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ELUCIDATING THE MECHANISMS UNDERLYING THE GENETIC BASIS OF EDWARD SYNDROME (TRISOMY 18): A REVIEW OF THE EVIDENCE

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Abstract

Edwards syndrome is also termed trisomy 18 syndrome. It is an autosomal chromosomal anomaly that occurs due to the presence of an extra chromosome 18. This anamoly was first observed in 1960 by Edwards and his colleagues. It was observed in a neonate who showed various congenital anomalies along with intellectual impairment. Smith et al. corroborated that the presence of an extra chromosome 18 is one of the causes of Edwards syndrome. Edwards syndrome is the second most frequent autosomal trisomy syndrome after trisomy 21. It is found to be living-born with an observed prevalence . However, it is more frequent since there is a high number of fetal losses or terminated pregnancies in cases diagnosed prenatally. As maternal age advances, the likelihood of having a baby with Edwards syndrome (Trisomy 18) also rises.The risk of repetition for a family who had children with full trisomy is approximately one in 100 cases. Edwards syndrome is observed to pose a vast clinical phenotype. Moreover, it is noticed that they have a very guarded prognosis. More than 130 anomalies of various systems such as heart, lungs, brain, skin, musculoskeletal, immune, etc. including almost all body systems, have been noticed in Edwards syndrome patients. It is found that their anomalies occur due to the presence of three copies of chromosome 18. Despite their extra copy of chromosome, the major chromosome observed is the trisomy of chromosome 18, that is observed to be free trisomy-18, which is related to non-disjunction, specially found in the mother's egg cells. Edwards syndrome is found to occur in almost 90 and 95 out of every 100 fetuses who expired in the embryonic or fetal periods of development. Their mean survival time for live-born children is found to range between 2.5 to 14.5 days . One of the primary features of Edwards syndrome is found to be gestalt dysmorphism. Moreover, it is observed that approximately 90 out of 100 the cases of Edwards syndrome occur with cardiac anomalies. More or less, 90 to 95 out of every 100 children suffering from Edwards syndrome tend to have intellectual impairments. Moreover, their features also include fixed flexion deformity of the limbs accompanying overlapping digits, presence of rocker-bottom feet, anomalies in the genitourinary or gastrointestinal tracts. Almost 90 out of 100 children with Edwards syndrome tend to have heart anomalies. Their mean survival time for live-born children is found to range

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between 2.5 to 14.5 days. Additionally, their features include fixed deformity of the limbs accompanied by overlapping digits, rocker-bottom feet, genitourinary anomalies, or anomalies of the gastrointestinal tracts. Almost 90 out of 100 children with Edwards syndrome tend to have cardiac anomalies. Moreover, approximately 90 to 95 out of 100 children suffering from Edwards syndrome tend to be intellectually impaired.

INTRODUCTION

Edwards syndrome is a relative common chromosomal disorder caused by an additional chromosome 18. Initially, travail-born infants were documented in 1960 (Smith et al., 1960) .The syndrome pattern consists of distinct pattern of major and minor anomalies, an evident risk of neonatal or infant mortality, and severe psychomotor retardation or psychosomatic impairment (Harnden et al., 1960). In the perinatal period, the diagnosis of this syndrome mainly depends on the presence of marked clinical abnormalities, such as poor fetal growth, distinctive facial features, typical hand posture, underdeveloped nails, a short big toe, a shortened sternum, and major congenital defects, particularly heart abnormalities. Postnatal disgnosis of Edwards syndrome can be confirmed by examining a standard G-banded karyotype, which reveals an additional chromosome 18 or, in some cases, a partial duplication of its long arm. In some individuals with trisomy 18, mosaicism has been observed in less than 95 out of 100 of the patients in the cited studies below; they present with a highly variable syndrome (Cereda, A., & Carey, J. C. 2012).

2. Epidemiology

Edward syndrome is the second most common autosomal trisomy syndrome, after trisomy 21. Some studies were found dealing with the prevalence of trisomy 18 that took place in various countries such as Australia, Europe, as well as in North America. Based on the various studies performed, it is determined that the live birth prevalence for trisomy 18 is between one in every three thousand six hundred to one in ten thousand with the most accurate estimate of one in six thousand (Rasmussen et al. 2003). It is widely recognized that the risk of fetal loss and stillbirth is high in trisomy 18 pregnancies, with the current prevalence of the condition being determined prenatally by maternal age screen or maternal serum marker screens with amniocentesis, with subsequent termination of pregnancy in a substantial proportion of cases. As a consequence, it could be assumed that the prevalence of Edward syndrome would be higher than that of live-born instances. A milestone study carried out in the United Kingdom in 1996 found that the total prevalence of Edwards syndrome was one in four thousand two hundred and seventy-two with a live-born frequency of one in eight thousand three hundred and thirty-three (Embleton et al., 1996); total frequency of Edwards syndrome found in Hawaii was one in two thousand one hundred and twenty-three with live-born frequency of one in seven thousand nine hundred for (Forrester & Merz, 1999). More recent research revealed that there was an increase in the total prevalence of Edwards syndrome by 369 percent in the last 20 years due to the rise in the maternal age; nevertheless, a fall in the live-born frequency of trisomy 18 was determined by the increase of prenatal diagnostic procedures used, with a substantial percentage of subsequent terminations of pregnancies. (Crider et al., 2008). In the mentioned recent research, the total prevalence of Edward syndrome was found to be one in two thousand five hundred for the United States, with a live-born frequency of one in eight thousand six hundred. In the United Kingdom, it was found to be one in two thousand six hundred with a live-born frequency of one in ten thousand. (Irving et al., 2011). Prevalence in females is more at birth in comparison to males, whereas this disparity does not exist if the ratio is calculated for the sex ratio among fetuses electively terminated (Crider et al., 2008). Additionally, the risk of fetal loss is more among males in comparison to females. Also, females had a better chances of survival in comparison to males (Rasmussen et al., 2003).

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3. Pathophysiology:

The physical and developmental abnormalities seen in Edwards syndrome are believed to result from having triple copies of two particular regions on the long arm of chromosome 18 (Balasundaram et al., 2021). Research suggests that the severe intellectual disability often seen in this condition is linked particularly to the extra genetic material (Balasundaram et al., 2021). On the other hand, an additional copy of the short arm of chromosome 18 does not seem to play a significant role in the main characteristics of Edwards syndrome (Balasundaram et al., 2021).

4. Prognosis

Trisomy 18 affects approximately one out of three thousands to one out of ten thousands live births (Cereda A & Carey JC, 2012).The syndrome involves pervasive congenital defects that simultaneously disrupt the formation and function of the brain, heart, lungs, and gut. More than half of affected infants exhibit craniofacial anomalies (Imataka G et al., 2016). Cardiac defects are particularly common, occurring in over ninety five individuals out of hundred with trisomy 18 (Courreges P et al., 2003). Around half of the affected infants live longer than the first week, while close to ninety out of hundred do not survive beyond their first year (Imataka G et al., 2016). Among those who survive, outcomes are often marked by profound developmental delay, limited ability to communicate with others, minimal independent mobility, and significant feeding difficulties. Many children also experience respiratory complications, including pulmonary disease, tracheomalacia, obstructive sleep apnea (Cereda A & Carey JC, 2012), and long-term oxygen dependence. Recent scrutiny suggests that past survival data may be skewed by a lack of active management, raising the possibility that more intensive neonatal care could have altered these outcomes. Some studies suggest that survival may be improving by surgries and diagnosis (Kosho Tet al., 2006). Similarly, a Canadian review of 254 individuals with trisomy 18 reported a survival of nine days and a almost ten individuals out of hundred can survive for ten years. Notably, among the thirty five children who underwent surgical interventions, survival at one year following the first surgery was sixty nine out of hundred(Nelson KE et al., 2016). However, the criteria used to determine surgical candidacy were not clearly described. Additionally, longer survival and variable clinical severity in some children may be partially explained by mosaic form (Tucker ME et al., 2007). Although trisomy 18 is still a life-limiting condition, improvements in medical care have greatly influenced survival and overall outcomes (Tamaki S et al., 2022). About half of all babies with trisomy 18 who reach full term are born alive, even though roughly forty out of hundered do not survive at a time delivery and nearly thirty three out of hundred of surviving babies are born prematurely (Tamaki S et al., 2022). Among infants who are born alive, about sixty to seventy five out of hundred live through the first seven days, twenty to fourty out of hundred survive the thirty days, and ten to nineteen out ot hundred reach their first birthday (Tamaki S et al., 2022). More recent research shows that when infants receive advanced medical care, including specialized hospital support and corrective heart surgeries can rise the one-year survival rate among thirty to fifty out of hundred individuals (Tamaki S et al., 2022). Female infants tend to survive longer than males, and children with mosaic trisomy 18 often have better long-term outcomes than those with the full form of the condition (Tamaki S et al., 2022). Most deaths result from severe heart problems caused by heart defects or from complications during respiration (Tamaki S et al., 2022).

5. Clinical Feature:

Edwards's syndrome can affect many parts of the body, resulting in many different health complications and serious medical challenges. (Goel et al., 2019)

5.1 Congenital heart disease:

Cardiac anomalies represent a highly prevalent clinical feature in neonates diagnosed with Trisomy 13 and 18 (Musewe et al., 1990). A subset of these pediatric patients may derive clinical benefit from either corrective or palliative cardiovascular surgeries performed shortly after birth or within the first few months of life (Balderston et al., 1990). Specifically, a significant number of infants with Trisomy 18 are born with large ventricular septal defects; these

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malformations carry a high risk of progressing toward heart failure, even when managed with the most advanced medical treatments available (Van Praagh et al., 1989).Research has shown that heart surgery can sometimes help patients with trisomy 13 or 18, but the risk of complications and death during or shortly after the procedure is higher (Costello et al., 2015).Research indicates that infants who need mechanical ventilation before surgery tend to have the poorest outcomes and often continue to require long-term ventilatory support (Cooper et al., 2019).Extracorporeal membrane oxygenation (ECMO) serves as a viable postoperative support mechanism following specific cardiac procedures, separate from the heart-lung machine used during the operation, but it is rarely needed for individuals diagnosed with Trisomy 13 or 18 (Furlong-Dillard et al., 2017). For these patients, clinical guidelines suggest that ECMO candidacy should be evaluated using the same criteria applied to the general surgical population, while ensuring that parents are informed about the higher risks of complications and mortality. (Furlong-Dillard et al., 2017) Documented cases demonstrate that ECMO has effectively stabilized neonates with Trisomy 13 or 18 suffering from transient non-cardiac conditions, such as meconium aspiration syndrome, with outcomes similar to survival rates observed across broader pediatric cohorts. Consequently, a diagnosis of T13 or T18 should be integrated into the clinical assessment for ECMO rather than serving as an automatic contraindication for the therapy (Alore et al., 2021).

5.2 Clinical Description:

Trisomy 18 typically presents with poor growth before birth, distinctive facial features, other minor physical differences, major congenital abnormalities, and significant delays in physical and cognitive development. (Baty et al., 1994) Growth restriction begins during pregnancy and continues after birth, often accompanied by feeding difficulties that may require tube feeding (Baty et al., 1994). Specialy developed growth charts are used to track the physical development of children with trisomy 18. (Baty et al., 1994)

6. Diagnosis:

The condition known as Fetal akinesia sequence, or Pena-Shokeir syndrome type I, is a seldom-seen disorder inherited through autosomal recessive traits disorder in which reduced fetal movement leads to characteristic features such as facial abnormalities (including a small jaw), multiple joint contractures, poor restricted intrauterine development, polyhydramnios, and pulmonary hypoplasia (Balasundaram, P., & Avulakunta, I. D. (2021)).Anemia is commonly seen in Edwards's syndrome and often results from problems in blood cell development along with the effects of chronic illness (Batinović et al., 2023).The severe iron-deficiency anemia required immediate treatment with a packed red blood cell transfusion, in line with recommended care for anemia in individuals with trisomy 18 (Watad et al., 2022).Central nervous system issues, including convulsive episodes, and unusual movements frequently occur among individuals with Edwards's syndrome and can greatly affect the patient's overall well-being (Outtaleb et al., 2020).Even with improvements in prenatal screening and diagnosis, the outlook for babies with Edwards's syndrome is still very poor, with most affected pregnancies ending in miscarriage or death shortly after birth (Yusrawati & Kartika, 2015).

The majority of Trisomy 18 instances are detected prenatally, often through diagnostic evaluations that consider maternal age alongside serological and sonographic assessments throughout the second trimester. (Kroes, Janssens, & Defoort, 2014) Before birth, Edwards syndrome may be indicated by slowed growth in the womb, excess amniotic fluid, missing or underdeveloped brain structures, fluid-filled cysts in the brain, a thickened neck area, a short and broad head, clenched hands with overlapping fingers, heart defects, a belly wall defect (omphalocele), and a single umbilical artery. (Kroes, Janssens, & Defoort, 2014) The assessment and diagnosis of trisomy 18 often start before birth. Blood tests during pregnancy can reveal low levels of certain substances, including serum biomarkers including AFP, hCG, and unconjugated estriol. (Staples, Robertson, Ranieri, Ryall, & Haan, 1991) Blood tests and the utility of molecular indicators is enhanced when integrated with standard sonography, like a thickened neck fold. (Zhen, Li,

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Yang, & Li, 2019) For instance, noninvasive prenatal testing using cell-free fetal DNA found in maternal circulation assists in the identification of chromosomal trisomy 18. When combined with ultrasound, noninvasive prenatal testing can be extremely accurate, correctly identifying trisomy 18 in all cases and reliably ruling it out by the second trimester. (Zhen, Li, Yang, & Li, 2019) Screening is important for these patients because multiple organ systems are often affected. (Cammarata-Scalisi et al., 2017) While clinical suspicion is often driven by phenotypic markers; however, karyotype analysis provides definitive verification of the trisomy, and chromosomal microarray offers granular genomic data, such as identifying mosaic forms is present. (Cammarata-Scalisi et al., 2017)

Common features of Edwards's syndrome frequently involve congenital cardiac defects present at birth, maturational delays, and nursing or oral intake complications, a smaller-than-average head (microcephaly), and atypical craniofacial characteristics such as inferiorly placed or unusually shaped auricles, a receding chin (micrognathia), a cephalad-pointing nasal tip, wide-set eyes, and blepharoptosis (Pereira et al., 2012).Other common differences can include a shorter breastbone, fluid-filled cysts in the brain (choroid plexus cysts), clenched fists with digits overlapping, hypoplastic digits or nails, missing radius bone, syndactyly of the second and third pedal digits, talipes equinovarus that curve outward (rocker-bottom feet), and in boys, undescended testicles or an abnormal opening of the urethra (hypospadias) (Crawford & Dearmun, 2016).Children with Edwards syndrome often have additional structural anomalies, like orofacial clefts or palate, kidney problems, heart malformations, and hernias in the groin or belly button (Carey, 2021).Sadly, almost ninety-five percent of these infants do not survive past their first twelve months of life, usually due to serious heart or brain abnormalities (Outtaleb et al., 2020).

7. Health supervision and management

Upon discharge from the clinical setting, infants with Edwards syndrome should have regular follow-up visits, particularly during the critical neonatal period and the initial months following birth, closely monitor their health (Cereda, A., & Carey, J. C. 2012).

7.1 Treatment

There is currently no cure for Edwards's syndrome (Balasundaram, P., & Avulakunta, I. D. 2021).Decisions about treatment for newborns with Edwards's syndrome can be ethically complex because of the high risk of mortality and the prognostic uncertainty regarding which neonates will achieve long-term survival (Balasundaram, P., & Avulakunta, I. D. 2021).Fatal outcomes in this population are primarily attributed to problems with the brain, heart, or lungs (Balasundaram, P., & Avulakunta, I. D. 2021).Care should be tailored to each child, with a strong focus on respecting the parents' wishes and making decisions that serve the best interests of the child (Balasundaram, P., & Avulakunta, I. D. 2021).In the past, trisomy 18 was often considered universally fatal, and newborns were not routinely resuscitated at birth (Neumar et al., 2015).However, current guidance from leading pediatric authorities and updated neonatal life support protocols now supports providing active management including resuscitation in the delivery room, rather than automatically withholding care (Neumar et al., 2015).

8. Family Support and Ethical Considerations:

Trisomy 18 and other severe disorders have a strong emotional impact on families affecting many aspect of social and familial life (Surve et al., 2024; Ñarca et al., 2021).Families of these children frequently face socioeconomic problems such as low income, barriers to specialized medical care and developmental programs, and various societal challenges (Şarca et al., 2021; Zhang et al., 2022).Due to the ongoing focus on the children's welfare, the intricacy of congenital abnormalities significantly impacts familial bonds and domestic stability, affecting interpersonal connections (Andrade et al., 2022).To manage their children's physical, cognitive and emotional development and help their community involvement, parents and families must have a thorough understanding of the syndrome and continuous support. Acquiring professional clinical assistance and mental health resources is a continuous frequently difficult

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requirement particularly in areas where healthcare services are limited (Andrade et al., 2022; Surve et al., 2024; Ñarca et al., 2021; Vijayalakshmi et al., 2021; Zhang et al., 2022).Orthothanasia is part of the ethical approach to palliative care, which aims to protect patients general well-being and dignity while allowing them to face death with some peace.Misthanasia, euthanasia and disthanasia are other terminology used when discussing about palliative care.According to Pimenta et al. (2006), misthanasia is the term for mistakes in behavior, dysthanasia refers to the implementation of medical procedures that extend biological life without providing therapeutic benefit or improving the patient's condition (Pimenta et al., 2006), and euthanasia involves the intentional shortening of a patient's life to mitigate suffering (Pimenta et al., 2006) which is illegal in Brazil.In a multidisciplinary and integrative approach, proper orthothanasia treatment incorporates scientific knowledge and calls for technical proficiency including human and ethical awareness. Since everyone has to interact with patients who are dying at some time in their professional lives, it is ideal for all healthcare workers to integrate into practice (Pimenta et al., 2006).

9. Prevention and Risk Reduction:

For families who have already experienced a child with complete Trisomy 18, the likelihood of the condition recurring in a subsequent pregnancy is generally estimated at 1% (Carey, 2010). Medical records include rare instances where parental mosaicism was the underlying factor (Beratis et al., 1972; Gersdorf et al., 1990; Tucker et al., 2007; Ukita et al., 1997). Research also indicates that different types of chromosomal trisomies can manifest across multiple births within the same family (Baty et al., 1994). Empirical data suggests that while the risk of recurrence is typically below 1%, this figure still exceeds the baseline risk expected for the mother's specific age group (De Souza et al., 2009; Uehara et al., 1999). Depending on whether one of the parents has a genetic rearrangement (translocation or inversion), families with partial trisomy 18 may have a higher recurrence risk than individuals with the complete chromosomal form (Carey, 2010). In light of the fact that early identification is essential for improving prognosis, patients presenting with partial trisomy 18 (Starr et al., 2014).

10. Current research and future directions

Congenital cardiac malformations occur with high frequency in babies with trisomy 13 and trisomy 18. More than half of infants with trisomy 13 and the vast majority of those with trisomy 18 are affected. Some of these babies may benefit from heart surgery, either to correct the problem or to ease symptoms, performed soon after delivery or during the initial months of life (Costello, J. P., et al. 2015).For example, substantial ventricular septal defects especially prevalent among infants with T18 can lead to worsening heart failure even when the best possible medical treatment is provided. Research shows that heart surgery can offer meaningful benefits for some children with T13 or T18; however, these procedures are also linked to an increased probability of complications and mortality during and following the surgical event compared with other infants (Costello, J. P., et al. (2015)). Studies indicate that babies who need mechanical ventilation before heart surgery tend to have the worst outcomes and often continue to rely on ventilator support for a long time afterward. Although extracorporeal membrane oxygenation (ECMO) provides a specialized form of physiological support used after some heart surgeries is rarely used in infants with trisomy 13 or 18, it can still be considered when appropriate.As with other surgical candidates, the decision to use ECMO should be made carefully, with clear and compassionate counseling for parents about the elevated probability of adverse events and death linked to this treatment within this specific patient group (Furlong-Dillard, J. M., et al., (2017)). ECMO has been used successfully in some infants with trisomy 13 or 18 when they have non-cardiac conditions that are potentially reversible, such as meconium aspiration syndrome. In these situations, outcomes have been similar to those seen in other children who receive ECMO.This suggests that having trisomy 13 or 18 alone should not automatically rule a baby out for ECMO; instead, the genetic diagnosis should be considered alongside other clinical factors when deciding whether ECMO is appropriate (Alore, E. A. et al., (2021)).In certain situations, doctors may

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recommend palliative surgery instead of corrective surgery.The goal in these cases is not to fully fix the heart defect, but to enhance neonatal comfort and functional status.This approach can allow doctors to stop prostaglandin infusions which are used to keep the ductus arteriosus open in duct-dependent heart conditions make it possible for the baby to go home, and help relieve symptoms of congestive heart failure (Hollis,T. et al., 2015).

Conclusion

Edwards syndrome, also referred to as Trisomy 18, represents a infrequent chromosomal anomaly precipitated by the presence of a third copy of the 18th chromosome.It is linked to many physical abnormalities as well as a very high risk of early death.Survival rates for these infants rarely exceed the one-year mark, and only a small number live past five years. In our study, we describe a patient who survived to 16 years of age, far exceeding typical expectations.This unusual survival provides valuable insight for prognosis, counseling families, and planning medical care.Although more research is needed to understand why some patients live longer, cases like this help us better understand the long-term course of the condition, possible complications, and how care needs may change as individuals with Edwards syndrome grow older.Managing difficult airways and breathing problems was one of the biggest challenges for our patients during surgery.Even small problems with ventilation could quickly become life threatening.This case series gives a detailed, long term view of patients with full trisomy 18 throughout the surgical window and offers helpful guidance for doctors and families when making care decisions.

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