Edwards' Syndrome (Trisomy 18)

Synonym: trisomy E syndrome

Edwards' syndrome (trisomy 18) is a common autosomal chromosomal disorder due to the presence of an extra chromosome 18.

Genetics

- The Edwards' syndrome phenotype results from full, mosaic or partial trisomy 18q. Full trisomy 18 is the most common form occurring in about 94% of cases. In full trisomy every cell contains three full copies of chromosome 18.
- Mosaics can occur in about 5% of cases in which some cells are normal with 46 chromosomes and others have the extra chromosome. Partial trisomy 18 can (rarely) occur if a segment of chromosome 18 is present in triplicate, usually due to a balanced translocation carried by one parent.

Epidemiology

- Trisomy 18 is the second most common autosomal trisomy among liveborn children after trisomy 21.
- Various population studies across the world estimate live birth prevalence of trisomy 18 between 1 in 3,600 to 1 in 10,000 with the best overall estimate as 1 in 6,000 live births. Changes in prenatal screening and maternal age are having an impact on liveborn prevalence.
- In liveborn infants, it is more likely that the affected infant is female rather than male. This is thought to be due to the fact that male fetuses with trisomy 18 are more likely to be lost due to miscarriage or stillbirth.

Risk factors

- A personal or close family history of giving birth to an affected child increases the risk.
- Risk rises with rising maternal age. The live birth prevalence is constant until 30 years of age and then increases exponentially till 45 years of age before becoming constant again.
- A small positive association of paternal age with trisomy 18 (as seen in Down's syndrome) has also been observed.

Presentation

- Currently, most cases in the developed world are diagnosed antenatally based on screening by maternal age, maternal serum marker screening, or detection of sonographic abnormalities during second or third trimester. Antenatal diagnosis of trisomy 18 leads to termination of pregnancy in 86% of cases.
- The most common soft sonographic markers detected in late first or early second trimester are increased nuchal translucency thickness and absence or hypoplasia of the nasal bone, identifying two thirds of cases. The detection rate is increased further if reversed flow in ductus venosus and tricuspid regurgitation are assessed as well.
- Antenatal pattern of ultrasound findings in trisomy 18 have been well defined by many studies. One or more sonographic abnormalities are detected in over 90% of fetuses and two or more abnormalities are present in 55% of cases. The features described include:
  - Growth restriction.
  - Polyhydramnios.
  - Strawberry-shaped cranium.
  - Choroid plexus cyst.
  - Overlapping of hands fingers (2nd and 5th on 3rd and 4th respectively).
  - Congenital heart defects.
  - Omphalocoele.
  - Single umbilical artery.
- The clinical presentation of Edwards’ syndrome is characterised by antenatal growth deficiency, specific craniofacial features, major system malformations and marked psychomotor and cognitive developmental delay. Features that may be noted after birth include:
  - Low birth weight.
  - Craniofacial abnormalities:
    - Low-set and malformed ears.
    - Micrognathia (small jaw).
    - Prominent occiput and dolichocephaly.
    - Small facial features - eg, microphthalmia, microstomia.
    - Microcephaly.
    - Cleft lip and palate and/or narrow palate.
    - Coloboma of iris.
• Skeletal abnormalities:
  • Typical hand posture: clenched hands with index finger overriding middle finger and fifth finger overriding fourth finger.
  • Thumb aplasia.
  • Radial hypoplasia or aplasia.
  • Short sternum.
  • Hypoplastic nails.
  • Short, dorsiflexed hallux.
  • Prominent calcaneus (rocker bottom feet).

• Congenital heart defects: >90% have these - eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of aorta.
• Gastrointestinal abnormalities: eg, omphalocele, oesophageal atresia ± tracheo-oesophageal fistula, umbilical or inguinal hernia, diastasis recti, imperforate anus, pyloric stenosis.
• Urogenital abnormalities: eg, gonadal dysgenesis, cryptorchidism, prominent clitoris, horseshoe kidney, hydronephrosis, cystic kidneys, renal agenesis.
• Neurological problems: anencephaly, hydrocephaly and other brain malformations, severe learning disability, neonatal hypotonia followed by hypertonia, seizures and jitters.
• Pulmonary hypoplasia.

Differential diagnosis
  • The clinical pattern of Edwards’ syndrome is well defined and rarely misdiagnosed.
  • There are some overlapping features with Patau’s syndrome (trisomy 13), Pena-Shokeir syndrome type 1 or syndromes with fetal akinesia sequence, and with CHARGE syndrome: Coloboma, Heart defects, Atresia of the choanae, Restriction of growth and developmental delay, Genitourinary abnormalities and Ear anomalies.

Investigations and management
  • Cytogenetic studies and chromosomal analysis will confirm the diagnosis.
  • Organ systems will need specific investigation depending on the abnormality - eg, echocardiography for cardiac abnormalities, skeletal radiography, etc.
  • There are ethical issues surrounding the care and management of infants and children with Edwards’ syndrome. There is some agreement that management decisions should focus on the best interest of the child and pay due respect to parental opinion. A collaborative approach with openness among team members is recommended and guidelines for management in the neonatal unit have been proposed.
  • Treatment of a liveborn infant is generally supportive but life-sustaining measures are not always carried out. Considerable thought and discussion are recommended before undertaking measures such as surgical correction of abnormalities. Ideally a full informed discussion with parents, undertaken before the birth of the child, should inform management.
  • Feeding difficulties are common and often require tube feeding in neonatal period and gastrostomy in older children. Gastro-oesophageal reflux is common and can be a significant problem which is linked to recurrent aspiration and death.
  • Cardiac defects have traditionally been managed conservatively as they not usually regarded as a cause of early infant mortality although some studies report early development of pulmonary hypertension induced by heart defects having a significant role in early death. Recently, a large series of patients undergoing surgical management has shown that most children with Edwards’ syndrome tolerate heart surgery well.
  • Respiratory problems in the form of upper airway obstruction or apnoea may need specialist respiratory assessment and input, including sleep studies. Treatment options including home monitoring; oxygen can be arranged as necessary in individual cases in close discussion with parents. Some children may require tracheostomy for continued respiratory support.
  • Ophthalmological evaluation to detect common structural abnormalities is recommended. Treatment of eye defects is the same as in other children.
  • Audiological evaluation is recommended in all infants. Hearing aids can be used in those with sensorineural hearing loss.
  • Clinical and if necessary radiological evaluation of the spine to detect scoliosis, is indicated in children over 2 years of age. In older children with severe scoliosis, the surgical option needs to be considered.
  • Abdominal ultrasound to check for renal abnormalities should be done.
  • Screening abdominal ultrasound scans are recommended in older infants because of the high incidence of intra-abdominal tumours such as Wilms’ tumour and hepatoblastoma.
  • Neurological and developmental evaluation helps in assessing the need for physiotherapy and specialised developmental support. Seizure can usually be managed well with standard anticonvulsant treatment.

Natural history/prognosis
  • Perinatal and neonatal management for Edwards’ syndrome is complicated because of a number of reasons, including the severity of clinical presentation at birth necessitating urgent decision-making by doctors and parents as well as the well-recognised high mortality and significant developmental disability in the surviving children.
  • Incidence of preterm birth is high (35%) and 38.5% of fetuses die during labour.
  • A study from England and Wales estimated that for live births with full Edwards’ syndrome, the median survival time is 14 days. The chance of survival to the age of 3 months is 20% and to 1 year, 8%. The one-year survival time for live births with trisomy 18 mosaicism was 70%. Thus, one in five survive for three months or more and one in twelve survive for a year or more.
  • The major causes of death are sudden death due to central apnoea, cardiac failure due to cardiac malformations and respiratory insufficiency due to hypoventilation, aspiration, upper airway obstruction or a combination of these factors.
Further reading & references

- Although historically the practice has been to avoid active neonatal resuscitation, there is change in practice with many neonatologists intervening in accordance with parental wishes to support the baby. [12]
- A study from Japan has reported an increased median survival time of 152.5 days and a survival rate of 25% at one year in a group of infants with trisomy 18 offered full intensive care other than cardiac surgery. [13]

Screening and counselling

- In the event of antenatal or neonatal diagnosis of Edwards’ syndrome, parents need support and counselling which has to be realistic. Uncertainty about the outcome needs to be discussed and they have to be prepared for making decisions regarding resuscitation, intensive care and surgery. They should be given information about support groups such as SOFT - see below.
- If Edwards’ syndrome is due to an unbalanced translocation, both parents should undergo chromosomal analysis. It may be that the translocation in the infant occurred de novo but a balanced translocation may be found in one of the parents. This has significance for future pregnancies. Other family members may also be affected.
- Screening and/or prenatal diagnosis should be offered for future pregnancies.
- For full Edwards’ syndrome, the risk of recurrence in a future pregnancy is higher than the general population risk and estimated as less than 1%. [14] Risk may be higher if a parent carries a balanced translocation. Referral should be made to a geneticist as appropriate.
- Serum screening that is currently carried out for Down’s syndrome (trisomy 21) may help to identify not only fetuses at risk of Down’s syndrome but also those at risk of trisomy 13 and trisomy 18.
- A recent study looked at screening for trisomy 18 by using maternal age, fetal nuchal translucency, free beta human chorionic gonadotrophin (beta-hCG) and pregnancy-associated plasma protein-A, alongside screening for trisomy 21. More than 95% of trisomy 18 fetuses were detected. [15]
- Another study concluded that the addition of a trisomy 18-specific risk algorithm in the second trimester achieved high detection rates for aneuploidies other than Down’s syndrome. In this study, all patients had a nuchal scan in the first trimester, and those without cystic hygroma had a combined test (nuchal translucency, pregnancy-associated plasma protein-A (PAPP-A), free beta-hCG) and returned at 15-18 weeks for a quadruple screen using serum alpha-fetoprotein, total hCG, unconjugated oestriol (uE3) and inhibin-A. [16]
- Ultrasound: typical structural abnormalities may be detected on prenatal ultrasound and may raise the suspicion of Edwards’ syndrome. Examples include persistent abnormal hand/finger position, choroid plexus cysts, cardiac defects, two- vessel umbilical cord. [17, 18] A second-trimester anatomical screening by ultrasound appears to be a good method of detection. [19]

Prenatal diagnosis

- Amniocentesis or chorionic villus sampling is usually needed to make a definitive prenatal diagnosis.
- A systematic review evaluating the accuracy of non-invasive prenatal diagnosis using cell-free fetal DNA in maternal plasma has confirmed the high accuracy of this technique for trisomies. For Edwards’ syndrome, the sensitivity was calculated as 97.4% and specificity as 99.95%. [20]

Ongoing debate[21]

- There is increasing debate about what is the right way of caring and managing children with Edwards’ syndrome.
- While the conventional approach has been to withhold technological support, this has been questioned by some studies which have shown that 5-10% of children with Edwards’ syndrome live more than a year and that parents of such children report caring for them as satisfying and fulfilling.
- Recent studies have also analysed relevant issues including parental autonomy, best interest of the child standard, and quality of life.
- A balanced approach to counselling parents of newborns with trisomy 18 at the time of diagnosis is recommended. Counselling should include presentation of accurate survival figures, avoidance of language that assumes outcome, communication of developmental outcome that does not pre-suppose perception of quality of life, and respect for a family’s choice, whether it is comfort, care or intervention.

History[1]

Trisomy 18 was described by Edwards et al in April 1960 and by Smith et al in September 1960. It was John Edwards who gained the eponym.

Further reading & references

- **Support Organisation For Trisomy 18 and 13 (SOFT) UK**
- Cereda A, Carey JC; The trisomy 18 syndrome, Orphanet Journal of Rare Diseases, 2012.
8. Bruns DA; Caring for an infant with trisomy 18: A case study and guidelines, Clinical Nursing Studies

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