Short reports

Marshall-Smith syndrome: the expanding phenotype

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Abstract

We report a child of 3 years 9 months with the Marshall-Smith syndrome (MSS), characterised by the typical facial features, developmental delay, and advanced bone age. After the diagnosis was made at 5 months of age, careful observation for respiratory complications and failure to thrive was initiated. By 3½ years of age, although our patient had no life threatening respiratory complications, investigation showed significant upper airway obstruction, which has been successfully treated. Aggressive treatment for failure to thrive has also allowed her to maintain a weight on the 50th centile. The purpose of this report is to suggest that early diagnosis and aggressive management may improve the ultimate prognosis with respect to the respiratory and feeding difficulties seen in this rare syndrome.

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Infants with the Marshall-Smith syndrome characteristically present with facial dysmorphism, failure to thrive, and psychomotor retardation. Investigation shows marked acceleration of osseous maturation. Of the published cases, all except one¹ have had recurrent pulmonary complications and most have died in early infancy. In this paper, we present another child with the characteristic facies of this rare syndrome, together with advanced bone age and developmental delay. We discuss the management of her respiratory and feeding difficulties, which we believe has led to an improved prognosis. She also has optic nerve hypoplasia, optic atrophy having been reported only by Sperli *et al.*¹ and a severe hearing loss, only two children with mild to moderate conductive deafness having previously been described.² We believe both of these features are likely to be additional characteristics of this condition.

Case report

The proband, a female infant, was born at term by spontaneous vertex delivery, with a birth

weight of 2800 g (3rd centile). Her length was 52 cm (75th centile) and her head circumference 36.0 cm (just below the 90th centile). She was the first born child of healthy, non-consanguineous, white parents, who have subsequently had a healthy son. Initially breast fed, she was unable to suck or swallow adequately and was changed to formula milk. However, she continued to feed poorly and failed to thrive. At 6 weeks of age, the patient was admitted to hospital, with a weight of 2800 g, exactly equivalent to her birth weight and well below the 3rd centile. Despite nasogastric tube feeding, her weight gain remained inadequate and she was referred to the regional paediatric gastroenterology department for further assessment. On general examination at this time she was noted to have several dysmorphic features and there was increasing concern about her general development.

In view of these problems, at 4½ months of age the patient was referred to the clinical genetics department. On examination her

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Figure 1 Patient at 4½ months of age.

Figure 2 Wrist/hand x ray at chronological age of 18 weeks.

Figure 3 Patient at 2 years 9 months of age.

weight (tube fed) had increased to 5.7 kg (10th centile), her length was 63 cm (just above the 50th centile), and her head circumference 42 cm (approximately 75th centile). Facially she had a prominent, broad forehead, hypertelorism, and protuberant eyes with shallow orbits. She had a depressed nasal bridge, a flat midface, and a small, upturned nose. There was micrognathia and a flat occiput (fig 1). She was a snuffly baby with a small left nostril. On general neurological examination there was

poor head control and limb and truncal hypotonia, but increased reflexes and extensor plantar responses. At 21 weeks of age a Griffiths Mental Developmental Assessment confirmed global developmental delay. Her overall performance DQ was 56: locomotor 50, personal-social 68, hearing and speech 62, eye and hand coordination 73. An ophthalmological assessment showed asymmetrical optic nerve hypoplasia (right>left), the visual significance of which remains unclear. A hearing assessment using brain stem auditory evoked responses indicated severe to profound bilateral hearing loss (85 dB in the right ear, 75 dB in the left ear). This loss is partly the result of effusions which have been treated. The remaining loss has not been characterised and may be conductive, sensorineural, or mixed. A hearing aid has been fitted. A wrist x ray for skeletal maturation at a chronological age of 18 weeks showed a bone age of 1.9 years (fig 2) and a diagnosis of Marshall-Smith syndrome was made. In addition, the phalanges were wide and the epiphyses stippled, features typical of those seen in the Marshall-Smith syndrome.³ A cranial CT scan showed generalised ventricular dilatation, with relative sparing of the lateral frontal horns. There was no obvious abnormality of the nasal anatomy, excluding choanal atresia. A spinal x ray was normal, with no evidence of subluxation or dislocation. A barium swallow showed mild reflux, but pH studies were subsequently normal. Chromosome analysis showed a normal female karyotype (46,XX). Metabolic studies including urine glycosaminoglycans, urinary amino acids, organic acids, and oligosaccharides were normal. Patients with MSS may develop ventricular hypertrophy secondary to respiratory failure and therefore an echocardiogram was performed. This showed a small muscular VSD, not causing haemodynamic instability and no evidence of left or right ventricular hypertrophy.

At 14 months of age, the patient had a weight of 11.47 kg (75th-90th centile), a length of 79 cm (75th centile), and a head circumference of 49.5 cm (97th centile). She continued to be predominantly tube fed. She had particular difficulty with liquids but was able to take some semi-solid materials off a spoon. Her swallowing difficulties were therefore presumed to be neuromuscular in origin. She had severe global developmental delay, although her head control was gradually improving. With age she developed some facial and bodily hirsutism, and an asymmetrical head shape. Her skull x ray showed an abnormal appearance of the skull vault, suggesting overgrowth of the left side.

At 2 years 9 months of age (fig 3) our patient had suffered several mild upper respiratory tract infections over the winter months and her sleep was occasionally broken by snoring. She held her head hyperreflexed to the right. A resting oxygen saturation measurement was 95%, but overnight continuous saturation monitoring showed several desaturations to the mid 80s and low 90s with a corresponding rise in carbon dioxide measurement. A diagnosis of

Figure 4 Profile and lateral view at 3 years 8 months.

moderate to severe upper airway obstruction was made. Subsequent tonsillectomy and adenoidectomy resulted in normalisation of oxygen saturation.

At 3 years 8 months of age the patient is on the 50th, 50th, and 97th centiles for weight, height, and head circumference respectively. Her facial gestalt remains typical of Marshall-Smith syndrome (fig 4). Her solid intake is increasing and she is encouraged to finger feed, although the majority of her intake is now through a gastrostomy, which was inserted three months earlier. She remains severely globally developmentally delayed; she stands holding on to objects and will take a few steps with her hands held. She has a few simple signs although as yet only babble rather than words. Her general health is good with no further upper respiratory tract infections.

Discussion

In 1971, Marshall *et al*⁸ reported two infants with characteristic facial features who failed to thrive and who suffered early profound respiratory distress. They were severely globally developmentally delayed and they both had significantly advanced skeletal maturation. One child died in infancy from a haemorrhagic pneumonia. From this date until 1990, a further 16 cases of the Marshall-Smith syndrome have been published.⁵⁻⁹ The main features of the condition are summarised by Cohen.¹⁰ They include prominent forehead (15/18 patients), prominent eyes (17/18), flat nasal bridge (17/18), anteverted nares (15/16), micrognathia (14/18), hypertrichosis (7/18), choanal atresia/stenosis (3/17), advanced bone age (18/18), broad phalanges (17/17), failure to thrive (11/13), neurodevelopmental abnormalities (13/13), and structural brain abnormalities (7/14). The natural history of the

Marshall-Smith syndrome is for persistent respiratory difficulties, stridor, hyperextension of the neck, and obstructing tongue, and the majority of patients have died by 20 months of age from pneumonia, atelectasis, aspiration, or pulmonary hypertension.

In 1993, Hoyme *et al*² presented two long term survivors with the Marshall-Smith syndrome. The first patient, a male of 7 years, developed severe upper airway obstruction in early infancy, relieved following tracheostomy and partial glossectomy. The second patient, a girl of 8 years, required a tracheostomy at 2 years of age. More recently, Sperli *et al*¹ have reported a 5 year old boy with typical features of the Marshall-Smith syndrome, but without respiratory difficulties in early infancy.

Our patient has the characteristic facial features of the Marshall-Smith syndrome, together with accelerated skeletal maturation and mental retardation. By 3½ years of age, she had no life threatening respiratory complications, although she had several upper respiratory tract infections and nocturnal snoring. Surprisingly, investigation showed moderate to severe upper airway obstruction, which has been corrected by tonsillectomy and adenoidectomy. Following surgery, she has had no further respiratory embarrassment. Most of the previous reports of the Marshall-Smith syndrome also describe significant failure to thrive, and although our patient presented with this complication, intensive dietary management, including nasogastric feeding and gastrostomy, have allowed her to reach the 50th centile for weight for her age. We also believe that continuous overnight nasogastric feeds, rather than bolus feeds are likely to have reduced the frequency of respiratory complications by reducing aspiration. This must improve the ultimate prognosis. Lapenna and

Folger⁷ also suggested that relief of upper airway obstruction may result in improvement in developmental status, but unfortunately this has not been our experience.

The significance of optic nerve hypoplasia in our patient remains unclear, although she is being carefully reviewed by the paediatric ophthalmologists. Optic atrophy in the Marshall-Smith syndrome has previously only been reported by Sperli *et al.*¹ Our case represents the third child with the MSS in whom a hearing loss has been described. We suggest that optic nerve hypoplasia and hearing impairment may be additional characteristics of this rare syndrome.

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