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Case Report

Radio-Tartaglia Syndrome: A Rare Cause of Delay in Neurodevelopment – A Case Report

Maria Ximena Arteaga Pichardo[1*], Felipe Bernate[1], Juan Felipe Trujillo-Ángel[1], María Camila Santana Alba[1], María Paola Lubo[1], Natalia Avellaneda Perdigon[1], Lev Bladimir Ramirez[1], Daniel Jimenez[1], Sofía Atuesta Escobar[1], Isabel Fernandez Gonzalez [2], Luis Gustavo Celis Regalado[3]

1.Research Organization in Cellular Therapy and Metabolism, Facultad de Medicina, Universidad de La Sabana, Chía, Cundinamarca.
2.Medical Genetics Unit, Metropolitan Polyclinic, Caracas, Venezuela
3.Universidad de la Sabana, School of Medicine, Colombia.

ABSTRACT

Background: Radio-Tartaglia syndrome or RATARS is an unfamiliar disease caused by a heterozygous mutation of the SPEN gen in the 1p36 chromosome. Clinically, it is represented by global developmental delay and intellectual disability; however, it can also be associated with other relevant comorbidities that embark on the cardiovascular, gastrointestinal, musculoskeletal, integumentary as well as endocrinological systems.

Case Report: A 3-year-old pediatric male patient from Venezuela is referred to genetic counseling due to neurodevelopmental delay, microcephaly and dysmorphisms. The initial diagnostic impression consisted of Williams syndrome. Further studies revealed mild supravalvular stenosis, but no important changes in brain imaging or laboratory analysis. The patient's diagnosis was later replaced with RATARS after a complete exome sequencing revealed heterozygous SPEN pathogenic genes.

Conclusion: The diagnostic process of RATARS must become a pillar of further investigation given its uncertainty when clinically diagnosed hence the necessity of a clear confirmation through exome sequencing. This case report highlights the importance of genetic testing in patients with neurodevelopmental delay due to a possible but uncommon correlation with rare diseases such as RATARS.

Keywords: 1p36 gen, Neurodevelopment, RATARS, Radio-Tartaglia syndrome, SPEN, Williams syndrome

Introduction

Radio-Tartaglia syndrome or RATARS is an uncommon cause of neurodevelopmental delay. It is genetically manifested by a heterozygous mutation in the SPEN gene localized in chromosome 1p36.21-36.13 and faces an autosomal dominant inheritance (2). The chromosomal terminal deletions of this chromosome are the most frequently registered and have a vast variety of clinical manifestations. Nonetheless, there has also been documented to a lesser extent an increase in the number of copies and mutations in this chromosome (1). Aside from neurodevelopmental delay, RATARS is characterized by intellectual disability, behavioral and psychiatric features, language developmental delay, and craniofacial dysmorphism. Moreover, it is associated with cardiovascular, gastrointestinal, musculoskeletal, endocrine, and tegmental manifestations. (3). Information available about the distinctive features of this disease is scarce,

* *Corresponding author*: Luis Gustavo Celis Regalado, Universidad de la Sabana, School of Medicine, Colombia. Tel: +57 3005696115, Email: luiscelisr@yahoo.com

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delaying prompt management, screening of associated conditions, and life expectancy.

Case report

A male infant born at 39 weeks of gestation, his birth weight was 3350 gr (7.4 lbs), length of 51 cm (20 inches), and a cephalic perimeter of 32 cm (12.6 inches). The patient's milestones report a hand grip at 4 months, sedestation at 8 months, and walking at 13 months. By the age of 3 years, the patient is referred to genetic counseling due to neurodevelopmental delay associated with microcephaly and other dysmorphisms. Physical examination evidenced a cephalic perimeter between -1 and -2 standard deviations, arched eyebrows, 'V' shaped mouth, genu varus, flat valgus foot, and short nasal length. Details of the patient's genealogy are shown in Figure 1 and laboratory results are shown in Table 1 with no relevant alterations. The Neurology department confirmed language and neurocognitive developmental delay. An initial diagnosis of Williams syndrome was considered for which further genetic and cardiovascular studies (echocardiogram and DNA microarray) were requested. The echocardiogram reported a mild supravalvular aortic stenosis whereas the molecular analysis of complete exome sequencing (Table 2) described a heterozygous pathogenic SPEN gene, leading to a change in the initial diagnosis from Williams syndrome to Radio-Tartaglia Syndrome.

Ethical Approval

This study was conducted under the ethical principles of the Declaration of Helsinki to ensure the interests of the subjects OMB No. 0990-0279. Necessary information was provided, doubts were clarified and participants signed informed consents before starting the research.

Table 1. Laboratory studies and images taken from the patient and results

Study	Result
Brain Computed Tomography	Normal
Electroencephalogram	Normal
Lipid Profile	Normal
Electrolytes:Calcium and Phosphorus	Normal
Creatin Kinase	Normal
Karyotype	46, XY

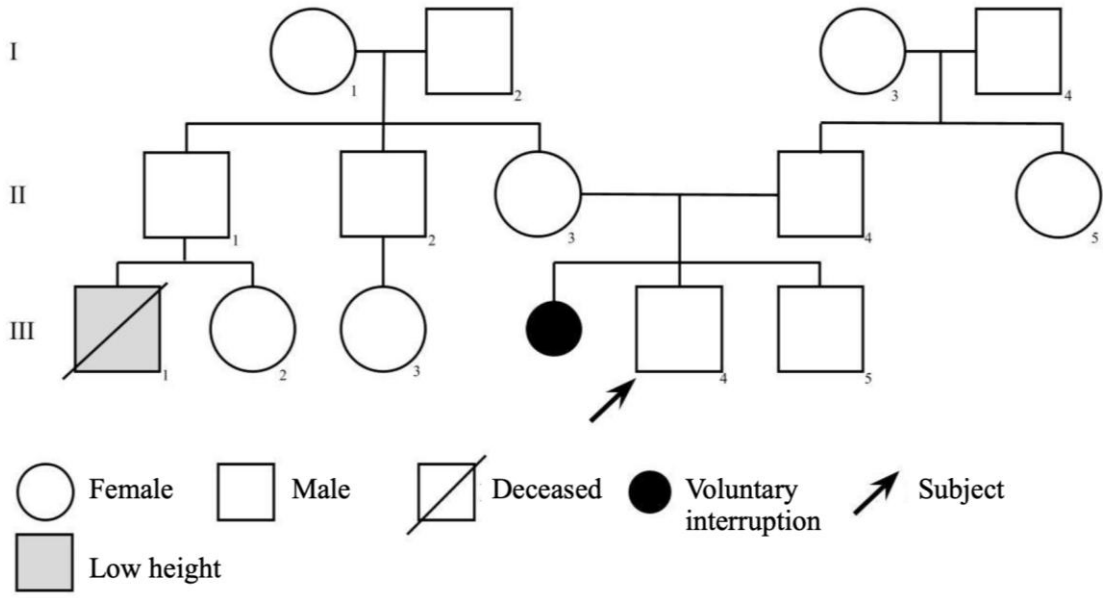

Figure 1: Genealogy of the patient

Table 2. Molecular analysis by exome sequencing

Diagnosis: Radio-Tartaglia Syndrome (RATARS)				
Gen	Position	Variation	Sequence	Copies
SPEN	chr1:15.928.739 - 15.928.741	TCA > T	p.Gln834Valfs*9 ENST00000375759	Heterocigosis (1 copy)

Discussion

The majority of genetic disorders that exhibit neurodevelopmental delay and intellectual disability at an early age must be determined by genetic sequencing. This is explained as advances in technology and the availability of high-resolution tests have demonstrated genetic heterogeneity between most genetic pathologies (4). The complexity in identifying promptly the pathology in this case report is influenced by the presence of only 45 cases of Radio-Tartaglia syndrome worldwide, making the establishment of a clear diagnosis challenging.

Mutations in chromosome 1p36 play a role in this genetic disorder, more commonly its terminal deletion which affects nearly 1 in 5000 born infants (1). Heterozygous truncated mutations in the SPEN gene in chromosome 1p36 are associated with Radio-Tartaglia syndrome (5). The SPEN gene is part of the tumor-suppressor gene family whose function is similar to that of the nuclear matrix as it organizes and integrates any transcriptional response that arrives at the cell (3). It is induced by hormones through interactions with other repressor genes, especially those involved in the remodeling of chromatin, histone deacetylases (HDAC), and the entrapment of transcriptional activators (4,6).

The SPEN gene has also been observed to play an important role in several processes in neuronal development. In rodent models, gene defects were found to produce a diminishment in brain mass, and a decrease in the thickness of the cerebral cortex and the hippocampus with subsequent ventriculomegaly (3, 4, 7, 8). In approximately 64% of cases of RATARS, important neurological abnormalities have been identified through imaging such as polymicrogyria, heterotopy, cerebellar atrophy, periventricular white matter abnormalities, corpus callosum agenesis, and tethered cord syndrome. Such neurological malformations entail clinical repercussions including developmental delay, psychiatric and behavioral abnormalities embarking autism spectrum disorder, aggressive behavior, and attention-deficit/hyperactivity disorder. Generalized hypotonia is present in 73% of cases, whilst oral motor abnormalities, gait ataxia, pyramidal signs, and seizures are expressed in a minority of cases (4).

A clinical study of 34 patients with RATARS, (Radio et al. (2021) diagnosed through genetic and Sanger sequencing in which heterozygous mutations of the SPEN gene (613484.0001-613484.0005) were reported. These mutations were found to not yet have been described in the gnomAD database as patients were verified through the GeneMatcher program (9) and DECIPHER database (10). The majority of the mutations occurred de *novo*, where there was no correlation between genotype and phenotype, and the methylation profile of the genome didn't show much difference between cells in the normal population compared to the patients in this clinical trial. There was a difference identified in chromosome X in which the role of the SPEN gene was suspected to influence in the inactivation and silencing of genes linked to this sex chromosome. This epigenetic finding, which manifests with syndromic characteristics, suggests a possible hallmark for the identification and classification of individuals with neurodevelopmental abnormalities. (4)

The haploinsufficiency of this gene contributes phenotypically in patients such as they present with craniofacial changes associated with frontal bossing secondary to delayed fontanelle closure, sunken eyes, broad, depressed nasal bridge, sharp jaw, micro/brachycephaly, and posteriorly rotated ears with low implantation (1,4). Despite phenotypical characteristics expressed in a high prevalence among patients with RATARS, the definitive diagnosis for this case report required genetic testing given the high rates of overlapping phenotypic and clinical features with other syndromes. (3, 4, 7, 8)

Williams syndrome is a fundamental differential diagnosis of RATARS. Notably, this syndrome was the first diagnostic impression in this case report until further additional exome sequencing was performed. Williams syndrome is an autosomal dominant multisystemic disorder caused by a microdeletion on chromosome 7q11.23, a region that contains 26 to 28 genes that include the ELN gene (11, 12). It consists of an array of signs and symptoms with phenotypic manifestations of dysmorphic facial features, intellectual disability, and arteriopathy.

Even though there are differences in etiology, the overlapping features between Williams and Radio-Tartaglia syndrome make a diagnosis based solely on clinical features poorly reliable. Supravalvular aortic stenosis is observed in approximately 70% of patients with Williams syndrome, a mild finding in this patient (13). This feature led to the first impression diagnosis of Williams given that RATARS's most common cardiac manifestations are focused on septal

defects, persistent ductus arteriosus or mitral regurgitation.

Both pathologies display developmental delay and intellectual disability as in this case report, which end up in psychiatric diagnoses such as ADHD, phobias, anxiety disorder, even aggressive behavior. The disorders mentioned above can be related to cerebral volume reduction in both diseases nonetheless, RATARS may express more complex neurological features such as polymicrogyria, cerebellar atrophy, corpus callosum agenesis, or tethered cord syndrome (4, 11). Axial hypotonia with peripheral hypertonia and increased deep tendon reflexes are typical of Williams syndrome whereas RATARS predominantly expresses generalized hypotonia with the presence of pyramidal symptoms and seizures.

As a final comparison point, facies from both Williams syndrome and RATARS are not distinctive, but suggestive of a genetic pathology. Williams syndrome has been described as having "elf-like" features with epicanthic folds, puffiness around eyes, small widely spaced teeth, small jaw,, and full cheeks (11,12,13). Whereas RATARS on the other hand presents with frontal bossing, telecanthus, arched elongated eyebrows, pointed chin, and dental abnormalities.

Conclusion

Radio-Tartaglia syndrome is an infrequent cause of neurodevelopmental delay and intellectual disability, associated with multiple systemic manifestations that share several characteristics with Williams syndrome as well as other genetic pathologies.

Because of its rare and low number of reported cases, the availability of information about the distinctive features of the disease is scarce, delaying prompt management, screening of associated conditions, and life expectancy. This challenges the necessity to further establish more clear parameters of the disease so that it does not go unnoticed.

Above all, the diagnosis of RATARS becomes a clear pillar for further investigation given the complexity level seen in this case: a patient with craniofacial dysmorphism and neurodevelopmental delay but normal laboratory analysis and brain images; a non-specific finding on the echocardiogram, leaving the child's diagnosis of RATARS to exome sequencing for a definitive diagnosis. Each patient's condition and symptoms are non-identical to each other hence this case report highlights the clear importance of genetic testing in the pathway to the diagnosis of rare diseases.

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Founding

No relevant financial relationship exists nor conflict of interests.

Conflicts of interest

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript..

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