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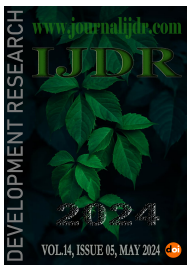

RESEARCH ARTICLE OPEN ACCESS

COGNITIVE AND BEHAVIORAL CHARACTERISTICS OF A PATIENT WITH DUBOWITZ SYNDROME

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ABSTRACT

Dubowitz Syndrome is a rare genetic disease and the clinical presentation is mainly characterized by pre and postnatal growth retardation, mental retardation, hyperactivity, eczema, short stature, microcephaly and facial and physical changes. Diagnosis is based on inspection of facial appearance, growth records, clinical observation of behavioral patterns and multiple clinical manifestations. We reported a patient with Dubowitz syndrome diagnosed through clinical-genetic examination treated with multidisciplinary therapies.

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INTRODUCTION

Dubowitz Syndrome (DS) is a rare genetic disease inherited in an autosomal recessive manner. It was described in 1965 by Dr. Victor Dubowitz and was designated as Dubowitz syndrome by Gorlin & Opitz in 1971 at the University of Wisconsin School of Medicine[2]. The cause of DS is not fully elucidated, but it has been observed that some affected individuals have mutations in the NSUN4 and LIG4 genes while others presents small DNA additions or deletions[4]. The clinical presentation is mainly characterized by pre and postnatal growth retardation, mild to moderate mental retardation, eczema, short stature, microcephaly and facial and physical changes. The typical face is with a sloping or high forehead, lateral thinning of the eyebrows, micrognathia, short palpebral fissures, ptosis, dysplastic auricular pavilions, a wide and flat nasal bridge, and a peculiar configuration of the mouth. In addition, patients may also present clinodactyly of the 5th finger, syndactyly of the 2nd and 3rd fingers and behavioral changes, being the most common hyperactivity and attention deficit[3]. The diagnosis is eminently clinical, being mainly based on inspection of facial appearance, growth records, behavioral changes and previous medical history, in addition to the exclusion of other genetic syndromes, with no laboratory tests to prove it. Several treatments can be proposed according to the conditions and needs of the patient. Drugs, surgery, or multidisciplinary therapies are used in some conditions. The objective of this report is to approach the particular characteristics of a patient with Dubowitz syndrome and highlight the importance of referring suspected patients to specialized genetic and neuropsychiatric follow-up for adequate management of cognitive, psychological and behavioral changes, improving the prognosis and quality of life of these patients.

Objective: The main objective is to report a rare genetic disease.

METHODS

Case report and brief literature review.

CASE REPORT

JCLS, male, 23 years old, Brazilian, born by vaginal delivery without complications and small for gestational age. Patient was referred by Primary Health Care to this service of the Association of Exceptional Parents and Friends (AEPF) to start multidisciplinary follow-up due to a condition compatible with Dubowitz Syndrome after previous genetic evaluation. The patient attended an outpatient consultation at

AEPF accompanied by his mother. The mother reported that she performed prenatal care properly and denied having gestational complications. She also denied the use of alcohol, cigarettes, and illicit drugs during pregnancy. She reported that the patient was born with heart disease, but was unable to report which one. In addition, she reported that in her family history includes a brother with cognitive delay. The mother reported that the patient is under neuropsychiatric follow-up due to psychomotor agitation and brought a medical report performed by a geneticist showing normal karyotype and fragile X for differential diagnosis, in addition to clinical manifestations of short stature, microcephaly, short palpebral fissures, micrognathia, clinodactyly of the 5th fingers bilaterally and previous history of eczema and constipation in the first year of life. Beyond that, impairment in neuropsychomotor development, dysarthria, cognitive deficits, with delay in the development of speech, reading and comprehension were observed. The patient's mother claimed that the patient was using Risperidone 3 mg every 12 hours and Imipramine 25 mg, 1 pill a day in the morning in view of psychomotor agitation, but due to the persistence of psychomotor agitation, medication adjustment was made in previous consultation replacing Risperidone per Quetiapine 25 mg every 12 hours. After drug introduction of Quetiapine, the patient had adverse effects with sialorrhea, agitation and disconnected speech. Therefore, a new medication adjustment was performed with Quetiapine being suspended and a decision to retake pharmacological therapy combined with Risperidone and Imipramine. Patient appeared for a return neuropsychiatric consultation showing stability of the clinical features and improvement of psychomotor agitation. He is under multidisciplinary follow-up with a speech therapist and psychotherapy for better management of cognitive and behavioral symptoms.

DISCUSSION

The global incidence of DS is not yet established, but it is rare. A case of Dubowitz syndrome was presented in a 23-year-old boy, diagnosed through clinical-genetic examination, after exclusion of other genetic syndromes. Diagnosis is commonly made in early childhood and is based on inspection of facial appearance, growth records, and clinical observation of behavioral patterns and multiple clinical manifestations. A physical examination with attention to growth parameters and craniofacial features is essential[4]. There is no laboratory test for diagnosis, presenting normal in most cases[8]. Differential diagnosis includes Bloom syndrome, Smith-Lemli-Opitz syndrome, Seckel syndrome, fetal alcohol syndrome, fragile X syndrome, and others in which eczema is a characteristic finding[9]. The main feature that distinguishes DS from Bloom syndrome is the facial appearance. In addition, Bloom syndrome characteristically presents telangiectatic erythema on the face. Fetal alcohol syndrome has minimal telecanthus, neural tube defect, absence of eczema, and a history of prenatal alcohol exposure. Mental retardation in Seckel syndrome may be more severe with distinctive facial features such as a "beak-like" nose protrusion[1]. Fragile X syndrome, an X-linked genetic disorder, is one of the causes of mental retardation, where more than 90% of affected children presents developmental delay and behavioral changes commonly associated with attention deficit hyperactivity disorder[7]. A review with 141 patients was published by Tsukahara and Opitz describing the main clinical features, including developmental delay, microcephaly, short stature, and characteristic facial and physical changes[9]. Facial appearance is considered the most diagnostic manifestation of the syndrome[6]. Micrognathia, a retraction of the chin, was present in more than 50% of cases and distinct abnormalities such as the shape of the face and eyes are common. Unnatural smallness of the eyes and common anomalies such as fifth finger clinodactyly, which is a permanent flexion of the finger, have been described[9]. A review of 51 publications from 1996 to July 2018 represented 63 individuals clinically diagnosed with DS and associated the eczema in 30 of 63 cases[4].

Clinical presentation may show overlap with mild or atypical forms of different syndromes associated with intellectual disability[4]. There is cognitive impairment and mild to moderate mental retardation is observed in about 50% of patients. However, severe mental retardation is rare. Abnormal behavior such as hyperactivity was described in 40% of patients as well as attention deficit and sleep disturbance[3]. Parrish and Wilroy identified severe delays with vocabulary as well as specific difficulties with numeracy, spelling, and motor coordination skills[5]. The phenotypic diagnostic features of DS in this patient included short stature, microcephaly, micrognathia and clinodactyly of the fifth finger, in addition to eczema and constipation in the first year of life. Other findings include psychomotor agitation and delayed neuropsychomotor development with cognitive impairment, speech delay, reading delay, and dysarthria. It is not known about the patient's prenatal growth since the mother was not followed up at this service. Suspected or diagnosed patients with DS are an opportunity for further investigations, clarifying genetic risks and related disorders[4]. The treatment of DS depends on the symptoms presented by patients. In children with language and cognitive difficulties, an individual education plan can be developed emphasizing areas of disability and need. Frequent speech therapy sessions can help with the development of language deficits. Occupational therapy and physical therapy can improve self-help skills. Regarding behavioral changes, medications used in attention deficit hyperactivity disorder (ADHD) have been shown to be effective along with psychotherapy. In this present case some of these methods were successfully used through follow-up with a speech therapist and psychotherapist, in addition to neurological and psychiatric methods through drugs treatment with Risperidone and Imipramine to control psychomotor agitation. Risperidone is useful for controlling behavior, especially when there is mental retardation.

CONCLUSION

We reported a 23-year-old patient with Dubowitz syndrome treated with multidisciplinary therapies managing his cognitive, psychological and behavioral features and improving his quality of life. In conclusion, the prognosis of patients with DS is good as long as the management of their clinical conditions is started early and maintained throughout life. For this reason, it is important to recognize the clinical characteristics and the consequent multidisciplinary follow-up.

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