

## Ehlers-Danlos Syndrome and Narcolepsy: An Incidental Relationship?

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### Abstract

Ehlers Danlos syndrome (EDS) is a collagenic disease that has often been associated with different types of sleep disorders ranging from insomnia to obstructive sleep apnea (OSA). EDS usually has associated fatigue and excessive daytime sleepiness (ES), thus narcolepsy should be excluded as a cause. Literature review suggests a high prevalence of hypersomnia disorders in this population. We present two sporadic cases presenting with typical symptoms of narcolepsy.

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## Introduction

Ehlers Danlos Syndrome (EDS) is a genetic disorder occurring in 1 in 5000 births, with predominance in females. Its multi-systematic effects are due to abnormal mutation of the connective tissue impacting skin (i.e., hyperextensibility), blood vessels, and joints (i.e., hyperflexible joints)<sup>1</sup>. Other associated abnormalities include psychiatric, cardiac, and gastrointestinal concerns. Excessive daytime sleepiness (ES), fatigue, and other sleep disturbances are frequently reported by patients with Ehlers Danlos Syndrome<sup>2,3,4</sup>. A 9-point Brighton scale has been used to aid in diagnosis of EDS. If four or more points are detected, the scale is considered positive. However, other hyperflexibility disorders such as Marfan's and osteogenesis imperfecta should be excluded.

Sleep disorders are very common in the EDS population ranging from insomnia to obstructive sleep apnea (OSA). Due to joint involvement, pain might interrupt sleep causing insomnia. Due to the associated cartilaginous defects, laryngo-tracheomalacia, chest deformities, scoliosis, dilated aorta causing tracheal compression, and vocal cord abnormalities, a higher prevalence of OSA is expected<sup>4,5,6</sup>. Other comorbid sleep disorders in this population include periodic limb movement disorder and circadian rhythm sleep disorders. Primary hypersomnia or narcolepsy was found in 21.3% of the population<sup>7</sup>.

Narcolepsy is a disorder characterized by excessive daytime sleepiness (ES), involuntary sleep attacks due to rapid eye movement (REM) intrusion, sleep paralysis and hypnagogic or hypnopompic hallucinations. Cases associated with sudden loss of muscle tone in the setting of strong emotions (i.e., cataplexy) are type 1, while lack of cataplexy is termed type 2. Aside from the clinical presentation, a confirmation by the presence of two sleep onset REM (SOREMs) on multiple sleep latency test (MSLT) is required. In narcoleptic individuals, an average sleep onset in the 5 naps of less than 8 minutes is expected signifying ES. In non-conclusive MSLT cases, a low or deficient CSF hypocretin can aid in diagnosis.

### Case Report

#### Case 1

A 12-year-old African-American female presented with a complaint of ES (Epworth Sleepiness Scale [ESS] = 15), with an onset of about two years prior to her initial evaluation. Her typical sleep patterns included going to sleep at 4pm and waking up at 6am. She would typically come home from school preferring to sleep rather than eat; her mother's attempts to wake her up for dinner were often unsuccessful. She would sometimes fall asleep during school, usually 5 times per day for about 15 minutes, at which time her teacher would wake her up. Eye lid drooping was noticed when she cried as well as when she laughed hard. This was sometimes associated with dizziness. The patient also experienced hypnagogic hallucination described as a "black shadow at the corner of the room". She reported infrequent sleep paralysis occurring once a month. Her swiss narcolepsy scale is -88 suggestive of narcolepsy with cataplexy.

The patient's body mass index [BMI] was within the normal range for her height (weight=49.40 kg, height=1.68 m, BMI=17.6) and aside from history of delayed speech requiring speech therapy at age 3, her neurological and other medical history was unremarkable. During examination, it was noticed that the patient also had elastic skin, long fingers, extensibility of the elbow, and symptoms of postural orthostatic tachycardia syndrome (POTS) with feeling dizzy if she was lying down and stood up too fast. She was referred to geneticist who diagnosed her with EDS. Leg length discrepancy, arachnodactyly, pes planus of both feet, tall stature and valgus deformity of the great toe were also noted. Genetic testing revealed a heterozygous variant in the COL9A2 gene (c.1061C>T). Her echocardiogram showed mild to moderate mitral insufficiency.

Due to suspected narcolepsy, polysomnography (PSG) with MSLT was conducted. At the time of the evaluation, she was not taking any medications other than multivitamins and an iron supplement. Results showed a normal PSG (total sleep time [TST]=438.5 minutes; sleep efficiency [SE]=90.1; REM latency=234.0 minutes) with no OSA (apnea hypopnea index [AHI] was 1.6). MSLT showed an average sleep latency of 2:08 minutes, with three SOREMs confirming the presence of narcolepsy. While her sleep during PSG was about 7 hours, that is not unusual given the routine

starting of the procedure at around 8pm, with about an hour for PSG setting and the arousal at 6am. Although neuroimaging and urine drug screen were not performed, both patient and her mother denied drug usage. Due to the lack of centers testing for cerebrospinal fluid (CSF) hypocretin, this investigation was not performed.

Initially, daily extended release amphetamine/dextroamphetamine 10mg was initiated; however, the patient continued to feel tired during the day and even more so at 15mg. Her prescription was switched to long-acting methylphenidate hydrochloride 27mg, but initially helpful, it stopped working after two months. Lisdexamfetamine 40mg was also tried but discontinued due to palpitations and chest pain. A retrial of the long-acting mixed amphetamine salts at a dose of 15mg yielded a good response.

#### *Case 2*

A 15 year-old Caucasian female was referred by her psychiatrist due to difficulty sleeping at night and ES. She struggled with depression after her father died in his sleep when she was seven. Although she would only see him on the weekends, they were close to each other. Around the anniversary of his death, she would often struggle more with her depression, having crying spells. Her appetite has been decreased and she lost 10 pounds over a six month duration, a year prior to her presentation. She was placed on sertraline 50mg daily by her psychiatrist and reported efficacy. Other stressors included losing her paternal grandparents and being bullied in school.

Her initial insomnia started when she was nine, after the death of her father. However, it later improved without treatment. It worsened again few months prior to her presentation, possibly precipitated by concussion associated with loss of consciousness while cheerleading. Her grades deteriorated to failing after being a B/C student. She reported going to bed around 10:30 or 11 pm, sleeping for about 2 hours at a time with at least 3-4 arousals per night. On weekdays, she would wake up at 5 am but on weekends would sometimes sleep until 3 pm if her mom did not disturb her. Due to her intermittent snoring at night, waking up gasping for air and trouble sleeping, PSG was conducted and showed an AHI of 11.3, with lowest oxygen at 85%. This

highlighted moderate to severe OSA and due to her large adenoids and tonsils, she had adenotonsillectomy. However, there was minimal change in her signs and symptoms. Over the course of treatment, medication trials included melatonin at 5mg, clonidine 0.1mg, doxepine at 20mg and even zolpidem 2.5mg nightly; all were unsuccessful. She complained of leg cramps and uncomfortable sensations mainly in her thighs. This was improved by rocking. In addition, there was family history of restless leg syndrome (RLS) in her paternal grandfather; thus, her ferritin level was tested and found to be at 22, and iron repletion was initiated. After normalization of the iron stores and due to continued RLS symptoms, ropinirole initially at 0.25mg was titrated slowly over a 2 month period to 2mg nightly which partially helped. Her initial PSG revealed mild to moderate periodic limb movements (PLMS) and a repeat sleep study after adjustment of medication resulted in a normal PLMS. Her blood work including complete blood work (CBC), basic metabolic panel (BMP) and thyroid stimulating hormone (TSH) were all within normal range. Due to her previous concussion history, magnetic resonance imaging of the head was performed and showed no abnormalities.

Due to her reported 14-16 hours of sleep, confirmed by fitbit data even in the two weeks prior to her PSG, narcolepsy was suspected. Symptoms consisted of weakness in her leg muscles and thighs when crying, followed by a feeling of needing to sit and later having to sleep (once every few weeks). Hypnagogic hallucination of seeing "black stuff" as if something went across the room occurring every few nights were also noted. However, no sleep paralysis was reported.

The patient's BMI was within normal range (height=1.65 m, weight=55.34 kg, BMI=20.3) and mental status exam revealed a well-kempt, cooperative young woman with depressed mood and slightly diminished alertness. In addition, examination revealed hyperextension of the fingers on both hands. She also had a history of joint pain, joint dislocation and frequent sprains and fractures as well overall discomfort with a need to stretch and "crack" various joints for relief. Other symptoms include orthostatic dizziness, mild scoliosis, and vomiting. She was referred to genetics where she was diagnosed with Ehlers Danlos

syndrome – hypermobile type. She had previously had a visual field and neurological exam done as part of a post-concussion evaluation, which noted no visual field defects or neurological abnormalities. Her second PSG was conducted after 4 months after surgery showing TST was 384 min, SE at 88%, AHI 1.6 and lowest oxygen was 96%. Although there was no snoring, frequent arousals were noticed. The third PSG with MSLT was conducted showing TST of 290.5 with REM latency of 57.5, SL of 2.9, and AHI was 3.1 with no oxygen desaturations. However, her arousal index was 24. Her MSLT showed moderate daytime hypersomnolence (average sleep latency of 6:45 minutes) with two SOREMs consistent with narcolepsy. Prior to the PSG, the patient was medicated with certerizine HCl, cholecalciferol, ferrous sulfate, hydroxyzine pamoate, mometasone furoate, Montelukast sodium, norethidrone ethinyl estradiol, omeprazole, ropinirole HCl, sertraline HCl, and zolpidem tartrate. However, to avoid the effects of her psychotropic medications on the sleep study, sertraline and zolpidem were discontinued two weeks prior to the study. It is not clear of why her third study showed a sleep duration of about 5 hours, compared to the previously conducted studies which were more than six.

Due to the confirmed narcolepsy, extended release mixed amphetamine salts at a dose of 10mg daily was initiated and showed significant improvement of symptoms. Although initially she had significant missed school days due to ES, after medication initiation, she did not miss any days and started to function better. The dose was later increased to 15mg because it was wearing off around noon. Her sleep pattern improved. She reported going to sleep at 10 pm after her cheerleading practice which occurred between 6-8:30 pm. She would go to sleep fast and would wake up at 6:20 am. Although she continued to nap daily (up to 2-3 hours), her daytime alertness improved, as did her grades.

## Discussion

The described cases illustrate a potential relationship between different sleep disorders including narcolepsy in patients with EDS. In a recently published retrospective review of 61 predominantly female children with EDS presenting to a tertiary care sleep clinic daytime fatigue occurred in 73.8%, ES was in 67.2%

and hypersomnia disorders in 21.3%<sup>7</sup>. It is important to exclude OSA since it is common in this population occurring at a rate of 39.4%, possibly highlighting the associated cartilaginous defects, laryngo-tracheomalacia, chest deformities, scoliosis, dilated aorta causing tracheal compression, and vocal cord abnormalities<sup>6</sup>. Similar to our second case, RLS/PLMS occurred in 18.0% of individuals, concurring with other conducted studies on narcoleptic individuals showing a higher prevalence of RLS/PLMS compared to non-narcoleptics. While subjective improvements of interrupted sleep improved with treatment of limb movements, it did not decrease the arousal index during PSG or daytime sleepiness.

A high rate of hypersomnia has been previously reported in EDS population, primary hypersomnia was found in 6.6%, and narcolepsy in 9.8%<sup>5</sup>. While this may be a prevalence over-estimation given the selection bias of EDS patients referred to a sleep center, our two cases concur with this possible relationship. It is important to note the commonality of fatigue and ES occurring at 73.8% and 67.2% respectively. While clinically, it is sometimes difficult to differentiate between primary hypersomnia versus narcolepsy, the high arousal index is commonly reported in narcoleptics but not in primary hypersomnia individuals. In addition, PSG with MSLT (showing short sleep duration and at least two SOREMs) and CSF hypocretin level are essential to confirm this differentiation. A common limitation, as highlighted by the second case, the PSG limited study duration given that most centers wake up patients at 6am. In the United States, CSF hypocretin testing is not available and we thus omitted it.

Research suggests these sleep disorders are seen more frequently in EDS than in the general population. Furthermore, the prevalence of narcolepsy in this population may be under-reported as symptoms of fatigue are common<sup>8</sup>. Additionally, cataplexy may be mistaken as POTS. However, it is important to note the high comorbidity of EDS and psychiatric disorders, with an overlap between hypersomnia as a symptom of depression versus narcolepsy as highlighted in the second case. Similarly, it is difficult to exclude the possible effect of head injury in case 2 as a possible cause for hypersomnia. Several cases of narcolepsy have been reported following head injury, possibly due to its effects on the hypothalamus. As in the second case,

depressed individuals have been associated with shorter REM latency and increased REM density. However, this is unlikely contributor in our presented cases. The use of actigraphy or sleep diary data prior to PSG would have been helpful. However, fitbit data was screened throughout treatment including the two weeks prior to the study. This method has not yet been clinically validated.

While PSG preceding MSLT in the second patient was short (about 5 hours), it is unlikely to be the reason for SOREMs occurrence in the third study as supported by recording from fitbit, previous PSG recording and her ES presentation during clinical examination. While a repeat study (PSG with MSLT) would have been more definitive, a decision to proceed with treatment was made due to her academic struggles the patient was facing as well as her request to seek rapid management.

An association between narcolepsy and EDS had not been explored in the literature to the same extent; however, the cases reported above as well as findings by Domany & colleagues suggest this may be a worthwhile focus for future research<sup>8</sup>. While symptoms of ES and dizziness (due to POTS vs. cataplexy) can be associated with EDS, the presence of the tetralogy symptoms including cataplexy, ES, sleep paralysis and hypnagogic hallucinations are more suggestive of a narcolepsy diagnosis.

### Conflict of Interest

None of the authors have any conflict of interest.

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