Oesophageal atresia, VACTERL association: Fanconi’s anaemia related spectrum of anomalies

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Abstract

Oesophageal atresia usually occurs without any genetic background. Three cases associated with Fanconi’s anaemia are reported. One neonate had growth retardation and numerous malformations including oesophageal atresia and four other components of the VACTERL association. In the two others, oesophageal atresia was isolated. In patients with such malformations an early diagnosis of Fanconi’s anaemia may have important genetic and therapeutic implications.

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Keywords: Fanconi’s anaemia; oesophageal atresia; VACTERL; chromosome breakage

Fanconi’s anaemia is a recessive autosomal condition (1/200 to 1/300 heterozygote frequency) involving bone marrow failure, congenital malformations (skeletal defects, especially radial ray aplasia, small stature, renal and genital malformations, microcephaly with microstomia, and microphthalmia), and a predisposition to malignancy.1 2 The high frequency of chromosome breakage, particularly apparent when the cells are incubated with chemical clastogens such as nitrogen mustard, diepoxybutane or chloromethine, constitutes the specific diagnostic test for this condition.1 2

Case reports

CASE 1

A boy who was small for dates (height: 43 cm, weight: 1700 g) presented in the neonatal period. He had no family history. Five of the component parts of the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula with oesophageal atresia, renal defects, and limb abnormalities): patent ductus arteriosus, type III oesophageal atresia (proximal blind oesophagus with distal oesophageal fistula), duodenal atresia, ectopic kidneys, hypoplasia, microcephaly, axillary muscles, and thumb hypoplasia were present. Full blood count was normal. Cytogenetic analysis with conventional G-banding techniques revealed a 46 XY karyotype. At the age of 19 months, a tracheo-oesophageal fistula was discovered which required surgery. The child’s growth was impaired, as was his cognitive development. At the age of 5, the appearance of ecchymoses led to the discovery of thrombocytopenia (platelet count: 50 × 109/l) associated with macrocytosis (mean corpuscular volume (MCV): 89 fl); a culture of blood lymphocytes exposed to diepoxybutane showed Fanconi’s anaemia characteristic breaks, gaps, rearrangements, and exchanges in 59/62 mitoses. As there is no identical histocompatible sibling, no bone marrow transplantation is planned in the immediate future.

CASE 2

An isolated and sporadic type III oesophageal atresia was diagnosed at the systematic neonatal examination in a full term 2200 g girl. Full blood count was normal. End-to-end anastomosis was performed on the first day of life. Growth and development were normal. The progressive onset at age 11 of non-regenerative macrocytic anaemia (haemoglobin: 36 g/l, MCV: 97 fl, reticulocyte count: 12 × 109/l) with thrombocytopenia (11 × 109/l) led to the diagnosis of bone marrow hypoplasia. There were cafe-au-lait spots on the neck and trunk, a triangular shaped face, and micrognathia. Nitrogen mustard chromosome testing revealed more than five Fanconi’s anaemia specific chromosomal lesions in 45/50 cells. Transfusion treatment has now begun, as has the process for selecting a bone marrow histocompatible unrelated donor.

CASE 3

A girl, born at full term weighing 3100 g, had an isolated and sporadic type III oesophageal atresia diagnosed on routine examination. Full blood count was normal. Gastrostomy and tension free end-to-end anastomosis were performed on the first day of life; an oesophago-pleural fistula occurred which eventually healed with pleural and oesophageal atresia. In view of severe chronic lung disease, a tracheo-oesophageal fistula was diagnosed at age 5 by simultaneous oesophageal and tracheal endoscopy. After surgical cure, a new oesophago-pleural fistula occurred, associated with thrombocytopenia (platelet count: 30 × 109/l), macrocytosis (MCV: 104 fl), and moderate bone marrow hypoplasia. Cytogenetic analysis of blood lymphocytes incubated with nitrogen mustard showed the Fanconi’s anaemia characteristic chromosomal rearrangement in 70 cells tested out of 100. Growth and development remained satisfactory at 12 years. There were mild dysmorphic features (fig 1). None of her siblings is HLA identical, and no allogenic bone marrow transplant is planned at present.

Discussion

No cases of Fanconi’s anaemia have been reported in the large series of patients with oesophageal atresia, despite long term follow-up and genetic analysis of blood lymphocytes incubated with chemical clastogens such as nitrogen mustard, diepoxybutane or chloromethine.
per, Butenandt, Carrere, et al

...by Paediatricians should be aware of these issues when investigating a neonate presenting with oesophageal atresia. The early diagnosis of Fanconi’s anaemia leads to specific management: transfusions, supportive care, routine screening for development delay and malignancies, family study (HLA analysis and search for Fanconi’s anaemia cytogenetic stigmata in siblings), umbilical cord stem cell sampling in a sibling, and search for an HLA identical unrelated donor. Appropriate genetic counselling should be given and antenatal diagnosis offered for a further pregnancy. 


cytogenetic analysis with clastogen agents in all neonates with oesophageal atresia before a prospective study assessing the frequency of Fanconi’s anaemia becomes available. We propose the indication should be similar to searching for trisomy 18 and 21 or other chromosomal abnormalities, at least for children with oesophageal atresia presenting with poor fetal growth or another malformation.

The relationship between congenital malformations, bone marrow failure, cancers, chromosomal breakages, and the five constituent groups in Fanconi’s anaemia is poorly understood. The embryogenesis of the oesophagus and trachea and their separation occur between days 21 and 32 after fertilisation and require considerable proliferation; we speculate an alteration common to embryogenesis and haematopoesis. In our cases 1 and 3 there was late relapsing secondary tracheo-oesophageal fistula, a complication reported in only 3–8% of patients with oesophageal atresia. It may be that the loss of Fanconi’s anaemia cell proliferative activity plays a part both in embryogenesis and in the occurrence of recurrent fistula.

The only curative treatment for Fanconi’s anaemia pancytopenia and the best preventive treatment for leukaemic evolution is allogenic bone marrow or umbilical cord blood transplantation from a HLA genotypically identical sibling. The chances of success for such treatment are greater the younger the child and the lower the number of pretransplant platelet transfusions. Work continues on bone marrow transplantation from alternative donors and on gene therapy. The early diagnosis of Fanconi’s anaemia leads to specific management: transfusions, supportive care, routine screening for development delay and malignancies, family study (HLA analysis and search for Fanconi’s anaemia cytogenetic stigmata in siblings), umbilical cord stem cell sampling in a sibling, and search for an HLA identical unrelated donor. Appropriate genetic counselling should be given and antenatal diagnosis offered for a further pregnancy. Paediatricians should be aware of these issues when investigating a neonate presenting with oesophageal atresia.


