American Journal of Medical Genetics 127A:277–287 (2004)

Möbius Sequence, Robin Complex, and Hypotonia: Severe Expression of Brainstem Disruption Spectrum Versus Carey–Fineman–Ziter Syndrome

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We report on nine unrelated children fitting a diagnosis of Carey–Fineman–Ziter syndrome (CFZS). All children presented with Möbius sequence, Pierre Robin complex (6/9) or micrognathia, and hypotonia. Some had primary hypoventilation, delayed development, and acral anomalies. The neuropathological investigations performed in two patients showed a combination of dysplastic lesions (neuronal heterotopias) and encephaloclastic changes consisting of small foci of necrosis with microcalcifications. The mother of a third child had severe trauma during her 2nd month of pregnancy. Based on a review of the literature on MS and CFZS, we suggest designating as "Robin–Möbius phenotype" a distinct clinical variant of MS with extensive brainstem involvement, Robin complex, hypotonia without specific muscle disorder, clubfeet and variable acral anomalies. This condition appears to bear a higher risk of mental handicap and perhaps a higher recurrence risk than "common" MS. Neuropathology and neuroimaging are suggestive, at least in some cases, of a vascular disruption, which could be exogenous, or secondary to a genetic predisposition. Etiologic heterogeneity seems likely and, in that respect, the original CFZS family could represent a private syndrome fitting on the "Robin–Möbius" spectrum. Despite the existence of two familial reports, recurrence risk is probably much lower than 25%, although exact figures cannot be extracted from the available literature.

KEY WORDS: Robin sequence; Möbius sequence; Carey–Fineman–Ziter syndrome; brainstem disruption; Poland anomaly; nosology

INTRODUCTION

Carey–Fineman–Ziter syndrome (CFZS) is a rare multiple congenital anomalies syndrome defined by a combination of Pierre Robin complex (PRC) and Möbius sequence (MS), associated with hypotonia and various other malformations [Carey et al., 1982]. It is speculated to be inherited as an autosomal recessive disorder (MIM 254940). To date, two pairs of sibs and two sporadic cases have been reported as having CFZS (see below). We describe here clinical data on nine new, unrelated cases, and present the neuropathological data on two of them. We review previous reports in light of a vascular disruptive hypothesis. The phenotypic spectrum of severity and the difficulty in discriminating CFZS from common MS are illustrated.

CLINICAL REPORTS

Patient 1

This girl was the first child of healthy Belgian parents born at 37 weeks gestation in a pregnancy that was complicated by oligohydramnios. The family history was unremarkable. There was no reported exposure to alcohol or teratogens. BW was 2,150 g (<3rd centile), BL was 48 cm (50th centile), and OFC was 32.8 cm (10th centile). Clinical examination at birth revealed a squared forehead with a median widow's peak, mild hypertelorism, flat nasal bridge, upturned nares, long, smooth philtrum, a thin upper lip, PRC, microglossia, posterior cleft palate, and a median dimple in the chin (Fig. 1C,D). She had short fingers and a right talipes equinovarus. Echocardiography showed a small, type 2 ASD that later closed spontaneously. No renal system abnormalities were noted on ultrasound. The neurological examination revealed gross hypotonia with poorly elicited and partially absent primitive reflexes, bilateral facial nerve palsies, absence of corneal reflexes, and external ophthalmoplegia. Initially there were

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Received 4 January 2001; Accepted 15 September 2001
DOI 10.1002/ajmg.a.20687

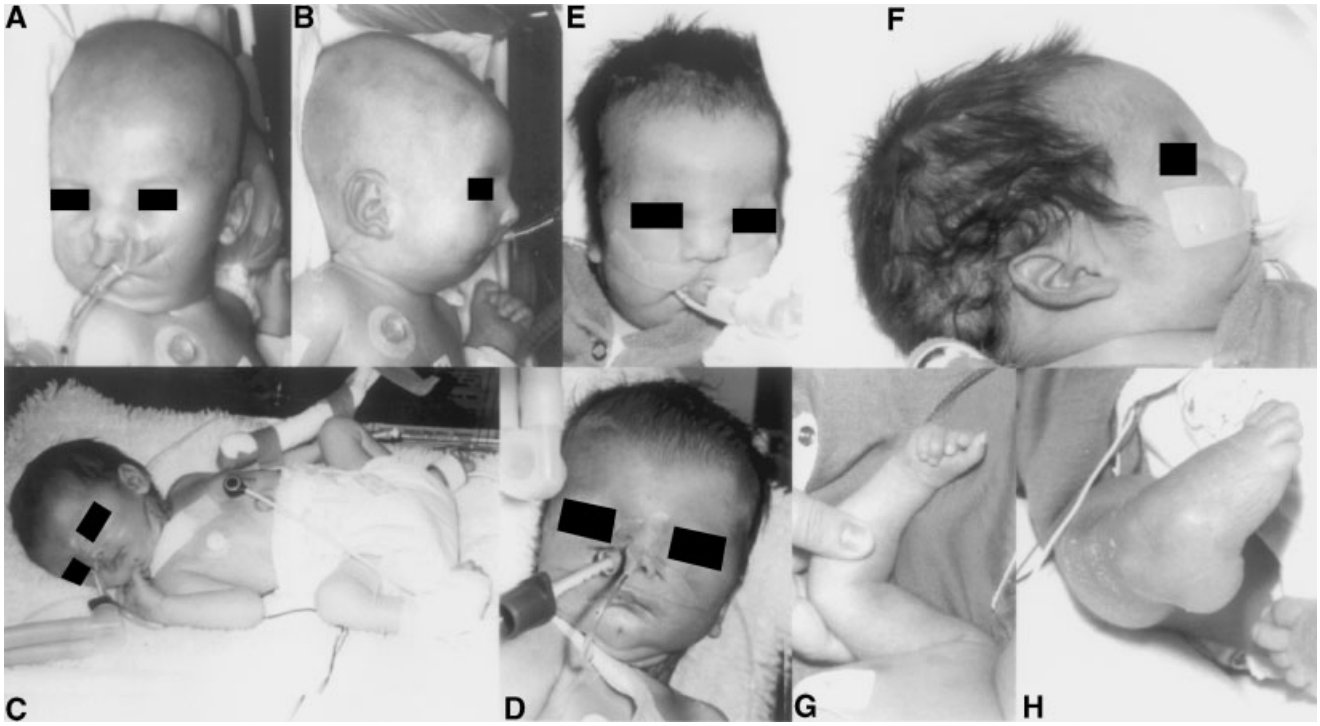

Fig. 1. Clinical appearance of patients in the neonatal period: (**A**, **B**) Patient 2; (**C**, **D**) Patient 1; (**E**–**H**) Patient 5.

absent myotatic reflexes. Swallowing was not possible, and feeding difficulties persisted until her death at 4½ months of age. EMG and auditory evoked potentials were normal.

Mechanical ventilation was required soon after birth because of hypoventilation. She was never weaned from the ventilator, although she became able to breathe efficiently when awake. She had several bouts of seizures that were controlled with phenobarbital. During her last weeks, she had several episodes of bradycardia with hypoxia, which finally lead her to death.

Several investigations were performed without conclusive results. This included extensive metabolic screening. Because of repeated increases of lactate and pyruvate in the urine and blood (but not in the CSF), a suspicion of mitochondrial dysfunction was raised. Studies of respiratory chain complexes I–V on fresh muscle biopsy and mtDNA screening were negative. Myotonic dystrophy was excluded by triplet analysis. Skin and peripheral blood chromosomes (G-banding, 500 band level) were normal. FISH studies excluded a del(22q11). Serial US examination and MRI investigations of the CNS showed progressive enlargement of the lateral ventricles and extra-axial subarachnoidal spaces, compatible with generalized CNS atrophy, and small, atrophic cerebellum. Radio-isotopic HMPAO SPECT scan of the brain showed a relative hypoperfusion of the frontal cortex, the anterior part of the cerebellum, and the brainstem.

At postmortem examination, the only unsuspected finding was abnormal segmentation of the lungs, with four lobes on the right side. Muscle histology (light and electronic microscopy) performed during the metabolic work-up was normal. Neuropathologic investigations (Fig. 2) showed normal supratentorial structures, and, in the cerebellum, a spongiosis of the Purkinje cell layer. There was a slight decrease of the number of neurons in the nucleus of cranial nerve III, and impressive changes in the midpons and medulla oblongata. At that level, multiple foci of necrosis were noted, with microcalcifications under the floor of the fourth ventricle. Several nuclei had a dysplastic aspect, with numerous heterotopias, especially at the level of the nucleus olivary principalis, but also in the subependymal area of the lower medulla oblongata and in the bulbopontine reticular formation. Several motor nuclei throughout the brainstem were hypoplastic or aplastic. There were no cortical anomalies.

Patient 2

This boy was the second child of non-consanguineous Belgian parents. There was no polyhydramnios and no reported exposure to alcohol or teratogens. BW was 3,270 g (50–75th centile), BL was 50 cm (75th centile), and OFC 36.2 cm (90th centile) at term. Prominent facial anomalies included: a high forehead, broad, flat nasal root, mild hypertelorism, bilateral epicanthus, apparent ptosis, upturned nose, PRC, and bilateral clubfeet (Fig. 1A,B). Because of recurrent apnea, mechanical ventilation was initiated at 3 days of age, and this remained necessary until his death at the age of 6 weeks. Due to the severity of the neurological impairment and the lack of progress, it was decided to suspend intensive care.

Initial neurological assessment revealed severe hypotonia, facial palsy, oculomotor palsy, complete absence of swallowing, and absence of reactivity to visual or auditory stimuli. Seizures were noted at day 3. Visual and somesthesic potentials were normal, as was the EMG. MRI showed bilateral ventricular dilatation and major bulbar and protuberential atrophy (Fig. 4).

Postmortem examination confirmed macroscopic CNS anomalies, and absence of visceral malformations. Microscopic neuropathological examination revealed dentato-ponto-olivary dysplasia. There were important anomalies of the brainstem, most severely affecting the nucleus olivari principalis,

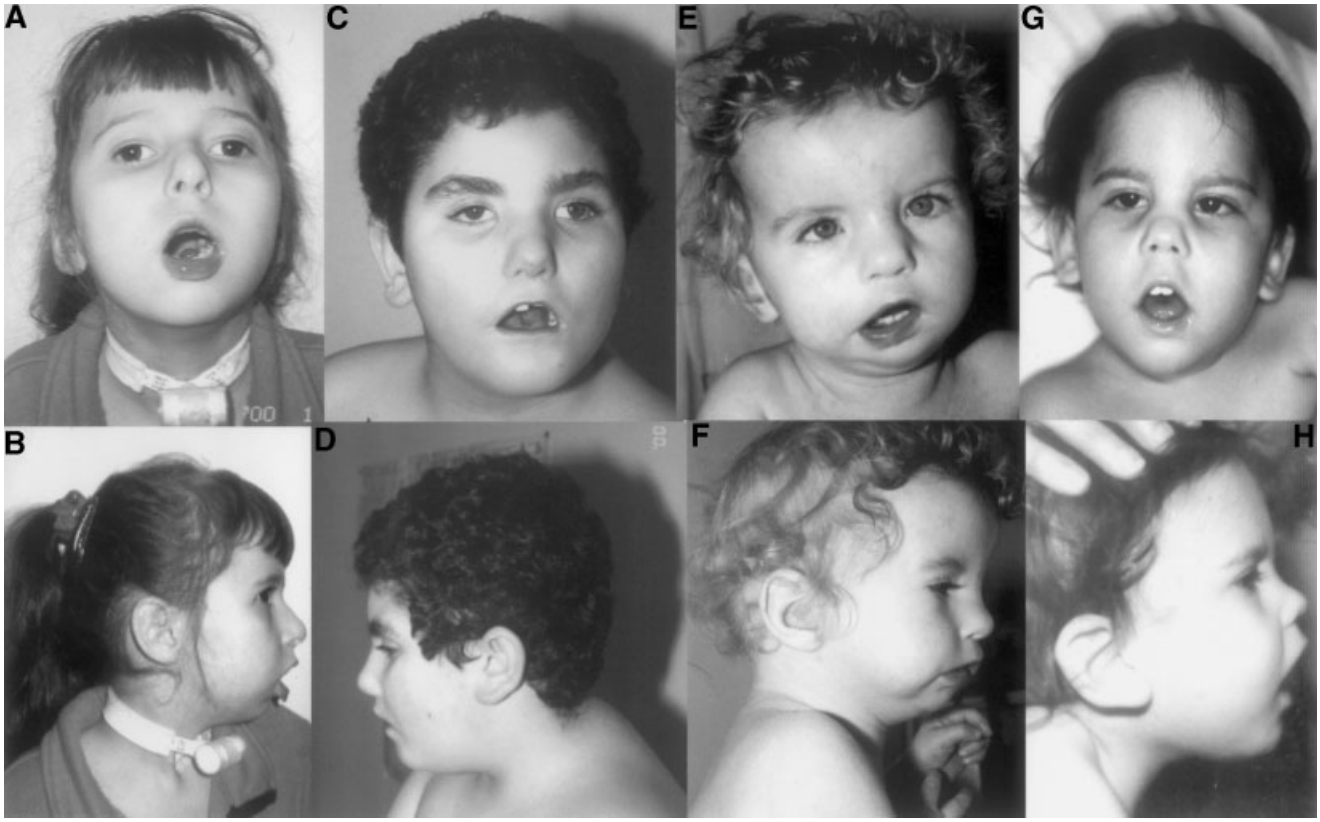

Fig. 2. Clinical appearance of patients in childhood: (**A**, **B**) Patient 8; (**C**, **D**) Patient 3; (**E**, **F**) Patient 6; (**G**, **H**) Patient 7.

the nucleus dentatus cerebelli, the pons, and all motor nuclei. Those nuclei were anarchically parsed in several smaller nuclei. In the posterior part of the pons, there were numerous vessels with enlarged perivascular spaces, and scattered areas of necrosis with microcalcifications and gliosis. In the cerebellum, several islets of neuronal heterotopias were present and the dentate nucleus was fragmented in five parts. There were no cortical anomalies. Muscle was not studied (Fig. 3).

Patient 3

This boy is the second child of normal, non-consanguineous Belgian parents of Italian origin. He has two normal sibs. During the 2nd month of pregnancy, the mother had a car crash, resulting in cerebral concussion, multiple rib fractures, and a splenic rupture that required emergency splenectomy. Gestational diabetes was noted during the third trimester. Birth weight at term was 4,330 g (>90th centile).

At birth, facial palsy, external ophthalmoplegia, PRC, and right talipes equinovarus deformity were noted. A diagnosis of Möbius syndrome was proposed. Motor milestones were delayed. Sitting unsupported was possible at age 2 years. Walking was acquired at age 4 years. Swallowing was persistently very difficult, even for liquids. At the age of 6, IQ was rated 30. A short description of this patient at age 3 was given by Lipson et al. [1996] as an example of Möbius syndrome induced by maternal acute hypotension.

At the age of 8½ years (Fig. 2C,D), he was 135 cm tall (+1 SD) and weighted 45 kg. OFC was 54.5 cm (+1 SD). He has severe mental retardation and severe verbal impairment. Swallowing was possible (sometimes with manual pressure) but chewing was a problem. He had fine motor coordination problems and difficulties with bimanual coordination. Language was limited to sounds, although verbal understanding of simple sentences or orders was satisfactory. The karyotype was normal.

Patient 4

This male infant was born to a 30-year-old G3P2Ab1 mother after a 38 week pregnancy complicated by maternal hypertension and IUGR, noted at 31 weeks. There was no reported exposure to alcohol or teratogens. He was delivered by emergency cesarean section for fetal distress during labor. Birth weight was 1,640 g (≪10th centile), length was 40 cm (≪10th centile), and OFC was 33 cm (25–50th centile). He was admitted to the NICU for severe hypotonia. Craniofacial features included scaphocephaly, large fronto-naso-palpebral nevus flammeus, downslanting palpebral fissures, epicanthic folds, short upturned nose, flat simple philtrum, thin upper lip, PRC (micrognathia, microglossia, and cleft soft palate), and crux cymbae. Hands were small with fifth finger clinodactyly, single palmar crease, proximally placed thumbs, and ulnar deviation. He had a left talipes equinovarus, a nevus flammeus of the left hemi-thorax, and micropenis (30 mm × 16 mm).

Head and cardiac ultrasonography, cranial CT scan, and MRI were normal except for absent posterior pituitary hyperintensity. ERG was normal. Visual evoked responses showed increased latencies compatible with a conduction defect. Brainstem auditory evoked responses also showed increased latencies. Ocular fundus examination and high-resolution karyotype were normal. FISH analyses for del(22q11) and del(13qter) screening were negative.

Severe feeding difficulties were noted with swallowing incompetence requiring gavage feeding for 18 months. He

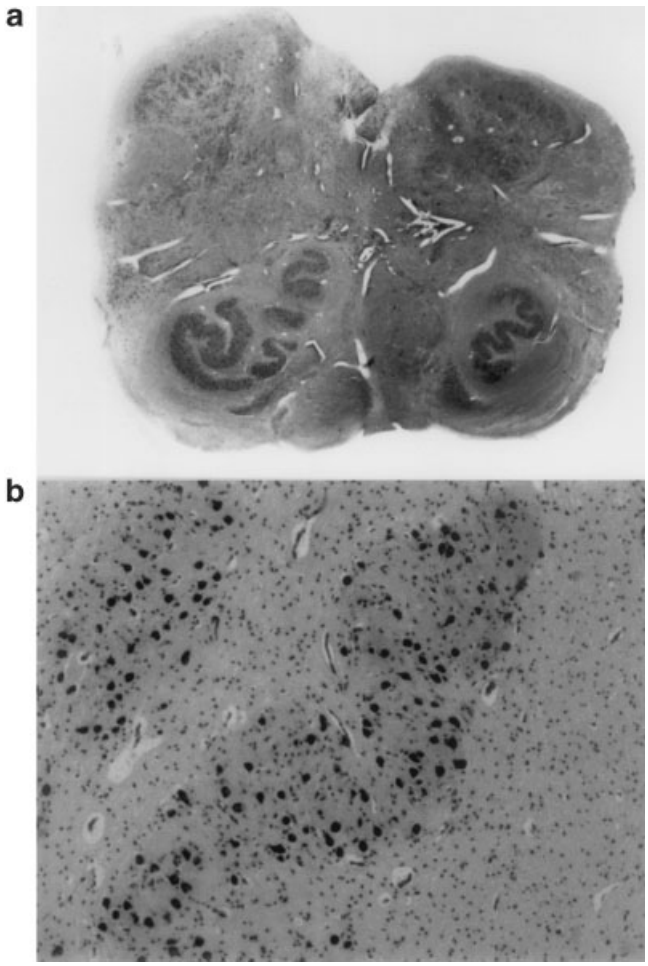

Fig. 3. Patient 1: Microscopic appearance of brainstem, (**a**) inferior olivary nucleus, fragmented aspect and absence of the normal architecture; (**b**) microcalcifications in the floor of the 4th ventricle.

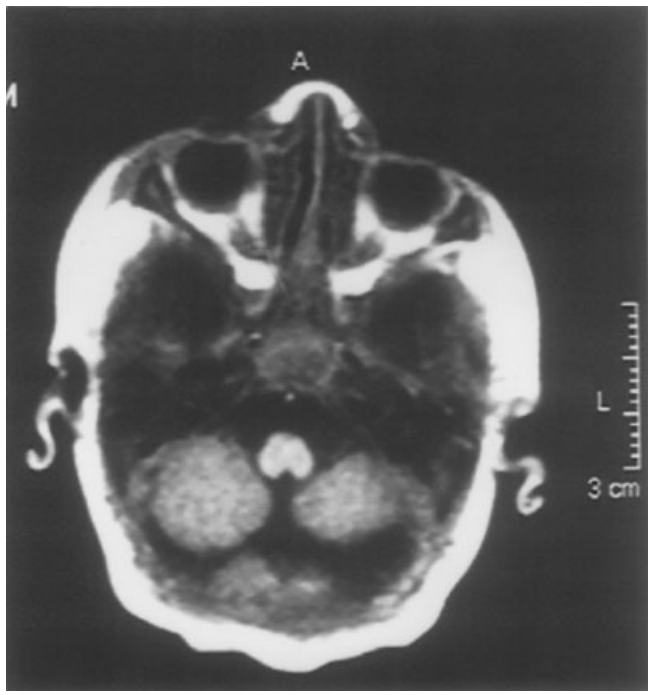

Fig. 4. Patient 2: MRI showing extreme atrophy of the brainstem.

had severe gastro-esophageal reflux and repeated episodes of aspiration pneumonitis prompting manometry that showed partial achalasia of the upper esophageal sphincter and asynchronous pharyngeal and sphincter function. He had surgery for an incarcerated inguinal hernia at 4 months of age. He had febrile seizures at 21 months. After normal testosterone secretion stimulation test with HCG, his micropenis was successfully treated with four injections of testosterone. Thyroid function and growth hormone stimulation testing was also normal.

His motor and language milestones were delayed. He sat at 1 year, and walked with assistance by 2 years. He had normal schooling, but he did need some help, which included intensive speech therapy. IQ was 95 at the age of 6 years, with poor verbal performance. At the last follow up, at age 8 years, he was of normal height, had prominent metopic suture with a narrow face and cranium, crowded teeth, and persistent small hands with total hand length of 10 cm (normal 11.5–14.5 cm).

Electromyographic studies of orofacial muscles at 3 months showed partial denervation of the facial muscles with a simplified trigeminal blink reflex. Palatal muscle activity was normal. There were signs of partial denervation of lingual muscles with absence of rhythmic suck. This was compatible with bilateral involvement of nuclei controlling the motor muscles of the 7th and 12th cranial nerves as well as the 5–7th internuclear relay, explaining poor central suck organization. Interestingly, there was no oculomotor involvement.

Patient 5

This boy was the 12th child born to a 38-year-old G14P10Ab3 woman. His parents are non-consanguineous Canadian aboriginals. The family medical history was unremarkable. Polyhydramnios and bilateral talipes equinovarus were noted on prenatal ultrasound scans. The pregnancy was further complicated by gestational diabetes and the mother was on thyroid replacement for hypothyroidism. There was no reported exposure to teratogens. Amniocentesis at 32 weeks gestational age showed a normal male karyotype, 46,XY.

He was born at 36 weeks gestation. Poor respiratory effort at birth necessitated intubation and assisted ventilation. Birth weight was 2,636 g (25th centile), length 46 cm, and head circumference was 36 cm (95th centile). He had a skull with a dolichocephalic appearance, low-set and posteriorly rotated ears, external ophthalmoplegia, facial diplegia, with poverty of facial movements, small eyelids, a broad nasal root, PRC, and an atrophic tongue (Fig. 1E–G). An ophthalmologic examination showed normal eye structure. There was a complete absence of the corneal reflex, and he has subsequently developed significant corneal abrasions. There was no gag reflex. A Poland anomaly of the right limb was present, consisting of a smaller right hand (Fig. 1G), syndactyly of the fingers, hypoplasia of the right pectoralis major, and shortened ribs of the right hemithorax. His left upper limb appeared normal, but the wrist was in a flexed position. In the lower limbs, bilateral talipes equinovarus was present (Fig. 1H). A tracheotomy was placed at 3 months. At 6 months, his weight was 6,220 g (5th centile), length was 65 cm (10–25th centile), and head circumference was 43 cm (25th centile). He was still ventilator dependent with a tracheostomy and was fed via a gastrostomy. He did not swallow and still had no gag reflex.

Developmentally, he was able to bring his hands to midline, clasped a rattle for a short period of time (he did not transfer), kicked his legs, and shook his arms. He did make some vocalizations and appeared to be responsive when stimulated. A formal developmental assessment at 7 months of age placed his development at a 16 week level.

Initial ultrasound of the head showed a subependymal cyst. Echocardiography and abdominal US were normal. Cranial MRI and CT scan suggested hypoplasia of the frontal temporal lobes. The brainstem and the cerebellum appeared shrunken. Small symmetric calcifications were noted in the dorsal pontine tegmentum extending downwards into the medulla. The location of the calcified lesions suggested involvement of the lower cranial nerve nuclei V–XII. A small hemorrhage in the germinal matrix and a subdural hemorrhage were also present. EEG findings suggested immaturity with lack of normal awake and sleep transitions. Excess sharp transients were reported over temporal regions, persisting until 6 weeks of age.

A muscle biopsy of the right quadriceps, done at 1 month of age, showed large ungrouped type I muscle fibers, scattered necrotic, contracted muscle fibers, evidence of mild fibrosis, and perimysial infiltration with mononuclear cells. Non-specific esterase activity was increased in the paranuclear regions of the myofibers. EM studies of the muscle indicated focal loss of Z discs and I bands and intramuscular nerve twigs composed of large thinly myelinated axons with reduplicated basement membranes suggesting demyelination and remyelination.

Patient 6

This patient was the third child of healthy, unrelated Romanian parents. The mother was 29-year-old and the father 42-year-old at time of birth. The pregnancy was uneventful. There was no reported exposure to alcohol or teratogens. Birth weight was 3,700 g (75–90th centile); birth length 50 cm (75th centile); and OFC 38 cm (>90th centile). When assessed at the age of 5 months, she was hypotrophic (length 2 −SD, weight 3.5 −SD). There was bilateral facial palsy with drooling and an expressionless face (Fig. 2E,F), lack of lateral ocular movements, apparent hypertelorism, PRC, and bilateral clubfeet. Brain CT scan showed mildly increased lateral ventricles and moderate bifrontal cortical atrophy. Ophthalmologic examination confirmed lateral gaze palsy. Karyotype was normal. At last follow up, at age $2\frac{1}{4}$ years, she had moderate mental retardation, with speech delay.

Patient 7

This girl was the first child of non-consanguineous French parents. The mother, aged 29 years, was of borderline intelligence. With a previous partner, she had a healthy child and two miscarriages. The father, aged 49 years, had eight children from a previous marriage. Two died in infancy (probable SIDS) and the six survivors all had developmental problems. Pregnancy was complicated by an episode of acute pyelonephritis at 20 weeks gestation. There was no reported exposure to alcohol or teratogens. Polyhydramnios was noted at 37 weeks. The child was delivered by cesarean section for breech presentation at 38 weeks. He weighed 2,600 g (10th centile), was 47 cm long (10th centile), and had an OFC of 33 cm (25–50th centile). Anomalies noted at birth included a dolichocephalic shape of the skull, bitemporal narrowing, ridged forehead, microretrognathia, high vaulted, not cleft palate, bilateral equinovarus deformity of the feet. Hypotonia and poor spontaneous movements were prominent. She was admitted to the NICU for recurrent bradycardias with cyanosis, and absence of sucking and swallowing reflexes. Investigations during the first weeks revealed paresis of the tongue and the pharynx, and severe gastro-esophageal reflux for which a Nissen fundoplication was required at 2 months of age. Brain MRI and renal ultrasonography were normal. Gastrostomy was performed at age 1 year. Clubfeet were surgically corrected at age 15 months.

At the last evaluation, at age 23 months (Fig. 2G,H), she was 77 cm tall (−3 SD) and had an OFC of 44.5 cm (−4 SD). Features included an elongated face, ridged metopic suture, downslanting palpebral fissures, a prominent nasal root, anteverted nostrils, a tented upper lip and downturned corners of the mouth, prominent micrognathia, and low-set, posteriorly rotated, normally shaped ears. Hands and feet were short, with spindle-shaped fingers and tiny toes. The 5th toenails were very small. She was able to crawl, but not to walk. Motor development was estimated at 12–15 months. Language was absent. There was bilateral facial palsy. The mouth was kept open, with continuous drooling. Sucking and swallowing were completely absent, and the tongue was immobile, with episodic fasciculations. Ocular abduction was limited. EMG of facial muscles confirmed denervation. Karyotype was normal. Myotonic dystrophy was excluded.

Patient 8

This girl was the first child of a 26-year-old mother and a 35-year-old father. The parents were of Caucasian ancestry, unrelated, and in general good health. Except for three episodes of syncope during the first trimester, pregnancy was uneventful. There was no reported exposure to alcohol or teratogens, and a prenatal ultrasound was normal. She was born at 41 weeks gestation. Birth weight was 3,245 g (50th centile) and birth length was 49 cm (25–50th centile). At the time of birth, she had no cry, absent suck, swallow and gag reflexes, minimal facial movements, and reduced eye blinking and abduction. She required ventilatory support and tracheostomy placement at the age of 1 month. Due to her poor feeding ability, she had a gastrostomy and a jejunostomy placed, Nissen fundoplication, and, because of recurrent aspirations, a Lindemann procedure (separation of trachea and larynx).

She remained on the normal growth curves for height, weight, and head circumference, but showed significant delays in motor skills. She began sitting at 8 months and was able to sit unsupported at about 14 months. She was able to walk with a walker age 2 years and to walk independently at age 5¼. She began to swallow effectively at age $4^{5}/_{6}$ years. She has exhibited gradual improvement of ocular muscles movements and tone.

When examined at age $4^{2}/_{3}$, she was 112.5 cm (90th centile), weighed 20.8 kg (90th centile), and had an OFC of 50 cm (50th centile). She had a long nose with broad nasal bridge and bulbous tip. There was bilateral reduced facial tone with minimal facial expression. Her lateral gaze was present bilaterally, although delayed, and she had left esotropia. Her mouth was held open. She had micrognathia, small tongue, high arched palate but no cleft. She had long fingers and toes bilaterally. X rays showed bilateral coxa valga. There was generalized asymmetric weakness and hypotonia (left worse than right), particularly in the trunk and neck. Deep tendon reflexes were normal. There was evidence of dysfunction involving muscles associated with cranial nerves V, VII, IX, X, and XII. She had unusual eye movements with abnormalities in smooth pursuits and saccades, defined as oculomotor apraxia with a supranuclear defect suggestive of a brainstem anomaly.

Cranial MRI studies in the newborn period and at age 5 years were normal. Audiometric assessment showed normal hearing but increased latency in response time. EEG and metabolic screening were unremarkable. Chromosomes showed normal 46,XX (500 bands). FISH for del(22q11) was negative. Using

sign language, she was able to construct 5–6 word sentences and to communicate using pictures. Verbal IQ, assessed using sign language, was 61 on the WPPSI.

Patient 9

This boy was the only child of non-consanguineous British parents. During pregnancy, it was noticed that there were reduced fetal movements and US scan showed bilateral talipes equinovarus and oligohydramnios. Amniocenteses showed a normal male karyotype. He was born at 37 weeks gestation. BW was 2,650 g (25–50th centile). At birth, it was noted there was a short umbilical cord, left sided facial weakness, and bilateral talipes. Further evaluation showed prominent veins over the left forehead, atrophy and weakness of the left tongue, high arched palate, normal hands, bilateral talipes, and hypotonia with poor muscle bulk. Facial electromyography showed relatively little electrical change in the facial muscles and orbicularis oculi but denervation of the left genioglossus. Brain MRI scan showed no asignificant abnormalities. Karyotype and biochemical studies, including CK has been normal. There has been some improvement of muscle tone. At 2 years of age, he can stand with support but is unable to walk and has very limited speech.

Follow up of Previously Published Patients

1) Patients of Carey et al. [1982] case. See accompanying Editorial.
2) Patient of Schimke et al. [1993] case. According to the author, the follow up of the child was better than foreseen at the time of their publication: muscle strength improved, walking was possible, and mental retardation was not as compromised as initially suspected, but the patient died of an acute respiratory problem [N.N. Schimke, personal communication, 2000].
3) Patient of Baraitser and Reardon [1994] case. The major problems beyond neonatal period were feeding difficulties, which continued up to his first birthday, but he did not require prolonged ventilatory support. At the age of 12, the patient continues to progress. He is moderately delayed and requires special help at school [R. Winter, personal communication, 1999].

DISCUSSION

CFZS is currently defined as a combination of MS, PRC, and "myopathic" hypotonia. Its delineation is based on two unrelated pairs of sibs and two sporadic cases. It is commonly considered to be an autosomal recessive condition. CFZS is the only syndrome identified when the combination of MS and PRC is searched for in databases. A diagnosis of CFZS was initially set up for Patients 1 and 2, but the expansion of the series and a critical review of the literature led us to think that the definition and nosology of cases with apparent CFZS could be much more complex. All the patients collected in this series were initially diagnosed as CFZS, based on this combination of key features. For five of them, a diagnosis of CFZS is sustained by the triad MS, PRC, and hypotonia (Table IA,B). Patients 7–9 have severe micrognathia rather than PRC but in other aspects, are very similar to Patients 1–6. Patient 8 shows supranuclear oculomotor apraxia. Patient 4 has no anomaly of the ocular movements but shows involvement of lower cranial nerves.

Nosology, Etiology, and Pathogenesis of MS

MS is commonly defined as the association of non-progressive facial palsy with abducens palsy. MS is causally and clinically heterogeneous. The term is usually used to describe children with aplasia or disruption of brainstem nuclei, [Henderson, 1939], but also for some children with peripheral nerve palsy or even myopathy. The older literature was reviewed in much detail by Henderson [1939] and the neuro-ophthalmological aspects by Danis [1945]. Succinct recent clinical updates are available [Legum et al., 1981; Kumar, 1990; Lipson et al., 1990]. By definition, MS includes facial palsy. This palsy may be asymmetric, and, when incomplete, affects the frontalis and periorbital muscles more than the lower muscles of the face. A closer look at the ophthalmological literature reveals that oculomotor dysfunction is variable and not limited to a cranial nerve VI nucleus palsy. Indeed, in the definition of MS, abducens palsy should better be termed abduction palsy, as patients with MS have been reported with pure abducens palsy (nerve VI palsy senso strictu), horizontal gaze palsy with preserved convergence (external ophthalmoplegia due to supranuclear lesion), complete horizontal gaze palsy [Danis, 1945], or even total oculomotor palsy resulting from nerves III, IV, and VI palsies [Hicks, 1943]. In his exhaustive review on MS, Henderson [1939], noted that 73% of patient with facial diplegia had abducens palsy and 25% had external ophthalmoplegia. Lingual and/or velar palsy (cranial nerves IX and XII) were recorded in over 30% and masseter palsy (cranial nerve V) in 7%. A series of 12 patients with severe congenital "dysphagia" has been reported among which 9 had bilateral facial palsy, and dysfunction of nerve pairs VII, IX, XI, and XII, but no ocular involvement [Renault and Couvreur, 1992]. Abnormal pregnancy, prematurity or neonatal distress were noted in 7 of 12 patients.

The most commonly proposed pathogenesis of MS is a local destructive process of brainstem nuclei. The brainstem nuclei that are involved in MS, undergo their more rapid embryonic development around the 4th and 5th week of development at the 10 mm stage. This could represent a susceptibility window, but insults occurring later in development should also be considered. Lesions of the posterior part of rhombomere 3 affect cranial nerve V; lesions of rhombomeres 4 and 5 result in MS (cranial nerves VI and VII); and lesions of the rhombomeres 6, 7, and 8 are responsible for deafness (cranial nerve VIII) and abnormal suction and deglutition that begins in utero and lead to the development of Robin sequence (cranial nerves IX, X, and XII) [Couly, 1983; Couly et al., 1994].

A variety of anomalies have been described in association with MS and are present in more than 50% of cases. Facial anomalies include micrognathia, broad base of the nose, epicanthus, and abnormal pinnae. Upper limb anomalies may be present in 15% of cases (syndactyly, brachydactyly, limb reduction, aplasia of the pectoralis major). Lower limbs are less often affected, but show a similar pattern of defects as the upper limbs and talipes. The presence of associated anomalies and of familial recurrence allowed authors to distinguish several phenotypes in MS, some of which representing distinct entities (defined by their inheritance pattern or associated anomalies). Others simply are clinical variants sharing a similar vascular disruptive pathogenesis, as for instance MS with Hanhart hypoglossia–hypodactyly (e.g., Patients 6 and 7 in Herrmann et al. [1976] with PRC, MS, and hypoglossia–hypodactyly). The most important and nosologically difficult is Poland–Möbius "syndrome" [Sugarman and Stark, 1973; Pierson et al., 1974], with an extreme variability in the expression. Many cases are sporadic and could represent simple variants of MS, whereas some cases show autosomal inheritance [Collins and Schimke, 1982; Rojas-Martinez et al., 1991; Larrandaburu et al., 1999]. Other syndromic forms of MS include MS with arthrogryposis multiplex, MS with peripheral neuropathy and hypogonadism, and CFZS. Among exogenous causes, misoprostol is known to induce both MS and limb deficiencies [Gonzalez et al., 1993]. MS has also been reported

TABLE IA. Summary of Findings in Literature Patients With CFZS

Case	Carey sib 1	Carey sib 2	Schimke	Baraitser	Ryan sib 1	Ryan sib 2	Sudarshan 1	Kuhn	Cortez case 1	Cortez case 2
Diagnosis	CFZ	CFZ	CFZ	CFZ	CFZ	CFZ	MS	MS	TNOH	TNOH
Sex	M	F	M	M	M	F	F	M	M	M
Hydramnios				?	?	+	+	+	+	+
Gestational age	39	38	Term	Term	37	38	Term	38	38	37
BW (g)/OFC (cm)	2,600	2,620	3,100	2,700/?	2,800	2,750	?/?	2,340/?	3,200/35.7	2,320/36
Outcome	Alive adult	Died 36 Y	Died	Alive 5½ Y	Died 8 M	Alive 10.6 Y	Died in infancy	Died 6 W	Died 2 W	Died 4 W
Parents' age (father/mother)	?/38		?	?/30	26/20		?/?	?/17	38/35	?/34
Sibship (affected/total)	2/4		?	?	2/2		1/6	1/1	1/2	1/4
Craniofacial										
Micrognathia	+	+	+	+	+	+	+	+	+	+
Cleft palate	+	+	+	−	−	−	+	+	+	−
Tongue hypoplasia	+	+	+	+	?	+	?	+	+	+
MS[a]	+	+	+	+	?	+	+	+	+	+
Hypertelorism	−	−	−	+			?	?	+	+
Downsl palp fissures	+	+	−	+	+	+	?	?	?	?
Ptosis	+	+	+	+	−	+	+	?	?	?
Epicanthic folds	+	+	+	−	?	+	?	?	?	+
Short triangular anteverted nose	+	+	+	+	+	+	?	?	?	+
Long, simple philtrum	+	+	+	+	+	+	?	?	?	?
Thin upper lip	+	+	+	?	+	+	?	?	?	?
Extremities										
Hand anomaly	Brachyd.	Brachyd.	Brachyd.	Brachyd.	?	+	−	−	Syndactyly	Left Poland
Dimples	Wrist	−	Knee	Wrist	?	?	?	?	?	
Clubfeet	−	Short Achilles tendon	+	+	−	+	?	+	+	+
Neurology										
OFC	Micro	Micro	NI	NI	Macro	Macro	?	?	NI	NI
Hypotonia	+	+	+	+	+	+	+	+	+	Hypertonia
Mechanical ventilation	−	−	+	−	−	+	+	+	+	+
Muscle hypoplasia	+	+	+	+	?	?	?	+	?	?
Scoliosis	+	+	−	−	−	+	?	?	?	?
Muscle histology	Normal	Normal	Mild, non-specific myopathic changes	ND	?	Type 2 fibre predominance	Normal	?	ND?	ND?
Brain anomalies	−(CT)	?	−(CT)	?	Ventricular enlargement (CT)	Cortical atrophy (CT)	Mild ventricular enlargement (NECR)	−(MRI/ NECR)	Cortex atrophy (MRI and NECR)	−(MRI and NECR)
Brainstem morphol. anomalies	?	?	−(CT)	?	+	Narrow brainstem (CT)	(3)	Y (4)	Y (1)	Y (2)
Brainstem calcifications[b]	?	?	−(CT)	?			+(NECR)	+(CT/NECR)	+(NECR)	+(NECR)
Development										
Motor development	Delayed	Delayed	?	Delayed	Delayed	Delayed	NA	NA	NA	NA
Mental development	Normal	Normal	Delayed	Normal	Delayed	IQ 57	NA	NA	NA	NA
Failure to thrive	+	+	−	+	+	−	NA	NA	NA	NA
Postnatal short stature	+	+	+	−	−	−	NA	NA	NA	NA

[a]Minimal criteria, facial palsy + oculomotor anomaly of any type.
[b]TNOH, tegmentary nocrosis and olivary hypoplasia syndrome. NECR, at necropsy CT or MRI, radiologically; (1) and (2), tegmental necrosis, olivary hypoplasia, hyperplasia of corpus pontobulbare, and arcuate nucleus; (3) necrosis of medial longitudinal fasciculus and genu of nerve VII, (4) fibrillary gliosis and calcification of nuclei VI, severe gliosis and loss of architecture of central portion of medulla with obliteration of nuclei V–XII, abnormal vasculature and neuronoglial heterotopias of the pons.

TABLE IB. Summary of Findings in Patients With CFZS of This Report

Case	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6	Pt7	Pt8	Pt9
Sex	F	M	M	M	M	F	F	F	M
Parent's age (F/M)		33/31	30/26	/30	44/38	42/29	49/29	35/26	–/–
Hydramnios	Oligo	–	–		+	–	+	–	Oligo
Gestational age (weeks)	37–38	Term	Term	38	36	40	38	41	37
BW/OFC	2,150	3,720	4,330/35.8	1,640	2,636	3,700	2,600	3,295/?	2,650/
Outcome	Died 4½ M	Died 6 W	Alive 9 Y	Alive 6 Y	Alive	Alive	Alive 2 Y	Alive 6 Y	Alive 2 Y
Sibship (affected/total)	1/1	1/3	1/2		1/11	1/3	1/1	1/1	1/1
Craniofacial									
Micrognathia	+	+	+	+	+	+	+	+	+
Cleft palate	+	+	+	+	+	+	–	HarchPt	HarchP
Hypoplastic tongue	+	+	+	+	+	Asym	–	+	+
Möbius sequence	+	+	+	+	+	+	+	+	+
Hypertelorism	+		+	–	+	+	–	–	+
Downsl palp fissures	+	+	+	+	+	+	+	–	–
Ptosis	+	+	–	+	–	Right	–	–	–
Epicanthic folds	+	–	+	+	+	+	–	–	–
Short triangular nose, antev. nares	+	+	+	+	+	+	+	+	+
Long, simple philtrum	+	+	+	+	+	+	+	+	+
Thin upper lip	+	+	+	+	+	+	+	+	+
Extremities									
Hand anomaly	Brachyd.	?	–	Brachyd.	Right Poland	–	Brachyd.	Long fingers	–
Dimples	?	Ankles	–	–	–	–	Elbows	–	–
Clubfeet	+	+	+	+	+	+	+	–	+
Neurology									
OFC (latest state)	NI	Macro	NI	NI	Normal	NI	Micro	NI	Normal
Hypotonia	+	+	+	+	+	+	+	+	+
Mechanical ventilation	+		–	–	+	–	–	–	–
Muscle hypoplasia	+	–	–	+	+	+	–	–	+
Scoliosis	–	–	–	–	–	–	–	–	–
Muscle biopsy	Normal	ND	ND	ND	Atypical (see text)	ND	ND	ND	ND
Brain anomaly			–(MRI)	–(CT)	Atrophy	Atrophy		–(MRI)	–(MRI)
Brainstem morphol anomalies	+(see text)	+(see text)	–(MRI)	–(CT)	Thin (MRI)	–(CT)		–(MRI)	–(MRI)
Brainstem calcifications	+	+		–(CT)	+(CT)	–(CT)		–(MRI)	–(MRI)
Development									
Motor development	Delayed	NA	Delayed	+	Delayed	Delay	Delayed	Delayed	Delayed
Mental development	Delayed	NA	Delayed	Normal	Delayed	Normal	Delayed	IQ 61	Delayed
Failure to thrive	+	NA	–	+	–	+	+		–
Postnatal short stature	–	NA	–	–	–	–	+		–

after maternal trauma in the first trimester [Reed and Grant, 1957, Patient 1; Steigner et al., 1975, Patient 1; Lipson et al., 1996].

Most cases of isolated MS are sporadic, and it is generally considered that MS is not genetically determined in most instances, hence, the low recurrence risk (2%). Nevertheless, there are familial observations of MS that clearly indicate Mendelian inheritance in selected families. Pure MS can be dominantly transmitted [Dotti et al., 1989] or recessively transmitted (four sibs in Beetz [1913]; two brothers in Thomas [1898], although in the latter family, dominant inheritance of Poland–Möbius with skipped generations could be possible). A potential gene for MS has been localized to chromosome 13, based on a cytogenetic anomaly, in a family labeled with MS but without nerve VI involvement and with camptodactyly [Ziter et al., 1977; Slee et al., 1991].

Neuropathologic aspects of MS are variable. A subdivision in four groups has been proposed: atrophy or hypoplasia of nerve nuclei (group 1), atrophy with neuronal degenerative process of the nerves III and VI (group 2), atrophy with foci of necrosis of the brainstem (group 3), or to anomalies outside the CNS and cranial nerves (group 4) [Towfighi et al., 1979]. The sporadic nature of MS allows speculation that the mechanism affecting the development of the rhombencephalon could be environmentally driven. Susceptibility of the brainstem to hypoxia has been has been reported in the past [Gilles, 1969; Norman, 1974]. It has been shown that MS could be the result of ischemic injuries of the brainstem in animals [Lipson et al., 1989], although experimental data have been criticized [Alderman et al., 1991]. This hypothesis is in accordance with the vascular, disruptive mechanism similarly advocated for Poland anomaly, and unifies the pathogenesis of Poland and Möbius syndromes [Bouwes, Bavinck, and Weaver, 1986]. The development of MS and limb defects after misoprostol exposure illustrates this vascular theory. The presence of calcifications in the floor of the 4th ventricle, observed in Patients 1, 2, and 4, and in some literature cases [Richter, 1958; Thakkar et al., 1977; Bouwes, Bavinck, and Weaver, 1986] may be a clue to this disruptive mechanism. An interesting patient with Poland–Möbius syndrome and central hypoventilation was reported with brainstem atrophy and calcifications visible on MRI [Fujita et al., 1991]. MS and PRC were recently observed in combination with splenogonadal fusion syndrome, and with a form of tetraperomelia that is reminiscent of Hanhart syndrome. Neuropathology showed disruptive anomalies and calcifications in both cases, and olivary dysplasia in one of them [Lammens et al., 1998]. The neuropathological investigations performed in our Patients 1 and 2 further support the disruptive hypothesis of Möbius syndrome. In both children, anomalies were detected from midpons to the transition area of the medulla oblongata with the cervical spinal cord, and showed two different features: dysplasia and clastic lesions. The primary dysplastic lesions consisted of neuronal heterotopias causing an important disruption of brainstem architecture (lower pontine tegmentum, formatio reticularis, nuclei of the 3rd, 4th, 7–10th cranial nerves, and nucleus olivaris inferior). Clastic changes consisting of numerous small foci of necrosis with microcalcifications, occurring in the floor of the fourth ventricle and in the subependymal areas.

Nosology, Etiology, and Pathogenesis of Pierre Robin Sequence (PRS) and Complex

The term Pierre Robin is widely used in medical literature, although the definition is highly variable among authors, extending from small mandible and U-shaped posterior cleft palate with upper airway obstruction due to glossoptosis to any situation with a combination of small mandible with high-arched or cleft palate. Even in its narrower definition, Robin anomaly remains pathogenetically and phenotypically heterogeneous. In a recent critical review published in this *Journal*, Cohen [1999] stressed the importance of distinguishing PRS from PRC. In PRS, malformation, deformation, or connective tissue dysplasia lead to micrognathia and/or retrognathia, which, in turn causes cleft palate and true glossoptosis. In PRC, micrognathia/retrognathia and cleft palate are present, but the respiratory compromise is secondary to another mechanism (CNS involvement) and does not result from the microretrognathia itself. In the sense defined by Cohen, none of the patients presented here have PRS but rather show PRC.

CFZS

Carey et al. [1982] described a brother and sister with PRC and MS, microcephaly and generalized muscle hypotonia, but normal intelligence. Those patients had an unusual facial phenotype that was not present in other cases nor in our series. Those patients have been followed for 20 years (see Editorial by Carey this issue).

Schimke et al. [1993] reported an affected 27-month-old boy with more severe muscle weakness ("congenital generalized non-specific myopathy") and talipes equinovarus. Baraitser and Reardon [1994] reported a further case in a 5-year-old boy and coined the eponym CFZS. Recently, Ryan et al. [1999] added a sib pair: one of the sibs died of aspiration at the age of 8 months; the second one was alive but mentally retarded (IQ 57) at age 10½ years, strengthening the hypothesis that CFZS could be a recessive disorder.

Some case reports not specifically diagnosed as CFZS were identified during our perusal of the literature. A combination of MS and PRC without acral anomalies was briefly noted in one previous report [Smith and Stowe, 1961]. Sudarshan and Goldie [1985], Patient 1, described a child with MS, PRC, absence of breathing and, at autopsy, midline necrosis and calcifications within the floor of the 4th ventricle. Another patient with MS, PRC, absence of breathing, contractures of ankles and knees, and talipes was shown to have hypoplastic brainstem with severe gliosis and calcifications of the nuclei of nerve VI and other territories [Kuhn et al., 1990]. These patients shares many similarities with the syndrome of tegmental necrosis and olivary hypoplasia that has been reported as a separate entity [Cortez and Kinney, 1996]. Two of the three newborns reported in this article had multiple nerve palsies consistent with MS and PRC (Patient 1) or high vaulted palate with micrognathia (Patient 2), microglossia, clubfeet, hypoventilation, and hypertonia. In both, neuropathology showed lesions restricted to the caudal pons: tegmental neuronal loss, gliosis and calcification, hypoplasia of inferior olivary nuclei, and hyperplasia of corpus pontobulbare, and arcuate nucleus. The authors favored a vascular pathogenesis, with an event occurring between 8 and 22 weeks (timing for migration of the neurons from the rhombic lip to the inferior olivary complex). Another case with tegmental necrosis, medullary and olivary hypoplasia, and apnea [Kinney et al., 1989] showed micrognathia, tongue atrophy, and no swallowing; this child had no oculomotor involvement but could belong to the same spectrum of anomalies as the entity we delineate here. Those case reports are summarized in Table IB. The two akinetic fetuses with MS, PRC associated with splenogonadal fusion in one, and peromelia in the other [Lammens et al., 1998] were excluded, although their phenotype could be pathogenically related.

Nosological Problem: CFZS or Brainstem Disruption Sequence?

The question of the delineation of CFZS as an entity distinct from MS was raised after neuropathological investigation of our two initial patients. The two deceased infants show the

CNS anomalies expected with the hypothesis of acquired disruption of the brainstem. In Patient 5, brainstem calcifications are an indirect marker for a similar vascular insult. The clinical history of Patient 3 makes him highly susceptible to suffer from the consequences of an intrauterine trauma. All the cases had major feeding difficulties and hypotonia, with some of them experiencing ventilation compromise. Our working hypothesis was that the CFZ phenotype was in fact only a variant of "common" MS, and could be described as Möbius syndrome with Robin complex and brainstem anomalies. PRC may be explained by lesions of the lower cranial nerves and thus not surprisingly associated with MS. The literature on MS repeatedly reports micrognathia, sometimes marked [Meyerson and Foushee, 1978]. Bifid uvula was present in 2/61 patients [Henderson, 1939] and cleft palate has been reported in some instances [Meyerson and Foushee, 1978, Patients E and G]. A combination of micrognathia and cleft palate associated with limb anomalies was present in three patients reviewed by [Herrmann et al., 1976]. Thus, PRC could be a marker for the severity of the disruptive process in the brainstem, rather than a specific clinical sign. This could suggest to the date of the initial insult before the 8th week of development.

The term "myopathy" has been used to describe CFZS, although no clear muscular defect was ever shown aside from generalized hypotonia. Muscle biopsy showed non-specific, mild anomalies in Carey's Patient 1 and atypical myopathic changes without specific architectural change, not explaining the important muscular weakness in our Case 5. Schimke's patient showed type 2 fiber predominance. In our Patient 1, muscular histology was considered normal.

Several acral anomalies are present in this series and in previous CFZS articles. Clubfeet, present in most of them, is probably a non-specific anomaly associated with reduced fetal movements. Indeed, 30% of patients with classic MS have clubfeet [Henderson, 1939] (inversely, 2/75 children with fetal akinesia sequence reported by Hageman et al. [1987] had MS. Patient 5 has Poland anomaly and thus overlaps with Poland–Möbius syndrome.

The facial appearance of several of these children is characterized by downslanting palpebral fissures, ptosis of the eyelids, epicanthal folds, upturned nose, low-set, posteriorly rotated ears, and lack of expression. Although this could represent face true facial malformation, it is more likely the result of facial muscle weakness and immobility (amimic face) rather than being a specific trait. Only the patients of Carey et al. have a specific facial appearance that became more obvious with time, as illustrated in the companion report. Interestingly, Carey's Patient 2, who had the full blown syndrome but was younger, did not have "the face" at a younger age, whereas it was present in adulthood. In our opinion, this facial appearance was not present in subsequent reports.

Repeated familial occurrence of CFZS contrasts with the sporadic nature of common MS. Obviously, this assertion has to be moderated. First, MS is a classical entity, defined 125 years ago, and contemporary cases likely to be published now are expected to be unusual in some way. Thus, there could be a bias to publish severe and/or familial cases. Another well known bias in clinical dysmorphology is the "founder effect" of a article: if a characteristic phenotype is delineated, we may expect "secondary" reports of this phenotype based on the original description. Thus, we cannot really evaluate how many children with sporadic "Robin–Möbius" phenotype are still hidden under the label of MS. Our experience is that this phenotype could be commoner than reported. If we consider MS to be a complex disorder with a small recurrence risk, the theory of multifactorial inheritance suggests that the recurrence risk is always small, but that the risk is higher when the proband has a more severe expression of the disorder. The report of Ryan et al. [1999] may just reflect this concept, rather than pointing to an autosomal recessive mode of inheritance of the condition.

CONCLUSION

We propose the name MS with PRC and brainstem anomalies (or "Robin–Möbius phenotype") for the combination of anomalies presented by our patients and by most patients reported as having CFZS. This clinically defined entity is, for us, a simple variant of MS with early and wide brainstem involvement explaining the associated anomalies: Robin complex, hypotonia without specific muscle disorder, and variable (but inconstant) acral anomalies. The most severe cases may lose their ability to control spontaneous breathing (Patients 1, 2, 5; and patients of Cortez and Kinney [1996]), whereas the least affected patients show regressive hypotonia and preserved intelligence. Neuropathology and neuroimaging of several cases point to a vascular disruption, either purely exogenous, or secondary to a genetic predisposition or a developmental anomaly of brainstem architecture. CFZS itself remains a private, possibly recessive syndrome, known only from the original family, distinct from MS with PRC and distinguished by its facial appearance, microcephaly, and presence of scoliosis.

When associated with PRC, MS appears to bear a higher risk of mental handicap and a higher recurrence risk than "common" MS, and these two observations justify distinguishing it as a distinctive variant. Despite the existence of familial reports, recurrence risk is probably much lower than 25%, although exact figures cannot be extracted from the available literature. We would encourage clinical geneticists to question the notation that: Möbius + Robin + hypotonia = a recessive disorder.

ACKNOWLEDGMENTS

We thank Prof. J.J. De Deyn (Neurology, Middelheim Hospital) and Dr. Ceuterick (Neuropathology, Antwerpen University) for their role in investigating Patient 1.

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