INTRODUCTION

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucination, and sleep paralysis. Narcolepsy is caused by damage of hypocretin producing neurons in the lateral hypothalamus. The association of narcolepsy with HLA DQB1*0602 and high incidence following H1N1 pandemic in China, vaccination with Pandemrix and an adjuvanted H1N1 vaccine suggests that pathophysiology of narcolepsy is involved in the immune system. This review focused on immunological associations and immunotherapy in narcolepsy.
Immunotherapy in Narcolepsy

How this activation modulates sleepiness and cataplexy. Decreased hypocretin in CSF suggests that more than 90 percent of hypocretin producing neurons are lost, and this process has begun at narcolepsy onset. Hypocretin-producing cell damage is selective and the melanin-concentrating neuron is not impaired in narcolepsy patients. Specific deletion is a basis for the autoimmune process.

Diagnosis can be made in definite clinical history but is limited, and polysomnography (PSG) and multiple sleep latency test (MSLT) are essential. PSG is needed to differentiate other sleep disorders such as obstructive sleep apnea syndrome that exhibit EDS, and MSLT is necessary to identify abnormal REM sleep transition during daytime naps. Narcolepsy was strongly suspected when MSLT revealed positive findings without other sleep disorders found in overnight PSG.

Main treatment strategy of narcolepsy is a symptomatic treatment. EDS is controled by wakefulness-promoting drugs such as modafinil or methylphenidate and these medications are associated with neurotransmitters of dopamine, serotonin and norepinephrine. Cataplexy is prevented by antidepressants (venlafaxine, floxetine, clomipramine and etc.) that inhibit re-uptake of norepinephrine. Cataplexy-producing cell damage is selective and the melanin-concentrating neuron is not impaired in narcolepsy patients. Specific deletion is a basis for the autoimmune process.

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However, these treatments are focused on the control of narcolepsy symptoms. Many researchers are conducting ongoing researches into treatment focusing on hypocretin depletion and hypocretin-producing neuron destruction. Therefore, in this paper, we reviewed the autoimmune pathophysiology of narcolepsy and immunotherapy.

The Immune System and Narcolepsy

Researchers have focused on the significance of the potential role of the immune system in narcolepsy onset for many years. A study of the relationship between the immune system and narcolepsy began with the discovery of strong association between human leukocyte antigen (HLA) and narcolepsy. HLA encodes various subtypes of major histocompatibility complex (MHC) class I and II proteins, and MHC triggers immune response by T cell receptor (TCR) activation through presenting foreign peptide to T cells during infection. HLA is associated with autoimmune diseases such as Graves’ disease, rheumatoid arthritis and type 1 diabetes.

HLA DQB1*0602 is found in 90 percent of patients with narcolepsy, and presence of this gene is known to increase the risk of narcolepsy by 200 times. The pathogenic mechanism of DQB1*0602 in narcolepsy is the destruction of hypocretin-producing neurons by interaction between specific TCR subtypes.

The autoimmune basis of narcolepsy, that was initiated by its association with HLA, has also revealed other mechanisms through research.

Second, there is a polymorphism of TCR alpha locus. TCR is expressed on the T cell surface and plays a key role in recognizing antigen by binding to HLA molecules on the surface of antigen presenting cells (APCs). Among them, alpha locus J region segment plays a crucial immunological role, and certain mutations of J region increase risk of developing narcolepsy.

The third mechanism is bystander activation of autoreactive T cells. During viral infection, cytotoxic T cells are polyclonally stimulated. The cytokines secreted from antigen-responsive cells around the infected site directly stimulate surrounding T cells. In this pro-inflammatory micro-environment, normal T cells, not pathogen-specific T cells, are stimulated and therefore damage hypocretin cells.

The fourth mechanism is molecular mimicry, that is characterized by structural similarity of pathogen and antigenic determinants of the host. This mechanism may occur at the cross reactive by helper T cells and MHC II/TCR synapse level. Activation of the cross-reactive TH1 of the microbial epitope and auto-antigen releases cytokines and chemokines and recruit activated monocytes and macrophages, leading to self-tissue damage. Subsequently, autoimmune disease persists from uptake by self-tissue antigen and APC. At MHC/TCR synapse level, this is caused by structural similarities between infectious agents (e.g., H1N1 and/or Streptococcus pyogenes) and hypocretin neuron autoantigen. MHC class II binding groove selects peptide fragments with specific amino acids in the context of DQA1*01:02–DQB1*06:02. The TCR recognizes the presented peptide with specific amino acid sequence and activates CD4 + T cells. However, the structure binding to MHC class II binding groove is similar to peptide fragments from infectious agents and hypocretin cell autoantigens, therefore the host binds and cross-reacts with CD4 + T cells instead of infectious agents, resulting in autoimmune response to hypocretin neurons.

Clinical cases that support this are large-scale narcolepsy outbreaks after influenza infection or H1N1 influenza vaccination in China and Northern Europe. In China, after the pandemic H1N1 influenza in 2009, diagnosis of narcolepsy tripled but has since declined. Most patients were not vaccinated, and natural occurring influenza. An infection is associated with occurrence of narcolepsy. Therefore, onset of symptoms of narcolepsy usually begins in late spring and is presumed to occur in spring through bacterial (Streptococcus pyogenes) or viral infection during winter. The titer of antibody to antistreptolysin O is high immedi-
ately after narcolepsy onset, that is the basis for the streptococcal infection to trigger the disease.42

In addition to influenza infection, vaccination also induces molecular mimicry. After the H1N1 vaccination of pandemic, AS03 (squalene, alpha-tocopherol) in Europe in 2009, narcolepsy occurred in considerable numbers of children and young adults in Finland.43 Finnish studies reported that narcolepsy diagnoses in children and young adults with DQB1*06:02 for eight months after vaccination were 12.7-fold higher when compared to those not vaccinated. In Sweden, Finland, Ireland, and the U.K., the incidence has increased in most cases between the age 5 and 19, that is seen as a genetically susceptible person.43,44

Other HLA-DQ alleles, HLA-DP and HLA class I also affect genetic susceptibility. Gene polymorphisms such as TCRA, TCRB, P2RY11, EIF3G, ZNF365, IL10RB-IFNAR1, cathepsin H and TNFSF4 that influence immune function, are associated with autoimmunity of narcolepsy.28

However, evidence of autoimmunity is related to cellular immunity, and humoral immunity is lesser known. Hypocretin specific antibodies have been studied, but only negative or inconclusive results have been reported.27 Recent studies have reported increased total IgG and hypocretin-specific IgM in narcolepsy patients, but this finding was not specific in narcolepsy patients with low hypocretin levels.45,46

In summary, the association of HLA DQB1*06:02, TCR alpha locus polymorphism, Streptococcus pyogenes, or influenza A or H1N1 vaccination is a unique autoimmune feature of narcolepsy.28

NARCOLEPSY TREATMENT OPTION BASED ON AUTOIMMUNITY

Narcolepsy is treated with a combination of behavioral and pharmacologic approaches.47,48 Non-pharmacological treatment is cost efficient with no adverse effects. Non-pharmacological treatment is critical considering pharmacological treatment is more effective if combined with non-pharmacological treatment. Behavioral treatment for EDS is to improve quality of sleep at night and take a nap for 15–20 minutes in the afternoon, that reduces EDS.49

The goal of conventional treatment is to reduce EDS and cataplexy. Treatment of EDS maintains alertness through central nervous system stimulants such as dextroamphetamine, methylphenidate that act as a mechanism of dopamine re-uptake inhibition and release and modafinil that is a selective dopamine re-uptake blocker. In the case of mild to moderate daytime sleepiness, modafinil is a viable choice. Side effects and abuse are less. Methylphenidate, dextroamphetamine, and amphetamine analogues are more potent than modafinil and side effects are more common. Cataplexy can improve through REM sleep suppression. Norepinephrine and serotonin are related neurotransmitters for REM sleep suppression. Tricyclic antidepressants (TCA) include imipramine and clomipramine, and selective serotonin-reuptake inhibitors include venlafaxine and fluoxetine, that are more effective than TCA, acting more selectively on the serotonergic transporter than TCA.

Sodium oxybate has a mechanism to activate GABAB receptors and is effective in treating cataplexy and EDS.24

These treatments have focused on each symptom control, and many studies have been conducted in recent advanced treatment focusing on autoimmunity that causes hypocretin production, neuron damaging or reduction of hypocretin.

Hypocretin replacement/supplement treatment is theoretically a viable method and various approaches have been studied. The method of administering hypocretin-1 that is more stable than hypocretin-2 to blood and CSF has an issue in that it is difficult to pass the blood-brain barrier. Another method of administering hypocretin to the brain is intranasal administration.50 However, this is an animal-based experiment and human-based studies will be needed.

In addition, gene therapy/cell transplantation has been studied. Gene therapy via hypocretin genes overexpressing was effective in mice.51 To transplant hypocretin-producing cells, transplanting of hypothalamus of a neo-natal rat into brainstem of an adult rat was conducted. However, the issue of graft survival, like Parkinson’s disease, must be solved.5

Immunomodulation treatment based on autoimmunity has also been studied. Steroid, immunoglobulin and plasmapheresis have been studied and immunoglobulin and plasmapheresis are effective.52-57

Studies on steroid therapy have been conducted on a dog and human. In dogs, frequency of cataplexy was reduced to 90 percent according to research, but some research reported that it was not effective. In the human study, an eight-year-old child was treated with prednisone, but it was ineffective.58-60

Plasmapheresis was administered in one patient and EDS and cataplexy improved, but recurred several weeks later. Symptoms improved after the second plasmapheresis and were successfully treated with sodium oxybate.52

The mechanism of autoimmune neurologic disorder of intravenous immunoglobulin has the following effects on auto-antibodies, 1) inhibition of complement binding and prevention of membranolytic attack complex formation, 2) modulation or blockade of Fc receptors on macrophages, 3) suppression of pathogenic cytokines and other immunoregulatory molecules.61 The effect of antibiotics is that IgG molecules in IVIg, that exhibit wide-range idiotypic and anti-idiotypic specificities, neutralize pathogenic auto-antibodies and prevent auto-antigen interaction. These mechanisms are targeted at pathogenesis associated with cellular and humoral immunity. In narcolepsy, a high dose of IVIg during the disease onset phase down-regulates T cell function, pathogenic cytokine and unidentified auto-antibody
**Table 1. Summary of all current narcolepsy cases treated by 1 g/kg/day for two days protocol**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Disease duration</th>
<th>Baseline 1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Our case</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt 2</td>
<td>10/F</td>
<td>3.5 mo</td>
<td>ESS: 9/24</td>
<td>ESS: 4/24</td>
<td>ESS: 8/24</td>
<td>ESS: 8/24</td>
<td>ESS: 4/24</td>
<td>Clinical improvement was not shown after 4th administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cataplexy: 3.5/d</td>
<td>3.5/d</td>
<td>3.5/d</td>
<td>1.5/d</td>
<td>2/d</td>
<td></td>
</tr>
<tr>
<td>Pt 3</td>
<td>8/F</td>
<td>8 mo</td>
<td>ESS: 4/24</td>
<td>ESS: 8/24</td>
<td>ESS: 8/24</td>
<td>ESS: 8/24</td>
<td>ESS: 4/24</td>
<td>No persistent effect of intravenous immunoglobulins in patients with narcolepsy with cataplexy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cataplexy: 2/d</td>
<td>2/d</td>
<td>2/d</td>
<td>2/d</td>
<td>2/d</td>
<td></td>
</tr>
<tr>
<td>Pt 4</td>
<td>45/M</td>
<td>9 yr</td>
<td>ESS: 23/24</td>
<td>ESS: 18.07 ± 4.3</td>
<td>ESS: 10.4 ± 2.9</td>
<td>ESS: 14.6 ± 1.7</td>
<td>Not performed</td>
<td>No persistent effect of intravenous immunoglobulins in patients with narcolepsy with cataplexy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cataplexy: 1–2/m</td>
<td>Cataplexy: rare</td>
<td>Cataplexy: rare</td>
<td>Cataplexy: rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ESS: 19 Cataplexy: &gt; 1/d</td>
<td>not performed</td>
<td>not performed</td>
<td>not performed</td>
<td>not performed</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cataplexy: 2/2</td>
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<td></td>
<td></td>
<td></td>
<td>Cataplexy: 3.5/d</td>
<td>not performed</td>
<td>not performed</td>
<td>not performed</td>
<td>not performed</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cataplexy: 5/d</td>
<td>not performed</td>
<td>not performed</td>
<td>not performed</td>
<td>not performed</td>
<td></td>
</tr>
</tbody>
</table>

ESS: epworth sleepiness, EDS: excessive daytime sleepiness.
and interferes with auto-antigen recognition.\textsuperscript{54,61} Immunoglobulin is the most common immunomodulation study in narcolepsy treatment, but it is inadequate compared to immunoglobulin therapy for other diseases. This may be due to the low prevalence of narcolepsy and high cost of immunoglobulin.

Knudsen et al.\textsuperscript{53} reported a case of successful treatment of patients with recent onset childhood narcolepsy and cataplexy with IVIg and a table summarizing cases treated with IVIg for narcolepsy was presented. Knudsen was treated with 1 g/kg/day for two days and five times at monthly intervals. However, the dose, duration, frequency, and additional medication of IVIg were variable for each patient in the table. Although IVIg is presumed to be effective, IVIg was not effective in some cases which is the reason for the lack of consensus in the protocol of IVIg treatment in narcolepsy.

Therefore, a systemic review of IVIg dose, treatment duration, and responses in narcolepsy patients is needed.

In 17 patients, the dose and treatment duration of IVIg were decided as 1 g/kg/day for two days\textsuperscript{53,56,62} or 0.4 g/kg/day for five days.\textsuperscript{57,62} According to previous reports, a total of 11 patients were treated with IVIg 1 g/kg/day for two days protocol (Table 1). The disease duration of the patients at the time of IVIg administration ranged from 15 days to 9 years. There were six males and five females. Ages ranged from 10–52 years old. Each patient received IVIg 1, 3 or 5 times. One patient received IVIg one time, and then took oral prednisolone for six weeks in addition to IVIg administration. A total of eight patients received IVIg three times, and one of them was treated with prednisolone too. Two patients received only prednisolone therapy five times.

One out of 11 patients was 52 years old and disease duration was not mentioned. IVIg was administered three times, but clinical improvement was not revealed. Ten patients had temporary or sustained improvement in symptoms (10/11, 90.9 percent). In symptomatic improvement, according to the number of administration, eight patients improved after the first administration, one patient had improved symptoms after the second administration, no patient improved in the third administration and one patient improved in the fourth administration. Six patients had sustained clinical improvement during follow up periods (6/10, 60 percent) and there were five patients with disease duration within six months and one patient was nine years (12/m, 10/m, 21/m, 12/f, 45/m, 10/m). Four of the six patients improved symptoms after the first administration (4/6, 66.6 percent) and each patient had improved symptoms after the second and fourth administrations. Follow-up test for MSLT or maintenance of wakefulness test (MWT) was conducted in nine patients. Three patients underwent MSLT, two patients underwent MWT and five patients underwent MSLT and MWT. In patients that performed only MSLT, one patient revealed improvement (1/3, 33 percent). Two patients that underwent MWT revealed improvement of MWT findings. None of the patients that underwent MSLT and MWT improved the outcome. There was no correlation between clinical parameters and sleep parameters in evaluation of treatment efficacy and this was known in past reports.\textsuperscript{57,63}

The efficacy of IVIg treatment is related to disease duration and onset age.\textsuperscript{54,55,57} Shorter disease duration and younger age make for better efficacy but there is no definite criterion for disease duration and onset age, and depending on literature, effects of treatment, timing and age, on effectiveness are inconsistent. Effect of treatment time on efficacy is based on the hypothesis that the shorter the disease duration, the lower the destruction of hypocretin-producing neurons by autoimmune. There is no evidence for normalization of hypocretin after IVIg treatment, but in patients with narcolepsy, CSF hypocretin level is generally low, suggesting that more than 90 percent of hypocretin-producing neurons are damaged.\textsuperscript{7,40,64} Patients with hypocretin levels in complete deficiency state did not have a positive effect with IVIg treatment, and hypocretin levels in early-treatment patients were higher than those in later course patients.\textsuperscript{53,56} Therefore, if hypocretin neuron is not completely destructive at time of treatment, the autoimmune process is reversible with IVIg treatment.

Serious side effects were not specifically reported in the previous case. Commonly known side effects of IVIg include thromboembolic events, migraine, aseptic meningitis, urticarial, pruritus, anaphylactic reaction, and renal tubular necrosis, but side effects reported in the case were infrequent flushes and headaches.

## CONCLUSION

The association of narcolepsy with HLA, TCR polymorphism, and large-scale development after influenza support autoimmune. TCR polymorphism and vaccination are unique autoimmune features of narcolepsy. Narcolepsy caused by this mechanism triggers severe daily disability due to EDS and cataplexy. However, most treatments administered in many clinics remain as symptomatic treatment rather than treatment by approach of pathophysiology. Use of long-term stimulants also have side effects.

Therefore, treatment based on underlying disease pathology and therefore a deeper understanding of the pathophysiology of narcolepsy is needed. Until now, cellular immunity had been clarified, but humoral immunity and antibody are unknown, therefore research is also needed on these subjects.

Although there are a limited number of cases treated by IVIg in narcolepsy, there have been reports of apparent clinical improvement in IVIg treatment. Guidelines and/or protocols including indication, dose and treatment duration should be established by research in fundamental treatment based on autoimmunity.
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CONFLICTS OF INTEREST

The authors have no financial conflicts of interest.

REFERENCES


