Reviewer’s report

Title: A diagnostic approach for defining Idiopathic Remitting Diabetes: a retrospective cohort study

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Reviewer: Beata Malachowska

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The manuscript entitled „A diagnostic approach for defining Idiopathic Remitting Diabetes: a retrospective cohort study” outlines an interesting clinical problem of remitting diabetes and describes an individual who showed the typical phenotype of this clinical entity. I do admit that the case is unusual and may pose a diagnostic and therapeutic challenge. The literature review part of the manuscript used to define the diagnostic criteria for remitting diabetes is very well done and the proposed guidelines may be readily used in clinical practice, with a possible consideration of remark number 5 below. The description of the case however does require some clarification and in depth diagnostics to fully rule out one of the monogenic diabetes subtypes, which seems to be the most likely explanation for the observed clinical trajectory demonstrated by the patient.

1. The addition of birth weight of the patient, her healthy siblings (is available), her mother and children, along with data on the children’s health and fasting blood glucose of seemingly healthy family members would rule out genetic causes.

2. I may not agree with the concept of not testing the patient for GCK mutations. Individuals with high HbA1c and hyperglycaemic crises and GCK-MODY had been reported, and the phenomenon could well explain the observed phenotype. Given that she was diagnosed at 15 years of age, GCK mutations should be considered as a causative or concomitant factor. Other MODY genes do seem less likely, although cases of patients with mild phenotype of monogenic diabetes have been linked to mutations of KCNJ11, ABCC8 and INS. Therefore, as a metabolic crisis event overlaid upon a monogenic defect is a likely explanation, there should be a strong urge to perform exome or whole-genome sequencing in this individual and her healthy/affected family members. I do understand that this may exceed the scope of the paper and there may be logistical or ethical concerns which I am not aware of precluding such studies in her family, but the notion of an exacerbated monogenic diabetes should be considered in more detail and genomic diagnostics should be discussed.

3. While I would do lean towards excluding type 1 diabetes, one should consider the possibility of performing anti ZnT8 antibody assay since, this kind of specific antibody was shown to be present in a subset of patients otherwise negative for other diabetic autoantibodies.

4. Had the patient been tested for any renal malformations using abdominal ultrasound? The presence of renal cysts would make HNF1B a top target for
diagnostics, but even with no renal structure alterations the gene could be considered a candidate for testing, since its mutations and deletions were also reported to cause diabetes before the manifestation of any renal lesions.

5. Given the availability of genomic testing methods and a growing number of pharmacogenetic treatment optimisation options and genetic counselling, one could suggest performing exome sequencing in patients with remitting diabetes, particularly if the probability of monogenic diabetes is high.

6. How likely is it in the Authors’ setting that amongst the patients treated within the centre there were individuals who had HbA1c >6.5% but missing or normal fasting glucose levels, before HbA1c was established as a diagnostic criterion? These patients would not be considered as having diabetes at that time and would not be considered as remitting should their HbA1c fell below the 6.5% level now. This, along with different timepoints of testing could lead to the underestimation of the frequency of remitting diabetes – this fact could be mentioned in the manuscript to strengthen its epidemiological outlook.

Minor issues
1. Was the HbA1c methodology constant throughout the follow up of the patient?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests