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

Y Perel, O Butenandt, A Carrere, R Saura, M Fayon, T Lamireau, P Vergnes

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.

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 microphthalmia), and a predisposition to malignancy. The high frequency of chromosome breakage, particularly apparent when the cells are incubated with chemical clastogens such as nitrogen mustard, diepoxybutane or chlorometine, constitutes the specific diagnostic test for this condition.

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, hypoplasias, micrognathia, and a normal chromosome complement (46 XY). The high frequency of chromosome breakage, particularly apparent when the cells are incubated with chemical clastogens such as nitrogen mustard, diepoxybutane or chlorometine, constitutes the specific diagnostic test for this condition. The diagnostic test has now begun, as has the process for selecting a bone marrow histocompatible unrelated donor.

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 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 oesophagopleural fistula occurred which eventually healed with pleural and oesophageal drainage. 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 oesophagopleural 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 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.
up, nor in rare cases of familial oesophageal atresia. The diagnosis of Fanconi’s anaemia is probably underestimated, since haematological signs may be moderate and occur very late. In recent reports, 40.5% of patients with Fanconi’s anaemia at diagnosis have no malformation, 43% have both malformations and pancytopenia, and 16.5% have malformations only; oesophageal atresia is reported in 1.4% and tracheo-oesophageal fistula in 3.5%. This contrasts with the frequency of 1/4000 or 1/3000 for this type of malformation in the general population.

Ten per cent of patients with Fanconi’s anaemia have at least three of the component parts of the VACTERL-hydrocephalus association. Several such malformation associations, later demonstrated cytogenetically to be Fanconi’s anaemia, have been reported. Our case 1 is different from previous cases as there is no hydrocephalus and survival was compatible with the appearance of pancytopenia. Although most VACTER (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula with oesophageal atresia, and renal defects) associations occur sporadically, we recommend systematic cytogenetic testing with clastogen agents if such an association is noted.

As in our cases 2 and 3, an isolated type III tracheo-oesophageal malformation may indicate Fanconi’s anaemia. The discrete signs of dysmorphic facies (fig 1) and the skin pigmentation abnormalities could have been detected earlier and suggested the diagnosis, but they are not constant characteristics. As yet, it is premature to recommend 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 haematopoiesis. 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.

Figure 1 Triangular shaped face, delicate features, and microphthalmia.