Reviewer's report

Title: SUR1 Mutation in Type 1 Diabetes: Autoimmunity Hinders Sulfonylurea Rescue of Diabetes Caused by SUR1 Mutation. Results from the Hvidore Study Group

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Reviewer: Wolfram JP Karges

Reviewer's report:

Comments to the authors

In this prospective observational study, a cohort of 261 pediatric patients with type 1 diabetes was followed for 12 months after diagnosis. Clinical and metabolic parameters and diabetes-related autoantibodies were longitudinally assessed. In addition, MODY and PNDM-associated genes were studied in 24 autoantibody-negative individuals. A SUR1 variant, identified in one patient, was expressed and functionally characterized in vitro.

Overall, this is a well designed and nicely performed study with important clinical observations. During the first 12 months after clinical diagnosis, antibody-negative patients have a more favourable clinical course and a higher degree of residual beta-cell function. All of these 24 individuals, except one, were found negative for variants of the five MODY and PNDM-associated genes studied. Accordingly, these patients were classified as having idiopathic type 1 diabetes, leaving open the question whether they were antibody-negative autoimmune cases, or had non-autoimmune etiologies.

In one individual, a novel ABCC8 missense mutation was identified. While this SUR1 variant was sensitive to tolbutamide in vitro, no beneficial effect of glibenclamide treatment was observed in the 13 year-old patient who had developed IA-2 antibodies 6 months after diagnosis. Apparently, this patient also developed GAD antibodies later on.

Comments

1. In the abstract and introduction, both aims of the present study are explicitly pointed out, i.e. the comparison of pediatric type 1A and 1B diabetes and the genetic contribution to type 1 B diabetes. This nice study provides answers to both questions. The title of the manuscript does not fully reflect these major findings of this study. This is also the case for the last two sentences of the abstract that focus on the findings from one patient. Changes of the title and the conclusions (abstract) are therefore advised.

2. In the last paragraph of page 21 it is stated that “mutations in ABCC8 can cause idiopathic diabetes” in the 13 year-old patient. The in vitro data clearly support a functional role of this gene variant. On the other hand, considering the
antibody data presented in the manuscript, there is little doubt that the 13 year-old indeed had autoimmune diabetes. It is therefore not essential to discuss to what extent diabetes in this patient has been caused by immune or non-immune mechanisms.

3. Effective sulfonylurea treatment requires intact beta cell function, as defined by C-peptide positivity. Treatment in the patient was performed 8 years after the initial diagnosis at a time when autoimmunity was far advanced and C-peptide was negative. It seems therefore not surprising that glibenclamide was ineffective at that time.

4. Figures 2B and 2C are derived from public database information and do not contain original data nor molecular modeling data. Inclusion of these figures is optional.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.