Dear Editor

We report a case of probable encephalitis presenting as narcolepsy with cataplexy, but with cyclical exacerbation and cognitive difficulties. Our patient continued to worsen despite treatment for narcolepsy and later was thought to have an immune-mediated encephalopathy. Treatment with intravenous gamma immunoglobulin (IVIG) led to complete recovery. Cyclic symptoms of narcolepsy with cataplexy are thus one presentation of probable immune-mediated encephalitis.

1. Clinical case

A 15-year-old otherwise healthy boy presented with several months of excessive daytime somnolence that followed a febrile illness involving myalgia and headaches. He had daytime hypersomnolence at baseline with monthly exacerbations lasting ~2 weeks when he would sleep 16–20 h a day. Though previously a high-achieving and physically active student, he now had difficulty concentrating and struggled in school. He had no hypersexuality, hyperphagia, or apathy, but did have diminished appetite. His father had restless legs syndrome, but the rest of his immediate family had no history of sleep disorders.

He saw a handful of specialists and had an extensive workup. Brain MRI was normal. Polysomnography showed sleep onset latency (SOL) of 47 min with sleep latency to REM of 197 min and no sleep-onset REM periods (SOREMPs); subsequent multiple sleep latency testing (MSLT) captured sleep in only 1 nap with SOL of nearly 20 min. Within 7 months of his presentation he developed paralysis on waking and weekly episodes of weakness with emotional events such as laughter and anger consistent with narcolepsy with cataplexy, but still did not fall asleep during the day, had no hypnagogic hallucinations, and did not have sleep fragmentation. He was seen at the Stanford Center for Narcolepsy where a repeat polysomnography showed SOL of 31 min, with one SOREM of 4.5 min. He was negative for HLA-DQB1*0602, an allele present in most patients with narcolepsy [1]. Lumbar puncture revealed oligoclonal bands which were also in his serum. CSF hypocretin level, which is typically low in narcolepsy [1], later returned as normal. His drowsiness and cognitive function improved some with a stimulant, but he continued to have cyclically-worsening hypersomnolence.

Due to his continued hypersomnolence at 10 months following his initial presentation and negative workup for narcolepsy or idiopathic hypersomnia, he returned to our clinic where we thought he likely had immune-mediated encephalopathy. A repeat lumbar puncture revealed no oligoclonal bands and CSF and serum later returned negative for all antibodies on the Mayo Autoimmune Encephalitis Panel (CSF and serum: NMDA receptor, voltage gated potassium channel, GAD65, GABA-B receptor, AMPA receptor, anti-neuronal nuclear antibody 1-2-3, anti-glial nuclear antibody, Purkinje-cell cytoplasmic antibody 1-2-3, amphiphysin CRMP-5 IgG; serum alone: N and P/Q calcium channels, muscle and neuronal AChR). He was treated with a course of IVIG at 2 g/kg over 5 days (400 mg/kg/day for 5 days). After the first day of treatment, he awoke with minimal somnolence and mental clarity that
he hadn’t felt in a year. Neurologic exam showed that his cognitive responses were faster and he was more engaging. He had symptom resolution within a few days and with his remarkable recovery returned to school full-time, achieving “A” grades. Seven months later he had recurrence of symptoms with headaches, hypersomnolence, sleep paralysis, and cognitive slowing, and his workup and brain MRI were again normal. He was treated with another course of IVIG with symptom resolution.

2. Discussion

This patient had symptoms of narcolepsy with cataplexy and cyclical exacerbation of chronic hypersomnolence that resolved with IVIG treatment, reflecting a probable immune-mediated encephalitis. Symptoms of narcolepsy and cataplexy in encephalitis are extremely rarely documented, but have been reported in a few cases of autoimmune encephalitis associated with Ma2 antibodies (2 of 34 cases in one series) [2]. Though our CSF autoimmune panel did not include anti-Ma2 antibodies, it is unlikely that our patient had encephalitis with anti-Ma2 antibodies since his brain MR and testicular examination were normal and most male anti-Ma2 cases have a testicular tumor, monophasic course, and abnormal brain MRI [2,3]. Since our patient’s serum and CSF autoimmune panel was negative, he is regarded to have had a probable seronegative immune-mediated encephalitis.

Our patient’s poor appetite and cyclical exacerbations of hypersomnolence following a febrile illness are strikingly similar to Kleine-Levin Syndrome (KLS), classically consisting of hyperphagia, hypersomnolence, and hypersexuality. However, our patient did not meet KLS diagnostic criteria per the International Classification of Sleep Disorders (ICSD) [4,5] as in absence of immunotherapy he did not return to baseline alertness and cognitive function between exacerbations. Furthermore, sleep paralysis and cataplexy are not features of KLS, and the time between episodes is typically months to years whereas in our patient without immunotherapy the time between exacerbations was ~2 weeks [4,6,7]. The pathophysiology of KLS is unknown, but an autoimmune etiology remains a consideration [4]. If our patient’s syndrome is considered a variant of KLS, then it is promising that immune-therapy might also be effective for treatment in KLS, which lacks consistently-effective treatment [4].

This case study shows that cyclic hypersomnolence with symptoms of narcolepsy with cataplexy is one presentation of probable immune-mediated encephalitis, and immune therapy can be considered for treatment and diagnostic confirmation, even if the patient is seronegative and brain MRI is normal [3]. A proposed algorithm for workup of antibody-mediated encephalitis includes screening for autoantibodies, EEG, MRI and possibly FDG-PET imaging, and a workup for systemic tumors [8,9]. With early suspicion of antibody-mediated encephalitis, empiric treatment should be considered as prompt treatment is associated with better outcomes [8,10]. Generally IVIG and plasmapheresis are preferred to steroids as they are unlikely to worsen infectious encephalitis or cloud diagnosis of a CNS lymphoma [10]. Additionally, patients may relapse typically with similar symptomatology, as in our case and within 2 years in 12% of anti-NMDAR encephalitis cases, thus follow-up remains important [10].

Author contributions

Rafer Willenberg: analysis & interpretation, drafting and revision of manuscript.
Jonathan Bui: conceptualization, interpretation, critical review and revision of manuscript

Author disclosures

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