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Late-onset diagnosis of SHINE syndrome in an adolescent with developmental delay: Case report

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Abstract

Sleep disturbances, hypotonia, intellectual disability, neurological disorders, and epilepsy (SHINE) syndrome is a rare autosomal dominant neurodevelopmental disorder. A mutation in the DLG-4 *gene* on chromosome 17 causes SHINE syndrome. SHINE are characteristic feature of the disease. This case recounts a 16-year-old female patient who presented with a longstanding history of developmental delay and intellectual disability since the age of two. At various points throughout her childhood, she was diagnosed with pervasive developmental disorder, autism spectrum disorder, attention-deficit hyperactivity disorder, and severe intellectual delay, undergoing extensive testing and imaging. Fourteen years after the initial presentation, additional genetic testing revealed a de-novo mutation in the DLG4 *gene*, confirming a diagnosis of SHINE syndrome. Due to its characteristic features, SHINE syndrome should be considered part of the differential diagnosis in children with unexplained developmental delays.

Keywords

SHINE syndrome, discs large MAGUK scaffold protein 4 (DLG-4) synaptopathy, postsynaptic density protein 95 (PSD-95)

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Educational objectives

- SHINE syndrome is a rare genetic condition caused by a mutation in the DLG-4 *gene*.
- Consider SHINE syndrome as a diagnosis in a patient with longstanding developmental delay.
- Sleep disturbances, hypotonia, intellectual disability, neurological disorders, and epilepsy are common characteristics of SHINE syndrome.
- Diagnosis of SHINE syndrome is made through genetic testing.
- There is no cure for SHINE syndrome. However, timely diagnosis can allow families and patients to receive specialized therapy and interventions earlier in life.

Introduction

Sleep disturbances, hypotonia, intellectual disability, neurological disorders, and epilepsy (SHINE) syndrome, also known as Disc large MAGUK scaffold protein 4 (DLG-4) related synaptopathy, is a rare autosomal dominant neurodevelopmental disorder caused by a mutation in the DLG-4 *gene* located on chromosome 17. The DLG-4 *gene* codes for postsynaptic density protein 95 (PSD-95). PSD-95 is a protein vital for synaptic transmission between neurons.[1,2,4] Synaptic transmission of signals is how neurons communicate with one another and, ultimately, how the brain communicates with the rest of the body.[4] Furthermore, The DLG-4 *gene* plays an important role in synaptic plasticity. Synaptic plasticity is the ability of synapses to change over time and plays an important role in childhood development and learning. The inability of neurons to communicate with one another and impaired synaptic plasticity contribute to developmental delay and intellectual disability in children.[4,12]

The exact prevalence of SHINE syndrome is not known; however, there are 53 confirmed cases of SHINE syndrome

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worldwide.[1,2,7] Characteristic features include SHINE. There is a strong association with autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD).[1,2] Identifying the etiology of intellectual disability and developmental delay is often complex and poses a challenge for pediatricians. The differential diagnoses for intellectual and developmental delay are broad. Genetic and chromosomal disorders, inborn errors of metabolism, congenital brain abnormalities, congenital infections, and environmental factors can cause intellectual and developmental delay.[5,13] As a result, caregivers of children with intellectual disabilities and developmental delays spend years searching for a cause. We present a case of an adolescent female with a history of developmental delay since the age of two that was recently diagnosed with SHINE syndrome.

Case presentation

Our case presentation is about a 16-year-old female who initially presented to the clinic for her annual well-child visit. Her mother expressed concern about longstanding developmental delay and intellectual disability since the age of two. Her mother reports that she can speak 30–40 words but cannot read and write and has difficulty retaining information. She is unable to combine words or speak in complete sentences. She can point and identify body parts. She can use utensils and feed herself. She can dress herself but has difficulty with buttons and tying her shoes. She walks and runs without any difficulty. Her mother reports that she is in special education classes focusing on developing life skills. She makes appropriate eye contact with the teacher at school but prefers to play alone. She has difficulty maintaining attention, even for short periods.

Mother reports that her pregnancy was uncomplicated, and the patient was born at term. There was no neonatal intensive care unit stay, and she did not require ventilatory support. She was briefly readmitted for phototherapy secondary to jaundice and discharged after the jaundice resolved. Her past medical history is significant for a small ventral septal defect diagnosed after birth, strabismus diagnosed at 3 years of age, and hypothyroidism at 10. Her strabismus was surgically corrected, and her hypothyroidism is well-controlled on Levothyroxine.

Her mother became concerned about the patient's development starting at three. Her primary concern was speech delay. At age three, she spoke only 2–3 words and would respond sporadically to her name. She had difficulty with sleep, specifically with sleep initiation. There is no reported history of loud snoring or apneic episodes. Her mother expressed concerns about the patient's ability to understand and follow commands. Although the patient made good eye contact, she preferred to play alone and engaged in repetitive spinning. There was no history of developmental regression.

Our patient was nonverbal during the visit. Physical examination shows that she is well-nourished and cooperative with her mother's help. No dysmorphic features were present. A cardiac exam revealed no murmurs, and she had a regular rate and rhythm. Lungs were clear to auscultation bilaterally. Neurological examination revealed significant hypotonia in the upper and lower extremities. Her sensation was intact, and her gait was stable. The musculoskeletal examination was significant for 5/5 muscle strength in all extremities, and no scoliosis was appreciated.

She had visits with multiple pediatricians and subspecialists throughout her childhood. She had an extensive workup performed for her developmental delay. Chromosomal microarray, sequencing for Rett Syndrome, Fragile X testing, plasma amino acids, urine organic acids, lactic acid, and ammonia levels were unremarkable. At the age of four, brain magnetic resonance imaging (MRI) showed mild plagiocephaly but was otherwise unremarkable. Multiple audiology screenings revealed no hearing loss. She did receive speech therapy and occupational therapy for several years of her life with minimal improvement. At various points throughout her childhood, she was diagnosed with pervasive developmental disorder based on previous DSM IV criteria, ASD, ADHD, and severe intellectual delay. Re-evaluation by neurology prompted additional genetic testing. Clinical exome gene sequencing revealed a de-novo mutation in the DLG4 *gene*. Genetic testing confirmed a diagnosis of SHINE syndrome 14 years after the initial presentation. Both parents underwent genetic testing and no mutations in the DLG-4 *gene* were found.

Our patient continues to follow up at our primary clinical for well-child supervision visits and sick visits. The diagnosis of SHINE syndrome has been shared with the school. She receives special education classes, speech therapy, and occupational therapy through her school. She continues to follow up with her endocrinologist for hypothyroidism. At her last neurology visit, she was referred to a specialized neurodevelopmental clinic at a tertiary academic center, and her appointment is pending.

Discussion

Identifying causes of developmental and intellectual delay is challenging and complex, and an underlying cause for developmental delay can take several years. A mutation in the DLG4 *gene* on chromosome 17 causes SHINE syndrome. The DLG4 *gene* codes for the PSD-95 protein and the PSD-95 protein plays a vital role in synaptic transmission between neurons.[4] Appropriate synaptic transmission between neurons plays a vital role in many different neurological processes, including the formation of focus, memory, and learning.[5] Difficulty with synaptic transmission between neurons helps explain our patients' cognitive difficulties.

SHINE syndrome has a variable clinical presentation. However, all patients have moderate to severe developmental

Table 1. Key characteristics and documented manifestations of SHINE syndrome.

Characteristics	Potential manifestations	Patient features
Sleep disturbances	Sleep onset and maintenance difficulties	Sleep onset difficulties
Hypotonia (movement disorders)	Joint laxity, dystonia, tremor, stereotypies, ataxia	Hypotonia
Intellectual disability	ADHD, ASD, developmental delay, motor or language regression	ADHD, developmental delay, and intellectual disability
Neurological disorders	Psychosis, migraine headaches, dystonia, tremor, strabismus, hyperopia, cortical blindness, atrophy or dysmorphia of the cerebellum, corpus callosum or hippocampus	Strabismus requiring surgery
Epilepsy	Generalized or focal seizures, epileptic encephalopathy	No known seizures to date

ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder.

delay or intellectual disability. Other common clinical findings are sleep difficulties, joint laxity, ocular abnormalities, gastrointestinal disturbances, hypotonia, epilepsy, movement disorders, and neuropsychiatric conditions.[1,2,4] Common neuropsychiatric conditions associated with SHINE syndrome include ADHD and ASD; our patient was previously diagnosed with both conditions. Although our patient did not have developmental regression, approximately 40% will have developmental regression of previously acquired milestones.[2] Regressions in motor and language development are the most common regressions seen in SHINE syndrome.[1] The appears to be an association between epilepsy and developmental regression in patients with SHINE syndrome. Our patient has sleep difficulties mainly related to sleep onset. Our patient has had a previous surgery for bilateral strabismus. As a child, our patient did engage in repetitive stereotypical behavior. Approximately, 53% of patients with SHINE syndrome have seizures, and there is no specific predilection to certain types of seizures.[1] Interestingly, our patient has not had any known seizures. An electroencephalogram (EEG) was ordered by her neurologist, but due to financial considerations secondary to the patient's insurance status, the EEG has been deferred.

Her most recent physical examination is significant for both hypotonia and joint laxity. She did not have any additional Marfanoid features. However, there has been an association with Marfanoid features in other cases. Seven Our patient has a history of hypothyroidism. She did have elevated thyroid peroxidase antibodies and was diagnosed with Hashimoto thyroiditis. It is unknown if her hypothyroidism is isolated or related to SHINE syndrome. There are no other known thyroid abnormalities in patients with SHINE syndrome. Our patient had a normal MRI scan that was performed at age five and was unremarkable. However, brain and cerebellar atrophy, thinning of the corpus callosum, and a dysmorphic hippocampus are features noted in other patients with SHINE syndrome.[3] Table 1 below shows common presenting features of SHINE syndrome and the features that our patient has.

While there is no cure for patients with SHINE syndrome, establishing an early and timely diagnosis is beneficial for both the patient and their family. Early diagnosis allows patient access to much-needed services, including speech, occupational, and physical therapy. Establishing an early diagnosis can also help avoid unnecessary recurrent labs and imaging. Timely diagnosis can also allow for appropriate genetic counseling, especially if the family plans to have additional children. Diagnosis of SHINE syndrome is made through genetic testing. An intellectual disability multigene panel that includes the DLG4 *gene* will diagnose SHINE syndrome.[1,2]

A multidisciplinary approach is needed to treat patients with SHINE syndrome. Assessment of developmental milestones should be performed at well-child check or other visits if there are concerns. A developmental evaluation includes an evaluation of gross motor, fine motor, speech, problem-solving, social and emotional milestones.[6] The clinician should note any signs of developmental regression. Refer children under 3 years to early childhood intervention with a history of developmental delay, and children with speech delay should receive an audiology evaluation.[6,10] Screen SHINE syndrome patients for both ASD and ADHD using a validated screening tool. Those who are diagnosed with ASD should receive applied behavioral analysis therapy. Consider behavioral modifications and stimulant medications in patients diagnosed with ADHD. Each patient should have an individualized learning plan to be reviewed annually with the parent.

Screen patients for seizures at each visit, and any concerning events warrant a 24-h EEG and consultation with a neurologist. Consider brain MRI for any abnormal findings on a neurological exam.[3] Often, a brain MRI is ordered before diagnosis. The pediatrician should assess sleeping patterns and behavior at each visit. It is essential to ask about sleep habits, insomnia, daytime sleepiness, and nighttime interventions. Pediatricians should counsel families on appropriate sleep hygiene and habits. Melatonin can be considered if behavioral modifications alone are not effective. Consider a referral for a sleep study if there are concerns for sleep apnea or narcolepsy. It is essential to discuss a sleep safety plan with parents.[11] Vision screening should be performed at wellness visits, and any concerns for strabismus or other eye abnormalities warrant evaluation by a pediatric ophthalmologist.[2]

Screening for scoliosis should be performed every 6 months, and the medical provider should assess joint laxity

and gait instability. Physical therapy can help improve motor function, and a referral to orthopedic surgery is recommended for severe scoliosis.[8] Finally, the care team should initiate a detailed transition plan from the pediatric medical home to an adult medical home. Transition planning discussions can start in early adolescence and last until the formal transfer of care, which usually occurs between 18 and 21. A multidisciplinary approach is recommended that involves the patient, parent, both the pediatric and adult medical provider, nurses, and case workers.[9]

Conclusion

This case highlights the challenge of finding an underlying cause of developmental delay in the pediatric population and illustrates the role that genetic testing can play in identifying an underlying cause. Consider SHINE syndrome as part of the differential diagnosis in any child with an unexplained developmental delay that is associated with sleep difficulty, hypotonia, intellectual disability, neurological disorders, and epilepsy. Our patient showed signs of developmental delay at the age of two and was diagnosed with SHINE syndrome at the age of 16.

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Author contributions

M. Z. contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agreed to be accountable for all aspects of work ensuring integrity and accuracy. I. C. contributed to design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agreed to be accountable for all aspects of work ensuring integrity and accuracy. S.C. contributed to design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethical approval

The University of Houston Tilman J. Fertitta Family College of Medicine does not require ethical or IRB approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient's legal guardian for their anonymized information to be published in this article.

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