Objective: To explore whether acute destruction of hypocretin cells in a patient with narcolepsy could be detected and if the course of the disease could be reversed or altered by the use of prednisone for immunosuppression.

Design: Case report.

Setting: A sleep-clinic population in a tertiary-care hospital

Patient: An 8-year-old boy with a very acute recent (< 2 month) onset of sleepiness.

Methods: Sleep studies; fluid-attenuated inversion recovery and gadolinium magnetic resonance imaging studies with a focus on the hypothalamus; examinations of cerebrospinal fluid for cytology, protein, and hypocretin-1 levels; and HLA typing were performed.

RESULTS AND CONCLUSION: Sleep evaluations were consistent with a diagnosis of narcolepsy. Hypocretin-1 was absent in the cerebrospinal fluid, and HLA-DQB1*0602 was present. All other results were within normal limits, and prednisone did not have any noticeable effects. Clinical manifestation of narcolepsy may occur when the hypocretin cell damage is too advanced to be reversible.

Citation: Hecht M; Lin L; Kushida CA et al. Report of a case of Immunosuppression with Prednisone in an 8-year-old boy with an acute onset of hypocretin-deficiency narcolepsy. SLEEP 2003;26(7):809-10.

INTRODUCTION

RECENT STUDIES HAVE SHOWN THAT THE PRIMARY CAUSE OF NARCOLEPSY IS A DEFICIENCY IN THE NEUROPEPTIDE SYSTEM HYPOCRETIN (OREXIN).1-5 Together with the established HLA-DQ association in the disorder,6 most current pathophysiologic models for narcolepsy involve an autoimmune-mediated destruction of hypocretin-containing neurons.4-7

HISTORY AND EXAMINATION

We had the opportunity to evaluate an 8-year-old boy 2 months after an abrupt onset of narcolepsy. The patient was referred to our tertiary sleep center by his pediatrician for possible narcolepsy. The patient was healthy until 2 months prior to presentation at our clinic. Onset occurred abruptly in less than 2 weeks and was characterized by overwhelming sleepiness and unexplained clumsiness. His classmates had nicknamed him “droopy.” On one occasion, he fell off his bicycle without any clear reason. The boy reported hearing voices at night but denied visual hallucinations. We could not elucidate a history of cataplexy or sleep paralysis from the patient or his mother. His nocturnal sleep was consolidated and extended approximately 10 hours. His family observed that his lucidations. We could not elucidate a history of cataplexy or sleep paralysis from the patient or his mother. His nocturnal sleep was consolidated and extended approximately 10 hours. His family observed that his legs twitched during sleep. The patient’s appetite had increased in the preceding 2 months and his mother noticed a sudden significant weight gain of approximately 3 kg.

The boy’s medical and surgical history were unremarkable except for a tonsillectomy and adenoidectomy at the age of 5. He did not have any medical problems, had not suffered any trauma, and was taking no medications. Snoring was not reported. A neurologist saw him shortly after the onset of the symptoms, and the patient’s examination results, routine blood tests, and electroencephalogram were reported as normal. Immunologic evaluation was normal, including normal complete blood cell count, quantitative immunoglobulins, and peripheral T-cell subset and B-cell numbers. His parents and 2 siblings were healthy. The patient lived in a supportive family environment.

On examination in our center, the patient appeared extremely sleepy and fell asleep repeatedly during the office visit. His airway was not crowded. Cardiopulmonary examination was unremarkable. Visually it appeared as if the patient never entirely lost his muscle tone during the observed sleep attacks.

Nocturnal polysomnography revealed a total sleep time of 451.3 minutes, normal nocturnal breathing, and 23.3 periodic limb movements per hour with 5.2 periodic limb movements per hour associated with arousals. A multiple sleep latency test followed, which showed a mean sleep latency of 0.6 minutes and sleep onset rapid eye movement periods during each of the 5 naps.

The HLA typing was positive for DQB1*0602. Cerebrospinal fluid (CSF) examination did not reveal pleocytosis, oligoclonal bands, or increased protein content. The testing of the hypocretin-1 in the CSF revealed very low levels, below the limit of detection using both the direct and extracted assays (< 40 pg/mL), confirming the diagnosis of narcolepsy.

Magnetic resonance imaging studies of the brain with gadolinium and fluid-attenuated inversion recovery did not reveal hypothalamic or any other lesions.

INTERVENTION

To our knowledge, this report is the first case of narcolepsy developing within 2 months of an abrupt onset. The patient did not have cataplexy, and we hypothesized that an autoimmune process, if responsible for the patient’s narcolepsy, could still be detected and possibly reversed. After consultation with the family and a pediatric immunologist, we initiated high-dose prednisone at 1 mg·kg-1·day-1 for 3 weeks. Steroids have been used for immunosuppression and have been shown to be effective in reversing symptoms in a number of autoimmune diseases, whether or not pathophysiology is believed to be primarily cell-mediated (e.g., multiple sclerosis) or antibody mediated (e.g., myasthenia gravis). We had the opportunity to evaluate an 8-year-old boy 2 months after an abrupt onset of narcolepsy. The patient was referred to our tertiary sleep center by his pediatrician for possible narcolepsy. The patient was healthy until 2 months prior to presentation at our clinic. Onset occurred abruptly in less than 2 weeks and was characterized by overwhelming sleepiness and unexplained clumsiness. His classmates had nicknamed him “droopy.” On one occasion, he fell off his bicycle without any clear reason. The boy reported hearing voices at night but denied visual hallucinations. We could not elucidate a history of cataplexy or sleep paralysis from the patient or his mother. His nocturnal sleep was consolidated and extended approximately 10 hours. His family observed that his legs twitched during sleep. The patient’s appetite had increased in the preceding 2 months and his mother noticed a sudden significant weight gain of approximately 3 kg.

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gravis). The boy experienced an additional weight gain of approximately 3 kg during the therapy; otherwise, the treatment was well tolerated. Repeated multiple sleep latency testing 3 weeks later after interruption of prednisone therapy was still highly abnormal (mean sleep onset of 0.0 minutes and sleep-onset REM periods in all 4 naps), and the family did not report any dramatic improvement. Repeat CSF examination still indicated undetectable hypocretin-1 levels, suggesting irreversible damage.

Symptomatic treatment with 100 mg of modafinil was instituted, and our recommendation included having the patient take a scheduled nap in the early afternoon. The boy’s sleepiness and school performance improved dramatically. His problems with balance (which might have been a presentation of sleep attacks) resolved. Approximately 1 year after the initial diagnosis, the patient returned with his mother after he began exhibiting recurrent episodes of tongue thrust with jaw dropping, without any clear association with emotions. We felt that this symptom could be an expression of sleep attacks, a side effect of stimulant treatment, or possible atypical cataplexy. Treatment with venlafaxine, an antidepressant used to treat cataplexy, was initiated at 37.5 mg per day, with dramatic effects on this atypical presentation of cataplexy.

DISCUSSION

This report illustrates the importance of evaluating narcolepsy as soon as possible after disease onset. We still hope that modification of the course of the disease can be achieved through therapeutic intervention. In this case, the use of immunosuppression did not reverse the symptoms. We could not detect any immune-related abnormalities in the CSF nor any local hypothalamic inflammation using available imaging techniques. Similarly, Matsuki et al. studied peripheral markers of inflammation and autoimmunity in 3 cases with recent (2-8 months) onset and could not detect any significant changes at baseline and during a 1-year follow-up study. These disappointing results suggest that clinical manifestation may occur most often when the hypocretin cell damage is too advanced to be reversible. In favor of this hypothesis is the finding of low or undetectable CSF hypocretin-1 levels in the only cases known to date that were studied within 1 year of narcolepsy onset; the 4 patients, all of whom had cataplexy, were aged 9 months and 6, 8, and 8 years. Alternatively, HLA association or hypocretin-cell destruction is not the result of an autoimmune process that responds to steroid therapy or not the result of an autoimmune process at all.

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REFERENCES