A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features

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Abstract

Twelve infants (six boys, six girls) with severe hypocalcaemic tetany or convulsions were seen over a three year period. Nine patients were symptomatic in the newborn period. Their hypocalcaemia was associated with hyperphosphataemia and very low concentrations of immunoreactive parathyroid hormone. None of the babies suffered from congenital cardiac disease. Cell mediated immunity, measured in five patients, was normal. There were no chromosomal abnormalities but all patients shared several dysmorphic features including deep set eyes, microcephaly, thin lips, beaked nose tip, external ear anomalies, micrognathia, and depressed nasal bridge. Mental retardation of varying degree was found in all patients. All had severe intrauterine and postnatal growth retardation. Four patients have died. The remaining eight patients are on treatment with vitamin D and calcium supplements with no change in their growth pattern. We believe that this association of congenital hypoparathyroidism with severe growth failure and dysmorphism represents a new syndrome.

Hypoparathyroidism represents a range of clinical and biochemical syndromes characterised by parathyroid hormone deficiency, hypocalcaemia, and hyperphosphataemia. Neonatal hypoparathyroidism is relatively common, occurring usually as a transient condition associated with well defined risk factors such as prematurity, perinatal asphyxia, and maternal diabetes.[1] Permanent congenital hypoparathyroidism is rare. Most cases are caused by defective embryogenesis of structures deriving from the third and fourth pharyngeal pouches and fourth branchial arch—namely the parathyroid glands, thymus, heart and aortic arch, and several facial structures. This constellation of findings is known as third-fourth pharyngeal pouch syndrome or DiGeorge's syndrome.[2]

In the past three years we have identified 12 patients with an unusual syndrome of congenital hypoparathyroidism associated with severe growth failure and dysmorphic features quite distinctive from those of DiGeorge's syndrome. The description of their clinical findings and laboratory investigations is the subject of this report which was presented in part at the 58th Annual Meeting of the Society for Pediatric Research, Washington DC, May 1988.[3]

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Accepted 29 June 1990

Patients and methods

RECOGNITION OF THE SYNDROME

The index case (case 1) was a 3 year old Saudi boy who was the product of a normal full term pregnancy and spontaneous vaginal delivery. His birth weight was 1500 g. Hypocalcaemic tetany was diagnosed in the first few days of life and was treated with oral calcium supplement and a vitamin D preparation. His parents were first degree cousins and had two older children in perfect health.

He was referred to our care at the age of 4·5 months because of repeated attacks of vomiting and convulsions. His weight was 2·5 kg and length 47 cm. Physical examination disclosed moderate dehydration and several dysmorphic features including microcephaly, micrognathia, thin lips, low set and posteriorly rotated ears, deep set eyes, depressed nasal bridge and beaked nose tip, and high arched palate. Examination of the heart and lungs showed no abnormalities and there was no abdominal visceromegaly. He had small hands and feet, micropenis, and unilateral cryptorchidism. He had normal blood urea nitrogen and creatinine concentrations and moderate hyponatraemia, which was corrected with appropriate treatment. His serum calcium concentration ranged from 1·5 to 1·7 mmol/l, and inorganic phosphate from 2·3 to 4·0 mmol/l. Parathyroid hormone, measured on five occasions, ranged between 10–30 pmol/l (normal 29–85 pmol/l) despite severe concomitant hypocalcaemia.

Two unrelated patients (cases 2 and 3) with similar phenotypic abnormalities had been seen by one of the authors (NAS) in the preceding 12 months. Both were found to have congenital hypoparathyroidism and severe growth failure. In the next two years, nine additional patients from eight unrelated families fulfilled the criteria for inclusion in this report.

LABORATORY METHODS

All patients had serial determinations of serum calcium, phosphate, magnesium, albumin, and creatinine concentrations in addition to routine laboratory studies. Parathyroid hormone was measured by radioimmunoassay against the mid region of the molecule utilising a commercial kit (INCSTAR Corporation). T and B lymphocyte quantitation, performed in five patients, was measured by monoclonal antibody with laser beam sorter. T lymphocyte function was measured by blastogenesis with several mitogens including pokeweed, phytohaemagglutinin, and concanavalin A.

Results

CLINICAL AND LABORATORY FINDINGS

Table 1 summarises the clinical and laboratory data of the 12 patients. Sex distribution was

Table 1 Clinical findings in patients with congenital hypoparathyroidism

Case No	Sex	Gestational age (weeks)	Birth weight (g)	Age		Consanguinity	Family history	Karyotype	Mental retardation	Additional data
				Onset of symptoms	Diagnosis					
1	M	Full term	1500	7 days	4 months	First cousins	Negative	46XY	Moderate	Recurrent vomiting, pyloric stenosis, operated
2	F	Full term	3000	25 days	25 days	First cousins	Positive	46XX	Severe	Esotropia, nystagmus, accessory auricle
3	M	Full term	1610	30 days	30 days	First cousins	Negative	46XY	Moderate	Death from fulminant pneumonia at 5 months of age
4	F	Full term	Low birth weight	3 months	3 months	First cousins	Negative	46XX	Severe	Esotropia
5	M	35	1650	1 day	1 day	First cousins	Negative	46XY	Moderate	Died at 7 months of age, pneumonia
6	F	Full term	2100	17 days	25 days	First cousins	Positive	ND	Moderate	
7	F	34	1400	4 months	4 months	First cousins	Positive	ND	Severe	Died at 2 years of age, sibling of case 8
8	M	Full term	2150	2 days	12 days	First cousins	Positive	ND	Severe	Sibling of case 7
9	M	32	2100	21 days	7 months	Fourth cousins	Positive	46XY	Severe	Bilateral corneal opacity, distal renal tubular acidosis, died at 9 months of age
10	F	30	1600	2 months	15 months	First cousins	Negative	46XX	Moderate	
11	F	36	1750	7 months	9 months	None	Negative	ND	Mild	
12	M	Full term	2000	15 days	2 months	First cousins	Negative	46XY	Mild	Chickenpox at 10 days of age

ND, not done.

equal. All but one patient (case 2) suffered from severe intrauterine growth retardation with birth weights ranging from 1500 to 2150 g. Five patients were born prematurely. Ten patients were born of parents who were first degree cousins. Four families had more than one child affected with a similar condition.

The presenting complaint in all patients was hypocalcaemic tetany or generalised convulsions, usually detected in the first few days or weeks of life. In two patients the onset of symptoms was delayed until the fourth and seventh month. Additional manifestations shared by all patients were severe growth failure and psychomotor retardation. Feeding disorders, vomiting, and diarrhoea were other common problems encountered.

The results of the biochemical investigations are listed in table 2. All patients had moderate to severe hypocalcaemia and hyperphosphataemia. The normal serum calcium found in case 11 was the result of treatment with vitamin D before her referral to our care. Three patients had a low serum magnesium concentration. The parathyroid hormone concentration was low in all patients despite concomitant severe hypocalcaemia. In cases 6 to 12 parathyroid hormone was reported as less than 30 pmol/l because this was the limit of detection of the assay. Renal function, judged from serum urea and creatinine concentrations, was normal in all patients. One patient had an associated distal renal tubular acidosis requiring alkali treatment.

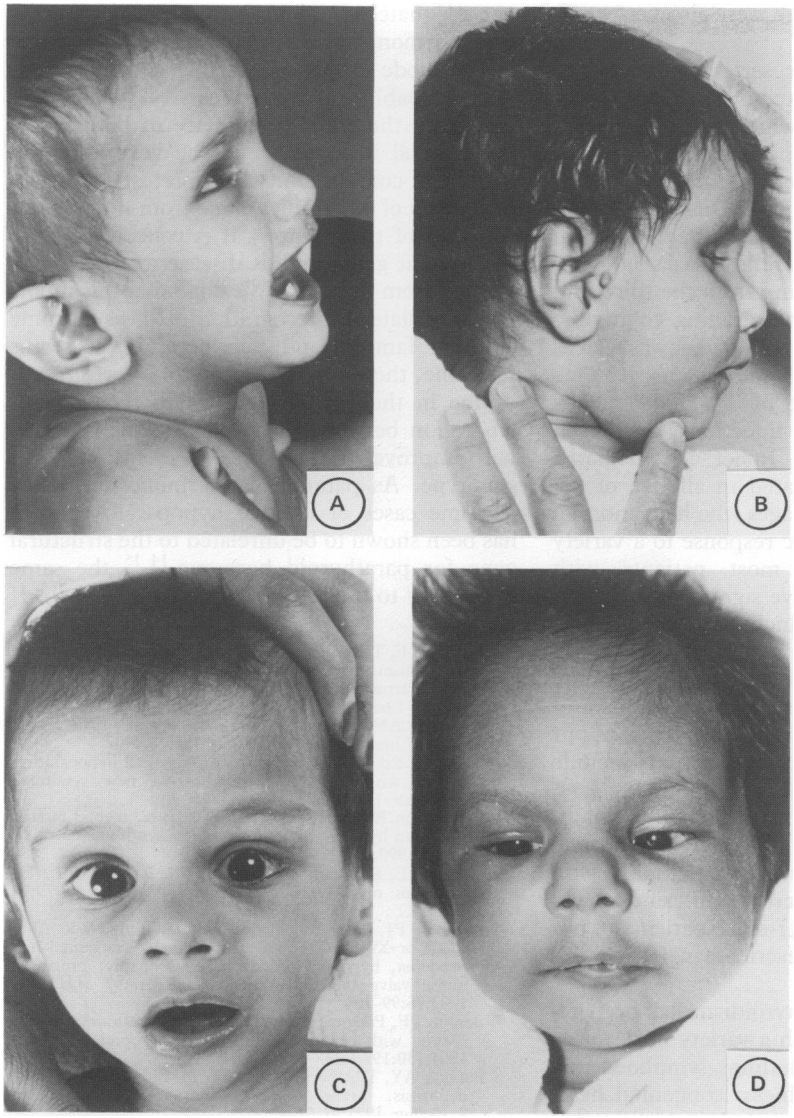
All patients had several dysmorphic features; these and other findings are summarised in table 3. The most characteristic were the craniofacial findings consisting of microcephaly, deep set eyes, thin lips, micrognathia, depressed nasal bridge with beaking of the nose

Table 3 Dysmorphic features and other clinical findings in 12 patients with congenital hypoparathyroidism and severe growth failure

Abnormal:	
Microcephaly	12
Deep set eyes	12
Thin lips	12
Beaked nose tip	10
Low set and/or posteriorly rotated ears	10
Micrognathia	10
Prominent forehead	10
Depressed nasal bridge	10
Small hands and feet	10
Microphthalmos	6
Esotropia	5
Micropenis	4/6
Cryptorchidism	2/6
Nystagmus	3
Epicanthic folds	2
Normal:	
Cardiovascular system	12/12
Absence of visceromegaly	12/12
Growth hormone	8/8
Thyroid function	7/7
T lymphocytes	5/5
Immunoglobulins	5/5

Table 2 Results of biochemical analysis of serum in patients with congenital hypoparathyroidism

Case No	Calcium (mmol/l)	Phosphate (mmol/l)	Magnesium (mmol/l)	Alkaline phosphatase (IU/l)	Parathyroid hormone (pmol/l)	Albumin (g/l)	Creatinine (μmol/l)
1	1·4	2·7	1·1	188	25	38	27
2	1·6	3·4	0·8	238	20·5	37	37
3	1·5	3·3	0·8	88	19	38	28
4	1·2	3·3	1·2	228	17	35	27
5	1·3	4·1	0·8	28	9·1	40	44
6	1·8	4·7	0·8	118	<30	42	40
7	1·75	3·2	0·8	18	<30	44	50
8	1·67	3·5	0·55	300	<30	41	44
9	1·35	3·2	0·6	216	<30	39	60
10	1·8	2·44	0·8	174	<30	42	46
11	2·29	2·45	0·8	260	<30	42	34
12	1·3	3·2	0·5	150	<30	40	35
Normal values	2·1–2·6	1·2–1·95	0·75–1·0	100–300	30–85	37–47	30–60



(A) Case 4: girl with deep set eyes, micrognathia, thin lips, and simple malformed posteriorly rotated ears. (B) Case 2: girl with prominent forehead, depressed nasal bridge, deep set eyes, micrognathia, thin lips, and preauricular tags. (C) Case 1: boy with deep set eyes, broad nasal bridge, prominent forehead, and micrognathia. (D) Case 5: boy with deep set eyes, epicanthic folds, broad nasal bridge.

tip, and external ear anomalies (figure). Small hands and feet and micropenis were also common. There were no cardiac abnormalities detected clinically or radiologically in any patient. Abdominal visceromegaly was absent in all. Thyroid function studies performed in seven of seven patients were normal. Growth hormone concentrations were normal in eight of eight patients. T and B lymphocyte functions were normal in all five patients tested.

Mental retardation of moderate to severe degree was encountered in 10 patients. The remaining two were considered to be mildly retarded. Computed tomography of the brain, performed in nine patients, showed mild to moderate ventricular dilatation in six and intracranial calcification in one. The remaining three were normal.

OUTCOME OF TREATMENT AND FOLLOW UP

All patients received vitamin D treatment in the form of $1,25(OH)_2$ D3 (calcitriol). Dosage ranged from 0·25 to 2·0 μg daily by mouth and was titrated against the serum calcium concentration. Several patients have developed hypercalcaemia which reverted to normal soon after reduction or withdrawal of calcitriol. In addition, they all received calcium supplements (50–100 mg/kg/day of elemental calcium). Two patients required oral magnesium supplements on a temporary basis. Aluminum hydroxide gel was used as phosphate binder in three patients with very high serum phosphate concentrations.

Severe growth failure and psychomotor delay has persisted in all patients despite normalisation of their biochemical abnormalities (table 4). Four patients have died during the course of this study: two from intercurrent infection (pneumonia), the other two from unknown causes.

Table 4 Follow up growth data in patients with congenital hypoparathyroidism

Case No	Birth weight (g)	Age (years)	Weight (kg)	Height (cm)	Weight (SD score)	Height (SD score)
1	1500	3·5	5·4	69·0	−5·8	−7·1
2	3000	5·5	6·4	76·0	−5·2	−7·2
4	Low birth weight	3·8	7·5	75·0	−5·4	−5·9
5	2100	1·3	4·8	59·0	−5·5	−7·6
7	1400	2·0	2·0	44·5	−7·6	−12·5
8	2150	1·0	4·0	52·5	−5·3	−9·0

Discussion

We consider that these 12 patients represent a new syndrome because of the association of severe prenatal and postnatal growth retardation, similar dysmorphic features, and the early clinical presentation caused by hypoparathyroidism, which was diagnosed on the basis of hypocalcaemia, hyperphosphataemia, and low serum concentrations of immunoreactive parathyroid hormone. Further support for this view is found in the report of a group of patients from Kuwait with the same characteristics.[4]

The most striking abnormalities shared by all our patients were the severe intrauterine (11/12) and postnatal growth retardation. Thus all patients have remained appeciably below the third centile for weight and height despite correction of their biochemical abnormalities with vitamin D treatment. Forced nasogastric feeding, tried in three patients, and parenteral nutrition in one, failed to promote any significant growth. This pronounced growth retardation may be appreciated by examining table 4, which shows the weight and height SD score of six long term survivors with this syndrome. In general height or length is more severely affected than weight. Case 2, the oldest in the series, weighed only 6·4 kg and measured 76 cm at 5·5 years of age.

All patients presented with several dysmorphic findings (table 3). The craniofacial features impart such a characteristic appearance on these patients (figure) that some were diagnosed at first sight by house officers who had seen examples before. Microcephaly, deep set eyes, and thin lips were present in all patients. Beaking of nose tip, micrognathia, prominent forehead,

and depressed nasal bridge were also very common abnormalities.

Several patients in the series were referred from other hospitals to exclude the diagnosis of DiGeorge's syndrome, which is also characterised by congenital hypoparathyroidism and facial dysmorphism. There are several differences between patients with DiGeorge's syndrome and those we have described. First, in DiGeorge's syndrome there is aplasia or hypoplasia of structures deriving from the third and fourth pharyngeal pouches leading to thymic aplasia and cellular immunodeficiency as well as hypoparathyroidism.[2 5] None of our patients showed clinical evidence of T cell deficiency such as chronic monilial infections, diarrhoea, rhinitis, or skin rashes. Intact cell mediated immunity was demonstrated in all five of the patients tested at various ages who had a normal T lymphocyte blastogenic response to a variety of mitogens. Second, most patients with DiGeorge's syndrome have significant congenital cardiac anomalies including conotruncal defects and aortic arch malformations.[5] Cardiovascular abnormalities were not seen in any of our cases. Third, the facial dysmorphism of DiGeorge's syndrome is quite unlike that of our patients. Commonly described features include hypertelorism, abnormal and pointed ears, anteverted nostrils, micrognathia, and antimongoloid slant. Of these, only micrognathia and possible ear anomalies were comparable with our cases. Lastly, the severe intrauterine growth retardation observed in 11 of 12 patients in our series is not a feature described in DiGeorge's syndrome.[2]

Congenital hypoparathyroidism has been reported in association with a variety of developmental anomalies, including lymphoedema, nephropathy, nerve deafness, congenital heart disease,[5-8] and chromosomal abnormalities.[9-11] Some of the reported cases may represent incomplete forms or variants of the third to fourth pharyngeal pouch syndrome of DiGeorge. More recently, congenital hypoparathyroidism has been reported in association with the Silver-Russell syndrome[12] and the Kenny syndrome of dwarfism, internal cortical thickening, and medullary stenosis of tubular bones.[13]

The pathophysiology of hypoparathyroidism in our patients and its association with the multiple abnormalities described remain elusive to us. With the available data, it is impossible to tell whether the parathyroid glands were absent or hypoplastic or whether they were present but not adequately producing or releasing parathyroid hormone into the circulation.

The mode of inheritance in this syndrome is most probably autosomal recessive. This is suggested by the equal occurrence in both sexes, the familial incidence, and the very high frequency of consanguinity. Of interest is the fact that seven of 12 families came from the western province of the country. It is conceivable that the mutant gene for this disease may have originated from that area. We hope that this report will stimulate the recognition of the syndrome in other families and elsewhere. If, as seems probable, there is a high gene dose for the syndrome in the Kingdom of Saudi Arabia, collaboration between the paediatricians involved will improve the chance of identifying the genotype. As parathyroid hormone deficiency in some cases of familial hypoparathyroidism has been shown to be unrelated to the structural gene for parathyroid hormone,[14 15] the same may apply to the syndrome we have described.

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