

Case Report

## DiGeorge syndrome presenting as late onset hypocalcaemia in adulthood

Philip C Johnston\*, Deirdre K Donnelly<sup>+</sup>, Patrick J Morrison<sup>+</sup>, Steven J Hunter\*

Accepted 15 May 2008

### ABSTRACT

We report a 29 year old female with mild dysmorphic facial features, presenting with late onset symptomatic hypocalcaemia in adulthood. The presence of hypoparathyroidism in association with a history of transient neonatal hypocalcaemia and velopharyngeal incompetence during childhood, prompted chromosomal analysis for DiGeorge Syndrome. *Fluorescence in situ hybridisation (FISH)* analysis revealed a deletion of chromosome 22q11.2. This case is unusual in that the patient remained asymptomatic apart from speech and language delay after the first few months of life and presented in adulthood without any associated immunological, cardiac or renal abnormalities. The diagnosis has important implications for health and family planning.

**Key Words:** DiGeorge syndrome, hypocalcaemia, late presentation, deletion 22q11.2

### INTRODUCTION

DiGeorge syndrome arises because of a microdeletion of chromosome 22q11.2, and in rare instances 10p13. Hypoplasia of the thymus and parathyroid glands, aortic arch as well as facial malformations and learning difficulties are common. We present a very rare case of DiGeorge syndrome presenting as hypocalcaemia in adulthood, without any associated immunological, cardiac or renal abnormalities.

### CASE REPORT

A 29 year old female, one of three children born to a non consanguineous caucasian couple presented initially to her general practitioner with a two year history of recurrent numbness and tingling in her hands and feet. This was associated on occasions with spasms of her toes. There were no obvious precipitating factors for her symptoms. Initial biochemistry testing revealed hypocalcaemia, the corrected calcium was 1.64mmol/L (ref range: 2.10-2.60mmol/L).

Her past medical history included transient neonatal hypocalcaemia 1.55mmol/L present when she was two days old, not associated with seizure activity. This responded to calcium and vitamin D replacement with a normalisation of her serum calcium 2.35mmol/L after one month. No hypocalcaemia was documented after this period, up until the age of twenty nine. Velopharyngeal incompetence was present in the form of nasal speech during childhood which subsequently resolved with speech and language therapy. The patient had learning difficulties but was now in full time employment. She had no history of cardiac or renal



Fig 1. Lateral view of the proband illustrating short philtrum with thin upper lip, low set ears, and mild micrognathia.

abnormalities. There was no significant family medical history and she had no children. She was referred to our endocrinology department by her General Practitioner.

On examination there was mild facial dysmorphism with a short philtrum, thin upper lip, low set ears, and mild micrognathia (Figure 1). Her nose was not unduly prominent or 'squared' as in classic cases of 22q deletion syndrome. Trousseau's sign was positive. Cardiovascular and respiratory examinations were unremarkable.

Parathyroid hormone was inappropriately normal at 36pg/ml (RR 10-65). The presence of hypoparathyroidism in association with a history of transient neonatal hypocalcaemia and velopharyngeal incompetence during childhood, prompted chromosomal analysis for DiGeorge syndrome. *Fluorescence in situ hybridisation (FISH)* analysis, using the Vysis N25 probe specific to the DiGeorge region, showed a deletion of chromosome 22q11.2 (Figure 2). Karyotyping of her mother and sister was normal. Her brother was not available for

\*Regional Centre for Diabetes and Endocrinology, Royal Victoria Hospital, Belfast, N. Ireland, BT12 6BA United Kingdom, and +Department of Medical Genetics,

A Floor, Belfast City Hospital Trust, Belfast, BT9 7AB, United Kingdom.

Correspondence to Dr Hunter

steven.hunter@belfasttrust.hscni.net

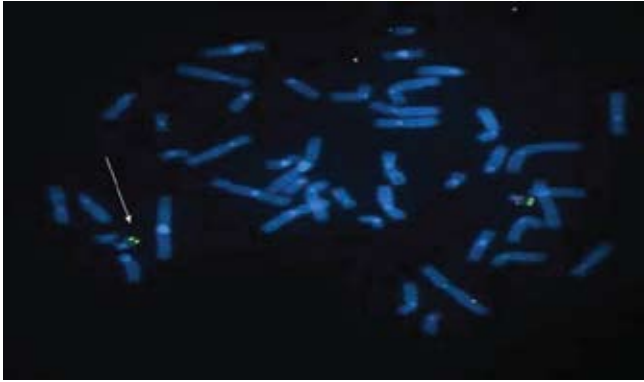


Fig 2. FISH analysis using the Vysis N25 probe specific to the Di-George region, showing a deletion of chromosome 22q11.2 (arrow).

testing (her father was deceased). This deletion was assumed to be sporadic although we cannot be conclusive without being able to test the father although neither he nor the brother had any facial features suggestive of 22q deletion syndrome from family photographs. The patient was informed of the diagnosis and placed on vitamin D and calcium supplementation, her serum calcium normalised. Further history obtained from the patient's mother confirmed no recurrent infections during childhood, immunological testing demonstrated a normal CD4 count of  $1.16 \times 10^9/L$  (RR 0.5 - 1.6) and a CD8 count of  $0.65 \times 10^9/L$  (RR 0.2 - 0.7). Measurement of T cell function, by in vitro lymphocyte stimulation revealed a PHA (T-cell stimulation index) of 46 units (normal >20). Transthoracic echocardiogram revealed no cardiac abnormalities. Renal ultrasound and DEXA (dual-energy X-ray absorptiometry scan) were normal.

## DISCUSSION

DiGeorge syndrome is associated with submicroscopic deletions of chromosome 22q11. Most cases arise as a *de novo* deletion, but in around 8% of patients the condition is familial with autosomal dominant inheritance<sup>1</sup>. Recent data has suggested that the incidence is close to 1 in 4000 live births, which reflects increased clinical awareness and enhanced genetic techniques<sup>2</sup>. The resulting syndrome is thought to result from a developmental defect that involves the third and fourth pharyngeal pouches, by defective migration of the neural crest cells during the fourth week of embryogenesis. Hypoplasia of the thymus and parathyroid glands, aortic arch as well as facial malformations and learning difficulties are

common<sup>3</sup>. The immune system is involved in around 80% of patients with a deletion of chromosome 22q11. Patients have reduced T cell numbers due to thymic hypoplasia, however T cell function tends to be preserved as evident in this case, apart from rare instances, 5% of patients who have no T cells. The absolute T cell number is not predictive of the incidence of infections<sup>4</sup>. Hypoplastic parathyroid glands associated with neonatal hypocalcaemia generally improves over the first year as the parathyroid glands hypertrophy, the asymptomatic period after childhood in this patient could be reflective of this. Many patients with DiGeorge syndrome require renal imaging to detect absent or dysplastic kidneys, vesico-ureteric reflux and nephrocalcinosis. Treatment options include calcium and vitamin D supplementation and in some severe neonatal cases, thymus transplantation<sup>5</sup>.

## CONCLUSIONS

This case is unusual, in that the patient remained asymptomatic apart from speech and language delay after the first few months of life and later presented in adulthood, without any immunological, cardiac or renal abnormalities associated with DiGeorge syndrome. The diagnosis has important implications for health and family planning. The diagnosis of DiGeorge syndrome should be considered in all patients who present with primary hypoparathyroidism even in the absence of the associated clinical characteristics of this syndrome.

The authors have no conflict of interest to declare in relation to the content of this manuscript.

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