

## SCIENTIFIC LETTER

## How to handle HMG-CoA lyase deficiency and type 1 diabetes? A challenging case report



### Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is an autosomal recessive disorder, caused by mutations in the *HMGCL* gene. This enzyme is important in the ketogenic pathway and in the last step of leucine catabolism, leading to inadequate ketone body synthesis and accumulation of toxic metabolites of leucine catabolism.<sup>1</sup> It occurs in 1 in 100,000 live neonates and is more common in Saudi Arabia, Portugal, Spain and Pakistan, with a high incidence of parental consanguineous marriage.<sup>2</sup> Although there is a considerable heterogeneity, it usually presents with vomiting, hypotonia and lethargy in the first year of life. Hypoketotic hypoglycemia, metabolic acidosis and hepatomegaly are common.<sup>3</sup> The primary aim of management is rigorous emergency management with a high carbohydrate intake during infections, avoiding extended fasting, with dietary protein, and possibly, fat restriction. Carnitine supplementation is usually prescribed.<sup>4</sup>

Type 1 diabetes (T1D) is a chronic disease wherein there is an absence of insulin production, resulting in hyperglycemia and, in severe cases, ketoacidosis. T1D requires painstaking efforts in order to reduce hyperglycemia while minimizing the risk of hypoglycemia. Most patients with T1D are treated with intensive insulin regimens, either via multiple day injections or continuous subcutaneous insulin infusion.<sup>5,6</sup> Good dietary adherence is necessary and is associated with better glycemic control in children with T1D, resulting in a reduction of the micro and macrovascular complications and the premature mortality associated with T1D.<sup>7,8</sup>

### Case report

We present a boy, diagnosed on the first day of life with HMG-CoA lyase deficiency, by early neonatal screening in view of a previous family history (a sister diagnosed by the national neonatal screening program 5 years earlier). The molecular study verified the presence of two mutations on the *HMGCL* gene – c.109 G>T (p.E37X) and c.505\_506delTC. According to the classification established by the American College of Medical Genetics and the

Association for Molecular Pathology in 2015, these mutations are categorized as strong evidence of pathogenicity (PS1).<sup>9</sup> Both mutations are present in a state of compound heterozygosity, and prior literature has already identified them as pathogenic, responsible for causing HMG-CoA lyase deficiency. Notably, both parents are carriers of one of the described variants; however, they exhibit no symptoms related to the condition. Apart from his sister, no other affected individuals have been reported in the family.

With a positive result and facing feeding difficulties he was admitted to the Neonatal Intensive Care Unit, where a 10% glucose infusion, carnitine and a leucine-free amino acids mixture were started. He was discharged on day 7 of life without any complications.

During his first years of life, no severe hypoglycemic episodes were described, but he still required hospitalizations, due to infections/food refusal, resolving with glucose infusion. He maintained avoidance of fasting, controlled lipid and protein intake, with an amino acid mixture low in leucine, cornstarch during the night and carnitine supplementation when needed, with good evolution.

At the age of 4, he was admitted to the emergency department with vomiting, polydipsia, polyuria and polyphagia. He had hyperglycemia of 422 mg/dL without ketoacidosis and type 1 diabetes was diagnosed. Low levels of c-peptide on diagnosis (0.5 ng/mL) confirmed insulinopenia. A scheme of long and short-acting insulin was started, but in order to prepare him for discharge, a continuous subcutaneous insulin infusion was implemented. The investigation showed negative autoimmunity, with negative antibodies to a variety of beta-cell components, such as glutamate decarboxylase-65, islet-antigen-2 and zinc transporter-8. Thyroid antibodies were also negative. He had a slightly positive tissue transglutaminase IgA, with HLA DR3-DQ2 and DR4-DQ8 also positive, but endoscopic biopsy of the duodenum did not confirm a suspicion of celiac disease. Despite the high-risk genotype for developing T1D, his sister, who shares the same genetic condition, did not undergo thorough screening due to her brother's diagnosis. However, she remains without any symptoms of T1D to date. Furthermore, there was no record of T1D in the family, and only the maternal grandfather had type 2 diabetes.

In the initial months, the patient's levels of HbA1c consistently persisted above 8%, accompanied by recurrent instances of hyperglycemia. This was attributed to the parents' reluctance to administer insulin due to the perceived threat of hypoglycemia. The solution entailed the

implementation of a hybrid, partially automated system, wherein the sole requirement was the introduction of the carbohydrates to be ingested. As a result of this modification, the parents exhibited a greater sense of ease, and metabolic control during the most recent appointment displayed significant improvement. Historically regarded as the "gold-standard," HbA1c has witnessed a shift in recent years with an increasing utilization of time in range (TIR) in routine clinical care.<sup>10</sup> In this case, although the total daily dose of insulin (including basal and boluses) remained consistent over time, averaging 11 units a day (0.5 U/kg/day), there has been a significant improvement in TIR. In the most recent endocrinology appointment, the patient demonstrated an impressive TIR of 66%, a substantial improvement, when compared to the initial levels of 20–30%.

Nowadays, besides the insulin treatment, he continues to maintain a protein- and lipid-controlled diet, cornstarch at night and carnitine supplementation. He has normal development and growth, progressing in the 15–50th percentile (WHO Growth Charts).

## Discussion/Conclusion

The co-occurrence of HMG-CoA deficiency and T1D, two almost antagonistic, complex, chronic diseases, in the same patient is extremely rare, and it is truly a great challenge to control and follow both pathologies in this child with the best results. The absence of ketone bodies can delay the identification of poor T1D control, but on the other hand, might minimize the risk of severe ketoacidosis. After reviewing the literature, there are reports of a single similar case in which a co-occurrence of the described pathologies was also observed. In this case, presented at the 21st European Congress of Endocrinology in 2019, the patient exhibited positive pancreatic autoimmunity (positive anti-glutamate decarboxylase antibodies) and a significantly older age at the diagnosis of T1D, with resultant greater ease in the therapeutic approach.<sup>11</sup>

It has been suggested that it may be reasonable to continue a night feed until the age of one year, but for older children, overnight fasting may be safe.<sup>12</sup> For HMG-CoA deficiency, safe overnight fasting is controversial, as is the optimal dietary approach, so the rigorousness of therapy is likely to be influenced by the severity of each case.<sup>4</sup> This particular case showed a child, in the early phases, very well controlled with a protein- and lipid-controlled diet only (plus carnitine supplementation). After the T1D diagnosis, and despite his glycemic instability, our patient is still avoiding fasting and taking cornstarch at bedtime, with continuous insulin infusion, in order to have a sustained energy supply to the cells that avoids lipid and protein catabolism.

The management of T1D has evolved substantially over the last decades, with the development of new therapeutics such as insulin pumps, continuous glucose monitors and the implementation of intensive insulin therapy. Despite these advances, childhood management of T1D remains very challenging.<sup>8</sup> None of the new therapeutic advances are automated, and, in this particular case, that is an important issue. In this family, the biggest concern was

always the occurrence of hypoglycemia, and the parents continue to promote a high intake of carbohydrates. It turns out that, even with a minimal decrease in the glycemic values observed in the glucose sensor in the interstitial fluid (still far from hypoglycemia), the child is offered fast-acting carbohydrates, resulting in a high number of hyperglycemias.

A long road lies ahead for the optimal glycemic control of T1D in this patient, requiring the support of the multidisciplinary team that works with the child and his family, to manage this challenge.

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