Journal of Neuro Psychiatry Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Evaluate the Evidence for Type 1 Narcolepsy as an Autoimmune Disorder

Pei-Chang Liu[1]*, Nancy Lentz[1], Chi-Chan Lee[1] and Nat Dumrongmongcolgul[1]

[1]Department of Medicine, Guam Regional Medical City, Dededo, Guam, USA

ABSTRACT

The presence of cataplexy and the loss of hypocretin neurons manifested as low serum or CSF hypocretin-1 levels distinguish narcolepsy type 1 (NT1) from other types of hypersomnias. Autoimmunity has long been proposed as the pathogenesis for NT1 for its association with HLA-DQB1*06:02 and an increase in incidence after 2009 H1N1 flu pandemic and Pandemrix vaccination. We critically evaluated the evidence through literature search from genetics, cell-mediated immunity, and humoral immunity perspectives to verify if NT1 is an autoimmune disease. The strongest evidence is the anti-tribbles homologue 2 (TRIB2) in which both the seroactivity and the loss of hypocretin neurons secondary to this autoantibody were observed, albeit through different studies. Cell-mediated autoimmunity is therefore confirmed. We were only able to identify partial evidence for cytotoxic autoimmunity in causing NT1. Further research is hence needed to explore if the hypocretin neuronal destruction can be due to cytotoxic T cells or other autoantibodies.

***Corresponding author**

Pei-Chang Liu, Department of Medicine, Guam Regional Medical City, Dededo, Guam.

Received: February 01, 2025; **Accepted:** February 05, 2025; **Published:** February 07, 2025

Keywords: Narcolepsy, Autoimmune, Cell-Mediated Immunity, Humoral Immunity, Hypocretin, Orexin

Introduction

Narcolepsy is a rare disease with a prevalence between 1/2000 and 1/5000, which is clinically categorized into narcolepsy type I (NT1) and type II (NT2). More than 80% narcolepsy cases are NT2, yet NT1 has a clearer clinical contour for the diagnosis requires hypocretin-1 concentration in the cerebrospinal fluid (CSF) to be either ≤ 110 pg/mL or < 1/3 of mean values from normal subjects with the same standardized assay [1]. as well as the presence of cataplexy, a sudden physical collapse in response to strong emotions, while NT2 has neither as criterion for diagnosis. Hypocretin-1 and hypocretin-2 are orexin peptides produced and secreted by the hypocretin neurons (HNs) in the posterolateral hypothalamus. The hypocretin receptors are mainly located in the hypothalamus and brainstem with neuronal projections throughout the cerebral cortex. Excitation of these receptors through binding with hypocretins promotes arousal and wakefulness, whereas hypocretin deficiency would cause sleepiness and cataplexy, and a common cause for hypocretin deficiency is the loss of HNs. NT1 is considered an autoimmune disease by many because:

- The prevalence for HLA-DQB1*06:02 is 90-98% in NT1 while it is only 15-25% in the unaffected population. Strong HLA association is often seen in autoimmune diseases such as ankylosing spondylitis with HLA-B27. HLA-DQB1*06:02 is also found to be associated with other autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus [2].
- Hypocretin deficiency in serum and CSF and the lack of sufficient HNs seen in autopsy [3]. are pathognomonic for NT1. Autoimmunity is therefore a putative mechanism for HN destruction.
- An increase in NT1 incidence was observed after the H1N1 influenza pandemic in 2009 and post-Pandemrix vaccination that led many to believe certain components of the influenza virus triggered autoimmune response for HN destruction.

Genetics

HLA-DQB1*06:02 is a major histocompatibility complex class II (MHC-II) gene, which constitutes the T cell receptor (TCR) to present peptides to the CD4+ T cells, and then both humoral and cell-mediated immunity paths can be activated. Other HLA polymorphisms including numerous other HLA-DP, -DQ, and -DR genes for MHC-II were also found associated with NT1 [4]. Even though no MHC class I gene association including HLA-A, -B, or -C has been established with NT1, the CD8+ T cells can still be activated via CD4+ T cells to exert cytotoxic effects on HNs. TCR gene polymorphism was also identified through genome-wide association study for TCR alpha chain J24 segment at rs1154155C [5]. and purinergic receptor subtype 2Y11 (P2RY11) at rs2305795A [6]. among the NT1 patients. J24 expression is increased on both CD4+ and CD8+ T cells while accentuated P2RY11 expression is seen on the CD8+ T cells among the NT1 patients. Although the enhancement of immune response is plausible through genetic evidence on CD4+ T cells and TCR, this does not mean that autoimmunity is bound to occur in NT1.

Cell-Mediated Immunity

CD4+ T Cell

Both humoral and cell-mediated immunity are anchored and driven through the helper T cells, known as the CD4+ T cells. CD4+ T cells transform B cells to plasma cells for antibody production and enable CD8+ T cells to fulfill cytotoxic and memory functions.

CD4+ T cells can also become memory T cells themselves. To confirm autoimmunity as the pathogenesis for narcolepsy, the CD4+ T cell reactivity toward the constituents of the HN needs to be assessed [7]. measured the CD4+ T cell reactivity against the hypocretin peptide among the patients with NT1. 3/15 patients (20%) showed hypocretin-specific CD4+ T-cell proliferation and none in the control (0%), yet the increase of reactivity did not reach statistical significance ($p = 0.2262$). No specific epitope on the hypocretin was identified for CD4+ T cell reactivity [8]. also reported lack of CD4+ T-cell reactivity (frequency <1:10,000) towards six different 15-mer peptides from prepro-hypocretin in 22 NT1 patients, expanding the studied antigen further from hypocretin to its original peptide [9]. eventually detected hypocretin-specific CD4+ T cell reactivity in all 19 NT1 patients with HLA-DQB1*06:02 as well as specific reactivity to another antigen in the HN, tribbles homologue 2 (TRIB2), was measured in 8/13 NT1 patients, while the healthy controls showed neither reactivity. As the activated CD4+ T cells were polyclonal, no specific epitope was identified. It is unclear why these studies offered contradictory results. Possible explanations include:

- The sample size was small in all three studies, probably due to the low prevalence for narcolepsy, so the results might not carry high validity [7]. might eventually show statistical significance if more patients were recruited.
- Each study utilized different measurements for cellular reactivity. It is likely that the cellular screen is more sensitive than carboxyfluorescein succinimidyl ester proliferation assay [7,8]. hence the last study was able to demonstrate more positive reactivity.
- The definition adopted to identify T cell reactivity was different among the three studies as well. Kornum and Ramberg both acknowledged seroactivity whereas Latorre authorizes positivity as long as reactivity is detected in either blood or CSF [9].

Autoimmune disease can be caused by environmental exposure that elicits dysregulated immune response. A common environmental trigger is infection, in which the immune response arisen by the pathogen in turn attacks one's own cells/tissues/organs due to cross reactivity or antigen resemblance. Vaccination can also result in autoimmunity through similar mechanisms. The narcolepsy incidence increased after the 2009 H1N1 influenza pandemic as well as the vaccination campaign in the Scandinavian region among the young people receiving the influenza vaccine Pandemrix. CD4+ T cells were then tested for the cross reactivity toward hypocretin [10]. who reported that higher frequency of circulating CD4+ T cells was observed against two hypocretin epitopes 56–68 and 87–99 among the narcoleptic patients compared to the healthy cohort after receiving the influenza vaccine containing pH1N1. The same group also identified a hemagglutinin epitope pHA1275–287 specific to the 2009 H1N1 strain as the homology to these two hypocretin epitopes. This provides a strong basis that H1N1 influenza may trigger autoimmune response toward hypocretin via molecular mimicry.

Memory CD4+ T cells are derived through MHC-II activation when interacting with the processed peptides, so we expect to see an increase in the memory T cells targeting specific self-antigens in autoimmune diseases [11]. observed contradictorily lower levels of memory CD4+ T cells among 31 NT1 patients who developed narcolepsy after the 2009 H1N1 pandemic and/or Pandemrix vaccination when adjusted for HLA DQB1∗06:02 and vaccination status. As the study only measured the count of memory CD4+ T cells carrying CD25, it is possible the counts of other subsets of memory CD4+ T cells targeting HN actually increased compared to the controls, but they were not measured, so autoimmunity cannot necessarily be negated by this result.

CD8+ T cell

The effector CD8+ T cells would destroy the cells that present pathogens or self-antigens after being activated by helper T cells, therefore these cytotoxic T cells may play a role in autoimmune diseases [12]. examined the blood samples from 20 NT1 patients and found that the CD8+ T cell autoreactivity was higher among the NT1 patients toward narcolepsy-relevant peptides compared to the cohort group. Yet, among the healthy controls, HLA-DQB1*06:02-negative individuals actually had higher CD8+ T cell reactivity than the ones with positive HLA-DQB1*06:02, which we do not have a good explanation for now, as HLA-DQB1*06:02 seems like a protective factor for cytotoxic autoimmunity. The same study [9]. mentioned earlier for CD4+ T cell reactivity also detected hypocretin-specific CD8+ T cells in several narcoleptic patients' blood and CSF, but it was uncertain if the result reached statistical significance. After all, the mouse model [13]. demonstrated that CD8+ T cells infiltrated into hypothalamus and specifically destroyed the hemagglutinin-labeled HNs. These mice then developed cataplexy and sleep attacks, and the symptoms worsened after repeated injection of CD8+ T cells. This study denotes that if CD8+ T cells can be activated through hemagglutinins like H1N1 infection, they may attack the hypothalamic HNs immunologically.

Humoral Immunity

When B cells are activated to plasma cells by the help of CD4+ T cells, they produce and secrete antibodies to implement humoral immunity. In autoimmune disease, these antibodies would neutralize, opsonize, and activate complements to lyse the self antigens [14]. reported that the polyclonal IgGs from the serum or CSF of the NT1 patients failed to stain the hypothalamic HNs in the rats while the nearby neuronal cells containing proopiomelanocortin and melanin-concentrating hormone were instead stained by the same IgGs [15]. found there was no difference in seroreactivity against the human prepro-hypocretin, hypocretin 1 and 2, N-terminal leader and C-terminal peptides of prepro-hypocretin between 34 NT1 patients and the healthy cohort. These two studies suggest that there is no direct seroreactivity toward the HNs and hypocretin peptides, but since there is evidence of autoimmunity toward the neighboring cells, the inflammatory response caused by the autoimmunity may still affect the HNs. A follow-up study to demonstrate the destruction of HNs by injecting the antibodies targeting the nearby cells is hence recommended.

Meanwhile, the autoantibody against TRIB2 has been suggested as a possible route for HN destruction in NT1 [16]. found a higher frequency of TRIB2 autoantibody presence among the Japanese NT1 patients than controls (26.1% vs 2.3%, $p<0.05$) [17]. also reported a higher TRIB2 autoantibody prevalence in NT1 patients who were HLA-DQB1*0602 carriers compared to the ones without cataplexy and controls (25% vs 3.5% vs 4.5%, $p<0.001$). Moreover, the presence of TRIB2 autoantibody was associated with a more recent onset of cataplexy (≤2.3 years), which may thus predispose to NT1 development [18]. observed that the highest TRIB2 antibody titers occurred at the onset of narcoleptic symptoms, followed by a plunge in the next 2–3 years, and then reached steady but still substantially higher levels among the N1 patients than the controls for decades. High TRIB2 antibody titer was also correlated with the severity of cataplexy.

[19] injected anti-TRIB2 IgGs collected from NT1 patients intraventricularly into mice, who then developed narcolepsy-like presentation four weeks later and the autopsy demonstrated absence of hypothalamic HNs compared to controls [20]. noticed that contrary to the previous study, the rats that developed TRIB2 antibody in the blood and CSF through immunization did not demonstrate change in the contents or cell counts of the HNs afterwards, albeit there was remarkable reduction of the hypocretin mRNA levels in blood and CSF. These two conflictory results raised two questions:

- Can the self-elicited TRIB2 antibodies destroy the HNs?
- Can TRIB2 antibodies cause narcolepsy phenotype through transcription modulation without damaging the HNs? In a separate animal model, the same group also saw the TRIB2 autoantibody titers increased after HNs were destroyed, so there is likelihood the cellular contents including TRIB2 were released after the HN death to trigger autoimmunity, given TRIB2 is an intracellular protein, and the HN loss is the reason than the result of TRIB2 autoimmunity.

Another evidence for humoral immunity was provided by the data from patients who developed narcolepsy after being vaccinated with Pandemrix [21]. reported that the anti-GM3 antibody was more frequently detected among the narcoleptic patients than healthy controls (14.6% vs 3.5%, p=0.047) and HLA-DQB1*0602 appeared to be a strong predisposing factor (p=0.016). GM3 is the ganglioside that exists on the various neuronal cells so autoimmunity against GM3 may lead to HN destruction. GM3 is part of a big family of gangliosides and most gangliosides bind to influenza virus hemagglutinin to facilitate viral entry into host cells, so when the human body develops immunological response toward hemagglutinins, anti-ganglioside autoantibodies may occur via cross-over autoimmunity. This same group also discovered that the total anti-ganglioside antibodies were more likely present in vaccinated than in unvaccinated cohorts (18.1% vs 7.3%, p=0.035). On the other hand [22]. identified a peptide in influenza nucleoprotein A on H1N1 influenza virus and Pandermix that shared protein residues with human hypocretin receptor (HCR) 2. When mixing the sera from the patients of vaccination-related narcolepsy, seroreactivity with both influenza nucleoprotein and HCR 2 was detected and it was more pronounced among the subjects receiving Pandermix than Focetria for the former has 3.57 times more influenza nucleoproteins. However, as HCRs are not located on the HNs themselves [23]. an animal study may be followed to demonstrate if injecting HCR antibodies would lead to the death of HNs.

Discussion

Given the genetic associations are indirect evidence, to verify the validity of autoimmune pathogenesis for NT1, three criteria below must all be fulfilled:

- The presence of immune autoreactivity against the constituents of HNs.
- The absence of HNs is verified. 3. The loss of HNs is secondary to immune autoreactivity. We will now examine cell-mediated (Table 1) and humoral immunity (Table 2) respectively. Cell-mediated immunity is further divided into CD4+ and CD8+ T cells for discussion.

There is fairly strong evidence that CD4+ T cell immunity exists in NT1 patients toward HNs for 3/4 studies showed autoreactivity toward hypocretin and its related peptides with 2/3 positive studies reaching statistical significance and one study revealed autoreactivity for TRIB2 with unclear statistical significance. Nevertheless, as CD4+ T cells are not involved directly in attacking HNs, the results from CD4+ T cells can only serve as indirect support for there has been no study performed to confirm the deprivation of HNs.

Similarly, immune autoreactivity from CD8+ T cells was demonstrated in 2 studies against hypocretin and its related peptides with both reaching statistical substantiality. There was one study demonstrating the HN loss owing to CD8+ T cells but their target was hemagglutinin instead, while no study has proved that NT1 patients would develop CD8+ T cell reactivity toward hemaglutinins. To sum up, we are not able to confirm the destruction of HNs is directly caused by the CD8+ T cell autoreactivity from NT1 patients.

Table 1: The Names Listed in the Table are the Principal Investigators for the Respective Studies. - : Negative Result; +: Positive Result.

Cell-mediated immunity				
T cell type	**CD4**		**CD8**	
T cell target	Hypocretin and related peptides	TRIB2	Hypocretin and related peptides	Hemagglutinin
Immune reactivity	+ Ramberger - Kornum + Latorre + Herrán-Arita	+ Latorre	+ Pedersen + Latorre	Lack of evidence
HN loss	Lack of evidence	Lack of evidence	Lack of evidence	+ Bernard-Valnet
HLA gene association	Yes		No	
TCR gene association	+rs1154155C		+rs1154155C +rs2305795A	

As for humoral autoimmunity, contrary to most belief, seronegativity was noted in 2/2 studies for hypocretin and related peptides, but seropositivity was shown for TRIB2, GM3, and nucleoprotein A, with TRIB2 autoantibody being identified in 3/3 studies as the strongest proof. Unfortunately there was no study confirming the absence of HNs could be resulted from either GM3 or nucleoprotein A autoantibody, whilst TRIB2 autoantibody again exhibited HN destruction, despite only in 1/2 studies. To conclude, autoimmune seroactivity toward TRIB2 can potentially lead to HN destruction, which corroborates the autoimmune hypothesis for NT1. Coupled with the evidence of CD4+ T cell immune autoreactivity toward TRIB2, every step of the humoral autoimmune loop against TRIB2 in NT1, from CD4+ T cell activation to HN destruction, has been validated via studies, albeit conducted by different groups.

Table 2: The Names Listed in the Table are the Principal Investigators for the Respective Studies. - : Negative Result; +: Positive Result.

Humoral immunity				
Autoantibody	Anti-hypocretin	Anti-TRIB2	Anti-GM3	Anti-nucleoprotein A
Cross-over	Hypocretin and related peptides	Tribbles homologue 2	Hemagglutinin-ganglioside	Hypocretin receptor
Immune reactivity	- Bergman - Black	+ Toyota - Kawashima - Cvetkovic-Lopes	+ Saariaho	+ Amhed
HN loss	Lack of evidence	+ Katzav - Tanaka	Lack of evidence	+ Bernard-Valnet

There have only been rare and sporadic studies on the pathogenesis of NT1 for two reasons. First, narcolepsy has very low incidence/prevalence hence it is difficult to recruit enough cases to reach statistical power on planning for study design. Second, the causal relationship between autoimmunity and the loss of HNs is quite challenging to be proven for the diagnosis of NT1 mandates the presence of very low serum or CSF hypocretin level so by the time the diagnosis is established, most HNs are destroyed already and the autoimmune destruction process has already completed. For the

same reason, the immunotherapy is often too late when the diagnosis is made, given the HNs are already wiped out. A retrospective cohort study confirmed that intravenous immunoglobins did not lead to symptomatic improvement among the pediatric NT1 cases [24].

Nonetheless, it is worth clarifying the exact pathogenesis for NT1. It may take up to 10 years between the symptom onset and the confirmation of diagnosis for NT1 [25]. so if NT1 indeed has autoimmune nature, empirical immunomodulation like treating other autoimmune disorders when symptoms first emerge may help prevent further HN destruction and clinical deterioration including cataplexy, yet due to the lack of sensitive diagnostic tool to identify NT1 early in the disease course, providing immunotherapy to patients with non-NT1 hypersomnia may cause more harm than good, so it is currently not recommended [26]. However, although both NT1 and NT2 are categorized under narcolepsy in the International Classification of Sleep Disorders, NT1 is possibly a distinctive disease from NT2. Some NT2 cases are actually the early phase of NT1 who have yet developed cataplexy [27]. and there may be opportunity to salvage the remaining HNs by halting further hypothalamic destruction if NT1 is truly driven by autoimmunity.

Conclusion

We reviewed the available studies in literature to determine whether NT1 is an autoimmune disorder and we have identified numerous indirect evidence that helper T cells and cytotoxic T cells may be involved in the pathogenesis of NT1, while stronger data supports that humoral immunity may directly participate in the autoimmune process for causing HN loss in NT1, especially the seroactivity against TRIB2. Further research is required to fill the knowledge gap in the cytotoxic immunity loop for autoimmune clarification in NT1. Randomized-control trial is also recommended for immunotherapy in confirmed NT1 patients and patients with hypersomnia symptoms but yet to meet the criteria for NT1 diagnosis to evaluate for efficacy and effectiveness, which can be an alternative path to verify the autoimmunity in NT1 pathology.

Reference

1. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, et al. (2002) The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 59: 1553-1562.
2. Kaushansky N, Ben-Nun A (2014) DQB1*06:02-Associated Pathogenic Anti-Myelin Autoimmunity in Multiple Sclerosis-Like Disease: Potential Function of DQB1*06:02 as a Disease-Predisposing Allele. Front Oncol 16: 4-280.
3. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, et al. (2000) Reduced number of hypocretin neurons in human narcolepsy. Neuron 27: 469-474.
4. Valizadeh P, Momtazmanesh S, Plazzi G, Rezaei N (2024) Connecting the dots: An updated review of the role of autoimmunity in narcolepsy and emerging immunotherapeutic approaches. Sleep Med 113: 378-396.
5. Hallmayer J, Faraco J, Lin L, Hesselson S, Winkelmann J, et al. (2009) Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nature genetics 41: 708-711.
6. Kornum BR, Kawashima M, Faraco J, Lin L, Rico TJ, et al. (2011) Common variants in P2RY11 are associated with narcolepsy. Nature genetics 43: 66-71.
7. Ramberger M, Högl B, Stefani A, Mitterling T, Reindl M, et al. (2017) CD4+ T-Cell Reactivity to Orexin/Hypocretin in Patients with Narcolepsy Type 1. Sleep 40: 1-9.
8. Kornum BR, Burgdorf KS, Holm A, Ullum H, Jennum P, et al. (2017) Absence of autoreactive CD4+ T-cells targeting HLA-DQA1*01:02/DQB1*06:02 restricted hypocretin/orexin epitopes in narcolepsy type 1 when detected by EliSpot. J Neuroimmunol 309: 7-11.
9. Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, et al. (2018) T cells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature 562: 63-68.
10. De la Herrán-Arita AK, Kornum BR, Mahlios J, Jiang W, Lin L, et al. (2013) CD4+ T cell autoimmunity to hypocretin/orexin and cross-reactivity to a 2009 H1N1 influenza A epitope in narcolepsy. Sci Transl Med 5: 216ra176.
11. Viste R, Lie BA, Viken MK, Rootwelt T (2021) Narcolepsy type 1 patients have lower levels of effector memory CD4+ T cells compared to their siblings when controlling for H1N1-(Pandemrix™)-vaccination and HLA DQB1∗06:02 status. Sleep Med 85: 271-279.
12. Pedersen NW, Holm A, Kristensen NP, Knudsen-Heier S, et al. (2019) CD8+ T cells from patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. Nat Commun 10: 837.
13. Bernard-Valnet R, Yshii L, Quériault C, Nguyen XH , Arthaud S, et al. (2016) CD8 T cell-mediated killing of orexinergic neurons induces a narcolepsy-like phenotype in mice. Proc Natl Acad Sci USA 113: 10956-10961.
14. Bergman P, Adori C, Vas S, Kai-Larsen Y, Sarkanen T, et al. (2014) Narcolepsy patients have antibodies that stain distinct cell populations in rat brain and influence sleep patterns. Proc Natl Acad Sci USA 111: 3735-3744.
15. Black JL 3rd, Silber MH, Krahn LE, Fredrickson PA, Pankratz VS, et al. (2005) Analysis of hypocretin (orexin) antibodies in patients with narcolepsy. Sleep 28: 427-431.
16. Toyoda H, Tanaka S, Miyagawa T, Honda Y , Tokunaga K, et al. (2010) Anti-Tribbles homolog 2 autoantibodies in Japanese patients with narcolepsy. Sleep 33: 875-878.
17. Kawashima M, Lin L, Tanaka S, Jennum P, Knudsen S, et al. (2010) Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. Sleep. 33: 869-874.
18. Cvetkovic-Lopes V, Bayer L, Dorsaz S, Maret S, Pradervand S, et al. (2010) Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. J Clin Invest 120: 713-719.
19. Katzav A, Arango M T, Kivity S, Tanaka S, Givaty G, et al. (2013) Passive transfer of narcolepsy: anti-TRIB2 autoantibody positive patient IgG causes hypothalamic orexin neuron loss and sleep attacks in mice. J Autoimmun 45: 24-30.
20. Tanaka S, Honda Y, Honda M, Honda K, Yamada H, et al. (2017) Anti-Tribbles Pseudokinase 2 (TRIB2)-Immunization Modulates Hypocretin/Orexin Neuronal Functions. Sleep 1: 40-41.
21. Saariaho AH, Vuorela A, Freitag TL, Pizza F, Plazzi G, et al. (2015) Autoantibodies against ganglioside GM3 are associated with narcolepsy-cataplexy developing after Pandemrix vaccination against 2009 pandemic H1N1 type influenza virus. J Autoimmun 63: 68-75.
22. Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, et al. (2015) Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med 7: 294ra105.
23. Wang C, Wang Q, Ji B, Yanyou P, Chao X, et al. (2018) The Orexin/Receptor System: Molecular Mechanism and Therapeutic Potential for Neurological Diseases. Frontiers in molecular neuroscience 11: 220.
24. Lecendreux M, Berthier J, Corny J, Bourdon O, Dossier C, et al. (2017) Intravenous Immunoglobulin Therapy in Pediatric Narcolepsy: A Nonrandomized, Open-Label, Controlled, Longitudinal Observational Study. J Clin Sleep Med 13: 441-

453.

25. Taddei RN, Werth E, Poryazova R, Baumann CR, Valko PO (2016) Diagnostic delay in narcolepsy type 1: combining the patients' and the doctors' perspectives. J Sleep Res 25: 709-715.
26. Giannoccaro MP, Sallemi G, Liguori R, Plazzi G, Pizza F (2020) Immunotherapy in Narcolepsy. Curr Treat Options Neurol 22: 2.
27. Bonvalet M, Ollila HM, Ambati A, Mignot E (2017) Autoimmunity in narcolepsy. Curr Opin Pulm Med 23: 522-529.