Reviewer’s report

Title: The course of diabetes in children, adolescents and young adults: does the autoimmunity status matter?

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Reviewer: Christiane Hampe

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This is an in-depth study of autoimmune and clinical parameters and their correlation in young T1D patients. The cohort represents almost all T1D cases in 0-24 year old patients (n=1209) in Lithuania diagnosed between 1990 and 2015.

The stated purpose of the study is the identification of patients that were misdiagnosed as T1D and could benefit from a re-classification and different treatment.

Indeed, ~10% of children diagnosed with T1D are later reclassified as having monogenetic forms of diabetes.

Their investigation finds 7.5% of the cohort to test negative for islet autoantibodies.

The correlation analysis confirms several previous findings: association of GAD65Ab with older age at onset, presence of GAD65Ab in patients after long duration of disease, inverse correlation of islet autoantibodies and disease duration, higher incidence of ketosis in islet autoantibody-positive patients, association of T1D with thyroid autoimmunity.

There are a few comments, which may help improve the study in its present form:

* The finding of higher frequency of autoantibody-negative individuals with retinopathy (after age adjustment) is of interest. The authors may want to discuss related findings (inverse relationship between GAD65Ab levels and severe retinopathy (Agardh D et al Diabetes Res Clin Pract. 1998, Miruma T et al Ophthalmology 2005).

* The phenomenon of autoantibody negative T1D (Type 1B or idiopathic) patients without monogenic diabetes has been described in the literature and accounts for ~5% of T1D patients. Inclusion of ZnT8 autoantibodies have further reduced the frequency of autoantibody-negative T1D patients. The possibility that some of the autoantibody-negative patients in the current cohort have in fact Type 1B diabetes needs to be addressed.

* Monogenic forms of diabetes often have normal C-peptide levels. It would be useful to know whether the autoantibody-negative patients in the current study have normal C-peptide levels.
* The authors mention in the discussion that insulin therapy in the majority of the patients may affect the measurement of insulin autoantibodies in these patients. Indeed, the detection of insulin autoantibodies (IAA) after initiation of insulin therapy is impossible as most patients develop insulin antibodies (IA) to endogenous insulin. To avoid confusion, the authors may use IA when referring to measurements made in patients that are on insulin treatment for at least 2 weeks and IAA when referring to those patients that are newly diagnosed and have either not yet received any insulin therapy, or have been on insulin treatment for less than 2 weeks.

* The authors point out that ZnT8 autoantibodies were not determined in the study, therefore it is possible that some of the autoantibody-negative patients have undetected islet autoimmunity.

* As the authors discuss, the lack of autoantibodies in patients with long duration of disease may be due to disappearance of autoantibodies over time. It would therefore be important to describe the findings of islet autoimmunity and correlations with age etc in newly diagnosed T1D patients (n=205 in the study) as a subcohort.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

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