Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor,

Thank you for your comments and reviewer feedback regarding our paper “A diagnostic approach for defining Idiopathic Remitting Diabetes: a retrospective cohort study”.

We were pleased both reviewers were positive and have made changes or given replies to the minor points they made. The replies are below and any changes to the manuscript, have been highlighted in the manuscript.

Reviewer’s comments: Charles Fox

Andrew Hattersley and his colleagues in Exeter have built on their pioneering work in MODY to become world leaders in the niche specialty of unusual forms of diabetes. When Christine Burren, a paediatrician in Surrey, found two brothers who apparently made a full recovery from Type 1 diabetes, she turned to Andrew to co-author the first report of Idiopathic Remitting Diabetes. This appeared in Diabetes Care in 2004 (ref 6).

Eleven suspected cases of this condition have since been referred to the Exeter team and they have now sifted carefully through this cohort and weeded out 10 cases leaving only one patient who fulfils their extremely rigorous criteria. One possible patient has been excluded as the BMI is >30 and 4 patients have not yet remained off insulin for > 4 years. So as time goes by, the pick up rate from this cohort may increase but the authors are right to stick rigidly to their definition. This is therefore a textbook example of how to define a new, albeit very rare, condition.

We thank the reviewer for his very positive comments.

Ref 19. It is customary to quote the date the website was accessed.

This has now been corrected in the manuscript. The reference now reads:

Reviewer’s comments: Beata Malachowska

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.

Our patient does not know her birth weight and we do not have her birth records. She has no siblings and her son, currently aged 3, is healthy. He does not have diabetes and had a birth weight of 3.54kg. Neither parent has had diabetes. This is now added into the manuscript with the statement: “Neither parent has had diabetes. She has no siblings but her son, currently aged 3, does not have diabetes.”

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.

Although we agree that GCK can contribute to a high HbA1c, the patient’s diabetes has remitted. Her fasting glucose was measured aged 27, the patient’s HbA1c was 30 mmol/mol and a fasting glucose of 4.5 mmol/l. These values are too low to be consistent with a glucokinase mutation: patients with GCK-MODY to have glucose values >5.5 mmol/l (Stride et al. Diabetologia 2002) and HbA1c >40 (Steele et al. PLoS One 2013). The patient was negative for mutations in HNF1A and HNF4A and MLPA has been done confirming there were no deletions in HNF1A, HNF4A, GCK or HNF1B. In response to the reviewer we have checked all the 29 known genes that result in monogenic diabetes using a targeted array (Ellard et al. Diabetologia 2013) and no mutations were found. We do not know how to interpret which, if any, of the 500 novel coding variants that would be found on exome sequencing are aetiological when you only have a single case. Therefore we do not think exome sequencing is appropriate.

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.
She has now been tested for ZnT8 as well as GAD and IA2 antibodies; these were all negative. Type 1 diabetes is defined as a progressive destruction of the beta-cells by WHO.

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.

Mutations and deletions in **HNF1B** have been excluded. Any imaging would be indirect and less accurate than genetic testing. HNF1B is a progressive disease that does not remit.

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.**

As the patient does not have diabetes the probability of monogenic diabetes is extremely low. We have excluded all known causes of monogenic diabetes by targeted capture. We do not know how to interpret which, if any, of the 500 novel coding variants that would be found on exome sequencing are aetiological when you only have a single case. Therefore we do not think exome sequencing is appropriate.

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 time points 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.

We agree that diabetes may have been missed if the appropriate diagnostic tests are not performed and if patients remit rather than progress they would not be detected later. At present there is no evidence to support this so we have not included it in our manuscript.

**Minor issues**

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

Our patient had HbA1c tested by 3 different assays between 1998 and 2012. The assays were aligned and hence comparable (initially with the DCCT and since 2009 to absolute values expressed as mmol/mol).

Kind regards,

Dr Tarig Babiker and Prof. Andrew Hattersley