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Vaccinations in early life are not associated with development of islet autoimmunity in type 1 diabetes high-risk children: Results from prospective cohort data

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ABSTRACT

Aims/hypothesis: Vaccinations in early childhood potentially stimulate the immune system and may thus be relevant for the pathogenesis of autoimmune diseases such as type 1 diabetes (T1D). We determined the association of vaccination burden with T1D-associated islet autoimmunity in children with high familial risk followed prospectively from birth.

Methods: A total of 20,570 certified vaccination records from 1918 children were correlated with time to onset of T1D-associated islet autoimmunity using Cox regression, considering multiple time periods up until age two years and vaccination types, and adjusting for HLA genotype, sex, delivery mode, season of birth, preterm delivery and maternal T1D status. Additionally, prospective claims data of 295,420 subjects were used to validate associations for the tick-borne encephalitis (TBE) vaccination.

Results: Most vaccinations were not associated with a significantly increased hazard ratio (HR) for islet autoimmunity (e.g. HR [95% confidence interval]: 1.08 [0.96–1.21] per additional vaccination against measles, mumps and rubella at age 0–24 months). TBE vaccinations within the first two years of life were nominally associated with a significantly increased autoimmunity risk (HR: 1.44 [1.06–1.96] per additional vaccination at age 0–24 months), but this could not be confirmed with respect to outcome T1D in the validation cohort (HR: 1.02 [0.90–1.16]).

Conclusions: We found no evidence that early vaccinations increase the risk of T1D-associated islet autoimmunity development. The potential association with early TBE vaccinations could not be confirmed in an independent cohort and appears to be a false positive finding.

1. Introduction

Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood, with worldwide increasing incidence [1]. The disease is preceded by a preclinical period of islet autoimmunity, which most commonly develops in early infancy [2,3]. Thus, factors that induce a strong immune response in early life might be relevant for the development of T1D-associated islet autoimmunity. We recently reported an association between the number of respiratory infections developed during the first year of life with increased risk of islet autoimmunity [4].

Vaccinations in early life are also of interest in this regard since they may reduce an individual's islet autoimmunity risk by protecting against specific infections or on the contrary, increase it by inducing a deleterious stimulation of the still immature immune system. Previous studies on this topic have been inconclusive, and evidence from prospective studies is scarce. Vaccinations against Haemophilus influenzae type B (HiB) have been found to be associated with increased T1D risk [5,6], and vaccinations against Bacille Calmette-Guerin (BCG) with accelerated disease progression [7], while measles vaccinations have been linked to reduced T1D risk [8–10]. Other studies have failed to detect associations

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between specific vaccinations and T1D [11–14], including two prospective studies that have been limited by a small number of events [15,16]. Studies with outcome islet autoimmunity are lacking, however.

In this study, we combined data from two large German prospective cohort studies of children at high risk for T1D with considerable follow-up to investigate the association of vaccinations with risk of islet autoimmunity development. As vaccinations were recorded together with their exact dates and certified, we were able to comprehensively examine associations between all facets of early childhood vaccination, including timing, type and cumulative vaccine load, with time to islet autoimmunity development, with a focus on vaccinations during the first two years of life.

2. Research design and methods

2.1. Study populations

Data from two ongoing German birth cohorts of healthy neonates with a familial increased risk of T1D, the BABYDIAB study and the BABYDIET natural follow-up study [17–19], were combined for association analyses of vaccination patterns and development of islet autoimmunity. Between 1989 and 2000, a total of 1650 offspring of patients with T1D were recruited for the BABYDIAB study and were followed for 23,856 patient years (median: 15.7 years). Between 2000 and 2006, 791 additional offspring or siblings of patients with T1D were screened in the context of the BABYDIET study and were followed by using the BABYDIAB protocol for 6358 patient years (median: 8.7 years). Of those 150 participated in the BABYDIET dietary intervention study and were randomized to gluten exposure at 6 or 12 months of age; the intervention had no effect on either islet autoimmunity or T1D [20]. The studies were approved by the ethical committee of Bavaria, Germany, and executed in accordance with the principles of the Declaration of Helsinki, including written informed consent by all participants.

Additionally, we analyzed data provided by the Kassenärztliche Vereinigung Bayerns (KVB, Bavarian Association of Statutory Health Insurance Physicians), which processes claims data for all statutorily insured patients in Bavaria, Germany (approximately 85% of the total Bavarian population). Just as in a previous analysis [21], 295,420 infants born between 2005 and 2007 were included and observed until March 2015 or last contact with a physician. Here, we used T1D as outcome variable, because the KVB data did not contain information about islet autoimmunity. Diagnosis of T1D, which was obtained using ICD-10 codes, and numbers of vaccinations against tick-borne encephalitis (TBE) were recorded in quarterly intervals.

2.2. Assessment of vaccinations and baseline risk factors

In Germany, every family is issued a vaccination passport or certificate shortly after their child's birth, where dates and types of all subsequent vaccinations are recorded at their time of occurrence, and certified by the physician's signature and stamp. As part of the BABYDIAB/BABYDIET studies, parents regularly provided a copy of their child's vaccination certificate, typically at scheduled visits corresponding to blood draw. Missing information was requested by phone. Date and type of each vaccination record were entered into a database together with the date when the vaccination certificate was seen. The focus of the current analysis lies on common vaccines recommended by the German Standing Committee on Vaccination (STIKO), which includes diphtheria, hepatitis B, HiB, pertussis, poliomyelitis, tetanus, measles, mumps, rubella, meningococcal, pneumococcal, varicella, TBE and influenza. Several vaccinations were typically given as a 3-fold compound (MMR: measles, mumps, rubella) or a 5/6-fold compound (diphtheria, HiB, pertussis, poliomyelitis, tetanus, and since 2001 additionally hepatitis B).

2.3. Outcome variables

Islet autoantibodies were measured in venous blood samples from scheduled visits. Children in the BABYDIAB study had scheduled visits at birth, and at age 9 months, and at 2, 5, 8, 11, 14, 17 and 20 years of age, whereas children in the BABYDIET study had 3-monthly visits from birth until the age of 3 years, and yearly until the age of 12 years. Measurement of islet autoantibodies in these studies has been described elsewhere [19,22]. Islet autoimmunity was defined as the development of persistent autoantibodies to one or more of the antigens insulin, GAD65, IA-2 or Zn-T8, with sample values above the 99th percentile of published population control children classified as positive. In case of single positive antibodies against insulin or GAD65, affinity and epitope reactivity was determined and children with low affinity antibodies ($<10^9$ L/mol) were not classified as islet autoantibody positive as these isolated antibody signals are not T1D specific and not associated with increased T1D risk [23,24]. Persistence was defined as positive in at least two consecutive samples. Islet autoantibody assays were evaluated according to the Diabetes Autoantibody Standardization Program [25].

2.4. Statistical analyses

Vaccination records were available for 1954 of the 2441 children recruited in both studies (80.0%; 1256 from BABYDIAB). A further 36 observations were excluded because of missing information about the HLA-DR3/4 genotype or preterm delivery, yielding a final sample size of n = 1918. The 1918 children accumulated a total of 20,570 vaccinations covering 61,784 vaccines with a median of 33 vaccines per child (range: 2–59). The last vaccination certificate was seen at a median age of 9.2 years, with 1837 children (95.8%) having complete documentation of vaccinations during their first two years of life. The documentation of vaccinations in the first two years of life did not differ significantly between children who did or did not develop islet autoimmunity at some time during follow-up, i.e. children who developed autoimmunity did not have more complete vaccination records.

Cox's proportional hazard model was used to compute hazard ratios (HRs) of time to islet autoimmunity and corresponding 95% confidence intervals (CIs) per additional vaccination in predefined time intervals. Additionally, we assessed associations with specific vaccinations in the last six months prior to islet autoimmunity, treating numbers of vaccinations as time-varying predictors [26]. Compound vaccinations were considered as separate vaccination events. All Cox models were adjusted for HLA-DR3/4 genotype, sex, delivery mode (Caesarean section/vaginal), season of birth (December-February, March-May, June-August, September-November), preterm delivery (<37 weeks of gestation) and maternal T1D status. In sensitivity analyses, we used a broader definition of HLA risk based on nine genotypes (including DR3/4, but additionally DR4/4, DR4/8, DR3/3, DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9) as defined by the TEDDY study [27] to check for potential confounding and effect modification. In another sensitivity analysis, we adjusted the TBE vaccination analyses additionally for TBE vaccinations administered in 2000 to take account for a potentially different vaccine which was temporarily available at that time.

For each type of vaccine, we computed the cumulative vaccine load during successively larger time windows, starting at birth with monthly increasing intervals up until age 2 years and performing a Cox regression of the association of the vaccine variables

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