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Case Report

Allan-Herndon-Dudley Syndrome with MCT8 Deficiency: A Case Report

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Abstract:

The Allan-Herndon-Dudley syndrome is caused by mutations in the SLC16A2 gene, responsible for encoding MCT8. Loss of function in the transporter can lead to a deficiency of TH necessary for brain development, causing significant issues for the affected individual. First described in 1944, this rare disease is linked to the X chromosome and exhibits a recessive inheritance pattern, predominantly affecting males. Key signs and symptoms include severe psychomotor retardation, axial muscle hypotonia, and profound cognitive impairment. Diagnosis is based on neurological clinical findings before the age of two, magnetic resonance imaging, and laboratory results. This study describes a clinical case of Allan-Herndon-Dudley syndrome in which the patient exhibited signs of the disease from early childhood. The patient was referred to a pediatrician at six months of age due to parental complaints of hypotonia, vomiting, and malnutrition. The mother reported that the patient lacked neck control and could not sit. Due to limited resources, the family had to relocate to another city for proper medical care. Treatment continued until the age of 8, after which the patient began attending the Association for the Development of Limited Children. During this time, there was some improvement, with the patient gaining head control and being able to eat with an adapted spoon. However, at the age of 22, despite physiotherapy, the patient started losing acquired movements. This deterioration led to the abandonment of the institution, as maintaining posture and sitting became challenging, exacerbating muscle atrophy and hindering social interaction. The family decided to return to their hometown during this period. In 2005, the Department of Biology at the University of São Paulo classified the patient as having Allan-Herndon-Dudley Syndrome. This diagnosis was based on the measurement of T3, T4, and TSH hormone levels, determined through immunofluorimetric assay. Presently, the patient weighs 34 kg, is 1.45m tall, exhibits hypertonia and a flexor pattern, and receives home-based treatment with a physiotherapist and various daily inhalations to alleviate respiratory discomfort.

Keywords: syndrome; allan-herndon-dudley; genetic alterations; MCT8; mental retardation

Introduction:

The thyroid gland is responsible for producing the hormones T3 and T4. Thyroid hormone (TH) plays a crucial role in the development of various tissues, including the Central Nervous System, and regulates energy metabolism throughout life. Most of its functions are carried out through the binding of T3 to nuclear TH receptors, requiring TH to enter the target cell membrane with the assistance of thyroid hormone transporter proteins. The most specific transporter identified to date is monocarboxylate transporter 8 (MCT8) (MASNADA et al., 2019).

Allan-Herndon-Dudley Syndrome (AHDS) is associated with mutations in the SLC16A2 gene, which encodes MCT8. It is characterized by elevated serum T3, normal low T4, and increased TSH levels, accompanied by severe intellectual and motor deficiencies. Problems are believed to arise from a loss of transporter function, leading to the crucial TH transport loss needed for brain development (ARMOUR et al., 2015).

AHDS was first described in 1944 by American geneticists William Allan, Nash Herndon, and Florence Dudley. It is an X-linked recessive condition, predominantly affecting males, making it challenging to estimate the prevalence in the population. However, the frequency is estimated at 1 in 10,000 males with mental retardation (SCHWARTZ et al., 2005).

Affected males exhibit severe psychomotor retardation, characterized by axial muscle hypotonia, spastic or dystonic quadriplegia, and profound cognitive impairment. Speech development is usually absent, and most patients cannot sit, stand, or walk without support. Other symptoms include athetoid hand and arm movements, paroxysmal dyskinesia, muscular hypoplasia, seizures, nystagmus, and secondary microcephaly (JANSEN et al., 2008).

Confirmation of the syndrome involves neurological clinical findings before the age of two, including hypotonia, feeding difficulties, developmental delays, intellectual disability, extrapyramidal findings (dystonia, choreoathetosis, paroxysmal movement disorders, hypokinesia, hypomimia), pyramidal signs, and late-onset seizures. Other features include thyroid dysfunction, poor weight gain, reduced muscle mass, craniofacial anomalies, and a distinctive facial appearance (SARRET; PETIT; TONDUTI, [s.d.]).

In children under five years, severely delayed myelination, simulating hypomyelination, can be observed in magnetic resonance imaging, which improves over time (SARRET; PETIT; TONDUTI, [s.d.]). Laboratory findings related to the thyroid include high serum levels of free T3, low serum levels of rT3, reduced T4 concentration, and normal serum TSH levels (HEUER, 2007).

Therapeutic approaches involve supportive care and symptom reduction, including physical, occupational, and speech therapies, medical treatment of dystonia and seizures (if present), and dietary supplementation. Orthopedic follow-up is necessary. The second form of therapy aims to restore correct TH signaling, intending to reverse hypothyroidism in tissues heavily dependent on MCT8 for TH uptake and protect tissues primarily relying on other TH transporters (GROENEWEG et al., 2016).

The objective of this case report is to present a man with Allan-Herndon-Dudley syndrome, a rare condition associated with the SLC16A2 gene, which encodes the monocarboxylate transporter 8 (MCT8). This syndrome, with an estimated prevalence of 1 in 10,000 men with mental retardation, is a recessive X-linked inherited disorder.

Given the scarcity of documented cases of this syndrome both nationally and internationally, and the limited number of published studies in Brazil, this report aims to fill a gap in the medical literature on Allan-Herndon-Dudley syndrome.

The main purpose is to thoroughly study the presented case, providing a detailed analysis of the symptoms, diagnostic methods employed, and treatment options implemented. Additionally, the intention is to establish comparisons with other cases described in medical literature to enhance understanding of the variability of this condition.

By sharing this case and its analyses, we hope to contribute to the advancement of medicine, facilitate early diagnosis, and increase awareness of Allan-Herndon-Dudley syndrome. We believe that enhanced knowledge can ultimately lead to significant improvements in the quality of life for individuals affected by this rare condition.

Case Description:

A 41-year-old male patient, Caucasian, Catholic, and single, was referred to a pediatrician at the age of six months due to parental complaints of hypotonia, vomiting, and malnutrition. The mother reported that the patient lacked neck control and was unable to sit. Various examinations were conducted with inconclusive results. Due to limited resources, the family had to relocate to another city to seek ongoing care for the case.

The father mentioned that when the boy was 3 years old, he received financial assistance from coworkers to take him to a capital city hospital for a metabolic disorders test, which proved inconclusive.

At the age of 6, according to physiotherapeutic evaluation, the patient exhibited generalized low muscle mass with uniform consistency in the lower limbs, showing impaired full extension of the knee and very pronounced flexion even with stretching treatment. The upper limbs presented more tonus-related impairment, and the most accentuated reflexes were the Moro reflex and toe-grasping reflex. Sitting balance was severely compromised, affecting safety due to the Moro reflex interference. The patient used medications for bronchitis treatment, including Ipratropium Bromide and Fenoterol. He experienced depressive episodes, avoiding necessary physical activities, showing apathy even during stimulating therapies (equine therapy, changes in decubitus, specific ground techniques).

This treatment continued until the age of 8, after which the patient started attending the Lumen Et Fides Child Development Association, which aims to assist children and adolescents with neuromotor and neuromuscular dysfunctions through therapeutic and educational activities. During this period, there was improvement; he could hold his head and eat with an adapted spoon. However, at the age of 22, despite ongoing physiotherapy, he began losing acquired movements, leading to his withdrawal from the institution due to an inability to maintain posture, sit, exacerbating the atrophy, and hindering social interaction. During this period, the family decided to return to their hometown.

Due to difficulties, the patient went through a period without physiotherapy and resumed at a local clinic, experiencing a continued decline in capabilities. In 2005, the Department of Biology at the University of São Paulo classified the patient as having Allan Herndon Dudley Syndrome, a result obtained through the measurement of T3, T4, and TSH hormone levels using immunofluorimetric assays.

Currently, the patient weighs 34 kg, is 1.45m tall, exhibits hypertonia and a flexor pattern, and maintains home-based treatment with a physiotherapist, along with daily inhalations to alleviate respiratory discomfort.

Discussion:

Described in 1944 by William Allan, Nash Herndon, and Florence Dudley, the MCT8-related syndrome, or Allan-Herndon-Dudley Syndrome (AHDS), poses challenges in terms of diagnosis and treatment. Due to its rarity and limited literature reports, finding professionals capable of providing precise and effective guidance to families of individuals with this syndrome becomes challenging (KIM et al., 2015).

Literature indicates that AHDS patients exhibit normal embryonic development and display the first signs of the syndrome in early childhood. Typically, patients manifest symptoms such as hypotonia, weakness, reduced muscle mass, developmental delays, ataxia, lack of ambition, and dysarthria. As the individual reaches adolescence and adulthood, a notable sign is below-normal body weight, evident since early childhood due to thyroid dysfunction. Height becomes compromised due to scoliosis and muscle contractures, with hypotonia ceasing and evolving into a spasticity pattern (SCHWARTZ et al., 2005).

The difficulty in diagnosing AHDS is linked to a lack of knowledge and epidemiological data about the syndrome. The hypothesis of AHDS is rarely considered based solely on the neurological characteristics presented by the patient. Therefore, it is necessary to conduct screening for males with X-linked mental retardation (ROMÃO et al., 2017; KIM et al., 2015).

The initial symptoms presented by the patient during the neonatal period are related to enzymatic deficiencies and metabolic disorders (ROMÃO et al., 2017). These alterations contribute to the individual's developmental delay. Consequently, the majority of cases receive a late diagnosis, determined by measuring T3, T4, and TSH, where T3 levels are elevated above reference values (KERSSEBOOM et al., 2013).

No effective treatment study has been presented for AHDS. However, as mentioned in the case, physiotherapy can be a way to improve the quality of life for individuals with the syndrome. Changes in decubitus, gait training, static and dynamic balance, specific ground techniques, and equine therapy may enhance the hypotonia condition. In cases of hypertonia, interventions aim to block abnormal reflex stimulation to normalize tonus and improve body composition, resulting in the adjustment of strength, flexibility, and range of motion. However, it evolves into a severe spasticity pattern (LEITE; PRADO, 2019).

Severe mental impairment should not hinder patients from participating in social activities and learning-stimulating activities. Limiting patients to activities of this nature can lead to low self-esteem, discouragement, and despondency, further impacting their way of life. It is crucial for patients to have support that enables interaction with their surroundings, with responsibility falling on family members, schools, child protective services, healthcare units, and philanthropic institutions (DÍAZ et al., 2009).

Conclusion:

Allan-Herndon-Dudley Syndrome is an exceptionally rare disease with limited cases documented in the literature. This study illustrates the symptoms of a patient with AHDS and a late diagnosis achieved through the measurement of T3, T4, and TSH. Concerning treatment, it can be concluded that there is no specific medication; only palliative treatments such as dietary supplements and physiotherapy are available to enhance the quality of life. The lack of knowledge regarding diagnosis, treatment, and coping mechanisms for the disease can have psychological effects on those who interact with the individual daily, including the syndrome sufferer who may experience depressive episodes. It is crucial to raise awareness among mothers about the possibility of having additional children with the syndrome.

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