Severe Silver-Russell syndrome

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SUMMARY Three children are described with severe Silver-Russell syndrome. Major medical problems occurred in the first two years of life in all three. Silver-Russell syndrome should be considered in the differential diagnosis of children with severe pre- and postnatal growth deficiency.

Silver-Russell syndrome is a well recognised condition of unknown aetiology presenting with intrauterine and postnatal growth retardation, body asymmetry, a normal head circumference, a small triangular face, downturned corners of the mouth, a small mandible in relation to the maxilla, and usually normal psychomotor development. The relative macrocephaly gives rise to a 'hydrocephalic' appearance. The fifth fingers are short and often incurved. In a study of the natural history of the syndrome, Tanner *et al*¹ followed the growth and development of 39 children. They found the height at referral (mean age 4.6 years) averaged -3.6 SD below the mean and remained at this level during subsequent growth. Only three of their cases had heights of -5.5 SD or below. They stated that it was likely that some 10% of cases might be missed because of relatively mild effects on pre- and postnatal growth, but it is equally likely that those at the other end of the scale, that is, with extremely severe growth deficiency, might not be diagnosed either because affected infants die early or because they are misdiagnosed. We report here three children with very severe pre- and postnatal growth deficiency.

Case reports

CASE 1

He was the third son born to a healthy, non-consanguineous 25 year old mother and 29 year old father of Caucasian origin. Severe intrauterine growth retardation was noted in pregnancy and spontaneous delivery occurred at 39 weeks' gestation. His birth weight was 1600 g (-4.7 SD), length 40 cm (-4.2 SD), and OFC 35 cm (50th centile). His

head appeared large in comparison with his body, his face was triangular, his sclerae blue, and the corners of his mouth turned downwards. There was bilateral fifth finger clinodactyly and a right transverse palmar crease. The penis was small and there was severe hypospadias; testes were palpable in the inguinal canals (fig 1). Ultrasound scan of his head

FIG 1 Case 1 at two weeks showing severe growth retardation but relatively normal head size.

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showed normal sized ventricles and an IVP showed a normal renal tract. Much of his first year and a half of life was spent in hospital with recurrent episodes of gastroenteritis and respiratory problems. Motor milestones have been extremely delayed, but he did eventually achieve head control at the age of two years 11 months and sat unsupported just after his third birthday. On his most recent examination at the age of three years six months (fig 2) he could 'bottom shuffle' and could just pull himself from sitting on a chair to a standing position. His speech development has been slow and he is able to say single words and short phrases. His comprehension is considered to be good and he feeds himself. He is able to do jigsaws with up to 30 large pieces and can sort blocks into colour groups. He is continent of urine and faeces in the daytime. In view of his extremely slow growth, and in spite of normal growth hormone studies, therapy with synthetic growth hormone was started at the age of two years and has continued since then.

His physical growth has continued to be extremely poor; at 14 months he weighed 3.09 kg (-7.7 SD), length 53.2 cm (-9.5 SD), and OFC 46.1 cm (10th centile). There was a slight discrepancy in the size of his feet with the right being smaller than the left. At

two and a half years he weighed 4.06 kg (-6.9 SD), length 60 cm (-8.5 SD), and OFC 48.2 cm (3rd to 10th centile). On this occasion his left leg measured 0.5 cm longer than the right and the left foot was 0.4 cm longer than the right. At three and a half years he weighed 5.84 kg (-6.2 SD), crown-heel length on the right was 69.3 cm (-6.9 SD) and on the left 69.5 cm, with a crown-rump length of 44.6 cm; his OFC was 50.5 cm (25th centile). Asymmetry of leg length and foot size was again noted with the left side being larger than the right (fig 3). There was also some asymmetry of the trunk, noticeable from the back, with the left side being larger than the right. His karyotype was normal male 46,XY.

CASE 2

This male was born at term after a normal pregnancy and delivery, birth weight 1760 g (-5 SD). He was the first child of a healthy 31 year old father and 26 year old mother, each of whom has a healthy child by previous marriages. Nasogastric tube feeding was required for the first two weeks of life and thereafter he fed well but failed to thrive and was investigated at the age of five months. He weighed 2.9 kg (-5.4 SD), length 52 cm (-6.5 SD), and OFC 40.1 cm (3rd centile). The anterior fontanelle measured 10 cm in the lateral diameter, the posterior fontanelle was open, and all the sutures were separated. Prominent veins and sweaty

FIG 2 Case 1 at three years six months showing large head in relation to rest of body.

FIG 3 Feet of case 1 at three years six months. Note left foot is longer and wider than right.

skin on the scalp were noted. He had small facial features with bilateral proptosis and blue sclerae. His mouth was small with downturned corners. The right arm and leg were thinner than the left and were shorter by 0.5 cm each. This limb asymmetry had been present since birth (figs 4 and 5). There were fixed flexion deformities of the right elbow and knee of 15°, right hip abduction was incomplete, and the second and third toes on the right foot were soft suggesting lack of ossification of their phalanges. The baby was alert, smiled responsively, and could hold objects. His head control was poor but he could roll from side to side. CT brain scan showed mild enlargement of all CSF spaces especially in the lateral ventricles, suggestive of a mild communicating hydrocephalus. Ultrasound head scans after birth had been normal.

At 13 months of age a ventriculoperitoneal shunt was inserted because of increase in both head size and ventricular dilatation documented on CT scan. This was complicated one month later by infection arising in the peritoneum, so the catheter was removed.

Recovery followed antibiotic treatment and a ventriculoatrial shunt was then inserted. Bilateral hydroceles and an umbilical hernia developed post-

FIG 5 Case 2 at five months. Note triangular face and large skull with prominent veins.

FIG 4 Case 2 at five months. Note asymmetry.

operatively. At 14 months a glucagon test was done. After fasting he was given 0.45 mg glucagon intramuscularly. A low blood glucose and the failure of blood glucose to rise after the injection suggested poor liver glycogen stores. Growth hormone rose to appropriate levels at 150 minutes but may have been expected to rise more rapidly in the face of the hypoglycaemia. Cortisol levels were appropriate. His growth has remained extremely poor despite a good appetite; at 19 months weight was 5.3 kg (-5.3 SD), length 61.3 cm (-7.3 SD), and OFC 47.3 cm (25th centile). The right leg was 3.7 cm shorter than the left. More recently, at three years eight months, his weight was 7.7 kg (-4.5 SD), length 72 cm (-6.6 SD), and OFC 52 cm (75th centile).

Motor milestones remained delayed at 19 months. Head control was poor and he was unable to sit alone or to roll over. If held upright he could bear his weight. He was alert, socially responsive, and had a four word vocabulary. At three years eight months he could walk with support and could talk in sentences with a large vocabulary. Photophobia has been a problem since about 16 months and is probably the result of corneal exposure secondary to proptosis. Karyotype is normal (46,XY) and skull x rays (at five months) showed Wormian bones.

CASE 3

Case 3 was the second child of a healthy, non-consanguineous 26 year old father and 27 year old mother. He was born at 37 weeks after a pregnancy

FIG 6 Case 3 at 15 months. Note large head and thin lips.

in which intrauterine growth retardation had been documented on ultrasound. Birth weight was 1300 g (-5.1 SD). Soon after birth congenital heart defects were diagnosed. There was a mid-muscular ventriculoseptal defect, an ostium primum atrial septal defect, and a patent ductus arteriosus. Associated congestive cardiac failure necessitated treatment with digoxin and diuretics and a pulmonary artery banding procedure was performed on day 2. During the first year of life he was admitted to hospital on several occasions for otitis media, respiratory tract infections, and poor weight gain.

At the age of six months his weight was 4.3 kg (-4.4 SD), length 58.5 cm (-3.3 SD), and OFC 44 cm (3rd centile). His cranial vault appeared large and he had a small, triangular face (fig 6). The forehead was prominent and he had a small mouth with downturned corners. Three teeth had erupted. Both fifth fingers turned in. The right arm and leg were longer than the corresponding limbs on the left. There was marked peripheral and central cyanosis and a thoracotomy scar. At 19 months the pulmonary artery was debanded and the ASD and VSD closed. Postoperatively he was dependent on the ventilator and he died 14 months later from an acute parainfluenza viral infection. Although he required ventilation most of the time he sat alone at two years four months and pulled himself to a standing position at two years six months. Full growth hormone studies were not completed since he could not tolerate extended periods without feeding, but preliminary testing was suggestive of growth hormone deficiency and replacement therapy was started at two years one month.

Discussion

It is evident from the three cases reported here that

the manifestations of Silver-Russell syndrome can be so severe that clinicians might be deterred from making the correct diagnosis. Case 1 was diagnosed in the newborn period but cases 2 and 3 were not specifically identified for several months after birth. Initially it was considered that they had a separate condition from Silver-Russell syndrome, but the appearance of the face and hands, the limb asymmetry, and the tendency of them all to sweat excessively over the head suggested that they are severe examples of Silver-Russell syndrome. The relatively normal intellectual development would also support the diagnosis.

The differential diagnosis includes the neonatal progeroid syndrome of Wiedemann-Rautenstrauch.^{2,3} The relatively large head, triangular facial shape, and visible veins on the head are shared by both conditions but asymmetry is not seen in the neonatal progeroid syndrome. Natal teeth are present in this syndrome as well as large hands and significant developmental delay. The progeroid syndrome is rare, but death in infancy seems to be the rule. Sibs have been reported with this condition and parental consanguinity, indicating autosomal recessive inheritance. Since recurrence of Silver-Russell syndrome within a family is unlikely, this is another important reason for differentiating the two conditions.

Structural malformations seem uncommon in reported cases of Silver-Russell syndrome and it may be significant that one of the children reported here had hypospadias, another hydrocephalus requiring shunting, and the other a congenital heart defect which was ultimately fatal. The hypospadias and congenital heart defect have been noted before, and in a study of 20 patients (14 boys and six girls) Angehrn *et al*⁴ noted severe hypospadias in one boy, slight hypospadias in another, and a ventriculoseptal defect in a further patient. Other published reports show a similar low level of such abnormalities. In 1985, Saal *et al*⁵ re-evaluated 15 patients between 2.9 and 13 years after initial diagnosis. At follow up, five of the 15 patients exhibited late catch up growth and it will be interesting to see whether the growth of our two surviving patients improves with time.

It seems likely that the spectrum of Silver-Russell syndrome must incorporate the severe cases described here. An important clinical feature, which should alert the clinician to the diagnosis, is that despite the serious delay in achievement of motor milestones, the children were mentally alert and socially responsive. If in a child with severe growth retardation body asymmetry is also present, severe Silver-Russell syndrome should be considered.

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