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CASE REPORT

Coffin Siris Syndrome associated with autism spectrum disorder and variant in arid1b.

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Abstract

Introduction: According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), the characteristics of Autism Spectrum Disorder (ASD) are defined as persistent impairment in reciprocal social communication and social interaction and restricted and repetitive patterns of behavior, interests or activities. Coffin-Siris syndrome (CSS) is a genetic condition characterized by classic dysmorphic features, developmental delays, and congenital anomalies. The variant in ARID1B is frequently linked to ASD and other neurodevelopmental disorders. **Objective:** To describe secondary ASD in a girl diagnosed with Coffin-Siris syndrome and establish the diagnosis through phenotype and genetic testing. **Case report:** Four-year-old girl presents neurological disorders (difficulties in communication, socialization and motor skills) and phenotypic characteristics (sparse hair, wide and flat nasal bridge, aplasia/ipoplasia of the nail of the fifth finger) and due to the clinical phenotype she was diagnosed with Syndrome de Coffin-Siris for medical genetics. The correct diagnosis enabled appropriate management of the patient. Therefore, we reinforce to pediatricians the importance of investigating this syndrome in cases of children who present neurodevelopmental disorders, accompanied by dysmorphia and language delay. **Conclusion:** Report that secondary autism is common in some genetic syndromes and emphasize the importance of diagnostic suspicion through phenotypic characteristics of ASD comorbid with a syndrome. This report highlights the importance and need for more research into the genetic background of these disorders to understand their complex etiology.

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INTRODUCTION:

Autism spectrum disorder (ASD) is defined as a neurodevelopmental disorder that manifests in the early years of life through behaviors that include challenges in social interaction, communication, and behavior.[1] The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* defines ASD as the occurrence of persistent impairments in communication and social interaction and the presence of restricted and repetitive patterns of behaviors, interests, or activities.[2]

The diversity of ASD, encompassing various subtypes and degrees of severity (levels 1 to 3), justifies its designation as a "spectrum."[1] Common impairments associated with ASD include intellectual disability (ID) (currently estimated in about 30% of cases) and attention deficit (occurring in about 30-40% of cases), as well as hypo- and/or hypersensory sensitivity, anxiety, depression, sleep disorders, motor skill delays, among others.[3]

Due to this great clinical heterogeneity, the presence of multiple signs, symptoms, and associated comorbidities, ASD can be considered a syndrome and not a disease per se, as it may have multiple etiologies. The term *syndromic autism* or *secondary autism* is used, therefore, to refer to cases of ASD that have a defined cause, as opposed to idiopathic autism, whose cause remains unknown. In this regard, a complementary investigative method that has stood out in determining the etiology of ASD is neurogenetic investigation.[3] One of the risk genes for ASD is ARID1B.[4]

Coffin-Siris syndrome (CSS) is a rare, clinically and genetically heterogeneous disease. Some reports have shown a ratio of four affected females to one male, with a prevalence of < 1/1,000,000 people.[5] It is characterized by classic dysmorphic features, developmental delays, and systemic anomalies. Genes in the BRG1-associated factor (BAF) complex have been shown to be causative, including *ARID1A* and *ARID1B*.[6] The most relevant mutation is in the *ARID1B* gene, accounting for up to 76% of CSS cases.[7]

In terms of its pathophysiology, CSS is caused by alterations in genes that encode the subunit of the SWI/SNF complex, known as the BAF (BRG1-associated factor) complex. Its function is chromatin remodeling, repairing DNA (deoxyribonucleic acid) that presents errors, i.e., it monitors all stages of cell duplication.[5]

In this context, *ARID1B* is a member of the switch/sucrose non-fermentable (SWI/SNF) complex responsible for chromatin remodeling, and it is highly expressed in the brain and embryonic stem cells. This complex is divided into Brahma-associated factor (BAF) and Polybromo-Brahma-associated factor (PBAF). Germline mutations in SWI/SNF complex subunits have been associated with autism spectrum disorder and neurodevelopmental disorders.[8]

Due to these mutations, individuals present with aplasia or hypoplasia of the distal phalanx or nail of the fifth digit and additional digits ("fifth digit syndrome"), phenotypic characteristics such as thick eyebrows, long eyelashes, broad nasal bridge, wide mouth with thick and everted upper and lower lips, abnormal position or shape of the ears, hirsutism, sparse hair, joint laxity, hypertrichosis, and moderate to severe intellectual disability. Congenital anomalies may include malformations of the cardiac, gastrointestinal, genitourinary, and/or central nervous systems (including Dandy-Walker variant, gyral simplification, and agenesis of the corpus callosum).[5]

Disorders caused by *ARID1B* are described as a spectrum that includes syndromic or nonsyndromic cases of ASD, ID, and CSS.[9] Although the overall prevalence is unknown, individuals with *ARID1B*-related disorders are also at increased risk for attention deficit hyperactivity disorder (ADHD) and epilepsy.[10]

After the discovery of *ARID1B* mutations as a monogenic cause of ID and ASD, preclinical research examining the neurobiological and developmental functions of the *ARID1B* gene accelerated. Recently developed mouse models of *ARID1B* variants successfully demonstrated many of the behavioral phenotypes of ASD and ID.[10]

The *ARID1B* variant is a frequent cause of intellectual disability (ID), autism spectrum disorder (ASD), and emotional disorders.[10] In 2010, a mutation in this gene was found in a patient who presented with agenesis of the corpus callosum, intellectual disability, and features of autism spectrum disorder.[11] Shortly thereafter, a separate research group identified eight additional patients with similar symptoms caused by *ARID1B* variants.[12] Since then, several studies have further validated and defined the important role of *ARID1B* mutations in neurodevelopmental disorders.[10]

Celen et al. (2017)[12], Shibutani et al. (2017)[13], and Jung et al. (2017)[14] recently developed mouse models with *ARID1B* variants. Two groups generated heterozygous mice by removing exon 5 of the *ARID1B* gene, while the other group removed exon 3. All methods resulted in frameshift mutations and loss of function of one gene copy. Each group conducted a variety of assays to characterize the following behavioral phenotypes: severe limitations in cognitive function, deficits in social interaction and communication, as well as repetitive and stereotyped behaviors.[12-14]

The results of these three studies showed that *ARID1B* heterozygous mice displayed most of the behavioral phenotypes seen in ASD and ID, thus providing a useful tool to advance and better understand the underlying pathology of these disorders.[12-14]

The findings of these studies highlight the crucial role that the *ARID1B* gene plays in normal brain development and behavior. Mutations in this gene cause developmental disorders, including ID, CSS, and ASD, as well as corpus callosum abnormalities. These discoveries further support the hypothesis that deficits in chromatin remodelers play a significant role in neurodevelopmental disorders.[10]

CASE REPORT

Female, three years old, daughter of healthy, non-consanguineous parents. Born by cesarean section, full-term, birth weight 3.6 kg, 52 cm in length, 37 cm head circumference, and Apgar scores of 8/10 (1st and 5th minutes of life). At birth, the first characteristics observed were neck hyperextension, hypotonia, weak sucking activity, and absence of the walking reflex. Brain magnetic resonance imaging showed partial dysgenesis of the corpus callosum associated with mild hypertrophy of the anterior commissure and subtle dysmorphism of the frontal horns of the lateral ventricles.

Regarding the child's development, she walked at 18 months and spoke her first words at two years of age, which caused concern for her parents. Evaluated by a pediatric neurologist, psychomotor developmental delay was noted, with significant difficulties in communication, socialization, and motor skills. The Childhood Autism Rating Scale (CARS) was applied, showing a score of 29 (borderline value). At two years and four months of age, she presented generalized tonic-clonic seizures, and treatment with sodium valproate was started. Electroencephalogram demonstrated epileptiform activity with generalized polyspike-and-wave complexes.

These findings correspond to known phenotypes of ARID1B-related disorders. In a study of 143 patients with an ARID1B spectrum, it was shown that both patients with ARID1B-CSS and those with ARID1B-ID presented autistic traits in more than 55% of cases. More than 83% of patients in both groups had impairments in social communication (19.7%), presence of repetitive (15.5%) and restricted (8.5%) patterns of behaviors, interests, or activities. Thus, the role of the ARID1B gene in normal brain development and behavior is recognized.[4]

On current physical examination, the child presented with sparse hair, facial features including thick eyebrows, long eyelashes, mild hypertrichosis, broad and flattened nasal bridge, wide mouth with slightly thick and hypotonic upper and lower lips, sialorrhea and difficulty with chewing movements, flat valgus feet, and aplasia/hypoplasia of the nail of the fifth digit. Due to the clinical phenotype, she received a diagnosis through medical genetics. Exome sequencing revealed a de novo heterozygous pathogenic variant (class 5) in the ARID1B gene, confirming the diagnosis. In some cases, the clinical presentation provides precise criteria for diagnosis. The gold standard for diagnosing syndromes leading to neurodevelopmental disorders is exome sequencing; however, this test is still very costly, which can make it inaccessible to many genetic centers.

Diagnosis may be delayed due to the absence of phenotypic features at birth, with physical characteristics becoming more evident as the child develops. This case reports a child with an early diagnosis and immediate initiation of treatment. It is noteworthy that early intervention therapies can result in significant gains in children's neuropsychomotor development. The earlier neurodevelopmental alterations are detected, the greater the neural organization capacity through neuroplasticity and the potential for cerebral myelination. Synaptic formation is faster and produces more satisfactory results in the early years of life. Moreover, early stimulation takes advantage of the windows of opportunity in the child's brain.

DISCUSSION

Autism Spectrum Disorder (ASD) and ASD-related characteristics may occur as part of certain genetic conditions, thus differing from primary ASD. The increase in ASD prevalence rates underscores the importance of investigating the syndrome's etiology. Approximately 20% of children with ASD will have a diagnosable genetic syndrome. Early detection of phenotypic characteristics and accurate, timely diagnosis, in combination with intervention, can benefit these children's development, quality of life, and social inclusion. Genetic consultation can help identify genetic syndromes and other morbidities frequently associated with ASD.

REFERENCES

1. Pereira D A. Tópicos Obrigatórios em Pediatria: diagnóstico por pediatras do Transtorno do Espectro do Autismo (TEA): um papel crucial na detecção precoce e intervenção adequada. Resid Pediatr. 2024;14(3): DOI: 10.25060/residpediatr-2024.v14n3-1264.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
3. Lin J, Antune FC, Mazzucchett L, da-Cost MA, Gonçalves CL. Investigação citogenética e molecular de casos de autismo atendidos em um ambulatório universitário no sul do Brasil. Resid Pediatr. 2023;13(1): DOI: 10.25060/residpediatr-2023.v13n1-638.
4. Jahnke-Majorkovits AC, Fauth C, Gander M, Sevecke K. Treatment of psychiatric comorbidities and interaction patterns in Coffin-Siris syndrome: A case report of a 4-year-old girl. Clin Case Rep. 2024 Feb 2;12(2):e8230. doi: 10.1002/ccr3.8230. PMID: 38314187; PMCID: PMC10837036.
5. Gritti, V. C.; Vieira, M. H.; Dorgievicz, V.; Habermann, M. A. M.; Bellaver, E. H. Coffin-Siris syndrome: a case report. Research, Society and Development, *[S. l.]*, v. 11, n. 15, p. e467111537637, 2022. DOI: 10.33448/rsd-v11i15.37637.
6. Vasko A, Drivas TG, Schrier Vergano SA. Genotype-Phenotype Correlations in 208 Individuals with Coffin-Siris Syndrome. Genes (Basel). 2021 Jun 19;12(6):937. doi: 10.3390/genes12060937. PMID: 34205270; PMCID: PMC8233770.
7. Figueira, Heliton & Medina, Pollyanna & Jesus, Giorge & Hanan, Aida & Sponchiado Júnior, Emilio Carlos & Hanan, Simone. (2021). Oral findings in Coffin-Siris syndrome: A case report. Revista Portuguesa de Estomatologia, Medicina Dentária e Cirurgia Maxilofacial. 62. 10.24873/j.rpemd.2021.03.826.
8. Bramswig NC, Caluseriu O, Lüdecke HJ, Bolduc FV, Noel NC, Wieland T, Surowy HM, Christen HJ, Engels H, Strom TM, Wieczorek D. Heterozygosity for ARID2 loss-of-function mutations in individuals with a Coffin-Siris syndrome-like phenotype. Hum Genet. 2017 Mar;136(3):297-305. doi: 10.1007/s00439-017-1757-z. Epub 2017 Jan 25. PMID: 28124119.
9. Van der Sluijs PJ, Jansen S, Vergano SA, Adachi-Fukuda M, Alanay Y, AlKindy A et al. The ARID1B spectrum in 143 patients: from nonsyndromic intellectual disability to Coffin-Siris syndrome. Genet Med. 2019 Jun;21(6):1295-1307. doi: 10.1038/s41436-018-0330-z. Epub 2018 Nov

8. Erratum in: Genet Med. 2019 Sep;21(9):2160-2161. doi: 10.1038/s41436-018-0368-y. PMID: 30349098; PMCID: PMC6752273.

10. Moffat JJ, Smith AL, Jung EM, Ka M, Kim WY. Neurobiology of ARID1B haploinsufficiency related to neurodevelopmental and psychiatric disorders. Mol Psychiatry. 2022 Jan;27(1):476-489. doi: 10.1038/s41380-021-01060-x. Epub 2021 Mar 8. PMID: 33686214; PMCID: PMC8423853.

11. Halgren C, Kjaergaard S, Bak M, Hansen C, El-Schich Z, Anderson CM, et al. Corpus callosum abnormalities, intellectual disability, speech impairment, and autism in patients with haploinsufficiency of ARID1B. Clin Genet. 2012 Sep;82(3):248-55. DOI: https://doi.org/10.1111/j.1399-0004.2011.01755.x.

12. Celen C, Chuang JC, Luo X, Nijem N, Walker AK, Chen F, et al. Arid1b haploinsufficient mice reveal neuropsychiatric phenotypes and reversible causes of growth impairment. Elife. 2017 Jul 11;6:e25730. DOI: https://doi.org/10.7554/eLife.25730.

13. Shibutani M, Horii T, Shoji H, Morita S, Kimura M, Terawaki N, Miyakawa T, Hatada I. Arid1b Haploinsufficiency Causes Abnormal Brain Gene Expression and Autism-Related Behaviors in Mice. Int J Mol Sci. 2017 Aug 30;18(9):1872. doi: 10.3390/ijms18091872. PMID: 28867767; PMCID: PMC5618521.

14. Jung EM, Moffat JJ, Liu J, Dravid SM, Gurumurthy CB, Kim WY. Arid1b haploinsufficiency disrupts cortical interneuron development and mouse behavior. Nat Neurosci. 2017 Dec;20(12):1694-1707. doi: 10.1038/s41593-017-0013-0. Epub 2017 Nov 6. PMID: 29184203; PMCID: PMC5726525.