

Hypoparathyroidism and 22q11 deletion syndrome

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Aims: To investigate a population of individuals with 22q11 deletion syndrome for hypocalcaemia.

Methods: A detailed clinical history enquiring into symptoms of hypocalcaemia and blood sampling to assess for hypocalcaemia and hypoparathyroidism, of patients outside the neonatal period known to have the 22q11 microdeletion from fluorescent in situ hybridisation studies was taken.

Results: Sixty one individuals were identified, of whom 23 were untraceable and one was unable to give informed consent. Biochemical investigations were performed on 27 subjects. Ten subjects had review of notes only. Four subjects had previously identified hypoparathyroidism. A new case of hypoparathyroidism was identified. Three subjects had borderline hypocalcaemia.

Discussion: In this population of patients with 22q11 deletion syndrome, 13% of the total or 30% of those biochemically assessed had evidence of reduced serum calcium concentrations. It is likely that 13–30% of patients with 22q11 deletion syndrome have possible hypoparathyroidism outside the neonatal period. Reported symptoms of hypocalcaemia did not correlate with biochemical evidence of persisting hypocalcaemia. We have shown that previously undiagnosed asymptomatic hypoparathyroidism occurs in patients with 22q11 deletion syndrome and conclude that screening of this population should be considered.

The 22q11 syndrome has a minimum prevalence of 13 per 100 000 live births, making it the most frequent contiguous gene deletion syndrome in humans and second only to trisomy 21 as a chromosomal cause of significant congenital heart disease.¹ Transient neonatal hypocalcaemia is a well recognised feature of individuals with 22q11 deletion syndrome. This syndrome includes DiGeorge syndrome,² velocardiofacial syndrome,³ and conotruncal anomaly face syndrome.⁴

Hypoparathyroidism is classically a transient feature in the neonatal period and more a characteristic of the DiGeorge syndrome subgroup of 22q11 deletion syndrome. Ryan and colleagues⁵ reported hypocalcaemia in 60% of subjects with 22q11 deletion syndrome, mostly in the neonatal period, but some in childhood; one patient was diagnosed aged 18 years. The natural history of hypocalcaemia remains poorly understood or defined. It has been shown to be both latent⁶ and overt⁷ in children and adolescents with 22q11 deletion syndrome. Adachi and colleagues,⁸ in reviewing their population of patients with hypoparathyroidism, found 10 of 14 children to have 22q11 microdeletion with an age of diagnosis of hypoparathyroidism between 9 days and 13 years.

The population of individuals with 22q11 deletion syndrome are cared for by many different specialists because of their variable phenotype. We hypothesised that in a population of patients in South Wales with known 22q11 deletion syndrome, it was probable that some may have undiagnosed hypoparathyroidism. The complications of chronic hypocalcaemia due to hypoparathyroidism may include lethargy, irritability, emotional lability, convulsions, cataracts, dental abnormalities, and calcification of basal ganglia and subcutaneous tissues. The treatment of hypoparathyroidism is relatively simple and can bring about profound clinical improvement.⁹ The aim of our study, therefore, was to investigate for hypoparathyroidism in a population of individuals outside the neonatal period known to have 22q11 deletion syndrome.

SUBJECTS AND METHODS

Patients known to have the 22q11 microdeletion from FISH (fluorescent in situ hybridisation) studies were eligible for

recruitment into the study. Patients with the 22q11 microdeletion were identified from registers held by the Institute of Medical Genetics, and the Paediatric Cardiology and Endocrine Services.

Investigation consisted of a detailed clinical history enquiring into symptoms of hypocalcaemia, blood sampling for measurements of serum concentrations of calcium (normal range for children 2.20–2.70 mmol/l and adults 2.2–2.6 mmol/l respectively), albumin (normal range 35–50 g/l), parathyroid hormone (PTH, normal range 0.9–5.4 pmol/l), phosphate (normal adult range 0.8–1.45 mmol/l), magnesium, and alkaline phosphate and a urine sample for estimation of the calcium:creatinine ratio. Any patient not able to attend for blood testing had review of their notes and biochemistry results for evidence of previous abnormalities of calcium biochemistry. Ethical approval was obtained from the South Glamorgan local research ethics committee.

RESULTS

Sixty one individuals were identified with 22q11 deletion syndrome, of whom 23 had no hospital records in our unit, were untraceable, or could not be contacted. One patient with psychiatric illness was unable to give informed consent. Biochemical evaluation was performed on 27 subjects, of whom four were already diagnosed with hypoparathyroidism. Ten subjects underwent review of their hospital notes only.

Table 1 shows patient details. The children with previously identified hypoparathyroidism on treatment were aged 0.01–0.36 years at diagnosis. Three of these had persistence of neonatally diagnosed hypoparathyroidism. Figure 1 shows the corrected serum calcium concentrations of those other patients who underwent biochemical assessment. The patients with borderline biochemistry all had marginally reduced serum calcium concentrations in the absence of increased PTH and phosphate concentrations. Two members of this group had normal serum calcium concentrations on repeat blood tests.

One patient in the normal group had a serum calcium concentration of 2.17 mmol/l, but with a slightly raised serum PTH concentration of 6.8 pmol/l and a serum phosphate concentration of 1.11 mmol/l, which did not suggest biochemical

Table 1 Details of subjects studied

	Median age in years (range)	Number of individuals	
		Biochemical assessment	Review of case notes
Hypoparathyroid (previously identified)	0.02(0.01–0.36)	4	0
Hypoparathyroid (identified by biochemical assessment)	32.9	1	0
Borderline biochemistry	16.8 (10.2–37.5)	3	0
Normal	9.1 (0.2–42.5)	19	10

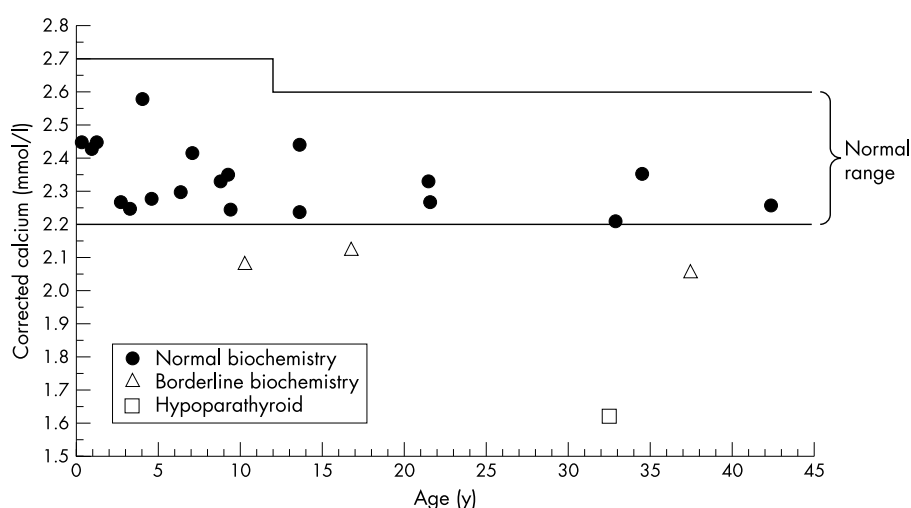


Figure 1 Relation between age and corrected serum calcium concentrations (normal range = mean \pm 2 SD, corrected calcium (mmol/l) = measured serum calcium (mmol/l) + ((40 – albumin (g/l)) \times 0.02)) of subjects not previously known to have hypoparathyroidism who underwent biochemical screening.

evidence of hypoparathyroidism. A further patient had a normal serum calcium concentration of 2.35 mmol/l, but with an undetectable serum PTH concentration and was assigned to the normal group in the absence of hypocalcaemia.

Of those who underwent biochemical investigations a new case of hypoparathyroidism was identified. This subject was 32 years old, under follow up by the cardiologists for a ventricular septal defect and had not previously undergone measurement of serum calcium concentration. He had learning difficulties, but was otherwise asymptomatic. Trousseau's sign could be elicited, but he had no other signs of hypocalcaemia. Biochemical investigations showed a serum calcium concentration of 1.62 mmol/l, phosphate 2.1 mmol/l, and PTH 1.3 pmol/l. He was subsequently treated with 1α -hydroxycholecalciferol.

Symptoms of possible hypocalcaemia in those who underwent biochemical assessment (excluding those previously diagnosed with hypoparathyroidism) were recorded and are shown in table 2. No patients were receiving anticonvulsant treatment.

Table 2 Symptoms of hypocalcaemia in the biochemically investigated group (excluding those previously diagnosed with hypoparathyroidism)

Symptom	% of patients with reported symptoms
Pins and needles	24
Unusual or unexplained weakness	18
Unusual or unexplained irritability	24
Muscle cramps or spasms	27
History of seizures	9

DISCUSSION

In this population of patients with 22q11 deletion syndrome, 13% had biochemical evidence of reduced serum calcium concentrations. These subjects accounted for 30% of those who underwent biochemical investigations. Furthermore, it is of interest that the distribution of serum calcium concentrations in apparently normocalcaemic individuals tends to fall within the lower half of the normal range (fig 1). Reported symptoms of hypocalcaemia did not correlate with biochemical evidence of persisting hypocalcaemia. However, serum calcium concentrations were not measured at the time of symptoms.

We have therefore shown that previously undiagnosed asymptomatic hypoparathyroidism occurs in patients with 22q11 deletion syndrome and conclude that serum biochemical screening of this population should be considered. Although patients with borderline biochemistry may represent normal individuals whose results fall more than two standard deviations below the mean, these subjects may be at increased risk of biochemically significant hypoparathyroidism and probably merit further monitoring of biochemistry in the future. Reported symptoms suggestive of hypocalcaemia and the urinary calcium creatinine ratio did not distinguish those with hypocalcaemia and would not be reliable screening methods. Our study is limited to patients who have largely received clinical follow up following their diagnosis of 22q11 deletion and who may therefore represent those who are clinically more severely affected by their gene deletion. The natural history of hypoparathyroidism in this syndrome is poorly understood given its variable clinical presentation. We suggest therefore, that prospective studies of children with 22q11 deletion syndrome are required to determine whether and how biochemical screening of this population for hypoparathyroidism should take place.

In the meantime, we would suggest that children with 22q11 deletion syndrome should have their care coordinated by paediatricians with an interest in the condition. Patients with 22q11 deletion require a protocol for follow up to ensure that all aspects of the variable phenotype are assessed with referral to the appropriate specialist when required. With regard to the risks for developing hypoparathyroidism we would suggest that families with 22q11 syndrome are aware of the symptoms that might occur with hypocalcaemia. Serum calcium estimation should be considered at the time of diagnosis of 22q11, when symptoms of hypocalcaemia occur, prior to surgery, and during pregnancy. Finally genetic investigation for 22q11 microdeletion should be considered in patients with idiopathic hypoparathyroidism.

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ARCHIVIST

Imaging after urinary tract infection reconsidered

Researchers in three US centres (Pittsburgh, Pennsylvania; Columbus, Ohio; and Boston, Massachusetts) have offered a minimalist view of the necessity for imaging studies after urinary infection in young children (Aljandro Hoberman and colleagues. *New England Journal of Medicine* 2003;**348**:195–202; see also editorial *ibid*: 251–2).

They studied 309 children aged 1 to 24 months with a first febrile urinary tract infection (10 or more white cells per cubic millimeter in uncentrifuged urine, 1 or more gram-negative rods per 10 oil-immersion fields, and 50000 or more colony forming units of a single pathogen from a catheter specimen). All 309 children had a renal ultrasound scan and a technetium-99m-labelled dimercaptosuccinic acid (DMSA) scintigram within 48 hours of diagnosis, 302 had a voiding cystourethrogram after 1 month and 275 had repeat DMSA scan and voiding cystourethrogram at 6 months.

The ultrasound scan was abnormal in 37 children (12%) but the abnormalities found were not considered to have affected treatment. Urinary tract obstruction was not found. (The authors of this paper attribute this to the use of antenatal ultrasound scanning but give no details of such scanning in their study population.) They recommend that ultrasound scanning should not be performed after a first urinary tract infection in children who have had an antenatal scan after 30 weeks gestation. The initial DMSA scans gave findings compatible with acute pyelonephritis in 190 children (61%). Only one child had a renal scar at that time. No child with a normal first DMSA scan had an abnormal follow up scan at 6 months. Twenty-six (15%) of 173 children with appearances of acute pyelonephritis on the first scan had renal scarring on the second but the extent of renal parenchymal involvement was small. These authors conclude that DMSA scanning is of limited value since it is unclear how the findings should influence treatment. They prefer to emphasise the importance of accurate diagnosis of urinary infection in subsequent febrile illnesses on follow up after a first urinary infection.

Voiding cystourography at 1 month showed vesicoureteric reflux in 117/302 children (39%). Fresh renal scarring occurred in 16/109 (15%) with reflux and 10/166 (6%) without. These authors point out that detecting reflux is only beneficial if prophylactic antimicrobial treatment prevents disease progression and that is unproved. (Their conclusion illustrates the ambiguity that can result from use of the passive voice. They state that “the use of voiding cystourethrogram is recommended” but do not make it clear whether it is recommended by themselves or by others.)

They are against the routine use of ultrasound scans. They probably favour the use of voiding cystourethrogram but qualify this approval with a call for further studies of the usefulness of prophylactic antimicrobial treatment. They suggest that a single DMSA scan is not useful and repeated DMSA scanning could probably be avoided by paying strict attention to the diagnosis and treatment of repeat urinary tract infections. The debate, which seems to have been going on forever, is obviously far from over.