Enterovirus vaccine induces good antibody response in children with increased risk to develop type 1 diabetes

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Purpose

The first vaccine against type 1 diabetes (T1D) -associated enteroviruses, group B coxsackieviruses (CVBs), has induced a strong antibody response among healthy adults in a phase 1 human trial. The ultimate target population of this PRV-101 vaccine comprises young children with increased genetic risk for T1D. Therefore, it would be important to know whether such children respond properly to enterovirus vaccines. The present study evaluates this question by analyzing the response to already licensed enterovirus vaccine, the poliovirus vaccine, in such children. The study is based on prospective design making it possible to study vaccine response before islet autoimmunity starts. This design also allowed as to study separately (the) two endotypes of T1D (first appearing autoantibody against either insulin or GAD) and compare case children with carefully matched control children.

Methods

Study subjects included children who have been followed from birth in the Type 1 Diabetes Prediction and Prevention (DIPP) study in Finland and who had been immunized by formalin-inactivated poliovirus vaccine (IPV, two vaccinations at age of 6 and 12 months) that represents similar inactivated whole virus vaccine technology as the inactivated Coxsackievirus B vaccine (PRV-101). Neutralizing antibodies against poliovirus 1 (Sabin strain) were analyzed using plaque reduction assay from two different case-control sets nested in the DIPP birth cohort:

The HLA Case-Control Set included samples taken at the mean age of 18 months (range 12.5-24.4 months) from 110 islet autoantibody negative and non-diabetic children who carried HLA-DQ genotypes that are associated with increased risk of T1D and comparable samples from 65 autoantibody negative control children who lacked such risk alleles. These groups were matched for the time of birth, sex and the city of residency. This set included altogether six genetic subgroups with high (N=35), moderately increased (N=47), slightly increased (N=28), neutral (N=28), mildly protected (N=14), and strongly protected (N=23) combinations of these HLA alleles (1). Those with neutral or protective alleles were considered as control children and those with slightly/moderately/highly increased risk were considered as case children.

The Islet Autoimmunity Case-Control Set included similar samples taken at the mean age of 18,5 months (range 12.5-24.4 months) from 111 children who developed multiple biochemical islet autoantibodies and 111 autoantibody negative control children who were individually matched for the time of birth, sex and the city of residency and who carried HLA-DQ genotypes that confer increased risk for T1D. The case children in this set included 54 children who developed IAA as the first appearing islet autoantibody (26% girls) and 57 children who developed GADA as the first-appearing autoantibody (40.4% girls) (2). The mean age of the IAA appearance in the IAA-first group was 21 months (range 17.2-24.8) compared to 59.8 months (50.6-69.1) of the GADA appearance in the GADA-first group (p<0.0001).

Summary of results

The levels poliovirus antibodies showed high variation between children (Fig. 1).

In the *HLA Case-Control Set* poliovirus antibodies were equally distributed in the six groups with HLA-DQ allele combinations conferring highly increased, moderately increased, slightly increased, neutral, mildly protective or strongly protective risk of T1D (Fig. 2). In addition, the antibody levels did not differ when the children with HLA-DQ alleles mediating increased risk of T1D were compared with pairwise matched control children with neutral or protective alleles (OR=1.03, 95%CI 0.9-1.2; p=0.642). Similar findings were obtained when children were stratified by the sex.

In the *Islet Autoimmunity Case-Control Set* poliovirus antibody levels did not differ between the islet autoantibody positive case children and autoantibody negative matched control children (OR=1, 95%CI 0.85-1.18; p=1; Fig. 3). The antibody levels did not differ between the case and control children in either IAA-first or GADA-first groups.

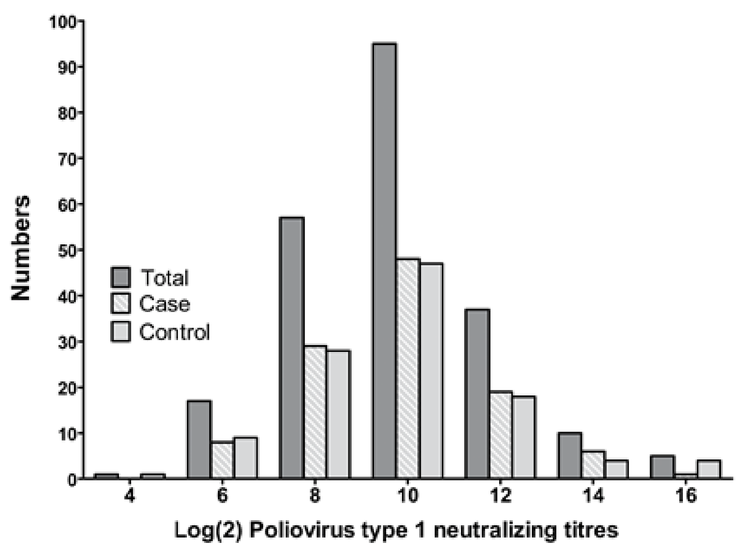

Figure 1. Distribution of neutralizing antibody levels against poliovirus type 1

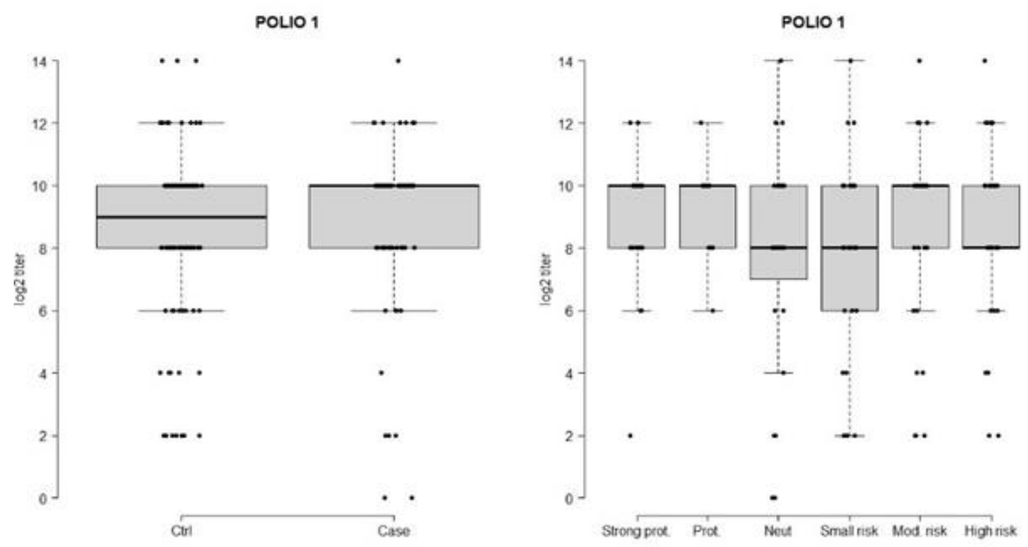

Figure 2. Neutralizing poliovirus 1 antibody levels in autoantibody negative non-diabetic children who had either increased (Cases) or decreased (Ctrl) HLA-DQ defined risk of T1D (left panel). Distribution of poliovirus antibody levels in the six subgroups with HLA-DQ alleles conferring varying risk for T1D ranging from strongly protective to high-risk (right panel).

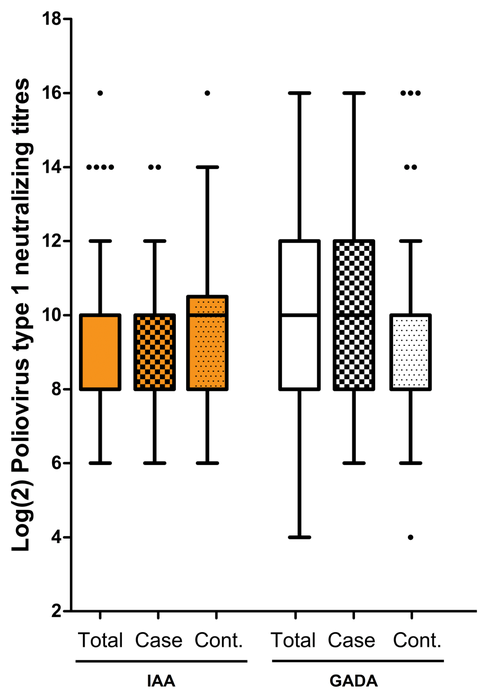

Figure 3. Neutralizing poliovirus 1 antibody levels in children with who developed either IAA or GADA as the first-appearing autoantibody and in their matched control children

Conclusions

The study shows that children who are genetically at risk to develop T1D mount a proper antibody response to inactivated poliovirus vaccine. Their vaccine response was comparable to that in control children who lacked T1D-associated HLA-DQ risk alleles. In addition, children who developed islet autoimmunity or T1D responded as well as autoantibody negative children.

References

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Conflict of interest statement: H.H. is the chairman of the board and a shareholder of Vactech Oy which develops vaccines against picornaviruses. HLA