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Thirteen Cases of Niikawa-Kuroki Syndrome: Report and Review With Emphasis on Medical Complications and Preventive Management

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Eight new and five previously illustrated patients with Niikawa-Kuroki syndrome (NKS) are compared to those in the literature, providing data on 183 cases. Eight patients had disproportionate microcephaly and in one autopsied patient there was frontal lobe atrophy, focal polymicrogyria, and a hypoplastic fourth ventricle. The metacarpophalangeal pattern profiles of three Caucasian patients with NKS were similar to that of a prior case report, but those of two Hispanic patients were more variable. NKS was eliminated by follow-up in nine suspect cases, highlighting the diagnostic value of findings such as arched eyebrows, long palpebral fissures, flat nasal tip, and prominent finger pads. One patient suspected of having NKS had a very different metacarpophalangeal pattern profile, supporting its diagnostic utility in selected cases. Higher frequencies of neonatal complications, abnormal dentition, hypotonia, and microcephaly were noted in non-Asian patients with NKS, while a higher frequency of skeletal anomalies was seen in Japanese patients. Complications affecting cognitive, visual, hearing, cardiac, renal, skeletal, immune, and endocrinologic functions are translated into a program for preventive management. X chromosome anomalies are the most compelling of diverse genetic changes seen in NKS, and this report adds another case to several possible instances of vertical transmission. The 108 non-Asian patients now reported emphasize the worldwide significance of NKS recognition. Am. J. Med. Genet. 79:112–120, 1998.

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INTRODUCTION

Following the description of a characteristic multiple congenital anomaly–mental retardation (MCA/MR) syndrome in ten unrelated Japanese children [Niikawa et al., 1981; Kuroki et al., 1981], the Niikawa-Kuroki syndrome (NKS) was thoroughly delineated in Japan with an estimated incidence of 1 in 32,000 infants [Niikawa et al., 1988]. The major findings summarized by Niikawa et al. [1988] include a characteristic face that was likened to a Kabuki theater mask, postnatal growth delay with short stature, mild to moderate mental retardation, dermatoglyphic abnormalities with frequent ulnar loops and prominent finger pads, and skeletal anomalies including scoliosis, vertebral anomalies, and congenital hip dislocation. The description of a South American girl by Koutros and Fisher [1982] led to recognition of NKS in occidental populations [e.g., Meinecke and Rodewald, 1989; Clarke and Hall, 1991; Philip et al., 1992; Schrander-Stumpel et al., 1994; Burke and Jones, 1995] with an increased appreciation of joint laxity, cardiac lesions, and urogenital anomalies. Here eight new and five previously illustrated patients with NKS are described, including one with sudden death and neuropathological studies. Preventive management guidelines are suggested for NKS based on the spectrum of complications in 183 patients.

CLINICAL REPORTS

The clinical data from 13 patients with NKS are summarized in Tables I and II; facial photographs are illustrated in Figure 1 (cases 1–8) or in a previous report (cases 9–13)[Schrander-Stumpel et al., 1994]. Results of routine chromosome studies were normal in all cases, and family histories were unremarkable unless explicitly mentioned (see cases 11 and 12).

Case 1 (Fig. 1A) is a Hispanic boy who was referred for evaluation of growth and developmental delay. He weighed 3,500 g after a 39-week gestation complicated

TABLE I. Physical Measurements and Parental Ages

	Patient													
	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean
Age (years)	3.75	2.25	6.50	0.58	2.17	1.80	4.00	10.0	1.10	1.10	1.65	9.00	5.50	3.80
Height (cm)	96	83	89	65	73	70	91	129	68	68	80	124	99	
Height age/age[a]	0.87	0.67	0.34	0.57	0.38	0.43	0.63	0.85	0.54	0.54	0.82	0.83	0.73	0.63
Weight (kg)	51.0	12.6	10.2	8.0	7.8	6.8	13.6	70.2	6.6	6.0	10.1	26.5	19.5	
Weight age/age	0.99	0.95	0.15	0.88	0.23	0.24	0.70	1.00	0.38	0.31	0.58	0.94	1.13	0.65
OFC (cm)	47.0	47.0	45.0	42.0	45.0	40.0	47.0	53.5	43.5	44.0	47.5	50.0	51.0	
OFC age/age	0.29	0.33	0.10	0.64	0.31	0.19	0.31	0.95	0.60	0.77	0.68	0.22	1.00	0.49
Mean PFL (mm)[b]	25	24	25	25	26	23	26	29	24	25	23	27	28	
PFL age/age	1.00	0.98	0.94	1.19	1.06	0.94	1.00	1.07	1.04	1.09	0.96	1.02	1.08	1.03
Developmental level	1.33	0.75	1.00	0.33	0.75	0.40	0.83	6.00	0.67	0.67	1.33	4.10	3.60	
Developmental	0.35	0.33	0.15	0.57	0.35	0.22	0.21	0.60	0.61	0.61	0.81	0.46	0.65	0.46
Maternal age (years)	27	36	18	32	17	20	28	35	27	27	21	22	28	26.0
Paternal age (years)	31	36	19	41	27	19	34	40	38	34	21	21	29	30.0

[a]Height age/age, age which is 50th centile/chronologic age.
[b]PFL, palpebral fissure length.

by diabetes mellitus in the last trimester. Neonatal problems included trigonocephaly with a prominent metopic ridge, hypotonia that necessitated gavage feeding, and jaundice treated with phototherapy. Results of laboratory studies on peripheral blood included normal chromosomes, ammonia, amino acids, acylcarnitine profile, and pyruvate. The venous lactate was mildly elevated (3.9 mmol/liter at age 6 months, upper limit 1.3) and calcium was low at 6.8 mg/dl, but both were normal at age 6 months. A head CT scan demonstrated hypotelorism and craniosynostosis of the metopic and sagittal sutures with normal brain and ventricles. Anomalies mentioned in the nursery records included microcephaly, trigonocephaly, bitemporal hollowing, parietal hemangiomas, receding forehead, prominent heels, broad space between the first and second toes, small testes with micropenis (1.5 cm), and a sacral dimple. After surgical correction of the craniosynostosis, the patient did well with improved growth and few illnesses. Physical examination at age 3 years 9 months (Tables I and II) showed mild spasticity with increased deep tendon reflexes, pectus excavatum, micropenis, and cryptorchidism.

Case 2 (Fig. 1B) is a Hispanic boy referred for evaluation of an unusual appearance with developmental and growth delay. He weighed 4,200 g after a term gestation complicated by bladder surgery at 7 months and gestational diabetes during the last trimester. After a nursery stay of 2 weeks because of pneumonia, jaundice, and poor feeding, he was healthy with normal hearing and vision screening results. Physical findings at age 19 months (Tables I and II) included cryptorchidism. Results of audiologic screening and cardiac and renal sonography were normal.

Case 3 (Fig. 1C) is a Hispanic boy referred for evaluation of growth and developmental delay. He weighed 2,800 g after a term uncomplicated gestation. Neonatal problems included poor feeding with gastroesophageal reflux. He had strabismus requiring surgery and chronic otitis with bilateral conductive hearing loss. Physical findings were documented at age 6 years and 3 months (Tables I and II) and had the anomalies listed in Table I. A TSH level was borderline low (0.42 m.i.u./ml; 0.49–5.66 normal), but the T4 (7.9 μg/ml) was normal. He had behavior problems including hyperactivity and self-stimulation.

Case 4 (Fig. 1D) is a Caucasian boy referred for evaluation of an unusual appearance with developmental delay. He weighed 3,390 g after a term gestation complicated by early hormonal treatment, valproic acid therapy, gestational diabetes in the last trimester, and late polyhydramnios. His mother had a normal son and four spontaneous abortions; two were with his father. Neonatal problems included tachypnea, poor feeding requiring gavage, and a patent ductus arteriosus and ventricular septal defect that resolved without surgery. Subsequent development and growth were delayed, and he had one hospitalization for fever. Physical findings at age 7 months (Tables I and II) included hypoplastic fingernails.

Case 5 (Fig. 1G) is a Caucasian boy referred for evaluation of growth and developmental delay. He weighed 2,450 g after a term, dizygous twin gestation with no problems. A nursery stay of 4 days was required because of initial hypoglycemia, cleft palate, and poor feeding. He had one episode of pneumonia and chronic otitis that required myringotomy tubes before cleft palate repair at age 14 months. Physical findings at age 26 months included a cleft soft palate. At age 27 months, the patient was found unresponsive in bed and died during transport to the hospital. The autopsy report noted blue sclerae, flat nasal tip, sacral dimple, enlarged right atrium and ventricle with right ventricular hypertrophy, and a horseshoe kidney. Neuropathology showed foreshortened frontal lobes, redundant gyration in the inferior frontal and lateral temporal lobes, and an enlarged fourth ventricle. The organic acids were abnormal with elevated 4-hydroxy-phenyllactate and 4-hydroxy-phenyl-pyruvate consistent with hepatic dysfunction; there was a modest elevation of urinary glutaric acid. The cause of death was pneumonia.

Case 6 (Fig. 1E) is a Caucasian girl referred for evaluation of growth failure and developmental delay. She weighed 3,300 g after a 38-week gestation and was born to a mother who had juvenile diabetes mellitus since age 15. A fetal ultrasound at 5 months gestation showed cardiac septal defects, and amniocentesis dur-

TABLE II. Manifestations of Patients With NKS*

	1	2	3	4	5	6	7	8	9	10	11	12	13	NKS	Not NKS	Asian	Non-Asian	All NKS (%)
General																		
Female sex	–	–	–	–	–	+	+	–	+	+	–	–	+	5/13	5/9	40/75	44/95	89/183 (49)
Low birth weight	–	–	–	–	–	–	–	–	–	–	–	–	–	0/13	4/9		4/21	4/34 (12)
Neonatal problems	+	+	+	+	+	+	+	+	+	+	–	+	–	11/13	3/9	13/65	*38/77*	62/155 (40)
Short stature	–	+	+	+	+	+	+	–	+	+	–	–	+	9/13	6/9	57/75	71/95	137/183 (75)
Frequent infections	–	–	+	–	+	+	+	+	+	–	–	+	+	8/13	3/9	31/57	43/67	82/137 (60)
Facial																		
Arched eyebrows	+	+	+	–	+	+	–	+	+	–	–	+	+	9/13	*1/9*	52/64	74/87	135/164 (82)
Ptosis	+	+	+	+	+	+	+	+	–	+	+	+	+	12/13	*2/9*		4/34	16/47 (34)
Long palpebral fissures	+	+	+	+	+	+	+	+	+	+	–	+	+	12/13	*4/9*	73/74	93/94	178/181 (99)
Blue sclerae	+	+	–	–	+	–	+	–	+	–	–	–	+	6/13	5/9	14/55	18/62	38/130 (29)
Everted lower eyelid	+	+	+	–	+	+	–	+	+	+	+	–	+	10/13	4/9	70/71	*79/91*	159/175 (91)
Strabismus	–	–	+	–	–	–	+	+	–	–	–	–	–	3/13	0/9	22/68	14/37	39/118 (33)
Broad nasal root	+	+	–	+	+	+	+	+	+	+	–	+	+	11/13	5/9		3/86	14/99 (14)
Flat nasal tip	+	+	+	+	+	+	+	+	+	+	–	+	+	12/13	*4/9*	53/69	58/76	123/158 (78)
Large ears	+	+	+	+	+	+	+	–	+	+	+	+	+	12/13	7/9	46/61	80/94	138/168 (82)
High/cleft palate	–	–	–	–	+	+	–	–	+	+	+	+	+	7/13	*0/9*	25/39	59/74	91/126 (72)
Abnormal dentition	–	+	+	–	–	+	+	+	–	+	+	+	+	9/13	3/9	33/73	*52/70*	94/156 (60)
Micrognathia	–	–	–	+	–	–	–	–	–	–	–	–	–	1/13	1/9	21/63	9/22	31/98 (32)
Limb/Skeletal																		
Prominent finger pads	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13	*3/9*	45/74	84/89	142/176 (81)
Brachy/clinodactyly 5	–	–	–	–	+	+	–	+	–	–	–	+	+	5/13	3/9	51/57	*51/73*	107/143 (75)
Hip dislocation	–	–	–	–	–	–	–	–	+	–	–	–	–	1/13	0/9	18/71	13/89	32/173 (18)
Scoliosis	–	–	–	–	–	–	–	–	–	–	–	–	–	0/13	0/9	26/69	*16/86*	42/168 (25)
Lax joints	+	+	+	+	+	+	+	+	+	+	–	–	+	11/13	7/9	50/63	40/60	101/136 (74)
Visceral anomalies																		
Cardiac anomaly	–	–	–	+	+	+	–	–	+	–	–	+	+	6/13	0/9	23/67	26/86	55/166 (33)
Urogenital anomaly	+	+	–	–	+	–	–	+	+	+	+	+	–	8/13	3/9	8/75	23/83	39/171 (23)
Neurologic problems																		
Mental disability	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13	7/9	71/73	87/95	171/181 (94)
Hypotonia	+	+	+	+	+	–	+	–	+	+	–	–	+	9/13	5/9	2/61	*34/58*	45/132 (34)
Microcephaly	+	+	+	–	+	+	+	–	+	–	–	+	–	8/13	6/9	3/57	*28/84*	39/154 (23)
Seizures	–	–	–	–	–	–	–	–	–	–	–	–	–	0/13	0/9	8/64	1/11	9/88 (10)

*Cases 1–13 with NKS, nine suspect cases with NKS excluded on follow-up (NonNKS); Non-Asian patients include 53 summarized by Schrander-Stumpel et al. [1994] (Koutros and Fisher [1982]; Braun and Schmid [1984]; Kaiser-Kupfer et al. [1986]; Pagon et al. [1986]; Sheikh et al. [1986]; Pe Benito and Ferreti [1989]; Halal et al. [1989]; Meinecke and Rodewald [1989]; Gillis et al. [1990]; Carciane et al. [1991]; Clarke and Hall [1991]; Philip et al. [1992]; Franceschini et al. [1993]; Hudgins et al. [1993]; Hughes and Davies [1994]; Say et al. [1993]; Schrander-Stumpel et al. [1993]; excluding cases 9–13 described here), two from Wulfsberg et al. [1994], seven from Burke and Jones [1995], five from Gálán-Gomez et al. [1995], 10 from Ilyina et al. [1995], two from Lynch et al. [1995], two from Li et al. [1996], two from Ho and Eaves [1997], and single cases from Stalder et al. [1991], Jardine et al. [1993], Fryns et al. [1994], Wellesley and Slaney [1994], Devrient et al. [1995, 1996], Hostoffer et al. [1996], Silengo et al. [1996], Van Hagen et al. [1996], Chu et al. [1997], Peterson-Falzone et al. [1997], Wappler and Standl [1997]. Asian patients include 60 summarized by Schrander-Stumpel et al. [1994] (Niikawa et al., 1988; Handa et al., 1991), three by Ikegawa et al. [1993], two by Ho and Eaves [1997], and single cases by Kadotani et al. [1984], Iwama et al. [1987], Kawada et al. [1990], Matsumura et al. [1992], Tawa et al. [1994], Wang et al. [1994], Watanabe et al. [1994], Ijichi et al. [1996], Kobayashi and Sakuragawa [1996], McGinniss et al. [1997]. Italic numbers in columns denote significant differences between NKS or non-NKS, Asian, or non-Asian patients as discussed in the text. Significance was assessed by the chi-squared test with the criterion of $P < 0.05$ with 1 degree of freedom.

ing the last trimester showed normal fetal maturity and a karyotype of 46,XX. Cyanosis and hypotonia were noted in the nursery, and she had poor feeding with frequent emesis, hospitalization for pneumonia at age 1 month, poor weight gain with hospitalization for failure to thrive at age 4 months, chronic otitis, lacrimal duct hypoplasia with chronic drainage, and a urinary tract infection at age 13 months. Medical evaluations included a neonatal echocardiogram showing atrial and ventricular septal defects that were corrected at age 7 months, normal renal ultrasound, and an auditory evoked response study demonstrating severe peripheral hearing loss in the left ear with normal mobility of the tympanic membrane. Physical findings (Tables I and II) were documented at age 21 months.

Case 7 (Fig. 1F) is a Caucasian girl referred for evaluation of a possible malformation syndrome. She weighed 2,800 g after a normal gestation and had early hypotonia with poor feeding in the nursery. Subsequent problems included gastroesophageal reflux treated with medications and thickened feedings, chronic otitis requiring myringotomy tubes, chronic sinusitis, and asthma. Evaluation at another center yielded a possible diagnosis of Langer-Giedion syndrome and documented a normal karyotype on blood and skin fibroblasts, normal urine organic and blood amino acid analyses, normal urine screening for mucopolysaccharides, and a normal skeletal survey. Physical findings (Tables I and II) were documented at age 4 years.

Case 8 (Fig. 1H) is a Caucasian boy referred for evaluation of developmental delay. He weighed 2,600 g after a normal gestation and cesarean section delivery. He required oxygen for resuscitation, with Apgar scores of 5 (1 min) and 8 (5 min), and the placenta was noted to be "dysfunctional." Clinical problems included strabismus, chronic otitis, early growth delay with stature at the 3rd centile until age 4 years, and severe speech delay with an "immature personality" that necessitated special education. Physical findings at age

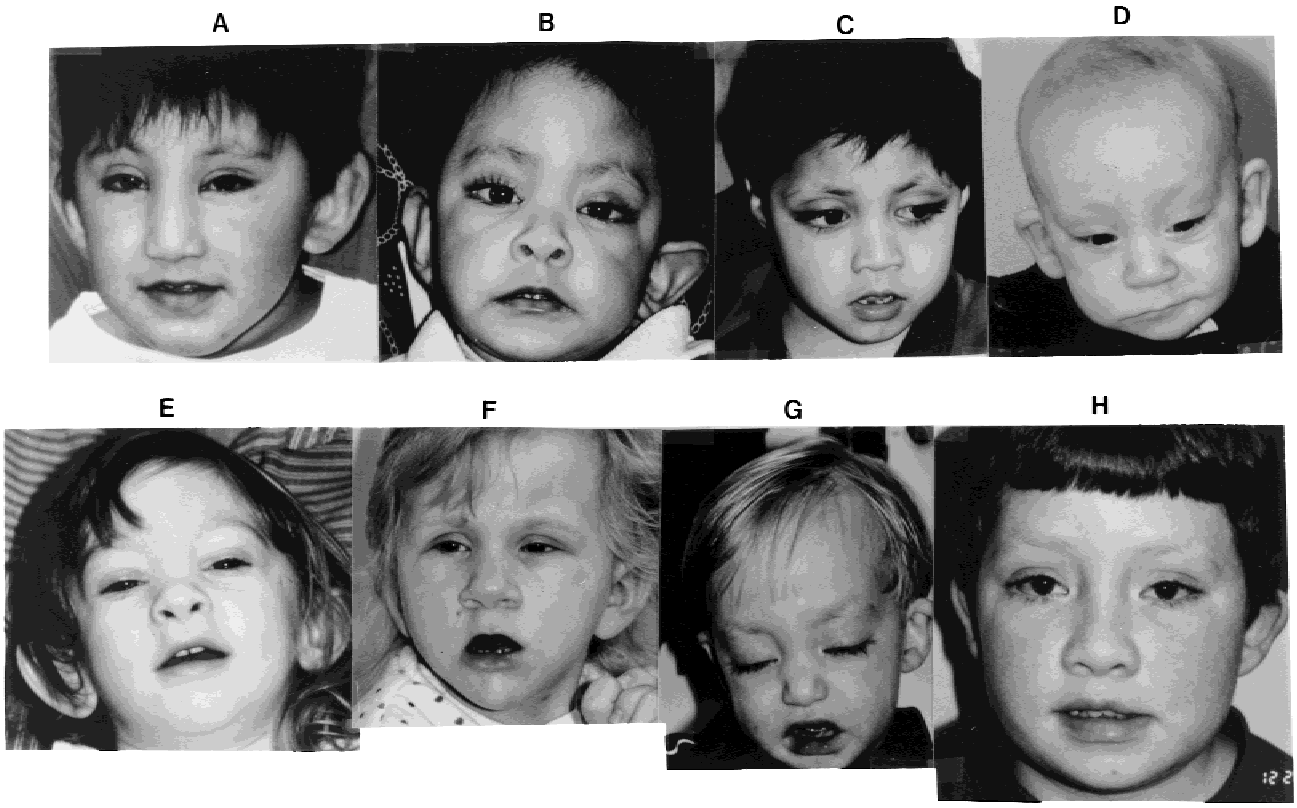

Fig. 1. **A–D:** cases 1–4; **E, F:** cases 6 and 7; **G:** case 5; **H:** case 8.

10 years (Tables I and II) included a pectus excavatum and a small penis (3.2 cm, <3rd centile). He had a normal karyotype, hand radiographs, and bone age. Endocrinology and ophthalmology evaluations at age 10 years and 3 months documented normal T4, TSH, FSH, and insulin growth factor-1 values with congenital palsy of the left superior oblique muscle and bilateral myopia with normal fundi. Treatments have included eye glasses and school psychology evaluations to promote inclusion.

Case 9 is a Caucasian girl referred for evaluation of growth and developmental delay. She weighed 2,320 g (50th centile) after a 34-week gestation complicated by polyhydramnios. Neonatal abnormalities included transient hypoglycemia and tachypnea, dislocation of the hips, and cardiac septal defects with dextroversion. Clinical problems included congestive heart failure requiring corrective surgery at age 5 months, velopalatine incompetence, congenital hip "dysplasia" requiring triple diapers until age 6 weeks, and chronic otitis requiring bilateral myringotomies. Physical findings at age 13 months (Tables I and II) included hypoplastic labia with a normal bone age. An audiogram demonstrated mild bilateral conductive hearing loss.

Case 10 is a Caucasian girl referred for evaluation of failure to thrive and a possible metabolic disorder. She weighed 2,080 g (60th centile) after a 33-week pregnancy complicated by gestational diabetes in the last trimester. Neonatal problems after a breech delivery included respiratory distress, bowel obstruction secondary to necrotizing enterocolitis, jaundice, and poor feeding due to hypotonia. She required nasogastric feedings for the first 7 months, and hospitalization at age 5 months had documented a cleft soft palate, bifid uvula, and bilateral duplication of the urinary collecting system without hydronephrosis. Physical findings at age 13 months (Tables I and II) included hypoplastic labia. Follow-up evaluation at age 3 years documented a similar degree of growth and developmental delay; normal laboratory studies have included an audiogram and bone age studies.

Case 11 is a Hispanic boy referred for evaluation of growth delay and an unusual facial appearance. He weighed 2,800 g (15th centile) after a 42-week uncomplicated gestation. His 23-year-old mother is small, had early failure to thrive, has a facial resemblance similar to that of the patient, and is employed as a consultant in office automation with a high school diploma; she did not comply with requests for childhood photographs. Physical findings at age 19 months (Tables I and II) included a cleft soft palate and hypoplastic scrotum. A renal ultrasound study showed bilateral renal duplication.

Case 12 is a Hispanic boy referred for evaluation of growth and developmental delay. He weighed 2,800 g (20th centile) after a 37-week gestation complicated by phenytoin and phenobarbitol therapy during the first 6 months due to maternal epilepsy. Labor was prolonged (20 hours), and neonatal resuscitation was required (Apgar scores of 4/6 at min 1/5). Neonatal problems included prematurity with respiratory distress, thrombocytopenia, jaundice, an imperforate anus with high

anorectal malformation and urethral fistula, sacral dimple with hemivertebrae at S2 and S3, increased pulmonary vascularity due to mitral valve stenosis, ventricular septal defect, coarctation of the aorta with subaortic stenosis, and patent ductus arteriosus. Subsequent medical events included a sigmoid colostomy with anorectoplasty at age 17 months, bilateral inguinal herniorraphy and orchiopexy, cardiac surgery at ages 2, 3, and 8 to correct the septal, aortic, and valvular defects, and the finding of urinary tract anomalies including shift of the right kidney inferolaterally with L-shaped fusion to a transverse, midline left kidney. A CT scan at age 5 years showed poor distinction of gray matter consistent with inadequate myelin deposition. Chronic otitis with multiple sets of myringotomy tubes led to the provision of hearing aids at age 8. Physical findings at age 9 years (Tables I and II) included a bifid uvula and a hypoplastic scrotum. Pertinent negative findings included normal nails and hair distribution with absence of facial signs from fetal hydantoin exposure. Behavioral problems included severe speech delay, short attention span, lack of toilet training, and "autism."

Case 13 is a Caucasian girl referred for evaluation of developmental delay. She weighed 3,050 g (25th centile) after a term uncomplicated gestation. Her 29-year-old father had Legg-Perthe hip dysplasia, strabismus, myopia, and loose joints as a child, but his photographs did not suggest the diagnosis of NKS. She had redundant neck skin, anomalous ears with cupped helices, and natal teeth without medical problems in the nursery, and a diagnosis of Ullrich-Turner syndrome was entertained. Childhood medical events included chronic otitis with conductive hearing loss, decreased palatal movement and the need for hearing aids, cardiology follow-up because of Ebstein anomaly and a bicuspid aortic valve, and fine motor deficits with mirror movements. Physical findings (Tables I and II) were documented at age 5.5 years.

RESULTS AND DISCUSSION

Table I lists selected physical measurements on 13 patients with NKS, and Table II summarizes their clinical and morphologic manifestations together with 95 non-Asian and 75 Asian patients from the literature. In Table I, measurement-appropriate ages (e.g., "height age") are divided by the chronologic age to determine the degree of growth or developmental retardation. The mean values demonstrate decreases in head circumference and developmental level that are more severe than those in height and weight. This severity of microcephaly (below 3rd centile in 8 of 13 cases) is comparable to other non-Asian patients (28/84 or 33%) listed in Table II, and contrasts with that (3/57 or 5.3%) in Japanese patients. Table II corroborates the report of Schander-Stumpel et al. [1994] by showing statistically significant differences in the manifestations of Asian (mainly Japanese) and non-Asian (mainly Caucasian) patients. Asians had higher frequencies of everted lower lids, brachy/clinodactyly of digit 5, and scoliosis, while non-Asians have significantly higher frequencies of neonatal problems, abnormal dentition, hypotonia, and microcephaly.

The five Hispanic children described in this article, together with three literature cases [Sheikh et al., 1986; Burke and Jones, 1995; Li et al., 1996], do not display significant differences in phenotype from Caucasian patients with NKS. Few African-Americans with NKS have been described, and the rebuttal by Mulvihill et al. [1989] concerning exclusion of their patient by Niikawa et al. [1988] emphasizes that the face may be less distinctive in these patients. Because subjective facial recognition is so crucial for diagnosis, variable ascertainment is a likely explanation for ethnic differences in the spectrum of NKS. Caucasian patients may acquire an "oriental" appearance [Schrander-Stumpel et al., 1994] but lack the "Kabuki" resemblance noted by Niikawa et al. [1981] in Japanese patients. The "Niikawa-Kuroki" eponym is therefore a more appropriate and unbiased name for the syndrome.

Table II also includes data on nine patients in whom the diagnosis of NKS was entertained but rejected after follow-up observation. The incidence of manifestations such as arched eyebrows, long palpebral fissures, flat nasal tip, and high or cleft palate was significantly decreased in the non-NKS patients. One patient presenting at age 9 months with large ears, unusual face, and growth/developmental delay is illustrated in Figure 2A; her subsequent improved growth and normal appearance at age 3.5 years (Fig. 2B) emphasize the value of specific findings such as long palpebral fissures and prominent fingerpads in distinguishing NKS from other syndromes with growth delay. Among the 13 patients with a presumptive diagnosis of NKS, case 7 is striking for her connective tissue laxity, aged appearance, sparse hair, and thin skin. She bears a strong resemblance to patient 1 of Pierpont et al. [1998] who had microcephaly, large ears, prominent finger pads, and dental anomalies typical of NKS. The plantar lipomatosis seen in the patient of Pierpont et al. [1998] was not present in case 7, and the overlapping findings emphasize the need for objective diagnostic measures in NKS.

A step toward the goal of objective diagnosis was reported by Meinecke and Rodewald [1989], who presented a metacarpophalangeal pattern profile analysis of an 8-year-old Caucasian boy with NKS. Figure 3 compares the latter profile (Fig. 3A) to those of five NKS patients from this report (Figs. 3B–F), the non-

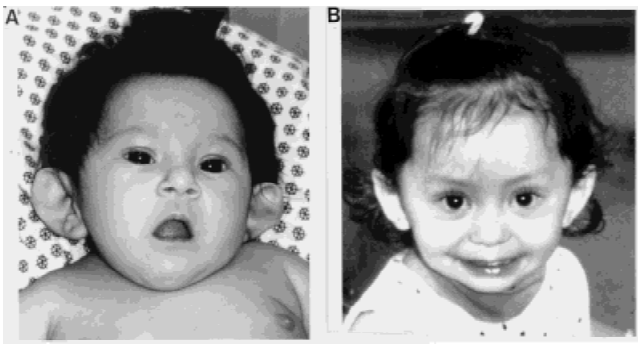

Fig. 2. Hispanic girl judged not to have NKS after follow-up. **A:** age 7 months; **B:** age 3 years.

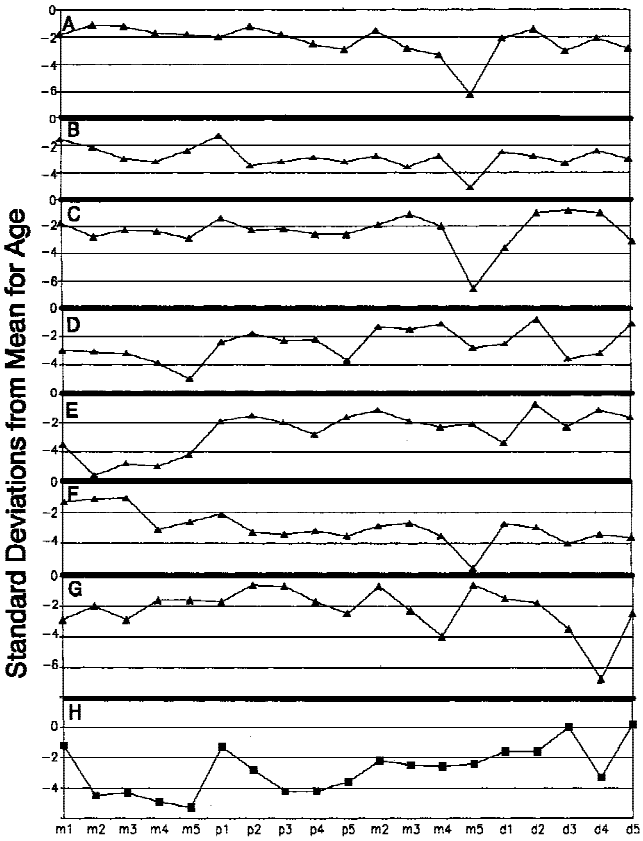

Fig. 3. Metacarpophalangeal pattern profiles calculated as described [Poznanski et al., 1972]; standard deviations for lengths of metacarpals (m1–m5) and proximal (p1–p5), middle (m2–m5), or distal (d1–d5) phalanges are shown. **A:** Caucasian boy age 8 years [Meinecke and Rodewald, 1989]; **B:** Caucasian girl age 1.1 years (case 10); **C:** Caucasian girl age 1.1 years (case 9); **D:** Hispanic boy, age 5.5 years (case 11); **E:** Caucasian girl, age 1.8 years (case 6); **F:** Hispanic boy, age 9 years (case 12); **G:** Girl with 45,X Turner syndrome, age 3 years.

NKS patient depicted in Figure 2 (Fig. 3G), and a patient with 45,X Ullrich-Turner syndrome (Fig. 3H). Profiles 3B, 3C, and 3F from young Caucasian girls (13, 13, and 21 months, respectively) all resemble that in Figure 3A, each having the valley expected from brachymesophalangy of digit 5. Profiles 3D and 3E, from Hispanic boys aged 2 and 9 years, are not as typical. Profile 3G from the non-NKS patient in Figure 2 is very different, as is profile 3H that reflects the short metacarpals expected in Turner syndrome. While the metacarpophalangeal pattern profile undoubtedly exhibits variability in NKS, as stressed by Schrander-Stumpel et al. [1994], the data in Figure 3 support utility in selected cases and the value of further investigation.

Occasional instances of familial transmission and associations with diverse chromosome anomalies have suggested a genetic cause of Niikawa syndrome. The mother of case 11 had facial findings of NKS with low-average stature and intelligence; she did not have obvious dental anomalies as reported in a mildly affected mother by Silengo et al. [1996]. The father of case 13 had some findings of NKS such as joint laxity and hip anomalies, but his facial appearance was not characteristic. These parents declined further evaluation. Other examples of vertical transmission may include the mildly affected father with hypodontia of the premolars reported by Halal et al. [1989], the several mothers cited by Niikawa et al. [1988] with facial resemblance to affected children, the mildly affected father of Kobayashi and Sakuragawa [1996], and several relatives with partial manifestations described by Ilyina et al. [1995]. Normal parental ages are documented in Table I and by Niikawa et al. [1988]; four families with consanguinity were noted in the latter report but not in other cases summarized in Table II. Diabetes mellitus occurred in four of 13 mothers described here, including one (case 6) with juvenile diabetes mellitus. Neonatal hypoglycemia was noted in case 5 and in four patients reported by Niikawa et al. [1988]. These findings may correlate with later endocrinologic abnormalities such as premature thelarche or growth hormone deficiency in NKS (Table III), but a primary role in etiology seems unlikely.

Chromosomal anomalies associated with NKS have included pericentric inversion of Y or ring Y(p11.2q11.2) [Niikawa et al., 1988], del(6q)/dup(12q) [Jardine et al., 1993], inv(4)(pterp12) [Fryns et al., 1994], pseudodicentric chromosome 13 in affected twin boys that was also present in their normal mother [Lynch et al., 1995], and balanced translocation 15q/17q in an affected male and facially similar mother [Gálan-Gómez et al., 1995]. Most enticing is the association of NK phenotype with ring X (p11.2q13) reported by Niikawa et al. [1988], McGinniss et al. [1997], and with 45,X Ullrich-Turner syndrome [Wellesley and Slaney, 1994] or low-grade 45,X mosaicism in the mother of an NKS patient [Van Hagen et al., 1996]. The chromosome 22q deletion typical of the DiGeorge-Shprintzen spectrum has been excluded in two patients by Li et al. [1996], but additional studies may be warranted since palatal and cardiac anomalies are frequent (Tables II and III). The 13 patients described here had normal routine karyotypes. Case 1 had normal blood amino acid and urinary organic acid profiles, and the abnormalities in case 5 probably related to his sudden death.

Complications of NKS are many, highlighted by the lethal pneumonia in case 5 and reports of immune dysfunction [Hofstoffer et al., 1996]. The latter patient had hypogammaglobulinemia first of immunoglobulin A, then M and G, and responded to intravenous immunoglobulin treatment. The patient of Hostoffer et al. [1996] also had immune thrombocytopenic purpura, as did the patient of Watanabe et al. [1994], and these findings substantiate the immune dysfunction suggested by the 58% of patients with chronic infections documented in Table II. The autopsy of case 5 also provided documentation of central nervous system pathology in NKS, since he had small frontal lobes, focal polymicrogyria, enlarged fourth ventricle, and delayed myelination. Chu et al. [1997] describe a temporoparietal subarachnoid cyst in a child with NKS, and Niikawa et al. [1988] reported brain "atrophy" in 2 of 51 patients. Although severe mental retardation is uncommon, Ho and Eaves [1997] document patients with autistic behavior, pervasive developmental disorder, and self-mutilation. Severe retardation seems more

TABLE III. Medical Complications and Preventive Management of NKS*

Category	Complications	Preventive management
General		
Neonatal	*Feeding,* metabolic problems[a]	Neonatal monitoring Evaluate feeding, skeleton
Growth	*Early failure to thrive,* adolescent obesity	Nutrition, growth checks
Learning/behavior	*Motor, cognitive delays,* autism, hyperactivity	Early intervention, family support School, behavioral evaluations
Craniofacial		
Eye	*Strabismus,* others[b]	Vision checks, ophthalmology referral
Ear	Chronic otitis, hearing loss	Hearing checks, audiology referral
Mouth	*Palatal, dental anomalies*[c]	Dentistry, speech therapy referrals
Surface		
Neck/trunk	Pectus excavatum, hernias	Evaluate thorax, inguinal region
Skeletal		
Cranial	*Microcephaly,* synotosis	Monitor head shape and growth
Axial	Cervical vertebral fusion, vertebral anomalies, *scoliosis*	Careful anesthesia Examine spinal curvature
Limbs	Patellar, hip dislocation	Monitor physical activity, joint laxity
Internal		
Digestive	Reflux, anal atresia, malrotation	Monitor feeding, gastrointestinal function
Cardiovascular	*Cardiac anomalies,*[d] mitral valve prolapse, aortic dilation	Echocardiogram in early infancy Monitor cardiovascular status
Endocrine	*Premature thelarche,* others[e] growth hormone deficiency	Monitor pubertal development Consider endocrine referral
RES[f]	*Susceptibility to infections,* hypogammaglobulinemia, ITP[g]	Monitor respiratory status
Excretory	*Urinary tract anomalies*	Renal ultrasound during infancy
Genital	Micropenis, cyptorchidism, hypoplastic labia	Examine genitalia Consider urology referral
Neuromuscular		
Central nervous system	Hypotonia, seizures	Early intervention Occupational therapy

*Italicized complications have a frequency >20%.
[a]Hypoglycemia, hypocalcemia.
[b]Cataracts, myopia, Peter anomaly.
[c]Cleft/high palate, velopalatine incompetence, speech dysarthria and/or dyspraxia.
[d]Aortic coarctation, aortic aneurysm, mitral valve prolapse, septal defects, tetralogy, transposition.
[e]Diabetes insipidus, ovarian failure.
[f]RES, reticuloendothelial.
[g]ITP, immune thrombocytopenic purpura.

common in non-Asian patients, and this may reflect the higher frequency of microcephaly documented in Table II.

Complications of the NKS are documented in Table II and summarized in Table III with a view towards preventive management. Skeletal, cardiac, and infectious complications have been well documented, and other problems include eye anomalies (strabismus, cataract, Peter anomaly); chronic otitis with hearing loss; cleft hard or soft palate (40% cited by Burke and Jones [1995])as well as velopalatine incompetence [Lan et al., 1995; Burke and Jones, 1995]; oromotor problems with speech dysarthria and dyspraxia [Burke and Jones, 1995] or hypernasal speech [Ilyina et al., 1995]; seizures or abnormalilities on electroencephalogram [Niikawa et al., 1988]; connective tissue abnormality evidenced by blue sclerae, joint laxity, patellar dislocation [Hudgins et al., 1993; Schrander-Stumpel et al., 1994] or even aortic aneurysm [Niikawa et al., 1988]; cervical and 12th rib anomalies including C3/C4 fusion [Niikawa et al., 1988]; thoracic anomalies such as elevated diaphragm or diaphragmatic hernia [Silengo et al., 1996]; gastrointestinal anomalies such as imperforate anus, malrotation, and rectovaginal fistula [Niikawa et al., 1988]; genital anomalies such as micropenis, cryptorchidism, or hypoplastic labia (cases 9 and 10); renal anomalies such as horseshoe kidney, duplication of the renal pelves, hydronephrosis [Schrander-Stumpel et al., 1994]; and endocrine findings such as neonatal hypoglycemia/hypocalcemia, premature thelarche, elevated follicle stimulating hormone, deficient growth hormone, and diabetes insipidus [Devrient et al., 1995; Tawa et al., 1994]. Coarctation of the aorta accounts for most of the cardiac anomalies in NKS [Hughes and Davis, 1994; Schrander-Stumpel et al., 1994], further suggesting a relationship between NKS and X chromosome excess or deficiency.

Table III utilizes knowledge of complications to present a plan for preventive management in patients with NKS. The incidence of vision and hearing problems, of developmental delay, and of cardiac anomalies is comparable to that of Down syndrome, mandating early intervention, infantile echocardiography, yearly assessment of hearing and vision, and attention to speech therapy as recommended on the Down syndrome checklist. Alertness for congenital hip dislocation and scoliosis is also justified by the frequencies in Table II, as is early and consistent dental care. Uro-

genital anomalies are frequent enough to be considered on yearly evaluations, and a renal ultrasound study should be considered in infancy and mandated after the first urinary tract infection. Pervasive delays of growth and development in some patients emphasize the need for regular pediatric monitoring with attention to school and financial issues.

In summary, NKS is an MCA/MR syndrome that is now described in more Caucasians than Asians, implying an incidence that approaches the 1 in 32,000 births estimated in Japan [Niikawa et al., 1988]. Thirteen cases have been encountered in one center over a 5-year period, and the diagnosis was strongly entertained in nine other children. These numbers place NKS with disorders such as the Noonan, Williams, Brachmann-de Lange, FG, and Shprintzen syndromes that frequently arise when evaluating the child with growth and/or developmental delay and an unusual appearance. The hypothesis of altered expression of X chromosome loci [McGinniss et al., 1997] points toward the development of an objective test for NKS, and it is likely that such testing will further augment estimates of disease prevalence. Awareness and early diagnosis of NKS is important because of the numerous opportunities for preventive health care.

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