

## Clinical Report

# Microcephalic Osteodysplastic Primordial Dwarfism With Severe Microdontia and Skin Anomalies: Confirmation of a New Syndrome

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**We report two related Thai children having a new syndrome of microcephalic osteodysplastic primordial dwarfism (MOPD). The findings which classify them as having MOPD include IUGR, microcephaly, prominent nose and nasal bridge, small pinnae, short stature, cone-shaped and ivory-epiphyses, delayed bone age, slender long bones, and abnormal pelvis. The findings that distinguish them as having newly recognized syndrome consist of severe microdontia, malformed teeth, single-rooted or rootless teeth, severely hypoplastic alveolar bone, café au lait spots, acanthosis nigricans, and areas of hypo- and hyperpigmented skin. The reported patients appear to have the same condition as the family reported by Kantaputra [2002: *Am J Med Genet* 111:420–428]. This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>. © 2004 Wiley-Liss, Inc.**

**KEY WORDS:** hyperpigmented skin; hypopigmented skin; hypoplastic alveolar bone; malformed tooth; microdontia; rootless tooth

## INTRODUCTION

In 2002, Kantaputra reported a newly recognized autosomal recessive syndrome of microcephalic osteodysplastic primordial dwarfism (MOPD). The uniqueness of that syndrome is the presence of dental, digital, and skin anomalies. The dental anomalies are striking, consisting of severe microdontia, opalescent and rootless molars, and an unerupted tooth. The mandibular premolars are unusually small and malformed, comprising many cusps. In addition, the alveolar process is severely hypoplastic. Digital anomalies include unusually long second toes, distal symphalangism of toes, and brachymesophalangy of fingers. Skin anomalies

include café au lait spots, and areas of hypo- and hyperpigmented skin. The hair is dry and sparse [Kantaputra, 2002]. After reviewing all previously reported cases of MOPD, we found that 12 cases of MOPD with microdontia have been reported (Tables I and II). We hypothesize that MOPD with severe microdontia with or without skin anomalies should be classified as a distinct entity.

We report on two related Thai patients with MOPD syndrome, who share many characteristic findings of the novel syndrome reported by Kantaputra [2002].

## CLINICAL REPORT

### Patient 1

Patient 1 was a 7-year-old boy. He was the only child of healthy, nonconsanguineous parents (Figs. 1 and 2a). He was born at term with weight 1,270 g (<3 centile; <−7.4 SD), length 37 cm (<3 centile; <−8.6 SD), and OFC 28 cm (<3 centile; <−3 SD). At the age of 3, his growth was moderately delayed with a development quotient of 42.

On examination at age 7, he was a cheerful boy with microcephaly, prominent nose and nasal bridge, small pinnae, high-pitched voice, and proportionate short stature (Fig. 2a). His height, weight, and OFC were 83 cm (<3rd centile; <−8.5 SD), 9.5 kg (<3rd centile; <−6 SD), and 41.5 cm (<3rd centile; <−5.5 SD), respectively. His upper and lower ratio was appropriate for age (1.1:1), but his arm span (73 cm) was relatively shorter than his height due to limited elbow extension. Limited abduction of the hips was observed. Clinodactyly of the fifth fingers, deep palmar creases, and medially-deviated toes were noted. Penis and testis were unremarkable. Hearing via auditory brainstem response (ABR) was unremarkable, and development remained globally delayed. Growth hormone secretion following clonidine stimulation at age 3 was normal. Karyotype was 46,XY.

Skin complexion was darker than that of his parents. There were areas of hypo- and hyperpigmentation of the skin which did not follow lines of Blaschko (Fig. 2a,b). The palms appeared hyperpigmented (Fig. 2c). Café-au-lait spots were observed on his body, hands, and thigh (Fig. 2b). Hair was normal.

Oral examination revealed normal shape and color of deciduous crowns. All teeth were mobile. Most deciduous incisors appeared to have premature exfoliation. The remaining deciduous teeth were slightly small. The permanent teeth, especially the maxillary and mandibular permanent incisors were extremely small. The mesiodistal width of a mandibular incisor was 3 mm. The mamelons of all incisors were prominent (Fig. 3a). The carabelli cusp of the maxillary second deciduous molar was large. The mandibular and maxillary right deciduous second molars exfoliated at age 5. The pharynx was very narrow.

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TABLE I. Clinical Manifestations of MOPD Patients With Microdontia With/Without Skin Anomalies

Mode of inheritance Gender	Cervenka et al. [1979]		Majewski et al. [1982]		Shebib et al. [1991]		Lin et al. [1995]		Majewski and Goecke [1998]		Seymen et al. [2002]		Kantaputra [2002]		Present cases	
	Pt1 AR M	Pt2 AR M	Pt1 Na M	Pt2 Na F	AR F	Pt1 AR M	Pt2 AR M	Pt1 AR M	Pt2 AR M	Pt3 Na M	Pt1 AR M	Na M	Pt1 AR M	Pt2 AR F	Pt1 AR M	Pt2 AR F
<b>Examination</b>																
<b>General</b>																
Age when reported (year)	8	11	2	3	7	10	15	2	2	2	7	18	16	8	9	
Weight (kg)	85	15	6.3	4.2	5.4	18	31	5	5	6.1	7	14	12	9.5	9.5	
Height (cm)	85	104	63.8	61	67	116	125	60.4	60.4	65.0	78	102	96	83	83	
OFC (cm)	41	44	37	31.5	37.5	47.5	48	40.4	40.4	41	40.5	43	41	38.5	38.5	
Dis/proportionate short	P	P	P*	P*	D	P	P	D	D	D	P	P	P	P	P	
Postnatal GR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Dev delay/MR	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	
Hypertonia	Y	Y	N	N	N	N	N	Y	Y	N	N	N	N	N	N	
High-pitched voice	Y	Y	Y	Y	Na	Na	Na	Y	Y	Y	N	N	N	Y	Y	
<b>Birth history</b>																
Birth weight (g)	1,040	1,500	1,280	1,150	1,250	1,700	1,480	1,320	1,320	1,300	800	1,000	1,000	1,270	920	
Birth length (cm)	34	Na	38	Na	30	Na	Na	37	37	39	35	Na	Na	37	31	
OFC (cm)	25.5	Na	27.5	Na	Na	Na	Na	28	28	27.5	25	Na	Na	28	24.5	
IUGR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
<b>Craniofacial</b>																
Microcephaly	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Craniosynostosis	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	
Strabismus	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	
Small/abnormal pinnae	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Prominent nose	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Small maxilla	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	
Micrognathic mandible	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Retrognathic mandible	Y	Na	Y	Na	N	Na	Na	Y	Y	Y	Y	N	N	N	N	
<b>Teeth</b>																
Microdontia of prim teeth	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Microdontia of perm teeth	Y	Y	Na	Na	Y	Y	Y	Na	Na	Na	Y	Y	Y	Y	Y	
Hypodontia	N	Na	Na	Na	N	N	N	Na	Na	Na	Y	N	N	N	N	
Taurodontism	N	Na	Na	Na	Na	Na	Na	Na	Na	Na	Y	N	N	N	N	
Malformed teeth	N	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	Y	Y	Y	Y	
Opalescent teeth	N	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	Y	Y	N	N	
Short root/rootless	Y	Y	Na	Na	Y	Y	Na	Na	Na	Na	Y	Y	Y	Y	Y	
Unrupted tooth	N	Na	Na	Na	N	N	N	Na	Na	Na	N	N	Y	N	N	
<b>Hair and skin</b>																
Dry/sparse hair	Y	Y	Y	Y	N	Na	Na	Na	Na	Na	Na	Y	Y	N	N	
Hyperhirsute	Y	Y	Na	Na	N	Na	Na	Na	Na	Na	Na	Y	N	N	N	
Skin hyperpigment	N	N	Na	Na	N	Na	Na	Na	Na	Y	Na	Y	Y	Y	Y	
Café au lait spots	N	N	Na	Na	Na	Na	Na	Y	Y	Y	Na	Y	Y	Y	Y	
Acanthosis nigricans	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	N	N	N	
Sclerotic skin	Y	N	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	N	N	N	
<b>Arms and hands</b>																
Bowed arms	Na	Na	N	Na	Y	N	N	Na	Na	Na	Y	N	N	Y	N	
Radial head dislocation	Na	Na	Na	Na	Y	Na	Na	Na	Na	Na	Na	Y	Y	Y	Y	
Clinodactyly V	Y	Y	Y	Y	Y	Na	Na	Y	Y	Y	Na	N	N	Y	Y	
<b>Legs</b>																
Bowed legs	N	N	N	N	N	Na	Na	N	N	N	Na	N	N	N	N	
Coxa valga	Na	Na	N	N	N	Y	Y	N	N	N	Na	Na	Na	N	N	
Coxa vara	Na	Na	Y	Y	Y	N	N	Y	Y	Y	Y	Na	Na	N	N	
<b>Genitalia (male)</b>																
Cryptorchidism	Y	N	N	—	—	Na	Na	Na	Na	Na	Na	N	N	N	—	
Small testis	Na	N	Y	—	—	Na	Na	Na	Na	Na	Na	N	—	N	—	
Small penis	N	N	Y	—	—	Na	Na	Na	Na	Na	Na	N	—	N	—	

TABLE II. Radiographic Findings of MOPD Patients With Microdontia With/Without Skin Anomalies

	Cervenka et al. [1979]		Majewski et al. [1982]		Shebib et al. [1991]		Lin et al. [1995]		Majewski and Goecke [1998]			Seymen et al. [2002]		Kantaputra [2002]		Present cases	
	Pt1	Pt2	Pt1	Pt2	Pt1	Pt2	Pt1	Pt2	Pt2	Pt3	Pt1	Pt2	Pt1	Pt2	Pt1	Pt2	
<b>Craniofacial</b>																	
Increased digital marking	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Y	Y	Y
Hypoplastic alv bone	Y	Y	Na	Na	Y	Na	Na	Na	Na	Na	Na	Na	Y	Y	Y	Y	Y
<b>Arms and Hands</b>																	
Angular carpal bone	Na	Na	Na?	Na	Y	Na	PIC	Na	Na	PIC	Na	Na	Na	Na	Y	Y	Y
Pseudoepiphysis of MC	Na	Na	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Na	Na	N	N	Y
Ivory epiphyses	Y	N	N	Na	Y	N	Y	Na	Na	N	Na	Na	Na	Na	Y	Y	Y
Cone-shaped epiphysis	N	N	N	Na	Y	Y	Y	Na	Na	N	Na	Na	Na	Na	Y	Y	Y
Delayed bone age	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
<b>Pelvis and legs</b>																	
Hypoplastic/narrow pelvis	Na	Na	Y	Y	Y	Y	Y	Y	Y	N	Y	Na	Na	Na	Y	Y	Y
Epiphysiolysis of hips	Na	Na	Y	Y	N	N	N	N	N	Na	Y	Na	Na	Na	Y	Y	N
Triangular of distal femoral epiphyses	Na	Na	Y	Na	Y	Y	N	N	Y	Y	Y	Na	Na	Na	N	N	N
Flaring of distal femoral metaphysis	Na	Na	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Na	Na	N	N	Y
<b>Feet</b>																	
Ivory epiphysis	Na	Na	Na	Na	Y	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	N	Y
Distal symphalangism of toes	Na	Na	Na	Na	Na	Na	N	N	Na	Na	Na	Na	Na	Na	Y	Y	N
<b>Chest</b>																	
Long/slender clavicles	Na	Na	Na	Na	Y	Na	Na	Na	Na	N	Na	Na	Na	Na	Y	Y	Y
Hypoplastic scapula	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	Na	Na	Na	Na	Y	Y	Y
11 ribs	Na	Y	Na	Na	Y	Na	Na	Na	Na	N	Na	Na	Na	Na	Y	Y	N

Y, present; N, absent; Na, not available.

Patients reported by Cervenka et al. [1979] were reported again in 1981 by Tsuchiya et al. [1981].

\*Disproportionately short during the early years of life.

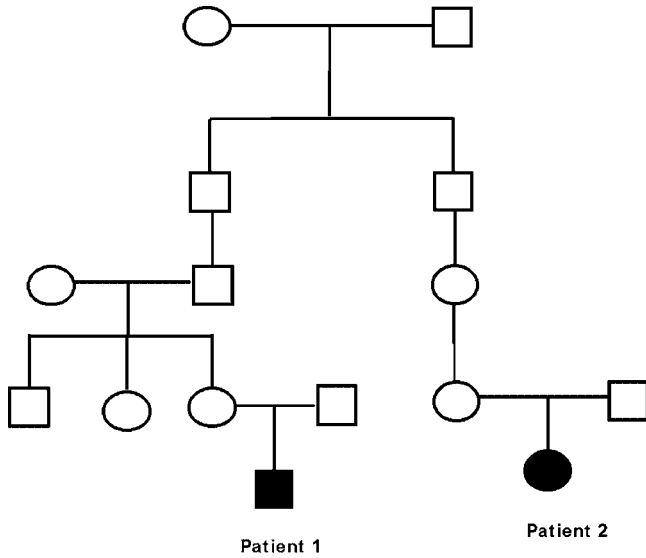


Fig. 1. Pedigree of the families.

Radiographic examination showed thin cranium. Molars were either single- and short-rooted, or rootless (Fig. 4a,b). Obliteration of the root canals was seen in all incisors (Fig. 5a,b). Alveolar process was severely hypoplastic and its cortical bone was not evident. Supernumerary maxillary right permanent molar was noted. All unerupted developing permanent teeth were malformed and very small mesiodistally. Digital marking of the skull was observed (Fig. 4a,b). Clavicles were long, straight, and slender. Scapulae were hypoplastic. There were 11 ribs on each side. The radius and ulna were slender. Radius was slightly bowed and the radial heads were dislocated. There was restricted supination and extension at the elbows.

According to Greulich and Pyle, the bone-age was delayed at age 3 years 3 months and estimated to around age 1 year (SD = 6.6 months). Middle phalanges of finger 5 appeared short and tapered proximo-distally. Epiphyses were observed only at the proximal phalanges of fingers 2–4 (see the online Figure 8a at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). At age 6, bone age was estimated to be of 5 years (SD = 9 months). Distal ulna was slightly short with ulnar deviation of the hand. Ivory epiphyses were observed at proximal phalanges of thumbs, all phalanges of fingers 3 and 4, and the middle and distal phalanges of fingers 2. Cone-shaped epiphyses of the proximal phalanges of fingers



Fig. 2. **a:** Patient 2 (left) and 1 (right). Note prominent nose and nasal bridge, dark skin, exotropia of Patient 2's eye. **b:** Dark skin with areas of hypo- and hyperpigmented macules and café au lait spot. **c:** Hyperpigmented palms.



Fig. 2. (Continued)

2–4 were observed (see the online Figure 8b at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). Pelvic radiograph demonstrated narrow iliac wings, flat acetabular sockets, thin and elongated pubic and ischial bones, and bilateral epiphysiolysis of the femoral heads (see the online Figure 6b at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). Foot radiograph showed hypoplastic distal phalanges of toes 2–4, ivory epiphyses of proximal phalanges 5, and distal symphalangism of toe 5.

### Patient 2

Patient 2 was a 9-year-old girl. She was the only child of healthy and nonconsanguineous parents (Figs. 1 and 2a). Her maternal great grandfather was the younger brother of the great grandfather of Patient 1 (Fig. 1). The patient was born at 32 weeks of pregnancy. Her birth weight, birth length, and OFC were 920 g (<3rd centile; <-1.7 SD), 31 cm (<3 centile; <-2.5 SD), and 24.5 cm (<3rd centile; -1.8 SD), respectively. At birth she suffered from mild respiratory distress syndrome, hyperbilirubinemia, and retinopathy of prematurity, and was in an incubator for 2.5 months. Growth hormone stimulation test with glucagon revealed peak of growth hormone of 2.6 ng/ml (norm >10 ng/ml). IGF1 = 0 ng/ml (norm 7–21 ng/ml). IGBP3 = 2,096 ng/ml. The results indicated primary growth hormone deficiency.

On examination at age 8, her height, weight, and OFC were 83 cm (<3 centile; <-8.9 SD; 50 centile of age 20 months), 8.3 kg (<3 centile; <-5.6 SD; 50 centile of age 17 months), and 38.5 cm (<3rd centile; <-8.8 SD; 50 centile of age 2 months), respectively. Physical examination revealed microcephaly, left esotropia, prominent nose and nasal bridge, and small pinnae (Fig. 2a). Proportionate short stature was noted with 1:1 upper and lower segment ratio. Hands, arms, feet, and legs were proportionately short. Arm span was 81.5 cm. Movement of the shoulders, elbows, wrists, hips, knees, and ankles was unremarkable. Palms were dry, and deep palmar and finger flexion creases were noted. Clinodactyly of the fifth fingers was observed. The hair and hearing were normal.

Like that of Patient 1, her skin complexion was darker than that of her parents. Also there were areas of hypo- and hyperpigmented macules in the skin of her chest and back (Fig. 2a). Acanthosis nigricans was observed around her neck and armpits. She sat, stood, walked, and ran at



Fig. 3. **a:** Patient 1. Extremely small maxillary and mandibular permanent incisors with prominent mamelons. **b:** Patient 2. Very small and yellowish permanent incisors with prominent mamelons.

ages 9, 18, 22, and 28 months, respectively, and she used single words at 18 months. Her voice was high-pitched, and global developmental delay was observed, with cheerful disposition. Intelligence quotient was 56 according to Stanford Binet form. Karyotype was 46,XX.

Oral examination demonstrated very small and yellowish teeth. Their mamelons were prominent (Fig. 3b). All teeth were mobile. The maxillary right second deciduous molar exfoliated at age 5. The maxillary left first permanent molar had occlusal caries. The maxillary labial frenum was thick. Her gingiva did not appear hyperpigmented like her skin, and was otherwise normal. The pharynx was narrow.

Radiographic examination showed thin cranium, rootless molars, and severely hypoplastic alveolar bone. Cortical bone of the alveolar process was not observed. Rootless molars appeared to float in loose alveolar bone. The crowns of all permanent molars were tapered occluso-cervically. Increased digital marking of the skull was noted (Fig. 4c,d). The dental pulps of all incisors appeared obliterated (Fig. 5c,d). Clavicles were long, straight, and slender. They appeared to be located in horizontal position. Scapulae were hypoplastic. At age 6, hand radiograph showed ivory epiphyses at all

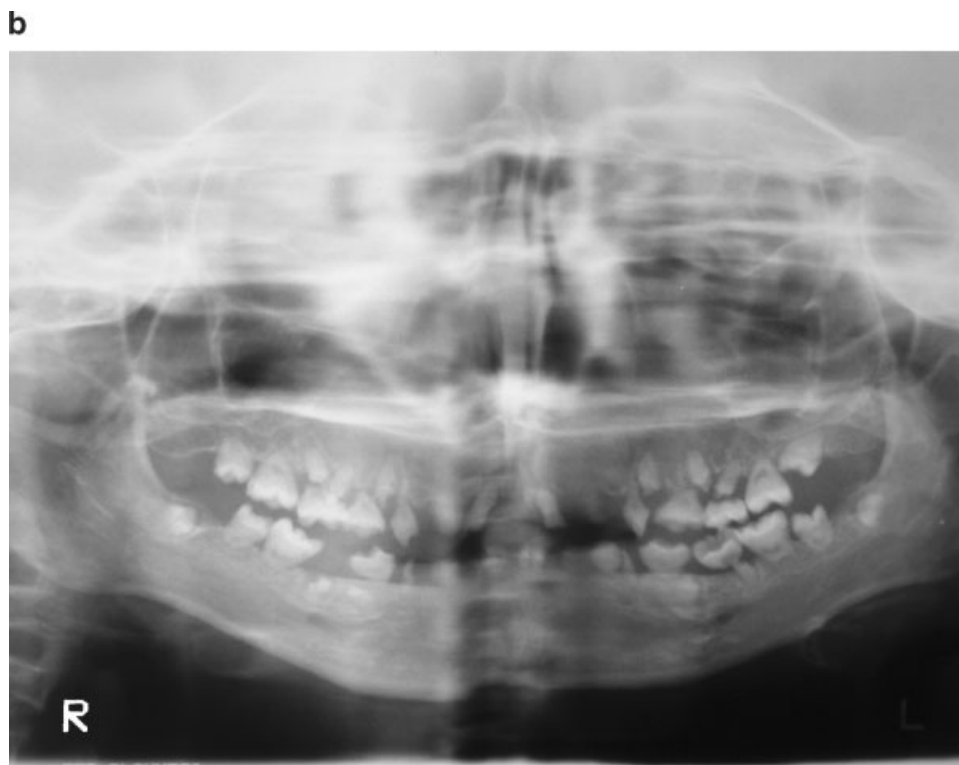
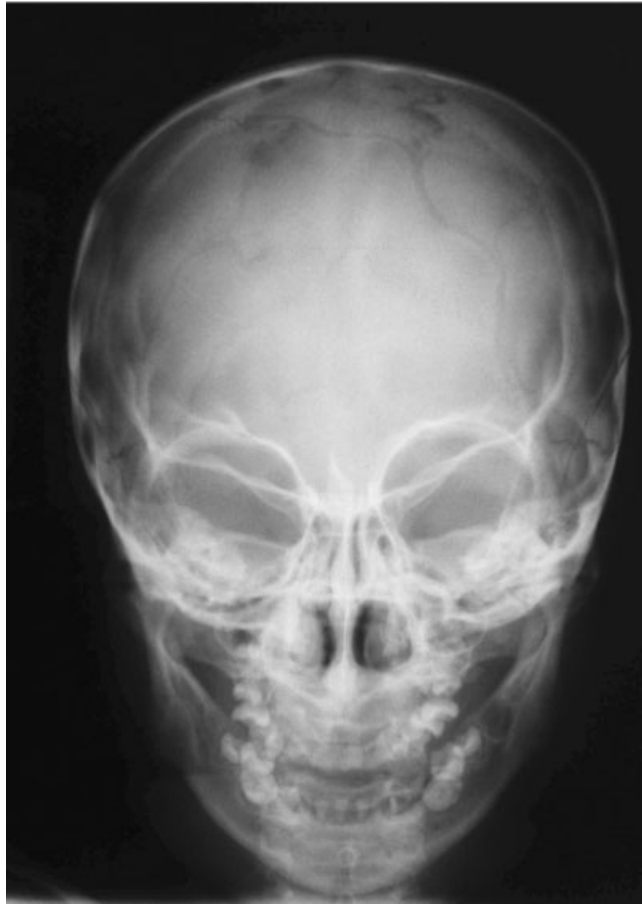


Fig. 4. Patient 1 (a) lateral cephalograph. Note increased digital marking of the skull. b: Panoramic radiograph. Supernumerary right maxillary permanent molar. Patient 2 (c) PA skull radiograph. d: Panoramic radiograph. Note single-rooted or rootless molars, severe microdontia of developing permanent premolars and molars, severely hypoplastic alveolar bone, and molar crowns converge occluso-cervically.

**c**



**d**

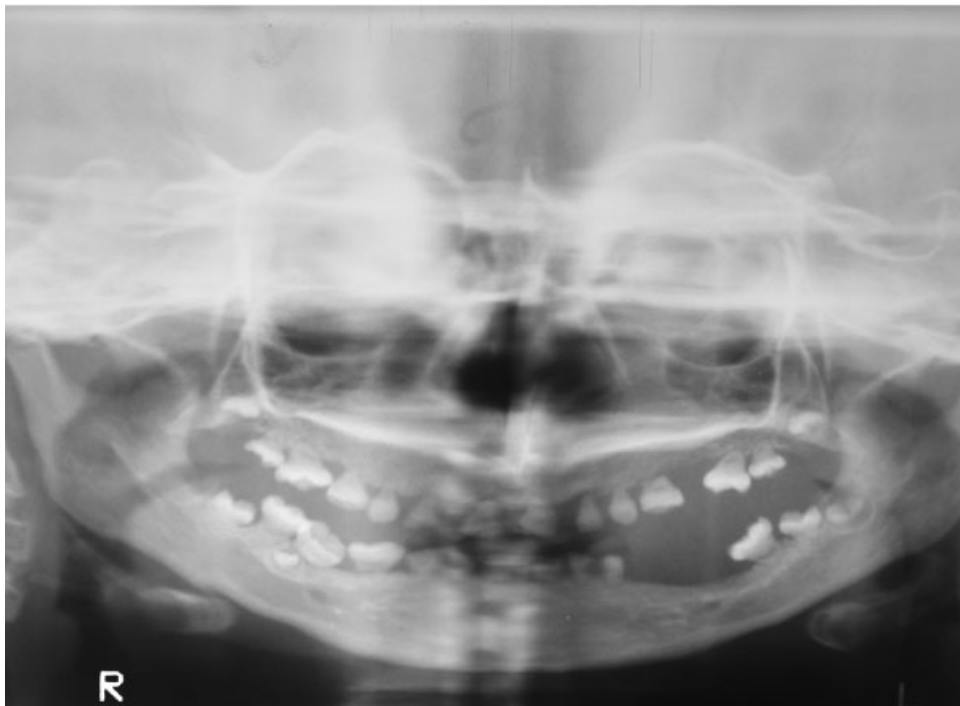


Fig. 4. (Continued)

**a**



**b**

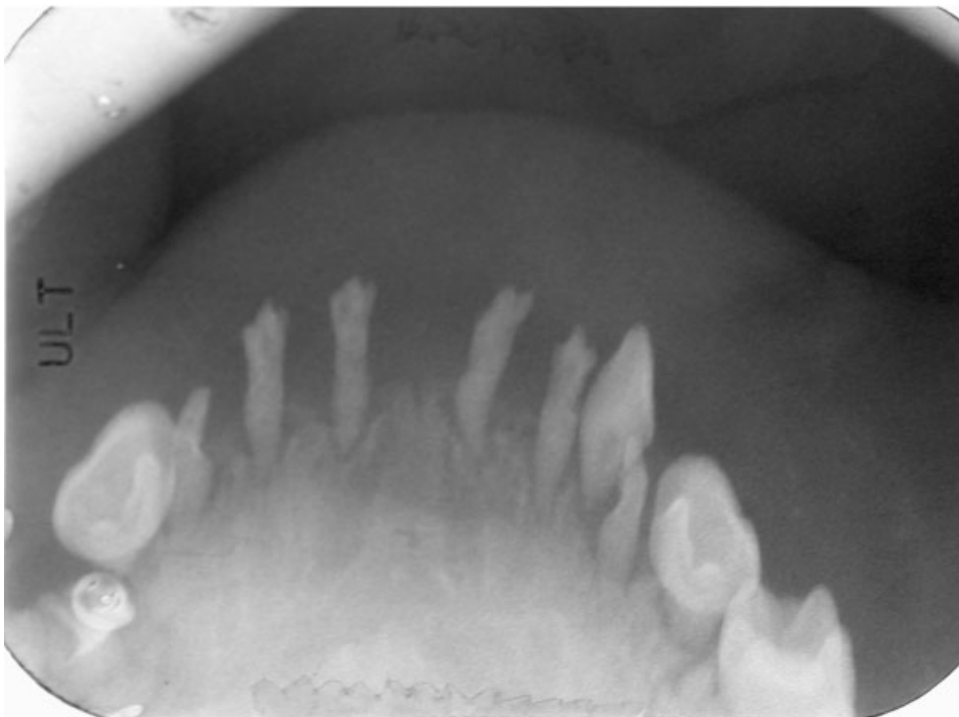
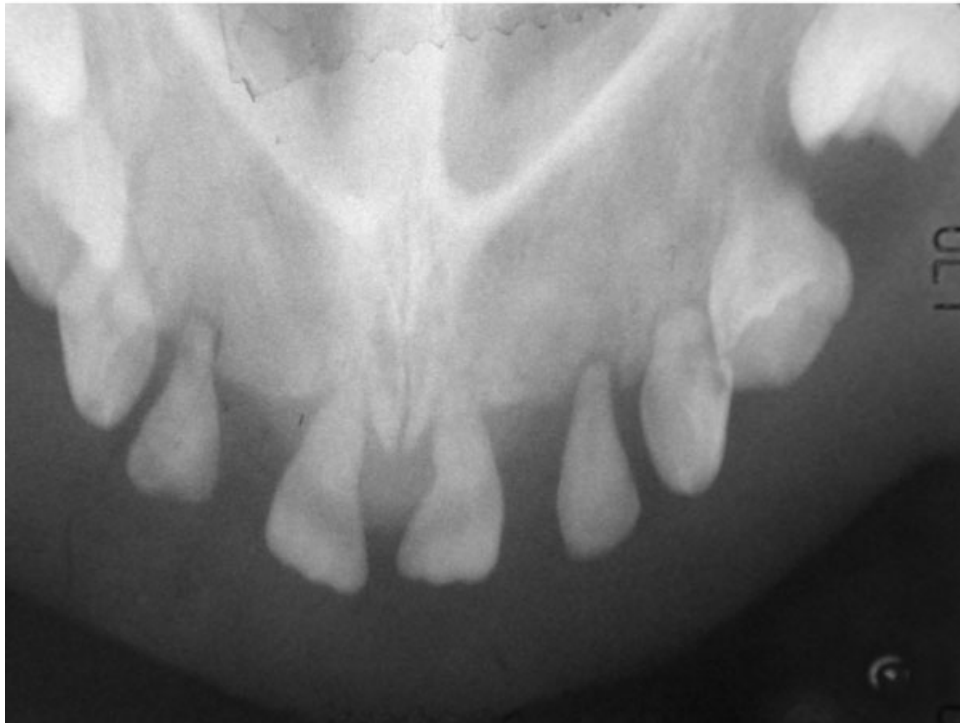


Fig. 5. Periapical radiographs of Maxillary and mandibular incisors of Patient 1 (a) and (b). Patient 2 (c) and (d). Note Severely hypoplastic alveolar bone. Obliteration of dental pulp chambers and root canals.

c



d

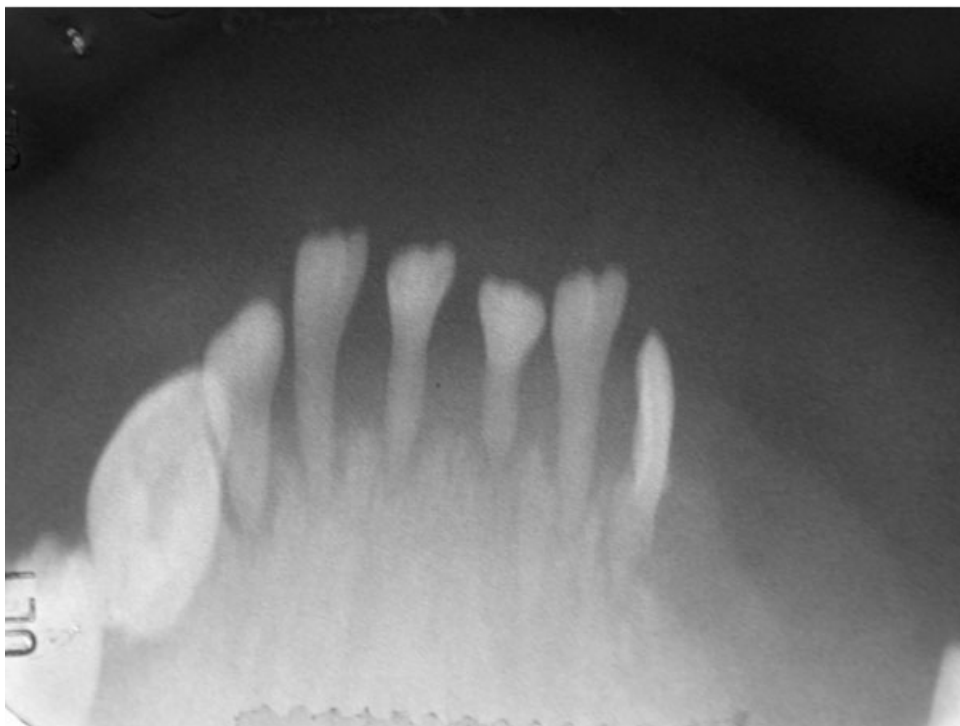


Fig. 5. (Continued)

phalanges except at the distal phalanges of her thumbs and the middle and distal phalanges of her 5th fingers, with bone age at 2.6–3 years (see the online Figure 8c at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). At age 8, ivory epiphyses were observed at all phalanges of the hands except for the distal phalanges of thumbs. Large pseudoepiphyses were noted at the proximal ends of metacarpals 2 and 5, and distal radial epiphyses appeared very dense (see the online Figure 8d at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). Eleven ribs were observed on each side. Like those of Patient 1, clavicles were straight and slender (see the online Figure 6a at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). Humerus, radius, ulna, tibia, and fibula were slender (see the online Figure 7b at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). Foot radiograph showed medially deviated toes and ivory epiphyses of all proximal phalanges and distal phalanges 2–5 (see the online Figure 9 at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>).

## DISCUSSION

We report on two additional Thai children affected with MOPD and severe microdontia, short and single-rooted molars, rootless molars, and severely hypoplastic alveolar bone, hyperpigmented skin, acanthosis nigricans, café au lait spots, and hypo- and hyperpigmented macules. The combination of dental and dermal features found in these two related children appears unique for MOPD. Interestingly, similar findings have recently been described in a Thai family living in the different part of Thailand [Kantaputra, 2002]. We are convinced that the syndrome found in our patients and that reported by Kantaputra [2002] represents a distinct entity.

Seckel syndrome and MOPD patients usually have normal teeth, and some affected patients even have large teeth [Seckel, 1960; Majewski, 1992; Kjær et al., 2001]. The permanent incisors found in the present patients especially those of Patient 1 were very small. Besides severe microdontia, these patients also had rootless or very short and single-rooted molars, with severely hypoplastic alveolar bone. We have reviewed the previously reported cases of MOPD with microdontia with or without skin anomalies and tabulated them in Tables I and II. Twelve MOPD cases were found to have microdontia. Seven of those had short roots or rootless teeth with severely hypoplastic alveolar processes (Table I). Based on both oral and skin manifestations, we believe the present cases and Thai sibs reported by Kantaputra [2002] have the same disorder.

It appears that the combination of severe microdontia, rootless molars, and severely hypoplastic alveolar bone, café au lait spots, hypo-hyperpigmented macules are the distinguishing features of this “newly” recognized syndrome. Seymen et al., 2002 reported a Turkish boy as having Seckel syndrome. However, with this phenotype and severe microdontia, hypodontia, abnormal molar roots, and hypoplastic

alveolar bones, we suspect that he might have the same condition as our patients and those reported by Kantaputra [2002].

The mode of inheritance of this new disorder is suspected to be autosomal-recessive as their maternal great grandfathers were brothers. However, the fathers of both patients denied consanguinity, but they all lived in the same village. While our patients share several features with Seckel syndrome and since it has recently been found that Seckel syndrome is caused by mutations in ATR, it is worthwhile to look for mutation in the gene [O’Driscoll et al., 2003].

## ACKNOWLEDGMENTS

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