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Editor's Note

In what I suspect will be the seminal paper on the Nicolaides-Baraitser syndrome, Sousa and colleagues comprehensively characterize and delineate the phenotype of the condition. From their work, which represented the collaboration of several clinical geneticists in Europe and the US, the syndrome is now established as a recognizable and discrete entity.

John C. Carey

Nicolaides–Baraitser Syndrome: Delineation of the Phenotype

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Nicolaides–Baraitser syndrome (NBS) is an infrequently described condition, thus far reported in five cases. In order to delineate the phenotype and its natural history in more detail, we gathered data on 18 hitherto unreported patients through a multi-center collaborative study, and follow-up data of the earlier reported patients. A detailed comparison of the 23 patients is provided. NBS is a distinct and recognizable entity, and probably has been underdiagnosed until now. Main clinical features are severe mental retardation with absent or limited speech, seizures, short stature, sparse hair, typical facial characteristics, brachydactyly, prominent finger joints and broad distal phalanges. Some of the features are progressive with time. The main differential diagnosis is Coffin–Siris syndrome. There is no important gender difference in occurrence and frequency of the syndrome, and all cases have been sporadic thus far. Microarray analysis performed in 14 of the patients gave normal results. Except for the progressive nature there are no clues to the cause.

Key words: Nicolaides–Baraitser syndrome; seizures; mental retardation; growth retardation; sparse hair; natural history; etiology; Coffin–Siris syndrome

INTRODUCTION

In 1993, pediatric neurologist Paola Nicolaides and clinical geneticist Michael Baraitser reported a 16-year-old girl with an unusual combination of signs and symptoms, and suggested this to be a separate and recognizable entity. Main clinical features were severe mental retardation, seizures, short stature, sparse hair, typical face, and prominent finger joints. Four other sporadic patients with a similar phenotype were subsequently described [Krajewska-Walasek et al., 1996; Morin et al., 2003; Witters and Fryns, 2003], and the name the Nicolaides–Baraitser syndrome (NBS), was suggested.

Here, we describe 18 hitherto unreported patients, and follow-up of the original and other published patients, in order to delineate the phenotype in more detail, and allow easier recognition of additional cases we discuss the differential diagnosis and possible etiologies.

CLINICAL REPORTS

The original patient is described in detail. The data on her and all other patients are summarized in Table I and illustrated in Figures 1–5. Only a short description of other patients is provided.

Follow-Up of Original Patient [Nicolaides and Baraitser, 1993]

The patient is now a 32-year-old woman. She is the only child of nonconsanguineous parents of British ancestry. The father died at the age of 60 years of colonic cancer. At 3 years the proposita had developed seizures which have continued through the years and included two episodes of *status epilepticus* (at 16 and 25 years, respectively), and increasing seizure frequency despite multi-medications. Her ability to use her hands and her general mobility decreased significantly. She could walk only very short distances, with a widely based gait, hips and knees flexed, and bent forwards. Most of the time she used a wheelchair. She developed obesity and constipation in puberty and adolescence.

Although formal testing has not been performed, her mental abilities were thought to have gradually deteriorated. She lost all language in early adulthood. She continues to have a very pleasant personality, prefers socializing with adults, loves going out, and enjoys music. She has bouts of laughter, sometimes inappropriately, and sporadic episodes of bad temper and aggression to herself and others, frequently related to the menses. Menarche was at the age of 16 years and menses were regular. Her sleep is erratic, awaking several times. She has no ventilation problems. She can feed herself independently.

Vesico-ureteric reflux has caused no problems using long-term antibiotic prophylaxis. She has myopia, and her hearing is normal. Her hair, which had always been sparse but with a normal distribution, had become more sparse and from 20 years onwards she had complete alopecia, except for a small area over the temples. Eyebrows were initially normal but became sparse with time. Her eyelashes and pubic hair have remained normal. Secondary teeth eruption and teeth morphology were normal. Skin wrinkling was progressive, mainly in the face, neck, and distal limbs. She had periods of eczema that affected her scalp mainly, had hypohidrosis and normal nails.

Physical exam at 32 years (Fig. 2) showed a friendly woman with proportionate short stature (height estimated 135 cm [<0.4th centile, exact measurement impossible]), truncal obesity (weight 58 kg) and microcephaly (OFC 51.8 cm [<0.4th centile]) (Fig. 2D,E). She had an aged appearance, almost no scalp hair, sparse eyebrows, normal eyelashes, prominent infra-orbital grooves, and numerous cheek folds. Her eyes were somewhat deeply set and she tended to keep them closed. She had brachycephaly, a narrow nasal bridge, broad nasal base and tip, thick flared alae nasi, low columella, broad and long philtrum, wide mouth, large protruding tongue, thick and everted lower vermillion, and frequent drooling. Intra-oral inspection was not possible. The lower third of her face was broad, and the shallow mandibular angle caused her chin to be prominent. The ears had thick, overfolded helices and underdeveloped attached lobules. Her neck was remarkably broad, with several skin folds. She had truncal obesity, and small mammae; her liver was 3.5 cm palpable below the lower costal margin, and there was a kyphoscoliosis. In general, she had a muscular build. Elbows had a slightly limited mobility; fingers had flexion deformities, their passive manipulation was painful but not significantly limited. She had loose skin over fingers and dorsum of the hands, prominent proximal inter-phalangeal joints, and

TABLE I. Summary of the Clinical Findings in 23 Patients With Nicolaides–Baraitser Syndrome

		Nicolaides and Baraitser	Krajewska-Walasek et al.	Morin et al. [2003]		Witters and Fryns	Present report																	
	Cases, No./total	[1993]	[1996]	Case 1	Case 2	[2003]	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5	Pat. 6	Pat. 7	Pat. 8	Pat. 9	Pat. 10	Pat. 11	Pat. 12	Pat. 13	Pat. 14	Pat. 15	Pat. 16	Pat. 17	Pat. 18
Epidemiology																								
Sex	13M + 9F[a]	F	M	F	F	F	M	M	F	M	M	F	M	M	M	M	M	M	F	F	M	M	F	F
Age[b]		32	19	6	22	20	9	2.3	7.3	8.4	12.1	4.8	7	20	16	13	13.7	3.9	16.0	17.1	3	6.9	13	13
Age father/mother[c]	30.2/27.3[d]	39/23	26/22	26/25	?/25	?/?	25/24	18/20	32/29	30/35	36/32	31/26	29/31	39/31	26/25	30/21	39/39	19/20	30/23	32/32	42/35	29/26	26/30	26/30
Growth	≤3%/total																							
At birth (weeks gestation)		40	40	?	?	35	39	39	39 + 5	41 + 3	38	36	36	39	39	Term	Term	40	38	40	40	35	40	40
Weight (g)	10/22	1,800	1,900	2,440	2,930	2,100	3,700	2,520	2,420	2,820	3,400	1,955	1,445	3,350	2,580	2,500	2,050	?	2,540	2,520	2,600	2,090	2,115	3,000
Length (cm)	7/14	?	48	46	46	46.5	?	?	49	47	52	?	?	?	46.5	46	45	?	45	45	47	?	?	51
OFC (cm)	5/14	?	32	31	34	31	?	34	?	32	?	?	?	?	34	33	32.5	?	?	33.5	34	34.5	31	33.5
Post-natal (age in years)		32	19	6	22	20	9.4	1.9	6.10	7.11	12	2.4	2.5	7	18	16	13	11	3.6	15	17	3	2.3	13
Weight (kg)	15/21	58	50	13	20	39	30.0	8.89	18.05	21.0	23.3	9.8	10.6	19.3	29.5	31	18.3	?	10	42	55	10.2	?	30
Height (cm)	13/23	135	158	99	130	169	128.7	77.2	111.4	118,5	127.8	85	84	116.4	139	144	118.5	129	92	152	154	83	82	152
OFC (cm)	19/23	51.8	52	46	52	53	50.3	48.4	49.9	49,6	52.1	44.7	45	49.9	51	53	49	52.1	47.8	51	54	49.2	47.5	52
Development																								
Delay (degree)	13[e]/23	Severe	Mod/Sev	Severe	Severe	Mod	Mod	Mod/Sev	Severe	Severe	Severe	Severe	Severe	Mild	Severe	Severe	Severe	Severe	Mod	Mod	Mod/Sev	Mod/Sev	Severe	Mod/Sev
Sits/walk independent (months)		6/18	8/24	?/No	?/18	?/?	10/16	12/no	8/14	9/24	6/15	9/16	9/14	9/19	?/<24	?/30	18/27	6/10	?/12	?/18	?/17	9/26	?/20	11/21
First words (months)	10[f]/23	2	3	None	None	?	2	None	None	None	1.6[g]	24	24	24	None	None	None	0.9[g]	3.9[h]	24	14	None	None	36
Seizures (age years)	16/23 (1.6[d])	+ (3)	−	+	+	−	−	−	+ (1.6)	+ (1.2)	+ (2.6)	+ (0.9)	+ (3)	−	+ (1)	+ (1.6)	+ (1.2)	+ (0.9)	−	+ (2)	+ (1.6)	+ (1.1)	+ (0.7)	No
Craniofacial features																								
Low anterior hairline	17/23	−	+	+	+	?	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	−
Sparse hair	22/23	+	+	+	+	(−)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prominent eyelashes	12/21	−	−	+	?	−	−	+	+	+	−	−	−	+	−	−	+	+	+	?	+	+	+	+
Triangular face (childhood)	19/20	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	+	?	−	+	?	+	+	+
Increased skin wrinkling	13/22	+	+	+	?	+	+	−	−	+	−	−	−	+	+	+	+	−	−	−	+Neck	+	+	−
Sagging periorbital skin	16/22	+	+	+	?	+	+	+	+	−	−	+	+	+	−	+	+	−	+	+	−	+	−	+
Narrow palpebral fissures	9/22	+	+	−	?	−	−	−	+	−	−	−	−	−	+	+	+	+	−	+	+	−	−	−
Down slant palpebral fissures	6/22	−	−	−	?	−	−	−	−	−	+	−	−	+	+	+	+	−	−	+	−	−	−	−
Narrow nasal bridge	12/22	+	+	+	?	+	+	+	−	+	−	−	−	−	+	−	−	+	−	+	+	−	+	−
Upturned nasal tip	19/23	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+
Thick alae nasi	22/22	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Broad nasal base	19/23	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Broad philtrum	21/23	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Long philtrum	20/23	+	+	−	(+)	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Large mouth	20/23	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Thin upper vermilion	19/23	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	−	+	+	+	+	+
Thick lower vermilion	22/23	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Widely spaced teeth	11/21	+	+	−	?	−	+	−	+	+	−	−	−	+	+	+	?	−	+	−	−	+	−	+
Trunc and limbs																								
Scoliosis	9/22	+	?	+	+	+	−	−	−	−	−	−	−	Minimal	+	−	−	−	−	+	+	−	−	+
Cryptorchidism	8/13	n.a.	+	n.a.	n.a.	n.a.	+	−	n.a.	+	+	n.a.	n.a.	+	−	+	−	+	−	n.a.	n.a	+	−	n.a.
Umbilical/inguinal hernia	6/23	−	+	−	−	−	−	−	−	+	−	−	−	+	−	+	−	−	−	−	−	+	+	−
Prominent IP joints	17/23	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	−	−	+	−	+	+	+
Prominent distal phalanges	15/22	+	+	+	+	?	+	+	−	−	+	+	+	+	+	+	+	−	+	−	−	−	−	+
Fetal finger pads	14/19	+	?	?	?	?	+	+	+ (Feet)	+ (Feet)	+	+	+	−	+	+	+	+	+	−	−	−	−	+
Sandal gap	12/20	−	+	?	−	?	−	+	+	+	+	+	+	+	−	−	−	+	−	+	+	−	−	+

Radiology																									
Bone age		Adv		Adv	?	?	?	Del	Del	Adv	Del	nl	?	?	Del (at 2 years)	n.a.	Del	Del	Adv	Del	?	nl	Del	nl	nl
Cone-shaped epiphyses	5/21	+		–	+	–	?	–	–	–	–	–	+	+	–	?	–	–	–	–	–	–	+	–	–
Short metacarpals/ metatarsals	14/23	+/+		+/+	+/?	+/?	–/–	+/–	–/–	+/–	–/–	+/–	–/–	–/–	–/–	+/+	+/–	+/–	+/–	–/–	+/+	+/–	–	–/–	–
Short phalanges	9/23	–		+	+	–	–	+	–	–	–	–	–	–	–	+	+	+	+	–	–	–	–	+	+ [Distal]
Other																									
Cardiac defect	2/23	–		–	–	–	–	–	[i]	–	–	[j]	–	–	–	–	–	–	–	–	–	–	–	–	–
Vesico-ureteral reflux	1/20	+		–	–	–	–	–	–	–	–	–	–	–	–	?	?	?	–	–	–	–	–	–	–
Poor mamma development	3/5	+		–	n.a.	+	?	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	–	n.a.	n.a.	n.a.
Eczema	8/23	+		–	–	–	–	+	–	+	+	+	–	–	–	–	–	–	+	+	–	–	–	–	+

[a]Twins counted as one patient here; [b]at present or when reported; [c]at time of birth; [d]mean values; [e]cases with severe mental retardation; [f]cases with absent speech; [g]speech lost later on; [h]just says one word; [i]persistent foramen ovale and mitral valve regur gitation; [j]double aortic arch; M, male; F, female; OFC, occipito-frontal circumference; IP, inter-phalangeal; Del, delayed bone age; Adv, advanced bone age; nl, normal; n.a., not applicable.

thick terminal phalanges (Fig. 3G). Knees were remarkably lax; feet showed short toes, thick halluces and fifth toes, and mildly shortened fourth metatarsals (Fig. 4G).

Conventional cytogenetic evaluation, multi-telomere FISH analysis, and CGH-microarray (1 Mb resolution) gave normal results. Plasma lipids were raised (total cholesterol 5.8 mmol/L [norm <5 mmol/L]; triglycerides 3.8 mmol/L [norm <3 mmol/L]). Liver and renal function tests, hormonal screening (luteinizing hormone; follicle stimulating hormone; 17-beta-oestradiol; prolactin; testosterone) gave normal results. Abdominal ultrasound confirmed hepatomegaly but was otherwise normal. Brain MRI at 29 years showed a small abnormal tangle of vessels in the frontal lobe. A full skeletal survey showed small neurocranium, limited calcification of the left choroid plexus and falx, large jaw, straight spine with loss of the physiological lumbar lordosis, mild platyspondyly, flat inter-vertebral discs, small pelvis, short femoral necks, broad distal radius, hands with small carpal bones, short metacarpals specially the fourth, over-modeled medial and distal finger phalanges, and feet with similar changes (Fig. 4E,F).

Follow-Up of Other Earlier Reported Patients

The Polish patient reported by Krajewska-Walasek et al. [1996] had died at the age of 25 years due to rupture of esophagus varices. The cause of the varices remained uncertain, no autopsy was performed [M. Krajewska-Walasek, personal communication, 2006]. The health of the two French patients reported by Morin et al. [2003] was excellent, without new physical problems, and without progression of existing signs and symptoms [Alain Verloes, unpublished work, 2008]. Also in the Belgian patient reported by Witters and Fryns [2003] general health was good, and no major new events had occurred since publication [Jean-Pierre Fryns, personal communication, 2008].

Previously Unreported Patients

Patient 1. Patient 1 was a 9-year-old British boy born after an uneventful pregnancy. He had a birth weight on the 75th centile and he stayed in the neonatal unit for 10 days because of poor movements. He had a somewhat delayed motor development and more marked delayed speech. At 2.5 years he was first evaluated: his height was at 25th centile, and he had microcephaly, reddish, but not sparse hair, eczema, and unusual face. It became clear that he had moderate mental retardation, very poor concentration, and some autistic features. He never had seizures, and general health was good.

He was re-evaluated at 6.10 years (Fig. 1G) and 9.4 years. He had wiry red hair (mildly sparse initially but almost normal at last evaluation), a frontal upsweep, slightly triangular face, decreased subcutaneous fat, high nasal bridge, mild hyperopia, upturned nasal tip, broad and shallow philtrum, wide mouth, and thick and everted lower vermilion. The distal phalanges of fingers and toes were broad, and fetal finger pads were evident (Fig. 3C). Height was at the 9th centile, weight on 50th centile, and he had microcephaly.

There were no cone-shaped epiphyses on X-rays of hands and feet, and no other major skeletal abnormalities. His MRI was normal, as were results of cardiac sonography, conventional cytogenetic studies, subtelomeric FISH and FISH 7q11.23

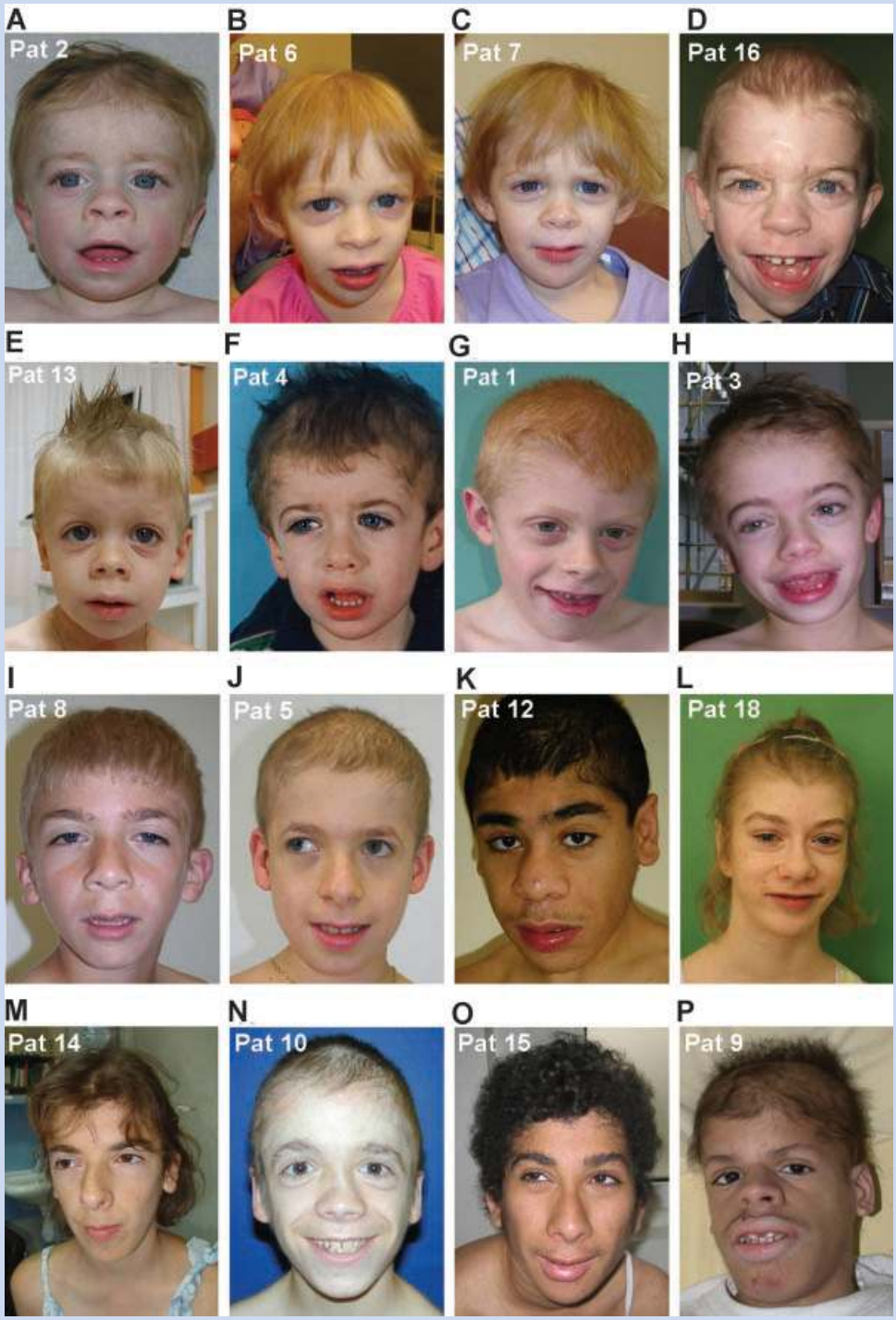

FIG. 1. Photo gallery of 16 patients with Nicolaides–Baraitser syndrome. Patients are arranged according to age. A: Patient 2 at 1.9 years; B: Patient 6 at 2.4 years; C: Patient 7 at 2.5 years; D: Patient 16 at 3 years; E: Patient 13 at 3.6 years; F: Patient 4 at 4 years; G: Patient 1 at 6.10 years; H: Patient 3 at 6.10 years; I: Patient 8 at 7 years; J: Patient 5 at 10 years; K: Patient 12 at 13 years; L: Patient 18 at 13 years; M: Patient 14 at 15 years; N: Patient 10 at 16 years; O: Patient 15 at 17 years; P: Patient 9 at 18 years. Remark the difficulty in evaluating the age and in some also gender based on facial features only.

locus, CGH-microarray (1 Mb resolution), screening for fragile X syndrome, urine aminoacids, organic acids, and glycosaminoglycans chromatographies.

Patient 2. This British boy had a low birth weight (at the 0.4th centile) but normal OFC (25th centile). He fed poorly and during his first year required several admissions for failure to thrive and feeding problems. His motor milestones were delayed, as was eruption of teeth (first tooth at 13 months). He had breath holding spells, and could have temper tantrums. No seizures were observed. At 1.9 years of age, his height was at 0.4th, weight below the 0.4th, and his head circumference at the 9th centile. He did not walk independently and had no speech. He had rather sparse hair, broad eyebrows, long eyelashes, and some fine hypertrichosis of face and neck. His face and limbs were otherwise very much like the other patients (Figs. 1A and 4A).

Cardiac sonography showed a small persistent foramen ovale, mildly thickened ventricular septum and trivial mitral regurgitation, renal ultrasound yielded normal anatomy. Skeletal survey at 13 months of age showed delayed ossification but otherwise normal bony appearances. Metabolic investigations (organic acids, plasma amino acids, lactate) gave normal results, except for a consistently abnormal acyl carnitine profile of doubtful significance (moderately raised levels of dimethylheptanoylcarnitine). Conventional chromosome studies and CGH-microarray (1 Mb resolution) also gave normal results.

Patient 3. This Northern Irish girl had intrauterine growth retardation (birth weight on the 0.4th–2nd centile and length on the 25–50th centile) and was noted at birth to have sparse hair with a low anterior hairline. The first months were marked by significant failure to thrive. Motor milestones were reached within normal limits but speech was significantly delayed. At 18 months she had a febrile convulsion and thereafter started to have seizure episodes.

At 2 years she was found to have a global developmental delay and marked lack of concentration. Facial features were characteristic (Fig. 2G), but fingers and toes were long and thin. Height was at the 2nd centile, and skull circumference at the 50th centile. She had seizures after the age of 1.6 years, using sodium valproate.

At 6.10 years she had no speech and still had very poor concentration. Parents described her as a happy child. She slept 11–12 hr per night. Height was at 10–25th, weight at the 3rd, and head circumference was at the 2nd centile. Her facial features and limbs were very similar to those in other patients (Fig. 2I,J), although fingers and toes were still long but did show somewhat thick and wide distal phalanges. There was generalized joint hypermobility. She disliked her fingers being moved. Parents reported periods of eczema, and in general a sensitive skin.

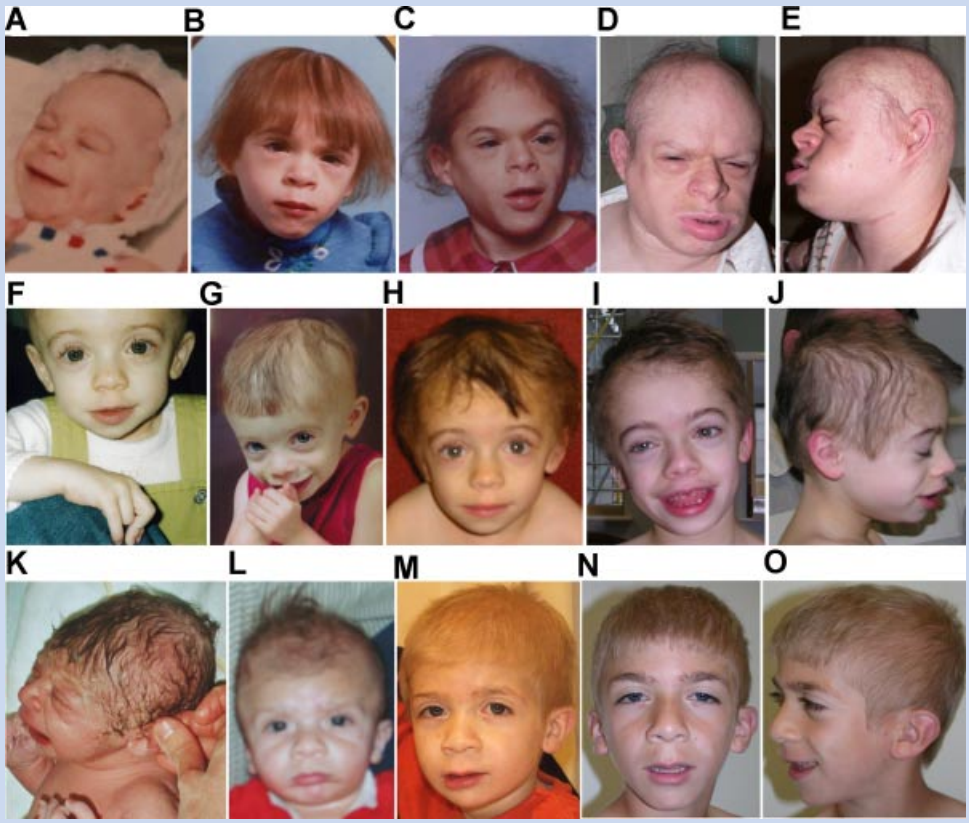

FIG. 2. Progression of facial features in Nicolaides–Baraitser syndrome. A–E: Original patient [Nicolaides and Baraitser, 1993] at 1 month (A), 6 years (B), 11 years (C), and 32 years (D,E) of age. Please note the broadening of the lower third of the face and the sparse air. F–J: Patient 3 at neonatal period (F), 2 years (G), 4 years (H), and 6.10 years (I,J). K,L: Patient 8 at birth (K), 1.6 years (L), 2.1 years (M), and 7 years (N,O).

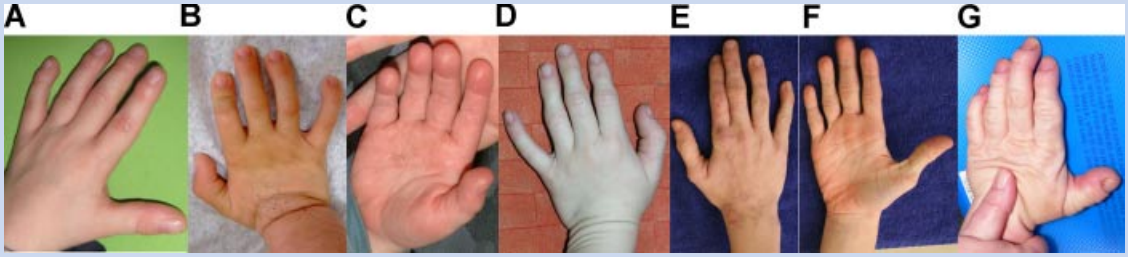

FIG. 3. Hands in Nicolaides–Baraitser syndrome. Patient 16 at 3 years (A), Patient 13 at 3.6 years (B), Patient 1 at 4.10 years (C), Patient 4 at 7.11 years (D), Patient 18 at 13 years (E,F) and original patient at 32 years (G). Please note the brachydactyly, prominent IP joints and distal phalanges, thickness of the distal tissues, fetal pads, multiple palmar and digital creases and wrinkled skin.

Urinary and plasma metabolic tests, hair microscopy, plasma cholesterol and triglyceride levels, CT scan of the brain, karyotype, MLPA for subtelomeric imbalances, and CGH-microarray analysis (1 Mb resolution) all yielded normal results. Hand X-rays showed ivory proximal epiphyses of the distal 2nd, 3rd, and 5th phalanges (Fig. 5B).

Patient 4. This British boy was born at term after an uneventful pregnancy, with a weight at the 9th centile, and length and skull circumference at the 0.4th–2nd centile. He was a poor feeder in infancy but did not require tube feeding. He was gradually noted to be globally delayed. From 14 months on he had had seizures. At 2.5 years he used no recognizable words, and all growth parameters were between the 2nd and 9th centiles. His scalp hair had become sparse, curly and of a very soft texture but he had slightly increased facial hair. He was found to have a right accessory nipple, umbilical and bilateral inguinal hernias, and some eczema, especially over the dorsum of the feet. At 7.11 years he was severely delayed, had no speech, and showed all features of NBS (Figs. 1F and 3D).

Investigations had included plasma and urinary metabolic studies including transferrins, lipid spectrum, biotinidase, copper and ceruloplasmin, C-peptide, and hair microscopy, karyotype, FISH for the 7q11.23 locus, and CGH-microarray studies (1 Mb resolution). All results were normal, as were echocardiography, MRI brain, and a skeletal survey. His bone age was delayed by 12 months when performed at a chronological age of 30 months.

Patient 5. This British boy had high birth weight and length (75th and 91st centiles, respectively). He developed stridor with apneic episodes, and was found to have a double aortic arch, which was repaired successfully at 4 months of age. Motor milestones were normal and he used his first words at 18 months. At 2.5 years he started having seizures, both absences and rigid tonic episodes. A few months thereafter he had a period of major seizures, and the EEG showed hypsarrythmia. Following this period there seemed to be a regression in his abilities, and he lost his speech. At 4 years he had significant developmental delay and autistic tendencies. Height was at the 3rd centile, and head circumference at the 75th centile. He had facial features similar to the other patients but in addition bilateral ptosis. His fingers were short but finger joints were normal. He had mild eczema.

At 12 years height and weight were further below the 3rd centile and head circumference had dropped to the 9th centile. He had very frequently seizures despite anti-epileptic treatment. He had severe retardation and had a very short attention span. Clinical features of face and limbs were very similar to those in other patients (Figs. 1J and 4D).

Conventional chromosome studies and fragile X testing gave normal results. Other investigations included liver and kidney

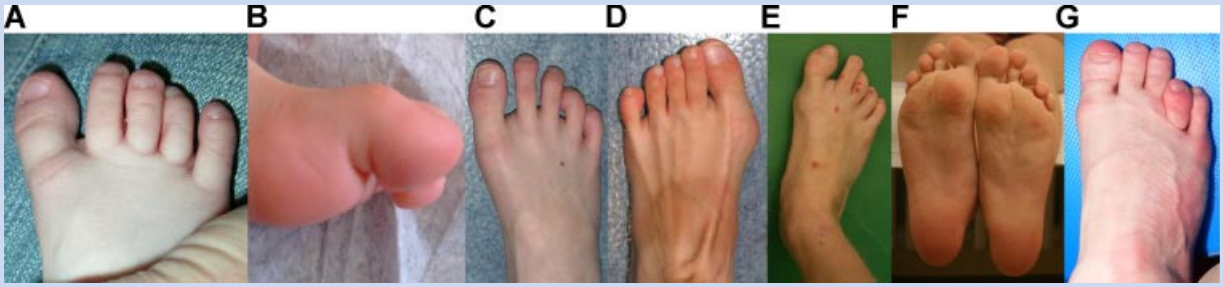

FIG. 4. Feet in Nicolaides–Baraitser syndrome. Patient 2 at 1.4 years (A), Patient 13 at 3.6 years (B), Patient 3 at 6.10 years (C), Patient 5 at 12 years (D), Patient 18 at 13 years (E,F) and original patient at 32 years (G). Please note the sandal gap, fetal pads, and thickness of the toes (especially the fifth toe).

function tests, thyroid hormone, biotinidase, isoelectric focusing of transferrin, plasma cholesterol and triglyceride levels, MRI of the brain, and electron microscopy of the hair, all without significant abnormalities. A skeletal survey showed ivory epiphyses of the distal 2nd and 5th phalanges of the fingers, and mild shortening of 4th and 5th metacarpal bones (Fig. 5C).

Patients 6 and 7 (Twins). Patients 6 and 7 are North American female monozygotic twins. During pregnancy hypertension developed and maternal alpha-fetoprotein levels were elevated. Amniocentesis showed a normal karyotype in both fetuses. At birth at 36 weeks weight was at the 9th centile in Patient 6 and below the 3rd centile in Patient 7. Initially both did well.

Patient 6 developed seizures and abnormal EEGs at 10 months. Motor milestones were reached normally, speech was delayed. At 2.4 years height was at the 2nd–9th centile, and head circumference below the 3rd centile. Facial and limb features were characteristic for NBS (Fig. 1B). In addition, she had downward slanted palpebral fissures. Cognitive development was considerably delayed and she used five words. At 3.6 years, her height and weight were at the 5–10th centile. Her head circumference was less than the 2nd centile. She was beginning to use 2–3 word sentences; however, most of her language was mimicking other individuals. There was little spontaneous speech.

Metabolic studies including lactate, pyruvate, plasma amino acids, and urine organic acids gave normal results. Creatine kinase levels were mildly elevated (284 U/L), and electromyography and nerve conduction studies showed no abnormalities. Sonography of heart and kidneys, hearing studies, CT scanning and MRI of the brain, conventional chromosome studies, and microarray studies (HapMap550Kv3) did not show abnormalities. X-rays of the hands showed cone-shaped epiphyses (Fig. 5A).

Patient 7 (Fig. 1C) did not develop seizures initially but otherwise clinical course, growth and development was identical to that in her twin sister. At 3 years she started having atonic seizures. At 3.6 years of age, she developed persistent seizures that were resistant to antiepileptic therapy. Her vocabulary consisted of about 50 words, and she was speaking in 2–3 word sentences with fairly good receptive language skills. Her overall development was more advanced than her twin sister. Her weight and height were at the 5–10th centile, and head circumference was below the 2nd centile. Similar additional studies including MRI of the brain and a microarray study (HapMap550Kv3) failed to show abnormalities. Zygosity testing confirmed monozygosity.

Patient 8. This Dutch boy was born with a normal birth weight (50th centile). He had mild feeding problems in the neonatal period, reached the motor milestones with mild delay but had more significant speech delay. Gradually height fell to the 2nd centile and skull circumference to the 10th centile. At the age of 9 months correction of a right sided inguinal hernia with orchidopexia was performed. He never had any seizures. At 2 years he was found to have mild developmental delay. His hair was wiry and sparsely implanted, and otherwise facial and limb features were very similar to the other patients (Fig. 2L,M). In addition he had a mild pectus excavatum, and four capillary hemangiomas. At 7 years he was moderately retarded, but with good concentration span and otherwise showed the classical phenotype at physical exam (Figs. 1I and 2N,O).

Extensive metabolic work-up including copper metabolism parameters, ophthalmologic exam, echocardiography, screening for *PTPN11* mutations, conventional chromosome studies and CGH-microarray (1 Mb resolution) showed no abnormalities. Skeletal X-rays showed a delayed bone age but otherwise were normal.

Patient 9. This boy was born at 39 weeks after an uneventful gestation, to nonconsanguineous Mauritanian/Moroccan parents whose family history was otherwise unremarkable and his five sibs were in good health. He had normal birth weight and length (2nd–9th centile) and OFC (25th). Inguinal hernia was treated surgically at age 6 months. He started to have tonic–clonic seizures at age 1 year. He was able to walk before the age of 2 years but his

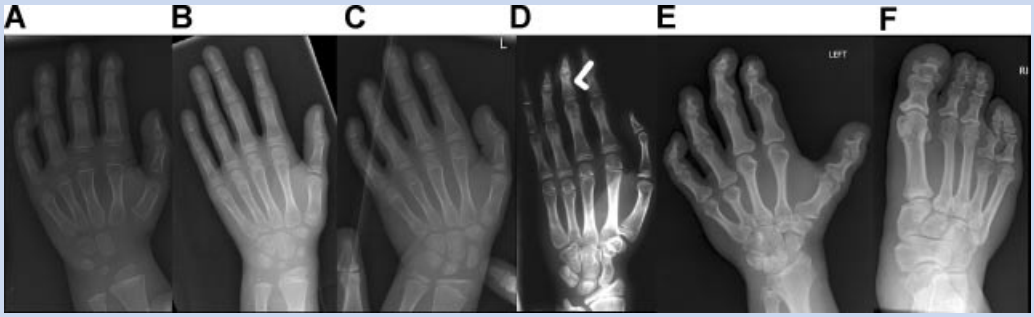

FIG. 5. Radiologic findings in Nicolaides–Baraitser syndrome. A: Left hand of Patient 6 at 2. 4 years. Please note generalized brachydactyly, slightly over-modeled metacarpals and mild cone-shaped epiphyses at medial phalanges; (B) left hand of Patient 3 at 6.10 years. Note normal length of the short tubular bones and ivory epiphyses at distal phalanges of the 2nd, 3rd, and 5th fingers; (C) left hand of Patient 5 at 12 years. Please note short and over-modeled metacarpals and phalanges, and ivory epiphyses at distal phalanges of 2nd and 5th fingers; (D) left hand of Patient 10 at 16 years. Note delayed bone age (corresponding to approximately 12 years), shortening of the 4th metacarpal, slightly over-modeled phalanges, ivory epiphyses, hypoplastic distal phalanges, and broad first metacarpal; (E) left hand and (F) right foot of the original patient at 32 years. Note striking over-modeled phalanges with signs related to previous cone-shaped epiphyses, brachydactyly, especially short 4th metacarpal and metatarsal bones, and broad distal radius with an exostosis.

psychomotor milestones were severely delayed: He never spoke, was totally dependent for basic cares, and he was not toilet trained. Progressive thoracolumbar scoliosis was diagnosed in late childhood, and finally surgically treated at age 20.

He was first evaluated in the genetic department when 18 years old. He had short stature and microcephaly (both at −4 SD). He had generalized amyotrophia predominating on the lower limbs and walked with difficulties. The face had a coarse appearance, with thick protruding vermilions and mild prognathism (Fig. 1P). Ears were small but normally folded. Hair was very sparse and slowly growing. Hands were short. Inter-phalangeal joints and large joints appeared enlarged but movements were not hampered. Skeletal survey did not show major changes. Formal IQ testing was not possible. His karyotype was normal, and CGH-microarray (44K oligo-array) failed to showed abnormalities.

Patient 10. This German boy is the first child of young healthy nonconsanguineous Caucasian parents. His birth weight was at −2.5 SD, length at −2.8 SD, and OFC at −2.0 SD. Inguinal hernias were surgically corrected at the age of 6 weeks, and umbilical hernia at 10 months. His motor development was retarded and his mental development severely delayed. He had no speech development and is not toilet trained. At age 19 months he developed grand mal seizures which were difficult to control and nearly resistant to pharmacotherapy.

Clinical examination at the age of 16 years showed typical NBS facial dysmorphisms (Fig. 1N) with sparse scalp hair but normal eyelashes and eyebrows, a low frontal hairline, a coarse triangular face with down-slanting palpebral fissures, a flat philtrum, a large mouth with thin upper and prominent lower vermilion, and low-set ears. He had short stature (−3.9 SD) and microcephaly (−2.1 SD). He had severe mental retardation and had no speech. He had cryptorchidism on the right side and had had a left orchidopexy. His hands and feet showed prominent joints with nontender, noninflammatory swelling, slightly large distal phalanges, and fetal finger pads. An X-ray of the left hand at the age of 16 years showed several anomalies (Fig. 5D) but no cone-shaped epiphyses.

Metabolic screening, thyroid hormone levels, CT and MRI of the brain and fundoscopy all gave normal results, as well as hair microscopy. Chromosome analysis, FISH subtelomeric screening and microarray analysis (250K SNP array) also gave normal results.

Patient 11. This boy was last seen at the age of 13 years. He is the second child of young healthy nonconsanguineous Caucasian parents. He was born at term with a birth weight at −3.6 SD, length at −3.3 SD, and OFC at −2.4 SD. His motor and mental development was retarded. At the age of 14 months he developed treatment resistant epilepsy. His growth pattern for length and OFC were continuously below the 3rd centile. Examination at the age of 3.5 years revealed a height at −2.1 SD, BMI below −2 SD and OFC at −3.4 SD. He had sparse scalp hair with a low frontal hairline but normal eyebrows and eyelashes. The face was coarse and triangular with down-slanting palpebral fissures, a short, upturned nose, a long, flat philtrum with a thin upper and prominent lower vermilion and a large mouth. Hands and feet showed prominent joints with noninflammatory swelling.

Clinical re-evaluation at the age of 13 years showed short stature (−4.7 SD) and microcephaly (OFC at −3.3 SD). The phenotype was marked by the dystrophy, the sparse hair, coarse face with typical NBS characteristics and severe mental retardation with epilepsy and absent speech.

A CT scan of the brain showed a large cisterna magna but no other abnormality. An X-ray of the left hand at the age of 12.5 years revealed a retarded bone age, brachydactyly and condensed/ivory epiphyses of middle and distal phalanges. Metabolic screening and chromosome analysis were normal.

Patient 12. This Turkish patient was found to have increased nuchal thickness prenatally. At birth hypospadias and unilateral cryptorchidism were noted. There were no neonatal problems, early motor milestones were normal. He used his first words at 10 months. At this age, he had a febrile convulsion and thereafter continued to have regularly seizures. His cognitive development declined and he lost speech. At 13 years he was severely retarded, had no speech, and was not toilet trained. He had autistic features in his behavior, and could show aggression towards himself and others. Despite the anti-epileptic treatment he had four to five tonic–clonic seizures per day. He was asthmatic and suffered from eczema and constipation. Height was at 0.4th–2nd centile and skull circumference at the 25th centile. He had sparse scalp hair, some secondary hair on face and trunk and no signs of puberty. His facial appearance resembled those of other patients, although his ethnic background made it somewhat less obvious (Fig. 1K). The feet were also typical but the hands showed only mild prominence of the inter-phalangeal joints and distal phalanges.

Biochemical investigations including biotinidase levels, very long chain fatty acids, plasma and urine amino acids, urine organic acids, urine glycosaminoglycans, white cells enzymes, isoelectric focusing of transferrin, liver and kidney function tests, plasma ammonia and lactate, yielded normal results. A brain MRI showed the left lateral ventricle to be larger than the right, without other anomalies. X-rays showed a normal spine, short metacarpals, and no cone-shaped epiphyses. Conventional chromosome analysis, testing for fragile X and CGH-microarray analysis (resolution 1 Mb) gave normal results.

Patient 13. This boy is the only child of young nonconsanguineous Swiss parents. He was born at 38 weeks after an unremarkable pregnancy. Intrauterine growth retardation was noted at birth (weight at 2nd–9th and length at 0.4th–2nd centiles). Postnatal growth for all parameters remained below the 3rd centile. Major feeding problems started at 4–5 months of age, with a very poor appetite and selective food habits. Gross motor development was in the normal range, but receptive and expressive speech were severely delayed. The boy was stated to have been able to say three words at 2.5 years, but at 3.9 years he only spoke one word. He was very active, most of the time happy and hypersociable, being able to go away with completely strangers. On the other hand, he also had a tendency to be at times in his own world. Hyperacusis had been noted since infancy. Severe generalized atopic dermatitis was present since age 7 months. Hair growth was initially normal, but has slowed down in the recent past months. Hair texture had become finer with time.

At examination at 45 months, main findings were growth retardation (−4.2 SD) and microcephaly (−2.8 SD), severe eczema, characteristic facial phenotype (Fig. 1E), absent speech, fine sparse hair, macrostomia, broad terminal phalanges with fetal pads of

finger and toes (Figs. 3B and 4B) and excessive palm skin. His behavior was reminiscent of Williams syndrome.

Blood karyotype, array-CGH (Agilent 244K, approximately 80 kb resolution), serum calcium, cholesterol, triglycerides, heart and abdominal ultrasound scans, as well as a skeletal survey did not show any abnormality, except a delayed bone age.

Patient 14. This French girl was born after an uneventful pregnancy, with a birth weight and length at the 10th centile and head circumference at the 5th centile. Already at birth somewhat sparse hair was noted, otherwise the neonatal period was uneventful. She had a moderate delay in reaching the motor milestones, but speech impairment was more marked. Her growth continued to be along the 10th centile, and her skull gradually became microcephalic. From 2 years on she started to have seizures. She developed several behavioral traits fitting autism. At 14 years she received therapy with finasteride (a 5 alpha-reductase inhibitor) to increase hair growth, which was successful. At 15 years she had height at the 9th centile, microcephaly (<3rd centile), only limited sparseness of her hair, but otherwise the typical facial and limb characteristics of NBS (Fig. 1M). The lack of subcutaneous fat tissue was marked, also in the limbs. She had secondary pubic hair, poor mammary development, and no menses.

Additional investigations included liver and kidney function tests, plasma cholesterol and triglyceride levels, immunological studies, urinary excretion of amino acids, hair microscopy, extensive hormonal studies (thyroid hormone, testosterone, estradiol, androstedione, LH, FSH, prolactine, cortisol), ophthalmologic exam, cardiac sonography, and brain MRI. The latter showed decrease bulk of white matter; otherwise the studies gave normal results. Conventional chromosome analysis showed a normal female karyotype.

Patient 15. This Moroccan patient was born with a low birth weight and length (2nd–9th) and OFC (25th centile). The neonatal period was uneventful but after 1 year of age she gradually developed feeding difficulties. Motor milestones were reached just outside normal limits, speech was more severely delayed. At 18 months she started to have generalized tonic–clonic seizures. Already during infancy she was stated to have sparse hair and an unusual face. She also developed a scoliosis in early childhood.

At 16 years she was a moderately to severely delayed adolescent with significant behavior problems, mainly autistic traits and periods of aggression. She spoke in short phrases. Growth parameters were normal (25–50th centile). She had sparse hair that had become less expressed with time according to mother, and she had also secondary facial hair (Fig. 1O). Hair distribution elsewhere was normal. She had normal mammary development and regular menses. She resembled other patients with NBS, although probably due to her ethnic background somewhat less typical. She did not have broadness of the lower 1/3 of the face and she had myopia. She had a significant dorso-lumbar scoliosis and a hypopigmented abdominal skin patch. Her fingers were not short and showed no increase of soft tissues at the distal phalanx, nor were there prominent joints, but she had shortened 4th and 5th metacarpal bones. Her feet were flat, she had sandal gaps and thin, striated nails of the halluces.

X-rays showed the short 4th and 5th metacarpals, scoliosis and flat inter-vertebral disks, and short femoral necks. Other additional investigations, all normal, included conventional cytogenetic analysis, CGH-microarray (1 Mb resolution), brain MRI, plasma ammonia, lactate, redox studies, urinary organic acid chromatography, isoelectric focusing of transferrin, and hair microscopy and metabolic hair studies.

Patient 16. Patient 16 was the second child to nonconsanguineous Caucasian British parents, with negative family history. Asymmetric intrauterine growth restriction was diagnosed on ultrasound scan at 35 weeks gestation. His birth weight at 38 weeks gestation was at the 0.4th centile and his head circumference at the 50th centile. Undescended testes, hypertrichosis and an umbilical hernia were noted at birth. He was a slow feeder who took small volumes and this resulted in a pediatric referral at 3 months. At 4 months he had an inguinal hernia repair and unilateral orchidopexy with a second orchidopexy at $2^1/_2$ years. He presented with tonic seizures associated with apnea at 13 months of age and was found to have an abnormal EEG with continuous bilateral slow wave activity and occasional high amplitude bilateral sharp waves. A brain MRI was within normal limits. Seizures were initially difficult to treat but good control was achieved with increasing doses of sodium valproate and clobazam.

He was first seen at 19 months of age. He was able to sit but was not yet walking or pulling to stand. He had a social smile but no speech or babble. His weight was just below the 0.4th centile, his height was on the 2nd centile, and head circumference was on the 2nd centile. He had low, straight eyebrows, blue eyes, long eyelashes, slight synophrys, a low frontal hairline, and a long philtrum. There were deep palmar creases, slightly broad thumbs, and bulbous finger tips with slight swelling of the distal inter-phalangeal (DIP) joints. There was also some hair on his back. Investigations including chromosomes, FISH for 1p telomere deletion and Williams syndrome ophthalmic assessment and metabolic studies (urine GAGs, thyroid function, organic acids, and amino acids) were normal. A skeletal survey showed cone-shaped epiphyses in the proximal phalanx of the 3rd and delayed bone age (at 29 months of chronological age, bone age of 15–20 months).

On review at 3 years, there had been a coarsening of his facial appearance and his scalp hair was sparser although it needed to be cut regularly (Fig. 1D). His head circumference was between the 2nd–9th centile while his height and weight were below the 0.4th centile. The swelling of his DIP joints was more obvious (Fig. 3A), and he continued to have deep palmar creases. He was noticed to have a high threshold for pain. There was no evidence of a scoliosis. He still had no speech but did have limited understanding. He was active with a short attention span. His epilepsy was under good control.

Patient 17. This boy is the third child of healthy unrelated parents originating form Bangladesh. His older siblings are healthy. He was born at term after an uneventful pregnancy. He had an umbilical hernia at birth. He developed seizures at 7 months of age which were initially thought to be due to sleep apnoea, but persisted after tonsillectomy and adenoidectomy. He was delayed in all his early motor milestones. Since improved seizure control his developmental progress seemed improved.

His growth parameters have remained small with OFC below the 0.4th centile and height on the 2nd centile. At 4 years of age he has sparse hair, a low anterior hairline, long eyelashes, arched eyebrows, long palpebral fissures, and a triangular face. He has a thin upper

vermilion and full lower vermilion. He has generalized joint laxity, bilateral single palmar creased and has long slender fingers with mildly prominent inter-phalangeal joints. Hand X-ray did not demonstrate cone-shaped epiphyses.

Metabolic investigations including lactate, very long chain fatty acids and biotinidase were normal, as were karyotype, telomere testing, and fragile X. Permission to publish photographs was not obtained.

Patient 18. She was the first child of nonconsanguineous German parents. She was born at term after an uneventful pregnancy with normal birth growth parameters. Already during infancy she was started to have atopic dermatitis. Her motor milestones and speech were delayed, but she learned to speak in short sentences. She developed progressive scoliosis in late childhood. She never had any seizures. Behavior abnormalities became more pronounced with age and were characterized by hyperactivity and trichotillomania.

At physical examination at age of 13 years height was at the 25–50th centile and OFC at the 10–25th centile. She had sparse hair, heavy eyebrows, broad nasal tip, a flat philtrum, full lower vermilion, long appearing fingers with broadened tips in all directions, prominence of inter-phalangeal joints, unilateral clinodactyly of the fifth finger, broad halluces, mild hypertrichosis of the face and back, and severe eczema (Figs. 1L, 3E,F, and 4E,F). Brain MRI and EEG gave normal results. An X-ray of the left hand at age of 4 years showed a hypoplastic distal phalanx V. Ophthalmologic examination, cardiac and renal ultrasound examinations showed no abnormalities. Metabolic screening, chromosome analysis, and array-CGH analysis (244K oligonucleotide array, Agilent, 70–100 kb resolution) yielded no abnormalities.

DISCUSSION

The pertinent clinical data of all earlier reported and presently described patients with NBS are presented in Table I. At present there is no "gold standard" for NBS, so the diagnosis has to be based on the experience with the phenotype. The major features are summarized in Table II and described below in more detail.

Growth

Ten of 22 NBS patients had low birth weight at birth. Thirteen of 23 patients have short stature, being of prenatal onset in at least 7 patients. Growth less than the 50th centile occurs all patients. There is no evident disproportion. Microcephaly of variable degree is found at birth in 5/14 patients but later on in 19/23 cases.

Face

The facial features may be subtle in younger patients, and at that age show resemblance to Williams syndrome. Indeed, four patients have been tested for this entity. There is evident progression of the phenotype and coarsening of the facial traits with age. We have been struck by the difficulty to estimate the patient's age by just looking at the face (Fig. 1).

The face is typically triangular. Palpebral fissures have a normal width, tend to be narrow, and may show some downward slanting. Eyelashes are frequently dense and prominent. The nose has a narrow bridge, the nasal ridge broadens inferiorly somewhat, and the tip has a normal width and is upturned. The nasal base is broad, the nares thick and anteverted. The philtrum is broad and usually long, the upper lip over the premaxilla tends to project anteriorly. The upper vermilion is relatively thin, the lower vermilion is thick and everted. The mouth tends to be wide. With time skin under the orbits becomes grooved and sagging (Fig. 2). There can also be wrinkled skin at the cheeks, especially when smiling. A few individuals showed wrinkled skin at the neck as well. In the course of time, a broadening of the lower third of the face develops, especially at the angle of the mandible. The neck may become broad too.

TABLE II. Major Features of Nicolaides–Baraitser Syndrome

Mild prenatal growth retardation
Mild postnatal growth retardation
Severe developmental delay
Severely impaired speech
Seizures
Microcephaly
Sparse hair
Progressive skin wrinkling
Thick, anteverted alae nasi
Long and broad philtrum
Large mouth
Thin upper and thick lower vermilion
Progressive prominence of distal phalanges
Progressive prominence of inter-phalangeal joints
Short metacarpals–metatarsals

Hair

Sparseness of the scalp hair can be regarded as one of the major features of NBS. At birth, the patients are noted to have a low anterior hairline with facial hypertrichosis, especially over the temples. With time, this feature may decrease but can also persist. Sparse scalp hair (with normal texture) is usually already noted in the neonatal period and is progressive, especially in the second decade. Growth rate itself seems normal, only quantity decreases. Adults have very limited hair. This is not a constant feature. The sparseness of hair may be quite mild and may even improve with time. In four patients hair color is red. Hair microscopy was done in eight patients and results was normal or without significant abnormalities. The eyebrows and lashes are normal at first. Eyebrows may decrease to some extent, eyelashes remain almost always prominent. Pubic hair develops normally.

Skin

The skin is frequently noted to be pale and sensitive. Subcutaneous veins are easily seen, probably related to poor subcutaneous fat tissue observed mainly at face and limbs and which may be progressive with age. The wrinkling of the skin in the face can also be present in the distal limbs and sometimes in the neck. Eczema is

present in eight patients and it tends to be severe. In one patient hypohidrosis was noted. Adult females have poor mammary development. One patient had an extra nipple. Teeth and nails do not show unusual features.

Limbs and Joints

Initially, clinical findings in the hands and feet may be subtle. Gradually distal phalanges become broader in all directions. Fetal pads can also be present. The most typical feature is the development of prominent inter-phalangeal joint swellings. At first these seem symptomless but some older individuals dislike passive movements of their fingers. The feet show sandal gaps and progressive thickening of the distal toe tissues is less pronounced but still similar to that found in the fingers, especially at the 5th toe.

X-rays show cone-shaped epiphyses only infrequently (5/21). Phalanges can be over-modeled or show metaphyseal flaring. Short phalanges, metacarpals, or metatarsals are frequent, especially of the 4th and 5th ray. Bone age is variable, and is found to be either normal (4/16), delayed (8/16), or advanced (4/16).

Some patients also have prominent large joints, especially the knees. With time, lower limbs may become amyotrophic. Scoliosis is present in a few patients. X-rays show mild platyspondyly and flat inter-vertebral discs. Furthermore, a small pelvis, pubic bone hypoplasia, small femoral heads and short femoral necks can be seen infrequently.

Other Physical Features

Cryptorchidism is present in most males. Cardiac problems (double aortic arch; mitral valve regurgitation; thick ventricular septum; small persistent foramen) are found infrequently. Other infrequent findings are vesico-ureteric reflux, mild dyslipidemia, abnormal carnitine profile, and umbilical and inguinal hernias.

Development and Behavior

All patients follow a delayed development which is usually severely delayed but sometimes it is less delayed. Especially language is highly impaired. Several patients never develop any speech. Three patients lost their speech in the course of time. Major motor milestones can be acquired within normal limits or be delayed, but usually not very delayed.

Many patients are described by their parents as being happy and generally very friendly. Some patients, however, develop also temper tantrums and periods of aggression. Frequently, patients have features known to occur in autism, although in none of the here described patients this diagnosis was formally made. Other features noted in some patients include short attention span and high threshold for pain. In older individuals slowing down of movements has been reported by parents.

Epilepsy

The majority of patients (16/23) have epilepsy. Seizure type is variable, even within a single individual. Seizures start in average around 1.6 years, not uncommonly progressively get worse, and require multiple anti-epileptic drugs, often with limited effects. In some patients there seems to be a coincidence of the deterioration of mental abilities with the occurrence of seizures. However, in the affected identical twins described here, in one a cognitive decline co-occurred with the start of seizures, while in the other the same decline occurred but seizures only started 2 years later. This suggests that a single process causing the deterioration of cognitive abilities can also be responsible for the seizures, but not a causal relation with the seizures themselves. EEGs are usually not significantly abnormal, and no specific abnormalities are known to be present.

Differential Diagnosis

If the typical Nicolaides–Baraitser phenotype is present in an individual, the phenotype is relatively easy to recognize from childhood on and differentiation from other entities should not provide problems. In patients with atypical phenotypes several other conditions should be considered [Gorlin et al., 2001].

Coffin–Siris syndrome is characterized by mental retardation, sparse hair, coarse facial features, growth restriction and epilepsy, which can be similar to NBS. Coffin–Siris syndrome differs in the presence of severely hypoplastic or absent fifth finger nails with or without hypoplasia of the terminal phalanges, the absence of the swelling of the finger joints, short metacarpals and broad terminal phalanges, and internal organ malformations are more common. Facial features can be very similar, however, especially at a young age, and we have encountered a patient with a phenotype which shows considerable overlap and whom we could classify as Coffin–Siris syndrome only after very careful evaluation (Fig. 6).

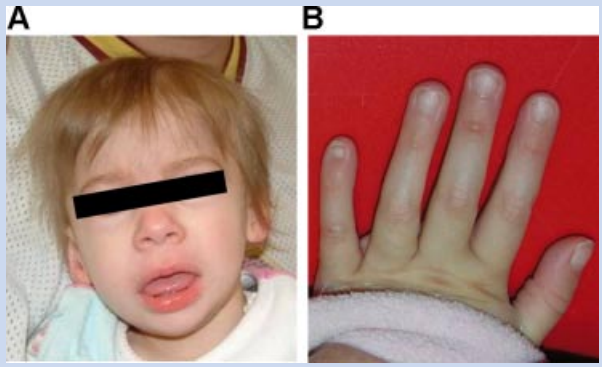

FIG. 6. Example of a difficult to classify patient (not included in the described cohort). Patient has features of both Nicolaides–Baraitser syndrome (NBS) and Coffin–Siris syndrome (CSS). The girl, aged 2 years, had moderate to severe developmental delay, no speech, post-natal growth retardation and microcephaly, failure to thrive necessitating a gastrostomy. Facial and hair characteristics resemble NBS although not completely classical (A). She had marked joint hypermobility and a hypoplasic left fifth finger nail fitting CCS (B). There was no brachydactyly. We made the probable diagnosis of CSS but admit the overlap with NBS.

The two sibs with sparse hair, unusual facial appearance and mental retardation described by Dennis and Cohen [1980] have some features of NBS and have been considered a mild form NBS [Morin et al., 2003]. However, facial features are different, the developmental delay is less, the sparseness of the hair did not increase but decreased with age and other features such as short stature, microcephaly or typical hand and feet anomalies were absent. In our opinion these sibs have a different entity.

Other overlapping conditions are biotinidase deficiency, the (micro)deletion 2q37 and, to a lesser extend, trichothiodystrophy. In all additional investigations will allow exclusion. In Cornelia de Lange syndrome there can be overlapping features such as the severe mental retardation, the facial hypertrichosis, the upturned nose with anteverted nares, the long philtrum, the relatively thin upper vermilion and the growth restriction, but the marked prenatal growth retardation and microcephaly, eyebrows, nasal bridge, shape of the lower vermilion, skin, and ulnar defects, and the difference in clinical course should allow easy differentiation. As already stated, some facial and behavior features may evoke Williams syndrome, especially at younger ages. Other entities that show resemblances have been discussed elsewhere [Nicolaides and Baraitser, 1993].

Etiology

Etiology of NBS remains unknown. It is described in persons with different ethnic backgrounds (the present 23 patients are from 13 nations and 4 continents). There is no significant difference in occurrence in males and females (M/F = 13:9 [identical twins counted as a single patient]), no familial cases are known except the present (molecularly proven) monozygotic twins, and parental consanguinity has not been reported. Mean paternal age (30.2 years; n = 20) is not increased. Chromosome analysis has shown a normal karyotype in all patients, and microarray analysis gave normal results in 14 patients. In our opinion NBS is likely to be either caused by a (very) small microrearrangement, or by a heterozygous dominant de novo mutation in a single gene. Recurrence risk seems to be (very) low. As long as the cause of NBS remains unknown it will remain difficult to estimate the full spectrum of this entity and to diagnose patients with milder phenotypes.

CONCLUSION

The present study confirms NBS as a distinct entity but with some variability in signs and symptoms. There is evidence of a continuum in the phenotype and a division in a classical/severe and atypical/mild phenotype, as proposed by Morin et al. [2003], was not well possible. The long-term follow-up of the original patient provides precious data for our understanding of the natural history of the condition. Recurrence risk is low. NBS has been considered a very rare condition, but the present series gathered over a short period of time may indicate it to be markedly underdiagnosed. The detailed phenotype analysis may hopefully help in recognizing further patients, and stimulate a search for the cause.

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