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Case Report

De Novo Variant in MAPK8IP3 Gene in the Differential Diagnosis of Global Development Delay. Case Report

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Abstract

Introduction: Global development delay has a high prevalence and heterogeneity in the world population. With the advancement of technology and the detection of pathogenic variants detected by exome sequencing, genes related to this condition could be identified and collaborated for further clinical clarification. Among the studied genes, the MAPK8IP3 gene became an attractive candidate due to its performance in neuronal axonal transport. This case report was approved by the Ethics Committee of Universidade Metropolitana de Santos.

Case Report: The present case refers to an 8-year-old male patient presenting with a global developmental delay with no body dysmorphia. Cerebellar ataxia, muscle hypotonia and intellectual impairment were important clinical impairments. Brain MRI and complementary exams were normal. The genetic study showed a *de novo* heterozygous pathogenic variant in the MAPK8IP3 gene. Symptomatic treatment with multi-professional rehabilitation was instituted with partial improvement of symptoms.

Keywords: *De Novo Variant; MAPK8IP3 Gene; Global Development Delay*

Introduction

Global development delay has a high prevalence and heterogeneity in the world population. With the advancement of technology and the detection of pathogenic variants detected by exome sequencing, genes related to this condition could be identified and collaborated for further clinical clarification. Among the studied genes, the MAPK8IP3 gene became an attractive candidate due to its performance in neuronal function, such as axonal transport leading to progressive cell damage. Experimental evidence indicates that the MAPK8IP3 gene product is involved in: Kinesin-I interaction, which acts in axonal transport; Formation of scaffolding that helps to regulate the signal transduction of the Janus Kinase cytokine signaling pathway.

Methods

The report of this case was submitted and approved by the ethics committee of Universidade Metropolitana de Santos.

Case Presentation and Discussion

The present case refers to an 8-year-old male patient, son of non-consanguineous parents, presenting with a global developmental delay with no dysmorphia.

The mentioned patient was born at term and by cesarean delivery with Apgar 9 in the first minute and 10 in the fifth minute. During the gestational period, there was evidenced mild pyelic-ureter junction stenosis, which normalization six months after birth.

The hypotonic tone was found from early childhood, associated with axial and appendicular incoordination and dysmetria after the first 4 years of life having been suggested as cerebellar ataxia. Nystagmus evoked by the gaze position and convergent strabismus of the left eye was also observed.

The language was quite compromised, showing greater severity in expression. Vocalization occurred only by phonemes, worsening in moments of anxiety or confrontation. The patient had a low tolerance threshold for frustrations, expressing repressed feelings with bites and pinches in himself and family members.

The presence of intellectual deficit was also observed and with important school damage, especially in literacy. Several clinical and complementary neurological evaluations were performed, including laboratory, graphic (electroencephalogram) and imaging (brain and spinal cord magnetic resonance imaging) with no alterations.

The exome genetic study was performed and showed a "*de novo*" heterozygous pathogenic variant Chr16:1.756.419G>T in the MAPK8IP3 gene. This variant promotes the replacement of the glutamate amino acid at position 27 by a stop codon (p.Glu27); This autosomal dominant inheritance condition variant also has been recently described in the medical literature associated with neurodevelopment disorders with or without structural brain anomalies such as global developmental delay from childhood, intellectual disability, speech delay, ataxia and epilepsy [1,2].

About half of affected individuals also have central nervous system malformations such as cerebral and cerebellar atrophy, tapered corpus callosum and white matter volume reduction [1,2].

Although the complementary exams performed in this patient were normal, the clinical picture demonstrated the need for genetic investigation for the differential diagnosis. The finding of the pathogenic variant in the MAPK8IP3 gene was postulated to be associated with this patient's global developmental delay.

Multiprofessional treatment was performed with physiotherapy, speech therapy, occupational therapy, psychology, as well as hippotherapy. Pedagogical teaching was started with multidisciplinary team support, as well as a therapeutic assistant in the school environment. Drug treatment was instituted with aripiprazole at a dose of 5 mg daily to stabilize behavior and mood with an adequate response.

Clinical and rehabilitation treatment resulted in partial improvement of neurological symptoms.

Figure: *A and C- Muscle hypotonia; B- Eye strabismus.*

Conclusion

Global developmental delay without body dysmorphia is a challenge due to the heterogeneity of clinical presentation. With the advent and development of neurogenetics, many etiologies were then better understood. The study and inclusion of the MAPK8IP3 gene should be encouraged in these patients, especially in individuals with global developmental delay from childhood, intellectual disability, speech delay, ataxia and epilepsy.

Author Disclosures

Joseph Bruno Bidin Brooks declares that he has no conflict of interest.

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