

Narcolepsy – Genes, Infections and Vaccines: the Clues for a New Autoimmune Disease

María-Teresa Arango MSc^{1,6}, Shaye Kivity MD^{2,3,4}, Joab Chapman MD PhD² and Yehuda Shoenfeld MD FRCP (Hon.) MaACR^{1,5}

¹Zabludowicz Center for Autoimmune Diseases, ²Rheumatic Disease Unit and ³Department of Neurology and Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Israel

⁴Borenstein Talpiot Medical Leadership Program 2013, Sheba Medical Center, Tel Hashomer, Israel

⁵Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

⁶Doctoral Program in Biomedical Sciences, Universidad del Rosario, Bogota, Colombia

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Narcolepsy is a sleep disorder resulting from the lack of orexin, an essential neurotransmitter involved in the equilibrium between sleep and wakefulness. Postmortem analyses of narcoleptic patients demonstrate the loss of orexin-producing neurons in the hypothalamus. As a consequence of this disruption, narcoleptic patients suffer from uncontrollable sleep attacks characterized by a rapid eye movement (REM) sleep pattern which is not preceded by the non-REM stage. In some patients the sleep disturbance is accompanied by other symptoms, such as cataplexy (loss of muscle tone), sleep paralysis and hallucinations [1].

Currently, narcolepsy is considered a rare disease with a world prevalence ranging from 25 to 50 per 100,000 people [2]. Its prevalence varies from one region to another, suggesting the importance of genetic and environmental factors [1]. In recent years scientists and clinicians have suspected that narcolepsy has an autoimmune nature, mostly due to its strong association with specific polymorphisms in immune related genes. Namely, the allele frequency of human leukocyte antigen (HLA) DQB1*06:02 among narcoleptic patients is 82–99% [1], while only 12–38% of healthy individuals are carriers. Later reports found additional associations between narcolepsy and other gene polymorphisms (e.g., TCR α) [3]. However, the fact that the rate of disease concordance among monozygotic twins is between 20% and 35% suggests that, as in other autoimmune diseases, environmental factors play a key role [1].

ENVIRONMENTAL ROLE: AH1N1 VACCINE, INFLUENZA AND STREPTOCOCCAL INFECTIONS

The relation between infections and autoimmunity is well documented. The best example is streptococcal group A (SGA)

bacterial infection, which is able to generate super-antigens that may stimulate autoreactive B and T cells leading to the production of autoantibodies (e.g., rheumatic fever). Moreover, SGA infections have also been related to other autoimmune neurological conditions, as well as to the presence of autoantibodies against neuronal proteins. Data suggest an association between infections, mainly *Streptococcus* sp. or influenza virus, and the onset of narcolepsy [4]. Childhood streptococcal throat infections were shown to be a risk factor for narcolepsy, and elevated anti-streptococcal antibodies were demonstrated in the sera of newly diagnosed narcoleptic patients [1,5].

Most striking was the discovery of a temporal association between narcolepsy and sleep-related disturbances, and the AH1N1 infection and its vaccination. In the 1918 H1N1 influenza pandemic, an increase in sleep disturbances as well as extreme sleepiness were noted in flu patients [1]. Ninety-one years later, a seasonal pattern of H1N1 infection in the 2009 Chinese pandemic was followed by a parallel increment in the incidence of narcolepsy, which returned to the usual incidence later [1,5]. However, the strongest evidence of an environmental association with narcolepsy was observed after immunization with the AS03-adjuvanted AH1N1 vaccine after the AH1N1 2009 pandemic [5]. This vaccine was designed based on the A/California/7/2009 (H1N1) v-like strain, and it was the one most used in Europe and the only one that contained the adjuvant AS03 [6]. Initially, an increment in narcolepsy cases related to the H1N1 vaccine was documented in Finland in 2010. As a result, a retrospective epidemiological analysis of historical reports and medical records demonstrated that the AS03 H1N1 vaccine was a risk factor for narcolepsy in Finland, Denmark, Sweden, France and England [6]. This association seemed to be stronger in genetically susceptible individuals, as HLA evaluation of new cases of narcolepsy/cataplexy post-vaccination showed they were mainly carriers of DQB1*06:02 [1,5]. Thus, the mechanisms by which the vaccine may be involved were explored. A recent study suggests that α -tocopherol (a component of the adjuvant AS03) may influence neuronal mouse cells, inducing over-production of orexin peptides as well as increased activity of the proteoso-

mal system. Masoudi et al. [7] suggest that this up-regulation might lead to the presentation of orexin peptides by the HLA, inducing an autoreactive response.

IMMUNE SYSTEM INVOLVEMENT IN NARCOLEPSY

Despite the recent reports of higher levels of inflammatory cytokines (i.e., granulocyte colony-stimulating factor and interleukin-8) in the plasma of narcolepsy patients [8], there is no evidence of an inflammatory process, including lymphocytic infiltration in the hypothalamus. A major obstacle is the inability to analyze brain specimens of patients at early stages of the disease [1,5]. The genetic polymorphisms associated with the disease are related to the immune system, and two of them are related to antigen presentation: the HLA DQB1*06:02 and the TCR α polymorphism. This may indicate the importance of the T cell response in the pathogenesis of narcolepsy, as it interacts directly with the HLA. It is possible that in predisposed individuals pathogenic T cells escape from the central tolerance process in the thymus. As a result, these cells may be able to be stimulated by external factors such as H1N1 vaccine or infections and finally evolve into an autoimmune response against orexin neurons. In fact, functional analyses of CD4+ lymphocytes from narcoleptic patients, but not from controls, showed that these cells were able to recognize orexin peptides when they were presented by dendritic cells (homozygous for DQA1*01:02/DQB1*06:02 haplotype); however, the authors failed to repeat these results [9]. Nevertheless, these controversial results do not clarify the mechanisms by which orexin peptides may be presented by CD4+ cells since it is currently unknown whether or not lymphocytes infiltrate the brain in narcolepsy patients. Furthermore, the role of CD8+ should also be further clarified, as should the mechanism whereby these cells pass the blood-brain barrier (BBB) [1,5].

The importance of B cell-mediated response has also been evaluated in narcolepsy. So far, three independent studies have shown that passive immunization with antibodies from narcoleptic patients can induce narcoleptic behavior and activity in mice [1,10], but none of them evaluated the sleep pattern of the immunized animals. Our group passively transferred total immunoglobulin G (IgG) from narcoleptic patients into mice brain, by intracerebroventricular injection. This procedure induced narcoleptic-like attacks and other behavioral changes in the mice and demonstrated the loss of orexin neurons in their hypothalamus [10]. Nonetheless, similar to the involve-

ment of T lymphocytes, the mechanism by which antibodies can induce narcolepsy is not known; neither is the identity of the specific autoantigen involved [5].

CONCLUSIONS

It is well known that the development of an autoimmune disease in genetically susceptible individuals can be triggered by contact with specific environmental factors, especially infections. Autoimmune diseases develop through four stages: inherited factors, interaction with environmental factors, breakdown of autoimmune tolerance defined by the appearance of autoreactive B or T cells, and the clinical stage when the disease is active. For narcolepsy, heritable factors as well as the relationship with environmental factors are well documented. However, the two final stages are not understood. Further research in this field is essential to understand the mechanisms by which the orexin neurons are lost in the brain of narcolepsy patients.

Correspondence

Dr. Y. Shoenfeld

Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-8070

Fax: (972-3) 535-2855

email: shoenfel@post.tau.ac.il

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“I have been very happy, very rich, very beautiful, much adulated, very famous and very unhappy”

Brigitte Bardot (born 1934), French former actress, singer and fashion model, who later became an animal rights activist

But what is happiness except the simple harmony between a man and the life he leads?”

Albert Camus (1913-1960), French-Algerian Nobel Prize-winning author, journalist, and philosopher. His views contributed to the rise of the philosophy known as absurdism