Prolonged survival in Edwards syndrome with congenital heart disease: a case report and literature review

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Abstract

Edwards syndrome or trisomy 18 is a complex entity that involves the musculoskeletal, craniofacial, cardiovascular, and neurological systems. Its genetics are varied, presenting both in a complete and mosaic type. Survival rarely exceeds the first year of life. Its phenotype characterization is not pathognomonic, so karyotype is essential for diagnosis, prenatally by amniocentesis and cordocentesis by FISH technique. We present the case of an eight-year-old girl who has survived with this condition despite presenting tetralogy of Fallot and serious cardiac malformations. Diagnosis began with prenatal screening ultrasound at 16 weeks and detailed ultrasound, with amniocentesis and amniotic fluid karyotype, with a result of 47 XX+18. She has been treated by multiple medical specialties, due to musculoskeletal, joint, neurological, metabolic, and cardiovascular complications that have limited her quality of life. The management of these patients requires a multidisciplinary medical team, and counseling for parents should include aspects related to survival, frequent complications, and risk-benefit to be evaluated before subjecting the minor to complex or corrective surgical interventions.

Main messages

- Trisomy 18 is a complex syndrome, with phenotypic findings and a 47 XX + 18 karyotype and an estimated prevalence of one per 6000 to 8000 newly born children.
- Survival beyond five years of age is not typical, and only limited publications report cases of patients older than five years old in the world.
- The clinical case of an eight-year-old female who has survived despite severe heart disease and other musculoskeletal, cardiovascular, neurological, and nutritional complications is described.
- This is a rare report, when comparing to the existing literature, that adds to the understanding of this trisomy in terms of patient survival and phenotype characteristics, an important aspect for establishing adequate diagnostic and therapeutic actions.

Introduction

Trisomy 18 syndrome or Edwards syndrome is a polymalformative condition that is produced by the existence of three chromosomes 18. The complete genotype occurs in 95% of cases, either by non-disjunction or by translocation. Although an incomplete genotype is also described in 5% of cases, it may be a mosaic or a partial trisomy[1]. Trisomy 18 is the second most common autosomal chromosomal

disease after Down syndrome (also termed trisomy 21). The estimated global prevalence is 1 in 6000 to 8000 newborns and its frequency increases in elderly mothers[2].

Patients with trisomy 18 have high mortality from the moment of birth and as time passes, the chances of survival are less, mainly due to congenital heart disease. Only 5 to 10% of patients live past the first year of life. After five years, few cases of survival have been reported in the literature[3], since of those who manage to survive beyond one year of life, only up to 12% present survival[2,3].

The diagnosis of trisomy 18 can be made prenatally through detailed ultrasound detecting anatomical malformations and through amniocentesis or cordocentesis tests for karyotyping or fluorescent in situ hybridization[4]. After birth, it is diagnosed by peripheral blood G-band karyotype[5,6]. Early diagnosis also includes hormonal determinations prior to conducting invasive studies[7].

We present the case of a patient diagnosed with trisomy 18 with a survival greater than five years, which is rare compared to the survival rate reported in the literature; in addition, the patient showed the joint presence of severe congenital heart disease and multiple typical and atypical manifestations of the syndrome. The objective is to provide information about the knowledge of this trisomy in terms of phenotypic characteristics and patient survival, which is of importance in the field of genetics, an important aspect to establish correct diagnostic-therapeutic actions.

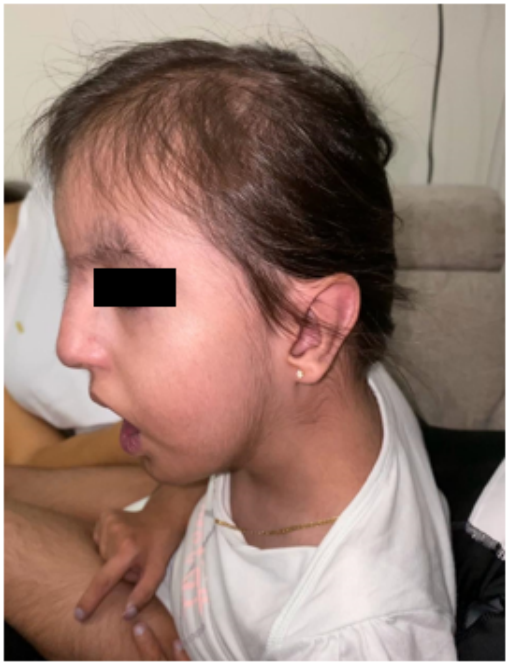
Clinical case

We evaluated an eight-year-old female patient from Pereira, a daughter of non-consanguineous parents, whose mother was aged 36, and the father 35 years at the time of the patient's conception. The patient is the product of the sixth pregnancy since the first two pregnancies ended in spontaneous abortion while the third through fifth took a normal course with no aneuploidies. The mother attended a total of seven prenatal check-ups, had a full-term delivery at 39 weeks, received no additional counseling on sexual and reproductive health, and did not receive a preconception consultation.

The patient received interdisciplinary management by pediatrics, nutrition, cardiology, orthopedics, and genetics for years before the consultation, with limited evolution in her development. Clinical data in this report were collected retrospectively from a follow-up and control consultation by a new pediatrician due to her underlying pathology (trisomy 18), in 2020. The physical examination presented the following anthropometric measurements: height 99 centimeters, weight 12 kilograms, body mass index 12.2 kilograms per square meter, with a diagnosis of chronic severe protein-calorie malnutrition—throughout her life she has remained in lower percentiles for her age, despite previous treatments with food supplements.

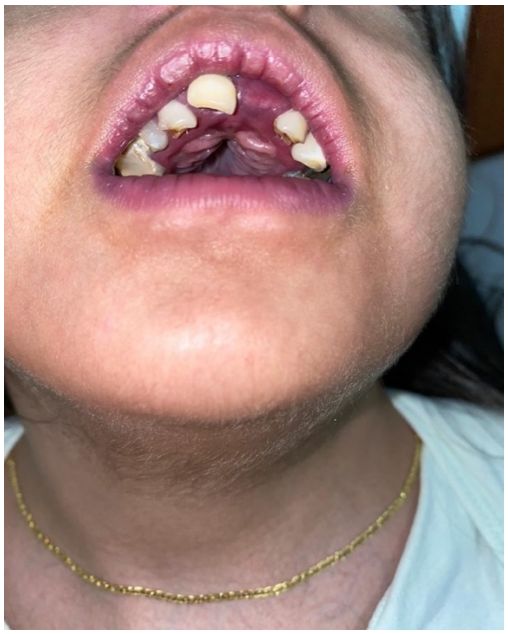
Regarding the phenotypic findings, the following were found: hypertelorism, plagiocephaly, micrognathia with low implantation pinnae (Figure 1); palatal fissure and narrow palatal arch (Figure 2); eyebrows full of synophrys, hypertrichosis (Figure 3); hypoplasia of the nostrils, short neck, scoliosis, congenital bilateral hip dislocation with limitation of abduction and flexion greater than 90 degrees; left clubfoot and right talus-valgus foot with marked muscular atrophy (Figure 4); hands with ulnar deviation with second and fifth fingers superimposed on the third and fourth and digital clubbing (Figure 5); retractions in the knees and ankles, hypertrichosis, hypotonia, and central cyanosis. On cardiac auscultation, a 4/6 mid-systolic murmur was found in all auscultatory foci.

Figure 1. Photograph of the head.



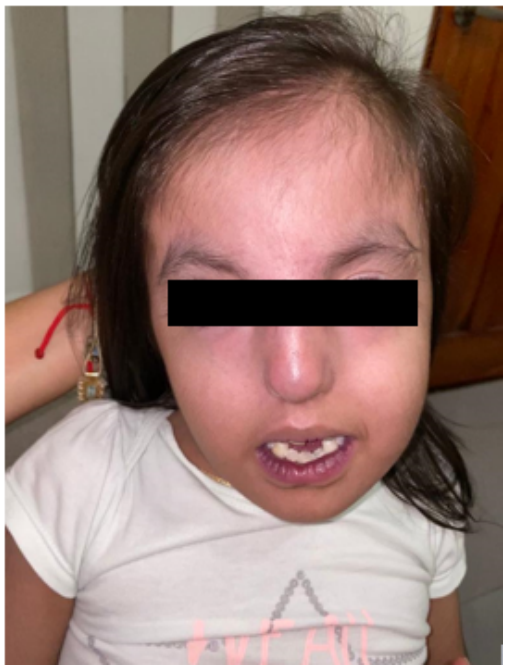
Left lateral photograph of the head. Plagiocephaly, micrognathia, and low-set, dysmorphic, posteriorly rotated ears can be observed.
Source: Photo taken by the authors with the patient's parents' permission.

Figure 2. Photograph of the oral cavity.



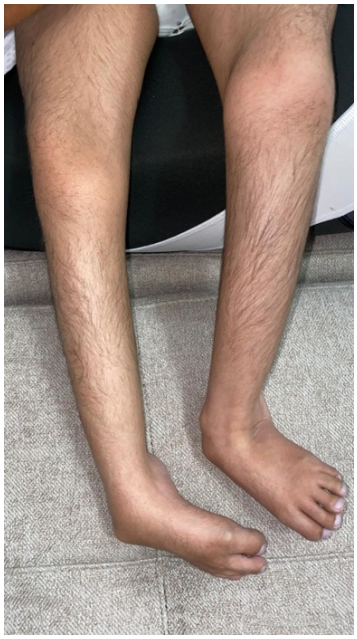
Oral cavity. A cleft palate and a narrow palatal arch can be observed.
Source: Photo taken by the authors with the patient's parents' permission.

Figure 3. Photograph of the face.



Hypertrichosis, crowded eyebrows with synophrys and central cyanosis are evident.
Source: Photo taken by the authors with the patient's parents' permission.

Figure 4. Photograph of lower limbs.



Left clubfoot and right talus-valgus foot, also with marked muscle atrophy.
Source: Photo taken by the authors with the patient's parents' permission.

Figure 5. Photograph of both hands.

Hands with bilateral ulnar deviation with second and fifth fingers superimposed on the third and fourth, digital clubbing, and peripheral cyanosis.
Source: Photo taken by the authors with the patient's parents' permission.

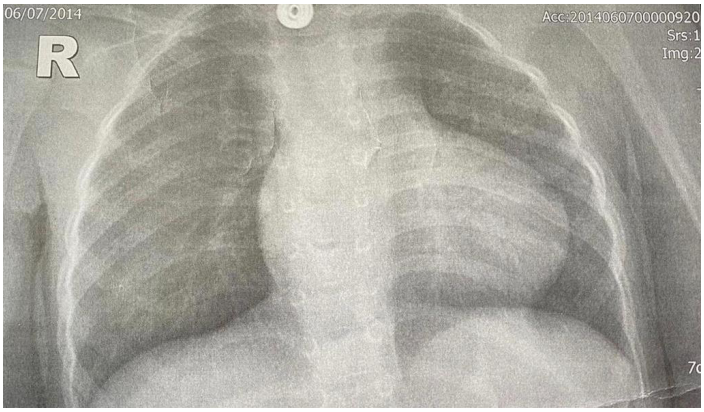
A screening ultrasound performed at week 12 revealed a fetus with a cystic appearance, septate at the level of the neck, generalized foot edema, pericardial effusion, probable interventricular septal defect at the level of the cross of the heart, finding regurgitation on tricuspid Doppler and in the ductus venosus, reverse flow. Furthermore, the nuchal translucency was found to be increased. Chorionic villus biopsy was requested before week 14 or amniocentesis from week 16. A karyotype of amniotic and fetal fluid was performed using fluorescent in situ hybridization technique, with a result of 47 XX + 18 in all the mitoses analyzed, clinically compatible with trisomy 18.

A detailed ultrasound was performed where tubular bones between 3 to 4 weeks younger for gestational age and an estimated fetal weight below the third percentile stood out. At the heart level, an associated septal defect in the intermembrane space of 2.8 millimeters was observed. Arch of the aorta artery evidenced apparently normal right ventricular outflow tract. In extremities, angulation of the foot was observed with respect to the legs. Additionally, megacisterna magna and polyhydramnios were detected.

At birth, she presented phenotypic symptoms and malformations compatible with trisomy 18. Because the patient had a survival greater than 3 months, it was necessary to establish whether the trisomy was free or in mosaicism; to that end, a cytogenetic study with R-band was requested in peripheral blood to define a karyotype with a 47 XX + 18 result in a count of 20 metaphases, which is, a free trisomy 18. The cytogenetic analysis was performed on the parents and a mosaicism was found in the mother 46 XX / 47 XXX.

Tetralogy of Fallot was identified from birth, which explains oxygen saturation levels not exceeding 80%. The echocardiogram revealed ventricular and interatrial septal defect, 45% riding aorta, reverse patent foramen ovale, severe pulmonary valve stenosis with a peak gradient of 77 millimeters of mercury, and a dilated pulmonary artery trunk. With closure of the ductus arteriosus after the third month of life, during the first year she had five follow-ups by pediatric cardiology, the patient used home oxygen for 24 hours a day in the first three months. In the second year of life cardiomegaly was observed in the chest radiograph (Figure 6).

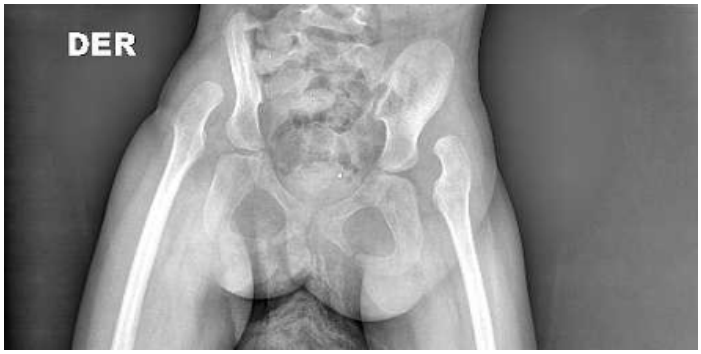
Figure 6. Chest X-ray.



Chest X-ray in anteroposterior projection, taken at 2 years old, showing moderate cardiomegaly with enlargement of the right cavities.
Source: Image collected by the authors with the patient's parents' permission.

At seven months of life, a bilateral equinovarus, cavus deformity associated with soft tissue disease, was described. Images of the pelvis were taken as shown in Figure 7. At 11 months, she received a resting cast with knee flexed at 80°, after which an improvement of the forefoot adduct of 20° was found. At 17 months, a Dennis Brown splint was indicated. At five years, progression was identified with mobility of the hips with flexion up to 90° and abduction of 10°, kyphosis at the thoracolumbar junction, for which it was concluded that the patient had a paralytic dislocation of her hips, scoliosis, and deformity in both feet that do not require surgical intervention.

Figure 7. Pelvic X-ray.



There is evidence of flattening of the acetabular roofs and an increase in the right acetabular angles by 33 centimeters and left by 27 centimeters, associated with loss of Schenton's arches and the relationship of the ossification nucleus of the femoral head with the acetabulum, angulation of the drops of tears, these findings are related to developmental dysplasia of the hip.
Source: Image collected by the authors with the patient's parents' permission.

Severe central hypotonia was documented from birth and psychomotor retardation secondary to chronic hypoxia due to complex heart disease from the first months of life. By transfontanellar ultrasound at three months of life, verticalization of the frontal horns and probable signs of dysgenesis of the corpus callosum were observed, without other alterations of the midline or hemorrhagic involvement. The brain MRI study at two years reported normal intracranial content, however, changes typical of chronic hypoxia that marked cerebral cortical atrophy at the bilateral frontotemporal level and delayed myelination expected for age were identified. At the moment, the patient does not pronounce syllables; she only emits sounds and her social responsiveness is through a smile; she holds her head and does not make movements; and on physical examination she has a left hearing loss, being able to understand simple commands without sphincter control.

Currently, the patient is eight years old, has not presented seizures, and is under medical management—since it was considered that she was not a candidate for cardiovascular surgery due to her unfavorable prognosis for life. Renal or digestive malformations have not been documented in ultrasound studies.

For the publication of the clinical case, informed consent was obtained from the patient's parents.

Discussion

The literature reports that the majority of fetuses with trisomy 18 evolve to death. If they survive until birth, the majority die in the first year of life[8]. Female carriers have a greater probability of survival for longer periods, mainly those with chromosomal defects due to mosaicism[9]. Although there is evidence of long-term survival, it is documented in case reports and not population studies; even so, it should be taken into account that these patients have a high degree of dependence and severe psychomotor retardation[10-13].

A higher probability of mortality has been reported during the first week of life, with a higher probability in some countries such as Israel and Argentina[14,15]. Most of these infants were born preterm and the longest survival was achieved up to 39 days with a median of two days[14,15].

In a population-based study performed in the United States, five-year survival was found to be around 12%, and those who survived the first year of life were more likely to survive to five years. The conditions related to higher survival were being female, having full-term births, and being children of non-Hispanic black mothers[16]. In another study where a group of neonatologists that were surveyed regarding the prenatal diagnosis of trisomy 18, the majority of them agreed with a minimum survival of one week and a maximum of one year, where the best prognosis at the neuro-developmental level would be deep mental retardation, and where they would only offer palliative care[17,18].

The main complications that cause mortality are heart disease, central apnea, and respiratory failure[19,20], which is why the survival of this eight-year-old patient is striking, is that she has severe congenital heart disease, which is rare in patients with trisomy 18, is not undergoing surgery, and considering that less than 4% of cases survive after one year of life[2,9]. The management of these patients throughout their lives includes invasive treatment measures such as cardiopulmonary resuscitation for their pre-existing conditions, enteral nutrition supporting, use of oxygen, and corrective surgeries for neurological or gastrointestinal defects mainly[21].

The main phenotypic defects described are prominent occiput, narrow bifrontal diameter, low set ears, palpebral fissures, narrow oral opening, and palatal arch, micrognathia, and hirsutism; of which, this patient presented the majority. Plagiocephaly and hypoplasia of the nose identified in the patient are not clearly described in the literature. From the findings at the skull level, among others, hypertelorism and cleft palate are described; both identified in the patient[2,9].

In the cardiovascular system, there are frequent manifestations such as patent ductus arteriosus and defects of the atrial and ventricular

septa, and for moderately frequent manifestations, defects of the aortic and pulmonary leaflets or pulmonary stenosis are described. In the less frequent there are anomalies of the coronary arteries. Tetralogy of Fallot, dextrocardia, and coarctation of the aorta, of which the patient presented the first from birth, are conditions that are present in less than 10%[2,9].

According to abdominal and pelvic findings, malformations include umbilical or inguinal hernias, omphalocele, Meckel's diverticulum, esophageal atresia, imperforate anus, ectopic kidney, double ureter, Wilms tumor, or polycystic kidney. The patient did not present any of these conditions[2,9]. 50% of children have been reported to show positional foot deformities. Scoliosis is common in older children and can progress between the ages of five and 10. Congenital hip dislocation has been described in the pelvis, which represents a rare condition and is present in this case. Other reported malformations include fused vertebrae, pectus excavatum, syndactyly of the third and fourth fingers and toes, short neck, scoliosis, ulnar or radial deviation, and clubfoot, of which our patient presents the last four, in addition to digital clubbing which is not mentioned in literature[2,9].

Patients with trisomy 18 are more likely to survive if they undergo cardiac surgery[21,22]. In a study by Cooper et al., it was found that cardiac surgery was associated with better survival in patients with trisomy 18 (Odds ratio: 0.2; $p = 0.02$)[23], however, treatment must be individualized to each patient[24]. In this patient, performing any cardiac procedure or surgery was not recommended due to the poor prognosis, considering the risk-benefit as well as the ethical aspects and the informed consent. On the other hand, oxygen therapy for the symptomatic management of heart failure was administered to the patient only for the first months of life.

Patients with trisomy 18 in more than 50% of cases present seizures usually in the first year of life[25-28]. Neurologically, they are also described: scant myelination, hydrocephalus, defects of the corpus callosum, and megacisterna magna. In this case, the findings presented the latter two, in addition to hypotonia, a condition not reported in the literature[2,9], which commonly describes hypertonia accompanying this syndrome[6].

Although the most common genotype is complete trisomy in all cells, mosaicism and partial trisomy also exist; the phenotype expressed later is the result of this additional genetic material. However, there is no defined pathognomonic spectrum of trisomy 18 since the clinical manifestations can be diverse. It has been postulated that there are critical regions on chromosome 18 for a phenotype to result in patients with mosaicism where the clinical picture is usually less severe. The manifestations depend on the proportion of normal and affected cells, although this has not been corroborated since the phenotype is usually variable and it is difficult to establish the percentage of cells with trisomy 18. In some cases, parents do not have any history of chromosomopathy, an entity that can be transmitted or have a new appearance. This information should be considered when conducting genetic counseling to parents, in addition to explaining that complete trisomy can recur in a future pregnancy with a probability of 1%. In this case, the diagnosis of the patient is a free trisomy 18, although, in the karyotype carried out, only twenty metaphases were observed and not one hundred, as is usual[6,11,29,30].

The frequency of gross abnormalities detected sonographically in fetuses with trisomy 18 varies with gestational age, and their occurrence ranges from 53% at 17.5 weeks of gestation until 67% from 17.5 to 24 weeks[31]. Nuchal involvement, either due to increased translucency (in the first trimester) or the fold (in the second), is the most reliable and widely used ultrasound marker of trisomies. In this clinical case, an increase in nuchal translucency was identified in early ultrasound. Regarding the cystic aspect of the fetus, the most frequent alteration is hygromas found in the first trimester, which are associated with a trisomy, while in the second trimester it is often related to monosomy X[31-33]. Another frequent marker in trisomies is alterations in the nasal bone[31] in the first-trimester ultrasound of the patient; this structure was referred to as normal. The absence of nasal bone in trisomy 18 has been found to range from 53% to 60%[34].

Concerning the Doppler characteristics, reverse venous flow, and tricuspid regurgitation are identified. The frequency of these defects is 58% and 33.3% in patients with trisomy 18, respectively[34-36]. In detail ultrasound in the second trimester, the patient presented an estimated fetal weight below the 3rd percentile. Studies have detected aneuploidy in 20% of fetuses small for gestational age[37,38].

Other abnormalities identified on ultrasound include choroid plexus cyst, neural tube defects, ventriculomegaly, strawberry-shaped skull, multisystem defects (facial, cardiovascular, gastrointestinal, urogenital), two-vessel umbilical cord, limb abnormalities, cistern abnormal magna, absent corpus callosum or cerebellar hypoplasia, and polyhydramnios[32]. Of the above, the patient presented the latter four in the prenatal screening.

Finally, it should be noted that the girl lives with both parents and they have been her permanent caregivers since birth since the patient is completely dependent for life's basic daily activities. It has been shown that there is an adequate family support network.

Conclusions

The case of an 8-year-old female patient with a diagnosis of trisomy 18 and severe congenital heart disease is reported, in consideration of the fact that there are few reports showing survival greater than 5 years, especially if it is associated with severe and infrequent heart malformations. In addition, she presented manifestations not described in the literature such as plagiocephaly, hypoplasia of the nasal fossae, clubbing, and hypotonia. Considering that this condition is infrequent and of atypical presentation, its description is necessary. The comprehensive approach to these patients requires intervention with various medical specialties. Counseling for parents should be carried out individually, taking in mind the prognosis and complications of the patient.

Notes

Authorship contributions

VLR, EGM: Conceptualization, methodology, research, preparation of the manuscript. VGZ, FAB: Methodology, research, review, and editing of the manuscript, visualization.

Competing interest

The authors completed the ICMJE conflict of interest declaration and declare that they did not receive funds for the realization of this article; the authors do not have financial relationships with organizations that may benefit from the published article in the past three years and do not have other relationships or activities that may influence the publication of the article.

The forms may be solicited by contacting the corresponding author or the editorial of this journal.

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Ethics
The consent as required by *Medwave* for the publication of this case report, including the presented images, has been signed by the patient's tutor. The authors declare that the patient's privacy was respected according to the CIOMS norms on privacy. Informed consent was obtained from the patient's parents. A copy of the consent was given to the editorial team of this journal.

From the editors
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