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CASE REPORT

Symptomatic hypoparathyroidism based on a 22q11 deletion first diagnosed in a 43-year-old woman

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ABSTRACT

Congenital hypoparathyroidism usually manifests in early childhood with hypocalcaemia with or without clinical characteristics. This report describes a Caucasian woman who, at the age of 43 years, was diagnosed with dysgenesis of the parathyroid glands due to a *de novo* microdeletion in chromosome 22q11 or DiGeorge syndrome. This syndrome is characterised by a considerable variability in clinical symptoms, including heart defects, thymic hypoplasia and mental retardation. Our patient presented with generalised convulsions due to extreme, symptomatic hypocalcaemia. The convulsions had been apparent for 18 months at the time of the diagnosis. Remarkably, whereas parathyroid hormone levels were undetectable, the 1,25-dihydroxy vitamin D level was normal. Chromosome 22q11 deletion was confirmed by fluorescence *in situ* hybridisation analysis.

KEYWORDS

22q11, DiGeorge, hypocalcaemia, hypoparathyroidism

CASE REPORT

A 43-year-old Caucasian woman was evaluated for thrombocytopenia. She had been suffering from convulsions for 18 months before presentation, for which antiepileptic agents were prescribed with insufficient response. At the time of presentation of the seizures bilateral calcifications were seen in the basal ganglia and cerebellum on CT scanning of the brain. The patient's history also included bronchitis, bilateral surgery for cataract and a significant learning disability. Her medication consisted of levetiracetam and salbutamol.

At physical examination we saw a woman of short stature who was noted to have subtle facial dysmorphisms (*figure 1*), i.e. a high forehead, a long philtrum, mild ptosis and

Figure 1. *Close up photograph of the patient with hypoparathyroidism, showing the high forehead, a long philtrum, mild ptosis and upslanting palpebral fissures*

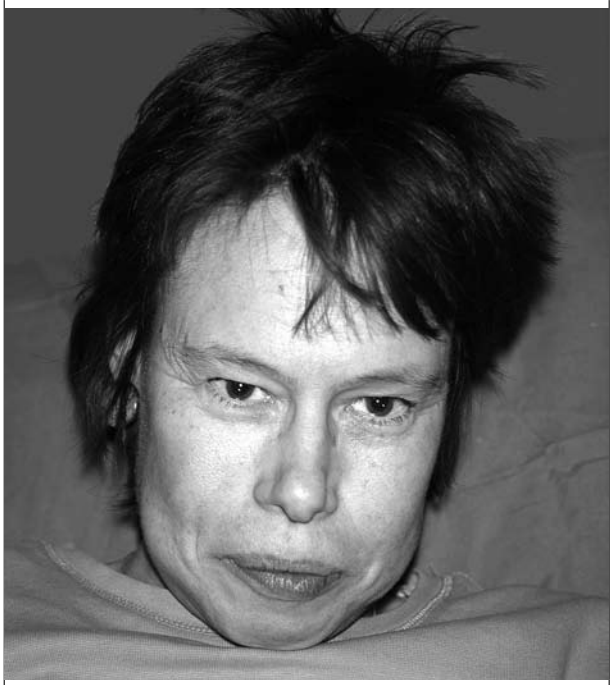


Photo with permission from patient.

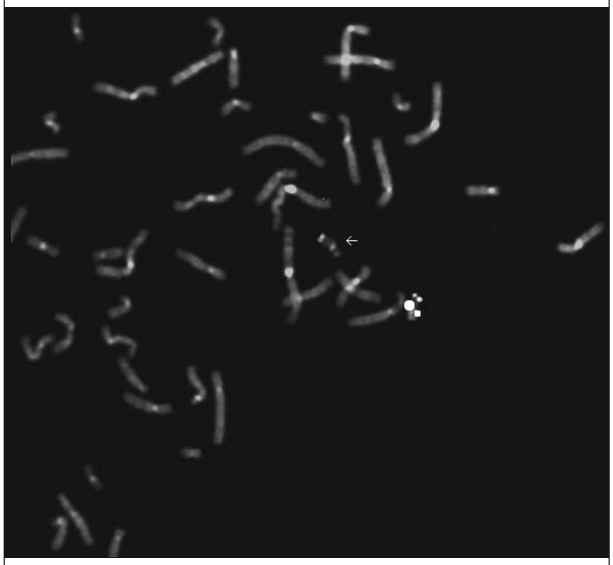
upslanting palpebral fissures. Examination of the heart and lungs was without abnormal findings but there was a remarkable hypoplasia of the breasts. Abdomen and external genitals were normal and inspection of the extremities showed no abnormalities. The patient gave oral consent for publication of this case report.

Blood tests showed a marked thrombocytopenia with a mildly lowered red cell count and a normal white cell count with normal differential. Kidney function was slightly impaired, but potassium and sodium were normal. There was an extreme hypocalcaemia of 1.27 mmol/l (ionised calcium 0.58 mmol/l) at a normal albumin level. Serum magnesium was low at 0.47 mmol/l. A spot urinary calcium was 0.54 mmol/l, which was considered to be elevated as related to the serum calcium concentration as the patient was unable to collect a 24-hour urinary sample. Hormonal measurements included a normal thyroid-stimulating hormone, mildly lowered 25-hydroxy vitamin D level, a normal 1,25 dihydroxy vitamin D level and an undetectable concentration of the parathyroid hormone (PTH). PTH levels remained undetectable after correction of hypomagnesiaemia. The diagnosis of hypoparathyroidism with extreme hypocalcaemia, resulting in seizures was made. The differential diagnosis comprised both acquired and congenital hypoparathyroidism. There was no evidence for acquired hypoparathyroidism, i.e. surgery, infections, or storage diseases. Congenital causes of hypoparathyroidism can be differentiated into several rare disorders. For example, it can result from destruction of the parathyroid glands due to an autoimmune process. Congenital hypoparathyroidism can be found in association with other endocrinopathies or specific developmental and mitochondrial disorders.[1]

Based on the hypoparathyroidism and the dysmorphic phenotype, the possibility of chromosome 22q11 deletion syndrome was suspected. Standard chromosome analysis showed a normal karyotype. Fluorescence *in-situ* hybridisation analysis was performed according to previously established methods[2] with biotine-labelled cosmid probes 122B5 and M51, demonstrating a deletion for chromosome 22q11.2 (DiGeorge/Shprintzen region) (*figure 2*).

Electrocardiography showed a mildly prolonged QT interval and a transthoracic echocardiogram revealed normal cardiac chambers and normal outflow tracts. To analyse the patient's thrombocytopenia, a bone biopsy was performed. Pathological examination revealed a mild marrow fibrosis with normal maturation and count of all haematopoietic cell lines. These findings are consistent with excess platelet turnover as is sometimes seen in levetiracetam use, but have also been mentioned as a part of the 22q11 deletion syndrome.[3] Conventional X-rays of the hands turned out to be normal and bone mineral densitometry was performed, also showing values in the normal range.

Figure 2. *Fluorescent in-situ hybridisation (FISH) using the cosmid probe 122B5 (white), shows a deletion of the DiGeorge/Shprintzen region on one chromosome 22q11.2*



The BAC probe CTD-3018K1 (red) is a subtelomeric probe and is used as a control probe. This probe shows hybridisation signals on both chromosomes 22.

Levetiracetam was stopped and the patient was initially treated with 1 µg calcitriol, which was tapered off, 1 g calcium, 1448 mg magnesium hydroxyde and 25 mg hydrochlorothiazide daily. The convulsions disappeared as the serum calcium concentration rose to normal at 2.05 mmol/l.

DISCUSSION

Hypoparathyroidism due to congenital agenesis or hypoplasia of the glands typically becomes apparent in early childhood and is a rare finding in the adult patient. This case report describes a 43-year-old patient with complete hypoparathyroidism due to chromosome 22q11 deletion syndrome, a congenital condition that results in hypoplasia of the parathyroid glands and is usually diagnosed in early life. In addition to the biochemical findings, some clinical characteristics, such as subtle facial dysmorphisms, short stature and mental impairment, pointed to this syndrome. It was only when the patient developed thrombocytopenia, probably due to the use of anticonvulsant drugs, that the serum calcium levels were evaluated and a severe hypocalcaemia, which had probably been present for years, was found. This eventually resulted in the diagnosis of 22q11 microdeletion syndrome.

Cerebral calcifications are relatively common in hypoparathyroidism and its aetiology has not been completely elucidated. It may be related to the duration of

hypocalcaemia and hyperphosphataemia more than to the lack of parathyroid hormone itself.[4]

The 22q11 deletion syndrome, also known as the DiGeorge syndrome, Shprintzen syndrome or velo-cardio-facial syndrome, was first described in 1965 in children with the triad of hypoparathyroidism, recurrent infections and thymic hypoplasia.[5] As a consequence of the microdeletion, there is a congenital failure in the development of the derivatives of the various pharyngeal arches and pouches.[6] Approximately 1/7500 live births are affected by this deletion, which typically occurs *de novo*, making it the most common contiguous gene deletion syndrome in humans.[3]

In addition to the originally described triad, a wide variety of clinical findings may accompany the 22q11 deletion syndrome. Most patients, in contrast to our patient, have structural heart disease[3,7] and more or less obvious dysmorphisms of the face and are therefore diagnosed in early childhood. A striking feature of the patient in this case report is the time of diagnosis, at the age of 43. She became symptomatic at age 41, when she developed generalised seizures. To the best of our knowledge, our patient is the eldest person in whom the syndrome has been diagnosed. A similar case was described in a 32-year-old patient a few years ago.[8] A plausible explanation for the late-onset symptomatic hypocalcaemia is inadequate parathyroid reserve, in which PTH secretion may be sufficient to maintain normocalcaemia in normal conditions, but is unable to create an adequate response in the situation of hypocalcaemic stress, which for example can occur during ageing, surgery, infection or pregnancy.[9] Symptomatic hypocalcaemia, however, rarely develops because of the compensatory increase in the PTH secretion, which is defective in our patient.

Of interest is the absence of structural changes in the patient's bone. Most patients with chronic depletion of PTH develop abnormalities in bone mineralisation, i.e. increased bone mineral density,[10] though skeletal abnormalities are only prevalent in 17 to 19% of patients with DiGeorge syndrome.[11] We do not have a plausible explanation for this finding, but suppose that in our patient parathyroid function deteriorated over time by mechanisms that are unknown. On the other hand, it can be envisaged that she could maintain low calcium levels by the extrarenal hydroxylation of 25-hydroxy vitamin D. This is supported by the finding of low normal 1,25-dihydroxy vitamin D levels in our patient.[12]

CONCLUSION

Hypoparathyroidism first diagnosed in adulthood may, in rare cases, be due to parathyroid gland hypoplasia, secondary to the chromosome 22q11 deletion syndrome. The diagnosis could be missed due to either the unfamiliarity of physicians with the syndrome or the variable and sometimes subtle phenotype. Because chromosome 22q11 deletion is relatively common, the diagnosis should be considered in patients with idiopathic hypoparathyroidism because of the potential benefit that can be derived from genetic counselling.

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