ACCSCIENCE PUBLISHING

Gene & Protein in Disease

CASE REPORT

Autoimmune thyroid disease in narcolepsy: A case report

Chaofan Geng[1], Zhenzhen Yang[2], and Hongju Zhang[1,3]*

[1]Henan University People's Hospital, Henan Provincial People's Hospital, Zhengzhou 450003, China

[2]Fuwai Central China Cardiovascular Hospital, Henan Provincial People's Hospital, Zhengzhou 450003, China

[3]Zhengzhou University People's Hospital, Henan Provincial People's Hospital, Zhengzhou 450003, China

Abstract

While the previous studies have discussed the association of narcolepsy with autoimmune diseases, autoimmune thyroid disease (IATD) has rarely been described in patients with narcolepsy. The association of narcolepsy with thyroid disease is intriguing for speculating the causal or coexisting autoimmune disorder. We report a case of narcolepsy Type 1 with IATD, presenting with excessive daytime sleepiness (EDS), cataplexy attacks, and unexplainable weight gain. Oral modafinil and sodium oxybate were used for treatment and prevention. During the 1-year follow-up, the patient's EDS and cataplexy attacks improved. However, the patient developed hypothyroidism and was subsequently prescribed with thyroid replacement therapy.

Keywords: Autoimmune thyroid disease; Narcolepsy; Mechanism; Autoimmunity; Case report

***Corresponding author:**
Hongju Zhang
(hongjuz@sina.com)

Citation: Geng C, Yang Z, Zhang H, 2023, Autoimmune thyroid disease in narcolepsy: A case report. *Gene Protein Dis,* 2(1):235. https://doi.org/10.36922/gpd.v2i1.235

Received: October 25, 2022
Accepted: December 19, 2022
Published Online: January 11, 2023

1. Background

Narcolepsy is a chronic sleep disorder, primarily associated with excessive daytime sleepiness (EDS), cataplexy attacks, sleep paralysis, and hypnagogic hallucinations[1,2], which affects one in every 2,000 individuals[3]. Autoimmune-mediated destruction of hypocretin neurons is thought to be the main pathophysiological mechanism of narcolepsy[4,5]. More than 98% of narcolepsy patients with cataplexy are *HLA-DQB1*06:02* positive[6,7]. Although the previous studies have reported the association of narcolepsy with autoimmune diseases[8], no reports of autoimmune thyroid disease (AITD) have ever been described in patients with narcolepsy. Furthermore, the pathogenesis of narcolepsy-associated autoimmune disorders has yet to be established. In this report, we present a case of narcolepsy with AITD as comorbidity.

2. Case presentation

A 14-year-old female patient presented to the hospital with a 5-year history of EDS, inexplicable weight gain, and cataplexy attacks. The patient reported that she often falls asleep during class, while doing her homework, or using her cellphone without any obvious cause, and then wakes up after 3 – 5 min; she also reported that whenever she was emotionally agitated, she would experience a transient weakness in both lower

limbs, causing her to fall down, but would be relieved after a few seconds; she also experienced sleep fragmentation at night with excessive dreams. At the same time, she was surprised to find that her body weight had increased by approximately 25 kg within a year. A standard neurological examination and a neuropsychological assessment of the patient were performed by a neurologist. She scored 18 points on the epworth sleepiness scale, which was used to assess the degree of subjective sleepiness[9], and 12 points on the Pittsburgh Sleep Quality Index, suggesting average sleep quality. The magnetic resonance imaging and magnetic resonance angiography of her brain were normal. She was otherwise well with no significant comorbidity or family history of neurological illness. Given these clues, polysomnography (PSG) and multiple sleep latency test (MSLT) were performed on the patient to further clarify the diagnosis. PSG study showed a total sleep time of 579.5 min, sleep efficiency of 76.5%, and apnea-hypopnea index of 1.7/h, which can exclude obstructive sleep apnea (Table 1). Her MSLT showed a mean sleep latency of 0.7 min and four sleep-onset rapid eye movement periods (SOREMPs) in five naps without notable sleep paralysis. Her cerebrospinal fluid hypocretin-1, measured by enzyme-linked immunosorbent assay, was 71.54 pg/mL. In addition, she was found to be *HLA-DQB*06:02* positive. According to the International Classification of Sleep Disorders, 3rd edition (ICSD-3), we diagnosed the case as narcolepsy Type 1 (NT1).

Laboratory tests for the patient, including complete blood count, renal function, electrolytes, cardiac enzymes, liver enzymes, sex hormones, fasting growth hormone, autoimmune encephalitis antibody, immunoglobulin, and complement tests, were all normal. However, her serum 25-hydroxyvitamin D (25(OH)D) level was 12.45 ng/mL (normal range >20 ng/mL), and her thyroid function test showed abnormally high levels of thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) (Table 2). Her thyroid gland was normal in texture and size. Following-up with the patient's past medical history, the patient had not consumed any antithyroid drugs. There was also no antecedent history of thyroidectomy, neck radiotherapy, and radioactive iodine (^{131}I) therapy for hyperthyroidism. Based on her medical history and laboratory tests, she was diagnosed with AITD. Given the patient's normal thyroid function, no treatment was administered. Only modafinil was prescribed to improve the patient's sleep symptoms. After a year of follow-up, the patient's sleep symptoms and thyroid function were re-evaluated. We found a significant improvement in the patient's EDS; however, she developed hypothyroidism. Otherwise, there was also significant improvement in her cataplexy attacks. Following a discussion with the patient and her family members, the patient was started on thyroid replacement therapy so as to achieve a euthyroid state, while still receiving modafinil.

The research protocol of this study was approved by the Research Ethics Committee of Henan Provincial People's Hospital, and the participant signed the written informed consent forms.

3. Discussion

The previous studies have found that the prevalence rate of immunopathological diseases is higher in patients with narcolepsy[8,10,11]. Cataplexy, in particular, is often associated with comorbid immunopathological diseases associated with narcolepsy[8]. However, to the best of our knowledge, this is the first case of narcolepsy with AITD. According to the ICSD-3 diagnostic criteria for narcolepsy, this case was not difficult to diagnose. In addition, the previous studies have also demonstrated that weight gain, in particular, is often related to narcolepsy with cataplexy[12-14]. Impaired feeding behavior, including binge eating, nocturnal eating, and increased food cravings, may contribute to this phenomenon[15]. In addition, abnormal energy metabolism and reduced spontaneous activity are also important factors that contribute to the altered body mass index[16].

AITD is characterized by the dysfunction of thyroid tissue by antibody-mediated immune inflammation[17]. TPOAb and TgAb are the main thyroid autoantibodies that cause thyroid destruction and suppression of function. They are sensitive indicators for the diagnosis and prognosis of autoimmune thyroid disease[18]. Elevated levels of TPOAb and TgAb are early manifestations in patients with Hashimoto's thyroiditis (HT) and may have initiated certain pathophysiological changes in the thyroid gland, albeit the normal thyroid function occasionally.

Table 1. Result of PSG

	TST (min)	AWN/h	WASO (%)	SE (%)	N1 (%)	N2 (%)	N3 (%)	REM (%)	AI (event/h)	PLMI (event/h)	AHI (event/h)
Value	579.5	4.0	13.4	76.5	29.2	43.4	11.9	15.5	6.1	0.4	1.7

PSG: Polysomnography; AHI: Apnea-hypopnea index; AI: Arousal index; AWN/h: Awakenings per hour; N1, N2, N3: Standard non-rapid eye movement sleep stages; PLMI: Periodic limb movement index; REM: Rapid eye movement sleep; REML: Rapid eye movement sleep latency; SE: Sleep efficiency; TST: Total sleep time; WASO: Wakefulness after sleep onset

Table 2. Laboratory studies

Variables	Baseline value	Normal range
T_3	1.36 ng/mL	0.91–2.18 ng/mL
T_4	7.02 μg/dL	5.91–13.2 μg/dL
FT_3	6.11 pmol/L	3.93–7.7 pmol/L
FT_4	14.24 pmol/L	12.6–21 pmol/L
TSH	2.38 uIU/mL	0.51–4.3 uIU/mL
TgAb	12.1 IU/mL	0–4 IU/mL
TPOAb	243.53 IU/mL	0–9 IU/mL

T_3: Triiodothyronine; T_4: Thyroxine; FT_3: Free triiodothyronine; FT_4: Free thyroxine; TGAb: Thyroglobulin antibody; TPOAb: Thyroid peroxidase antibody; TSH: Thyroid stimulating hormone

In this case, the patient's thyroid function was normal on admission but she tested positive for thyroid antibodies. The previous studies have suggested that abnormal thyroid function may be preceded by prolonged thyroid autoimmune abnormalities and that most thyroid function abnormalities are predominantly hypothyroid[19]. In this case, despite the short follow-up period, abnormal thyroid function was observed after a year, thus suggesting that annual screening of thyroid function is necessary for narcolepsy patients with positive thyroid antibodies.

It is noteworthy that although the exact mechanisms leading to neuronal destruction in narcolepsy remain unclear[20], environmental trigger, genetic factors, viral infections, and autoimmunity have been found to be associated with the pathogenesis of narcolepsy[21,22]. Epidemiological studies have reported a significant six to nine times increase in incidence of narcolepsy in 2010[23], and analyses have suggested that the cause of the increased incidence in 2010 may be closely related to H1N1 influenza infection in the winter of 2009 and the AS03-adjuvanted influenza A vaccine[23-25]. Studies have also found an association between upper respiratory tract *Streptococcus pyogenes* infection and narcolepsy[26]. In addition, the association of narcolepsy with human leukocyte antigen (HLA) has been extensively investigated, in which the frequency of *HLA-DQB1*06:02* and *HLA-DQA1*01:02* motifs has been found to be associated with the onset of the disease[27]. However, there is a growing body of evidence supporting the hypothesis that narcoleopsy is a T cell-mediated autoimmune disease that attacks hypocretin neurons[21,28].

There are different mechanisms to explain the causal relationship between narcolepsy and autoimmune diseases. One explanation for the observed association between narcolepsy and AITD is the common immunological pathogenetic pathway. The previous studies have shown that patients with one autoimmune disease are usually at an increased risk of developing another autoimmune disease[8]. *HLA-DRB1*0803* and *DQB1*0601* haplotypes have been found to be strongly linked with AITD[29]. We suspect that HLA-related homologous genes could make it easier for specific autoantigens to be presented to self-reactive T cells, leading to defects in peripheral autoimmune responses and resulting in autoimmune diseases. All in all, narcolepsy and AITD may share common susceptibility genes, thus supporting the hypothesis that common genetic variants lead to immune dysregulation and autoimmune susceptibility. However, the specific susceptibility loci and genes shared by narcolepsy and AITD remain unknown, thereby requiring further research in this area.

Vitamin D has been shown to be an immunomodulatory hormone[30]. Although the patient was measured for Vitamin D deficiency in our case, we were unable to infer with certainty the cause of the deficiency. At present, the relationship between Vitamin D and narcolepsy is understudied, and the findings are inconsistent[31,32]. Interestingly, the previous studies have found that Vitamin D deficiency contributes to the development of AITD[33]. T cells have immunomodulatory properties[34].

Maintaining the T helper 17 cell/regulatory T cell (Th17/Treg) balance that occurs during chronic inflammation is an important key point in the treatment of autoimmune diseases[35]. A growing body of evidence has demonstrated that Vitamin D is associated with the inhibition of Th17 cell differentiation and the upregulation of Tregs[36].

In addition, the previous studies have demonstrated that pro-inflammatory cytokines interleukin 6 (IL-6) is upregulated in narcolepsy patients[37]. This finding supports the hypothesis that inflammation is associated with the pathophysiology of narcolepsy[38]. Cytokines are involved in the pathogenesis of thyroid disease; they play a role in the immune system and directly target thyroid follicular cells[39]. Cytokines also have certain roles in promoting and suppressing the development of autoimmune diseases[40]. We hypothesize that appetitive-regulating cell-associated antigens may be expressed in thyroid tissue; thus, when Th17/Treg ratio imbalance and immune balance disruption occur, the corresponding antibodies produced against hypocretin neuron-associated antigens will act on the thyroid tissue and promote the development of AITD.

4. Conclusion

Given that both narcolepsy and AITD have a basic defect in immune regulation as a shared, similar disease mechanism, thyroid autoantibodies and thyroid function should be checked regularly to facilitate early detection and treatment of abnormal thyroid function and to prevent complications. Nevertheless, we lack

sufficient data to demonstrate whether AITD is more likely to occur in narcolepsy patients. Therefore, the future studies should focus on autoimmune disorders in larger sample sizes of narcolepsy patients to explore the pathophysiological mechanisms of narcolepsy with immunopathological diseases. This would allow us to better understand the significance of immune-related processes in the pathophysiology of these disorders.

Acknowledgments

None.

Funding

No funding was received in drafting this manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

Data curation: Chaofan Geng
Writing – original draft: Chaofan Geng, Zhenzhen Yang
Writing – review & editing: Hongju Zhang

Ethics approval and consent to participate

The research protocol of this study was approved by the Research Ethics Committee of Henan Provincial People's Hospital. The patient/participant provided a written informed consent to participate in this study.

Consent for publication

A written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Availability of data

The data presented in the study can be obtained from the corresponding author on reasonable request.

References

1. Bassetti CL, Adamantidis A, Burdakov D, *et al*., 2019, Narcolepsy-clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nat Rev Neurol*, 15(9): 519–539.

   https://doi.org/10.1038/s41582-019-0226-9

2. Postiglione E, Antelmi E, Pizza F, *et al*., 2018, The clinical spectrum of childhood narcolepsy. *Sleep Med Rev*, 38: 70–85.

   https://doi.org/10.1016/j.smrv.2017.04.003

3. Luo G, Yogeshwar S, Lin L, *et al*., 2021, T cell reactivity to regulatory factor X4 in Type 1 narcolepsy. *Sci Rep*, 11(1): 7841.

   https://doi.org/10.1038/s41598-021-87481-8

4. Andlauer O, Moore HT 4th, Hong SC, *et al*., 2012, Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. *Sleep*, 35(9): 1247–1255F.

   https://doi.org/10.5665/sleep.2080

5. Liblau RS, Vassalli A, Seifinejad A, *et al*., 2015, Hypocretin (orexin) biology and the pathophysiology of narcolepsy with cataplexy. *Lancet Neurol*, 14(3): 318–328.

   https://doi.org/10.1016/s1474-4422(14)70218-2

6. Kachooei-Mohaghegh-Yaghoobi L, Rezaei-Rad F, Sadeghniiat-Haghighi K, *et al*., 2020, The impact of the HLA DQB1 gene and amino acids on the development of narcolepsy. *Int J Neurosci*, 132(7): 706–713.

   https://doi.org/10.1080/00207454.2020.1835903

7. Bourgin P, Zeitzer JM, Mignot E, 2008, CSF hypocretin-1 assessment in sleep and neurological disorders. *Lancet Neurol*, 7(7): 649–662.

   https://doi.org/10.1016/s1474-4422(08)70140-6

8. Martinez-Orozco FJ, Vicario JL, Villalibre-Valderrey I, *et al*., 2014, Narcolepsy with cataplexy and comorbid immunopathological diseases. *J Sleep Res*, 23(4): 414–419.

   https://doi.org/10.1111/jsr.12143

9. Johns MW, 1991, A new method for measuring daytime sleepiness: The epworth sleepiness scale. *Sleep*, 14(6): 540–545.

   https://doi.org/10.1093/sleep/14.6.540

10. Peraita-Adrados R, Lammers GJ, De Andres C, *et al*., 2013, A patient with narcolepsy with cataplexy and multiple sclerosis: Two different diseases that may share pathophysiologic mechanisms? *Sleep Med*, 14(7): 695–696.

    https://doi.org/10.1016/j.sleep.2013.03.015

11. Ekbom K, 1966, Familial multiple sclerosis associated with narcolepsy. *Arch Neurol*, 15(4): 337–344.

    https://doi.org/10.1001/archneur.1966.00470160003001

12. Schuld A, Hebebrand J, Geller F, *et al*., 2000, Increased body-mass index in patients with narcolepsy. *Lancet*, 355(9211): 1274–1275.

    https://doi.org/10.1016/s0140-6736(05)74704-8

13. Cohen A, Mandrekar J, St Louis EK, *et al*., 2018, Comorbidities in a community sample of narcolepsy. *Sleep Med*, 43: 14–18.

    https://doi.org/10.1016/j.sleep.2017.11.1125

14. Poli F, Pizza F, Mignot E, *et al*., 2013, High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. *Sleep*, 36(2): 175–181.

    https://doi.org/10.5665/sleep.2366

15. Chabas D, Foulon C, Gonzalez J, *et al*., 2007, Eating disorder and metabolism in narcoleptic patients. *Sleep*, 30(10): 1267–1273.

https://doi.org/10.1093/sleep/30.10.1267

16. Zhang M, Thieux M, Inocente CO, *et al*., 2022, Characterization of rapid weight gain phenotype in children with narcolepsy. *CNS Neurosci Ther*, 28(6): 829–841.

https://doi.org/10.1111/cns.13811

17. Huang KH, Tai MC, Lee LC, *et al*., 2018, Positron emission tomography/computed tomography scan of Vogt-Koyanagi-Harada syndrome with associated autoimmune thyroid disease: A case report and literature review. *Medicine* (*Baltimore*), 97(9): e0047.

https://doi.org/10.1097/md.0000000000010047

18. Radetti G, Gottardi E, Bona G, *et al*., 2006, The natural history of euthyroid Hashimoto's thyroiditis in children. *J Pediatr*, 149(6): 827–832.

https://doi.org/10.1016/j.jpeds.2006.08.045

19. Umpierrez GE, Latif KA, Murphy MB, *et al*., 2003, Thyroid dysfunction in patients with Type 1 diabetes: A longitudinal study. *Diabetes Care*, 26(4): 1181–1185.

https://doi.org/10.2337/diacare.26.4.1181

20. Wiendl H, Gross CC, Bauer J, *et al*., 2021, Fundamental mechanistic insights from rare but paradigmatic neuroimmunological diseases. *Nat Rev Neurol*, 17(7): 433–447.

https://doi.org/10.1038/s41582-021-00496-7

21. Pedersen NW, Holm A, Kristensen NP, *et al*., 2019, CD8+ T cells from patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. *Nat Commun*, 10(1): 837.

https://doi.org/10.1038/s41467-019-08774-1

22. Mahlios J, De la Herran-Arita AK, Mignot E, 2013, The autoimmune basis of narcolepsy. *Curr Opin Neurobiol*, 23(5): 767–773.

https://doi.org/10.1016/j.conb.2013.04.013

23. Wijnans L, Lecomte C, de Vries C, *et al*., 2013, The incidence of narcolepsy in Europe: Before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. *Vaccine*, 31(8): 1246–1254.

https://doi.org/10.1016/j.vaccine.2012.12.015

24. Han F, Lin L, Warby SC, *et al*., 2011, Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol*, 70(3): 410–417.

https://doi.org/10.1002/ana.22587

25. Partinen M, Kornum BR, Plazzi G, *et al*., 2014, Narcolepsy as an autoimmune disease: The role of H1N1 infection and vaccination. *Lancet Neurol*, 13(6): 600–613.

https://doi.org/10.1016/S1474-4422(14)70075-4

26. Aran A, Lin L, Nevsimalova S, *et al*., 2009, Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. *Sleep*, 32(8): 979–983.

https://doi.org/10.1093/sleep/32.8.979

27. Mignot E, Lin L, Rogers W, *et al*., 2001, Complex HLA-DR and-DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *Am J Hum Genet*, 68(3): 686–699.

https://doi.org/10.1086/318799

28. Mahoney CE, Cogswell A, Koralnik IJ, *et al*., 2019, The neurobiological basis of narcolepsy. *Nat Rev Neurosci*, 20(2): 83–93.

https://doi.org/10.1038/s41583-018-0097-x

29. Li L, Liu S, Yu J, 2020, Autoimmune thyroid disease and Type 1 diabetes mellitus: Same pathogenesis; new perspective? *Ther Adv Endocrinol Metab*, 11: 2042018820958329.

https://doi.org/10.1177/2042018820958329

30. Bellan M, Andreoli L, Mele C, *et al*., 2020, Pathophysiological role and therapeutic implications of Vitamin D in autoimmunity: Focus on chronic autoimmune diseases. *Nutrients*, 12(3): 789.

https://doi.org/10.3390/nu12030789

31. Dauvilliers Y, Evangelista E, Lopez R, *et al*., 2017, Vitamin D deficiency in Type 1 narcolepsy: A reappraisal. *Sleep Med*, 29: 1–6.

https://doi.org/10.1016/j.sleep.2016.05.008

32. Carlander B, Puech-Cathala AM, Jaussent I, *et al*., 2011, Low Vitamin D in narcolepsy with cataplexy. *PLoS One*, 6(5): e20433.

https://doi.org/10.1371/journal.pone.0020433

33. Wang J, Lv S, Chen G, *et al*., 2015, Meta-analysis of the association between Vitamin D and autoimmune thyroid disease. *Nutrients*, 7(4): 2485–2498.

https://doi.org/10.3390/nu7042485

34. Alamo A, Condorelli RA, La Vignera S, *et al*., 2019, Autoimmune thyroid disease following treatment with alemtuzumab for multiple sclerosis. *Int J Immunopathol Pharmacol*, 33: 2058738419843690.

https://doi.org/10.1177/2058738419843690

35. Zhao R, Zhang W, Ma C, *et al*., 2021, Immunomodulatory function of Vitamin D and its role in autoimmune thyroid disease. *Front Immunol*, 12: 574967.

https://doi.org/10.3389/fimmu.2021.574967

36. Bishop EL, Ismailova A, Dimeloe S, *et al*., 2021, Vitamin D and immune regulation: Antibacterial, antiviral, anti-inflammatory. *JBMR Plus*, 5(1): e10405.

https://doi.org/10.1002/jbm4.10405

37. Mohammadi S, Mayeli M, Saghazadeh A, *et al*., 2020, Cytokines in narcolepsy: A systematic review and meta-analysis. *Cytokine*, 131: 155103.

https://doi.org/10.1016/j.cyto.2020.155103

38. Dauvilliers Y, Jaussent I, Lecendreux M, *et al*., 2014, Cerebrospinal fluid and serum cytokine profiles in narcolepsy with cataplexy: A case-control study. *Brain Behav Immun*, 37: 260–266.

https://doi.org/10.1016/j.bbi.2013.12.019

39. Mikos H, Mikos M, Obara-Moszynska M, *et al*., 2014, The role of the immune system and cytokines involved in the pathogenesis of autoimmune thyroid disease (AITD). *Endokrynol Pol*, 65(2): 150–155.

https://doi.org/10.5603/ep.2014.0021

40. Ganesh BB, Bhattacharya P, Gopisetty A, *et al*., 2011, Role of cytokines in the pathogenesis and suppression of thyroid autoimmunity. *J Interferon Cytokine Res*, 31(10): 721–731.

https://doi.org/10.1089/jir.2011.0049