

Long-Term Outcome of a Series of Patients With Narcolepsy Type 1 and Comorbidity With Immunopathological and Autoimmune Diseases

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Abstract

Background: The aim of this study was to evaluate the long-term outcome of our series of narcolepsy type 1 (NT1) patients with comorbid autoimmune diseases (ADs) and other immunopathological diseases (IDs), focusing on the incidence of new ADs and IDs in this sample.

Methods: A longitudinal observational study was conducted over 6 years (2014 - 2020) in a series of 158 Caucasians NT1 patients (96 males; mean age: 50.1 ± 19.0 years) from the previous study. All but one case (familial case) were HLA-DQB1*06:02-positive. The diagnosis of narcolepsy was made according to the International Classification of Sleep Disorders (ICSD-3).

Results: Twenty-one patients have been diagnosed with a new ID, 10 of them with an AD (autoimmune thyroid disease, psoriasis, rheumatoid arthritis, transverse myelitis, granuloma annulare, primary biliary cirrhosis, alopecia areata and antiphospholipid syndrome), and 11 with other IDs (allergic rhinitis, allergic asthma, atopic dermatitis, food allergy, contact dermatitis and drug allergy). One patient was diagnosed with two new ADs. We found IDs in 46 patients (24 females and 22 males) and the overall prevalence in this series is actually 29.11%; 22 of them (13.92%) had an AD, with a percentage higher than estimated in the general population.

Conclusions: The prevalence of AD/ID is high in our series, suggest-

ing that NT1 might arise on a background of generalized susceptibility to immune-mediated processes. The occurrence of an ID can in turn influence the development of others in genetically predisposed individuals, which explains the increased associations observed in this long-term study.

Keywords: Autoimmune diseases; Comorbidity; Epidemiology; Immunopathological diseases; Narcolepsy with cataplexy; Narcolepsy type 1

Introduction

Narcolepsy type 1 (NT1) is caused by a deficiency in hypothalamic neurotransmission through a selective loss of hypocretin-producing neurons [1]. This mechanism of neural destruction potentially indicates an autoimmune pathogenesis, although the existence of autoantibodies has been reported, their relevance is unclear and recent studies suggest that NT1 is a T-cell-mediated disease [2]. T cells have been found, and they target not only hypocretin neurons but also other molecules. The role of environmental factors as a trigger in genetically predisposed subjects has also been suspected. H1N1 influenza and H1N1 vaccinations have also been related to narcolepsy onset [3]. According to Lernmark, the timing of detecting the autoimmune response is important to understand the possible role of environmental factors. "First, an etiological trigger may be a common virus infecting beta cells or with antigens inducing beta cell cross reactivity. Afterwards, an autoimmune reaction may occur in response to beta cell apoptosis or autophagy resulting in autoantigen-specific T cells and autoantibodies" [4].

Evidence suggests that autoimmune diseases (ADs) tend to co-occur in an individual and within the same family, so that patients with an autoimmune disorder are at higher risk of a second AD, and the concept of an autoimmune diathesis is now widely accepted [5]. The association between allergic and ADs is having considerable interest. ADs have been mapped to many shared loci with variable specificities to different diseases. Several population-based studies have demonstrated positive associations between different ADs, allergic diseases, and even between both types, and the concept

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Table 1. Autoimmune and Other Immunopathological Diseases Observed in Our Narcolepsy Type 1 Series (N = 158) and Their Prevalence in Spain (2020)

	Previous (2014 - 2015)	New (2020)	Frequency (%)	Prevalence in Spain (2020)
Autoimmune diseases				
Multiple sclerosis (MS)	1	-	0.63	65/100,000 [8]
Systemic lupus erythematosus (SLE)	1	-	0.63	40 - 50/100,000 [9]
Idiopathic thrombocytopenic purpura (ITP)	1	-	0.63	Unknown
Psoriasis	2	3	3.16	2.3% [10]
Crohn's disease	2	-	1.26	1.9/100,000 [11]
Ulcerative colitis	1	-	0.63	8/100,000 [12]
Multinodular goiter autoimmune (MNGA)	1	-	0.63	0.8-6.4% (by sex) [13]
Autoimmune thyroid disease (Hashimoto)	2	1	1.89	Up to 33% in > 70 years [14]
Celiac disease	1	-	0.63	0.27% [15]
Type B insulin resistance syndrome (IRS-B)	1	-	0.63	Unknown
Idiopathic recurrent facial palsy (IRFP)	1	-	0.63	Unknown
Peyronie's disease	1	-	0.63	Unknown
Antiphospholipid syndrome	1	1	1.26	Unknown
Rheumatoid arthritis	-	2	1,26	0.3-1.6% [16]
Granuloma annulare	-	1	0.63	Unknown
Primary biliary cirrhosis	-	1	0.63	0.023% (Madrid) [17]
Transverse myelitis	-	1	0.63	Unknown
Alopecia areata	-	1	0.63	Unknown
Other immunopathological diseases				
Allergic rhinitis	12	5	10.75	Unknown
Allergic asthma (extrinsic)	6	1	4.43	3-7% [18]
Atopic dermatitis	4	1	3.16	2-14% [19]
Food allergy	3	1	2.53	1-3% [20]
Contact dermatitis (heavy metals, animals)	1	1	1.26	2-11% (nickel) [21]
Drug allergy	-	3	1.89	Unknown

of shared autoimmunity has gained acceptance. Furthermore, recent studies have identified loci with overlapping effects on ADs and allergies. For this study, AD means autoimmune disease taken from American Autoimmune Related Diseases Association (AARDA), whereas all immune-mediated disorders - apart from AD - will be named immunopathological diseases (IDs).

We previously published our series of patients with NT1 to evaluate the comorbidity with AD and other ID, including allergy diseases, and we found that 16.6% had one or more ID-associated [6].

In a later case-control study, with the same series, we found a higher frequency of ID (n = 30, 18.99%), and the results demonstrated that there was a significantly higher frequency of AD in NT1 patients (odds ratio (OR) = 3.17, P = 0.040) compared to a control group in the Community of Madrid [7].

The aim of this study was to evaluate the long-term outcome of our series of NT1 patients with an AD and other IDs,

focusing on the incidence of new ADs and IDs in these patients.

Materials and Methods

This longitudinal observational study was conducted at the Sleep Disorders Units of San Carlos University Hospital and Gregorio Marañon University Hospital in Madrid (Spain) over a period of 6 years (2014 - 2020). One hundred and fifty-eight Caucasian NT1 patients from our previous studies were included (96 males (60.7%); mean age: 50.1 ± 19.0 years; range 9 - 89 years). All but one familial case were HLA-DQB1*06:02-positive. NT1 patients were diagnosed using the International Classification of Sleep Disorders (ICSD-3, AASM, 2014). For the assessment of the AD/ID, patients were asked using a comprehensive list of these diseases and symptoms. The past medical history and the medical reports from other specialists were

reviewed and confirmed in all cases. The regular follow-up visits of the NT1 patients varied from 3 to 6 months. Once the presence of other AD/ID was confirmed, patients were systematically asked about the age at onset of the AD/ID, before the onset of the first symptom of narcolepsy - excessive daytime somnolence (EDS) in our series - simultaneously with EDS, or subsequent to the onset of EDS.

Control group of subjects from the general population

This control group is detailed in our previous study published in 2016 and were selected from the companions and non-consanguineous relatives of patients assisting to our outpatient clinics, matched by gender and age with the NT1 patients [6]. The control group was not medicated. They completed a specific questionnaire with two separate sections: a sleep questionnaire, the Epworth Sleepiness Scale (ESS) to discard the presence of narcolepsy; and specific questions about diseases separated by organs and systems, including allergic processes. A hospital medical specialist (neurologist, rheumatologist, pulmonologist, internal medicine, etc.) to confirm the information personally interviewed all subjects. Questionnaires with uncertain or not verified diseases, presence of sleep paralysis, hypnagogic hallucinations or ESS scorings ≥ 10 , were discarded. Four hundred and thirty-four questionnaires were collected, from which 151 were finally selected [7].

Statistical analysis

Categorical variables were described using frequencies and percentages, and quantitative variables were described using means and standard deviations. The Mann-Whitney and Pearson χ^2 tests were used for the parametric comparison, and the Fisher's exact test was used to evaluate the severity of cataplexy. Differences were considered as statistically significant if $P < 0.05$.

The local Clinical and Research Ethics Committees approved the study. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Twenty-one NT1 patients have been diagnosed with a new ID over a 6 years period, 10 of them with an AD (psoriasis: $n = 3$, Hashimoto's thyroiditis: $n = 1$, antiphospholipid syndrome: $n = 1$, rheumatoid arthritis: $n = 2$, granuloma annulare: $n = 1$, primary biliary cirrhosis: $n = 1$, transverse myelitis: $n = 1$, alopecia areata: $n = 1$). In addition, 11 patients were diagnosed with other ID (allergic rhinitis: $n = 5$, allergic asthma: $n = 1$, atopic dermatitis: $n = 1$, food allergy: $n = 1$, contact dermatitis: $n = 1$, drug allergy: $n = 3$).

One of 21 NT1 patients was diagnosed with one new AD (rheumatoid arthritis) and one new ID (granuloma annulare), another one with one AD in addition to an allergy (alopecia

areata and allergic asthma), and one more with two allergies (Table 1) [8-21].

The current prevalence of ID in our sample is 29.11% ($n = 46$, 24 females and 22 males), 13.92% of them ($n = 22$) with at least one AD, and 19.62% ($n = 31$) with other ID, a percentage higher than estimated in the general population (Table 1).

In addition, this number of NT1 patients with IDs represents an increase of 53.3% in 6 years of follow-up visits.

In this series of NT1 patients, HLA-DQB1*06:02 was positive except in one familial case (DQB1*06:03) diagnosed as having an idiopathic thrombocytopenic purpura [22]. The estimated prevalence of DQB1*06:02 in Madrid, where this study has been carried out, is 15% [23].

The analysis of the temporal relationship between the EDS onset and the presentation of the AD/ID showed that in 17 cases (36.9%), the diagnosis of the AD/ID preceded the EDS, and in four (8.6%), both EDS and AD/ID appeared simultaneously. In 21 cases (45.6%), the AD/ID started after NT1 and in the remaining four cases (8.6%), the temporal relationship was unknown (in two patients the age at onset of EDS and in other two the age at onset of the ID).

Discussion

It has been suggested that some ADs, including multiple sclerosis (MS), share susceptibility genes [24]. Ekblom first described familial cases of MS and NT1 in four families [25], and we have recently published a new family case [26].

MS patients have a greater risk for other ADs compared to the general population [27]. Using MS and NT1 as an example, it is clear that the susceptibility to these diseases results from interaction of genes, environment and gene/environment. Our patient with NT1, who developed an MS 3 years later, is an example to illustrate this hypothesis [28].

Another case of NT1 comorbid with a transverse myelitis of possible autoimmune etiology developed after the onset of a typical NT1 is a relevant example. This case might help to provide a better understanding of the implications of immune-related processes in the pathophysiology of these diseases [29]. Except for the previously mentioned neurological AD and others not mentioned in this article, no studies so far have reported an association between NT1 and other non-neurological ADs. In this series, the prevalence of ADs - compared to the general population - was high (13.92%), suggesting that the disease might arise on a background of generalized susceptibility to autoimmunity. Besides, in 17 cases (36.9%), the AD preceded the first NT1 symptom of narcolepsy.

Barateau et al, in a multicentric study of hypersomnolence and immune-based disorders (autoimmune, inflammatory and allergic diseases), concluded that compared with controls, AD frequency was higher in patients with narcolepsy without cataplexy (narcolepsy type 2), whereas allergies were more common in idiopathic hypersomnia and the authors hypothesized on immune dysregulation mechanisms [30].

We demonstrated a higher frequency of ADs in our series of 158 patients with NT1 compared with a sample of the Spanish general population ($P = 0.04$). The association with other

allergic diseases was also high, although the difference was not significant [6].

A study in 468 narcolepsy pediatric patients also found an increased frequency of allergic conditions, which was higher in patients with cataplexy compared to those without cataplexy. The study hypothesizes that Th2 cellular hyperactivation against autoantigens would cause IgE-mediated allergy and hypersensitivity [31]. The study, however, does not evaluate the presence of AD, and the discrepancies with our study observed in the severity of cataplexy could be explained because we only included NT1 patients in our study. In addition, the most important marker for cataplexy - the allele DQB1*06:02 - varies in percentage in different ethnic populations (Caucasian, Asiatic and Amerindian).

A more recent population-based study from Taiwan found a significant association (OR = 3.1, $P < 0.001$) between asthma and narcolepsy [32].

An interesting case of a 19-year-old Asian American female with NT1 and AD presented to the allergy clinic for evaluation of food and environmental allergies. Her medical history was significant for diagnosis of atopic dermatitis at age 9, in which shortly after, she began having symptoms of narcolepsy. Authors pointed that “both diseases may share an immunological connection, which can complicate treatment, and management options as physicians must take into account what the standard pharmacological intervention is and how it can impact other disease processes” [33].

The association of NT1 and alopecia areata - an autoimmune dermatological disorder - was described in 1992, although new case reports have been presented and the autoimmune association has not been established definitively [34, 35].

Another epidemiological and clinical interesting study in Slovakia found the presence of autoimmune disorders and allergies increased in the narcolepsy group (OR = 1.46, resp. 1.63). Hashimoto thyroiditis was the most frequent autoimmune disorder associated with NT1 [36].

Conclusions

The prevalence of AD/ID is high in our series, suggesting that NT1 might arise on a background of generalized susceptibility to immune-mediated processes. The occurrence of an ID can in turn influence the development of others in genetically predisposed individuals, which explains the increased associations observed in the long-term study, and strengthens the idea of an autoimmune pathogenesis. Further studies will be necessary to identify clinical and genetic associations between NT1 and AD/ID and, perhaps, it would allow detecting the more severe cases in the early stages of the disease, providing an opportunity for immune-modulating therapies.

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Conflict of Interest

The authors have no conflict of interest to declare regarding this study.

Informed Consent

The patients signed an informed a consent form.

Author Contributions

Rosa Peraita-Adrados, MD, PhD: conceptualization; methodology, formal analysis, data curation, writing original draft; review and editing reviewing and editing the draft. Francisco J. Martinez-Orozco, MD, PhD: conceptualization, formal analysis, data curation, writing - review and editing the original draft. Miguel Fernandez-Arquero, MD, PhD: methodology, formal analysis, data curation, review the original draft. Jose L. Vicario, PhD: methodology, formal analysis, data curation, review the original draft. Laura Lillo-Triguero, MD: methodology, formal analysis, data curation, review the original draft. Elena Ameyugo, MD: data curation, review the original draft. All authors approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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