Case Report
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Scoliosis in Carey-Fineman-Ziter Syndrome: Clinical Course, Association with Pierre Robin Sequence and Treatment

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Abstract

Objective – We present a female patient with Carey-Fineman-Ziter Syndrome (CFZS) and 4 patients with Pierre Robin sequence who developed a progressive thoracic scoliosis in early child life. **Material and Methods** – We reviewed the medical notes and spinal radiographs of these 5 patients who were treated for progressive scoliosis, underwent a posterior spinal fusion and were followed in our service to skeletal maturity. **Results** – We describe the patients' response to treatment including bracing which was unsuccessful, and scoliosis correction. We compared the evolution of scoliosis and surgical outcome between the patient with CFZS and our 4 patients with Pierre-Robin sequence and hypotonia who were managed for scoliosis under our care in order to understand possible aetiological relations between the underlying myopathic condition and the development of scoliosis. **Conclusion** – Scoliosis in children with CFZS and Pierre Robin sequence occurred in early childhood with rapid progression around puberty and poor effectiveness of bracing. We suggest that generalised hypotonia is a likely causative factor in the development and rapid deterioration of scoliosis in these 2 conditions. Spinal surgery through a posterior spinal fusion produced excellent deformity correction and functional outcomes that were maintained through to skeletal maturity in all 5 patients.

Key Words: Carey-Fineman-Ziter Syndrome ▪ Pierre Robin Sequence ▪ Moebius Sequence, Hypotonia, Scoliosis, Surgical Treatment, Spinal Fusion, Genetics.

Introduction

Carey-Fineman-Ziter syndrome (CFZS) is an autosomal recessive condition due to homozygous or compound heterozygous mutations in the myomaker gene (MYMK) (1). It represents a rare slowly progressive congenital myopathy, characterised by the Moebius (facial paralysis and ophthalmoplegia) and Pierre Robin sequences (facial abnormalities including micrognathia, glossoptosis and commonly cleft palate) (2). Additional phenotypic characteristics include the Poland sequence (unilateral absence of pectoralis muscles and syndactyly), hypotonia, muscle hypoplasia with axial and appendicular weakness, delayed motor development, congenital club feet and short stature (2-4). Scoliosis has been reported as extracranial feature in CFZS but there is no information on the type of deformity or treatment (2-5.

We present a case series of 5 patients; one patient had CFZS, developed a progressive primary thoracic scoliosis that required bracing at a young age and surgical treatment during adolescence. We describe the course of spinal management and follow-up to skeletal maturity. We compare the type and evolution of scoliosis, as well as outcome of surgery to a consecutive group of 4 patients with Pierre Robin sequence and hypotonia treated under our care in an attempt to understand any possible

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aetiological relation between the underlying condition and the development of scoliosis.

Methods

We reviewed the medical notes and radiographs of one patient with CFZS and 4 patients with Pierre Robin sequence treated in our National Spinal Deformity Service for scoliosis. Institutional review board (IRB) support was received for this study by the Hospital Research Board. All 5 patients' data has been inserted in the British Spine Registry which is the National Database for surgical patients with spinal conditions in the United Kingdom.

Results

Patient with CFZS

A British Caucasian female patient aged eight years and nine months presented with a right thoracic scoliosis. She was diagnosed with CFZS soon after birth based on her phenotypic features. Her parents were non-consanguineous. Whole-exome sequencing did not identify mutations in the MYMK gene. She had ophthalmoplegia, micrognathia, a submucous cleft palate that did not require treatment, bilateral facial paralysis with impaired swallow and speech, as well as dysarthria related to her tongue movements. She also had bilateral mild sensorineural hearing loss with additional left sided conductive hearing loss, learning disability and hypotonia. She attended a specialist school for children with learning disability. She was treated for bilateral congenital club feet initially with serial casting/splinting and subsequently with bilateral tendo-Achilles lengthening and tibialis anterior tendon transfers at age 5 years. She has been wearing an ankle-foot orthosis ever since. She had no other congenital joint contractures. She had unilateral absence of the pectoralis muscles on the right side and underwent release of right hand syndactyly at age 7 years. At age 8 years, a baseline respiratory assessment was organised including sleep studies which showed short-lasting central apnoeic episodes with good oxygen saturation and no obstructive sleep apnoea. An EEG excluded seizure activity overnight. She never required nocturnal non-invasive respiratory support. She has been on melatonin to improve her sleep. There was no family history of neuromuscular/syndromic conditions or scoliosis.

Scoliosis was first noted by her parents at age 4 years. She was referred to our service at age eight years and nine months when her parents thought that the deformity was deteriorating. At first presentation to our clinic, she was pre-menarchal with height 123 cm, arm span 120.5 cm, body weight 26.7 kg, and BMI 17.6 kg/m^2. She had a primary right thoracic and compensatory left lumbar scoliosis which was producing rib prominence on the right posterior chest wall. There was thoracic translocation towards the right side causing waistline asymmetry and prominence of the left hemipelvis. There was also elevation of the right shoulder. She had normal thoracic kyphosis and lumbar lordosis. There were no abnormalities or pigmentation of the skin and subcutaneous tissues overlying the spine. Spinal movements were pain free with no tenderness on palpation. Ankle dorsiflexion was restricted bilaterally due to her clubfeet deformity. Neurological examination showed normal muscle power/sensation and symmetrical tendon reflexes with reduced tone in all 4 limbs.

Initial spinal radiographs showed a primary right thoracic scoliosis extending from T4-T10 measuring 54° and a secondary left lumbar scoliosis extending from T11-L4 measuring 28° (Fig. 1A). There were 11 thoracic and 6 lumbar vertebrae but no other congenital vertebral anomaly. Thoracic kyphosis and lumbar lordosis were within normal limits but the patient was in positive global sagittal balance (Fig. 1B). The iliac apophyses had not appeared with Risser grade 0 and open triradiate cartilage bilaterally, indicating a significant amount of remaining spinal growth. The hips had normal appearance with congruent joints and well-contained femoral heads (Fig. 1A).

Bracing was instigated to delay the need for surgical correction and preserve spinal/chest development. A custom-moulded thoracic Boston brace

was used. The patient tolerated the underarm brace until the age of 12 years when she was growing rapidly as part of her pubertal growth spurt. The thoracic scoliosis had deteriorated to 81° indicating a rate of progression of 0.7°/month (8.2°/year) during bracing (Fig. 1C-D). The primary thoracic curve was rigid with flexibility index 17% (Table 1). Surgical treatment was planned and a preoperative review was organised to assess co-morbidities that could increase morbidity of the procedure.

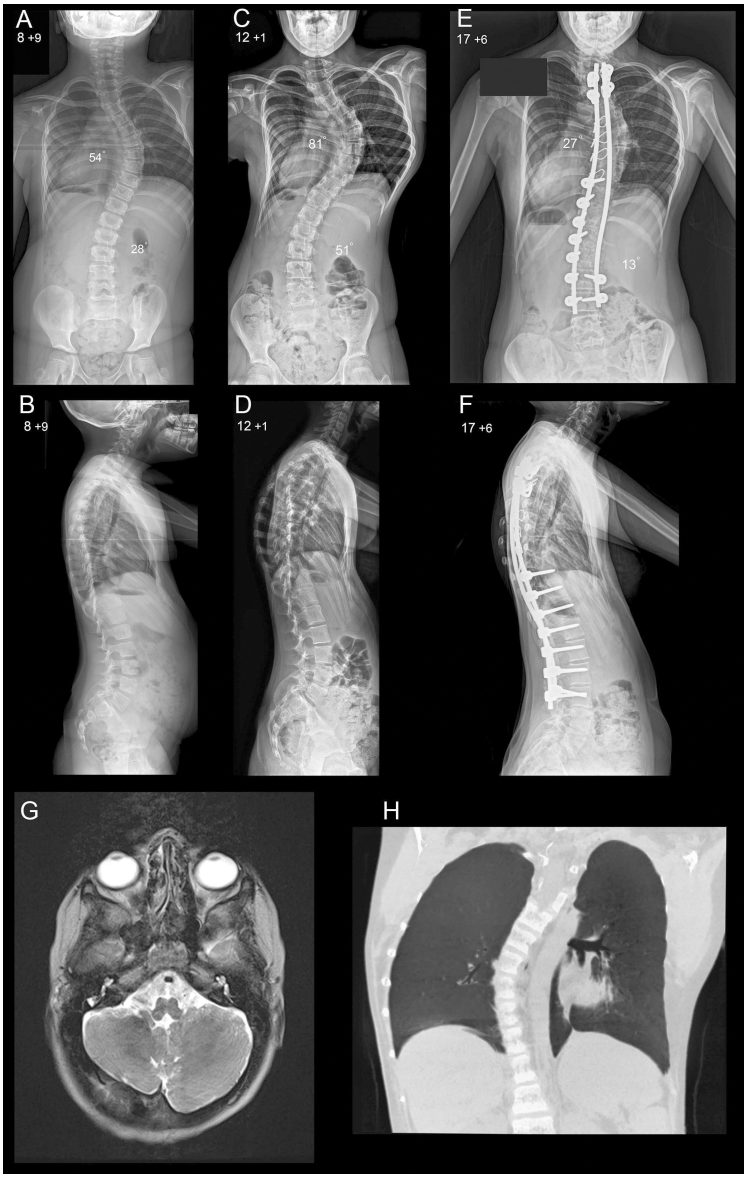

Fig. 1. *Preoperative and lateral spinal x-rays at initial clinical presentation (A-B). The scoliosis progressed despite bracing across the primary right thoracic and secondary left lumbar curves and required surgery (C-D). Excellent deformity correction and a balanced spine in the frontal and lateral planes was achieved and maintained at follow-up (E-F). MRI of the brain showed right cerebellar hypoplasia (G). CT of the chest demonstrated segmental collapse of the left lower lobe (H).*

Magnetic resonance imaging (MRI) of the head/spine showed hypoplastic right cerebellum but no other intracranial/intraspinal anomaly and no spinal stenosis (Fig. 1G). Cardiac assessment including ECG and echocardiogram showed a structurally normal heart with good function.

On respiratory evaluation, she was noted to have coarse crepitations on auscultation that did not respond to antibiotics (azithromycin). A CT of the chest found segmental collapse of the posterior basal segment of the left lower lobe with bronchial dilatation but no focal pulmonary pathology or bronchiectasis (Fig. 1H). A bronchoscopy showed normal anatomy of the upper/lower airways with increased inflammation and secretions; increase in the number of lipid laden macrophages seen in the pathology sample was consistent with possible aspiration. A lung biopsy did not show abnormalities. She was placed on anti-reflux treatment. Spirometry tests were incomplete as the patient could not cooperate due to her facial paralysis. The plan was for provision of non-invasive ventilation (NIV) and chest physiotherapy postoperatively. An anaesthetic review did not identify significant upper airway abnormalities. Preoperative blood tests including full blood count, urea and electrolytes, liver function tests, C-reactive protein and coagulation screen were normal. Serum creatinine kinase was mildly elevated (500 U/L).

Table 1. Scoliosis Data in Our Group of 5 Patients (one Patient with CFZS and 4 Patients with Pierre Robin Sequence and Hypotonia)

Patient group	Initial presentation (age, scoliosis)	Presentation at surgery (age, scoliosis)	Rate of primary TH scoliosis progression before surgery	Postoperative scoliosis at skeletal maturity	FI (TH scoliosis); Surgical time/blood loss	CI (TH scoliosis); Complications
Patient with CFZS	8.8 years; TH: 54°; L: 28°	12.1 years; TH: 81°; L: 51°	0.7°/month; 8.2°/year	TH: 27°; L: 13°	17%; 120 min/ 6% EBV	67%; None
Patient 1 with Pierre Robin sequence/ hypotonia	2.1 years; TH: 22°; L: 18°	13.9 years; TH: 86°; L: 36°	0.45°/month; 5.4°/year	TH: 18°; L: 14°	29%; 130 min/ 18% EBV	79%; None
Patient 2 with Pierre Robin sequence/ hypotonia	12.9 years; TH: 58°; L: 35°	13.7 years; TH: 72°; L: 41°	1.4°/month; 16.8°/year	TH: 8°; L: 8°	33%; 120 min/ 12% EBV	89%; None
Patient 3 with Pierre Robin sequence/ hypotonia	3 years; TH: 18°; L: 27°	10.6 years; TH: 85°; L: 62°	0.7°/month; 8.8°/year	TH: 30°; L: 20°	29%; 120 min/ 16% EBV	65%; None
Patient 4 with Pierre Robin sequence/ hypotonia	2.4 years; TH: 28°; L: 15°	12.8 years; TH: 65°; L: 37°	0.3°/month; 3.6°/year	TH: 14°; L: 6°	29%; 150 min/ 15% EBV	78.5%; None

TH=Thoracic; FI=Flexibility index (%): ([pre-operative scoliosis angle – supine maximum traction scoliosis angle] / preoperative scoliosis angle) × 100; CI=Correction index (%) = ([pre-operative scoliosis angle – post-operative scoliosis angle] / pre-operative scoliosis angle) ×100; EBV= Estimated blood volume; L=Lumbar.

The patient underwent a posterior spinal fusion from T3-L4 with pedicle hook/screw, sublaminar wire and rod instrumentation, and bone graft. The spine was exposed subperiosteally to the tips of the transverse processes and extensive facetectomies were performed to increase curve flexibility. No congenital vertebral abnormalities were identified. The scoliosis was corrected using a double rod construct with rod derotation and apical translation towards the midline. This was followed by decortication of the posterior elements and onlay of locally harvested autologous and allograft bone in order to achieve fusion across the instrumented levels. Multimodal intraoperative spinal cord monitoring was performed recording transcranial electrical motor (MEP), as well as cortical and cervical somatosensory (SSEP) evoked potentials and EMGs which was stable throughout. We noticed no abnormality in EMGs and no change in amplitude or latency of SSEPs/MEPs during surgery. The patient did not develop malignant hypethermia during surgery.

The patient was transferred to the intensive care unit (ICU) extubated postoperatively on NIV support. She was discharged to the ward 4 days after surgery with no oxygen support requirements. She had nutritional supplementation overnight through nasogastric tube feeds. There were no neurological abnormalities and the patient mobilised with the support of an underarm spinal jacket. She was discharged 7 days after surgery, had a satisfactory cosmetic result and made an uneventful recovery. Postoperative radiographs showed excellent deformity correction and a balanced spine in the coronal/ sagittal planes. At latest follow-up, 5 years post-surgery, she had completed her growth, had no complaints of her back and had returned to her normal activities. Repeat x-rays showed the instrumentation in good position with no loss of correction and no evidence of pseudarthrosis (Fig. 1E-F). The patient was due to have reconstruction of the right anterior pectoral region to improve cosmesis.

Patients with Pierre Robin Sequence

Comparison of the type of scoliosis, rate of curve progression, response to bracing and surgical treatment between the patient with CFZS and 4 of our surgical patients with Pierre Robin sequence and

hypotonia is demonstrated in Table 1. There was no family history of neurological or syndromic conditions on any of our patients with Pierre Robin sequence; they were all coming from non-consanguineous families. All 5 patients developed a primary thoracic and secondary lumbar scoliosis which progressed rapidly during puberty with poor response to brace treatment (custom-moulded thoracic Boston brace). They underwent extensive preoperative assessment followed by scoliosis correction through a posterior spinal fusion which was uneventful and achieved satisfactory clinical outcomes.

Discussion

CFZS is a rare genetic disorder with a spectrum of clinical presentations but key phenotypic features involve the Moebius and Pierre Robin sequences. There are less than 20 patients reported worldwide (1). The condition was described in 1982, in 2 siblings who had facial characteristics in keeping with the Moebius and Pierre Robin sequences.[6] Moebius sequence is defined by ophthalmoplegia and facial paralysis caused by bilateral congenital paralysis of the abducens and facial nerves (7). Pierre Robin sequence predominantly affects structures in the face and neck with cleft palate, micrognathia and glossoptosis being common abnormalities (8). A patient with typical features of CFZS and unilateral absence of pectoralis major muscle, a feature indicative of Poland sequence has also been reported (9). Ryan et al. (3) described a series of affected siblings who presented with musculoskeletal anomalies including generalised myopathy, brachysyndactyly and congenital clubfeet. Our patient presented with phenotypic appearance of Moebius, Pierre Robin and Poland sequences allowing early clinical diagnosis of the condition.

The genetic abnormalities underlying CFZS relate to MYMK. This is a gene on the long arm of chromosome 9 that encodes a plasma membrane protein fundamental for myoblast function. The protein regulates the fusion of myoblasts to form multinucleated myotubules, the structural basis of skeletal muscle development. Di Gioia et al. (1) showed the autosomal recessive inheritance pattern of the genetic mutation in the MYMK gene to be the cause of the fundamental clinical and pathologic features of CFZS. Reduced function, not complete absence of the MYMK gene is found in CFZS; it has been suggested that total absence of the MYMK gene may be incompatible with life but this remains to be confirmed in humans (1). The consequence of impaired MYMK function is marked muscle fibre hypertrophy despite overall reduced muscle mass. This indicates a defect in the fusion of myoblasts during embryonic development that results in reduced numbers of individual muscle fibres leading to hypertrophy of the residual few fibres and generalised muscle weakness (10). Mutations in the MYMK gene were not identified in our patient who had whole-exome sequencing.

Brain MRI can assist the diagnosis of CFZ. In a previous report, brain anomalies included marked hypoplasia of the pons and cerebellum with the severity of clinical presentation being incompatible with life beyond infancy (11). In the original and follow-up descriptions of 2 siblings with CFZS by Carey et al. (2, 6) normal brain scans were reported. Both patients survived into adult life suggesting that absence of intracranial anomalies may be a protective factor prolonging life expectancy in CFZS. Our patient had right cerebellar hypoplasia but no other intracranial anomalies and survived beyond adolescent age with no major morbidities.

Musculoskeletal anomalies are prevalent in CFZS affecting the upper limbs in around 15% of patients with syndactyly, brachydactyly and aplasia of the pectoralis major muscle being the most common (12). Unilateral right hand syndactyly occurred in our patient and required surgical release at age 7 years. Lower limb deformities are less common with bilateral congenital clubfeet being reported (3, 12). Diagnosis of congenital clubfeet was made in-utero using ultrasound scanning and was associated with oligohydramnios (12). Similarly, in our patient, congenital clubfeet was found at the 20-week gestation scan with no abnormalities in amniotic fluid and required orthotic and surgical treatment.

Scoliosis has been mentioned as a feature of CFZS in a few patients but there is no previous report on the type of deformity or treatment (2, 3, 5). Patients with Moebius sequence have been described to develop mild scoliosis which did not necessitate surgery (7). There is only one report on the anaesthetic considerations in a patient with Pierre Robin sequence who underwent spinal surgery for cervicothoracic kyphoscoliosis (13).

We presented the evolution of deformity, results of bracing and scoliosis correction in a patient with CFZS and compared to our patients with isolated Pierre Robin sequence and hypotonia who underwent scoliosis correction. To our knowledge, our series of 5 patients is the first to report on scoliosis treatment in both conditions. Bracing was applied in our patient with CFZS and in 3 of the 4 patients with Pierre Robin sequence who presented at a young age in order to slow down deformity progression and delay surgery for a later age while preserving spinal and chest growth. In all 4 patients who were braced, scoliosis progressed rapidly as they approached puberty when surgical correction was indicated to prevent pain and respiratory complications, as well as improve cosmesis. It is possible that the decisive aetiological factor in the development and progressive nature of spinal deformity among these children was the presence of generalised hypotonia which was a feature seen in all 5 patients. Low muscle tone was the common denominator in these 5 children that may have resulted in the development of scoliosis during periods of rapid skeletal growth as the spine was unable to resist gravity in the upright position in the presence of poor muscle control resulting in a pathological curvature. The thorough preoperative assessment allowed a multidisciplinary approach that optimised perioperative care. Scoliosis correction through a posterior spinal fusion was uncomplicated in all patients whose postoperative course included initial ICU stay with NIV and total hospital stay of 7-8 days. Excellent deformity correction was achieved and maintained during follow-up with all children monitored beyond skeletal maturity.

Conclusion

Early onset scoliosis can develop in children with CFZS and Pierre Robin sequence possibly as the result of generalised hypotonia. The spinal deformity has an aggressive course and shows little response to bracing, especially as the children progress into puberty. Scoliosis surgery through a posterior spinal fusion can produce excellent deformity correction and satisfactory clinical results which are sustained beyond the end of growth.

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