the psychosis subgroup, these limitations reduce mechanistic interpretability and increase the risk of type I error. Future prospective studies should incorporate systematic assessment of these variables to clarify their role in shaping sleep–wake patterns and psychiatric outcomes in pediatric NT1.

Despite these limitations, our results provide preliminary evidence supporting the existence of a distinct clinical phenotype in pediatric NT1. This subtype is not exceptional, with several percent of our population being affected. Future prospective studies will be essential to confirm this emerging phenotype, further address its genetic predisposition, and tailor early interventions aimed at improving long-term psychiatric outcomes in NT1. Ultimately, identifying and characterizing this NT1-psychotic phenotype may represent the first step toward a nosologically meaningful subtype, which has implications for early diagnosis, monitoring, and personalized intervention.

## 5. Conclusion

The coexistence of primary psychiatric disorders, such as schizophrenia, with NT1 presents substantial diagnostic and therapeutic challenges, including the risk of misdiagnosis, inappropriate treatment, and poorer psychosocial outcomes, such as social withdrawal and mood dysregulation.

Given the influence of sleep–wake disturbances on psychiatric presentations, clinicians should remain alert to the possibility of overlapping or misattributed symptoms during routine evaluations. In particular, distinguishing between primary psychotic disorders and psychotic features secondary to NT1 is essential to guide appropriate management.

Premorbid features, such as social withdrawal, obsessive thinking, or cognitive rigidity, coupled with positive first-degree family history for psychiatric disorders, may represent early indicators of emerging psychiatric complications in NT1.

Taken together, our findings support the existence of a distinct clinical NT1-psychotic pediatric phenotype, marked by core psychotic symptoms, reduced CSF hypocretin-1 levels, and pronounced sleep–wake instability. Early recognition of this phenotype may facilitate more accurate diagnosis, enable timely and targeted interventions, and ultimately improve long-term outcomes for affected children.

## CRedit authorship contribution statement

**Valentina Baldini:** Writing – original draft, Methodology, Data curation, Conceptualization. **Martina Gnazzo:** Writing – original draft, Methodology, Data curation. **Francesco Biscarini:** Writing – original draft, Methodology, Investigation. **Oliviero Bruni:** Writing – original draft, Validation. **Giorgia Varallo:** Writing – original draft. **Michel Lecendreux:** Writing – review & editing. **Emmanuel Mignot:** Writing – review & editing. **Diana De Ronchi:** Writing – review & editing. **Asia Shahbaz:** Writing – review & editing. **Stefano Vandi:** Writing – review & editing, Methodology. **Fabio Pizza:** Writing – review & editing, Supervision, Formal analysis, Data curation. **Giuseppe Plazzi:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

## Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2026.109246>.

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