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Case report: early onset narcolepsy initially misdiagnosed as obstructive sleep apnea syndrome

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ABSTRACT

Background. Narcolepsy is a chronic neurological syndrome, which is characterized by excessive sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis during the rapid eye movement period of sleep. This disease is commonly diagnosed within adulthood. However, the first symptoms often appear in childhood and/or adolescence. Pediatric cases of narcolepsy generally remain unrecognized and undiagnosed. Clinical heterogeneity, prolonged onset and diverse symptoms contribute to the delay in diagnosis and treatment in childhood.

Case. This report describes a case of narcolepsy in an 8,5-year-old male patient who was misdiagnosed as obstructive sleep apnea syndrome and many other diagnoses at different hospitals over a period of 3 years before the correct diagnosis was made.

Conclusions. Narcolepsy in children is a rare neurological syndrome, which can occur with uncommon and atypical clinical presentations. In our case report we aimed to highlight pediatric narcolepsy, which could help to make more appropriate approaches and prevent misdiagnoses or diagnosis delay in these cases.

Key words: narcolepsy, polysomnography, multiple sleep latency test, misdiagnosis.

Narcolepsy is a rare chronic neurodegenerative disease caused by autoimmune destruction of hypocretin (orexin) producing neurons in the lateral hypothalamus. It's characterized by chronic excessive daytime sleepiness and cataplexy; which is loss of muscle tone that is typically triggered by strong emotional stimuli. Hypnagogic or hypnopompic hallucinations, behavioral changes, sleep paralysis, vivid dreams and frequent nocturnal awakening, weight gain, and cognitive impairment are less commonly associated symptoms.[1] Usually, patients experience some, but not all of these symptoms; only 10% of individuals with narcolepsy have the four cardinal symptoms of narcolepsy all together (paroxysmal sleep, cataplexy, hypnagogic hallucination, and sleep paralysis).[1]

Even the exact etiology of narcolepsy is still unclear, multiple genetic and environmental factors may underlie the mechanism of hypocretin neuron loss, through autoimmune processes. After the adjuvanted pandemic influenza A (H1N1) in 2009, there was a significant increase in narcolepsy prevalence within both infected and vaccinated populations.[2] Many studies showed evidence of autoimmune and molecular mechanisms associated with flu antigens, modulated by genetic factors, which can trigger narcolepsy.[3]

The clinical heterogeneity and relative rarity of narcolepsy in childhood often leads to a misdiagnosis of narcolepsy as depression, epilepsy, and other disorders. Misdiagnosis of children with narcolepsy can interfere with their normal growth and puts them at increased risk of life-threatening accidents.

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We will present a case report of early onset pediatric narcolepsy, with a history of multiple previous misdiagnoses over a period of 3 years till the proper diagnosis and treatment were made in Ağrı State Hospital's child psychiatry and pediatric neurology clinics.

Case Report

Our patient was an 8,5-year old male, who was brought to our outpatient clinic by his parents due to excessive daytime sleepiness with no gross nocturnal symptoms.

According to his family; the patient's complaints had started at the age of 5 and they first sought medical advice after 6 months of the symptom's onset. Initially, they reported low energy levels, desire to sleep, and loss of interest in daily activities. Sudden and recurrent episodes of sleep started over time, gradually increasing to 2-3 times per day, with about 30 minutes as duration for every episode. Once his family tried to wake him up during these sleep attacks, the patient became irritable and agitated.

According to his medical history, a wide range of tests and examinations were conducted at three different hospitals over a period of 3 years, and many diagnoses were considered, like iron deficiency anemia and depression.

Finally, through only Polysomnography (apnea-hypopnea index was found as 13.9), he was diagnosed with severe obstructive sleep apnea syndrome due to adenoid hypertrophy and referred to an ear, nose, throat (ENT) clinic, where tonsillectomy and adenoidectomy were performed in 2017. According to his parents, after the operation his symptoms gradually worsened and sleep attacks increased. Over the course of time, he became more irritable, forgetful, less active, and started to gain weight despite having a normal diet.

His father reported similar symptoms during his childhood, which spontaneously stopped at the age of 14 without receiving any medical advice. Laboratory method insufficiency prevented the autoimmune workup evaluation for the father. The patient was 142cm tall (>90th percentile) and weighed 38 kg (>90th percentile). On mental status examination, he was irritable and had difficulty concentrating but was fully conscious and orientated. His behavior was appropriate and well-coordinated with normal intelligence and insight appropriate for his age. During the examination, he had slurred speech and on occasion his eyes closed with no response to loud noises.

Blood tests (including CBC, blood chemistry, iron, ferritin, vitamin D and B12), chest radiograph, and electrocardiogram were normal. Cranial CT/MRI performed to rule out intracranial pathologies (like encephalitis and multiple sclerosis) were also normal. No epileptiform discharges were found in the electroencephalogram (EEG).

The overnight polysomnography (PSG) showed an increased number of awakenings, with a total of 7 minutes of wakefulness after sleep onset. The latency to sleep onset was 5.1 minutes, and rapid eye movement (REM) sleep latency was 4.5 minutes, without sleep apnea or periodic limb movements (Table I). After getting enough sleep (≥6h), the daytime Multiple Sleep Latency Test (MSLT) revealed severe daytime sleepiness with sleep onset REM periods (SOREM) in all 5 naps on the MSLT (Table II).

Autoimmune work up including human leukocyte antigen (HLA) typing was not done to confirm the diagnosis (the proper method was

Table I. Sleep study results.

Total sleep time	451 min
Wake after sleep onset	7 min
Sleep onset	5.1 min
Sleep efficiency	97.4%
Number of awakenings	10 min
NREM 1	5.1 min
NREM 2	7.1 min
NREM 3	25.6 min
REM Latency	4.5 min
Apnea-hypopnea index	0.4

Table II. Mean sleep latency test (MSLT) results.
MSLT/Nap Sleep Data

Start time	Stop time	Sleep latency (min)	REM latency (min)	Total sleep time (min)
08:01	08:17	0.5	1.5	16
10:00	10:17	1.0	0.5	15.5
12:08	12:26	0.0	2.0	17.5
14:01	14:18	0.0	5.5	17.5
15:48	16:09	2.5	5.5	19
	Average:	0.8	3	17.1

not available in our facility's laboratory), but the diagnosis of narcolepsy without cataplexy (type 2) was obvious based on medical history, PSG, and MSLT results.

With written consent of his parents the patient was started on modafinil 50 mg/day (stimulant agent), his symptoms resolved, and his diurnal sleep was significantly reduced. No significant difficulties in his daily life or school attendance remained.

Discussion

Narcolepsy is a lifelong disorder that most commonly begins in the first or second decade of life. About one-third of patients become symptomatic at the age of 15 years, and up to 5% of cases begin before the age of five years.[2] Our patient's symptoms started at the age of 5 years.

In a retrospective study, the time between symptoms onset and diagnosis in patients with narcolepsy was found to be about 10 years on average.[4] In our case this duration was about 3 years.

The prevalence of narcolepsy in the general population varies between 20 to 50 cases per 100,000 across different studies with a bimodal peak for age at onset (15 years and 35 years) with no detectable male-female differences.[2] A study estimated the incidence rate in children aged 5-19 years as 0.83/100,000 person-years in Europe.[5] In an American study the overall incidence of narcolepsy was found as 0.74 in 100,000. The incidence rates were found variable among different age groups, with highest incidence rate in the second decade (3.84 per 100,000), followed by the 3rd and 4th decades, and the lowest incidence rate was found in the 1st decade of age.[6]

Narcolepsy is classified as type 1 (narcolepsy with cataplexy) or type 2 (narcolepsy without cataplexy). Reduction in the numbers of hypocretin-producing neurons, and low levels of hypocretin-A in the cerebrospinal fluid (CSF) was founded in about 90% of cases of type 1.[7] The cause of narcolepsy type 2 is unknown, although only 20-30% of these patients have low CSF orexin-A levels.[7] This disorder may result from less extensive loss of the orexin neurons, about half of these individuals may later develop cataplexy, suggesting progression of the disease.[8]

Hypocretin is an excitatory neuropeptide transmitter, which plays a role in promoting wakefulness, energy consumption and food intake, by modulating serotonin, histamine, and other neurotransmitters.[2] The loss of hypocretin producing neurons occurs in narcolepsy is secondary and specific to patients with HLA-DQB1*0602 allele, which may act as an antigen presenter to the T cell receptors. Most narcolepsy type-1 patients (76-98%) and 40-60% of patients with narcolepsy type-2 are positive for HLA DQB1*0602 allele.[2]

Compared to normal the population, the risk of narcolepsy in patient's first-degree relatives is increased by 10-40 folds (1-2%) which suggests a genetic predisposition to narcolepsy.[9] Even though our patient's father reported similar

symptoms during his childhood, his diagnoses was not clear.

The exact underlying mechanism of hypocretin neurons loss is unknown, but recent studies suggest that autoimmune-mediated mechanisms may cause this loss, with major roles of both environmental and genetic factors.[3] Multiple environmental factors are considered as possible triggers for narcolepsy, including upper respiratory tract infections, influenza, neurotoxic metals, major psychological stress, hormonal changes during puberty and smoking.[10-12]

Auto-antibodies against Tribbles Homolog 2 (TRIB2) were appointed in narcolepsy patients, supporting the autoimmune hypothesis.[13] Also, elevated anti-streptolysin O (ASO) antibodies and anti-DNAase B (ADB) antibodies in patients with narcolepsy were found, suggesting an autoimmune process triggered by streptococcal infection.[14]

This underlying mechanism, can be triggered by other infections too, such as in H1N1. Many recent studies have reported increased cases of narcolepsy in Europe and Asia after the H1N1 pandemic, especially in children and adolescents. This increment seems to be related to influenza infection itself in China, and Pandemrix vaccination in Europe.[5,10,15] A cross immune reaction occurs after flu infection, involving antigens of multiple hypocretin-producing neuron epitopes, and possibly CD8+ T cell cytotoxic killing of hypocretin-producing neurons.[3]

According to the American Academy of Sleep Medicine (2005)[16], symptoms of narcolepsy with cataplexy include: (a) recurrent daytime naps that occur almost daily for at least three months, and (b) sudden loss of postural muscle tone in association with intense emotion (cataplexy). Administering the Multiple Sleep Latency Test (MSLT) after overnight polysomnography (PSG) can assist in the diagnosis of narcolepsy. The presence of one or both of the following confirms the diagnosis: (a) a mean sleep latency of <8 minutes and two or more sleep onset REM periods (SOREMPs) based on MSLT performed after at least six hours of sleep during the previous night. (b) CSF Hypocretin-1 concentration <110 pg/ml.

In our case, MSLT revealed severe daytime sleepiness with SOREM in all 5 naps and mean sleep latency of 0.8 minutes, which confirm the diagnoses of narcolepsy without cataplexy.

The cardinal symptoms of narcolepsy include paroxysmal sleep (100%), cataplexy (70%), hypnagogic hallucination (25%), and sleep paralysis (5%), as in our case usually, patients experience some, but not all, of these four symptoms.[17] About two-thirds of patients experience transient paroxysmal sleep only, and one-third of patients have one of the other three symptoms in addition to paroxysmal sleep.[17]

Obesity and precocious puberty are common in children with narcolepsy, in addition within a few years of diagnosis, approximately two-thirds of these children become overweight or obese, which can cause severe and irreversible secondary health problems in these cases.[18]

At the initial examination our patient's height and weight were found to be over the 90th percentile, which became within normal ranges (50-75 percentile) after 7 months of modafinil treatment. Also, narcolepsy could be secondary to systemic disease or neurological insults targeted at the hypothalamus, such as multiple sclerosis, brain injury, neurocysticercosis, encephalomyelitis, tumors, and cerebrovascular accidents. Carbon monoxide poisoning and congenital disorders like Prader-Willi, myotonic dystrophy, and Neimann-Picks have also been associated with narcolepsy.[19] Secondary narcolepsy was ruled out in our case by running blood tests, EEG and imaging studies.

Due to the prolonged onset and atypical symptoms in children, the diagnosis of narcolepsy could be more difficult and could result in delayed diagnosis and treatment. Associated with immunological mechanisms, there is a potential increased risk of narcolepsy

during or after the Covid-19 pandemic, such as that which occurred in the H1N1 pandemic. This case highlights the wide presentational variety of uncommon psychiatric and neurological conditions of pediatric narcolepsy. After excluding secondary narcolepsy; to rule out the possibility of narcolepsy and to decrease complications and similar misdiagnosis; we recommend conducting sleep monitoring, polysomnography, and multiple sleep latency tests in all cases with excessive sleep of unknown etiology in children. Accurate diagnosis and treatment depend on taking detailed medical histories and being aware of the atypical presentations of uncommon psychiatric/ neurological conditions, particularly in children.

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