DiGeorge Syndrome Presenting as Hypocalcemia in an Adult Woman

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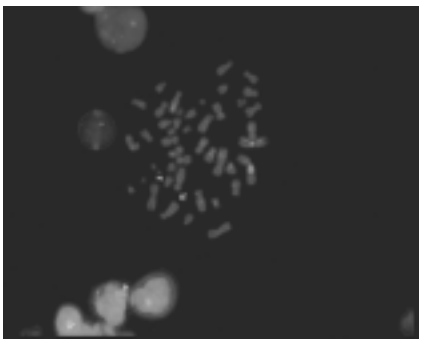
In 1968 Angelo DiGeorge, an American pediatrician, described a syndrome of congenital thymus absence with resulting immunologic consequences, concurrent hypoparathyroidism and cardiac abnormalities. This syndrome now carries his name and is caused by chromosome 22q11.2 deletion (DiGeorge syndrome chromosome region, or DGCR). As is the case with most genetic disorders, DiGeorge syndrome is usually diagnosed in early childhood. We describe an adult woman presenting with symptomatic hypocalcemia, ultimately diagnosed as DiGeorge syndrome.

Patient Description

A 47 year old woman was admitted with a one week history of progressive weakness and involuntary hand movements. She reported similar symptoms occurring occasionally since childhood, but never sought medical attention for this problem. Past medical history was remarkable for primary infertility. She had immigrated to Israel from the Ukraine 3 years prior to her admission. She is the younger of her parent's two children and was unaware of any similar symptoms in family members. Her physical development was normal, but learning difficulties encountered during the school years required her placement in an institution for mentally retarded children.

Physical examination revealed an obese adult woman in no apparent distress. Her vital signs were normal. She had subtle dysmorphic features, including low set ears, wide nasal bridge and a small fish-like mouth. Oral examination revealed no teeth, and white plaques resembling Candida on the tongue. Bilateral cataracts were observed. Heart, lungs and abdomen examination was normal. She had positive Trousseaux sign, and the neurologic examination showed mild symmetric weakness. Her electrocardiogram and chest X-ray were unremarkable. Blood tests revealed hypocalcemia (calcium 6.6 mg/dl) and hyperphosphatemia (phosphate 5.5 mg/dl); serum albumin was normal. Twenty-four hour calcium excretion in urine was low, 12 mg/24 hr (normal 100–300). This value remained low even after initiation of calcium and vitamin D3 treatment. Parathyroid hormone level was low, 2.6 (normal 7–53). Thyroid-stimulating hormone was elevated, 6.1 (normal 0.39–4) with normal free thyroxine. ACTH stimulation test and levels of lactate hydrogenase, follicle-stimulating hormone and prolactin were all within normal limits. Titers of antithyroid autoantibodies were anti-TPO 587 IU/ml (normal 0–50) and anti-thyroglobulin-Ab 2,996 IU/ml (normal 0–100). Serum protein electrophoresis showed normal distribution of protein fractions. Computed tomography of the brain showed symmetric calcifications of basal ganglia and centrum semiovale, consistent with long-standing diseases involving calcium metabolism. There was a normal amount of circulating B and T lymphocytes with a CD4+/CD8+ ratio 2:1. Transthoracic echocardiography was normal.

The diagnosis of polyglandular autoimmune syndrome type I was considered because of the association of hypoparathyroidism, infertility and oral findings consistent with candidiasis. However, the adrenal function test was normal, and there was no history of recurrent infections with Candida



FISH analysis of the patient's lymphocytes using the DiGeorge probe (Tuple1-Q-BIOgene) showing a deletion of 22q11.

Cytogenetic study (FISH) revealed 22q11.2 deletion [Figure]. Based on probable lifelong hypocalcemia, abnormal facies and the typical 22q11 deletion, a diagnosis of DiGeorge syndrome was reached. She was treated with oral supplementation of vitamin D3, calcium and L-thyroxin and was discharged to outpatient follow-up.

Comment

DiGeorge syndrome is a frequent chromosome abnormality, with an estimated birth prevalence in Europe of 1:4,000. It is second only to Down syndrome as a cause of congenital heart defects [1]. Nearly 80% of cases represent *de novo* mutations; translocations and autosomal dominant inheritance are the causes of the remaining cases. Although more than 90% of cases

have similar deletions in the DGCR, the phenotypic spectrum of DiGeorge syndrome varies greatly: from 10–25% of cases being asymptomatic to relatively few with severe hypocalcemia and immune deficiency leading to early death [2]. In 1993 Wilson proposed the acronym CATCH-22, describing frequent manifestations of 22q11.2 deletion – Cardiac abnormality, Abnormal facies, T cell deficit due to hypoplasia of thymus, Cleft palate and Hypocalcemia – along with chromosome 22 deletions. Mild mental retardation is also a common feature of the syndrome.

Disorders of the immune system are one of the hallmarks of DiGeorge syndrome. Both cellular and humoral components of the immunity might be impaired. Often, recurrent infections raise the suspicion of immune deficiency and ultimately lead to the correct diagnosis. With increasing age, various autoantibodies are found, occasionally producing clinical disease. Diabetes mellitus, anemia, idiopathic thrombocytopenic purpura and autoimmune thyroid disease (as in this case) are associated with the syndrome. The pathogenesis of these disorders has not been elaborated [3].

The treatment of DiGeorge syndrome is largely symptomatic. Calcium supplements and 1,25-cholecalciferol are indicated to treat hypocalcemia. Clefts may be submucous and should be actively sought. Cardiac defects are the usual focus of clinical management. Early echocardiography is essential in any child in whom other features suggest the diagnosis. Thymic transplantation is efficacious and well tolerated, and should be considered as treatment for infants with complete DiGeorge syndrome [4,5].

In summary, we describe a patient diagnosed with a mild form of DiGeorge syndrome late in life. This report underscores the importance of the special vigilance required when treating patients emigrating from medically under-served countries, particularly the need to consider pediatric diseases that may present in adult patients, as a full-blown syndrome, or, as in this case, in mild form.

DGCR = DiGeorge syndrome chromosome region

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