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"Oh My Sleeping Child" … Narcolepsy Type 1 in a 22-Month-Old Boy

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Abstract

Pediatric narcolepsy is a complex disorder with unique diagnostic challenges. It is diagnosed with a combination of clinical presentation, polysomnogram with multiple sleep latency test (PSG with MSLT), and occasionally, hypocretin-1 (orexin) levels in the cerebrospinal fluid (CSF). This report describes a 22-month-old boy experiencing excessive daytime sleepiness (EDS) and frequent falls. The patient was subsequently diagnosed with narcolepsy using hypocretin-1 (orexin) levels. The intent of this report is to establish the utility of using hypocretin-1 (orexin) levels to diagnose narcolepsy type 1 in children who are too young to undergo PSG with MSLT. To our knowledge, there are no reports of narcolepsy in a patient this young. Early recognition and treatment of narcolepsy in children younger than age five may lead to a substantial impact on their cognitive development and minimize potential long- term complications.

Keywords

excessive daytime sleepiness, hypocretin-1(orexin), pediatric narcolepsy, toddler

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Introduction

Narcolepsy is an extremely rare disorder in children. Narcolepsy usually presents with a tetrad of EDS, sleep paralysis, hypnagogic or hypnopompic hallucinations, and cataplexy.[1] Two types are recognized: 1) Narcolepsy type 1 - with cataplexy, caused by loss of hypocretin-1 (orexin); 2) Narcolepsy type 2 - without cataplexy with normal hypocretin- 1 (orexin).[2] Narcolepsy is seldom suspected in the pediatric population. Diagnosing narcolepsy in young children is further challenging, as clinically they have atypical presentations, and conventional approaches for diagnosis are often difficult to perform and interpret.[3]

In young children, the tetrad is often incomplete. The presenting symptoms of EDS can be vague and manifest as fatigue, low energy, difficulty concentrating, irritability and even hyperactivity and aggression.[4] PSG with MSLT, the standard diagnostic tool in adults, is hard to interpret and practically difficult to perform in young children, and alternative methods are needed.[5] While the incidence of narcolepsy in pre-pubertal children is not highly studied, one study found an incidence rate of 0.40 in children ages 0-9.[6] In another retrospective study of 51 children with narcolepsy, over half - the majority being African American children - showed disease onset prior to puberty.[5] We present a case of narcolepsy in a 22-month-old boy diagnosed via low levels of CSF hypocretin-1 (orexin) who was treated with dextroamphetamine with an excellent response. To the best of our knowledge, there are less than fifteen reported cases of narcolepsy type 1 with onset before age five and only three with diagnosis via CSF hypocretin-1 (orexin) levels.[7]

Case Presentation

A 22-month-old previously healthy and neurodevelopmentally normal African American male presented with a two-week history of progressively worsening fatigue and EDS. The

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patient did not have any recent infectious symptoms, sleep deprivation or vaccinations prior to presentation and did not show signs of early puberty. He would fall asleep when walking or eating several times daily. This led to frequent falls and the appearance of an unsteady gait.

On physical exam, vital signs were stable, and he was intermittently alert but with closed eyes. He was noted to be eating and appeared to be falling asleep. Gait was narrow based, but intermittently he would stumble/sway and exhibited unsteadiness; although, there was no concern for the presence of an overt movement disorder or classic signs of cataplexy. His general physical exam and the remainder of the neurologic exam was otherwise age appropriate.

His initial workup was normal including toxic, metabolic, infectious, and thyroid laboratory studies. Magnetic Resonance Imaging of the brain with contrast was normal and long-term electroencephalogram did not capture an awake background; sleep was recorded for the entire duration of the study.

He was discharged from the hospital without a unifying diagnosis, but narcolepsy was suspected as a cause of his presentation for which he was evaluated by sleep medicine. A PSG was obtained which showed moderate obstructive sleep apnea (OSA). However, his degree of OSA did not explain his EDS. PSG with MSLT was not obtained given his age. Lumbar puncture was completed to obtain CSF hypocretin-1 (orexin) levels which were <50 pg/ml, consistent with narcolepsy type 1 thus providing an explanation for his EDS. HLADQB1*06:02 was positive, further supporting the diagnosis of narcolepsy. Whole exome sequencing reveled a heterozygous C > T change of maternal origin, on nucleotide 1287 on the DNMT1 gene (NM_001130823.3):c.1287C > T, p.Tyr429=, not suspected to alter the tyrosine residue at this amino acid position but unknown if the change could affect splicing.

EDS was causing a hindrance to the patient's speech development, and he was having multiple falls, so the decision to treat was made despite lack of age-approved treatment guidelines. He was started on the lowest dose of dextroamphetamine (2.5 mg), and quickly showed significant improvement.

Since starting dextroamphetamine, his overall quality of life significantly improved. He was no longer demonstrating EDS, with increased alertness and interactivity. He is now seen every 3-6 months and tolerates the dextroamphetamine without significant adverse side-effects and is making developmental gains. He continues in speech therapy for a mild speech delay but is otherwise neurodevelopmentally age-appropriate.

Discussion

Narcolepsy in a toddler is rare and hence a challenge to diagnose and treat but is important to recognize as early intervention is essential for proper neurodevelopment. Narcolepsy is often mistaken for other behavioral disturbances in young children and hence is likely underdiagnosed.[3]

Diagnostic criteria for narcolepsy type 1 are the same for children and adults, according to International Classification of Sleep Disorders by the American Academy of Sleep Medicine. The patient must present with periods of irrepressible sleep with a mean latency of 8 min on PSG with MSLT, with evidence of sleep-onset rapid eye movement periods and clear cataplexy and/or CSF hypocretin-1 (orexin) deficiency (110 pg/mL or less than one-third of the normative values).[8] As PSG with MSLT is practically difficult in toddlers because of their immature sleep-wake cycle in comparison to adults, PSG with MSLT should not be used as the only diagnostic tool. There are no standard values for MSLT in the very young child, thus this was not used.[9] In a study of narcolepsy in 51 prepubertal children, in the five children that were under age 5, a PSG with MSLT was not obtained.[10]

Loss of hypocretin is understood as being the main driver behind narcolepsy with cataplexy.[11] Given the difficulties of PSG with MSLT in the young child, obtaining CSF hypocretin-1 (orexin) should be strongly considered if there is a high clinical suspicion. In our literature review of the few cases under age 5, CSF hypocretin-1 (orexin) was not consistently examined, and although this is more invasive, it should be obtained when narcolepsy is on the differential diagnosis. In one study of 16 Japanese patients with narcolepsy and 12 with idiopathic hypersomnolence, three of the patients were prepubescent (6-10 years old) and had narcolepsy type 1 clinically and confirmed with PSG with MSLT.[12] Hypocretin-1 (orexin) levels were measured, and all had low to undetectable levels. Hypocretin deficiency was thought to be an early finding in the disease as they were measured soon after disease onset.[12] Evidence also suggests a strong association between narcolepsy and HLA DQB1*0602 as was found in the above study. However, the role of genetics is not fully understood and not currently mandatory for diagnosis.[11] Although pathogenic alterations in the DMNT1 gene have been reported in adults with narcolepsy, the exact variant found in our patient has not been identified to be causative and therefore was reported as a variant of uncertain significance. However, our patient's clinical picture matches the profile of other DNMT1-related narcolepsy cases and therefore this variant may indeed be pathogenic in our patient.

We present this case for multiple reasons, most importantly, to bring awareness to the presence of this rare condition at such a young age, to avoid misdiagnosis. Various neuropsychiatric symptoms (mood disturbances, irritability) and co-morbidities (such as attention deficit/hyperactivity disorder, oppositional defiant disorder) as well other developmental delays and a transient movement disorder (with 'active' and 'negative' motor symptoms such as swaying and falls respectively, as was seen in our patient) can occur in a child with narcolepsy.[7,13] Therefore, it only seems logical that the earlier narcolepsy is identified and treated, the better the neuropsychiatric and neurodevelopmental outcomes will be.[7]

European guidelines and expert statements on the management of narcolepsy in adults and children suggest scheduled naps as well as first line monotherapy with sodium oxybate (strong recommendation) or modafinil, methylphenidate, amphetamine derivatives (weak recommendation) or pitolisant (very limited data).[14] In the United States, stimulant medications are not approved under age 3. Despite its off-label use,

it is important to consider treatment with low dose stimulants even in toddlers, as this case demonstrated safe and effective use of dextroamphetamine in a child younger than age 2.

In conclusion, an accurate diagnosis of narcolepsy in a toddler is easily accomplished by testing hypocretin-1 (orexin) levels in the CSF which will then allow timely intervention and may thus minimize neurocognitive delays in the long term.

Authors Contribution

B Giourgas: contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy. A Morgan: contributed to acquisition, analysis, and interpretation, drafted the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy. S Bhatia: contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, critically revised the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Informed Consent

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References

1. Park EG, Lee J, Joo EY, Lee M, Lee J. Narcolepsy in a three-year-old girl: A case report. *Brain & Development (Tokyo 1979)*. 2016;38(1):139-141. doi:10.1016/j.braindev.2015.06.003
2. Dye T, Gurbani N, Simakajornboon N. Epidemiology and pathophysiology of childhood narcolepsy. *Paediatr Respir Rev*. 2018;25:14-18. doi:10.1016/j.prrv.2016.12.005
3. Kwon S, Jang K, Hwang S, Cho M, Seo H. Narcolepsy with obstructive sleep apnea in a 4-year-old Korean girl: A case report. *J Korean Med Sci*. 2013;28(5):792-794. doi:10.3346/jkms.2013.28.5.792
4. Chung IH, Chin WC, Huang YS, Wang CH. Pediatric narcolepsy—A practical review. *Children (Basel)*. 2022;9(7):974. doi:10.3390/children9070974
5. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: A retrospective study of 51 children. *Sleep*. 2010;33(11):1457-1464. doi:10.1093/sleep/33.11.1457
6. Silber MH, Krahn LE, Olsone EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted county, Minnesota: A population-based study. *Sleep (New York, NY)*. 2002;25(2):197-202. doi:10.1093/sleep/25.2.197
7. Veneruso M, Pizza F, Finotti E, et al. Child neurology: A case series of heterogeneous neuropsychiatric symptoms and outcome in very early-onset narcolepsy type 1. *Neurology*. 2022;98(23):984-989. doi:10.1212/WNL.0000000000200666
8. Sateia MJ. International classification of sleep disorders-third edition: Highlights and modifications. *Chest*. 2014;146(5):1387-1394. doi:10.1378/chest.14-0970
9. Winter E, Prendergast M, Green A. Narcolepsy in a 2-year-old boy. *Dev Med Child Neurol*. 1996;38(4):356-359. doi:10.1111/j.1469-8749.1996.tb12101.x
10. Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. *Ann Neurol*. 1998;43(1):135-142. doi:10.1002/ana.410430125
11. Miskoff JA, Chaudhri M. A case of off-label sodium oxybate in an 11-year-old with narcolepsy. *Curēus (Palo Alto, CA)*. 2019;11(2):e4057. doi:10.7759/cureus.4057
12. Kanbayahi T, Inque Y, Chiba S, et al. CSF Hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. *J Sleep Res*. 2002;11(1):91-93. doi:10.1046/j.1365-2869.2002.00284.x
13. Plazzi G, Pizza F, Palaia V, et al. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. *Brain*. 2011;134(Pt 12):3477-3489. doi:10.1093/brain/awr244
14. Bassetti CLA, Kallweit U, Vignatelli L, et al. European guideline and expert statements on the management of narcolepsy in adults and children. *J Sleep Res*. 2021;30(6):e13387. doi:10.1111/jsr.13387