Editorial

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Narcolepsy: An Autoimmune Disease

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Editorial Note

Narcolepsy is a persistent sleep condition that usually begins in infancy or adolescence. It affects around 1 in 2000 people and has serious implications for patients, primarily owing to Excessive Daytime Drowsiness (EDS). Social stigma, somatic and mental comorbidities, problems acquiring an education and retaining a career, and a lower quality of life are all issues. Narcolepsy has significant socioeconomic implications. Narcolepsy symptoms include excessive daytime drowsiness, fragmented REM sleep episodes, disrupted nocturnal sleep, and unusually fast transitions into REM sleep. Cataplexy, a very specific symptom of narcolepsy, affects approximately two-thirds of all identified narcoleptic patients. Cataplexy is characterized by a rapid decrease of muscular tone caused by emotions such as laughing, joking, and, on rare occasions, rage.

Narcolepsy is one of several central hypersomnia that include Narcolepsy Type 1 (NT1), Narcolepsy Type 2 (NT2), and Idiopathic Hypersomnia (IH). The loss of hypocretin (HCRT, also known as orexin) generating cells in the lateral hypothalamus is a key discovery in NT1, as evidenced by a low level of HCRT-1 in Cerebrospinal Fluid (CSF). Despite clinical and electrophysiologic similarities, NT1 has a separate aetiology from NT2 and IH since CSF-HCRT-1 is normal in the latter. Furthermore, cataplexy and certain electrophysiologic abnormalities are linked to NT1.

The Autoimmune Theory of NT1

NT1 is caused by a particular loss of HCRT-producing neurons in the lateral hypothalamus, and numerous recent findings support the notion that NT1 is caused by an autoimmune process. For many years, the NT1 autoimmune hypothesis was largely based on genetic correlations with certain HLA alleles and other immune-related locations. In fact, narcolepsy has one of the strongest HLA correlations known, with more than 98% of patients having the MHC-II allele HLA-DQB1*06:02. Several studies have indicated the existence of autoantibodies in NT1, although despite some encouraging results, none of them have been consistently identified in NT1.

Auto-reactive NT1 T-cells

The discovery of auto-reactive CD4+ T-cells in blood samples from NT1 patients was a major advance in NT1 research recently. The significant connection with the MHC-II allele HLA-DQB1*06:02 suggests that CD4+ T-cells have a role in the development of NT1. However, CD4+ T-cells are unlikely to trigger neuronal death for a variety of reasons. To begin with, CD4+ T-cells are not cytotoxic in general. Second, unlike MHC-I, MHC-II has never been found on neurons. Third, a study of an NT1 animal model demonstrated that CD8+ T-cells, not CD4+ T-cells, may destroy hcrt neurons. This is corroborated by the discovery of postmortem hypothalamus CD8+ T cell infiltration in a case of NT1 caused by anti-Ma–associated diencephalitis. The infiltration of CD8+ T cells was linked to the total loss of hypocretinergic neurons. In patients and healthy controls, auto-reactive CD8+ T lymphocytes target narcolepsy-relevant peptides provided predominantly by HLA-B*18:01, HLA-B*51:01, and HLA-C*04:01. The frequency of auto-reactive T cell clones is lower in HLA-DQB1*06:02 positive controls compared to NT1 patients and HLA-DQB1*06:02 negative controls, indicating that the lack of auto-reactive T cells in healthy HLA-DQB1*06:02 positive people may play a protective function.

Although the presence of more auto-reactive CD8+ T cells in patients suggests a role for CD8+ T cells in disease progression, the autoimmune nature of NT1 has yet to be established. CD8+ T cells are involved in a complicated interaction with many other immune system cells, and further research is needed to completely understand the etiology of NT1. It is likely, for example, that auto-reactive CD4+ T cells, which appear to be more specific for NT1, are required for the activity of auto-reactive CD8+ T cells.

Increased Risk of NT1 by Childhood Infections

Infection with *Streptococcus pyogenes* has been proposed as a potential infectious cause for NT1. Other viral causes may also be involved. During the 2009-2010 flu seasons in China, there was a temporal relationship between a peak in H1N1 Influenza

A (swine-flu) infections and a surge in NT1 incidence 3-6 months later. Following the 2009 H1N1 Influenza A pandemic, numerous European nations began vaccination efforts, which resulted in a higher incidence of NT1 in Finland, Sweden, Norway, Ireland, France, and the United Kingdom. This rise in the prevalence of narcolepsy was linked to a particular H1N1 vaccination, Pandemrix. Despite the fact that the relative risk was typically considerable (3-12.7 fold), the prevalence of NT1 remained low (1 case per 16,000 vaccinated individuals). It has been proposed that an influenza infection/vaccination is simply one of several shocks to the HCRT neurons required for complete development of NT1.

Immunosuppressive Treatment for NT1-Concerns and Drawbacks

The main clinical concern with NT1 is whether immunosuppressive medications can stop or slow the illness down. It has been demonstrated that the loss of HCRT is still occurring in certain individuals close to the start of symptoms, indicating a significant clinical need for immunomodulatory therapy alternatives. Corticoids and intravenous immunoglobulin, on the other hand, have largely demonstrated a dismal lack of effectiveness. These treatments primarily target the humoral immune system. The lack of effectiveness implies that antibodies play only a minor role in NT1 development. Instead, future NT1 immunotherapy should focus on T-cell immunity. A few such therapies are already in clinical trials for the treatment of multiple sclerosis, and future research should look into the benefit of such T-cell-directed immunotherapy in animal models of T-cell mediated HCRT neuron destruction, with the goal of strengthening the case for a drug trial in NT1 patients near the start of the disease. Such investigations have yet to be launched. The discovery that illness onset and cell death are often quick and complete (particularly in patients with extremely low or undetectable CSF HCRT-1)-likely within days or weeks-poses a problem for NT1 immune mediated treatments, as is the frequent diagnostic delay. Patients with moderate HCRT levels, on the other hand, may be candidates for such therapy. Finally, if the cause of the cellular damage is understood, a vaccination may be unnecessary; nevertheless, it is still unknown which component initiates the autoimmune cascade. Additional study is required, which should include more data on the disease's natural course.