

Trisomy 18 – When the Diagnosis Is Compatible With Life

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Abstract

Trisomy 18 is an autosomal chromosomal disorder characterized by the presence of an extra 18 chromosome. In the last decades, and as the therapeutic options have become more relevant, the medical community witnessed a paradigm shift on the offer of treatment to these children.

This is a retrospective, cohort study that strives to characterize the clinical path and survival of the children with the diagnosis of trisomy 18, accompanied in a tertiary pediatric hospital between 1995 and 2020.

Six children were identified with trisomy 18, two of them mosaic (33,3%) and four were females (66,7%). All had cardiovascular, cognitive and physical development anomalies or minor congenital anomalies (n=6, 100%) and most presented musculoskeletal anomalies (n=5, 83,3%) and feeding difficulties (n=4, 66,7%). Four children (66,7%) were reliant on devices or equipment and all needed chronic medication (n=6, 100%). Two children (33,3%) were submitted to surgical interventions. Four children (66,7%) were hospitalized in the last year of life. A decision of limitation of therapeutic effort was present in three cases (50%) with one child being referenced to pediatric palliative care (16,7%). One-month, one-year and ten-year survival were 66,7% (n=4), 33,3% (n=2, both mosaic), and 16,7% (n=1, mosaic) respectively.

Conclusions: Knowledge on the clinical picture is of great importance regarding the neonatal care and the decisions about invasive treatments, which can involve ethical issues, highlighting, concurrently, the need for attempted referral of these children to pediatric palliative care teams.

What Is Known

- *The increase in survival and the high mortality and morbidity that trisomy 18 entails causes a need for careful deliberation on the offer of intensive treatment.*

What Is New

- *Most recent studies prove that the designations of “incompatible with life” or “lethal” are not adequate to characterize trisomy 18 establishing a need to change this mindset.*
- *The development of specialized pediatric palliative care teams in the last decade and the early referral can give new perspectives and insights to promote the most adequate individualized advanced care plan.*

Introduction

Trisomy 18, also known as Edwards' Syndrome, was first described in 1960 as an autosomal chromosomal disorder resulting from an extra 18 chromosome. (1, 2)

A 2019, worldwide study indicated the total prevalence of trisomy 18 to be of 4.08 per 10,000 births and a prevalence of live births of 1.07 per 10,000 births. This reflects the reality that most parents who have a pregnancy with a fetus diagnosed with trisomy 18 turn to an elective termination of pregnancy and that those who choose instead to continue the pregnancy are often confronted with the outcome of a stillbirth. (3, 4)

Genetically, trisomy 18 can present itself as a full extra chromosome, a partial trisomy (18q), or a mosaic, translating on a spectrum of clinical findings and different survival outcomes on the children diagnosed with this syndrome. (2) Therefore, several anomalies may be present, with cardiac anomalies presenting as the most prevalent, as they are identified in approximately 80-90% of cases, followed by musculoskeletal defects and nervous system anomalies. Digestive system defects are also essential to identify for planning treatment and feeding options for these children after birth. (2, 4-6)

In the past, a diagnosis of trisomy 18 was set to be "incompatible with life", where the death of the infant was to be expected, making the offer of intensive treatment not a viable option. Therefore, palliative approach was presented as the only possibility for these children and their families. (7, 8)

Over the past decades, medical centers started to offer parents the chance of seeking treatment in cases that might benefit from the correction of congenital anomalies, especially cardiac anomalies, contributing to an increase in the survival of these children. (6, 7, 9, 10)

The increase in survival and the high mortality and morbidity that this syndrome entails causes a need for careful deliberation on which cases may benefit from intensive treatment, notwithstanding assistance by pediatric palliative care teams. This can be achieved through an anticipated care plan, by the multidisciplinary team, always taking into consideration the clinical evolution of the child throughout time, as well as the family's expectations, beliefs and treatment goals. (2, 6, 7)

This study strives to characterize the clinical path of the children with the diagnosis of trisomy 18 who were accompanied in a tertiary pediatric hospital from 1995 to 2020, identifying the comorbidities of these individuals, the procedures they were submitted to and evaluate the presence of therapeutic limitation plans, referral to a pediatric palliative care team and survival study.

Materials And Methods

This is a cohort retrospective study that compiled all cases of children diagnosed with trisomy 18 who were accompanied in a tertiary pediatric hospital from 1995 to 2020. All children who had a diagnostic code (International Classification of Diseases, Ninth Revision or Tenth Revision [ICD-9 or ICD-10] and Orphanet nomenclature of rare diseases) for trisomy 18 (ICD-9, 758.2 or ICD-10, Q91.0-Q91.3 and ORPHA:3380) were included. Children with irreconcilable data error, including uncertain genetic diagnosis not matching with trisomy 18, were excluded. Neonates who died in the early neonatal period were not included in this study. Additional diagnostic and clinical data were obtained using the databases of the departments of Pediatric Cardiology, Pediatric Intensive Care, Medical Genetics and Pediatric Medicine.

Regarding the children who were followed in a hospital other than the hospital in which the study was conducted the information was complemented, whenever possible, through access to the respective hospital's clinical file and consultation of clinical records.

We proceeded to create an anonymized database with the variables of interest, using IBM SPSS Statistics Version 27.0 (NY, USA), reporting data through descriptive analysis. Kaplan-Meier Curves were created using to assess 1-month, 1-year and 10-year survival probability.

Demographics (gender, year of birth), prenatal factors (fetal abnormalities, presence of prenatal diagnosis), neonatal factors (gestational age at birth, birth weight), cytogenetic status, age of cytogenetic diagnosis, diagnoses, comorbidities and death aspects were included in the analysis. Treatment factors such as surgeries, chronic medication, devices/equipment dependence, specialties involved in treatment and hospital admissions in the last year of life, as well as treatment decisions (limitation of therapeutic effort and reason for non-execution of therapeutic procedures) were accessed and examined. Reference to pediatric palliative care team in the hospital in which the study was conducted was also a variable in our study, even though this team only started functions in 2016.

Fetal growth restriction was defined as an estimated fetal weight that is less than the 10th percentile for gestational age of the 2013 Fenton growth chart for preterm infants. The records of diagnoses and comorbidities were reliant on the available clinical files and/or coding of the respective diagnoses.

Approval was obtained from the Ethics Committee of the hospital in which the study was conducted.

Results

Six children with trisomy 18 were liveborn between 1995 and 2020 and, by the time of conclusion of this study, one child was alive. Detailed individual case description with most of the variables studied can be found in Appendix 1. The most common cytogenetic status found was full trisomy (n=4, 66,7%), with mosaicism being detected in the remaining cases (n=2). Among these children, 66,7% were female (n=4) and half were term infants (n=3, 50%). Despite all children having been diagnosed with fetal growth restriction, none had prenatal diagnosis of trisomy 18.

One child (16,7%) was diagnosed with trisomy 18 in the first week of life, four children (33,3%) were diagnosed between the first week and first month of life and one child was diagnosed at 15 months of age (16,7%, mosaic).

Further description of all baseline and prenatal characteristics, as well as all primary and secondary diagnoses can be assessed in Table 1.

Table 1. Clinical Characteristics of Trisomy 18 Children

Total No.	6
Cytogenetic Status No. (%)	
Mosaic	2 (33,3%)
Full Trisomy	4 (66,7%)
Year of Birth, No. (%)	
1995 - 1999	1 (16,7%)
2000 - 2004	1 (16,7%)
2005 - 2009	1 (16,7%)
2010 - 2014	1 (16,7%)
2015 - 2020	2 (33,3%)
Gender No. (%)	
Female	4 (66,7%)
Male	2 (33,3%)
Gestational Age at Birth	
≤37 weeks	2 (33,3%)
37 - 40 weeks	3 (50,0%)
≥40 weeks	1 (16,7%)
Birth weight, kg, No. (%)	
≥2,5	3 (50,0%)
[1.5-2.5]	3 (50,0%)
<1.5	0 (0%)
Primary and Secondary diagnoses, No. (%)¹	
Cardiovascular	6 (100%)
Respiratory	2 (33,3%)
Neurological	4 (66,7%)
Abdominal	2 (33,3%)
Genitourinary	2 (33,3%)
Ophthalmological	3 (50,0%)
Cranial	2 (33,3%)

Musculoskeletal	5	(83,3%)
Cognitive and physical development	6	(100%)
Minor congenital anomalies	6	(100%)
1 Children may be included in more than 1 category.		

The number of organ systems with congenital anomaly diagnoses varied between 3 and 8 systems, with a mean of 6 systems affected per child. All children presented cardiovascular, cognitive and physical development anomalies, as well as minor congenital anomalies (n=6, 100%). The most common cardiovascular anomalies included ventricular septal defects, patent ductus arteriosus (both n=5, 83,3%), atrial septal defects (n=4, 66,7%), arterial hypertension, pulmonary hypertension and aortic anomalies (all n=3, 50%). The most observed minor congenital anomalies were short palpebral fissures and low set ears (both n=4, 66,7%) followed by retrognathism (n=3, 50%). Five children (83,3%) had musculoskeletal anomalies. Overlapping fingers (n=3, 50%) was the most diagnosed in this group of anomalies. Subsequently to these systems, the most detected anomalies were neurological anomalies (n=4, 66,7%), with megacisterna magna and hypotonia (both n=3, 50%) as the most frequent. Ophthalmological anomalies were found in half the cases (n=3, 50%), with microphthalmia as the most commonly found one (n=2, 33,3%). Genitourinary, respiratory, abdominal and cranial anomalies were present in less than half the cases (n=2, 33,3%). In the studied cases, the most common comorbidity found was feeding difficulties, affecting four out of six children (66,7%), followed by failure to thrive (n=2, 33,3%). All main diagnoses identified and their respective frequency are present on Appendix 2.

The full list of specialties that were involved in treatment in both the tertiary pediatric hospital and the hospital of residence area of the children can be observed on Appendix 3. It was identified between 2 and 9 different specialties per child, with a mean of 4. Cardiology and Genetics were the specialties that most accompanied the children from this study.

Out of the six children, four (66,7%) were reliant on, at least, one device or equipment. The four children above mentioned had a median of 2 devices or equipment needed per child, with a maximum number of 3 devices per child. In one case it was not possible to establish the dependence on equipment or devices.

All of the four children who needed equipment assistance were dependent on a nasogastric feeding tube and had some form of respiratory support (both n=4, 66,7%), including oxygen therapy (n=3) and mechanical ventilation (n=2, non-invasive ventilation in one and both non-invasive and invasive in the other). All cases had at least one medication on their therapeutic table, mainly diuretics (n=5) and antihypertensive medication (n=3). There was a median of 1,5 medications (minimum 1- maximum 5) per child.

Two of the children had some kind of surgical intervention done. One child had a patent ductus arteriosus ligation performed at 3 months old (corrective surgery) and survived to 9 years of age. The other child

had an adenotonsillectomy done at 4 years old (for treatment of obstructive sleep apnea syndrome) and a Meckel's diverticulectomy at 8 years old and is still alive, being 12 years old at the time this study was concluded. Of the four cases that were not submitted to surgery, one had a decision for non-execution of therapeutic procedures as a result of the child's poor prognosis.

In the last year of life, four children (66,7%) had hospital admissions and had not been discharged home since birth. Two children (50%) had one intensive care unit admission and one child (16,7%) had two admissions. These hospital admissions had a mean total duration of 49 days (14-98 days), with a total mean length of stay in the intensive care unit of 9 days (8-10 days).

A decision of limitation of therapeutic effort, with a do not resuscitate order, was present in half the cases (n=3, 50%), with one of those also having a decision to withdraw the previously instituted therapy (invasive ventilation and oxygen therapy). All three children died less than 3 months after birth, with two of them even before 1 month of age. In the remaining 3 cases (50%) it is unknown if any decision was made. Out of the three children eligible (born or alive after 2016), only one child (33,3%) was referred to the palliative care team for symptomatic control and advance care planning.

By the conclusion of this study, only one child is still alive. This child continues to be accompanied by the medical specialties of Cardiology and Orthopedics following up on the diagnosis of aortic valve dysplasia managed with symptomatic treatment and scoliosis managed through conservative treatment. Despite the diagnosis of global developmental delay, this child was able to finish the 4th school year at the age of 11 years old.

Statistical analysis registered a median age of death of 62 days (minimum 14 days – maximum 9 years). This analysis also indicated a total 1-month, 1-year and 10-year survival of 66,7%, 33,3% and 16,7%, respectively. Kaplan-Meier curves of 1-year and 10-year survival are presented in Fig. 1.

Regarding the children with full trisomy 18 (n=4), their life span ranged from 14 to 98 days of age, with half (n=2) dying before 1 month of age (full trisomy 1-year survival: 0%). One mosaic reached a life span of 9 years, and the other child is still alive at the time of conclusion of this study. (mosaic 1-year survival: 100%; 10-year survival: 50%). Cause of death was identified in three children as all of them suffered from cardiac arrest. Concerning the place of death, from the total of 5 children that died, 4 children (80%) died in a hospital setting (one in the Intensive Care Unit), while in the remaining case it was not possible to retrieve that information.

Discussion

Over the last 25 years, we identified six children with a diagnosis of trisomy 18, with the majority being female and term infants, findings that are in accordance with numerous studies. (5, 6, 10–12).

In our study, neither of the children had prenatal diagnosis which makes an impossibility to reflect on what approach would have been taken in view of the clinical complexity, wishes and expectations of the

parents, in the presence of prenatal diagnosis.

The great majority of anomalies found correlate with the usually described phenotype on trisomy 18 children.

All cases had a diagnosis of fetal growth restriction throughout the pregnancy, a frequent ultrasound finding documented in previous literature regarding intrauterine anomalies with fetuses with trisomy 18. (10, 13–15)

As found in other studies, in the six cases reviewed, cardiovascular and musculoskeletal anomalies occur with a high prevalence. (4–6) The high prevalence of ventricular septal defects, atrial septal defects and patent ductus arteriosus in the children in this study confirms, once again, the high prevalence of these anomalies in children with trisomy 18. (9, 10, 16)

As corroborated by several articles, the need for ventilatory support, oxygen and feeding assistance is something common throughout children with trisomy 18, and the children in our study are not exception. (10, 17, 18) These needs and medical complexity might be translated on long lengths of stay of hospital admissions. (19, 20) In addition, many studies show a relevant proportion of children discharged home and requiring specialized home care assistance. (21)

Despite the prevalence of such defects, cardiac intervention was performed in only one child (16,7%), namely a patent ductus arteriosus ligation. This proportion is reflected by other reports, in which 7-26% of the children had cardiac surgeries performed. (6, 10, 16, 22) Other studies reveal that infants may undergo major surgeries, not only cardiac surgery but others as gastrointestinal surgery and neurologic procedures. (6, 10, 21, 22)

It is needed to have into consideration that, even if corrective surgery might not be appropriate in certain cases, it is known that surgical intervention contributes to a decrease in-hospital mortality and makes it possible to achieve home care more easily. (22)

The new paradigm shift on the offer of corrective surgery for congenital anomalies has contributed, in the last decade, to increasing numbers for 1-year survival, ranging between 8% and 29% (with a Japanese multicenter study reporting as high as 43%) and 5-year survival, varying between 7,7% and 12,3%. A 9,8% 10-year survival rate was also reported recently. (3, 4, 6, 10–12, 23)

Previous studies state longer survival in children with mosaicism in comparison to the ones presenting with full trisomy, which is in accordance with our findings. Indeed, this might be a consequence of the absence of major congenital anomalies in mosaic children. (23, 24) Although our study has not shown survival beyond 3 months of life in children with full trisomy 18, some studies demonstrate that survival in these individuals can extend beyond 5 years, despite the high associated morbidity. (5, 12, 23, 25, 26)

Independently of their cytogenetic status, this is proof that the designations of “incompatible with life” or “lethal” are not adequate to characterize trisomy 18, as previously reported, and establishes the need to

change this mindset emphasizing the need of improving comfort and quality of life, independently of their length, as well as end-of-life care.

Most parents will have difficulty in understanding the medical aspects, clinical characteristics and treatment needs of trisomy 18 children, resulting in a need for a trustful, honest communication between parents and physicians, validating the parent's hopes and fears, which will, in turn, potentiate conscient, deliberate decisions regarding the children, based on a better understanding of their needs and improving their quality of life as much as possible. (26–29)

A weapon when tackling the difficult decisions that might surge may be the early implementation of specialized pediatric palliative care teams as they can assist in the prenatal and birth plans, postnatal care plan and giving new perspectives and insights to promote the most adequate treatment through an individualized advanced care plan, helping decrease futile therapy, discussing complex ethical issues and working on the child's best interest. Family expectations, beliefs and cultural background are a focal piece of advanced care plans and end-of-life care. (7, 29–31)

As the paradigm shift on management and treatment options for trisomy 18 continues, all new reports, studies and revisions of current literature contribute to the foundation of the development of future guidelines that may assist in providing personalized care to these children and their families, throughout disease progression and including bereavement support.

On account of this study being restricted to a single center in which only six cases were identified, it may be impossible to generalize these findings and conditioned statistic options. As medical records from other hospitals cannot be accessed in some cases, it was difficult to obtain further information from the hospital of the area of residence.

Due to the retrospective nature of this study, diagnoses and comorbidities may have been underdiagnosed.

In our study, neither of the children carried a trisomy 18 prenatal diagnosis, which may have resulted in a smaller number of major congenital anomalies in these children resulting in a better prognosis.

Declarations

Funding:

Not applicable.

Conflicts of interest:

The authors declare that they have no conflict(s) of interest.

Code availability:

Not applicable.

Authors' contributions:

All authors were responsible for the conception of this study. CS and MCF contributed toward the acquisition of data. CS wrote the manuscript. JS and CC had a major contributor in reviewing it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval:

Approval was obtained from the Ethics Committee of *Centro Hospitalar e Universitário de Coimbra*.

Consent to participate:

Not applicable.

Consent for publication:

All authors authorise publication.

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Figures

Figure 1

1-Year and 10-Year Survival

Supplementary Files

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