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Microcephaly, short stature, and developmental delay associated with a chemotactic defect and transient hypogammaglobulinaemia in two brothers

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SUMMARY Two brothers presented with unusual facial features, microcephaly, developmental delay, and severe postnatal growth retardation. They both developed eczema in infancy and have had recurrent infections. Additional physical findings in both boys included hypogonadism, flexion contractures, hypoplastic patellae, and scoliosis. Their facial similarity was striking with sloping foreheads, beaked noses, large, protruding ears, and micrognathia. Low levels of serum gammaglobulins and defective chemotaxis were present in both boys in infancy. The hypogammaglobulinaemia was transient and improved, reaching normal levels by 3½ years and 15 months, respectively. Defective chemotaxis and recurrent infections have persisted to the present. Both parents were normal. The mode of inheritance was not clear, as both X linked and autosomal recessive patterns were possible. Although patients with congenital malformations who also had immunodeficiency have previously been reported, immune system abnormalities, especially those of a transient nature, may frequently go unrecognised.

Several patients with immune deficiency and congenital malformations have been reported.[1–5] We describe a family in which two brothers have hypogammaglobulinaemia, defective chemotaxis, and multiple congenital anomalies including primary microcephaly, joint contractures, severe growth retardation, and developmental delay (table 1). A survey of published reports failed to disclose a similar association of abnormalities.

Case reports

CASE 1

The proband was the product of a term pregnancy complicated by hypertension in late gestation. His birth weight was 4000 g and Apgar scores were 6 and 9 at one and five minutes, respectively. At birth, he had unusual facies, microcephaly, and anal stenosis. Chronic feeding problems, poor weight gain, atopic dermatitis, and recurrent respiratory infections were apparent by 2 months of age.

At 4 months of age, he weighed 4675 g, his length was 55 cm, and head circumference was 37 cm, all

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TABLE 1 *Clinical features.*

	Case 1	*Case 2*
General		
Postnatal growth deficiency	+	+
CNS		
Developmental delay	+	+
Flexion contractures	+	+
Cranium		
Microcephaly	+	+
Craniosynostosis	+	–
Sloping forehead	+	+
Ears		
Large, protruding	+	+
Nose		
Beaked, prominent	+	+
High nasal bridge	+	+
Mouth		
Carp shaped	+	–
High arched palate	+	+
Micrognathia	+	+
Anus		
Stenosis	+	–
Extremities		
Dislocated hips	+	–
Hypoplastic patellae	+	+
Spine		
Scoliosis	+	+
Genitalia		
Small penis	+	–
Small testes	+	+
Skin		
Eczematous lesions	+	+
Decreased subcutaneous fat	+	+

well below the 3rd centile. He had sparse hair, and the scalp was covered with large scales. A sloping forehead, large, protruding ears, a beaked nose with a broad nasal bridge, prominent eyes, and micrognathia gave him a most unusual facial appearance (fig 1). A fine pinpoint rash covered his protuberant abdomen and many weeping excoriated lesions were noted in the flexion creases of the knees, elbows, and neck. There was a marked decrease in subcutaneous fat over the entire body. Deep creases were present in the palms and oedema was noted over the dorsum of the hands and feet. The hips were subluxated and mild flexion contractures of the knees were present.

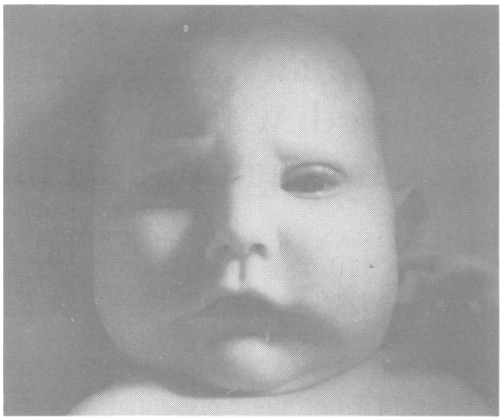

FIG 1 *Case 1 at 3 months of age.*

Laboratory studies

Routine urine and blood studies were normal. Serum zinc levels in the patient and his parents were normal, as were thyroid function studies and plasma cortisols. A TORCH screen was negative. Chromosome studies with Giemsa banding and dermatoglyphs showed no abnormalities. Serum growth hormone level was normal. Hand pattern profile analysis showed a small hand for his age, with short first, second, third, and fifth metacarpal bones. Gross and microscopic appearance of the hair was normal. An EEG was also normal.

Skull radiographs showed synostosis of the left coronal suture and the posterior aspect of the sagittal sutures, which was surgically corrected. Adenoidal tissue was noted to be diminished. Radiological studies of the remainder of the skeleton showed no abnormalities. CT scan of the brain showed a mild left frontal atrophy.

Immunological studies

Serum immunoglobulins were quantified by nephelometry.[6] The IgG and IgA levels remained low up to 3½ years of age at which time both reached normal levels. The percentage of B cells, determined by recording surface immunoglobulin bearing lymphocytes, was depressed (table 2). Serum anti-B titre was normal at 3½ years.

Total lymphocytes and percentage of their subpopulations[6] were normal. Lymphocyte function as indicated by phytohaemagglutinin (PHA), pokeweed (PWM), and concanavalin A (ConA) stimulated blastogenesis[6] was normal.

Delayed type hypersensitivity skin tests to phyto-

TABLE 2 *Results of immunological studies*

	Age (mth)	*B cells (%)*	*T cells (%)*	*Serum immunoglobulins (mg/dl)*			*Chemotaxis (%)*	
				IgG	*IgA*	*IgM*	*PMNL*	*MNL*
Case 1	4	ND	ND	180	10	58		
	6	ND	ND	158	<3	36		
	10	6	67	136	10	12	0	0
	15	2	51	279	14	92	0	0
	18	3	55	182	<3	51	3	15
	24	2	42	346	<3	63	ND	ND
	32	ND	ND	415	20	53	0	ND
	42	3	62	540	35	46	1·25	1·1
Case 2	1	7	42	490	<3	44	0	6
	7	5	34	65	<3	52	2	0
	15	ND	ND	391	37	116	ND	ND
	26	5	56	820	45	185	0	0
Normal values		11–22	44–62	1–3 mth 244–661	10–40	15–50	3–13	2–9
				4–6 mth 180–579	15–42	29–107		
				7–9 mth 322–579	19–109	35–140		
				10–18 mth 390–1400	25–168	40–180		
				2 y 590–1400	35–168	47–184		
				3–4 y 600–1575	40–235	51–201		

ND=not done.

haemagglutinin (0·5 N), candida (1:10 000 dilution), and PPD (10 and 50 IU) were negative, while reaction to streptodornase-streptokinase (20 units) was depressed. At 3½ years of age, immunisation with pneumococcal polysaccharide and tetanus antigens demonstrated a normal antibody response. Erythrocyte adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) determinations showed raised ADA and normal PNP levels (table 3).

Leucocyte chemotaxis, measured in a Boyden chamber,[6] was markedly depressed (table 2). A nitroblue tetrazolium test gave normal results. C3 and C4 levels were normal.

This patient has been examined on several occasions; he is now 7 years of age. During his last visit at the age of 6½ years, he was 98·4 cm in length, weighed 13·5 kg, and his head circumference was 44·5 cm, again all well below the 3rd centile. He still suffers from recurrent infections, including herpes and bacterial pneumonias, although his most recent serum immunoglobulin levels were within the normal range. Eczematous skin lesions with excoriation are still prominent. Additionally, a linear naevus like lesion has developed during the last 18 months extending from the right mid upper arm across the chest. His facial features remain unchanged (fig 2). Both tympanic membranes were opaque but were not actively draining. Two central and two lateral incisors were missing and *x*-rays of the mouth showed that several permanent teeth were also missing. He had multiple dental caries. The penis was small and two small masses approximately 0·5×0·3 cm were palpated in the scrotum, probably representing rudimentary testes. There were flexion contractures of the elbows, dislocated hips, marked laxity of the knees, and an inward deviation of the lower ends of the femora (fig 2). The patellae could not be seen on *x*-rays nor could they be palpated. He also had tight heel cords bilaterally, but otherwise the lower extremities were not spastic. The toenails were discoloured, indicating fungal infection. His vocabulary consisted of several single words, but no word combinations were heard.

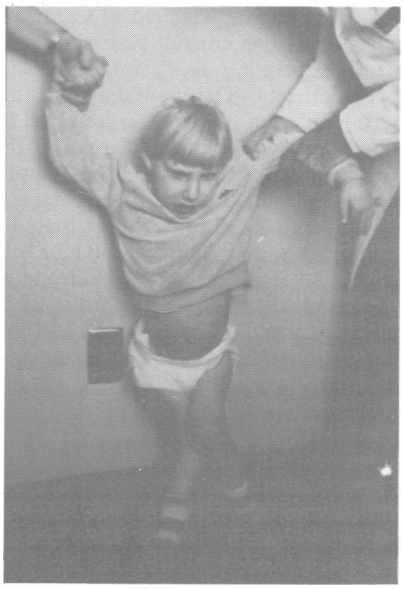

FIG 2 *Case 1 at 6½ years of age.*

TABLE 3 *Other laboratory studies.*

	Case 1	*Case 2*
Skin tests		
PHA	—	—
Candida	—	—
PPD	—	—
SD–SK	↓	↓
Response to immunisation*		
Tetanus toxoid	Normal	Normal
Pneumococcal polysaccharide	Normal	Normal
Complement		
C3	Normal	Normal
C4	Normal	Normal
Enzyme studies		
Erythrocyte ADA	Normal	↑
Erythrocyte PNP	Normal	Normal
Serum growth hormone level	Normal	Normal
Bone age	Delayed	Delayed
Karyotype	46,XY	46,XY

*These studies were done after serum gammaglobulin levels became normal.

CASE 2

The younger brother was born at term after a pregnancy complicated by bleeding and contractions for the last two months. The mother was found to be a gestational diabetic. The birth weight was 5·32 kg, length 51·5 cm, and head circumference 33 cm. The Apgar scores were 9 at one and five minutes. At birth, he was noted to bear a striking facial resemblance to his brother, with a sloping forehead, prominent nose, deep set eyes, and micrognathia. Initially, he progressed well, but by 3 months of age he had recurrent respiratory infections, similar to though less severe than those of his brother.

Physical examination at 11 months of age showed a small, slender child. His height was 69·1 cm, weight 7·5 kg, and head circumference 40·4 cm, all below the 3rd centile. Although his hips clinically did not appear to be dislocated, *x*-rays of the pelvis showed the acetabular roofs to be shallow. He was also noted to have very lax knee joints and mild atopic eczema. When last seen at 5 years of age, he was able to walk, was toilet trained, and had considerably more language than his brother. He

was 100·2 cm in length, weighed 13 kg, and his head circumference was 45 cm (all below the 3rd centile for age). His primary teeth were in place. The tonsils were present. The genitalia were those of a prepubertal male but the testes were small (0·5×0·5 mm). The extremities were malformed with inward deviation of the lower ends of the femora, most marked on the right in spite of corrective surgery (fig 3). The patellae could not be palpated and the knees appeared to be somewhat enlarged. No signs of spasticity involving the lower extremities were noted, although his heel cords were tight. His gait was quite abnormal in that he had considerable inward deviation of both knees, more marked on the right than the left. He had mild flexion contractures of the elbows.

Laboratory studies

Routine urine and blood studies and blood and urine amino acid screening were normal. Serum growth hormone level and chromosome analysis with Giemsa banding were also normal. The results of the immunological studies were somewhat similar to those seen in his brother and are shown in table 1.

A skull film showed some thickening of the calvarium in the frontal region, but no pathological calcifications; the sutures were open. A CT scan was suggestive of cortical atrophy in the right parietal area; the density of the falx was prominent posteriorly.

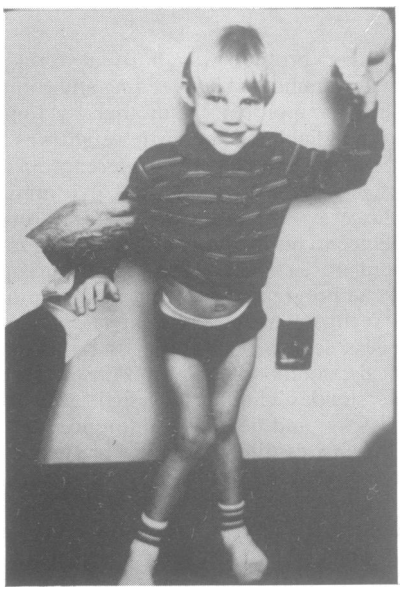

FIG 3 *Case 2 at 4 years of age.*

Family history

The mother was 20 and the father was 22 at the time of the birth of their first child. There was no consanguinity and both were in good health, although mildly obese. A family history of developmental delay, atopic dermatitis, or recurrent infections was specifically denied. However, the son of a paternal half-brother was said to have craniosynostosis, bilateral hip dislocation, and anal stenosis. His subsequent growth and development was reportedly normal.

Growth and development

These children have been followed for over five years. Both were of normal weight at birth with very poor growth patterns in early infancy and are now parallel to but below the 3rd centile for both height and weight. The microcephaly in both boys is striking. The craniotomy done on the older child did not result in accelerated head growth.

Cognitive abilities in case 1 remained at age level on the Mental Scale of Bayley until he was 16 months of age when they dropped slightly. Subsequent evaluation at 29 months showed a further decrease into the borderline range of ability. Scores on the motor component of the Bayley test were consistently low because of limited ambulation. A marked expressive language delay was present despite adequate hearing. During his final testing at 3½ years of age, he was functioning considerably below his age level with cognitive as well as motor development index being under 50.

The younger boy is less severely disabled physically although he too has striking microcephaly. His initial evaluation with the Bayley Mental Scale showed abilities in the low normal range, but he seems to be losing ground steadily. He walks reasonably well. He also has adequate hearing with poor expressive language.

Clinically, the major problem encountered by both of these children consists of recurrent infections, predominantly of the upper respiratory tract, accompanied by otitis media and herpes. The older brother tends to have high fever and a protracted course with his illnesses.

Discussion

We have presented two male sibs with defective chemotaxis and transient hypogammaglobulinaemia associated with multiple congenital malformations, developmental delay, and severe growth retardation with normal serum growth hormone levels. IgG and IgA values were low initially and remained so until

3½ years of age in the older boy and 15 months in the younger. The quantity and in vitro function of T cells were normal. It may be that the immunological findings in these children represent a variant of transient hypogammaglobulinaemia of infancy.[7] However, our patients in addition have defective chemotaxis and, despite normal serum immunoglobulins, they continue to have frequent infections.

The association of multiple congenital malformations and immunodeficiency is intriguing.[5] Recently such an association has been postulated in 20 patients with severe craniofacial anomalies.[6] However, all were sporadic cases. Congenital malformations have been described in a few patients with transient hypogammaglobulinaemia. None of them had the type of malformations seen in our patients.[7]

These brothers are very similar physically. Their condition is obviously genetic and appears to affect adversely both overall mental development and physical growth, as well as the orderly maturation of the immune system. The exact mode of inheritance is not clear; both X linked and autosomal recessive inheritance would be equally possible from the available data. Similarly, the possibility of a small undetectable chromosomal abnormality (for example, a deletion) being responsible for the clinical findings observed in these children cannot be excluded at this time. It is particularly relevant that the father's half-brother's child also reportedly had anal stenosis, craniosynostosis, and joint contractures.

The findings in these patients as well as those in published reports suggest that an association of immunological abnormalities and birth defects may not be fortuitous and may frequently go unrecognised.

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