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RESEARCH LETTER

Progression from single to multiple islet autoantibodies often occurs soon after seroconversion: implications for early screening

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Abbreviation
IQR Interquartile range

To the Editor: Multiple islet autoantibodies mark a pre-clinical stage of type 1 diabetes, with 70% progression to clinical diabetes within 10 years of seroconversion [1]. Broad application of screening for multiple islet autoantibodies may, therefore, become an attractive instrument to identify asymptomatic type 1 diabetes and prevent severe metabolic disarrangements and ketoacidosis. In contrast to multiple islet autoantibodies, only a minority of children who are, and remain, single islet autoantibody-positive develop type 1 diabetes within 10 years of follow-up. Nevertheless, many multiple islet autoantibody-positive children are likely to have transitioned from single to multiple islet autoantibodies. We [2, 3], and others [4] have reported that multiple islet autoantibody-positive children frequently seroconvert in the first 2 years of life, but little is known of the timing of transition from single to multiple islet autoantibody positivity. This knowledge is important for the design of screening and re-screening strategies. Here we analysed the prospectively followed German BABYDIAB/BABYDIET birth cohort [2, 5] to address this.

Children in the BABYDIAB/BABYDIET studies were routinely tested for islet autoantibodies at the ages of 9 months and 2 years, and every 3 years thereafter; children who were positive for one or more islet autoantibodies were tested every 6 months. In a subgroup of children with high genetic risk participating in the BABYDIET intervention study, routine testing for islet autoantibodies was carried out at 3 month intervals from the age of 3 months to 3 years and annually thereafter. Persistent islet autoantibody positivity was defined as a positive result for the same islet autoantibody in at least two consecutive samples.

A total of 227 children (114 boys) in the cohort developed persistent islet autoantibodies. Of these, 62 (27.3%) were multiple islet autoantibody positive already at their seroconversion sample and had a median age at seroconversion of 2.2 years (interquartile range [IQR] 1.97–5.02 years). The remaining 165 were single islet autoantibody positive at seroconversion and had a median age at seroconversion of 5.01 years (IQR 1.89–8.13 years, $p=0.01$). A total of 55 (25.2%) children transitioned from single to multiple islet autoantibodies during 8 years of follow-up. The longest observed period of multiple islet autoantibody positivity was 7.36 years after the seroconversion sample. The rate of

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conversion from single to multiple islet autoantibodies was highest in the first 2 years after seroconversion (11.5/100 person-years) and declined rapidly to less than 5/100 person-years after 4 years of follow-up (p=0.003 within 2 years vs within 4 years, Fig. 1a). Of the 55 children who converted from single to multiple islet autoantibodies in follow-up, 38 (69%) did so within 2 years of their seroconversion sample. In total, 100 (85%) of the 117 multiple islet autoantibody-positive children had already reached this stage within 18 months of their seroconversion sample. Progression to multiple islet autoantibodies was higher in children who first seroconverted by age 5 years than in children who first seroconverted after age 5 years (p=0.001 at seroconversion, p=0.008 at 1 year after seroconversion, p=0.021 at 2 years after seroconversion), but again, progression from single to multiple islet autoantibodies was highest and most frequent early after seroconversion regardless of whether the children first seroconverted early or late (Fig. 1b). Similarly, progression from single to multiple islet autoantibodies was higher in children with the HLA DR3/DR4-DQ8 or DR4/4-DQ8 genotypes than in children with other genotypes (p<0.001), but again progression was highest early after seroconversion in both HLA genotype groups, with transition to multiple islet autoantibodies after 2 years predominantly seen in children with the high risk genotypes (Fig. 1c). Development of diabetes (Fig. 1d) was faster in children who became multiple islet autoantibody positive before the age of 5 years (64%) than in children who became multiple islet autoantibody positive after age 5 years (36%; p=0.014), and faster in children who became multiple islet autoantibody positive within 2 years of initial seroconversion (60%) than in children who became multiple islet autoantibody positive >2 years after seroconversion (36%; p=0.02).

The findings indicate that multiple islet autoantibodies largely appear close to initial seroconversion in children with a family history of type 1 diabetes. Initial seroconversion is often within the first 2 years of life in children who develop multiple islet autoantibodies and progression to diabetes appears to be linear early in these children [1]. On the basis of these findings we suggest the following guidelines: (1) a

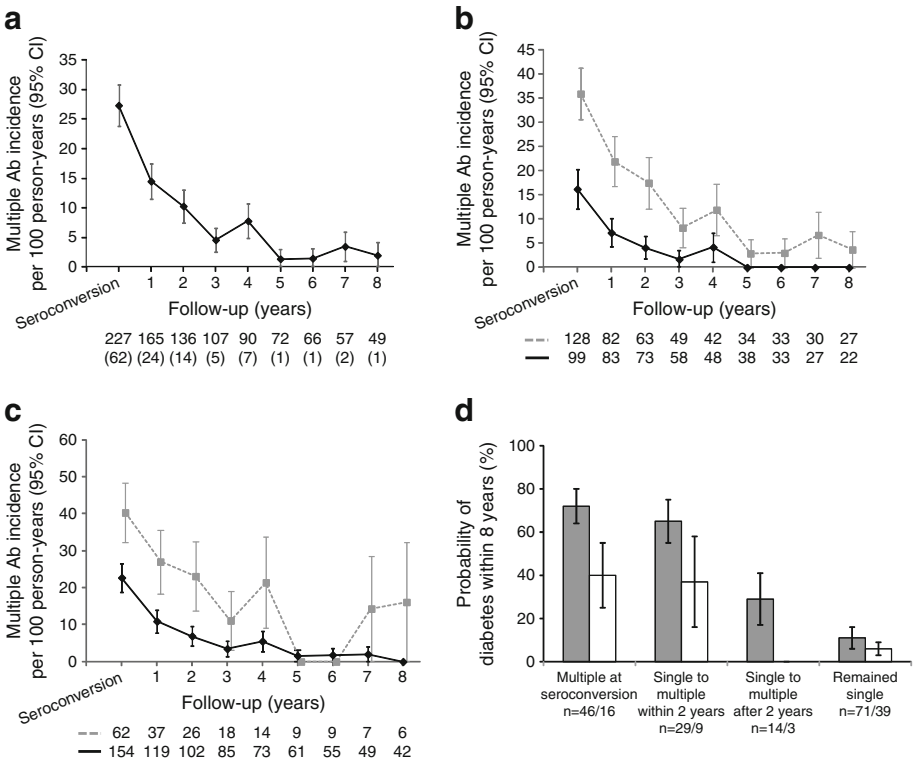

Fig. 1 Incidence of multiple islet autoantibodies (cases per 100 person-years) in children from the BABYDIAB/BABYDIET cohort. (**a**–**c**) Incidence is shown from the time of seroconversion to the appearance of multiple islet autoantibodies for the total cohort (**a**), stratified for children who first seroconverted by age 5 years (grey dashed line) and in children who first seroconverted after age 5 years (black line) (**b**) and children who had HLA DR3-DR4-DQ8 or DR4-DQ8/Dr4-DQ8 genotypes (grey dashed line) vs children who had other HLA DR/DQ genotypes (black line) (**c**). Numbers under the abscissa are the number of children still followed at each time point, with the number of children who developed multiple islet autoantibodies in each time interval shown in parentheses. Ab, autoantibody. (**d**) Cumulative risk for the development of type 1 diabetes from the age of seroconversion is shown with respect to autoantibody status at seroconversion and follow-up and in relation to age at islet autoantibody seroconversion (grey bars, seroconversion age before or at age 5 years; white bars, seroconversion after age 5 years); numbers under the categories refer to children with seroconversion age before or at age 5 years (left) and after 5 years (right). Error bars represent SE

screen at around 2–4 years of age to identify a large proportion of the children who become multiple islet autoantibody positive during childhood and (2) follow-up screening around 2 years later in children who are single islet autoantibody positive or restriction of follow-up testing to those at high risk as defined by HLA genotype. These guidelines could change as more information about autoantibody seroconversion is obtained. The data also indicates that intervention in single islet autoantibody-positive young children to prevent multiple islet autoantibodies will be logistically difficult because of the rapid progression in most cases who become multiple islet autoantibody positive. These findings, which are supported by those of the DIPP study [3], will eventually enable the implementation of a cost-effective early islet autoantibody screening programme in the population at large.

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Contribution statement RC acquired and reviewed the data, undertook statistical analysis and interpretation of the results and drafted the manuscript. EG contributed to acquisition, analysis and interpretation of data and contributed to the writing of the manuscript. CW undertook statistical analysis and interpretation of the results and contributed to the writing of the manuscript. PA provided input to the statistical analysis and contributed to the writing of the article. EB provided major input to analysis and interpretation of data and contributed to the writing of the manuscript. AGZ designed the study, is Principal Investigator of the BABYDIAB study, provided input to the analysis and contributed to the writing of the manuscript. All listed authors approved the final version of the manuscript. AGZ takes responsibility for the integrity of the work as a whole.

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