Hypoparathyroidism and 22q11 deletion syndrome

S C Taylor, G Morris, D Wilson, S J Davies, J W Gregory

T he 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. Transient neonatal hypocalcaemia is a well recognised feature of individuals with 22q11 deletion syndrome. This syndrome includes DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome.

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 colleagues 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 latent and overt in children and adolescents with 22q11 deletion syndrome. Adachi and colleagues, 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. 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 phosphatase 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, 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.
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 others 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.

**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.

### Table 1: Details of subjects studied

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

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

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of patients with reported symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pins and needles</td>
<td>24</td>
</tr>
<tr>
<td>Unusual or unexplained weakness</td>
<td>18</td>
</tr>
<tr>
<td>Unusual or unexplained irritability</td>
<td>24</td>
</tr>
<tr>
<td>Muscle cramps or spasms</td>
<td>27</td>
</tr>
<tr>
<td>History of seizures</td>
<td>9</td>
</tr>
</tbody>
</table>

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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.

References

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