Narcolepsy with Cataplexy in Early Childhood

Don Hayes, Jr, MD

Summary: Narcolepsy is a rare neurologic sleep disorder with morbidity associated with functional impairment and frequent delay in diagnosis. Symptoms typically manifest in adolescence or early adulthood, but diagnosis of narcolepsy has been reported in early childhood. Diagnosis rates are as low as 50% of the total population of patients with narcolepsy and are delayed as much as 10 years after disease onset due to inadequate patient-physician communication and/or misdiagnosis. I present the complexity of diagnosing narcolepsy in early childhood in a patient with cataplexy that started soon after independent ambulation at age 10 months. Clin Pediatr. 2006;45:361–363.

Introduction

Narcolepsy profoundly impairs the lives of patients and often is not diagnosed until 10 years after disease onset.1 Diagnosis rates are estimated as low as 50% of the total population with narcolepsy.1 The age of onset is typically between 15 and 30 years, but onset of symptoms has been reported before age 10 and after age 55.2 Narcolepsy affects control of sleep and wakefulness and manifests rapid eye movement (REM) sleep episodes at sleep onset and REM-like activity during wakefulness.3-5 The hallmark clinical presentation is excessive daytime sleepiness with other clinical symptoms including cataplexy, hypnagogic and/or hypnopompic hallucinations, and sleep paralysis.3-5 Cataplexy is the abrupt loss of muscle tone provoked by a strong emotion. Auditory or visual hallucinations occur during sleep transition at sleep onset (hypnagogic) or sleep offset (hypnopompic). Sleep paralysis is the inability to move or speak for a few seconds or minutes at sleep onset or offset. Prevalence of narcolepsy is 0.02% to 0.05% of the general population.6,7 The multiple sleep latency test (MSLT) is considered the standard test to diagnose narcolepsy and entails nocturnal polysomnography followed by a 4 to 5 daytime naps during which sleep latency is measured.8 Narcoleptics have short mean sleep latencies, often 5 minutes or less, with 2 or more sleep-onset REM periods (SOREMPs).

Patient Report

An 8-year-old male presented with continuing narcosis with occasional staring spells. He was initially evaluated at age 2 years with poor sleep quality, inattention, aggressiveness, and episodes of falling down of unknown etiology. These falling episodes began soon after onset of independent ambulation at age 10 months and were associated with crying. His developmental milestones were appropriate for age. At that time, he was diagnosed with attention deficit and hyperactivity disorder with sleep difficulties, but his mother was reluctant to continue stimulant therapy with dexedrine without a definitive diagnosis. She pursued other evaluations at other medical institutions with multiple electroencephalograms without epileptiform activity ever being identified. Computed tomography and magnetic resonance imaging of the brain were normal. Neuropsychological testing placed him at borderline intelligence. Metabolic work-up was negative.

Daytime hypersomnolence began at 4 years of age but was progressing despite several trials of stimulants and other medications including methylphenidate, dextroamphetamine, pemoline, dexedrine, clonidine, thioridazine, and nortriptyline. Venlafaxine was started at 7 years of age with significant improvement of hyperactivity and staring spells. At 8 years of age, a multiple sleep latency test (MSLT) was performed at a small community clinic, and it questioned narcolepsy but the study failed to meet diagnostic standards. Nocturnal polysomnography (NPSG) and MSLT were performed at our sleep center before his clinic appointment. The venlafaxine therapy was not stopped before the NPSG due to the mother’s request. The NPSG revealed normal sleep latency, low sleep efficiency at 83%, prolonged REM latency at 390 minutes, with low REM density at 6% of total sleep. There was no evidence of sleep-disordered breathing or periodic limb movements. His 4-nap MSLT following the NPSG revealed a sum sleep latency of 3.5 minutes with average sleep latency of less than 1 minute. Sleep latencies for each individual nap were 0.5 minutes, 1.5 minutes, 1 minute, and 0.5 minutes. He had 4 SOREMPs with REM latencies of 4 minutes, 2.5 minutes, 2.5 minutes, and 2.5 minutes. The MSLT confirmed severe REM dysregulation consistent with narcolepsy. During his evaluation in clinic, he reported severe hypersomnolence that improved with sleep and cataplexy with complete loss of postural muscle tone due to sudden emotional changes. Hypnagogic hallucinations and sleep paralysis started 2 years earlier. His examination revealed a somnolent 8-year-old right-handed male with an otherwise normal physical and neurologic examination and body mass index of 28. He was begun on stimulant therapy with dexedrine extended and immediate release in addition to continuing venlafaxine. Human leukocyte antigen (HLA) typing was positive for DQB1*0602. At follow-up, he had breakthrough hypnagogic hallucinations, so venlafaxine was changed to the extended release preparation with resolution of symptoms.
Discussion

The pathophysiology of narcolepsy is described as abnormal hypocretin (orexin) neurotransmission from the lateral hypothalamus. Undetectable levels and rarely elevated levels of hypocretin-1 were described in cerebrospinal fluid (CSF) of narcoleptics.9–12 Selective loss of hypocretin messenger RNA and immunoreactivity was reported in the hypothalamus of six patients.13,14 Common treatment for narcolepsy is psychostimulants for excessive sleepiness and antidepressants including tricyclic antidepressants and selective serotonin reuptake inhibitors for cataplexy.

The majority of cases of narcolepsy are sporadic, but twin and family studies demonstrated genetic factors.3,7 Hypocretin-1 deficiency in CSF was found in both familial and sporadic cases of narcolepsy.15 The risk of narcolepsy for relatives of patients with sporadic narcolepsy is 20 to 40 times higher than the general population, suggesting a genetic component.7 There is close association of narcolepsy with HLA allele DQB1*0602.16–18 This association suggests an autoimmune etiology. Further studies confirmed that HLA-DQB1*0602 is positive in 90% to 100% of patients with definitive cataplexy but is decreased with atypical cataplexy or no cataplexy.5,17 Within cataplectic patients, there is significant variation in HLA association (70–100%).5,17 Autoimmunity as a possible etiology was further demonstrated with a recent study by Smith and colleagues19 that described a functional autoantibody in narcolepsy compared to normal control subjects.

Another diagnostic tool is now available to help in the clinical evaluation of narcolepsy. Mignot et al.20 reported that CSF hypocretin-1 levels below 110 pg/mL were diagnostic for narcolepsy and values above 200 pg/mL were normal. Mean CSF hypocretin level for patients with narcolepsy with cataplexy was 47.5 ± 9.7 pg/mL, narcolepsy without cataplexy was 270.9 ± 24.8 pg/mL, essential hyporsomnia was 308.9 ± 9.9 pg/mL, and for controls was 363.2 ± 16.3 pg/mL.20 HLA-DQB1*0602 frequency in this study group was 93% for narcolepsy with cataplexy, 56% for narcolepsy without cataplexy, 52% for essential hyporsomnia, and 17% for controls.20 Hypocretin-1 deficiency was present in six narcoleptic children (ages 6 to 16 years) with mean CSF levels of 79 pg/mL.21

Narcolepsy is difficult to diagnose in the adolescent and adult population but is even more difficult in the very young child as illustrated by this case. Retrospectively, this patient likely had cataplexy soon after independent ambulation at 10 months of age and continued to have similar episodes of complete postural tone several years later. Psychostimulant therapy was not helpful in early childhood, but his clinical course significantly improved when venlafaxine was started. His suppressed REM density and prolonged REM latency on NPSG was due to venlafaxine, which suppresses REM sleep. HLA typing may have been helpful earlier in the clinical course. Due to delay in diagnosis, this patient suffered from significant morbidity and was thought to have borderline intelligence. Presently with adequate therapy, he is an above average student with a goal of attending college.

Conclusions

This case illustrates the difficulty of diagnosing narcolepsy in the early childhood period. Physicians must be cognizant of behavioral problems in early childhood as possible manifestations of sleep disorders and include narcolepsy in that differential diagnosis. The MSLT continues to be the standard test to diagnose narcolepsy, but narcolepsy cannot be excluded in the absence of positive findings. Other diagnostic tests are available that may be helpful in the early childhood period, including HLA typing for the DQB1*0602 allele and CSF hypocretin-1 levels, particularly if cataplexy is present. At this delay in diagnosis is imperative in avoiding significant morbidity in the young child.

References