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X-Linked Adrenoleukodystrophy and Newborn Screening: an experience of extended screening for families in the city of São Paulo

AUTORES: Fernanda de Castro Monti Rabelo, Rodrigo Rezende Arantes, Bruna Glaucia Farah, Matheus Augusto Araújo Castro, Fabio Aires, Vanessa Catarine Silva Abreu Ribeiro dos Santos, Fernanda Aparecida Ronchi, Cristina Soares Ferreira, Vinícius de Morais Gomes, Luciana Regina Ruano Gaspar Garcia, Giselle Yuri Hayashi, Carlos Eugênio Fernandez de Andrade, Athenê Maria de Marco Mauro, Fernando Kok, Clarissa Bueno.

NOME DAS INSTITUIÇÕES: Instituto Jô Clemente (IJC), Faculdade de Medicina da Universidade De São Paulo e Secretaria Municipal De Saúde.

BACKGROUND

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal genetic disorder caused by mutations of the ABCD1 gene in which the central or peripheral system and adrenal cortex are involved. Males with X-ALD have a 30-35% risk of developing cerebral adrenoleukodystrophy until 12 years old, which can be prevented by early recognition and treatment, and an 80% lifetime risk of developing adrenal insufficiency. We describe the experience of the first 40 months in newborn screening in São Paulo city and the results of extended screening for families.

METHODS

Newborn screening was performed using tandem mass spectrometry, in which were analized C26:0, C26:0LPC and C24:0LPC. Second-tier testing with a next-generation sequencing (NGS) panel of genes carefully selected to confirm positive-screens. Genetic counseling was performed in all cases submitted to the genetic panel. Whenever a variant of unknown significance (VUS) was found, segregation in the mother or sibling and measurement of very long chain fatty acids (VCLFA) in blood were performed. Positive and indeterminate cases were referred to a dedicated outpatient clinic in a tertiary hospital. All positive cases are being monitored by international and research protocols.

RESULTS AND DISCUSSION

From May 2021 to December 2024, 302480 newborns were screened through the newborn screening program, and 46 (45 boys/ 1 girl) were referred to genetic confirmatory testing and genetic counseling.

A girl who presented a compatible biochemical profile already had seizures at birth and was diagnosed with the p.Ile370Asnfs*2 variant in the PEX1 gene.

A boy who underwent genetic testing was ruled out with variants in the ABCD1 gene but was diagnosed with XXYY syndrome, as an incidental finding.

Three patients had variants in the ABCD1 gene and had their families screened for other children at risk:

A copy number variation (CNV), a deletion of exons 6 to 10 classified as pathogenic, was identified. This boy had a 13-year-old brother under investigation for intellectual disability and the same variant was confirmed. The MRI showed a Loes score of 12 points and therefore, guidance was given to the parents.

The p.Met403Thr variant classified as LP was identified in a patient who is an only child and in his mother.

A VUS (p.Asp674His) was identified in a boy and his older 9-year-old brother who had increased VCLFA in the blood. Despite presenting adrenal alteration, this brother's MRI remains unchanged.

Discussion: This study highlights the importance of neonatal screening carried out within a program in which the screened newborn is guaranteed confirmatory exams, specialized monitoring, and adequate genetic counseling.

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