Continuation of a case report

We previously reported on two male sibs with an unknown syndrome which included microcephaly, seizures, mental retardation, congenital heart disease, and skeletal abnormalities. The subsequent clinical course and necropsy findings of one of the boys (sib 2) contribute substantial information to the original report.

At 15 months of age he had findings of a large atrial septal defect with significant left to right shunt and signs of congestive heart failure. At 22 months of age he was admitted to the hospital in status epilepticus of new onset for which no etiology was determined. At 29 months of age he had new and striking findings of pulmonary artery hypertension not previously observed. Cardiac catheterisation showed marked pulmonary artery hypertension with markedly raised pulmonary vascular resistance (10 units/m²) and a small left to right atrial shunt. The ventricular, septal defect was closed. Oxygen breathing failed to reduce pulmonary vascular resistance. At 36 months of age he required oxygen up to 4 l/min because of increased tachypnoea, respiratory distress, and lack of energy. At 39 months of age he suddenly deteriorated and was dead on arrival in the emergency department of a local hospital.

Necropsy findings showed marked right ventricular hypertrophy and dilatation, dilatation and hypertrophy of the main pulmonary artery and its branches, and hypoplasia of the left atrium, left ventricle, and the entire aorta. There was a 2 cm atrial septal defect partially closed and no ventricular septal defect. The right ventricular wall thickness was 1.7 cm, the left ventricular wall thickness was 0.7 cm (normal). The aortic diameter was 0.9 cm at the root, 0.6 cm at the arch, and 0.5 cm at the descending thoracic aorta while the diameter of the pulmonary artery was 1.5 cm. Histologically, there was diffuse intimal and medial proliferation of the pulmonary arterial walls severely constricting, and in some cases obliterating, the vascular lumina, compatible with an advanced degree of pulmonary vascular occlusive disease (figs 1 and 2).

The rate of progression and severity of this patient's pulmonary vascular occlusive disease in the absence of a large ventricular septal defect make us speculate whether this particular syndrome may include or predispose to advanced pulmonary vascular disease. The older brother has a small atrial septal defect but neither clinical nor echocardiographic evidence of pulmonary artery hypertension.

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Figure 1  Small pulmonary artery; medial hypertrophy and intimal thickening almost obliterating the lumen. (H and E stain.)

Figure 2  Small pulmonary artery; elastic lamina duplication and intimal thickening. (Elastic tissue stain.)

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Absent fibula and craniosynostosis: a 25 year follow up

For many rare syndromes good information on the natural history is often lacking. It is essential to have this in order to provide accurate counselling. In 1972 I reported two brothers with congenital absence of the fibula, craniosynostosis, cryptorchidism, and bilateral simian creases (McKusick No 21855). Recently I had the opportunity to re-examine the proband who is now 25 years of age.

He had had bilateral craniectomies for the coronal craniosynostosis, multiple operations for strabismus, repair of a right inguinal hernia, placement of tubes in the nasolacrimal ducts which were stenosed, and an abnormal exploration for undescended testes. At laparotomy bilateral intra-abdominal testes were found at the lower poles of the kidneys. There was no anatomical way of placing the testes in the scrotum.

Secondary sexual characteristics first developed at 14 years and he began to shave regularly at 16 years. At present he shaves daily and has a fully masculine phenotype with male pubic hair distribution and normal penile size. The empty scrotum is normally pigmented. The plan now is to remove the intra-abdominal testes, place prostheses in the scrotum, and maintain him on testosterone therapy. A recent serum testosterone level was normal (22.7 nmol/l). He has had two operations to improve his deformed feet.
Initially he was thought to be mentally retarded, which was based on developmental testing and a pneumoencephalogram at 10 months which was suggestive of cerebral atrophy. He walked independently at 2 years. He spent his first 1 to 2 years in an institution for the mentally retarded but was then placed in a foster home. At school age it was evident that he was not retarded and he returned to live with his parents. At the age of 7 he had one grand mal seizure but has had none since. A brain scan at that time was normal. Vertebral radiographs disclosed fusion at C2-3. He completed grade XII in a regular high school programme, did two years of college, and is presently in an electronics technology programme. He is a bright, alert, apparently happy, well adjusted man despite his early institutional and foster home experiences including many admissions to hospital.

His general health is good. Examination disclosed the following: height 156.5 cm (height age 13), head circumference 52.8 cm (<2 centile), arm span 150 cm, markedly overweight, left esotropia, normal visual acuity, bilateral ptosis left more than right, flat midface, prominent nose, and normal ears. His skull is markedly brachycephalic (figure) and he has a high V shaped palate with single uvula and mobile soft palate. There is malocclusion with an open bite and he has only 21 teeth consisting of primary and permanent teeth. His speech is normal. He has bilateral simian creases and bilateral short fifth digits, the thumbs appear stubby, and four out of 10 digits show loop radial patterns, three have wheels, and three loop ulnar patterns. They all show a very high pattern intensity. The ATD angles are 45° and 43°. His lower limbs are normal above the knee; below that he has markedly hypoplastic calves with feet in valgus position and virtually no movement at the ankles. There is normal sensory distribution in the lower limbs.

In summary, this young man has done extremely well and if geneticists encounter similar cases they can at least give some positive information about the possible outcome. I realise, of course, that this is only one case but, nevertheless, the knowledge does provide some sort of guidance to other geneticists.

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Mild pulmonary, but severe hepatic disease in a cystic fibrosis patient homozygous for a frameshift mutation in the regulatory domain of the CFTR

The clinical phenotype of cystic fibrosis (CF) patients is very variable and it has been suggested that patients lacking the cystic fibrosis transmembrane conductance regulator (CFTR) have milder lung disease than those having an altered CFTR.1-3 However, on the basis of the large variation in lung function in patients homozygous for the most common CF mutation, AF508, and W1282X homoyogotes,4 it was concluded that most CF patients have a common phenotype, but that other genetic and environmental factors may modify the clinical phenotype.4,5 We describe a patient, homozygous for a frameshift mutation in the regulatory (R) domain of the CFTR, who presented with mild lung disease but severe hepatic and pancreatic involvement. The mutation, 2184delA (deletion of A at position 2184 together with an A to G substitution at position 2183 in exon 13) was originally characterised by D Bozon and L-C Tsui (personal communication) and was found in both parents of our patient in a screening programme of non-AF508 CF chromosomes with denaturing gradient gel electrophoresis, followed by sequencing.

The boy was born at term in December 1977, birth weight 3500 g, to healthy, non-consanguineous parents. Cystic fibrosis presented neonatally with meconium ileus which was treated surgically. CF was confirmed by positive pilocarpine iophotophore sweat test at 10 days. Conventional treatment for CF was given. The clinical course of the lung disease was mild. At the age of 5 years a nasal polypectomy was performed. Liver function tests altered from this age onwards. Hepatomegaly was observed two years later. He was admitted to hospital at the age of 11½ years for intravenous antibiotic treatment because of pulmonary infection. Pseudomonas aeruginosa was isolated from sputum cultures soon after this, but not repeatedly. At 13½ years he was asymptomatic with discrete clubbing, hepatomegaly of 4 cm, and pubertal state A1PIG2. Weight and height were between the 10th and 25th centiles. Respiratory function tests for FVC, FEV1, and PEFR were 89%, 83%, and 76% of predicted, respectively.

Schwachman score was good (80-100) as was the Chrispin-Norman score at 41.33 ALT (71 IU/l, normal <29 IU/l) and γGT (106 IU/l, normal <40 IU/l) values were raised. Ultrasonographic investigations showed marked liver and pancreatic steato-cirrhosis.

In conclusion, we present a patient homozygous for a frameshift mutation in the R domain of the CFTR. He has severe pancreatic and hepatic symptoms, but his lung disease is mild. The 2184delA mutation predicts a stop codon 38 amino acids further in the same exon of the CFTR, but it is not known whether this mutation results in the total absence of the CFTR or in a partially functional protein. Study of the CFTR protein in different tissues will be necessary to resolve this. At the moment, the question remains whether these studies will clarify the difference in disease expression in tissues.