Ebstein anomaly associated with cri du chat (cat's cry) syndrome and 20q duplication

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SUMMARY

Ebstein anomaly is a congenital heart defect with a low prevalence and high mortality in the early stages of life. In medical literature, there is no reported association between Ebstein anomaly and cri du chat syndrome. Here, we report the case of a full-term newborn with a low weight for his age and who had a prenatal diagnosis of Ebstein anomaly and a postnatal diagnosis of cri du chat syndrome and 20q duplication detected on array CGH. The patient required medical treatment with inotropic support, high-frequency ventilation and nitric oxide, with an adequate response. Surgical intervention was not needed.

BACKGROUND

Ebstein anomaly is a congenital defect of the tricuspid valve in the septal and posterior valves, although it has been suggested that Ebstein anomaly may be cardiomyopathy with valve involvement rather than a primary valve disorder. Compared with other congenital heart malformations, Ebstein anomaly has a low prevalence at <1%, with variable signs and symptoms according to the degree of mitral valve compromise.[1–3] Diagnosis is reached in the postnatal stage based on echocardiogram, and treatment is either medications or surgery based on the newborn's conditions.[2] Cri du chat syndrome has an incidence rate of 1 in every 50 000 live births.[4] It is caused by a deletion on the short arm of chromosome 5. The phenotype is characterised by a delay in neurodevelopment, and approximately 30% of those affected have heart defects, more often finding a ventricular defect along with auricular defects in smaller proportion.[4 5] In global literature, there is no reported association between Ebstein anomaly and cri du chat syndrome; therefore, it is important to document this new association.

CASE PRESENTATION

The patient was a male newborn of 37 weeks' gestational age. The mother is a 28-year-old nutritionist from Bogotá with a history of hyperthyroidism treated with methimazole 10 mg/day and a previous pregnancy without complications. The father was healthy without consanguinity links with the mother. In the current pregnancy, the mother was prenatally diagnosed with intrauterine growth restriction and fetal malformations (Ebstein anomaly, interatrial communication, prenatal history of mega cisterna magna, ventriculomegaly and dysgenesis of the corpus callosum), with appropriate neonatal adaptation. The infant had an APGAR (appearance, pulse, grimace, activity, respiration) score of 6 at 1 min, 7 at 5 min and 9 at 10 min, with a birth weight of 2170 g (third percentile) and a length of 43 cm (third percentile). Physical examination revealed low-set pinna, right preauricular appendage, complete polydactyly of the fifth finger on the right hand and generalised hypotonia. Due to these findings, a decision was made to hospitalise the infant and initiate comprehensive management for the multiple malformations. In addition, a brain MRI scan was done due to persistence of central hypotonia and cat-like cry; the examination reported mega cisterna magna with no other abnormalities.

INVESTIGATIONS

Due to the multiple malformations and hypotonia, an array comparative genomic hybridization (CGH) was performed, which reported a terminal deletion of 18.3 megabases in 5p15.33-p 14.3 associated with cri du chat syndrome and a terminal duplication of 12.1 megabases in 20q 13.2-q 13.33. The two copy number variations diagnosed in the patient in accordance with The International System for Human Cytogenetic Nomenclature (ISCN) 2016 were as follows: arr[GRCh37]5p15.33p14.3 (113576_18439602) x1, 20q13.2q13.33 (50737522_62913645)x3.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the ductal-dependent cyanotic heart disease includes tetralogy of Fallot, pulmonary valve stenosis and hypoplastic left heart syndrome.[3 6–8] Based on prenatal history, Ebstein anomaly was suspected. A transthoracic echocardiogram was performed which confirmed the diagnosis of type B Ebstein anomaly, and due to it being a major malformation associated with a cry similar to the mewing of a cat, an array CHG was performed, which confirmed the diagnosis of cri du chat syndrome.

TREATMENT

The patient required inotropic support with dopamine at a dosage of 10 μg/kg/min and dobutamine at 10 μg/kg/min for 2 days, with high-frequency ventilation for 6 days, nitric oxide at 20 parts per million for 3 days, fentanyl 5 μg/kg/hour for 6 days for sedation, and vecuronium bromide 1 μg/kg/min for 3 days for relaxation, and conventional ventilation for 7 days. Moreover, he required management with supplemental oxygen through a 4 L high-flow cannula with dynamic FiO2 between 30% and 50%

for 2 days, then a 1/32 low-flow nasal cannula until adequately tolerated. The patient showed deterioration in respiratory pattern, with chest X-ray showing cardiomegaly and signs of pulmonary oedema, with hepatomegaly resulting from heart failure and requiring management with oral sildenafil 0.5 mg/kg every 4 hours, furosemide 0.5 mg intravenously every day for 3 days, spironolactone 1 mg/kg/day orally, oral captopril 0.1 mg/mg every 8 hours and oral digoxin 5 μg/kg/day. Subsequently, the patient showed improvement in symptoms of heart failure. With regard to the kidneys, the patient had adequate urinary output and his kidney function was within normal limits. Right kidney agenesis was reported on abdominal ultrasound. He required first-line antibiotics, that is, ampicillin 100 μg/kg every 12 hours and amikacin 15 mg intravenously for 7 days, until his blood culture results turned negative. Subsequently, due to findings of kidney malformation, daily aminoglycosides were discontinued, and piperacillin/tazobactam 100 mg intravenously every 8 hours for 14 days was prescribed instead. He then showed periumbilical discharge and clinical deterioration. Treatment with linezolid 10 mg/kg intravenously every 8 hours and meropenem 20 mg/kg intravenously every 12 hours for 10 days was initiated, with a new blood culture set and umbilical discharge culture both showing negative results. Integral management was performed with music, physical, occupational and phonoaudiological therapy for the newborn. Paediatric psychiatry assistance was also provided for the family during hospitalisation.

OUTCOME AND FOLLOW-UP

At 9-month follow-up, delay in psychomotor development was evident. The patient has had two hospitalisations during the follow-up period due to acute respiratory infections, which were managed in the hospital for approximately 5 days. To this day, the paediatric cardiology department conducts follow-up with medical management. No surgical intervention was required.

DISCUSSION

Ebstein anomaly is a congenital heart defect with tricuspid valve dysplasia and displacement towards the septal valve and atrialisation of the right ventricle, although it has been suggested that Ebstein anomaly may be cardiomyopathy with valve involvement rather than a primary valve disorder. Compared with other congenital heart defects, Ebstein anomaly has a low prevalence at <1%, and is associated with variable signs and symptoms, with a life expectancy of 40 years. It can be associated with mitral valve prolapse and left ventricular non-compaction.[9]

The partial or total deletions of the 5p arm are associated with the 5p deletion syndrome or cri du chat syndrome. This alteration in chromosome structure is present in 1 out of every 15 000–50 000 live births, as it is one of the most frequent contiguous gene deletion syndromes.[10] It is characterised by a monotone cry, facial dysmorphism and delay in growth and development. Other alterations associated with the phenotype of the deletion are shown in a highly variable manner and depend to a large extent, although not entirely, on the area involved.[4 11] The case reported here has characteristics frequently found in other patients with deletion, such as hypotonia (72% of those affected), mega cistern magna, ventriculomegaly and corpus callosum dysgenesis (30% of those affected), unilateral kidney agenesis (6%–18% of those affected), anomalies of the genitourinary tract (4%–21% of those affected), and congenital heart defects (30% of those affected).[4] With respect to the heart defects, our patient, in addition to relatively frequent findings in people affected by cri du chat syndrome, such as interatrial communication and large patent ductus arteriosus, which are two of the most frequently reported heart development alterations in people with cri du chat,[7 8] also exhibited Carpentier's type B Ebstein anomaly, which to the best of our knowledge has occurred for the first time in a case of 5p deletion.

Table 1 Genes annotated in the heart development class of the Gene Ontology database which map in the altered chromosomal regions of the reported patient

Gene	Chromosome	Band
IRX4	5	p15.33
DNAH5	5	p15.2
SALL4	20	q13.2
BMP7	20	q13.31
GATA5	20	q13.33

The other chromosomal alteration identified was a terminal duplication of the long arm of chromosome 20. This duplication is not extremely frequent and has only been reported in a few cases. The phenotype of the affected individuals includes moderate delay in development, craniofacial dysmorphism, dysmorphism in the lip and cleft palate, and congenital heart defects such as interventricular communication and aortic coarctation.[5 6] Ebstein anomaly has not been reported in people with duplication either.

To determine the potential candidate genes responsible for a particular heart alteration in a patient, a bioinformatic analysis was performed for chromosomal regions with deletion and duplication. In accordance with version 38 of the human genome, in the lost region of the short arm of chromosome 5, 300 annotated genes were found, whereas the duplicated region of the long arm of chromosome 20 had 235 genes. After determining which of these 535 genes were annotated in the Gene Ontology (GO) database, heart development under class GO:0007507 was identified.[12] From the 535 genes in the class mentioned, two genes map in the deleted region of chromosomes 5 and 3 in the duplicated region of chromosome 20 (table 1).

Ebstein anomaly can be presented as an isolated malformation or as part of a syndrome with other malformations. Although the aetiology is unknown, some families have been described to present reoccurrence of the illness and have also reported showing association with some genetic syndromes.[9] The former supports the hypothesis of possible genetic alterations associated with the appearance of the disease. From studies on people with isolated or syndromic Ebstein anomaly, it is possible to find potential candidate genes such as NKX2.5, HATA4, MYH7 and TPM1.[9 11] All of these play an important role in the embryonic development of the heart. Although the genes related with the embryonic heart development in the altered chromosomal regions of the patient have not been previously linked with candidate genes for Ebstein anomaly, in examining the protein interaction database STRING,[12] it was found that the protein products of four of these interact with GATA4 and NKX2.5.

The unbalanced chromosomal rearrangement in the patient could have originated from a de novo mutation or inherited from one of the parents with a balanced translocation. If an unbalanced chromosomal rearrangement is diagnosed in a child, it is always necessary to assess the parents' karyotype to provide adequate genetic counselling. In the present case, the parents refused analysis of their chromosomes because they had no plans of having more children and did not want to have this information. Additional genetic studies in the family were not performed.

Our hypothesis is that the combination of haploinsufficiency of the genes in the deleted region of the short arm of chromosome 5 with the gene dose increases the effect, resulting from trisomy of the long arm of chromosome 20, and generates disruption in the regulatory mechanisms of the embryonic heart development mediated by GATA4 and NKX2.5, resulting in the development of the patient's phenotype.

Patient's perspective

I am grateful for the opportunity of my child to be the person described in this article. In this way, other people can know the pathology of my son.

Learning points

- The identification of the genetic causes of Ebstein anomaly has proved to be evasive, probably due to the genetic heterogeneity underlying the phenotypic heterogeneity of the disease.
- This case report represents a breakthrough in the characterisation of patients with Ebstein anomaly and in the search for its candidate genes.
- The phenotypic presentation of Ebstein anomaly in a patient with cri du chat syndrome for the first time can be explained by the interaction with one or several of the genes involved in the 20q duplication.

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