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AGENESIS OF CORPUS CALLOSUM, CARDIAC, OCULAR, AND GENITAL SYNDROME. CASE REPORT

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Palabras clave: Malformaciones del Sistema Nervioso; Agenesia del Cuerpo Calloso; Tetralogía de Fallot; Anomalías Craneofaciales; Megalencefalia; Hidrocefalia; Cadherinas.

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RESUMEN

Introducción. El estudio etiopatogénico de las malformaciones tanto mayores como menores, así como su identificación, son requisito indispensable para el pediatra ya que es el médico de primer contacto en la atención natal y postnatal de gran parte de los recién nacidos. El síndrome genital, ocular, cardiaco y de agenesia del cuerpo calloso (ACOGS por sus siglas en inglés) es una entidad compleja y de muy baja incidencia, causada por mutaciones del gen *CDH2* en el cromosoma 18q12. Las anomalías de esta patología se pueden expresar en varios sistemas: a nivel ocular con complicaciones como la anoftalmia y la microftalmia, a nivel cardiaco puede presentar problemas en la comunicación interventricular y a nivel cerebral se pueden presentar patologías como la ventriculomegalia, la agenesia del cuerpo calloso, entre otras.
Presentación del caso. Recién nacido con antecedente prenatal de macrocefalia diagnosticada por ultrasonido pélvico, quien es remitido al Servicio de Pediatría de una institución de segundo nivel de complejidad en la ciudad de Acapulco (México) por dificultad respiratoria. A su ingreso se identificó macrocefalia, soplo cardiaco y criptorquidia, además de dificultad respiratoria manejada con fase ll de ventilación. Se realizó ultrasonido transfontanelar y tomografía axial de cráneo, cuyos hallazgos fueron coincidentes con agenesia del cuerpo calloso, hidrocefalia e hipoplasia cerebelar. En el ecocardiograma realizado se identificó una Tetralogía de Fallot. Dichos resultados, sumados al conjunto de anomalías encontradas, fueron consistentes con ACOGS.
Conclusión. El ACOGS es un conjunto heterogéneo y poco común de malformaciones mayores recientemente descrito en la literatura, que se debe sospechar en aquellos pacientes con alteraciones cardiacas, genitales y del tubo neural.

ABSTRACT

Introduction: The etiopathogenic study of major and minor malformations, as well as their identification, is imperative for pediatricians since they are the first contact physicians in the natal and postnatal care of most newborns. The agenesis of corpus callosum, cardiac, ocular, and genital syndrome (ACOGS) is a complex disorder with a very low incidence, caused by mutations of the *CDH2* gene on chromosome 18q12. The anomalies associated with this condition can be found in several systems: anophthalmia and microphthalmia in the eye, problems in the ventricular septal defect in the heart, and problems in the brain such as ventriculomegaly, agenesis of the corpus callosum, among others.
Case presentation: A newborn with a prenatal history of macrocephaly diagnosed by pelvic ultrasound was referred to the pediatrics service of a secondary care institution in the city of Acapulco (Mexico) due to respiratory distress. On admission, macrocephaly, heart murmur, and cryptorchidism were observed, in addition to respiratory distress that was managed with phase 2 ventilation. Transfontanelar ultrasound and axial tomography of the skull were performed, with findings consistent with agenesis of the

corpus callosum, hydrocephalus, and cerebellar hypoplasia. In the echocardiogram performed, a tetralogy of Fallot was identified. These results, together with all the anomalies found, were consistent with ACOGS.
Conclusion: ACOGS is a heterogeneous and uncommon group of major malformations recently described in the literature, which should be suspected in patients with cardiac, genital, and neural tube defects.

INTRODUCTION

The study and identification of malformations, both major and minor, are fundamental requirements for all pediatric medical personnel, as proper identification of these malformations will allow establishing a therapeutic approach in a timely manner. Likewise, the study of these malformations should focus on the review of existing information about the associations or characteristic phenotypes of specific syndromes, as in the case of Down syndrome (Trisomy 21), in which Hall's criteria are considered to establish the suspicion of the disease, or in the review of physical features or defects, such as type 1 shortening of the nasolabial fold (thin upper lip) that children with fetal alcohol syndrome exhibit (1,2).

Central nervous system (CNS) malformations are the leading cause of disability of higher neurological and developmental functions in children. Although they are usually not accompanied by craniofacial abnormalities, alterations in the shape of the head and skin lesions over the dorsal midline are a sign of CNS-associated anomalies (3). As in the case of encephalic malformations, there are other genital conditions, such as cryptorchidism, that are common in several syndromes such as prune belly syndrome (4) and complex cardiopathies.

The following is the case of a newborn with a diagnosis of ACOGS identified at a secondary care hospital.

CASE PRESENTATION

A 48-hour-old newborn was admitted to the pediatric emergency department of a secondary care hospital in the city of Acapulco (Mexico) after being born in the labor and delivery department. His medical records reported a 29-year-old mother and a 27-year-old father, apparently healthy, with 2 children aged 7 and 4 years old, also healthy. Both parents had a basic education and a low socioeconomic status, and came from Coahuayutla, Guerrero (Mexico), a settlement with a population of approximately 1300 inhabitants.

The mother received prenatal care from the second month of gestation at a local hospital and reported taking folic acid and ferrous sulfate during pregnancy. While pregnant, she presented pelvic inflammatory disease and was treated with vaginal suppositories. It was also reported that macrocephaly had been observed in the fetus in the fifth and last gestational sonogram performed.

The baby was born in a rural community hospital due to failure to thrive. His Apgar score was 8 at 1 minute after birth and 9 at 5 minutes. The Silverman-Anderson severity test yielded a score of 0. Due to weak suction, and because there were not enough supplies in the secondary care unit, he was referred 6 hours after birth to the Hospital General de Acapulco, a secondary care institution.

On admission, stage 2 ventilation with continuous positive airway pressure was initiated due to the patient's respiratory distress. Upon physical examination, a grade 2 holosystolic murmur in the area of auscultation of the mitral valve was detected, so it was decided to perform a chest X-ray 4 hours after admission (Figure 1), which revealed a raised cardiac apex located to the left, excavated pulmonary artery, severe dilatation of the right atrium, and decreased pulmonary vasculature. A 12-lead electrocardiogram was also performed, showing sinus rhythm with right axis deviation and tall R wave in V1.

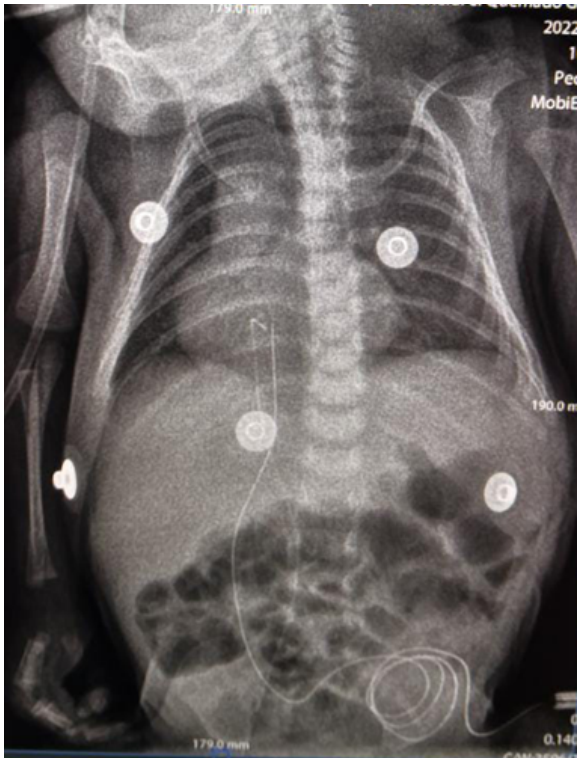

Figure 1. Anteroposterior chest X-ray. Decreased pulmonary vasculature and a cardiothoracic ratio >0.6 were observed, which was defined as cardiomegaly. Dilatation of the right heart cavity and cardiac silhouette with boot-shaped morphology were also evident.

Source: Image obtained while conducting the study.

Furthermore, given the macrocephaly, wide anterior and posterior fontanels (6x6cm and 2x2cm respectively) and perinatal history, a computed tomography (CT) scan of the brain was performed 24 hours after admission (Figures 2 and 3),

showing hydrocephalus with dilation of the fourth ventricle and hypoplasia of the cerebellar tentorium. Therefore, a medical consultation with the neurosurgery department was requested 2 hours after receiving the results of the CT scan. Taking into account the imaging findings, the neurosurgery department decided to perform a ventriculoperitoneal shunt.

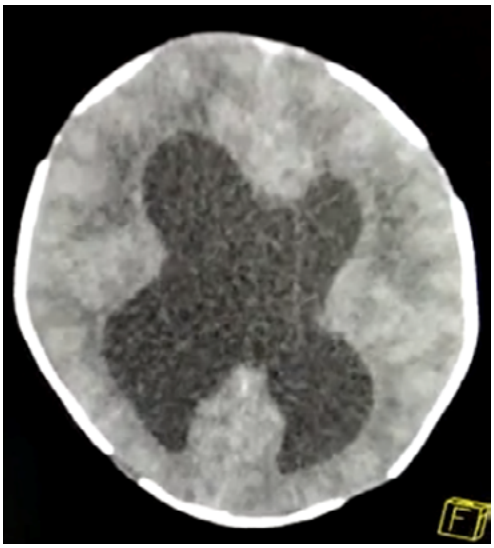

Figure 2. Transverse CT scan of the skull. Large dilatation of the lateral ventricles can be seen.

Source: Image obtained while conducting the study.

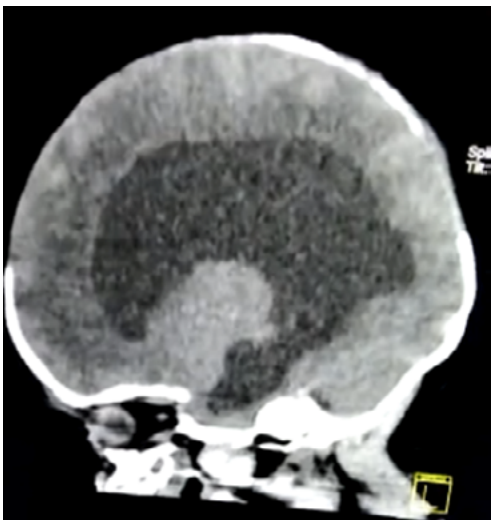

Figure 3. Longitudinal CT scan of the skull, parietal region. There is evidence of significant dilatation of the first, second, and third ventricle.

Source: Image obtained while conducting the study.

On the fourth day of hospitalization, a conventional echocardiogram was performed, revealing levocardia with left cardiac apex, atrial situs solitus, atrioventricular concordance, and left ventricular hypertrophy. Moreover, a 10mm interventricular septal defect and a mixed left-to-right shunt were observed. Pulmonary artery pressure was 7mm with a maximum gradient of 35 mmHg, and aortic overriding was 50%. A small patent ductus arteriosus was also observed. In view of these findings, tetralogy of Fallot (TOF) was suspected.

Throughout his hospital stay, the pediatrics service made an assessment of a large number of anomalies found: prominent forehead, low-set ears, sunken eyes with entropion, thin lips and low palpebral fissures, hypoplasia of the rectus abdominis muscles, and bilateral cryptorchidism. It was initially considered that the patient could have prune belly syndrome, also referred to as Eagle-Barrett syndrome; however, this idea was ruled out after identifying TOF and agenesis of the corpus callosum (detected on CT), alterations that are not typical of prune belly syndrome given that they are major malformations on their own.

Given these findings, the patient was reclassified with a dysmorphic syndrome under study. After an exhaustive literature review in books on genetics, dysmorphology and pediatrics, ACOGS was established as the condition seen in the neonate, which is actually a newly described disorder.

On the tenth day of hospital stay, oxygen therapy was completely withdrawn. It was therefore decided to refer him to a pediatric specialty hospital for comprehensive surgical treatment of complex heart disease and congenital hydrocephalus, and to establish a multidisciplinary approach with the areas of pediatric cardiothoracic surgery, pediatric anesthesiology and pediatric critical cardiovascular and genetic medicine, since there were insufficient resources for his care at the institution.

DISCUSSION

ACOGS is a neurodevelopmental syndromic disorder characterized by global developmental delay and/or intellectual disability, agenesis or hypoplasia of the corpus callosum, and craniofacial, ocular, cardiac and genital abnormalities. It was first described in 2019, and there is no quantified incidence or prevalence, with only 13 cases described in the literature (5).

Its etiology is attributed to a heterozygous mutation with autosomal dominant inheritance of the *CDH2* gene of chromosome 18q12 (5), which encodes the synthesis of N-cadherins, calcium-dependent transmembrane proteins that allow cell-cell adhesion (6). In the neural epithelium, N-cadherins play an essential role in neural development, including proliferation and differentiation of neural progenitor cells, neural tube formation, synaptogenesis, neuronal migration, and axon elongation (6). In addition to neural tissue, it has also been identified that N-cadherin is expressed

in many other tissues, such as the heart, where it is involved in the coupling and communication of cardiac myocytes. Furthermore, given the high prevalence of corneal alterations in patients with this syndrome, Accogli *et al.* (6) concluded that the activity of N-cadherins is fundamental in the development of the structures of the anterior chamber of the eye (6).

The diagnosis of this syndrome has been ascertained by identifying the mutated gene in patients with a wide range of major malformations and global neurodevelopmental delay, with this group of symptoms being the most prevalent in the cases described to date (6). The patient of the reported case presented adequate and symmetrical primitive signs since birth, so further follow-up should be made to verify the presence of neurodevelopmental delay.

This syndrome is characterized by numerous encephalic alterations. In the report by Accogli *et al.*, (6) it is observed that, among the cases studied, both agenesis of the corpus callosum (77%) and hypoplasia of the corpus callosum (11%) are found. Besides callosal malformations, hypothalamic adhesions, periventricular nodular heterotopias, interhemispheric cysts communicating with the third ventricle, hypoplastic or dysplastic cerebellar tentorium, mega cisterna magna and even atretic parietal cephalocele have been found (6).

In ACOGS, the heart also exhibits different malformations, including atrioventricular canal, aortic coarctation, pulmonary artery hypoplasia with dextrocardia, and tricuspid valve regurgitation, this being the first case report describing a patient with TOF. In fact, in this dysfunction, TOF is expected in genes encoding proteins that regulate cell adhesion and migration, since the most accepted and investigated etiopathogenic hypothesis of this condition has to do with mutations in the *NKX2.5* gene. This gene is an orchestrator for cell migration during embryogenesis, so its aberrant function correlates with an abnormal development of the conotruncal portion of the heart (7-9).

On the other hand, the patient's cryptorchidism is consistent with what has been found in the literature, as it is the most frequent genital malformation in children affected by the N-cadherin mutation. There is also a report of an affected patient with micropenis (4).

Half of the patients in the study by Accogli *et al.* (4) exhibited ocular defects such as Peters anomaly, strabismus, unilateral ptosis with Duane syndrome, and congenital cataracts. In the case reported here, multiple craniofacial features were encountered (prominent forehead, low-set ears, sunken eyes with entropion, thin lips, and low palpebral fissures). More than half of these anomalies have also been characterized in 11 of the 13 patients with ACOGS described in the literature (5,6).

In addition to the anomalies that form the acronym for this syndrome, musculoskeletal malformations have also been identified which, to date, have remained in the upper dorsal portion of the body, with one patient with shoulder muscle agenesis and two patients with Sprengel deformity (6). The patient in this

report was diagnosed with abdominal muscle hypoplasia due to the presence of skin flaps or folds that were evident at the time of examination and palpation of the abdomen.

Neurodevelopmental disorders, autism spectrum disorders, and even self-injurious behaviors have been consistently noted in the prospective longitudinal follow-up of patients (6). In the case presented, no alterations of the patient's primitive reflexes were observed, and due to his age at the time of the study, it was not possible to determine alterations in his neurodevelopment.

The presence of the aforementioned malformations, and the absence of other typical chromosomopathies such as trisomy 13, 18 and 21, helped to establish the clinical diagnostic suspicion (and based on imaging studies) of ACOGS. The unavailability of a basic and/or extended genetic study, such as the determination of a karyotype or exome, restricts the certainty to corroborate a different etiopathogenesis.

CONCLUSIONS

All pediatricians must be skilled in the identification and clinical correlation of malformations. ACOGS is a rare malformation syndrome recently described in the literature, characterized mainly by neural tube defects, craniofacial anomalies, and cardiac, ocular and genital abnormalities with subsequent neurodevelopmental and intellectual impairment, resulting from defects in cell adhesion and migration. This case report describes a patient meeting the clinical criteria for the diagnosis of ACOGS and describes the first case of TOF within this group of anomalies, adding a complex variant to the phenotype of diseases caused by defects in cell adhesion.

ETHICAL CONSIDERATIONS

Informed consent was obtained from the patient's mother.

CONFLICTS OF INTEREST

None stated by the authors.

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