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Co-occurrence of anxiety and depressive symptoms, suicidal thoughts, and hopelessness in patients with narcolepsy type 1

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ABSTRACT

Objective: To assesses the prevalence and co-occurrence of anxiety, depressive symptoms, suicidal thoughts, and hopelessness in patients with narcolepsy type 1 (NT1).

Patients/Methods. In this cross-sectional study, 127 patients with NT1 (mean age 38.2 ± 15.5 years, 53.5 % female) and 131 controls (mean age 37.4 ± 14.3 years, 59.5 % female) matched for age, sex, and education, filled in the following validated questionnaires: Beck Depression Inventory-II (BDI), State-Trait Anxiety Inventory (STAI), and Beck Hopelessness Scale (BHS). Comparisons between groups and multivariable logistic regression analyses were performed.

Results: Patients with NT1 presented significantly higher scores in BDI, suicidal thoughts (BDI-item-9), STAI-trait, STAI-state, and BHS than controls. Adjusted for age, sex, and educational level, NT1 was significantly associated with depressive symptoms (BDI≥13; OR 3.23, 95%CI 1.71–6.10), trait anxiety symptoms (STAI-trait≥38; OR 1.91, 95%CI 1.14–3.21), co-occurrence of BDI≥13 with STAI-trait≥38 (OR 2.72, 95%CI 1.47–5.05), and with STAI-state≥38 (OR 2.24, 95%CI 1.17–4.30), and moderate to severe hopelessness (BHS≥9; OR 2.95, 95%CI 1.55–5.63).

Conclusions: Patients with NT1 present a multidimensional psychiatric burden and comorbidity between symptoms of depression and anxiety and suicidal thoughts, a concern that deserves tailored interventions.

1. Introduction

Narcolepsy type 1 (NT1) is a central disorder of hypersomnolence [1] associated with anxiety and depressive symptoms in 19–53 % and 13–35 % of patients, respectively [2,3]. These associations have an impact on the NT1 severity and therapeutic options [4].

Anxiety and depression also share some pathogenetic mechanisms and therefore can often coexist [5]. This association is common in the general population, in primary care, and in physically ill patients and implies higher symptom severity and persistence [6,7]. However, few studies have addressed the prevalence of anxiety and depression comorbidity in patients with narcolepsy, and found this association in more than 20 % of cases [8,9], and more frequently in women [9] Comorbidity may foster suicidal ideation, frequent in patients with narcolepsy who have depression [2,4].

The present study aims to increase our knowledge by assessing the co-occurrence of the presence of anxiety, depressive symptoms, suicidal thoughts, and hopelessness –as yet unexplored in the hypersomnia area– in patients with NT1 versus controls.

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Abbreviations:

BDI = Beck Depression Inventory-II
BHS = Beck Hopelessness Scale
ESS = Epworth Sleepiness Scale
NT1 = narcolepsy type 1
STAI = State-Trait Anxiety Inventory

2. Methods

2.1. Participants and procedures

The cross-sectional study included adult patients with diagnosis of NT1 (established with night-polysomnography, multiple sleep latency test, and cerebrospinal fluid hypocretin-1 dosage according to the International Classification of Sleep Disorders-3rd edition) [1] participating in the "Psychological impact of Narcolepsy" study [10], recruited during routine outpatient visits at the Narcolepsy Center of the IRCCS – Istituto delle Scienze Neurologiche di Bologna. All patients were followed up and treated at the Narcolepsy Center by the same team of neurologists specialized in central disorders of hypersomnolence. A control group, matched for age, sex, and educational level was recruited from people without sleep disorders who accompanied their relatives to neurology outpatients' clinics [10].

The study was approved by the local Ethical Committee (Comitato Etico Interaziendale Bologna-Imola, protocol number: 16,181). All participants provided their written informed consent.

Psychiatric symptoms were investigated with the following validated questionnaire.

- Beck Depression Inventory-II (BDI) with the severity of depressive symptoms categorized as mild (13–18 points), moderate (19–29 points), and severe (>30 points) [11]. Item 9 of the BDI (BDI-item-9), concerning suicidality risk, was also considered as an isolated item [11];
- State-Trait Anxiety Inventory (STAI) [12], which assesses state and trait anxiety symptoms as slight (30–37 points), moderate (38–44 points), and serious (≥45 points) [13];
- Beck Hopelessness Scale (BHS), the score of which measures the severity of hopelessness, ranging from mild (4–8 points), to moderate (9–14 points), to severe (15–20 points) [14].

Clinical features of NT1 were explored in the patients' group with the Epworth Sleepiness Scale (ESS) [15] and a structured clinical interview assessing the presence of core NT1 symptoms, age at onset and at diagnosis, and current pharmacological treatment.

2.2. Statistical analysis

The Kruskal-Wallis test was used to compare continuous variables (presented as median [inter-quartile range]) and the Chi-square test was used to compare categorical variables (presented as numbers and percentages) between patients and controls. The post-hoc analyses were adjusted for multiple comparisons using Bonferroni method. Correlations between BDI, STAI, and BHS were assessed with Spearman's Rho. Multivariable logistic regression models evaluated the relation between depressive symptoms (i.e., BDI≥13) [16], symptoms of trait and state anxiety (i.e., STAI≥38) [13], their combination, moderate-to-severe hopelessness (BHS≥9) [17] (dependent variables) and NT1, age, sex, and lower educational level (independent variables), expressed as Odds Ratio (OR) with 95 % Confidence Interval (95%CI). Within the NT1 group, clinical features were compared between patients stratified by the presence BDI-item-9≥1, and BHS≥9. P-values ≤0.05 were considered statistically significant.

Analyses were performed using STATA SE 14.

3. Results

One-hundred-twenty-seven patients with NT1 (39 [24–48] years, 53.5 % female) and 131 controls (35 [24–48] years, 59.5 % female) were included. Among patients, 92.3 % were under treatment for narcolepsy, 27 on low-dose antidepressants as anticataplectic (clinical features of patients are reported in Supplemental Table 1).

Patients with NT1 presented significantly higher scores than controls on BDI, STAI-trait, STAI-state, and BHS. Patients with NT1 had more frequent BDI≥13 ($p = 0.004$), BDI-item-9≥1 ($p < 0.001$), BHS≥9 ($p = 0.002$), STAI-trait≥38 ($p = 0.015$). No differences emerged in frequencies of STAI-state≥38 ($p = 0.559$). Patients also showed significantly higher rates of coexistence of BDI≥13 with both STAI-trait≥38 and STAI-state≥38 than controls (Table 1). BDI, BDI-item-9, STAI-trait, STAI-state, and BHS were significantly correlated with each other in both NT1 and controls (Supplemental Table 2).

Adjusting for age, sex, and educational level, NT1 was significantly associated with BDI≥13, STAI-trait≥38, co-occurrence of BDI≥13 with both STAI-trait≥38 and STAI-state≥38, and associated with BHS≥9, while it was not associated with STAI-state≥38 alone. Older age was associated with BHS≥9, while male sex was inversely associated with BDI≥13, STAI-trait≥38, STAI-state≥38, and for their co-occurrence

Table 1
Depressive symptoms, suicidal thoughts, anxiety, and hopelessness: comparisons between patients and controls.

	Narcolepsy (N = 127)	Controls (N = 131)	
	Median (IQR) or N (%)	Median (IQR) or N (%)	*P-value*
BDI score	9 (3–18)	5 (1–11)	<0.001
BDI level			**0.002**
Absent <13	86 (67.7 %)	113 (86.3 %)	
Mild 13-18	18 (14.2 %)	8 (6.1 %)	
Moderate 19-29	15 (11.8 %)	9 (6.9 %)	
Severe ≥30	8 (6.3 %)	1 (0.8 %)	
BDI item 9 level			**<0.001**
"I do not have thoughts of killing myself" = 0	100 (80.0 %)	125 (96.9 %)	
"I have thoughts of killing myself, but I would not carry them out"=1	19 (15.2 %)	3 (2.3 %)	
"I would like to kill myself"=2	5 (4.0 %)	1 (0.8 %)	
"I would kill myself if I had the chance" = 3	1 (0.8 %)	0 (0.0 %)	
STAI-trait anxiety score	43 (34–51)	38 (32–46)	**0.009**
STAI-trait anxiety level			**0.025**
Absent <30	16 (12.6 %)	21 (16.0 %)	
Mild 30-37	30 (23.6 %)	46 (35.1 %)	
Moderate 38-44	27 (21.3 %)	31 (23.7 %)	
Severe ≥45	54 (42.5 %)	33 (25.2 %)	
STAI-state anxiety score	36 (32–49)	34 (29–42)	**0.011**
STAI-state anxiety level			**0.003**
Absent <30	19 (15.0 %)	38 (29.1 %)	
Slight 30-37	55 (43.3 %)	43 (32.8 %)	
Moderate 38-44	15 (11.8 %)	26 (19.8 %)	
Serious ≥45	38 (29.9 %)	24 (18.3 %)	
BHS score	5 (3–10)	4 (2–6)	**<0.001**
BHS levels			**0.002**
Absent <4	47 (37.0 %)	62 (47.3 %)	
Slight 4-8	41 (32.2 %)	52 (39.7 %)	
Moderate 9-14	23 (18.1 %)	16 (12.2 %)	
Serious 15-20	16 (12.6 %)	1 (0.8 %)	
Coexistence of BDI≥13 and STAI- trait≥38	40 (31.5 %)	20 (15.3 %)	**0.002**
Coexistence of BDI ≥13 and STAI- state≥38	32 (25.2 %)	18 (13.7 %)	**0.020**

Legend: BDI, Beck Depression Inventory-II; BHS, Beck Hopelessness Scale; STAI, State-Trait Anxiety Inventory. In bold: P-value <0.05.

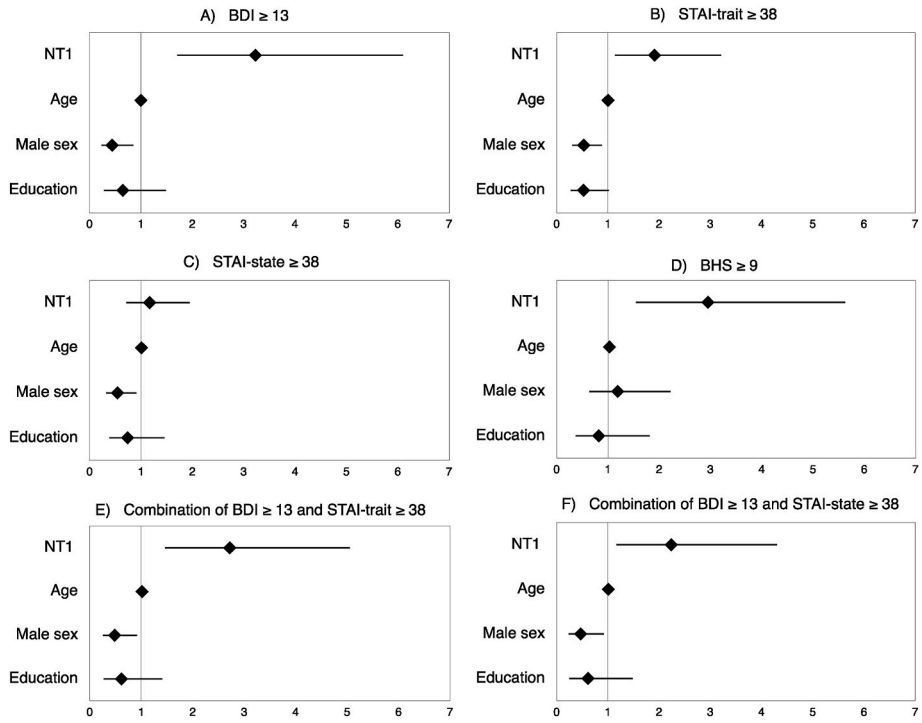

Fig. 1. Multivariable analysis of the relation between narcolepsy and depressive symptoms, anxiety, hopelessness and comorbid symptoms of depression and anxiety, expressed as odds ratio and 95 % confidence interval.
Legend: NT1, narcolepsy type 1; BDI, Beck Depression Inventory-II; BHS, Beck Hopelessness Scale; STAI, State-Trait Anxiety Inventory.

(Fig. 1; full results of multivariable analysis are presented in Supplemental Table 3).

Within the NT1 group, patients with BDI-item-9≥1 more frequently had hallucinations than patients who scored 0. Patients with BHS≥9 were older at recruitment and at disease onset and had more hallucinations and disturbed nocturnal sleep than those with BHS<9. No differences in terms of medications for narcolepsy emerged, except for a lower frequency of sodium oxybate in patients with BHS≥9 vs those with BHS<9 (Supplemental Table 4).

4. Discussion

The study confirmed the high prevalence of depressive symptoms, alone and combined with symptoms of anxiety, in a large group of Italian patients with NT1, while the presence of a control group allowed us to estimate the risk of their occurrence associated with NT1. Suicidal thoughts were also confirmed as highly prevalent in patients with NT1. Hopelessness was for the first time explored in NT1 and was found to occur as a moderate-to-severe feature.

The co-occurrence of anxiety and depression is widely known in general psychiatry [5] and this comorbidity is associated with worse outcomes than isolated depression, regardless of employed definitions [7,18]. In the context of narcolepsy, it was detected in 27 % of patients in a small group of patients with and without cataplexy (using Zung Depression Scale and Zung Anxiety Scale) [8], and reported in 22 % of 87 patients with NT1 evaluated with Hospital Anxiety and Depression Scales [9]. These uncontrolled studies did not distinguish between state anxiety (i.e., a temporary emotional state characterized by feelings of apprehension and tension) and trait anxiety (i.e., a stable disposition towards anxiety) [12]. Differentiating between state anxiety and trait anxiety allows for accurate monitoring of progress. Changes in state anxiety show immediate intervention effects, while changes in trait anxiety indicate long-term improvements in coping [12]. Chronic trait anxiety can exacerbate symptoms and hinder recovery in chronically ill patients [12]. In our population of patients with NT1, depressive symptoms co-occurred with moderate state anxiety in one out of five and trait anxiety in nearly one-third. Patients with NT1 had a two-fold higher risk of experiencing both depressive symptoms and anxiety compared to controls, and females with NT1 were at a higher risk for both, consistently with previous findings [8,9]. Our study assessed comorbidity of symptoms of anxiety and depression exclusively through questionnaires. However, the STAI may not fully differentiate between depressive symptoms and anxiety due to symptom overlap and similar etiology [19], highlighting the need for further investigation, potentially using clinical interviews.

Patients with NT1 presented higher BHS scores and had almost threefold higher odds of at least moderate hopelessness compared to controls. Hopelessness is a dimension associated with suicidal ideation and suicide risk with high sensitivity and low specificity [20]. According to the literature, the presence of suicidality (consisting of suicidal ideation and behavior) is significantly higher in patients with narcolepsy type 1 and 2 compared to controls [2]. Barateau et al. employing BDI-item-9 found suicidal thoughts in almost 23 % of untreated patients with NT1 and in 14.4 % of those who were treated [4]. The confirmation of the non-negligible occurrence of suicidal thoughts found in our population supports the need for screening and early intervention. BDI-item-9 could represent a valuable tool for this screening purpose, as proposed [4].

Patients with risk of suicidality presented a more severe neurological picture in terms of hallucinations and disturbed nighttime sleep, in line with previous evidence [4]. The mechanisms of this relation can only be hypothesized, as the cause of comorbidity of anxiety and depression in NT1. A more severe disease could directly impact the patient's mood, but also depression and anxiety could contribute to worsening nocturnal sleep quality. It has also been proposed that low hypothalamic hypocretin-1 plays a pathogenic role in psychiatric comorbidity since a reduction of hypocretin-1 activity was correlated with depression [21]. Data on anxiety disorders are less striking, but hypocretin-1 neurotransmission could play a role in stress-induced behavior and defense response [21].

Alternatively, psychoactive medications for NT1, the impact of the

psychological distress and socio-economic difficulties of NT1 could contribute to the development of psychiatric symptoms [2,22]. In our cohort, no significant associations emerged between pharmacological treatment and suicidal thoughts and hopelessness. This lack of association should be interpreted cautiously, as it is known that medications for narcolepsy can have psychiatric side effects and can be associated with depressive symptoms [23]. The numerosity of subgroups was limited (especially for BDI-item-9≥1) so we could not consider combinations of treatment and dosages. Additionally, the treatment choice could have been influenced by the pre-existing psychological status of the patient. Further studies specifically designed on this topic are needed.

These results, considered together, point to the need for a multidimensional and multidisciplinary approach to the treatment of NT1, which should not only be focused on core NT1 symptoms but also on the psychiatric morbidity and psychological dimension. When possible, it is convenient to use structured evidence-based psychological interventions such as cognitive-behavioral therapy in patients with narcolepsy [24], also to avoid medications (benzodiazepines, sedative antidepressants) that may worsen sleepiness. The importance of facing psychiatric morbidity is strengthened by prospective evidence that, in NT1, mood disorders remain stable over time [25] and can be associated with impaired quality of life and socio-occupational dimensions [22,25].

We acknowledge some limitations. The cross-sectional design of the research does not allow for investigation of the mechanisms beyond psychiatric comorbidity in patients with NT1. The lack of validated tools to assess NT1 severity when the study was designed, and the little number of patients without a pharmacological treatment limits the robustness of the findings on the relation between psychiatric symptoms, NT1 severity, and treatment. Information about ongoing psychotherapy or patient support groups was not systematically collected and could not be included. It is a necessary topic for future, possibly longitudinal, investigation, as these interventions can improve the psychological well-being of these patients [24]. The lack of a psychiatric clinical interview prevented the diagnosis of depression and anxiety disorder according to international criteria. However, the validated questionnaires employed are suitable to be administered in clinical practice to screen for the presence and assess the severity of symptoms, before referring the patient to a psychiatrist. Finally, the control group was constituted by the patient's relatives, who may carry a higher environmental and genetic risk for depression and anxiety symptoms than the general population.

In conclusion, this report emphasizes the considerable burden of psychiatric symptoms associated with NT1, including depression, anxiety, suicidal thoughts, and hopelessness, underscoring the necessity for integrated assessments and treatments of neurological and psychiatric aspects. Future prospective studies should focus on elucidating the mechanisms underlying these associations and developing tailored interventions, especially for gender- and age-specific care, to enhance mental health in patients with NT1.

Data availability statement

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

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CRediT authorship contribution statement

Francesco Biscarini: Writing – original draft, Investigation, Data curation, Conceptualization. **Chiara Bassi:** Writing – original draft, Investigation, Data curation, Conceptualization. **Marco Menchetti:** Writing – review & editing, Investigation, Conceptualization. **Corrado Zenesini:** Formal analysis. **Valentina Baldini:** Investigation. **Christian Franceschini:** Writing – review & editing. **Giorgia Varallo:** Writing – review & editing. **Elena Antelmi:** Writing – review & editing. **Luca Vignatelli:** Methodology, Data curation. **Fabio Pizza:** Writing – review & editing, Supervision. **Giuseppe Plazzi:** Writing – review & editing, Project administration. **Francesca Ingravallo:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Giuseppe Plazzi reports a relationship with Jazz Pharmaceuticals that includes: board membership. Giuseppe Plazzi reports a relationship with Bioprojet that includes: board membership. Giuseppe Plazzi reports a relationship with Centessa Pharmaceuticals, LLC that includes: board membership. Giuseppe Plazzi reports a relationship with Takeda Pharmaceutical Company Limited that includes: board membership. Giuseppe Plazzi reports a relationship with Idorsia Pharmaceuticals Ltd that includes: board membership. Fabio Pizza reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory. Fabio Pizza reports a relationship with Jazz Pharmaceuticals Inc that includes: speaking and lecture fees. Fabio Pizza reports a relationship with Bioprojet that includes: travel reimbursement. Elena Antelmi reports a relationship with Bioprojet that includes: speaking and lecture fees and travel reimbursement. Elena Antelmi reports a relationship with Jazz Pharmaceuticals Inc that includes: speaking and lecture fees and travel reimbursement. Elena Antelmi reports a relationship with Polifarma that includes: speaking and lecture fees. Francesco Biscarini reports a relationship with Bioprojet that includes: travel reimbursement. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2024.09.023.

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