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Carey-Fineman-Ziter (CFZ) Syndrome: Report on Affected Sibs

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We describe a sib pair with craniofacial anomalies, micrognathia, Möbius sequence, generalised myopathy, relative macrocephaly, and developmental delay. They appear to have the Carey-Fineman-Ziter syndrome (MIM 254940), which has been reported in only four children, a sib pair and two sporadic cases. This report on an additional affected brother and sister pair supports autosomal inheritance as the likely cause. These cases also confirm that scoliosis, talipes equinovarus, and a non-specific primary myopathy are important manifestations of Carey-Fineman-Ziter syndrome. Am. J. Med. Genet. 82:110–113, 1999.

KEY WORDS: Carey-Fineman-Ziter syndrome; Möbius sequence; congenital myopathy; central hypoventilation

INTRODUCTION

The Carey-Fineman-Ziter (CFZ, MIM254940) syndrome was first described by Carey et al. [1982]. They reported a brother and sister sib pair with hypotonia, Möbius sequence, Robin sequence, facial anomalies, delayed motor milestones, and failure to thrive. Two other children have since been reported as having the CFZ syndrome. We have recently seen a 10-year-old girl who bears a remarkable similarity to these published case reports. Her deceased brother undoubtedly had the same condition.

CLINICAL REPORT

Case 1

Case 1 was the first child born to healthy nonconsanguineous parents, age 26 and 20 years at the time of conception. He was born spontaneously by vaginal delivery at 37 weeks gestation, with a birth weight of 2.8 kg (10th centile). He was noted to be macrocephalic with a large anterior fontanelle. He also had a small nose, apparently low-set ears, prominent forehead, micrognathia, and a high arched palate (Fig. 1). He had an expressionless myopathic face due to bilateral facial diplegia. Feeding problems secondary to bulbar palsy were present from birth. He required gavage feeding and failed to thrive from age 2 months. He was generally hypotonic and hyporeflexic. A single generalised seizure occurred at age 3 months. Development was markedly delayed and his head circumference (OFC) fell from the 98th to the 50th centile by 8 months. He died from aspiration pneumonia at 8 months.

Chromosome analysis showed an apparently normal 46,XY karyotype. Serologic tests ruled out cytomegalovirus, toxoplasma, herpes simplex, and rubella infection. Results of abdominal ultrasound studies, cerebrospinal fluid studies, full blood count, electrolytes, lysosomal enzymes, organic acid, and amino acid analysis were normal. Computer tomographic (CT) head scan showed minor non-progressive enlargement of the left lateral ventricle. Electroencephalogram brainstem-evoked responses were normal. Conduction studies of the seventh cranial nerve were normal, excluding peripheral seventh nerve palsy and consistent with a supranuclear defect. Fundoscopy examination and electroretinogram (ERG) were normal bilaterally. Visual evoked response latencies were slightly prolonged. Permission for autopsy was refused. There was no significant family history. The parents had had one previous pregnancy resulting in miscarriage at 21 weeks of gestation, following maternal appendectomy for perforated appendix. The post-autopsy and chromosome analysis on this fetus were normal. Both parents are of low normal intelligence. Parental chromosomes were apparently normal. Electromyogram studies on the mother were normal.

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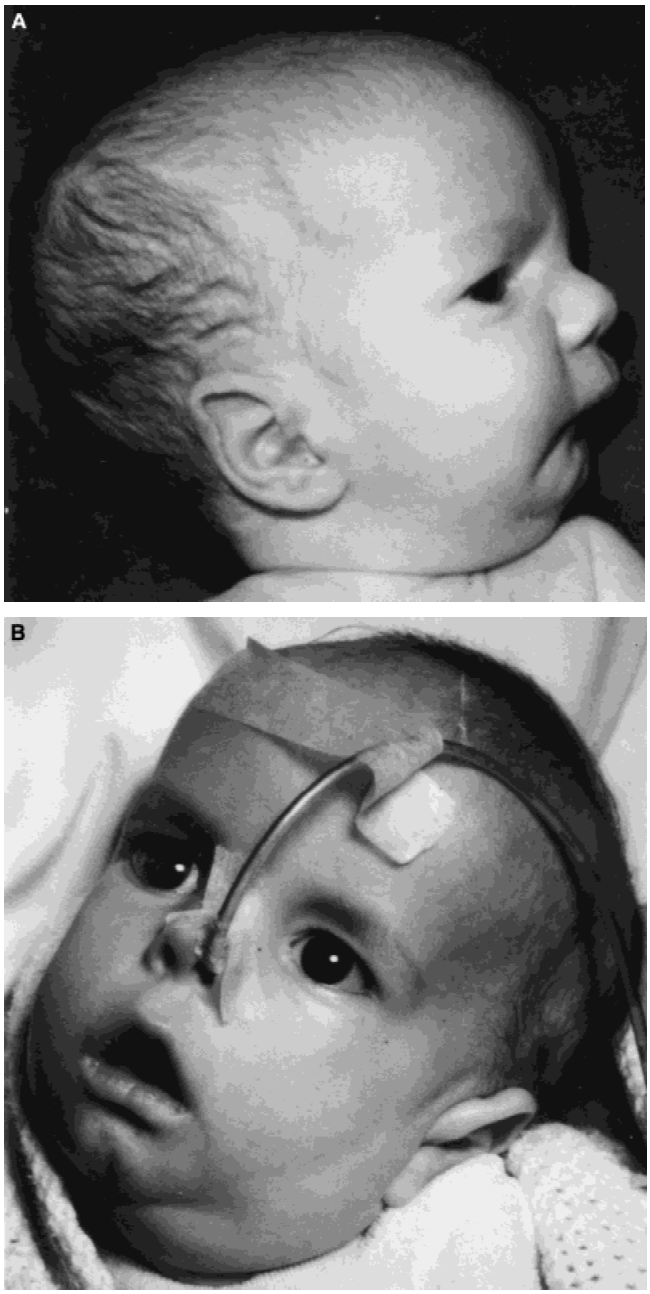

Fig. 1. **(A)** Lateral and **(B)** frontal photographs of Case 1 showing macrocephaly, frontal bossing, myopathic face, micrognathia, and low-set posteriorly angulated ears. A nasogastric tube was required for severe feeding difficulties.

Case 2

Case 2 is the younger sister of Case 1 and was born at 38 weeks gestation with a weight of 2.75 kg (10th centile), OFC of 37 cm (>97th centile), and length of 50 cm (50–75th centile). The pregnancy had been complicated by polyhydramnios. She was noted to have an appearance similar to that of her brother with hypertelorism, a large bulky forehead, pouting lips, micrognathia and a small tongue, apparently low-set posteriorly rotated ears, and a bilateral facial nerve palsy. In addition, she had a scoliosis, a tuft of hair at the base of her spine, and a left talipes equino valgus deformity. She had a feeble cry, and paucity of movements. Congenital bulbar palsy necessitated gavage feeding and later gastrostomy insertion. She required tracheostomy and noctural ventilation was required for long periods of time in the first 18 months of life due to central hypoventilation.

CT head scan at 20 months showed "cortical atrophy" and a narrow brainstem. She was generally hypotonic and her development was delayed. Muscle biopsy documented a myopathy with type 2 fiber predominance and electrophysiology studies of both peripheral nerves and facial nerves were normal. Chromosome analysis showed an apparently normal 46,XX karyotype.

Nocturnal ventilation has been required over the intervening years. Recurrent episodes of pneumonia secondary to her bulbar palsy resulted in bronchiectasis, chronic collapse and consolidation of her left lower lobe, necessitating left lower lobectomy, at age 9 years. She has recently developed an oxygen requirement. She had a mild left nonprogressive hearing loss. She had moderate mental retardation with a developmental quotient assessed as 57, age 10.3 years.

Examination at age 10.6 years showed height and weight on the 50th centile and OFC on the 90th centile. She had a bossed forehead, macrocephaly, thick eyebrows, short nose, low set ears, high arched rugose palate, and slightly asymmetrical face (Fig. 2). She had short fourth fingers bilaterally, a short fifth metacarpal, and a proximally inserted thumb. She had a marked kyphosis and mild scoliosis which did not require any active intervention. Her left leg was shorter with decreased muscle bulk compared with her right leg. She walked independently with the aid of fixed ankle orthoses for valgus deformity of her left foot. Tone was mildly reduced and reflexes were present but quiet.

Full blood count was normal as were electrolytes, arterial blood gases, and urinary amino acids. Electrocardiogram was normal apart from mild right ventricular hypertrophy secondary to chronic lung disease. Eye review demonstrated a complicated ophthalmoplegia bilaterally and hypermetropia of one eye. DNA analysed for myotonic dystrophy expansions using the method described by Warner et al. [1996] was normal. Sterol analysis was normal, excluding inborn errors of cholesterol metabolism.

DISCUSSION

Both sibs have micrognathia and high arched palate, Möbius sequence with supranuclear dysplasia of the seventh and tenth nerves, hypotonia, macrocephaly, apparently low-set posteriorly angulated ears, and developmental delay. The brother also had failure to thrive and the sister left talipes and scoliosis.

Searches for a unifying syndrome consistently suggested the CFZ syndrome (MIM 254940), an autosomal recessive condition comprising congenital nonprogressive myopathy, Möbius sequence, and Robin sequence, hypotonia, unusual facies, and growth delay (see Table I). This condition was first described by Carey et al. [1982], when they reported a brother and sister with

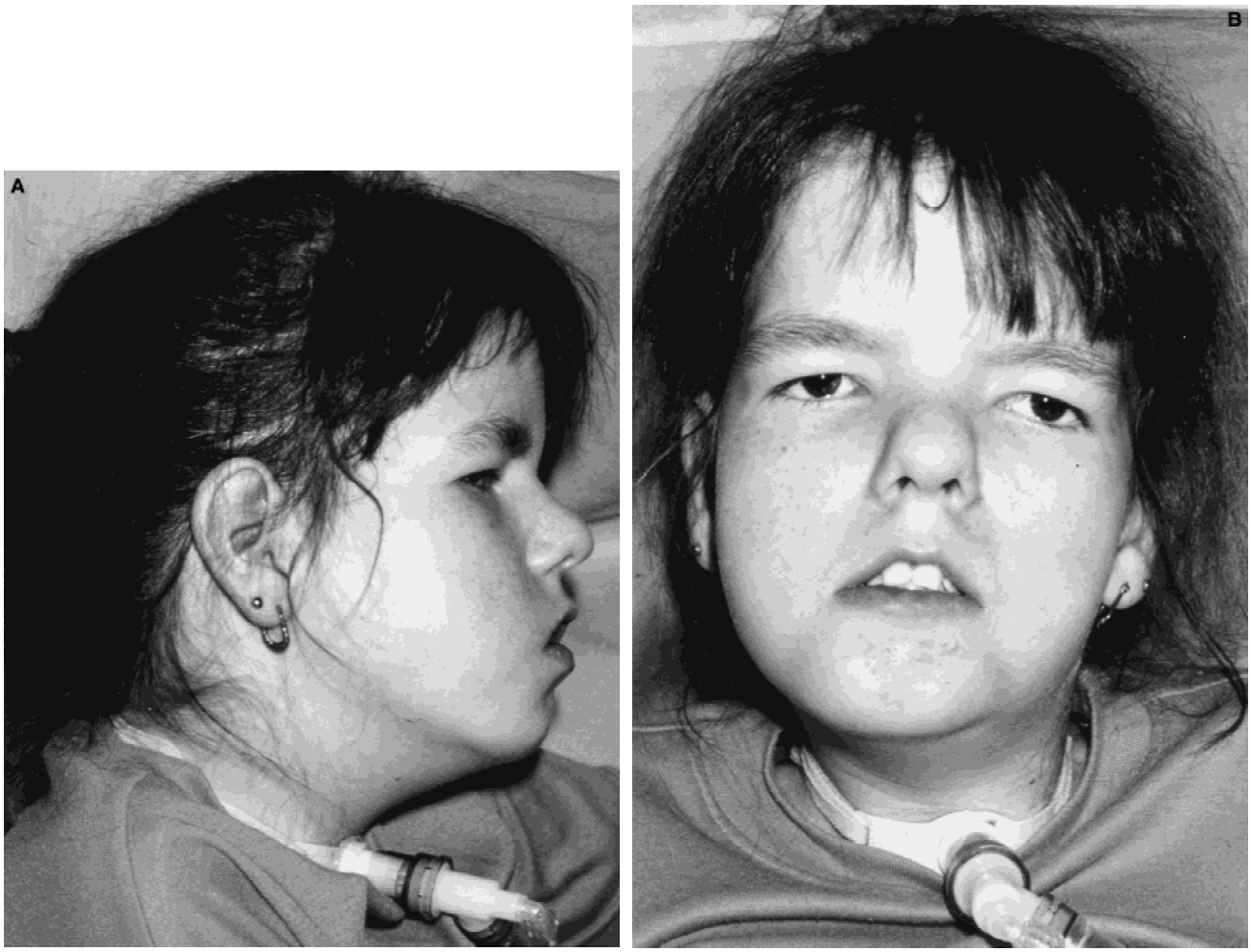

Fig. 2. **(A)** Lateral and **(B)** frontal views of Case 2 showing a short bulbous nose, downslanting palpebral fissures, low-set ears, and myopathic facies. Note that a tracheostomy tube is in situ to facilitate nocturnal ventilation due to central hypoventilation.

normal intelligence with the above manifestations. Schimke et al. [1993] reported a further case, a 27-month-old boy with more severe muscle weakness and talipes. Baraitser and Reardon [1994] described a fourth case, a 5-year-old boy. Three of the cases had a similar facial appearance. Interestingly, in the original report, Case 2 does not facially resemble the other cases, but does have cleft palate, nerve palsies, and

TABLE I. Clinical Manifestations of CFZ Syndrome

	Carey et al. [1982]		Schimke et al. [1993]	Baraitser and Reardon [1994]	This report	
	Case 1	Case 2			Case 1	Case 2
Developmental delay/mental retardation	–	–	–	–	+	+
Short stature	+	+	+	–	–	–
Feeding/swallowing problems	+	+	+	+	+	+
Microcephaly	+	+	–	–	–	–
Facial weakness	+	+	+	+	+	+
Ptosis	+	+	+	+	–	+
Downslanting palpebral fissures	+	–	+	+	+	+
Ophthalmoplegia	+	+	+	+	?	+
Triangular nose	+	+	+	+	+	+
Small jaw	+	+	+	+	+	+
Cleft palate	+	+	+	–	–	–
Brachydactyly	+	+	+	+	?	+
Hypotonia	+	+	+	+	+	+
Talipes	–	–	+	+	–	+
Scoliosis	–	+	–	–	–	+
Central hypoventilation	–	–	–	–	–	+

myopathy. As Case 2 is the oldest patient described this may reflect a developing facial appearance that the younger patients will "grow into."

It is also interesting that although all previous cases were associated with motor delay, all had normal intelligence. Case 1 did have delayed motor development but died in infancy. Case 2 had delayed global development, with an IQ of 57. Developmental delay, as seen in Case 2, may be part of the spectrum of abnormalities, as no significant episodes of hypoxemia were recorded.

The mechanism of inheritance is likely to be autosomal recessive, given that both parents had normal karyotypes and were phenotypically normal and that a further sibling pair was reported by Carey et al. [1982].

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