Child Neurology: Common Occurrence of Narcolepsy Type 1 and Myasthenia Gravis

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Neurology® 2024;103:e209598. doi:10.1212/WNL.0000000000209598

Abstract

Narcolepsy with cataplexy and myasthenia gravis are both chronic neurologic conditions causing symptoms of muscle weakness, often affecting facial muscles, and have both been attributed to an immune-mediated etiology. We report an adolescent girl diagnosed with both conditions and discuss possible shared mechanisms and the diagnostic challenges presented by her case to inform and aid clinicians managing children and young people with these rare conditions.

Introduction

Narcolepsy is a chronic neurologic condition characterized by daytime periods of an irrepressible increased need to sleep caused by dysregulated REM sleep. Narcolepsy is divided into 2 phenotypes classified by the presence or absence of cataplexy, historically referred to as types 1 and 2, respectively.[1] Cataplexy is defined as a sudden loss of muscle tone triggered by a strong emotional stimulus, such as laughter, as a dysregulation of the skeletal muscle atonia generated during REM sleep. The presentation of cataplexy varies between complete loss of postural tone[1] and subtler manifestations including knee-buckling and head-drop. "Cataplectic facies" can be seen manifesting as repetitive mouth opening, tongue protrusion, and ptosis, but, interestingly, is not always associated with an emotional trigger.[2] Cataplectic symptom severity often correlates with daytime sleepiness severity and often improves when the sleepiness is controlled.

Myasthenia gravis (MG) is an autoimmune disorder characterized by fatigable muscle weakness in either a generalized or localized distribution. MG often has a predominantly proximal pattern and nearly always includes ocular symptoms such as ptosis and/or extraocular muscle involvement.[3] Ocular involvement is often unilateral or asymmetric and may be the only presenting feature in 10%–20% of cases.[3] MG is primarily associated with IgG antibody–mediated disruption of postjunctional proteins, typically targeting the acetylcholine receptor (AChR) or, less frequently, muscle-specific kinase or other proteins.

Case Report

A 10-year-old girl was referred to the sleep clinic with 2 years of excessive daytime sleepiness and irresistible sleep attacks. She reported episodes of changes in muscle tone affecting her face, trunk, and lower limbs with falls to the ground triggered by laughter. She had an age-appropriate bedtime of 20:00-20:30 hours. She reported lucid dreaming, but no hallucinations or sleep paralysis. No infectious, immunologic, or emotional triggers preceded onset of her symptoms. However, she was significantly overweight, with a BMI of 36.3 at presentation. She was the first child of nonconsanguineous parents with no significant family history. She was born at term by spontaneous delivery in good condition and had a normal developmental history. Academically, she was above average at school.

Actigraphy identified regular bedtime at 20:30 hours with normal 24 minutes average sleep-onset time and 11 hours sleep opportunity per night. Her polysomnography (PSG) identified a

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AChR = acetylcholine receptor; **MG** = myasthenia gravis; **MSLT** = multiple sleep latency test; **PSG** = polysomnography; **SOREMP** = sleep onset REM period.

total sleep time of over 9 hours with a notable sleep-onset REM latency of 2.5 minutes arising from the first stage of N1, REM within 15 minutes being defined as sleep-onset REM period (SOREMP) (Figure). She underwent the multiple sleep latency test (MSLT) and slept in all 4 nap opportunities with a mean sleep latency of 0.3 minutes; each nap included REM sleep (average of 1.6 minutes after sleep onset, again satisfying criteria for SOREMPs) with 2 of the REM periods arising from N1. Blood test for the HLA-DQB1*06:02 allele associated with narcolepsy was also positive. A diagnosis of narcolepsy with cataplexy was made based on her overnight SOREMP and her positive MSLT, supported by her compatible HLA allele. A lumbar puncture for hypocretin levels was not undertaken because it was not believed to add to her diagnosis or her subsequent management.

A management plan was agreed that included 1 or 2 daily scheduled 20-minute naps, psychoeducation for the young person and the school, and commencement of prolonged release methylphenidate. Despite increasing doses of methylphenidate, there was only mild improvement of her symptoms of hypersomnolence. Cataplexy also persisted in the form of daily collapses; therefore, modified release venlafaxine was eventually added in keeping with European guidelines.[4]

By the time the patient had turned 12 years, she was experiencing ptosis of the left upper eyelid, which was worse at the end of the day. This was initially attributed to her cataplexy, which was not being controlled medically despite ongoing pharmacologic optimization. She was seen by an optician for a routine eye check, who felt the ptosis was fatigable and would warrant further investigation. After referral to the pediatric ophthalmology department, acetylcholine receptor antibodies were found to be elevated (0.75 nmol/L; normal range 0.0–0.45 nmol/L).

She was reviewed by pediatric neurology where limb fatiguability was elicited after 1 minute of sustained shoulder abduction. Ptosis fatiguability on sustained upward gaze seemed to be present but was more difficult to elicit because of her excessive daytime sleepiness as she struggled to remain awake and keep her eyes open. Neurologic examination was otherwise normal. She had no urinary or bowel-related symptoms, nor any visual or hearing difficulties. She had some difficulty in swallowing solids and liquids but no choking episodes. She complained of headaches. She was started on pyridostigmine at 60 mg 5 times daily. Chest MRI was undertaken as part of her routine workup to screen for thymoma, which was normal, as well as a head MRI considering her headaches and increased weight. Both scans were normal.

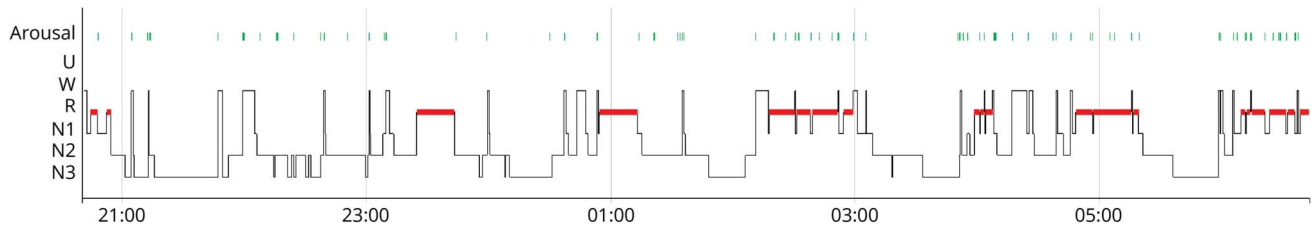
Improvement of her ptosis was noted after pyridostigmine was commenced. Further immunosuppressive treatment with steroids was deferred, considering her improvement.

Discussion

This case illustrates an unusual clinical challenge in that the confirmed diagnosis of narcolepsy with cataplexy obscured the perception and interpretation of her fatiguability and facial symptoms that were in fact because of a second diagnosis of MG. The ptosis on the background of already existing facial symptoms of cataplexy was initially considered part of her original diagnosis, and her cataplexy medication was initially further titrated to response before the diagnosis of myasthenia was suggested by an optician review, prompting further investigations and a dedicated review by a pediatric neurologist.

Although clinical examination and findings of fatiguability suggested a diagnosis of MG, this was challenging because of persistence of cataplectic symptoms and excessive daytime

Figure Hypnogram Generated From Our Patient's PSG Demonstrating Rapid Sleep-Onset Time (SOT), With Rapid Sleep-Onset Latency and First REM Cycle in Red Arising From N1



There is general fragmentation of sleep. This is a typical hypnogram for narcolepsy. U, undefined sleep stage; W, wakefulness; R, REM sleep; N1, NREM stage 1; N2 NREM stage 2; N3 NREM stage 3.

sleepiness; the ice pack test, commonly applied in the diagnosis of MG, would be unhelpful because it results in a similar improvement of cataplexy-related ptosis.[5] The difficulty in differentiating the 2 is also illustrated in another case in the literature of a young child presenting with distal muscle weakness and ptosis, which was initially confused for neuromuscular disorder, but subsequently found to be due to narcolepsy with cataplexy.[2] Subtle differences between the 2 presentations are summarized in eTable 1.

The diagnosis of narcolepsy in children and young people requires PSG and a MSLT to identify SOREMPs, defined as evidence of REM sleep within 15 minutes of sleep onset.[1] First REM sleep period onset from non-REM sleep level 1 (N1) or wakefulness is more likely in narcolepsy than other forms of hypersomnolence.[6] The HLA-DQB1*06:02 allele is present in almost all cases of narcolepsy with cataplexy and supports diagnosis but has low specificity, found in 12%–25% of the general population.[7]

The diagnosis of MG can be established based on suggestive clinical symptoms, immunoassay confirmation of causative antibodies, neurophysiologic evidence of disrupted neuromuscular transmission, and/or response to treatment with acetylcholinesterase inhibitors. Repetitive nerve stimulation and an increased jitter on single-fiber EMG may also support the diagnosis, but are challenging in children and not routinely performed if other findings are already supportive of the diagnosis.[3] Thymus imaging to screen for thymoma is required in all cases of MG.

On review of the literature, we identified only one small case series of 2 adult women with a comorbid diagnoses of narcolepsy and MG (in one case associated with ocular symptoms.)[8] Both had negative AChR antibody results and were diagnosed on neurophysiologic studies. In both cases, diagnosis of MG preceded that of narcolepsy, which presented without cataplexy.[8] In both cases, narcolepsy was diagnosed based on PSG and MSLT findings.[8]

Co-occurrence of 2 rare conditions MG and narcolepsy with cataplexy raises the question about potential commonality of underlying mechanisms. MG is well recognized as autoantibody-mediated and mainly B-cell driven,[3] whereas narcolepsy is more associated with T-cell–mediated loss of hypocretin-secreting neurons,[9] as such specific antibodies to hypocretin receptors are very rare.[10] A strong association between narcolepsy and HLA-DQB1*06:02 has been documented,[7] and an increased risk of developing narcolepsy with cataplexy has been noted after exposure to *streptococcus pyogenes* or H1N1 outbreaks and H1N1 ASO3-adjuvanted vaccine (Pandemrix).[7]

Autoimmune diseases tend to coexist more often than due to chance, and there is some evidence of increased risk of immunopathologic disease in individuals with narcolepsy[11] with a particularly increased prevalence of allergy in children with narcolepsy with cataplexy.[12] Some evidence in adult retrospective studies also suggest a relationship between narcolepsy and autoimmune disorders, such as alopecia areata, psoriasis, and autoimmune thyroiditis, but without statistical significance when accounting for other autoimmune diseases in control groups.[13] MG has also been associated with other immune-mediated non-neurological manifestations in adult cases, including alopecia, gastrointestinal disturbance, and minimal change nephrotic syndrome.[14]

Conclusion

This case highlights an unusual presentation of 2 very rare conditions with clinical features that are difficult to distinguish. Because both disorders are rare, diagnostic overshadowing may occur whereby the presence of either MG or narcolepsy might reduce scrutiny for other disorders. Although the co-occurrence is likely to be exceedingly rare, we would advise caution to clinicians when reviewing the progress of cataplectic symptoms of children and young people with narcolepsy and to consider other differential diagnoses if symptoms do not respond to treatment or are not fully consistent with the typical presentation of narcolepsy with a low threshold to involve other professionals with relevant expertise.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* November 13, 2023. Accepted in final form June 3, 2024. Submitted and externally peer reviewed. The handling editor was Resident & Fellow Deputy Editor Ariel Lyons-Warren, MD, PhD.

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