Monozygotic twins discordant for narcolepsy type 1 and multiple sclerosis

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Published in:
Neurology: Neuroimmunology & Neuroinflammation

DOI:
10.1212/NXI.0000000000000249

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
MONOZYGOTIC TWINS DISCORDANT FOR NARCOLEPSY TYPE 1 AND MULTIPLE SCLEROSIS

Narcolepsy type 1 (NC1) is a neurologic sleep disorder caused by the loss of hypothalamic neurons that produce the sleep–wake regulating neuropeptides, the hypocretins (orexins). The pathogenesis is believed to be mainly autoimmune, based on the observation of a 95% to 100% association with the HLA-DQB1*06:02 allele, and on the recent strong indication of antigen presentation to T cells as central factors. In Caucasians and Asians, the DQB1*06:02 allele is tightly linked to the HLA-DRB1*15:01 allele, which itself is associated with multiple sclerosis (MS), a CNS autoimmune disorder. Herein, we describe a DRB1*15:01/DQB1*06:02-positive monozygotic twin pair discordant for NC1 and MS.

Case report. In 2004, a 34-year-old, otherwise healthy Caucasian man (twin A) was diagnosed with narcolepsy NC1, 19 years after the onset of sleepiness. At the time of diagnosis, he presented severe daytime sleepiness (Epworth Sleepiness Scale score of 22/24), hypnagogic hallucinations, and dream enactment during sleep (REM sleep behavior disorder), but no cataplexy or sleep paralyses. Sleep investigations confirmed narcolepsy: the polysomnography was normal except for REM sleep without atonia, which was consistent with the reported dream enactment; the Multiple Sleep Latency Test showed a mean sleep latency of 6 minutes, with sleep-onset REM periods in 4 of 4 naps. He was hypocretin-deficient (CSF hypocretin-1: 58 pg/mL, compared with normal levels of ≥200 pg/mL) and his HLA type was DRB1*15:01/13:01; DQB1*06:02/06:03. In 2008, cataplexy triggered by laughter and surprise evolved. In 2011, serologic tests confirmed Epstein-Barr/cytomegaloviral infection and he experienced temporary leg paraesthesia, from which he quickly and fully recovered. Neurologic examinations, MRI of the brain and spinal cord, and measurement of the immunoglobulin G (IgG) index gave normal results. Oligoclonal bands were absent. The low CSF hypocretin-1 level was unchanged.

In 2006, his brother (twin B) was healthy, with a normal Epworth Sleepiness Scale score (8/24) and no narcoleptic symptoms. He declined to participate in sleep investigations, but was confirmed to be DRB1*15:01/13:01; DQB1*06:02/06:03-positive. In 2010, he developed bilateral hand/forearm paraesthesia. MRI of the brain and neck revealed >9 demyelinating periventricular lesions and a hyperintense lesion at the C2 level. Definite MS was diagnosed according to the 2010 revised McDonald criteria and on the recent strong indication of antigen presentation to T cells as central factors. In Caucasians and Asians, the DQB1*06:02 allele is tightly linked to the HLA-DRB1*15:01 allele, which itself is associated with multiple sclerosis (MS), a CNS autoimmune disorder. Herein, we describe a DRB1*15:01/DQB1*06:02-positive monozygotic twin pair discordant for NC1 and MS.
none of which overlap, have been reported and account for some of the missing heritability in both diseases. However, the present monozygotic twin A, who, when last examined, still had isolated NC1 without signs of comorbid MS, and twin B, who still had isolated MS without signs of secondary NC1, had an asymptomatic DRB1\*15:01/DQB1\*06:02 homozygote father and an asymptomatic DRB1\*15:01/DQB1\*06:02-negative mother. This strongly suggests that a shared genetic background of DRB1\*15:01/DQB1\*06:02 is not sufficient to account for a predisposition to either of these autoimmune CNS disorders. Additional predisposing genes are most likely uncommon since comorbidity is rare, but environmental factors, for example, bacterial or viral infections, are believed to be equally important in the pathogenesis of autoimmune disorders. Pandemrix is a vaccine whose effect is reduced in patients with MS treated with immunomodulatory drugs such as glatiramer acetate or natalizumab but not in patients on interferon \(b\). Given the dramatic increase of NC1 cases following H1N1 vaccinations with Pandemrix (GlaxoSmithKline), our present twin case and cases of comorbid MS and NC1 after H1N1 vaccination could be valuable for further studies of the genetic background and specific triggers (or drivers) of autoimmunity in these CNS disorders.

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Author contributions: S.K., P.J.J., B.R.K., and S.G. designed the study. S.K. and N.M.I. handled patients and CSF/blood samples. P.J.J. analyzed the sleep investigation data. S.G. and S.K. measured the hypocretin levels. N.T., N.M., and Z.T. handled the genetic samples and designed and performed the genetic tests. S.K., P.J.J., and B.R.K. wrote the manuscript. Z.T., N.M.I., and N.M. revised the manuscript.

Study funding: No targeted funding.

Disclosure: P.J. Jennum’s institution received a research grant from UCB. B.R. Kornum received research support from UCB. N.M. Isa, S. Gammeltoft, N. Tommerup, and N. Morling report no disclosures. Z. Türner received research support from the Lundbeck Foundation. S. Knudsen served as a member of the scientific panel for sleep disorders, received research support from and served as an expert consultant for the Norwegian State. Go to Neurology.org/nn for full disclosure forms. The Article Processing charge was paid by Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias.

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Received February 27, 2016. Accepted in final form May 6, 2016.

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Neurol Neuroimmunol Neuroinflamm 2016;3;
DOI 10.1212/NXI.0000000000000249

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