What can Global Developmental Delay Conceal? Apropos of a Case with a Genetic Cause

Ana Braslavsky and Valentina Riveros
Servicio de Clínica Pediátrica. Hospital Italiano de Buenos Aires. Buenos Aires, Argentina

ABSTRACT

A six-year-old boy presents with a history of language delay that led his parents to make multiple consultations. At first, we interpreted his condition as part of a global developmental delay. Subsequently, the patient presented seizures and episodes of metabolic decompensation, and since then, he had to be followed up by neurology, genetics, and metabolism services. Finally, after several complementary studies, following a trio exome analysis, we diagnosed chromosome 7q11.23 microduplication syndrome, which explains his global developmental delay and neurological symptoms.

Key words: Global developmental delay, chromosome 7q11.23 microduplication syndrome.

INTRODUCTION

Neurodevelopmental disorders are alterations in neurodevelopment that begin in childhood. Developmental delay is one of them, which refers to acquiring maturational patterns with the expected sequence but at a slower rate than usual. It may involve one specific area (motor skills, language, sociability, cognition, and activities of daily living) or more than one area, in which case the condition is called global developmental delay (GDD), the prevalence of which is 1-3% of the population[1,2].

There are several risk factors for its development, both genetic and environmental, and the latter, in turn, can be classified into prenatal and postnatal. Ten percent of cases are associated with monogenic syndromic causes, 5% with rare chromosomal alterations, 5% with variations in the number of copies of parts of the genome, and another 5% with penetrant genetic variations. The remaining 75% is due to unknown multifactorial causes with environmental factors modulating gene expression[3].

Here is the case of a child diagnosed with GDD of genetic cause.

We conducted the report according to the legal regulations on ethical issues to protect the subject's dignity, identity, integrity, and welfare, and respect for his human rights and fundamental freedoms throughout the production process. We obtained informed consent.

PATIENT PRESENTATION

We have a 6-year-old boy, the fourth child of a non-consanguineous couple, born in Korea, with no relevant perinatological history and standard neonatal metabolic and auditory screening. From the motor aspect, he presented cephalic support at three months, sitting at seven months, standing at 13 months, and walking at 15 months, with adequate pondostatural development and physical examination without pathological findings.

The parents, concerned about the lack of verbal language (Korean and Spanish), consulted their pediatrician at thirteen months of age. As he presented smiling socially, responding to sounds, babbling, pointing, and responding to his name, we took a watchful waiting approach. At fifteen months, he had an atypical febrile seizure. He underwent evaluation by Child Neurology, who requested a video electroencephalogram (VEEG)

Author for correspondence: ana.braslavsky@hospitalitaliano.org.ar, Braslavsky A.

Received: 03/17/23 Accepted: 07/24/23 Online: 09/29/2023

DOI: http://doi.org/10.51987/revhospitalbaires.v43i3.223

How to cite: Braslavsky A, Riveros V. What can Global Developmental Delay Conceal? Apropos of a Case with a Genetic Cause. Rev. Hosp. Ital. B.Aires. 2023;43(3):143-146.

ISSN (Online) 2314-3312

that revealed no pathological findings, a brain MRI with epilepsy protocol, and a brain CT scan, which reported mild asymmetry of the lateral ventricles in favor of the left side.

Thus, he started medication with phenobarbital and diphenylhydantoin until he was 24 months old.

He continued to have poor language and social interaction difficulties at two years of age, so we referred him to a pediatric neurodevelopmental specialist. He underwent the national screening test (PRUNAPE*) and the modified questionnaire for early detection of autism (M-CHAT**), failing in all areas of both tests.

We referred him to Mental Health and performed the Autism Diagnostic Observation Scale (ADOS***), which reported a picture not compatible with autism spectrum disorder with an overall score of 7 for a cut-off point of 10, reflecting alterations in reciprocal social interaction.

We arrived at the diagnostic impression of a picture of GDD with a severe language impairment.

We indicated speech therapy, occupational therapy, and psychology. We also performed a brainstem auditory evoked potentials test with no pathological findings. At two and a half years of age, the child presented with a picture of acute deterioration of the sensorium in the context of ketosis and hypoglycemia. He was studied again by the Child Neurology Service.

A CT scan of the brain showed no changes concerning the previous one, and an MRI of the brain and angiography (MRA) of intracranial vessels showed hyperintensity in the frontal horn of the left ventricle.

At the same time, a VEEG reported frequent synchronous and asynchronous bilateral temporooccipital sharp waves compatible with electrical seizures, which revealed benign childhood epilepsy. Given these findings, he started treatment with phenytoin and oxcarbamazepine until age four.

Due to the presentation of GDD associated with episodes of metabolic decompensation without apparent cause and epilepsy, he started follow-up by the Metabolism and Genetic Services.

A karyotype test showed no abnormal results, and blood tests showed metabolic acidosis with increased b-hydroxybutyrate with metabolites compatible with mitochondrial disease and positive organic acids in urine.

At the same time, due to the background described above and the suspicion of mitochondrial disease, we requested a complete trio exome study with the mitochondrial genome, which showed a de novo 7q11.23 duplication with no significant variants in the mitochondrial genome, a result compatible with 7q11.23 duplication syndrome, which justified the neurodevelopmental delay and the neurological compromise of the child. At six years of age, the child attends elementary school accompanied by an integrative teacher.

He continues to undergo occupational therapy, assisted by professionals in speech therapy, neurolinguistics, and psychology.

DISCUSSION

Microduplication syndrome 7q11.23 is a rare autosomal dominant disorder caused by partial duplication of the long arm of chromosome 7 comprising 26 genes. It is estimated to affect 1 in 7500-20 000 live births. Seventy-three percent of those diagnosed have the disorder due to a de novo genetic alteration, while the remaining 27% have an affected parent.[4] The main diagnostic suspicion is due to a delay in expressive language development. The phenotype is highly variable, and no particular clinical expression is required to establish the diagnosis[5]. Table 1 shows the characteristics described in patients diagnosed with 7q11.23 microduplication syndrome. Figure 1 shows the patient presented in this case, evidencing in the image that he has a broad forehead and triangular face.

The first molecular cytogenetic description was published by Somerville et al. (2005) 6,7, based on a patient with severe expressive language delay and certain dysmorphic features in the context of a family with a history of attention and academic difficulties. Afterward, Van der Aa et al. (2009)8 referred to 14 patients with chromosome 7q11.23 duplication syndrome, whose most consistent clinical finding was speech delay. Morris et al. (2015)8, in turn, reported the clinical features, medical problems, and natural history of 64 patients with the present syndrome. In this last study, the most common indication for genetic testing was developmental delay, followed by autism spectrum disorder.

The diagnosis of GDD involves screening for heterozygous duplications of 1.5 to 1.8 megabases (Mb) of the critical region of chromosome 7 (q11.23), the same region deleted in Williams-Beuren syndrome.[4] Historically, G-banding karyotyping was the standard test for detecting chromosomal normalities in the study of GDD. This method allowed the cytogeneticist to visualize and analyze chromosome number or rearrangement of chromosomes, including gains (duplications) and losses (deletions), generally over 5Mb.

Today, molecular cytogenetics (chromosomal microarrays or whole exome sequencing) is the test of choice for such conditions [5,10], as it provides a much higher resolution (less than 5 Mb) than karyotyping, which increases the sensitivity for detecting small deletions or duplications. Another technique available for the study of deletions or duplications is fluorescence in situ hybridization (FISH), with the disadvantage of being performed for a specific genome region of interest (a single syndrome)[9].

* A simple test designed to screen for inapparent developmental problems in children under six years.
** A screening tool that parents respond to to assess the risk of autism spectrum disorder.
*** Standardized, semi-structured assessment instrument of communication, social interaction, and play or imaginative use of materials for individuals suspected of a diagnosis of autism or other pervasive developmental disorder.

Table 1. Phenotypic characteristics of the 7q11.23. duplication syndrome.[5,65,6]

Craniofacial features	Macrocephaly, brachycephaly, broad forehead, straight eyebrows, sunken eyes, long eyelashes, thick nasal tip, low insertion of the columella, short nasolabial fold, micrognathia, thin upper lip vermilion, ogival palate, minor ear abnormalities.
Neurodevelopment	Speech disorders: apraxia, dysarthria, phonological disorders, expressive language delay with average age of first words at two years. Behavioral problems: anxiety disorders, phobia, separation anxiety, selective mutism, oppositional disorder, autism spectrum disorders. Intellectual disability.
Cardiovascular	Patent ductus arteriosus, septal defects, aortic dilatation.
Endocrinologic	Growth hormone deficiency
Neurologic	Hypotonia, adventitial movements, gait and stability disturbances, coordination disorders, seizures, hydrocephalus, high pain tolerance. MRI findings include ventriculomegaly, thinned corpus callosum, increased extraaxial space, decreased white matter, delayed myelination, posterior fossa cysts, and cerebellar vermis hypoplasia.
Gastrointestinal	Sucking problems in the neonatal stage, requirement of gastrostomy, chronic constipation.
Genitourinary	Hydronephrosis, unilateral renal agenesis, cryptorchidism.
Musculoskeletal	Joint hyperlaxity

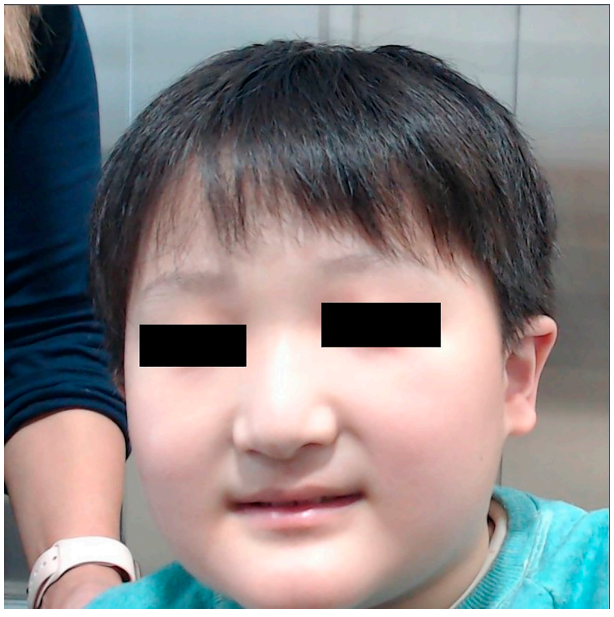

Figure 1. Facial phenotypic characteristics in a patient with chromosome 7q11.23 microduplication syndrome.

The relevance of reporting this case is that we should consider the uncommon causes of a frequent pathology, such as global developmental delay. When finding a patient with GDD associated with some comorbidity, such as seizures, or when there is a phenotype with dysmorphias, we must consider that there may be a genetic cause behind it. In this way, an early etiological diagnosis is possible, which in the case of the patient referred to is chromosome 7q11.23 duplication syndrome. This pathology has several comorbidities that need investigation to diagnose and treat them promptly and thus improve the patient and his family's quality of life.

Acknowledgments: To Dr. Julio Busaniche, Dr. Muriel Naymark and Dr. Alfredo Eymann of the Servicio Pediatría del Hospital Italiano de Buenos Aires.

Conflicts of interest: the authors declare no conflicts of interest.

REFERENCES

1. Sociedad Argentina de Pediatría. Comité de Crecimiento y Desarrollo. Guía para el seguimiento del desarrollo infantil en la práctica pediátrica [Guide for monitoring children's development in pediatric practice]. Arch Argent Pediatr. 2017;115(3):s53-s62. https://doi.org/10.5546/aap.2017.s53.
2. Soto Insuga V, González Alguacil E, García Peñas JJ. Detección y manejo del retraso psicomotor en la infancia. Pediatr Integral. 2020; 24(6):303-315.
3. Hervás A, Maristany M, Salgado M, et al. Los trastornos del espectro autista. Pediatr Integral. 2012;16(10):780-794.
4. González Lajas JJ, García Cruz JM. Trastornos del lenguaje y la comunicación. En: AEPap, editors. Congreso de Actualización Pediatría 2019. Madrid: Lúa Ediciones 3.0; 2019. p. 569-577.
5. Mervis CB, Morris CA, Klein-Tasman BP, et al. 7q11.23 Síndrome de duplicación. 25 de noviembre de 2015 [actualizado el 25 de marzo de 2021]. En: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): Universidad de Washington; 1993-2021.

6. Morris CA, Mervis CB, Paciorkowski AP, et al. 7q11.23 Duplication syndrome: physical characteristics and natural history. Am J Med Genet A. 2015;167A(12):2916-2935. https://doi.org/10.1002/ajmg.a.37340.
7. Somerville MJ, Mervis CB, Young EJ, et al. Retraso severo del lenguaje expresivo relacionado con la duplicación del locus de Williams-Beuren. Nuevo Ing J Med. 2005;353:1694-1701.
8. Van der Aa N, Rooms L, Vandeweyer G, et al. Fourteen new cases contribute to the characterization of the 7q11.23 microduplication syndrome. Eur J Med Genet. 2009;52(2-3):94-100. https://doi.org/10.1016/j.ejmg.2009.02.006.
9. Strong E, Butcher DT, Singhania R, et al. Symmetrical dose-dependent DNA-methylation profiles in children with deletion or duplication of 7q11.23. Am J Hum Genet. 2015;97(2):216-227. https://doi.org/10.1016/j.ajhg.2015.05.019.