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SCIENTIFIC LETTER

Alterations in NeuroD1. Infrequent cause of infantile and juvenile diabetes

Alteraciones en el NeuroD1. Causa infrecuente de diabetes infantil y juvenil

Maturity-onset diabetes of the young (MODY) is part of the differential diagnosis of diabetes in the paediatric population and becomes relevant in those patients with a family history of diabetes in more than two consecutive generations (including gestational diabetes), an initial finding of hyperglycaemia without ketoacidosis and in those with a negative autoimmune pancreatitis study. It requires a confirmatory genetic study.[1,2] Of the 14 subtypes described to date, mutations in the NEUROD1 gene make up the MODY-6 subtype. It accounts for a very small percentage (<1%) within the 1–6% that MODY diabetes represents in all paediatric patients with diabetes.[3,4] However, it is estimated that both MODY-6 and the MODY diabetes group are underdiagnosed, with the alterations being attributed to type 1 or 2 diabetes.[1]

NEUROD1 mutations were initially linked to the onset of type 2 diabetes.[5] It is now known that homozygous mutations in the NEUROD1 gene are associated with severe manifestations (such as neonatal diabetes and neurodevelopmental disorders) due to expression of this gene in the central nervous system.[6] It is the heterozygous mutations that cause the onset of diabetes in childhood or youth and, more rarely, have been associated with neurodevelopmental disorders.[7] NEUROD1 is involved in the maturation of beta cells, in the pancreatic transcription of insulin by binding to its promoter, in addition to playing a role in glucose homeostasis by binding to and activating the promoter of sulfonylurea receptor 1 (SUR1), glucokinase (GCK), glucose 6-phosphatase catalytic subunit and PAX6.[8]

We present two clinical cases of MODY-6 diabetes with onset in the paediatric age.

The first case was a five-year-old Caucasian girl with no history of interest (physical examination without dysmorphism and normal psychomotor development and weight-to-height ratio) with a finding of hyperglycaemia in tests carried out according to preoperative protocol. She had no cardinal symptoms. A blood glucose profile was performed with basal glucose levels between 100 and 160 mg/dl and postprandial levels between 140 and 200 mg/dl. Her laboratory tests showed glycosylated haemoglobin (HbA1c) of 7%, C-peptide 1.26 ng/ml and negative anti-insulin, anti-GAD and anti-IA2 antibodies. HLA was determined, with no predisposition to developing type 1 diabetes mellitus. A molecular study of monogenic diabetes was performed, revealing a missense mutation (p.Arg158Cys c.472 G>A) in the NEUROD1 gene not previously described and also present in the father. She had a long history of diabetes on the father's side, although the father had not been diagnosed. The patient suffered a worsening of her blood glucose control and the appearance of cardinal symptoms during follow-up, as well as an increase in HbA1c (8.5%), so it was decided to start sulfonylureas (gliclazide 30 mg a day), despite which good control was not achieved. Therefore, insulin therapy was started with a basal-bolus regimen and a low-carbohydrate diet, with control improving since then. No complications have been observed since diagnosis (less than one year).

The second case was a seven-year-old girl, also Caucasian, who presented with hyperglycaemia in lab tests carried out in the gastroenterology department (follow-up for necrotising enterocolitis with intestinal resection in the neonatal period) and adequate weight-to-height ratio and psychomotor development. She had a 3-week history of cardinal symptoms (polyuria and polydipsia) and vaginal candidiasis on physical examination. Laboratory tests revealed HbA1c of 7.3% and negative anti-insulin, anti-GAD and anti-IA2 antibodies. Given the suspicion of monogenic diabetes due to significant family history of diabetes with negative antibodies (her mother was diagnosed with diabetes at 11 years of age, initial control with oral antidiabetics and start of insulin therapy from the age of 15 along with a history of diabetes in the maternal line), HLA was determined, which was not predisposing for type 1 diabetes mellitus, and a molecular study of monogenic diabetes was performed, with a mutation in NEUROD1 observed (p.Met114Lys c.341T>A), also not previously described and present in the mother. Following that, treatment was started with glibenclamide 10 mg daily with good control. There have been no associated complications since diagnosis (six years).

Treatment guidelines recommend oral antidiabetics or insulin therapy.[1,9] The factors that influence the need for one treatment or another in each patient are not defined. This is because evidence is scarce as a result of its low prevalence. Disparate response to treatment with oral antidiabetics has been observed in patients from the same family (with the same mutation) and similar clinical characteristics, with insulin therapy required only in some cases. The reasons for disparate response to the same treatments are not fully clear. Various factors have been suggested, such as incomplete penetrance, increased insulin secretion in obese patients, or race or ethnicity with their different capacity for insulin secretion.[10] It has been observed that maternal inheritance of the mutation could predispose a

patient to the earlier development of diabetes due to factors such as the intrauterine environment of hyperglycaemia.[7] However, none of the factors stated allows us to predict which treatment will be suited to each patient, and this should be based on blood glucose controls and the appearance of complications such as diabetic ketoacidosis.

Nor has it been established what control should be performed in terms of the possibility of the onset of vascular complications. Cases of patients with MODY 6 diabetes and diabetic nephropathy with advanced-stage chronic kidney disease at early ages have been reported, although the greatest severity has been reported in patients with intellectual disabilities, which makes it difficult to establish how their self-care impacted on the development of their condition.[7]

More studies are needed in order to define how diabetes behaves in these patients and the benefits according to the therapies used. The low prevalence and the need for genetic confirmation for its diagnosis make it difficult to gather enough samples to achieve significant results.

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Cystic fibrosis-related diabetes: An interdisciplinary diagnostic and therapeutic challenge

La diabetes relacionada con la fibrosis quística: un reto diagnóstico-terapéutico interdisciplinar

Cystic fibrosis (CF) is the most common autosomal recessive hereditary disease in Caucasian people, with an incidence of one in 3000 live births, and is caused by mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene.

Abnormal lung function is the main factor responsible for the high mortality rate in patients with CF. However, advances in respiratory therapy and specialised treatment of CF over the last few decades have significantly increased these patients' life expectancy,[1] achieving current mean survival of more than 30 years. This increase in survival has led to an increase in extrapulmonary complications, with cystic fibrosis-related diabetes (CFRD) being the most common comorbidity. CFRD is a comorbidity caused by impairment of the endocrine pancreas and constitutes a determining factor in lung function as well as a marker of a worse prognosis and a higher mortality rate.[2,3] Its prevalence increases with age and its onset is usually preceded even years ahead by carbohydrate metabolism abnormalities, respiratory worsening and weight loss.[4] CFRD may be chronic or intermittent, and it is of multifactorial aetiology. CFRD treatment with insulin appears to improve these patients' respiratory and nutritional status.[5]

Lung transplantation is the only treatment available in end-stage lung disease. The incidence of CFRD in patients who require lung transplantation is 28.6%.[6]

The objectives of the study were to assess the diagnostic possibilities that might be offered by continuous glucose