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New Syndrome?

Postnatal Growth Failure, Microcephaly, Mental Retardation, Cataracts, Large Joint Contractures, Osteoporosis, Cortical Dysplasia, and Cerebellar Atrophy

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We describe two sibs with postnatal-onset growth deficiency, microcephaly, cataract, prominent supraorbital ridge, large joint contractures, severe osteoporosis, cortical dysplasia, cerebellar atrophy, and mental retardation. The combination appears to constitute a previously undescribed syndrome inherited in an autosomal recessive pattern.

KEY WORDS: growth failure; mental retardation; microcephaly; cataract; arthrogryposis; osteoporosis; cortical dysplasia; cerebellar atrophy

INTRODUCTION

There have been many MCA/MR syndromes with a combination of short stature, microcephaly, cataracts and mental retardation. These microcephalic dwarfism with cataract include CAMAK or CAMFAK syndrome (MIM 212540) (cataract, microcephaly, failure to thrive, arthrogryposis, and kyphoscoliosis) [Talwar and Smith, 1989]; cerebro-oculo-facio-skeletal (COFS) syndrome (MIM 214150) (growth failure, microcephaly, severe mental retardation, microphthalmia, cataracts, prominent nose, large ears, progressive joint contractures, camptodactyly, osteoporosis, and intracranial calcifications) [Pena and Shokeir, 1974]; microcephalic primordial dwarfism, Toriello type (MIM 251190) (growth deficiency, microcephaly, cataracts, mental retardation, enamel hypoplasia, immune deficiency, and delay of ossification) [Toriello et al., 1986]; Warburg micro syndrome (MIM 600118) (microcephaly, microcornea, cataracts, mental retardation, optic nerve atrophy, prominent nose, large ears, hypogenitalism, and hypotonia) [Warburg et al., 1993]; Martsolf syndrome (MIM 212720) (short stature, severe mental retardation, cataracts, hypogonadism, hypotonia, lax joints, and osteoporosis) [Harbord et al., 1989]; and ataxia-microcephaly-cataract (AMC) syndrome (MIM 208870) (ataxia, microcephaly, hypotonia, mental retardation, and cataracts) [Ziv et al., 1992].

We report on two children (a girl and a boy) in a sibship of four with another form of microcephalic dwarfism with cataract that is distinct from previously described syndromes.

CLINICAL REPORTS

Patient 1

The proband, a Thai girl, was the third child of a 31-year-old father and a 30-year-old mother. The parents were healthy and unrelated. Their first two children were normal and no other family members had short stature, mental retardation, or congenital anomalies. The proband was born at term after a normal pregnancy with a birth weight of 3,050 g (50th centile) and birth length of 51 cm (50th centile). Her OFC at birth was noted to be normal but the actual size was not available. No abnormalities were noted at birth. Since infancy, she gained weight poorly. Her weight at ages 2 months, 6 months, and 1.5 years were 3.9 kg (−2 SD), 4.8 kg (−3 SD), and 6.0 kg (−4 SD), respectively. Her

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length at the same ages were 55 cm (mean), 60 cm (−2 SD), and 66 cm (−5 SD), respectively. Her development had been delayed. She first rolled over at 4 1/12 years. At 9 years of age, she crawled, had to be held to stand, and walked without support for only 2–3 steps. She could build towers of seven blocks and follow simple commands. She had a vocabulary of approximately 10 words. Her deciduous and permanent teeth were normally erupted and developed. Her large joints were noted to have limitation of movement beginning at around 2 years of age. Besides bilateral lenticular cataracts, which were detected and extracted at 8 years, her general health had been unremarkable. She had never suffered from seizures or severe infections.

On physical examination at age 9 years, her weight was 13 kg (−4 SD), height 99.5 cm (−6 SD), and OFC 44.5 cm (−5 SD). She had prominent supraorbital ridge, prominent nasal root, and wide mouth (Fig. 1A). Her eyes were not deep-set, and teeth were normal. There were no abnormalities of the chest wall, genitalia, hands, or feet. Dermatoglyphics of her left and right hands from the first digit to the fifth digit were AUUUW and UAAUA, respectively. Her back was without scoliosis. Limitation of motion of the shoulders, elbows, hips and knees were noted: her elbows and knees could be extended to a maximum of approximately 170 degrees (Fig. 2A), but the wrist, ankle, and phalangeal joints were normal. There was no spasticity, and her motor power was normal with DTR of 1+. Plantar reflexes were down-going.

Besides bilateral cataracts, ophthalmologic examination showed normal anterior segment, fundus, retina, and the maculae. Hearing tests by pure tone audiogram (evaluated by head turning to a sound source) and brain stem auditory evoked potentials were normal. Devlopmental assessment by the Gesell Developmental Schedule showed a mental age of 20 months at a chronological age of 9 3/12 years. Other than severe osteoporosis, a skeletal survey was unremarkable. There was no kyphoscoliosis and the acetabular roofs were well formed without hip dislocation. Brain MRI showed microcephaly predominantly affecting the frontal lobes and marked cerebellar atrophy with possible atrophy of the pons, medulla and upper cervical cord (Fig. 3A). There were also multiple focal areas of abnormally thickened cortex of bilateral frontal and right parietal lobes and multiple small scattered hyperintense foci on T2WI and FLAIR images in subcortical white matter close to the vertex, suggestive of cortical dysplasia and the presence of gliosis in the underlying subcortical white matter. Cavum septum pellucidum was present. Myelination of white matter and corpus callosum appeared normal. She had a normal 46,XX karyotype. Serum levels of IgG (1,847 mg/dl; normal, 600–1,600 mg/dl) and IgM (285.7 mg/dl; normal, 38.4–148 mg/dl) were slightly increased, whereas that of IgA was normal. Serum levels of T4, free T4, TSH, FSH, LH, estradiol are all normal.

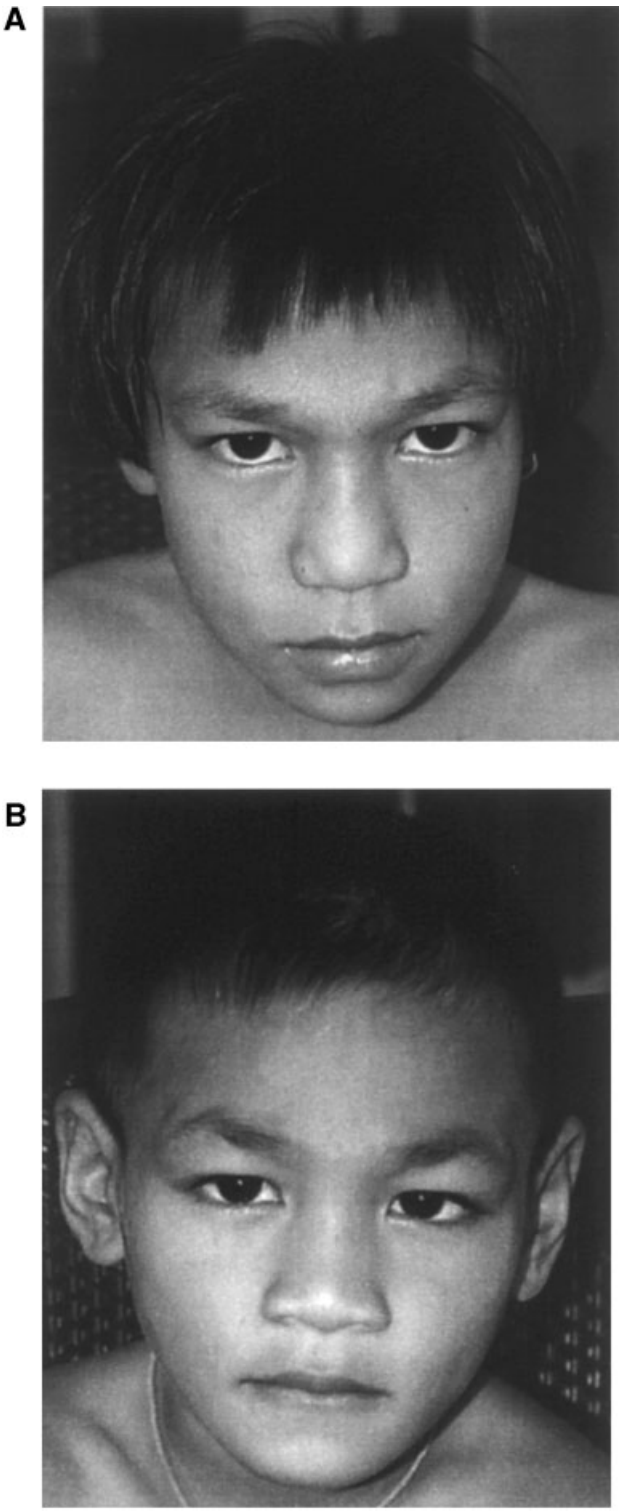

Fig. 1. The elder sister (**A**) and the younger brother (**B**). Note the triangular facies with prominent supraorbital ridge and prominent ears.

Patient 2

The younger brother of Patient 1 (P1) was delivered at term after a normal gestation. His birth weight was 2,900 g (−0.5 SD) with an unremarkable physical examination. His weight at ages 2 months, 6 months, and 1.5 years were 4.3 kg (−1 SD), 5.6 kg (−3 SD), and 6.5 kg (−4 SD), respectively. His length and OFC in

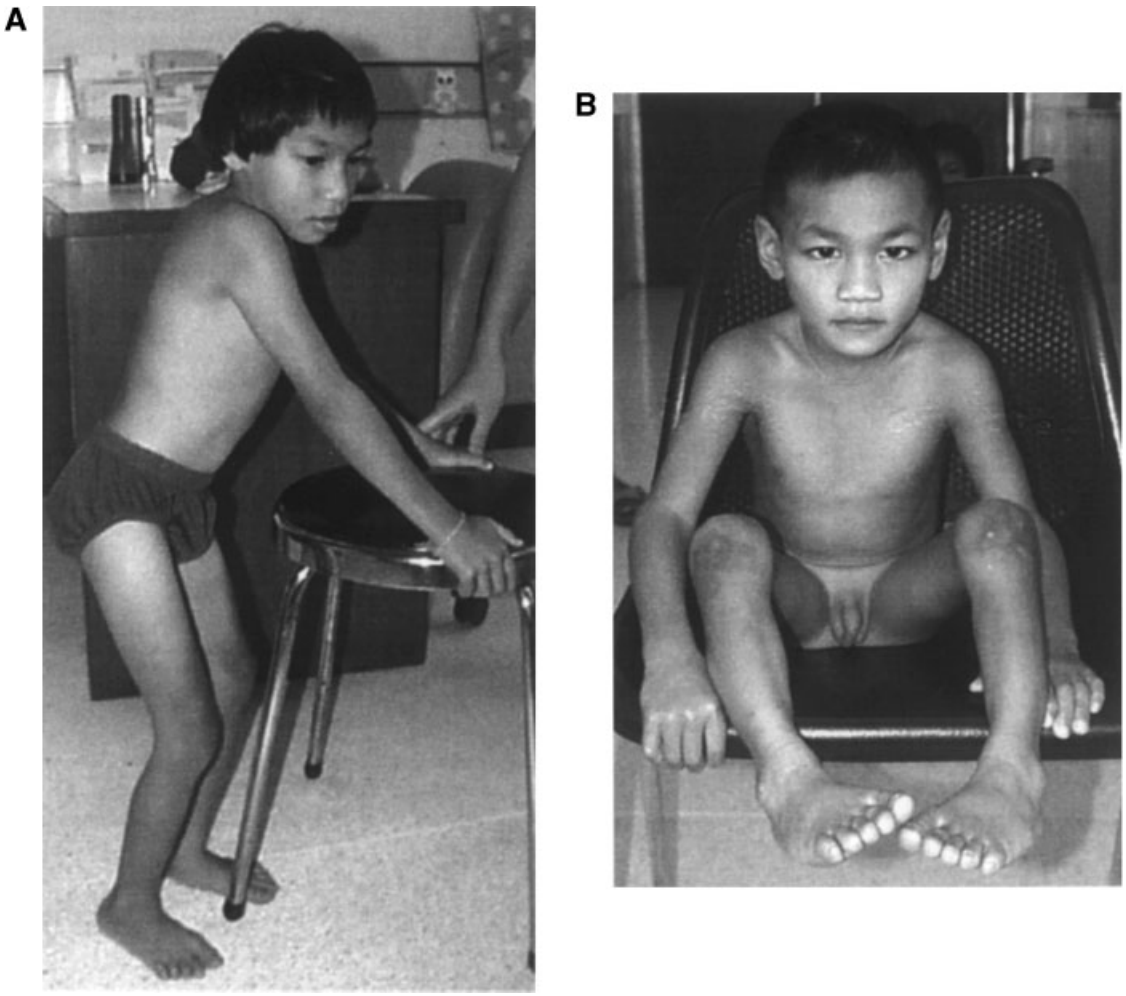

Fig. 2. Joint contractures, especially of the hip, knees and elbows in the sister (**A**), and normal male genitalia in the brother (**B**).

infancy were unavailable. His development had been delayed. At 6 years, he began to walk with some support, could follow simple commands but had no speech. Bilateral lenticular cataracts were diagnosed at age 3 years and removed. He developed tonic-clonic seizures at age 5 years. The frequency of the seizures was approximately twice a year. Except for an episode of acute diarrhea in infancy, he had never had a severe infection.

On physical examination at age 6 years, his weight was 10.5 kg (−4 SD), height 90.5 cm (−6 SD), and OFC 44 cm (−5 SD). He had a similar facial appearance to that of P1 but distinct from those of two other unaffected sibs. He had triangular facies, prominent supraorbital ridge, prominent ears, and prognathism (Fig. 1B). His genitalia was of a normal prepubertal male appearance (Fig. 2B). Dermatoglyphics of his left and right hands from digits 1–5 were WWUWW and WUUWW, respectively. The motion of his large joints was more severely limited than that of P1. His elbows and knees were extended to a maximum of approximately 160 and 150 degrees, respectively. Neurological examination showed normal muscle power, no spasticity, and DTR of 1+. Unlike his affected sister, he had positive bilateral ankle clonus and up going plantar reflexes. All other findings were similar to those of P1.

Developmental assessment by the Gesell Developmental Schedule showed a mental age of 13 months at a chronological age of 6 5/12 years. A skeletal survey showed severe osteoporosis without scoliosis. Results of an ophthalmologic examination and hearing tests were normal. Electroencephalography showed evidence of mild diffuse encephalopathy with no definite epileptiform activity. Brain MRI was similar to that of P1 with the addition of a 2×3 cm arachnoid cyst in the right temporal area (Fig. 3B–D). Proton MR spectroscopy of the occipital white matter showed normal spectrum.

DISCUSSION

The two sibs we described had a similar combination of malformations, i.e., postnatal growth failure, microcephaly with cortical dysplasia and cerebellar atrophy, severe mental retardation, prominent supraorbital ridge, cataracts, limitation of movement of the large

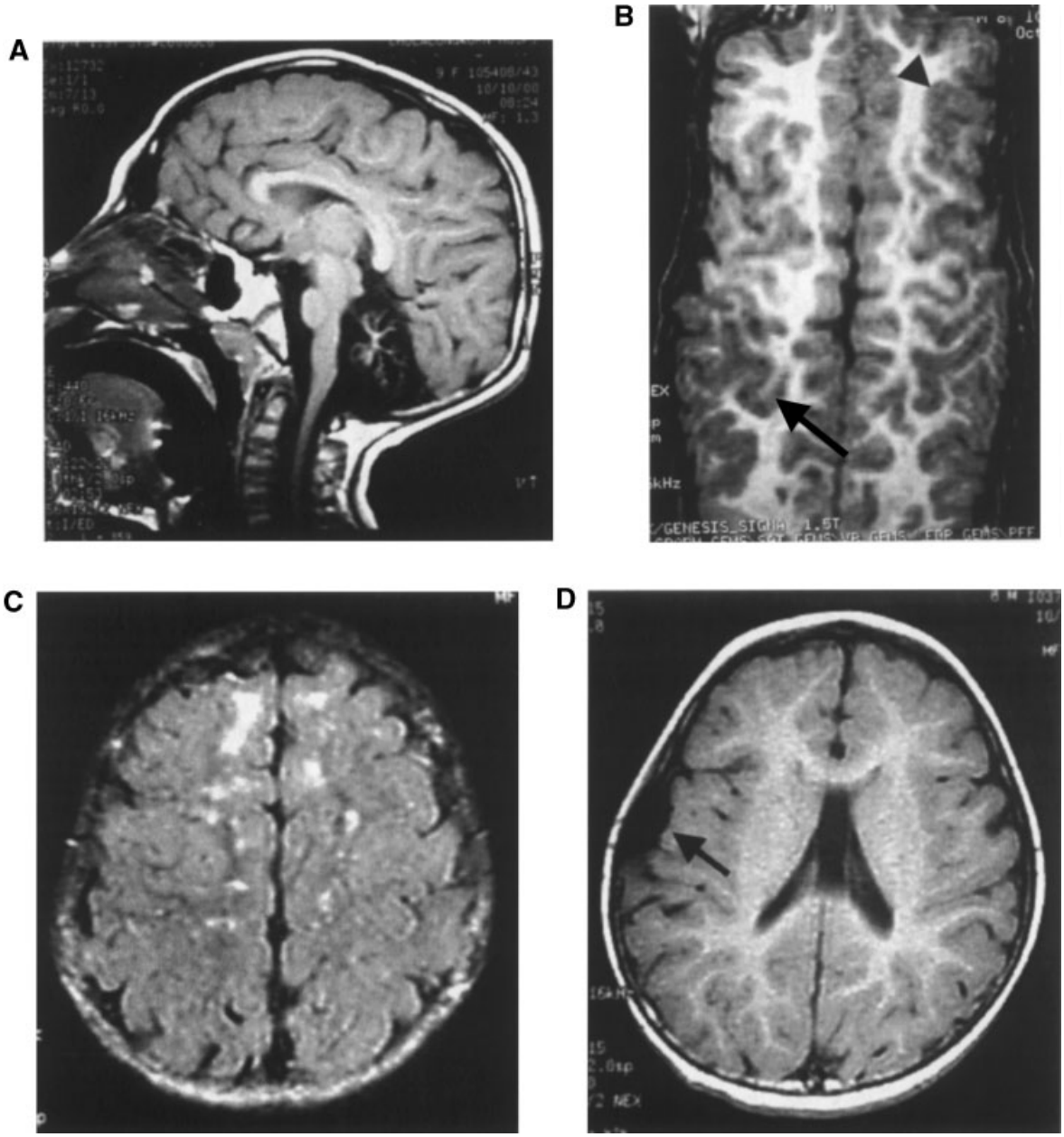

Fig. 3. Brain MRI of the elder sister (**A**) and the younger brother (**B–D**). A: Sagittal T1WI shows microcephaly and marked cerebellar atrophy with very prominent fissures between shrunken cerebellar folia and widened posterior fossa subarachnoid space. B: Reformation from volume gradient echo acquisition shows focal areas of thickened abnormal cortex with irregular "bumpy" gyral pattern in the left frontal lobe (arrow head) and right parietal lobe (arrow), suggesting cortical dysplasia. C: Axial FLAIR image shows small scattered hyperintense foci in the subcortical white matter. D: Axial T1WI shows an arachnoid cyst (arrow) in the right temporal area. Cavum septum pellucidum is also demonstrated.

joints, and severe osteoporosis. One of the children had seizures and an arachnoid cyst. We are not aware of such a combination of abnormalities seen in the sibs among known syndromes of microcephalic dwarfism with cataract and mental retardation. The fact that the two affected children were sibs without any affected family members suggests an autosomal recessive inheritance.

Syndromes from which differential diagnosis has to be made include CAMAK (CAMFAK) syndrome; COFS syndrome; microcephalic primordial dwarfism, Toriello type; Warburg micro syndrome; Martsolf syndrome; and ataxia-microcephaly-cataract (AMC) syndrome (Table I). CAMAK and CAMFAK syndromes are supposedly the same [Lowry et al., 1971; Sugarman, 1973; Scott-Emuakpor et al., 1977; Talwar and Smith, 1989]. Major features of these syndromes that are similar to those in our patients include severe mental retardation, microcephaly, cataracts, failure to thrive, and extreme osteoporosis. Patients with CAMAK syndrome are small at birth, however, and their growth is extremely slow, with one reported patient weighing

TABLE I. Clinical Manifestations of Syndromes with Microcephaly, Mental Retardation, Growth Failure, and Childhood Cataract*

Clinical findings	This report	CAMAK syndrome	COFS syndrome	Toriello syndrome	Micro syndrome	Martsolf syndrome	AMC syndrome
Growth failure	PO	PR	PR	PR	PO	PO	N
Large joint contracture	Y	Y	Y	N	Y	N	N
Osteoporosis	Y	Y	Y	N	N	Y	N
Prominent supraorbital ridge	Y	N	N	N	N	N	N
Cortical dysplasia	Y	N	N	NA	N	N	NA
Cerebellar atrophy	Y	Y	Y	NA	N	Y	NA
Spasticity	N	Y	N	N	Y	N	N
Demyelination	N	Y	Y	NA	NA	Y	NA
Kyphoscoliosis	N	Y	Y	N	Y	N	N
Hip dysplasia	N	Y	Y	N	Y	N	N
Hypogonadism	N	Y	N	NA	Y	Y	N
Abn NCV	N	Y	NA	NA	NA	N	NA
Inheritance pattern	AR	AR	AR	AR	AR	AR	AR

*AR, autosomal recessive; PO, postnatal; PR, prenatal; Y, present; N, not present; NA, information not available.

only 5,400 g at age 14 years. The sibs we reported weighed 13 and 10.5 kg at ages 9 and 6 years, respectively. In addition, patients with CAMAK syndrome typically do not develop to the stage of crawling, whereas our patients were able to walk with some support and follow commands; one of two had a limited vocabulary. In contrast to our patients, patients with CAMAK syndrome have severe spasticity, kyphoscoliosis, severe limitations of joint movement, and hip dysplasia. The facial features of the CAMAK syndrome that have been described as bird-like are markedly different from our patients. Neurologically, patients with CAMAK syndrome show a major defect in myelination both in the central and peripheral nervous systems [Talwar and Smith, 1989], whereas our patients had cortical dysplasia and cerebellar atrophy as the prominent feature with no evidence of demyelination. An arachnoid cyst present in one of our patients has not been reported in CAMAK syndrome.

Similar to our patients, patients with COFS syndrome have growth failure, microcephaly, severe mental retardation, cataracts, prominent nose, large ears, progressive joint contractures, and osteoporosis [Pena and Shokeir, 1974]. In contrast to our patients, however, patients with COFS syndrome have microphthalmia, deep set eyes, blepharophimosis, overhanging lips, scoliosis, hip dysplasia, camptodactyly, prominent heels, posteriorly placed second metatarsal, hypotonia, difficulty feedings, recurrent pulmonary infections, and delayed teeth eruption. In addition, patients with COFS syndrome typically have bilateral intracranial calcifications in the region of the basal ganglia, ventriculomegaly, demyelination, agenesis of corpus callosum, cortical atrophy, cerebellar atrophy, and optic nerve atrophy [Linna et al., 1982; Del Bigio et al., 1997; Meira et al., 2000]. Of these symptoms, our patients had only cerebellar atrophy. Prominent supraorbital ridges, prognathism, cortical dysplasia, and cavum septum pellucidum were present in our patients but not in patients with COFS syndrome.

As with our patients, patients with microcephalic primordial dwarfism, Toriello type [Toriello et al., 1986] have growth deficiency, microcephaly, cataracts, and mental retardation. The onset of growth deficiency is prenatal, however, whereas our patients were normal at birth. In addition, patients with microcephalic primordial dwarfism syndrome have clinodactyly, enamel hypoplasia, immune deficiency and generalized delay of ossification, which were not present in our patients. The limitations of joint movement and severe osteoporosis present in our patients has not been reported in patients with the microcephalic primordial dwarfism syndrome. Importantly, the facial features of patients with the microcephalic primordial dwarfism syndrome are receding forehead, downslanting palpebral fissures, and micrognathia that are markedly different from those of this study.

In Warburg micro syndrome [Warburg et al., 1993; Megarbane et al., 1999], signs include postnatal growth failure, microcephaly, severe mental retardation, childhood cataracts, and mild contracture as is similar to our patients. In contrast to our patients, however, patients with Warburg micro syndrome have microcornea, borderline micro-ophthalmus, small pupils with posterior synechiae, optic nerve atrophy, hypogenitalism, hypertrichosis, kyphosis, and spastic palsy with hip dislocation as prominent features. In addition, our patients had severe osteoporosis, which is not present in patients with Warburg micro syndrome.

Patients with Martsolf syndrome [Harbord et al., 1989] may have microcephaly, mental retardation, cataracts, postnatal growth failure, osteoporosis and seizures. In contrast to our patients, however, patients with Martsolf syndrome have hypogonadism, cardiomyopathy, marked hypotonia with exaggerated tendon reflexes, lax finger joints, lumbar lordosis and generalized cerebral atrophy and delayed myelination. Contractures were noted in our patients but not with Martsolf syndrome.

Patients with AMC syndrome [Ziv et al., 1992] have mental retardation, microcephaly, and cataracts. In contrast to our patients, however, patients with AMC syndrome have ataxia, hypotonia, and nystagmus as major features but do not show growth retardation, joint contractures, or osteoporosis. Psychomotor retardation is present in only one of three reported AMC patients.

In 1987, Bouwes Bavinck et al. [1987] reported a mother and her son with microcephaly, eye anomalies, short stature, and mental deficiency. Unlike our patients, the son had ptosis, blepharophimosis, low-set ears, hydroureters, hydronephrosis, cryptorchidism, and hyperextensibility of fingers and toes. The mother had several eye abnormalities including iris and choroidal colobomata, microphthalmia, microcornea, and no light perception-vision. In addition, they were only mildly mentally delayed. Patients with carbohydrate deficient glycoprotein syndrome have cerebellar atrophy [Grunewald and Matthijs, 2000]. The possibility of these two children having the classic form of the syndrome, however, has been ruled out by the normal transferrin analysis.

CONCLUSION

In summary, we report on two sibs with a previously undescribed autosomal recessive syndrome comprising postnatal-onset growth deficiency, microcephaly, mental retardation, cataract, prominent supraorbital ridge, large joint contractures, severe osteoporosis, cortical dysplasia and cerebellar atrophy.

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