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A Distinctive Feature of Coffin-Siris Syndrome: a Unique Clinical Case

Um achado distinto na Síndrome de Coffin-Siris: Um Caso Clínico Único

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Abstract

Dandy-Walker malformation (DWM) is a rare congenital malformation of the central nervous system in the posterior fossa, revealing hypoplasia or agenesis of the cerebellar vermis, upward rotation of cerebellar tentorium, and cystic enlargement of the 4th ventricle. Majority of cases are sporadic, but some result from Mendelian disorders, such as Coffin-Siris Syndrome (CSS). CSS includes intellectual disability, facial dysmorphism, congenital malformations and 5th digit nail or distal phalanx hypoplasia or aplasia, in some cases DWM. Our case presents a pregnant woman with prenatal malformations fitting CSS with DWM and complete agenesis of both 5th toes, not yet reported in literature.

Keywords: Dandy-Walker malformation; Coffin-Siris Syndrome; Prenatal evaluation.

Resumo

A malformação de Dandy-Walker (MDW) é uma malformação congénita rara do sistema nervoso central que afeta a fossa posterior caracterizada pela hipoplasia ou agenesia do vérmis do cerebelo, rotação superior do tentório do cerebelo, e pela dilatação quística do 4.º ventrículo. A maioria dos casos é esporádico, mas alguns podem resultar de doenças mendelianas, como a Síndrome de Coffin-Siris (SCS), A SCS caracteriza-se por uma perturbação do desenvolvimento intelectual, dismorfias faciais, malformações congénitas e hipoplasia ou aplasia da unha ou da falange distal do 5.º dedo, e nalguns casos MDW. Apresentamos o caso de uma grávida com malformações pré-natais compatíveis com SCS, porém com agenesia completa bilateral dos quintos dedos dos pés, uma alteração fenotípica ainda não descrita na literatura.

Palavras-chave: Malformação de Dandy-Walker; Síndrome de Coffin-Siris; Avaliação pré-natal.

INTRODUCTION

Dandy-Walker malformation (DWM) is a rare complex malformation of the nervous system involving the posterior fossa and cerebellum, with an estimated incidence of 1 in 10,000 to 30,000 births. The "classic triad" of DWM is defined by a complete or partial agenesis of the vermis, an enlargement of the posterior fossa with the upward displacement of the tentorium, transverse sinus, and torcular; and a cystic dilation of the fourth ventricle[1-5].

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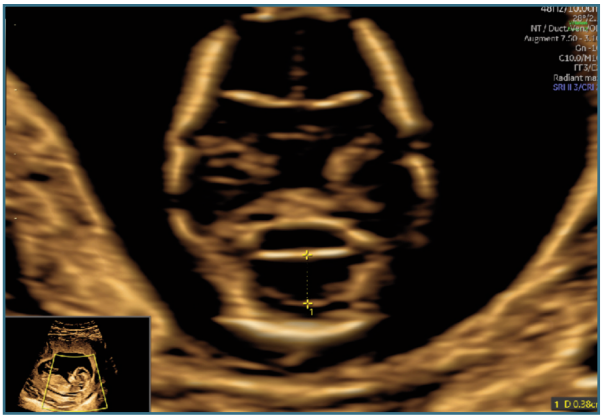

FIGURE 1. Ultrassonographic evaluation performed at 12 weeks and 4 days showing an enlarged fourth ventricle.

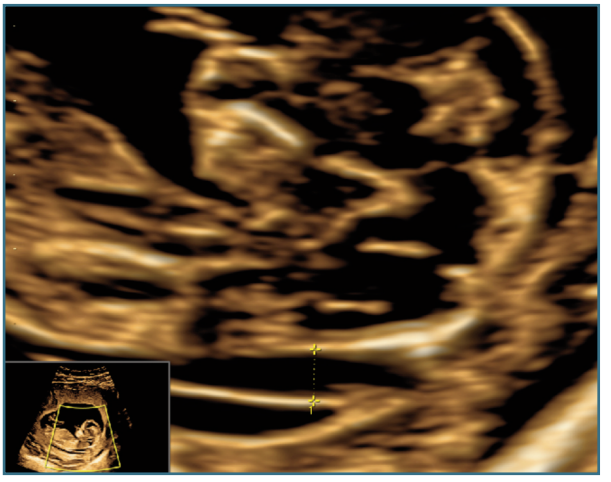

FIGURE 2. Ultrassonographic evaluation performed at 12 weeks and 4 days showing the midsagittal plan with an enlarged fourth ventricle and a suspected retrognathia.

Its etiology is multifactorial. Most cases occur sporadically without a known cause, but other factors, including environmental and genetic factors, can be responsible for causing this malformation. Coffin-Siris Syndrome (CSS) is a rare genetic disorder caused by pathogenic or likely pathogenic variants in one of several genes. Variants in the *ARID1B* gene are the most common known cause of the condition, following an autosomal dominant pattern of inheritance. The condition is not usually inherited from an affected parent but arises from new *(de novo)* variants in the gene that can occur at different developmental stages: pre-zygotically, in a parental gamete, or post-zygotically, the latter due to early embryonic mitotic error possibly resulting in somatic mosaicism[6,7].

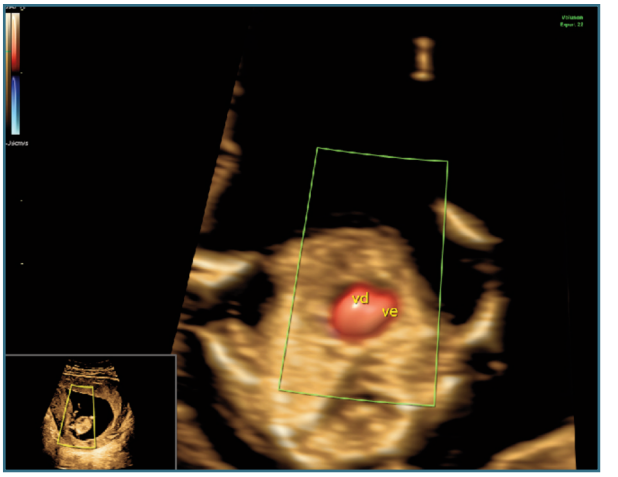

FIGURE 3. Ultrassonographic evaluation performed at 12 weeks and 4 days showing a suspected interventricular septal defect (vd: right ventricle, ve: left ventricle).

The signs and symptoms in CSS are variable. The hallmarks of this condition include developmental disability, from mild to severe intellectual disability or delayed development of speech and motor skills, abnormalities of the fifth fingers or toes (including aplasia or hypoplasia of the distal phalanx or nail) and characteristic dysmorphic features. Prenatally, the findings may be absent or few and nonspecific[8].

We present a case of a pregnant woman followed at our hospital with prenatal malformations fitting CSS who had a thorough radiological, genetic, and pathological evaluation.

CLINICAL CASE

A 31-year-old primigravida presented for a scan at 12 weeks and 4 days revealing nuchal translucency above the 99th percentile, absent nasal bones and an enlarged fourth ventricle (Figures 1 and 2), single umbilical artery, and a suspected ventricular septal defect (Figure 3). Chorionic villus sampling was performed with normal chromosomal microarray results. On the 17 weeks and 6 days scan, the 4th ventricle and the cisterna magna were enlarged (Figure 4), the cerebellar vermis was not identified, and there was an upward elevation of the tentorium, compatible with DWM, in addition to

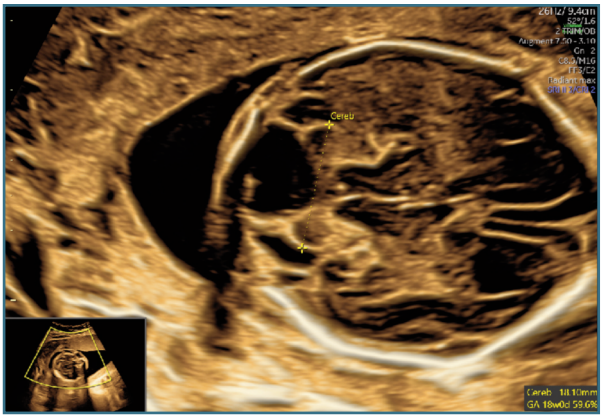

FIGURE 4. Ultrassonographic evaluation performed at 17 weeks and 6 days showing an enlarged fourth ventricle and cisterna magna, and a non identified vermix of cerebellum.

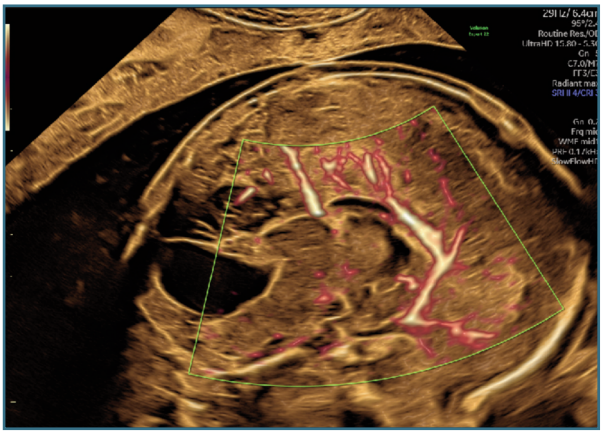

FIGURE 5. Ultrassonographic evaluation performed at 17 weeks and 6 days showing a suspected agenesis of the corpus callosum with an abnormal pericallosal artery.

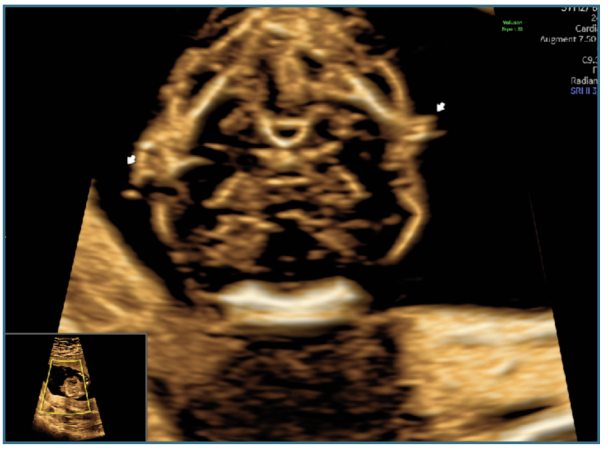

FIGURE 6. Ultrassonographic evaluation performed at 17 weeks and 6 days showing dysmorphic facial features (hypoplasia of the right ear).

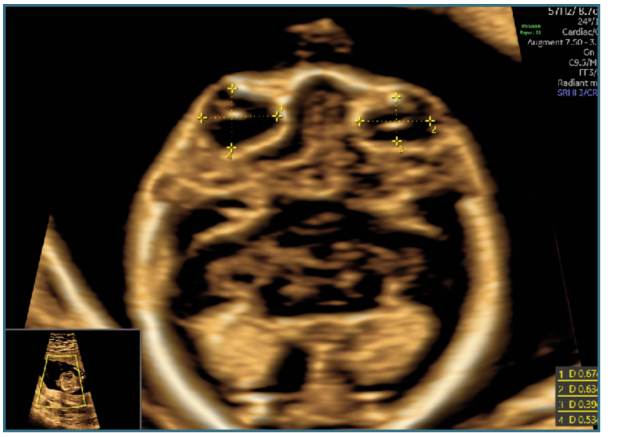

FIGURE 7. Ultrassonographic evaluation performed at 17 weeks and 6 days showing dysmorphic facial features (asymmetry of ocular globes).

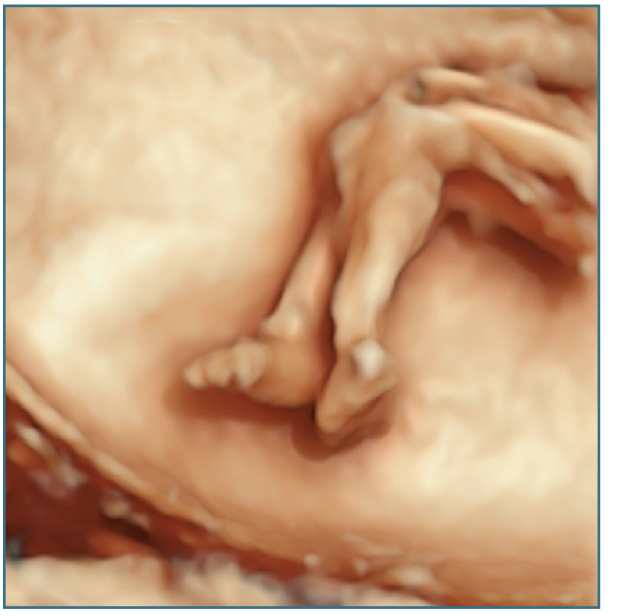

FIGURE 8. Three-dimensional ultrassonographic evaluation performed at 17 weeks and 6 days showing bilateral clubfeet.

a suspected agenesis of the corpus callosum (Figure 5) and dysmorphic facial features – hypoplasia of the right ear (Figure 6), asymmetry of ocular globes (Figure 7), retrognathia (Figure 2). Other findings, such as bilateral clubfeet (Figure 8), single umbilical artery (Figure 9) and ventricular septal defect were also present.

After a multidisciplinary meeting and a thorough counseling including members from the Obstetric and Genetics Departments, a termination of pregnancy was

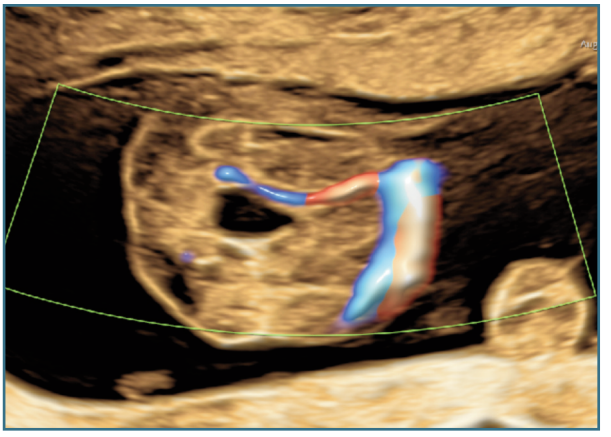

FIGURE 9. Ultrassonographic evaluation performed at 17 weeks and 6 days showing a single umbilical artery.

requested by the couple. The fetus was sent for pathological evaluation.

On fetal autopsy, a male fetus with an estimated gestational age of 17-18 weeks presented with multiple craniofacial, cardiac, and urinary congenital anomalies. Externally, the fetus had notable craniofacial findings included low-set ears (left posteriorly rotated and right hypoplastic), fused and downward-slanting palpebral fissures, hypertelorism, a hypoplastic nasal bridge with anteverted nostrils, a long philtrum, thin upper lip, complete median cleft palate, short lingual frenulum, and microretrognathia. Limb anomalies included bilateral syndactyly of the second to fifth fingers, with complete agenesis of the 5th finger of both toes, and bilateral clubfeet. Internally, the heart was rounded with a prominent interventricular groove, revealing a ventricular septal defect and right ventricular hypoplasia. The ventriculoarterial connection was normal, with confluence of the pulmonary artery branches. The kidneys were hypoplastic and the bladder was enlarged. Regarding central nervous system, the cerebellum was hypoplastic with non-identifiable cerebellar vermis, the corpus callosum was absent, and an enlarged cisterna magna was acknowledged.

Genetic evaluation through trio-whole exome sequencing (WES) identified a *de novo* heterozygous frameshift variant in *ARID1A* (NM_006015.6): c.31_56del (p.Ser11fs), classified as likely pathogenic and associated with Coffin-Siris syndrome-2 (OMIM# 614607)[9,10].

DISCUSSION

This case underscores the importance of a multidisciplinary approach, and the value of trio-WES, in the etiological diagnosis of fetuses with multiple congenital malformations. Genetic counselling was offered to the couple, regarding the low risk of recurrence and the possibility of prenatal diagnosis in future pregnancies, since *de novo* variants can have a small risk of parental germline gonadal mosaicism.

To our knowledge, this is the first report of complete agenesis of both 5th toes, which is a more extreme presentation than the usual limb defects.

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CONFLICT OF INTEREST

Authors declare they have no conflicts of interest.

INFORMED CONSENT

The patient gave informed consent for publication.

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