Two new cases of brazilian boys presenting a Rett-like phenotype due to FOXG1*:* case report and literature review

Dois novos casos de rapazes brasileiros que apresentam um fenótipo Rett-like devido a FOXG1: relato de caso e revisão da literatura

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ABSTRACT
Rett syndrome (RTT) is a rare neurodevelopmental disorder usually affecting females. Most typical forms of RTT patients are hemizygous for pathogenic variants in *MECP2.*

FOXG1 syndrome is a rare and severe neurodevelopmental disorder with a broad spectrum of clinical features which could be described as RTT-like. In this paper we describe two non related patients who presented with developmental delay, microcephaly and hyperkinetic movements. One of them had epilepsy. Diagnosis was made by exome analysis and highlights an uncommon differential diagnosis in developmental delay in children.

Keywords: rett syndrome, neurodevelopmental disorders, epilepsy, FOXG1.

RESUMO
A síndrome de Rett (RTT) é uma doença rara do neurodesenvolvimento que afecta geralmente o sexo feminino. As formas mais típicas de doentes com RTT são hemizigóticas para variantes patogénicas na MECP2. A síndrome FOXG1 é uma perturbação do desenvolvimento neurológico rara e grave com um amplo espectro de características clínicas que podem ser descritas como semelhantes à RTT. Neste artigo descrevemos dois doentes não relacionados que apresentavam atraso no desenvolvimento, microcefalia e movimentos hipercinéticos. Um deles tinha epilepsia. O diagnóstico foi feito através da análise do exoma e destaca um diagnóstico diferencial pouco comum no atraso de desenvolvimento em crianças.

Palavras-chave: síndrome de rett, perturbações do neurodesenvolvimento, epilepsia, FOXG1.

1 INTRODUCTION

Most typical forms of RTT patients are hemizygous pathogenic to *MECP2* mutation. Atypical cases are associated with mutations in X-linked cyclin-dependent kinase-like 5 (*CDKL5;* Online Mendelian Inheritance in Man (OMIM) #300203) or Forkhead box G1 (*FOXG1*; OMIM #164874), but some remain undefined. (KYLE SM, 2018)

Neurodevelopmental disorders have a broad spectrum of diagnosis. Some clinical characteristics such as developmental delay or regression, microcephaly, movement disorders and epilepsy are not specific but could highlight specific diagnoses such as RTT and FOXG1 syndrome.

We report two boys presenting developmental delay, microcephaly and hyperkinetic movements due to pathogenic variant in *FOXG1*.

2 PATIENTS REPORTS

CASE 1

A 4-year-old boy, son of a consanguineous couple, was referred to our department for investigation of developmental delay. Term infant, vaginal delivery, Apgar score

performed at 1 and 5 minutes was 8. He remained hospitalized for 8 days due to neonatal jaundice, underwent phototherapy with good response. Mother with bleeding and urinary tract infection during pregnancy properly treated, serology and gestational ultrasound showed no changes. He has significant global developmental delay, both in motor, he hasn't seated without support, with impairment in cognitive acquisitions, communication and social interactions. Currently, he didn't acquired speech, with poor eye contact, and no epilepsy. He also presents uncoordinated movement and restlessness of the four limbs, characterized as hyperkinetic ballistic movements, without pathologic plantar reflex. He had microcephaly, prominent ears and feet valgus. He underwent tests for fragile X Syndrome, microdeletions or duplications, analysis of subtelomeric regions and amino acid profile, which were normal. The Brain Computed Tomography (CT) scan and Brain Magnetic Resonance Imaging (MRI) showed microcephaly, mild dilatation of the ventricular system and arachnoid cyst. Genetic testing showed a heterozygous pathogenic variant in *FOXG*1 G>T p.Arg230Leu. He had follow-up at the neurogenetics outpatient clinic of a public and tertiary children's hospital in northeastern Brazil.

CASE 2

A 12-years-old boy, child of a non-consanguineous couple, was sent to our department because of developmental delay, hyperkinetic movement disorder and epilepsy. He was born term by cesarean section, Apgar score was normal. He had no perinatal abnormalities. He acquired head control at 9 months old, he sat and spoke his first words at 12 months old ("papa", "mama"); at 15 months old he started to walk with support, he was capable to point out what he wanted and to clapped his hands and said "bye". His first seizure occurred at 20 months of age and it was characterized by tonic deviation of the gaze associated with a generalized tonic-clonic seizure, evolving to *status epilepticus*. After that he had developmental regression. We weren't able anymore to sit without support and have no head control. He presented with a severe motor impairment characterized by spastic quadriplegia of spastic and global dystonia. He has head circumference 46 centimeters (z score = <-2sd) and anterior sialorrhea. Brain MRI shows nonspecific T2 hypersignal in frontal gyri and parietal lobes, suggesting late demyelination and mild compensatory enlargement of the supratentorial ventricular system. Genetics testing showed a heterozygous pathogenic variant in FOXG1 AC>A p.His318Thrpfs*.

3 DISCUSSION

Since the first report in 1966 (RETT, A 1966), Rett syndrome (RTT) is recognized as a rare neurodevelopmental disorder usually affecting females, with prevalence of approximately 1 in 10,000–15,000(WONG, LC 2019). RTT is characterized by an apparently normal prenatal and perinatal period followed by a stagnation in development and a severe regression in language and motor skills. (NEUL 2010) The clinical features of typical RTT are neurodevelopmental regression at approximately 1 year of age, including acquired spoken language and hand skills, along with the development of repetitive hand stereotypies and gait impairment. (WONG, LC 2019)

For the diagnosis of typical RTT, individuals must present the four main criteria, established by Neul and cols in 2010.

Table 1: Diagnostic criteria Rett syndrome

DIAGNOSTIC CRITERIA RETT SYNDROME Adapted by Niel and cols
Required for typical or classic RTT 1. A period of regression followed by recovery or stabilization 2. All main criteria and all exclusion criteria 3. Supportive criteria are not required, although often present in typical RTT
Required for atypical or variant RTT 1. A period of regression followed by recovery or stabilization 2. At least 2 out of the 4 main criteria 3. 5 out of 11 supportive criteria
Main Criteria 1. Partial or complete loss of acquired purposeful hand skills. 2. Partial or complete loss of acquired spoken language 3. Gait abnormalities: Impaired (dyspraxic) or absence of ability. 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
Exclusion Criteria for typical RTT 1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems 2. Grossly abnormal psychomotor development in first 6 months of life
Supportive Criteria for atypical RTT 1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis

7. Growth retardation
8. Small cold hands and feet
9. Inappropriate laughing/screaming spells
10. Diminished response to pain
11. Intense eye communication - “eye pointing”

However, those with several clinical presentations that do not fulfill all the diagnostic criteria are classified as having atypical RTT. (NEUL, JL 2010)

Ariani F. and cols 2008 were responsible for associate *FOXG1* variant to Rett-like phenotype, later described as a *FOXG1* syndrome which has many overlapping features of typical RTT but with differences in disease onset and symptoms (ARIANI F, 2008*;* NEUL, JL 2010). Since the first individual with *FOXG1* syndrome described in 2005, there have been up to 100 variants of *FOXG1* identified (WONG LC 2019). *FOXG1*, located on chromosome 14q12 (chr14: 28,765,388-28,770,27; GRCh38/hg38) has one coding exon, 4890 bp and belongs to the forkhead (FOX) family of genes. It consists of a 489-amino-acid protein in humans and contains a highly conserved domain spanning from the forkhead binding domain (FBD) to the C-terminus and variable N-terminus (KUMAMOTO T 2017). *FOXG1* is expressed in a variety of nervous system cell types and tissues, including the cerebral cortex, telencephalon, inner ear, retina, olfactory epithelial cells, and other neural and sensory tissues in mammals (PAULEY S, 2006; SHEN W, 2019).

FOXG1 syndrome is a rare and severe neurodevelopmental disorder caused by heterozygous *de novo* mutations in the gene encoding the transcription factor Forkhead Box G1 (*FOXG1*). (AKOL L, 2022) The disorder comprises a complex constellation of clinical features, including severe postnatal microcephaly, deficient social reciprocity, combined stereotypies and dyskinesias, epilepsy, poor sleep patterns and unexplained episodes of crying. (VEGAS N, 2018; KORTUM F, 2011).

Mitter et al 2018 found in an analysis of 83 patients with FOXG1 syndrome that motor development was delayed in all patients, according to our patients. Also, affected patients have a more severe form of presentation than RTT patients with respect to ambulation, reciprocity, receptive language, sleep disorder and lacking regression. (PAPANDREOU A, 2016) Additionally, FOXG1 syndrome is associated with Autism Spectrum Disorders (ASD) and *FOXG*1 variants are identified in patients with ASD (MARIANI, J. 2015)

Hyperkinetic movement disorders, main clinical feature of cases presented, have been recognized to be a key feature in FOXG1 syndrome since its original description (PAPANDREOU A, 2016). A wide variety of movement disorders has been identified in patients with *FOXG1* variant, most commonly dystonia (76%), choreoathetosis (88%) and orolingual/facial dyskinesias (80%). Stereotypies are present in 50% of patients affected: mouthing of toys, grasping, nail biting and, rarely, midline wringing. (WONG, 2016).

Epilepsy is diagnosed in 68–87% of subjects with FOXG1-related disorders (SPAGNOLI, 2021; MITTER D, 2017) and it was presented in just one presented here. Seltzer et al 2014 showed that the mean age of diagnosis of epilepsy in *FOXG1* duplications is significantly younger than that in deletion or intragenic variants (7.4 months of age vs 22.3 months of age). Multiple seizure types (including generalized tonic-clonic, myoclonic, and complex partial seizures with or without generalization) have been associated with *FOXG1* variants (SELTZER LE, 2014). Epilepsy in FOXG1 patients are often refractory to medications, but status epilepticus is rare (WONG, 2016).

There is a described fenotipe-genotipe association, nevertheless due the few cases described in literature, this correlation cannot be well described. Patients with N-terminal mutations and *FOXG1* deletions showed the highest global severity scores, while those with frameshift and nonsense variants showed the lowest global severity scores. (VEGAS N, 2018; PAPANDREOU A, 2016). Patients with the missense and C-terminal domain mutations tended to have lower global severity scores. (VEGAS N, 2018).

FOXG1 affects the early phase of cortical development by regulating progenitor cell proliferation and differentiation in the neocortex and is considered a key promoter of neocortical lamination. (HANASHIMA C, 2002;) The brain MRI in individuals with *FOXG1* duplications is typically normal; however, nonspecific findings, such as mild brain atrophy, thin corpus callosum, and delayed myelination, have been reported. (KORTÜM F, 2011). In case series, there was a variable incidence of abnormalities in MRI that included mild to moderate hypoplasia and partial or complete aplasia of corpus callosum (67- 95,6%) as well as delayed myelination (56%). Cortical anomalies included mild to moderate simplified gyral pattern and pachygyria (64,4 - 72%) (VEGAS N, 2018, MITTER D, 2017). In presented cases brain MR showed no abnormalities. Intragenic variants or duplications/deletions of *FOXG1* gene have been reported in the neurodevelopmental disorder, initially classified as “congenital RTT variant”. (CELLINI, E 2015).

Lack of access to genetic testing is a barrier to several appropriate diagnoses in Brazil. Improvement of knowledge and easier access to genetic testing could lead to higher diagnosis rates of FOXG1 syndrome.

4 CONCLUSION

Both patients presented in this document present criteria for RETT syndrome. However, unlike the typical cases in which a mutation in *MECP2* is identified, we identified pathogenic variations in *FOXG1* heterozygosity, which corroborates the diagnosis and causality of the same in relation to the clinical manifestations described.

These two cases presented confirm the prediction that the congenital variant of Rett syndrome can also be found in males, with clinical characteristics similar to the syndrome classically described in girls by mutation in *MECP2* and *FOXG1* such as postnatal microcephaly, disorder of the hyperkinetic movement that can manifest with manual stereotypies, important neuropsychomotor delay including language, neuroimaging alterations. Therefore, *FOXG1* screening should be considered in male subjects with these clinical features.

These cases point to an unusual cause of developmental delay, microcephaly, and hyperkinetic movement disorders in boys, as well as contributing to the description of the FOXG1-related syndrome. More studies are needed for characterization and for a better understanding of the syndrome.

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