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Case Report

Neurodevelopmental disorder associated with NARS1 gene mutation in a child with cerebral palsy

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ABSTRACT

Cerebral palsy is the most common cause of chronic motor disability in children. CP has a multitude of causes, including developmental, genetic, metabolic, ischemic, infectious, and acquired, all of which result in comparable neurologic symptoms. As of right now, the cause of CP remains unclear. Research has found a substantial link between low birth weight, birth hypoxia, and poor fetal position and placenta. When diagnosing children with cerebral palsy and determining its cause, brain imaging is crucial. The final diagnosis should consider many factors, including physiological, topographic, ICF/functional, and neuroradiological categorization, origin, time of injury, concomitant disorders, sequelae, and nutritional status. This assists with planning, management, counseling, progress tracking, and prognosis. We present a case of a 5-year-old child with cerebral palsy who has a complicated clinical presentation including delayed psychomotor development, dysmorphia, and a verified pathogenic variation in the NARS1 gene linked to a neurodevelopmental condition. The child has been receiving frequent monitoring and multimodal therapies, such as physical therapy, defectologist sessions, and omega fatty acid supplements. Genetic testing found a pathogenic variant in the NARS1 gene, emphasizing the significance of genetic screening for parents to prevent recurrence in future pregnancies. Collaboration with special education instructors and speech therapists remains active to meet the child's communicative and cognitive requirements.

Keywords: Cerebral palsy, NARS1 gene mutation, Disability, Therapy

INTRODUCTION

Cerebral palsy (CP) is the leading cause of persistent motor impairment in children. In 2007, an international committee defined cerebral palsy as a group of permanent movement and posture disorders caused by nonprogressive disturbances in the developing fetal or infant brain. CP can also cause disturbances in sensation, perception, cognition, communication, and behavior, as well as epilepsy and secondary musculoskeletal problems. The surveillance of cerebral palsy in Europe (SCPE) organization identifies five important features that define CP: an umbrella phrase, persistent but not unchanging, a disturbance of movement, posture, and motor function, caused by a non-progressive interference, lesion or aberration, and impacting the developing brain.[1]

CP is caused by a variety of etiologies, including developmental, genetic, metabolic, ischemic, infectious, and acquired, resulting in similar neurologic symptoms. Although CP was once thought to be a static encephalopathy, its neurologic characteristics, including mobility problems and orthopedic consequences including scoliosis and hip dislocation, can alter or worsen with time. Children and adults with cerebral palsy often achieve academic and occupational success without any cognitive impairment. The centers for disease control and prevention report that the prevalence of cerebral

palsy, the most prevalent and expensive kind of persistent motor impairment that starts in childhood, is 3.6 per 1,000 children, with a male to female ratio of 1.4 to 1.Most infants with cerebral palsy were delivered at term with simple labors and deliveries, according to the collaborative perinatal project, which tracked almost 45,000 children from in utero to age seven.In preterm newborns, intracerebral hemorrhage and periventricular leukomalacia (PVL) are the main lesions that cause cerebral palsy.[2] Prematurity and underweight are the most significant risk factors.[3]When diagnosing children with cerebral palsy and determining its cause, brain imaging is crucial.[4] More than 70% of cases with CP are classified as spastic. As of right now, the cause of CP is unknown. Research has indicated a strong correlation between issues such low birth weight, birth hypoxia, and improper fetal position and placenta.[5]

CASE REPORT

A 14-month-old was brought in for examination owing to delayed motor milestones and clonus in his left leg. The clinical examination indicated slight hypotonia of the body axis, spasticity in all four limbs, and microcephaly. Follow-ups indicated chronic developmental delays and motor deficits that were consistent with a cerebral palsy diagnosis. Despite receiving regular physical treatment and wearing a corset, the kid suffered from repeated relapses.

Figure 1: Cerebral palsy, with variations in posture.

At 2.5 years, the kid had spastic gait, wide-based walking, no expressive speech, and continuing psychomotor deficits. Despite therapies such as Bedoxin, and physical therapy, the child's developmental growth was restricted. Genetic testing revealed a pathogenic mutation in the NARS1 gene, which contributed to the complicated neurodevelopmental pattern described. By the age of five, the child had developed global hypotonia (Figure 1), microcephaly, and dysmorphic traits such as hypertelorism, small philtrum, and an open mouth phenomenon (Figure 2). Genetic investigation confirmed the pathogenic mutation in the NARS1 gene, providing additional support for the diagnosis.

Figure 2: Cerebral palsy patient and muscle tone.

In the patient, a pathogenic mutation, 1600S>T, r. (Arg534Ter) in the NARS1 gene, was found to be heterozygous. Because no DNA material from the parents is available for study, it is impossible to say whether the pathogenic variation was inherited from one of the parents or developed de novo. Pathogenic alterations in the NARS1 gene have been linked to a neurodevelopmental disease accompanied by microcephaly. Speech and gait impairments are inherited as autosomal dominant and recessive. This genotype is in addition to the patient's NARS1-associated neuro-developmental impairment.

DISCUSSION

Asparaginyl-tRNA synthetase1 (NARS1) belongs to the ubiquitously expressed cytoplasmic Class IIa tRNA synthetase family, which is necessary for protein translation. One research identified biallelic missense and frameshift mutations in NARS1 in seven children from three unrelated families who had microcephaly and neurological delay. Patient cells had decreased NARS1 protein, poor NARS1 activity, and impaired global protein synthesis. Cortical brain organoid modeling reveals lower proliferation of radial glial cells (RGCs), resulting in smaller organoids typical of microcephaly. Single-cell analysis revealed changed components of both astrocytic and RGC lineages, indicating that NARS1 is required for RGC proliferation.[6] Individuals with NARS1 defects exhibit global developmental delay (GDD) and intellectual impairment, which ranges from mild to profound. There are significant delays in language and motor development, and some people never achieve

independent walking. Microcephaly is seen in the majority of instances, and epilepsy is strongly connected with the disease. Seizures vary in kind. Some people have an ataxic gait, poor balance, and dysarthria, which may indicate the presence of further neurodegenerative processes. Peripheral neuropathy is present in certain cases, coupled with other dysmorphic characteristics such as deformed hands and feet, upslanting palpebral fissures, and skeletal deformities such as scoliosis. Impulsivity, repetition, and selective feeding routines are examples of behavioral features.[7]

Cerebral palsy is the most prevalent physical impairment, beginning in childhood. It affects around three out of every thousand live babies worldwide. The syndrome is linked to movement problems (spasticity, dystonia, and choreoathetosis), epilepsy, and sensory and cognitive deficits. As individuals become older, they are more likely to develop avoidable noncommunicable illnesses and die young. Pain and mental issues are common. Healthcare services throughout the transition from pediatric to adult care are frequently scattered and insufficient. Nonetheless, in a European research, teenagers with cerebral palsy reported a worse quality of life than matched controls from the general population in only one domain: social support and peer interactions.[8]

The damage done is static and irreversible, and it might be caused by a variety of circumstances, including hereditary and environmental causes. Although the damage is constant, the resulting symptoms are changeable and can alter over time. Intellectual impairment, hearing and vision deficiencies, dietary and feeding issues, respiratory infections, and epilepsy are all possible complications for children. Spasticity, muscular weakness, and immobility are major causes of secondary musculoskeletal disorders that affect muscle, tendons, bones, and joints. Children and their families' daily function, societal involvement, and quality of life are significantly impacted by CP throughout their lives.[9]

Clinical findings are the primary basis for diagnosing CP. Early diagnosis is achievable using a combination of clinical history, standardized neuromotor testing, and magnetic resonance imaging (MRI); nonetheless, in most clinical settings, CP is better diagnosed by the age of two. An MRI scan is used to determine the degree of brain lesions and to detect congenital brain abnormalities. Genetic diagnostics and tests for inborn metabolic abnormalities are recommended based on clinical results to detect particular illnesses. Because CP is linked to a number of related and secondary medical disorders, its treatment necessitates a multidisciplinary team approach. The majority of children with cerebral palsy develop into productive adults. Occupational therapy is an important part of the multidisciplinary treatment of people with cerebral palsy, and several studies have shown that it has long-term impact on improving fine motor skills. Occupational therapy focuses on improving fine motor skills in the upper extremities to help children conduct daily activities more effectively. Occupational therapists also work to organize children's play spaces, provide adapted equipment for self-care and learning, and change the child's learning environment to improve attention and information processing.[10]

CONCLUSION

This article demonstrates the complex interaction of cerebral palsy and genetic variables in forming the clinical presentation of neurodevelopmental disorders. Multidisciplinary treatment, which includes genetic counseling, physical therapy, and specialized schooling, is essential for delivering comprehensive care to children with complex developmental needs. Genetic testing for parents is critical for informed family planning and preventing recurrent pregnancies.

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