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Research Article

Can Islets Autoantibody Profile at Diagnosis of Type 1 Diabetes in Children and Adolescents Predict the Future Development of Hashimoto's Thyroiditis and Coeliac Disease?

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Abstract

Aim: This study aims to explore if any correlation exists between islets autoantibody profile at diagnosis in children and adolescents with type 1 diabetes and subsequent development of Hashimoto's thyroiditis and coeliac disease.

Materials and Methods: In this multicentre retrospective cohort study conducted in three hospitals, for children below 18 years of age diagnosed with Type 1 Diabetes (T1D) over a ten-year period between 1 January 2009 and 31 December 2018, electronic Medical Records (DMR) were looked at and analysed by using SPSS V24.0, for several data variables such as antibody profile (type and number of three antibodies-GAD, IAA and ZnTr8 present and their titres), demographical characteristics (BMI, gender, age of onset), severity of disease at presentation (DKA vs non-DKA and HbA1c value) and subsequent development of Hashimoto's Thyroiditis (HT) and Coeliac Disease (CD).

Results: Out of 218 children (male = 112, female = 103) tested during this study period, IAA was the most prevalent antibody found which was positive in 90 (41%) cases followed by GAD in 83(38%) and ZnTr8 in 34 (16%) children. Median age of onset of T1D was 7.709 years (range 1-17 years) and the mean HbA1c at presentation was 8.8% (range 5.5% - 14.6%). HT and CD were identified in 31 (12.8%) and 14 (5.8%) cases respectively in this cohort. Independent samples t-tests could not identify any significant difference in the GAD, IAA and ZnTr8 antibody levels for the children with or without HT{(M = 148.16, SD = 507.9) and (M = 117.6, SD = 402.2); t (103) = 0.275, p = 0.784 in GAD}, {(M = 514.46, SD = 1360.7) and (M = 316.86, SD = 972.02); t (99) = 0.697, p = 0.487) in IAA}, {(M = 309.63, SD = 397.76) and (M = 383.26, SD = 462.70) ; t (32) = 0.385, p = 0.703) in ZnTr8}. Likewise, there has not been any statistically significant difference for those with or without CD {(M = 57.9, SD = 107.5) and (M = 91.21, SD = 326.4); t (93) = 0.335, p = 0.739 in GAD}, {(M = 22.41, SD = 18.0) and (M = 420.87, SD = 1140.2); t (90) = 1.10, p = 0.274 in IAA}. One-way ANOVA {F (2) = .970, p = 0.382} could not identify any correlation between the number of antibodies present at diagnosis and subsequent development of HT. There was, however, a statistically significant difference recognised, as determined by a one-way ANOVA {F (2,112) = 3.305, p = < .05} for the number of antibodies present and development of CD. Post hoc comparisons using the Tukey test showed children presenting with all 3 antibodies were 3.87 times more likely to develop CD(p = 0.036).

Conclusion: IAA was the most prevalent islets autoantibody found in this study, followed by GAD and ZnTr8. All three antibodies were positive in 13% cases. Although, GAD, IAA and ZnTr8 antibody titres at diagnosis are not predictive of subsequent development of HT and CD, the number of antibodies present influences the future risk of CD but not for HT. Presence of all the three antibodies nearly quadruples the possibility of subsequent development of CD. As HLA typing is not a predictor of development of CD in children with T1D, this finding can influence the frequency of serology testing.

Keywords: T1D: Type 1 Diabetes mellitus; IAs: Islets Autoantibodies; GADA: Glutamic Acid Decarboxylase Antibody; IAA: Insulin Autoantibody; IA-2A: Insulinoma Antigen-2 Antibody; ZnTr8A: Zinc Transporter 8 Antibody; HT: Hashimoto's Thyroiditis; CD: Coeliac Disease

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Introduction

Type 1 Diabetes mellitus (T1D) is an autoimmune disease characterized by loss of insulin producing beta cells and, therefore, life-long requirement of exogenous insulin for survival. This is one of the most common chronic medical condition in children and young adults equally affecting both males and females with classical symptoms of polyuria, polydipsia and weight loss despite polyphagia [1]. Although, T1D affects nearly half a million population worldwide, fortunately, the overall incidence has not been rising over the last 15 years in Australia [2]. In individuals with a genetic predisposition (polymorphism in HLA locus and in gene producing insulin and PTPN22), an unidentified trigger initiates an abnormal immune response and the development of Islet Autoantibodies (IAs) directed against proteins such as insulin, glutamic acid decarboxylase, islet antigen 2, and zinc transporter 8, found on secretory granules within pancreatic beta cells [3]. T1D is also associated with other autoimmune diseases such as Hashimoto's Thyroiditis (HT), Coeliac Disease (CD), Addison's disease and rheumatoid arthritis. Development of IAs occurs before clinical diagnosis of T1D and many have multiple IAs present at diagnosis. Similarly, antibodies suggestive of other comorbid autoimmune conditions such as anti-TPO (for HT) and TTG, AGA, EMA (for CD) are already present in some cases of T1D at diagnosis. CD is associated withT1D in 4% - 9% of all cases and vice versa and both are two genetic disorders involving similar genes (HLA DQ2 and DQ8). CD usually develops within 10 years of T1D onset [4]. HT occurs in approximately 3-8% of the children and young adults with T1D, with an incidence between 0.3 and 1.1 in 100 children and teenagers with T1D per year [5]. In addition to the index case the family members have higher rate of development of HT and CD compared to general population. The presence of HT and CD in children with T1D may have an overall impact on the glycaemic control, health-related quality of life of the child and on the family as a whole. Unfortunately, there has not been any robust clinical or laboratory tool available to predict the future occurrence of HT and CD in children with T1D. Regular surveillance with the laboratory testing of thyroid function test (TSH, T4), anti-TPO antibody, anti-TTG and AGA etc in the asymptomatic phase is currently practiced for the timely identification of these comorbidities [6].

Islets Autoantibodies

Autoantibodies against Glutamic Acid Decarboxylase (GAD), insulinoma antigen-2 (IA-2A), insulin (IAA) and the most recently Zinc transporter 8 (ZnT8A) are commonly used biomarkers for T1D in both children and adults. Islet antibodies (IAs), measured by sensitive and specific liquid phase assays, are the key parameters of the autoimmune response monitored for diagnostics or prognostics in patients with T1D [7]. Islet Autoantibody Standardization Program, previously known as DASP, supervised by the Immunology of Diabetes Society, organized by the Trial Net Islet Cell Autoantibody Core Laboratory at the Department of Pathology of the University of Florida, USA controls the standard of ICA measurements. IA-2 and Zn T8 proteins are found on the membrane of Secretory Granules (SG), in addition to insulin contained within, while GAD 65 is found on the cytoplasmic site of Synaptic-Like Micro-Vesicles (SLMV). GAD is highly expressed in β cells and in a minority of α cells. GAD antibody is often present in the absence of diabetes such as in Autoimmune Polyglandular Syndrome (APS). IA-2 is a receptor type Protein Tyrosine Phosphatase (PTP) which is intrinsic to the membrane of SG responsible to influence insulin secretion, SG biogenesis and homeostasis and β-cell expansion. Insulin in the human is expressed almost exclusively in pancreatic beta cells. IAA have also been described in other autoimmune diseases like APS and Stiff-person syndrome. In β cells the uptake of zinc into secretory granules is mainly mediated by zinc transporter 8 (ZnT8) [8]. ZnT8 transporter is essential for the formation of insulin crystals in beta cells, contributing to the packaging efficiency of stored insulin [9].

Seroconversions of Islet Autoantibodies

Siblings of the index case of T1D are at risk of development of not only T1D but other associated comorbidities like HT and CD. Seroconversions occur very rarely before the age of 6 months in these at-risk children, and the peak of incidence of seroconversion takes place between 9 and 24 months of age [10]. The rate of seroconversion at 9 and 24 months were 18.5 and 21 new cases per 1000 high risk children per year, respectively, compared to 9.1, 5.1, and 6.9 seroconversions per 1000 high-risk children years at 5, 11, and 14 years of age [11]. The incidence of IAA at seroconversion peaked earlier and was significantly higher than that of GADA, IA-2A, and ZnT8A [11]. Multiple islet autoantibodies, when present, tends to occur in the younger age group. In around 70% of the cases, from single antibody at presentation to multiple antibody seroconversion happens in 2 years' time [12]. IAs show a predominance of immunoglobulins mostly of the IgG1 class for GADA, IA-2A, and in addition also of the IgG3 and IgG4 class for IAA, already at seroconversion as opposed to the sequential appearance of immunoglobulin M to IgG of a classical de novo immunization process [13]. Frequency prevalence of autoantibody positivity at onset of disease range in decreasing order was seen in >80% for GADA, ≥70% for IA-2A, ≥65% for ZnT8A, and >50% for IAA in a large population-based study [14]. In another study of 750 children with T1D living in Taiwan, 66.3% had GADA, 65.3% IA2A, 35.7% IAA, and 17.2% had no autoantibodies [15]. Those children with higher IAA or IA-2A antibody have a two to fourfold increase in risk of developing T1D within 10 years [16]. Female patients had significantly higher prevalence of GADA compared with male patients (72.3% vs. 59.7%, P = 0.00027) [15].

Materials and Methods

Three IAs (GADA, IAA and ZnTr8A) were tested among the children below 18 years diagnosed with T1D since January 2009 till 31st of December, over a ten-year period across the state of Tasmania in three different hospitals. In this multicentre retrospective cohort study electronic Medical Records (DMR) were looked at and collected data were analysed by using SPSS V24.0. Throughout the sites three IAs were tested and IA-2A was not included in the panel. Not every child had been tested for all three antibodies over. Antibody types, titres and number of antibody's present in each individual were looked at. Demographical characteristics (BMI, gender, age of onset), severity of disease at presentation (Diabetic Ketoacidosis vs non-DKA and HbA1c value) and subsequent development of HT and CD were explored to determine if the IAs profile based on type, number and the titres at diagnoses had any predictive correlation. HT was confirmed when the TSH level was higher than 10 m U/L in the presence of either anti-TPO or anti-thyroglobulin antibody who were being treated with thyroxine. Presence of tissue transglutaminase

Table 1: Demographics of participants.

Variable		
Total Gender Male Female Not specified	N = 218 n = 113 n = 103 n = 2	
Age at onset	M = 7.709 years (Range 1-17 years)	
HbA1C at presentation	M = 8.8% (Range 5.5% -14.6%)	
Initial Serological Investigations GAD positive IAA Positive ZnTr8Positive	 n = 83 (117) n = 90 (114) n = 34 (42)	 Reference Range > 1.45 Reference Range > 1.0 Reference Range
Associated Co-morbidities Hashimoto's Thyroiditis Coeliac Disease	 n = 31 (12.8%) n = 14 (5.8%)	

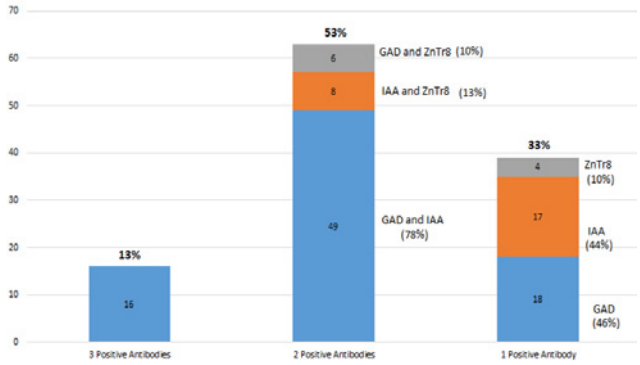

Figure 1: Number of cases presenting with 1, 2 or 3 positive antibody level results.

autoantibodies (TTG antibody), IgA and IgG antibodies to gliadin (AGA-IgA, AGA-IgG) were confirmed with the endoscopy and intestinal biopsy prior to the diagnosis of CD. Only confirmed cases of HT and CD were considered in this study. Ethics approval was obtained from the Tasmanian Health and Medical Research Ethics Committee (Ref: H0016509).

Results

We identified that 242 participants were eligible for this study. However, there was incomplete data for 24 cases, which were then excluded reducing the participant numbers to 218. The demographics for this population are described in (Table 1).

An independent samples t-test was performed to compare islets antibody levels in females and males (Table 2). There was no significant difference in the GAD antibody levels for females (M = 151.1, SD = 446.7) and males (M = 93.54, SD = 359.1); t (115) = 0.773, p = 0.441. Similarly, there was no significant difference in the IAA antibody levels for females (M = 315.4, SD = 961.4) and males (M = 351.26, SD = 1018.1). There was no significant difference in the ZNTr8 antibody levels for females (M = 414.68, SD = 513.5) and males (M = 363.24, SD = 513.5).

A Pearson's correlation coefficient was performed to assess the relationship between IAs and age of onset of disease. There was no significant correlation between GAD antibody levels and age of onset (r = -.06, n = 64, p = .638). Also, there was no significant correlation between IAA antibody levels and age of onset (r = .088, n = 68, p = .475). There was, however, a weak, positive, non-significant correlation found between ZnTr8 antibody levels and age of onset (r = .142, n = 23, p = .518)) (Figure 1).

From a total of 218 cases where antibody levels were measured in 120 of these, 13% of patients presented with a positive result for all three antibodies- GAD, IAA and ZnTr8, 53% of patients presented with a positive for 2 antibodies and 33% of patients presented with a positive result for one antibody (Figure 1). GAD-IAA has been the most frequent combination when two IAs are positive at diagnosis (Figure 2).

The antibody fractions are presented in (Figure 2), highlighting the difference in numbers between patients who presented with normal range GAD, IAA and ZnTr8 antibody levels and those with increased antibody levels. 18% presented with a normal range GAD antibody level when tested whereas 15% presented with a normal range IAA antibody level. When tested for ZnTr8, only 13% presented with a normal range ZnTr8 antibody level. It is noted that towards the late years there has been a positive trend to include the ZnTr8 in the panel to test for T1D at diagnosis.

Independent samples t-tests were performed to compare IAs in those with or without HT and also for those with or without CD (Table 3). There was no significant difference in the GAD antibody levels for children with HT (M = 148.16, SD = 507.9) vs for those with normal thyroid function (M = 117.6, SD = 402.2); t (103) = 0.275, p = 0.784. Similarly, no significant difference found in the IAA antibody levels for those with HT (M = 514.46, SD = 1360.7) and without HT (M = 316.86, SD = 972.02); t (99) = 0.697, p = 0.487). Also, there was no significant difference in the ZnTr8 antibody levels for children with hypothyroidism (M = 309.63, SD = 397.76) and euthyroid participants (M = 383.26, SD = 462.70); t (32) = 0.385, p = 0.703).

There was no significant difference in the GAD antibody levels for

Table 2: Islet Autoantibody and Gender.

Gender	N	GAD Mean	*p*	N	IAA Mean	*p*	N	ZnTr8 Mean	*p*
Female Male	38 45	210.7 86.3	0.195	41 49	392.4 444.4	0.822	15 19	525.1 439.7	0.615

Table 3: Autoantibody and Serological Investigations.

Auto-antibody	N	GAD Mean	*p*	N	IAA Mean	*p*	N	ZnTr8 Mean	*p*
Thyroid Function Test Positive Negative	 17 88	 148.16 117.6	0.784	 18 85	 514.46 316.86	0.487	 7 27	 309.63 383.26	0.497
Coeliac Disease Present Absent	 11 84	 57.9 91.2	0.739	 10 82	 22.41 420.87	0.274	 0 26	 301.94	**

Figure 2: Numbers of cases by antibody level.

those with confirmed CD (M = 57.9, SD = 107.5) and those without CD (M = 91.21, SD = 326.4); t (93) = 0.335, p = 0.739. There was no significant difference in the IAA antibody levels for positive coeliac participants (M = 22.41, SD = 18.0) and negative participants (M = 420.87, SD = 1140.2); t (90) = 1.10, p = 0.274. The ZnTr8 antibody profile was unable to be determined as there were insufficient participants. The number of cases in each antibody category are shown in (Figure 1). There were no statistically significant differences between group means as determined by one-way ANOVA (F (2) = .970, p = 0.382) for number of antibodies present at time of diagnosis and HT. There was, however, a statistically significant difference identified between groups as determined by a one-way ANOVA (F (2,112) = 3.305, p = < .05) for the number of antibodies present at the time of diagnosis and the presence of CD. Post hoc comparisons using the Tukey test showed that there was a significant difference between 1 positive antibody and 3 positive antibodies (p = 0.036) with patients presenting with 3 positive antibodies are 3.87 times more likely to have CD than those presenting with only 1 positive antibody.

Discussion

At presentation, it is a traditional clinical practice to test for the islet autoantibody profile, both the types of antibody and the titre, to confirm the diagnosis of T1D. Although, the IAs can be negative in cases of T1D, it raises the suspicion of Maturity Onset Diabetes of Young (MODY) which is not an autoimmune condition. Screening for IAs for at risk children, such as for parents and sibling, is currently practiced in research settings. The benefits of screening for IAs in this group include identifying the children who are likely to develop T1D, decreasing the incidence of Diabetic Ketoacidosis (DKA) at presentation, initiating insulin therapy sooner in the disease process with the aim to delay or prevent progression [17]. The utility the IA testing for the index cases for any other clinical information is quite limited. The presence of islets autoantibodies at diagnosis did not predict micro vascular complication in a large study [18]. T1D usually has a preclinical symptomless phase identified by circulating IAs, but the rate of progression to diabetes remains uncertain. In a multi-centre study, the progression to T1D at 10-year follow-up after IA seroconversion was seen in 69.7% (95% CI, 65.1%-74.3%) cases when multiple IAs were present compared to 14.5% (95% CI, 10.3%-18.7%) of children with a single IA present [19]. Risk of diabetes in children who had no IAs was negligible 0.4% (95% CI, 0.2%-0.6%). Progression to T1D in the children with multiple IAs was faster for children who had islet autoantibody seroconversion younger than age 3 years (hazard ratio [HR], 1.65 [95% CI, 1.30-2.09; P < .001. Although the appearance of autoantibodies does not usually follow any distinct pattern, the presence of multiple autoantibodies in less than 3 years old has the highest positive predictive value for development of T1D [20,21]. Similar trend for CD is also seen in our study, the presence of multiple IAs has nearly 4 times higher incidence for CD in children with T1D than with single IA. The progression of IAs and T1D differs among races/ethnicities in at-risk individuals, which is lower in Hispanic compared with non-Hispanic White at-risk individuals, however, no gender preference identified. Younger age, presence of multiple antibodies and certain race increase the possibility of development of T1D in at risk individual, whether this is also applicable to other comorbidities that remains to be answered. What factors predict the possibility of future development of HT and CD is the larger question.

In this article we explored whether specific antibody profile have any predictive correlation with the subsequent development of CD and HT. Antibody levels were found not to be useful in this regard. The number of antibodies, however, seems to be positively correlated with the future occurrence of CD, but not with HT. Presence of all three IAs increased the probability nearly four times the likelihood of CD than with single antibody positivity. In our cohort 13% children with T1D did have all three antibodies positive. Most of the children and adolescents in this study had two antibodies positive in various combinations, seen in 53% cases, followed by 33% of cases where only one antibody was positive. The commonest combinations were GAD-IAA (78%), IAA-ZnTr8 (13%), followed by GAD-ZnTr8 seen in 10%. Nearly 13-18% of cases antibodies were negative when tested for. Those who are negative or positive with single antibody the future likelihood of development of CD is minimal. There has been a clear association between specific HLA haplotypes and development of IAs. In particular, GADA are associated more strongly with the HLA DR3-DQ2 haplotype, while IAA and IA-2A are more associated with the HLA DR4-DQ8 haplotype [11]. The frequency of Coeliac Disease (CD)-specific HLA genotypes, HLA-DQ2, HLA-DQ8 or both is positive in the vast majority (>80%) of patients with T1D and therefore, screening for coeliac-specific HLA genotypes as a first-line test is not a suitable method to predict likely development of CD in T1D. Regular screening for coeliac-specific antibodies in T1D remains standard of current clinical practice [22].

As an autoimmune disease, T1D can be associated with other autoimmune disorders such as autoimmune thyroid disease, coeliac disease, and Addison's disease. The presence of autoantibodies was evaluated with special regard to the control of diabetes and to the clinical status of the patient. Autoantigens of the small intestine - Tissue Transglutaminase Autoantibodies (ATTG), IgA and IgG antibodies to gliadin (AGA-IgA, AGA-IgG) were evaluated by ELISA. The screening of autoantibodies in type 1 diabetic patients could reveal subclinical cases of AITD or coeliac disease. Subclinical forms of these disorders have no influence on diabetes control [5]. In this elevated TPOA and EMA levels at diagnosis of T1D predict the development of HT and CD, respectively. In children with negative antibody titres at diagnosis, screening at 2-year intervals is recommended [18].

Limitations

1. Inconsistency in pathological tests requested during this 10-

year study period. Not all of them have been tested for all the three antibodies.

2. Another limitation is the availability of pathology data – some of the cases may have had their antibody levels done but the data was not available though he DMR or through the pathology lab (e.g. may have been done interstate or through a private provider).

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