pretable and identical in the twins. The affirmative probability for monozygosity in the twins was estimated at more than 99.9%.

Patient 2

A girl was born at 34 weeks' gestation with a birth weight of 2,675 g to a 34-year-old G3P2 mother and a 29-year-old father. She was hospitalized at ages 6 days and 5 months due to gastroenteritis and again at age 9 months for pneumonia. Lower central incisors erupted at 4 months. She held her head at age 4 months, rolled over at 7 months, sat at 11 months, walked at 16 months, and spoke at 18 months.

At age 10 months, she measured 65 cm (−2.5 SD), weighed 5.2 kg (−2.5 SD), and had an OFC of 40.5 cm (−2.5 SD). She had sparse hair, long eyelashes, eversion of the lateral lower eyelids, hypertelorism, prominent ears, a depressed nasal tip, and micrognathia (Fig. 2A). There were two symmetrical nodules with a pit in the center of each nodule on her lower lips with discharge (Fig. 3A). Her narrow, high-arched palate with incomplete cleft was surgically corrected at 15 months. She had a right single transverse crease, brachydactyly, single creases and clinodactyly of bilateral fifth fingers, and prominent finger pads. A pilonidal sinus was present. Her developmental quotient (DQ) was 78. She had epiphora due to obstruction of bilateral lacrimal ducts. Bone age was normal. The serum TSH level was increased (8.94 μU/mL; normal, 0.3–4.1 μU/mL) at age 10 months but normalized at 18 months, and T4 and free thyroxine (FT4) were normal at both ages. Immunoglobulin A (IgA) was decreased (< 22.5 mg/dL; normal, 30–180 mg/dL), while other immunoglobulins were normal. Her and her parents' chromosomes were normal.

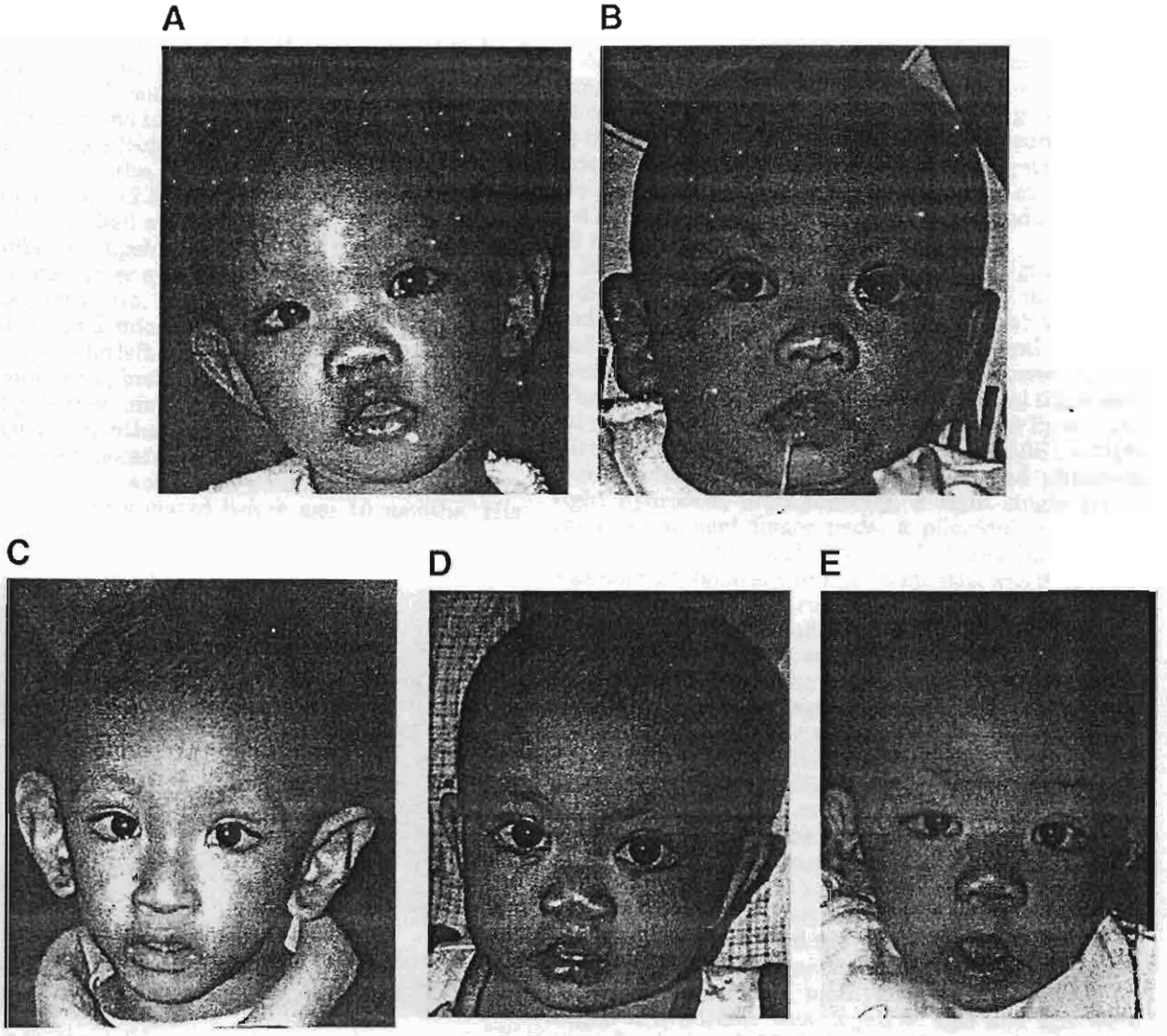

Fig. 2. Facial appearance of patients 2 (A), 3 (B), 4 (C), 5 (D), and 6 (E).

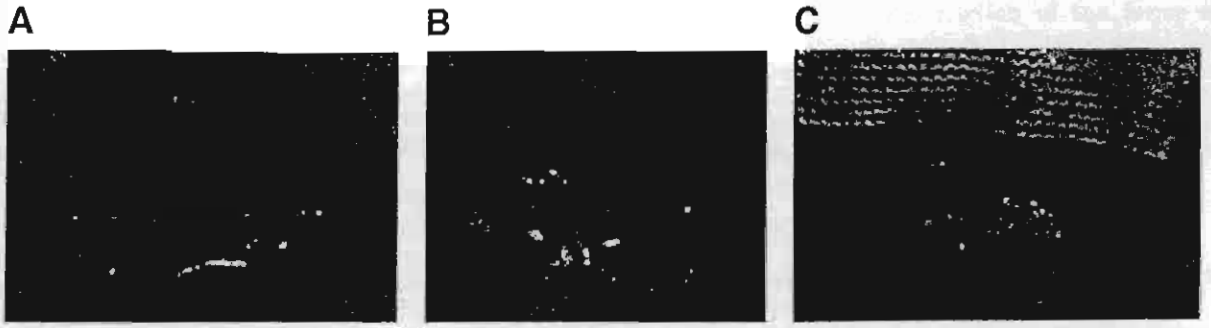

Fig. 3. Symmetrical lower lip nodules with central pits in patients 2 (A) and 4 (B), and lower lip pits without nodules in patient 5 (C).

Patient 3

A boy was born after uncomplicated pregnancy at term with a birth weight of 2,900 g to a 24-year-old G1P0 mother and a 25-year-old father. Lower central incisors erupted at age 2 weeks. At 2 months, he was hospitalized for pneumonia. He held his head at 3 months and rolled over at 4 months. His mother had long palpebral fissures and bowed eyebrows but had normal growth and intelligence (Fig. 4). No other family members were affected.

At age 4 months, he measured 59 cm (−1.5 SD), weighed 4.3 kg (−2.5 SD), and had an OFC of 37.5 cm (−2.5 SD). He had sparse lateral one-third eyebrows, long eyelashes, upslanted palpebral fissures, eversion of the lateral lower eyelids (Fig. 2B), prominent ears, a depressed nasal tip, two lower central incisors, a cleft soft palate, and micrognathia. A grade II/VI systolic murmur over the left chest wall was present. He had an umbilical hernia, brachydactyly, and prominent finger pads. A pilonidal sinus was present. His DQ was 97. Bone age at 4 months was appropriate for his chronological age. An echocardiography revealed a mild form of coarctation of the aorta and patent ductus arteriosus that spontaneously closed before age 10 months. His chromosomes and immunoglobulin levels were normal. FT4 at age 4 months was normal, but TSH was slightly high (4.49 μU/mL; normal, 0.3–4.1 μU/mL).

Fig. 4. Patient 3 and his parents. Note the facial similarity between the patient and his mother.

Patient 4

A boy was born at term after an uncomplicated pregnancy to a 34-year-old G2P1 Thai mother and a 35-year-old father. Birth weight was 3,500 g. After birth to the age 2 8/12 years, he had frequent pneumonia and urinary tract infections requiring 13 hospitalizations. He held his head at 3 months, rolled over at 5 months, sat at 14 months, spoke at 14 months, pulled to stand at 18 months, and walked at 26 months.

His length was 85 cm (−1.5 SD), weight 9,700 g (−2 SD) and OFC 45 cm (−3 SD) at age 32 months. He had sparse hair and lateral one-third eyebrows, long and thick eyelashes, upslanted palpebral fissures, eversion of the lateral portion of the lower eyelids (Fig. 2C), prominent ears, a depressed nasal tip, bilateral preauricular pits, two symmetrical lower lip nodules with a pit in the center of each nodule (Fig. 3B), a high-arched palate, and micrognathia. He had phimosis, right hydrocele, brachydactyly, a right single transverse, prominent finger pads, a pilonidal sinus, and mild generalized hypotonia. His DQ was 66. Hearing was normal. Bone age at age 15 months was 9 months. Renal ultrasound, intravenous pyelography, voiding cystourethrography, and cortical scintigraphy (Tc-99m 2,3-dimercaptosuccinic acid [DMSA]) revealed a double collecting system of the left kidney with moderately dilated pelvicalyceal system and vesicouretororenal reflux of the left lower moiety. The double collecting system and ureteropelvic junction obstruction of the left kidney was surgically corrected at age 2 5/12 years. Echocardiography and cardiac catheterization revealed a moderate-size perimembranous ventricular septal defect (VSD) with pulmonary hypertension. The VSD was surgically closed at age 13 months. Due to recurrent pneumonia, computerized tomography of the chest was performed and revealed normal lung parenchyma and airways. His G-6-PD was deficient. Chromosomes were normal: 46,XY. *FMR1* methylation PCR analysis for fragile X syndrome was negative. IgG and IgA were normal, whereas IgM (169.3 mg/dL; normal, 36.8–144 mg/dL) was slightly increased.

Patient 5

A girl was born at term to a 29-year-old G2P1 mother and a 31-year-old father. The pregnancy was uncomplicated. Birth weight was 2,400 g. She held her head at age 3 months, rolled over at 6 months, but was unable to grasp things or sit at 7 months.

At age 7 months, she measured 63 cm (−1.5 SD), weighed 6.0 kg (−2 SD), and had an OFC of 42.5 cm (mean). She had arched and sparse lateral one-third eyebrows, long and thick eyelashes, eversion of the lateral portion of the lower eyelids (Fig. 2D), prominent ears, a depressed nasal tip, bilateral complete cleft lip (surgically corrected at age 7 months) and palate, and micrognathia. There were lower lip pits without nodules (Fig. 3C). She had brachydactyly, clinodactyly, and hypoplastic middle phalanges of the fifth fingers, prominent finger pads, a pilonidal sinus, and a hairy hyperpigmented macule. A café-au-lait spot (0.5 cm) was present at the left abdominal wall. Her DQ was 71. Chromosomes were normal.

Patient 6

A boy was born at term with a birth weight of 3,030 g to a 29-year-old G2P1 mother and a 46-year-old father. The pregnancy was complicated by maternal gestational diabetes mellitus, which could be controlled by diet alone. He had neonatal hypoglycemia requiring intravenous glucose for a few days. Lower central incisors were erupted at age 4 months. He held his head at age 4 months, but was still unable to roll over at 5 months.

At age 5 months, he measured 65 cm (mean), weighed 7.4 kg (+0.5 SD), and had an OFC of 40 cm (−1 SD). He had aplasia cutis (0.8 cm) on the occipital area, sparse lateral one-third eyebrows, long and thick eyelashes, eversion of the lateral portion of the lower eyelids (Fig. 2E), prominent ears, a depressed nasal tip, bilateral preauricular pits, two lower central incisors, a narrow and high-arched palate, and a cleft uvula. He had brachydactyly, clinodactyly and single creases of the fifth fingers, prominent finger pads, a pilonidal sinus, and a hairy hyperpigmented macule.

DISCUSSION

We described six Thai children with KS and some interesting clinical and genetic characteristics. All six children showed the five cardinal manifestations of the syndrome (Table I), with the exceptions of patient 6, with normal weight and length at age 5 months, and patient 3, with normal development at age 7 months. They included typical peculiar facies, dermatoglyphic abnormalities with persisting fingerpads, skeletal anomalies including brachydactyly, mild to moderate mental retardation, and postnatal growth deficiency. The growth of patient 6 may yet prove deficient in the second half of infancy, like other patients with typical KS [Niikawa et al., 1988]. Other associated abnormalities in the six children included cleft lip/cleft palate (patients 2, 3, and 5) [Burke and Jones, 1995], congenital heart defects (patients 3 and 4), hearing loss (patient 1) [Igawa et al., 2000], delayed bone age (patient 1) [Niikawa et al., 1988], kidney anomalies (patient 4), and abnormal immunoglobulin levels (patient 2) [Hostoffer et al., 1996].

Three (patients 2, 4, and 5) of six patients we described had lower lip pits with occasional clear discharge. Patients 2 and 4 also had lower lip nodules. *The nodules of both patients were symmetrical. Of 246 patients reported with KS, only four had lower lip pits* [Franceschini et al., 1993; Kokitsu-Nakata et al., 1999; Makita et al., 1999]. The lower lip pits are also present

TABLE I. Clinical and Laboratory Findings in Six Children*

	Patient number							
Clinical findings	1	2	3	4	5	6	Total	Niikawa et al. [1988]
Sex	M	F	M	M	F	M		M:F = 1:1
Age (years)	9	1	7/12	2	9/12	5/12		
Growth failure	+	+	+	+	+	−	5/6	73%
Developmental delay	+	+	−	+	+	+	5/6	92%
Typical face	+	+	+	+	+	+	6/6	100%
Lower lip pits and nodules	−	+	−	+	+	−	3/6	
Cleft palate	−	+	+	−	+	−	3/6	41%
Early eruption of lower central incisors	−	+	+	−	−	+	3/6	
Congenital heart disease	−	−	+	+	−	−	2/6	32%
Fingertip pads	+	+	+	+	+	+	6/6	78%
Skeletal abnormalities	+	+	+	+	+	+	6/6	92%
Pilonidal sinus	−	+	+	+	+	+	5/6	
Hearing loss	+	−	−	−	NA	NA	1/4	24%
Urinary tract anomalies	−	−	NA	+	NA	−	1/4	12%
Abnormal Ig levels	NA	+	−	−	NA	NA	1/3	
Normal chromosomes	−	−	−	−	−	NA	5/5	
Hyperthyrotropinemia in infancy	NA	+	+	NA	NA	NA	2/2	
Others						Cleft lip	Aplasia cutis	

*NA, data not available.

n van der Woude syndrome (VWS) (MIM 119300). The ossibility that KS could be caused by a microdeletion, ncluding the VWS type 1 critical region at 1q32-q41, as been excluded [Makita et al., 1999].

Pilonidal dimples have been described with KS Franceschini et al., 1993; Makita et al., 1999], but not n the 62 patients reported by Niikawa et al. [1988]. ecause pilonidal dimples were present in five (patients -6) of six patients, with two of them (patients 5 and 6) ith hairy hyperpigmented macules on the sacral area, e propose that this finding is a part of clinical mani-stations of KS, and probably related to sagittal cleft-g of vertebrae [Niikawa et al., 1988].

The lower central incisors erupted before age months in three of six patients (2 weeks, 4 months, nd 4 months for patients 3, 2, and 6, respectively). lthough dental anomalies are frequent and variable in atients with the syndrome [Matsune et al., 2001], to ur knowledge, early eruption of the two lower central cisors has not been described.

Several hormonal abnormalities have been described KS, including growth hormone (GH) deficiency, evated follicle-stimulating hormone (FSH) and pro-ctin [Niikawa et al., 1988; Franceschini et al., 1993], ntral diabetes insipidus [Tawa et al., 1994], and ngenital hypothyroidism [Kawame et al., 1999]. We served hyperthyrotropinemia in two of the three tients examined for this complication (patients 2 and . The increased TSH was normalized after infancy in tient 2.

The mother of patient 3 had a facial appearance miniscent of KS (Fig. 4). Kuroki et al. [1981] sugges-d that the syndrome is inherited as an autosomal minant trait in which affected individuals represent w mutations. Dominant inheritance of the syndrome as supported by more than 10 families in which ere was a facial resemblance between a patient and e parent [Niikawa et al., 1988; Halal et al., 1989; ina et al., 1995; Kobayashi and Sakuragawa, 1996; engo et al., 1996; Tsukahara et al., 1997; Wilson, 98; Courtens et al., 2000].

Monozygotic twin boys concordant for KS have been orted, and have reinforced the belief that KS has a netic basis [Lynch et al., 1995]. On the other hand, r patient 1 had an unaffected monozygotic twin. tient 1 had all five cardinal features of KS, whereas unaffected twin had none. Their monozygosity was pported by molecular studies. The presence of dis-dant monozygotic twins argues against, but by no ans excludes, monogenic disorders. There have been ny instances of monozygotic twins discordant for mo-genic disorders, including spondylocostal dysostosis n Thienen and van der Auwera, 1994] and oral-ial-digital syndrome type 1 [Shotelersuk et al., 1999]. eral causes for such discordance have been sugges-, including postzygotic, posttwinning, and somatic tation [Shotelersuk et al., 1999].

n summary, we described six Thai children with KS. ver lip pits with or without symmetrical lower lip ules and pilonidal sinus were much more common ur series than previously described. Early eruption he two lower central incisors, transient hyperthyr-otropinemia in infancy, and aplasia cutis were observed. A mother had a facial appearance similar to her affected son. However, we also described discordant monozygotic twin boys with KS, arguing against autosomal dominant inheritance.

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บทความที่ 4

American Journal of Medical Genetics 116A:164–169 (2003)

New Syndrome?

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

Vorasuk Shotelersuk,[1]* Tayard Desudchit,[1] and Nitaya Suwanwela[2]

[1]*Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and Hospital, Bangkok, Thailand*
[2]*Department of Radiology, Faculty of Medicine, Chulalongkorn University and Hospital, Bangkok, Thailand*

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. © 2003 Wiley-Liss, Inc.

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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*Correspondence to: Vorasuk Shotelersuk, MD, Division of Endocrinology, Genetics, and Metabolism, Department of Pediatrics, Sor Kor Building 11th floor, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.
E-mail: vorasuk.s@chula.ac.th

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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. Developmental 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.

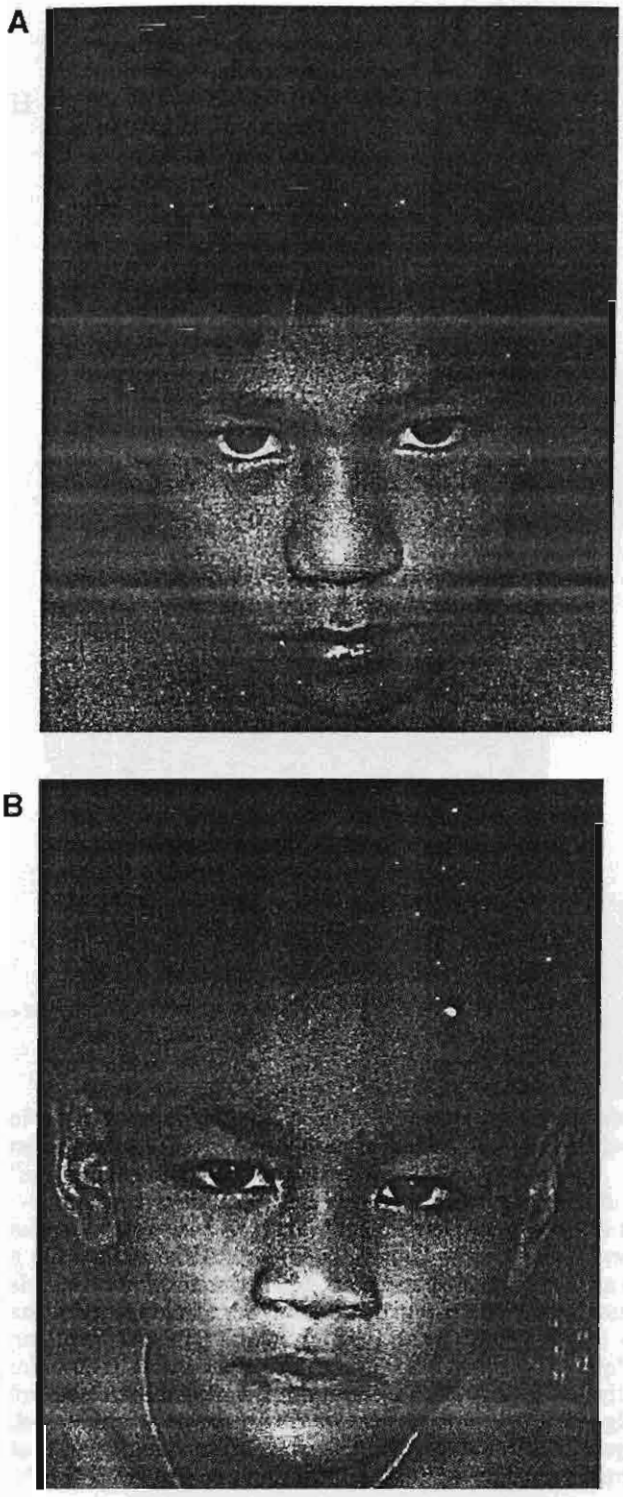

Fig. 1. The elder sister (A) and the younger brother (B). Note the triangular facies with prominent supraorbital ridge and prominent ears.

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

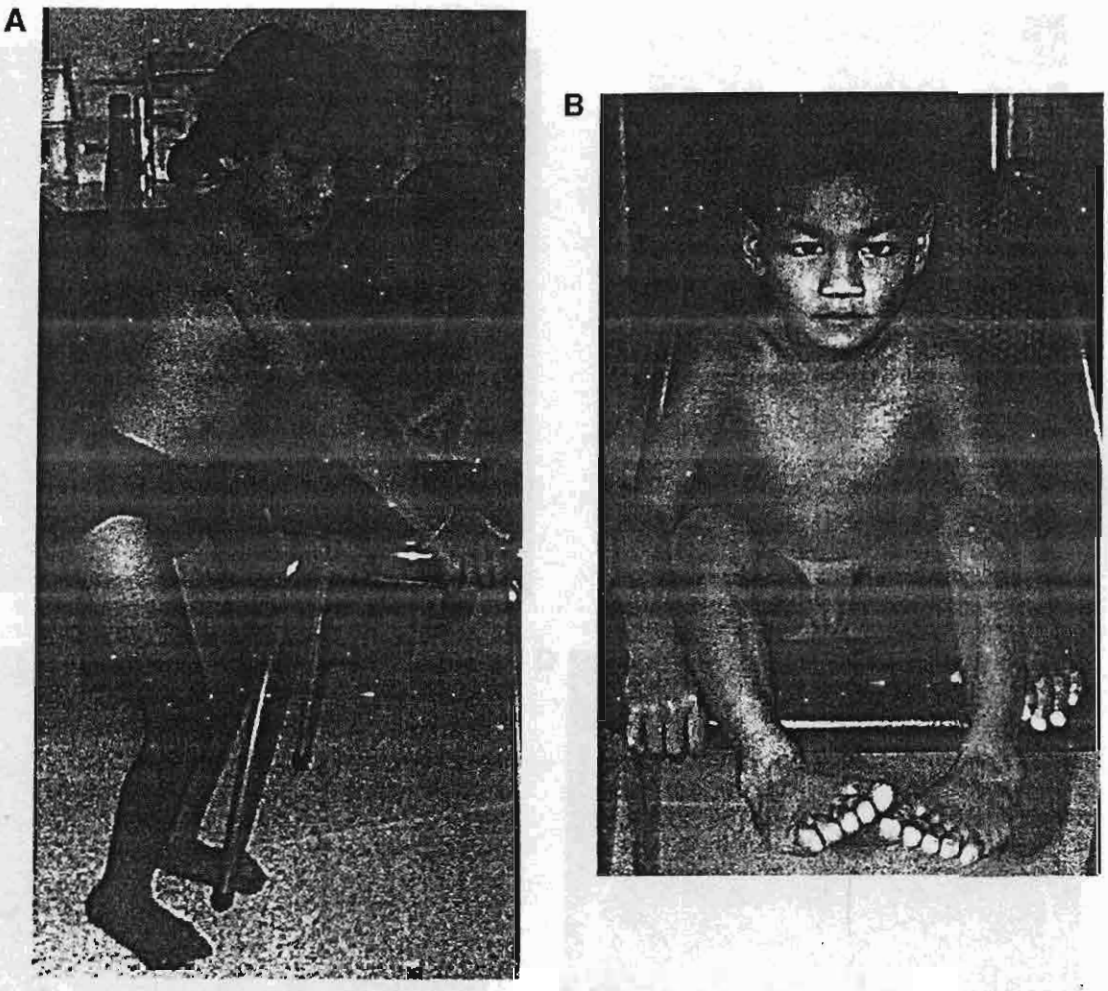

Fig. 2. Joint contractures, especially of the hip, knees and elbows in the sister (A), and normal male genitalia in the brother (B).

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

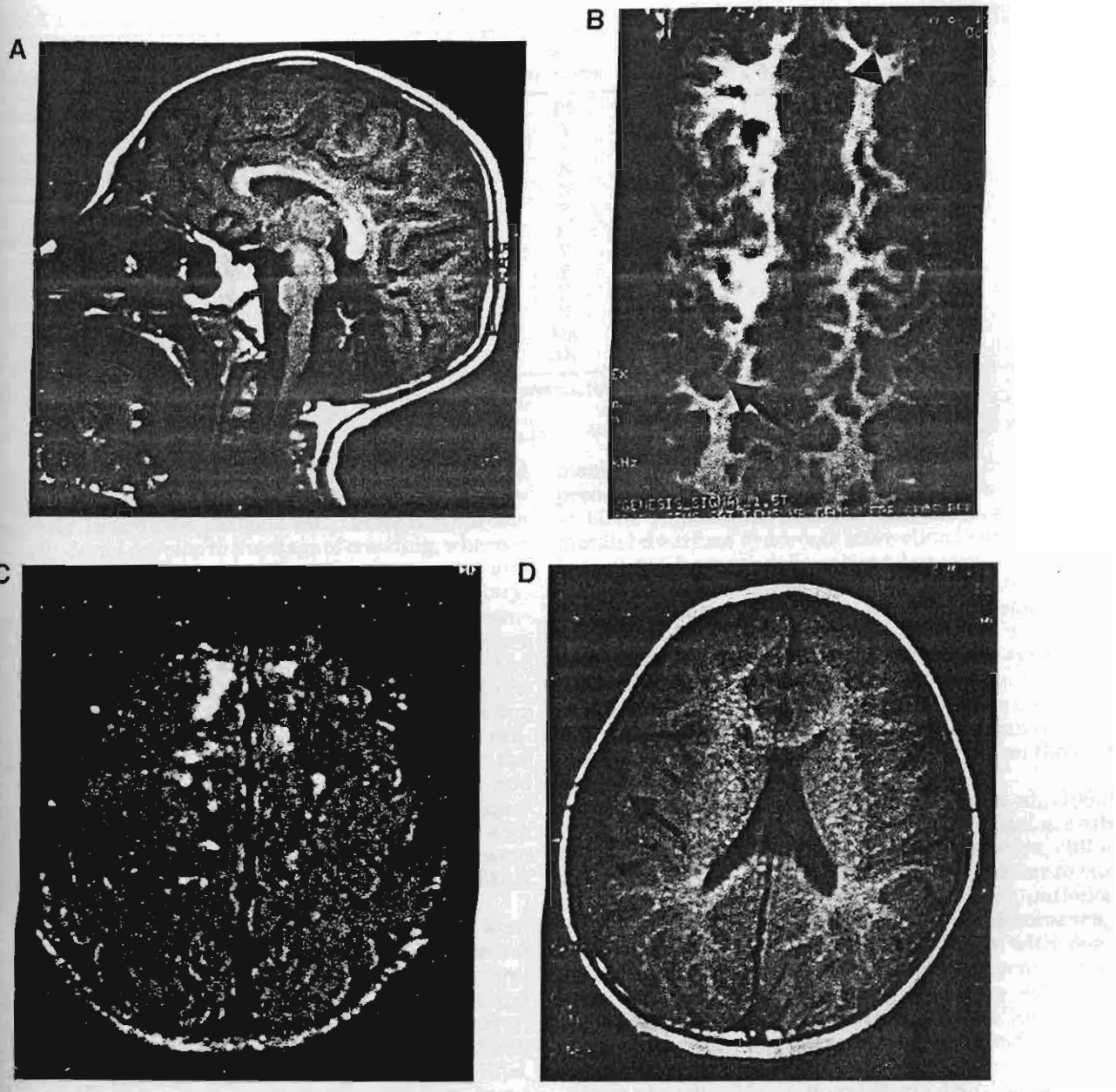

Fig. 3. Brain MRI of the elder sister (A) and the younger brother (B–D). A: Sagittal T1WI shows microcephaly and marked cerebellar atrophy with very prominent fissures between shrunken cerebellar folia and widened posterior fossa subarachnoid space. B: Reformation from volume gradient echo acquisition 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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บทความที่ 5

Clinical, Pathological, and Electron Microscopic Findings in Two Thai Children with Pompe Disease

VORASUK SHOTELERSUK, M.D.*,
PAIROJ CHOTIVITAYATARAKORN, M.D.*,
VANNEE WATTANASIRMKIT, B.Ed.**,
PENPAN NUAYBOONMA, B.Sc.**,
PONGSPEERA SUWANGOOL, M.D.**
SHANOP SHUANGSHOTI, M.D.**,
WICHIAN CHOUWSRIKUL, M.D.**,
SUPANG MANEESRI, M.Sc.**,
CHOOSAK VIRATCHAI, M.D.**,

Abstract

The authors report on a Thai boy who first presented at age 7 months and an unrelated Thai girl in her neonatal period with hypotonia, cardiomegaly and hepatomegaly. Their chest roentgenograms showed markedly enlarged hearts, EKGs showed abnormally shortened PR intervals with gigantic QRS complexes, and electron microscopic studies of their skin samples showed glycogen accumulations surrounded by membranes. The boy died at age 22 months and the girl at age 9 months due mainly to cardiorespiratory failure. Autopsy of the girl showed marked accumulation of glycogen in the liver, heart and numerous additional tissues including her brain. The clinical, pathological, and electron microscopic findings of these two children are consistent with the diagnosis of Pompe disease.

Pompe disease is an autosomal recessive disorder of glycogen metabolism resulting from deficiencies in activity of the lysosomal acid α-glucosidase. Definite diagnosis of the disease can be made from a biochemical test or a mutation analysis. To the authors' knowledge, no service laboratories in Thailand offer the tests. Because Thai children have occasionally been reported to be affected by Pompe disease, an attempt to establish a definite diagnostic test for Pompe disease in Thailand should be encouraged. With a definite diagnosis, the proper genetic counseling and prenatal diagnosis could be offered to the families.

Key word : Glycogen Storage Disease, Pompe Disease, Electron Microscopy

SHOTELERSUK V, SHUANGSHOTI S, CHOTIVITAYATARAKORN P, et al
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* Department of Pediatrics
** Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.