Prevalence of autoantibodies in children newly diagnosed with type 1 diabetes mellitus

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is an increasingly encountered chronic illness in Saudi Arabia. It is known to have an immune-mediated pathogenesis, which results in the loss of insulin-secreting β-cells responsible for maintaining normal blood glucose levels. The three main autoantibodies identified to play a role in the pathogenesis are islet cell antibodies (ICA), insulin autoantibodies (IAA) and glutamic acid decarboxylase antibodies (GAD). This study aims to determine at what age during childhood the autoantibodies ICA, IAA and GAD are most prevalent, and identify any correlation between their presence and the severity of the initial clinical presentation. Medical records of children diagnosed with T1DM in Riyadh in 2000–2007 were reviewed, and a total of 98 patients were included in the study (age range: 1–12 years, mean: 6.6 years, equal numbers by gender), of which 49% presented with diabetic ketoacidosis (DKA). Results showed that 67% were positive for ICA, 36% for IAA and 84.4% for GAD. The presence of ICA was predominant in children aged under six years. The presence of ICA and GAD in the absence of IAA was associated with more severe clinical presentation.

KEY WORDS: Autoantibodies.
Child.
Diabetes mellitus, type 1.
Prevalence.

Introduction

The incidence of type 1 diabetes mellitus (T1DM) has gradually increased in most Western countries since the 1940s.[1] The onset of the disease is probably triggered by one or more environmental agents, and the process usually progresses over many months or years, a period during which the patient is asymptomatic. Type 1 diabetes is also known to have an immune-mediated pathogenesis, which results in the loss of insulin-secreting β-cells. The three main autoantibodies that have been identified as playing a role in the pathogenesis of T1DM are islet cell antibodies (ICA), insulin autoantibodies (IAA) and glutamic acid decarboxylase antibodies (GAD).[2,3]

The predictive characteristics of ICA have been more closely defined than IAA and GAD.[4] It has also been recognised that the antibodies convey different levels of diabetes risk.[1] The presence of a single autoantibody may not increase risk appreciably, but the presence of multiple antibodies adds significantly to the risk of diabetes.[5] Also, the autoantibodies differ in their prevalence, correlation with each other, and their level of risk for T1DM.[2] The presentation of patients with T1DM varies; however, typical presenting symptoms include polyphagia, polydipsia, polyuria, weight loss, fatigue and diabetic ketoacidosis (DKA).

Type 1 diabetes is an increasingly encountered chronic illness in Saudi Arabia and it comprises the majority of cases of diabetes seen in childhood.[6] The prevalence of T1DM varies from one region to another across the country, with the highest prevalence in the central region.[6]

The aim of this study is to determine the prevalence of autoantibodies in children with T1DM and identify any correlation between their presence and the severity of the initial clinical presentation.

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Materials and methods

This retrospective study was conducted at a tertiary care academic hospital in Riyadh, Saudi Arabia, on patients seen between January 2000 and December 2007.

Patients

Children aged ≤12 years diagnosed with type 1 diabetes mellitus were included. All cases of type 2 diabetes mellitus and secondary hyperglycaemia were excluded. Children who initially presented to, or whose diagnosis was made at, another hospital were also excluded from the study.

Data collection

Patient medical records were reviewed. Demographics, clinical presentation and the results of laboratory investigations were gathered, including presence or absence of autoantibodies.

The clinical presentation was considered to be severe if the child presented with DKA, which was defined as pH<7.3 and/or bicarbonate <15 mmol/L and a random glucose value >11.1 mmol/L.

Autoantibody testing

Testing for GAD and IAA was performed by a referral laboratory (Biocentia) in Germany. The method used was a radioimmunoassay (RIA) technique performed on serum samples (reference range: <1.0 unit/mL).

Testing for ICA was performed in-house using an indirect immunofluorescence assay (IFA; GB Alphadia, Belgium)), as previously described,[7] again on serum samples.

Data analysis

The age of the children was categorised into two groups: preschool group (age range: 1–5.9 years) and school age group (age range: 6–12 years). The type of autoantibody, gender and clinical presentation were then identified for each group. The data were analysed using SPSS software (Statistical Package for the Social Sciences, version 17). The χ^2 test was used and the presence of autoantibodies was correlated to the severity of presentation between the different subject groups.

Results

Ninety-eight patients were identified as having T1DM (age range at diagnosis: 1–12 years; mean age of 6.6 years; male to female ratio: 1:1) (Table 1). Approximately half of the samples 48 (49%) were from patients who presented with DKA (Table 2). Twenty patients (41.7%) were aged <6 years and 28 patients (58.3%) were aged six to 12 (Table 2). Out of these patients in the DKA group, 22 (45.8%) were male and 26 (54.2%) were female (Table 3).

In the 98 patients, ICA, IAA and GAD antibodies were tested in 94, 25 and 32 patients, respectively, and 63 (67%) were positive for ICA, nine (36%) were positive for IAA and 27 (84.4%) were positive for GAD.

Three of the patients were positive for all three antibodies, but they were not in the DKA group and were <6 years of age. Two patients were positive for ICA and IAA (mean age: 4.4 years [SD±3.7]). Seventeen patients were positive for ICA and GAD (mean age: 5.4 years [SD±2.9]). Out of these 17 patients, seven (41.1%) were in the DKA group.

Of the 63 (67%) patients who tested positive for ICA antibodies, 38 (60.3%) were <6 years old and 25 (39.7%) were in the six to 12 year age group (Table 4). The *P* value for both age groups was 0.108, and more females were ICA-positive than males (33 and 30, respectively [$P=0.423$]). In those who were ICA-positive, 31 (49.2%) presented with DKA (14 males, 17 females [$P=0.611$]). Of these, 15 patients (48.4%) were aged <6 year and 16 (51.6%) were in the six to 12 age group.

Of the nine (36%) patients who tested positive for IAA antibodies, five (55.5%) were aged <6 years and four (44.4%) were in the six to 12 age group (age range: 1.7–11 years; mean age: 6.43 years [SD±2.9]; $P=0.847$) (Table 4). There was a similar number of males and females (five and four, respectively). In patients who were IAA-positive, three were in the DKA group, one was aged <6 years and two were in the six to 12 age group.

Of the 27 (84.4%) patients who tested positive for GAD antibodies, 14 (51.8%) were aged <6 years and 13 (48.1%) were in the six to 12 age group (Table 4). More males than females were GAD-positive (16 and 11, respectively). In those who were GAD-positive, 12 (44.4%) patients presented with DKA (seven males, five females). In the group with DKA, five were aged <6 years and seven were in the six to 12 age group (mean age: 6.8 years, $P=0.174$).

Table 1. Frequency of type 1 diabetes mellitus by age and gender.

Age	Male	Female	No (%)
<6	22	31	53 (54.1)
6–12	27	18	45 (45.9)
Total	49	49	98 (100.0)

Table 2. Prevalence of diabetic ketoacidosis by age group.

Age	No (%)
<6	20 (41.7)
6–12	28 (58.3)
Total	48 (100.0)

Table 3. Diabetic ketoacidosis by gender.

Gender	No (%)
Male	22 (45.8)
Female	26 (54.2)
Total	48 (100.0)

Table 4. Prevalence of antibodies (IAA, ICA and GAD) by age group.

	IAA	ICA	GAD
Age	No (%)	No (%)	No (%)
<6	5 (55.5)	38 (60.3)	14 (51.8)
6–12	4 (45.5)	25 (39.7)	13 (48.1)
Total	9 (100.0)	63 (100.0)	27 (100.0)

Discussion

In the present study, it was observed that the presence of autoantibodies was more prevalent in T1DM patients with a younger age of onset (<6 years). In several European studies, it has been shown that the prevalence of autoantibodies is higher in females then in males;[8,9] however, in the present study IAA and GAD antibodies were detected more frequently in males, but this trend would need to be confirmed in further study of a larger number of patients.

Furthermore, this work demonstrated a high prevalence of ICA in patients with T1DM in both age groups studied, which is a similar finding to that reported by others.[10] The present study also showed that the prevalence of ICA was higher in preschool children and those of school age. This increased prevalence could possibly be explained by genetic susceptibility to T1DM.[11]

Insulin autoantibodies are known to emerge as the first autoantibodies in the vast majority of patients who are shown to have two or more autoantibodies during their first

few years of life.[11] In the present study, however, approximately half of those who tested positive for IAA were aged <6 years.

In this study, the prevalence of T1DM with GAD was high. This may account for the apparently higher prevalence of GAD in the group aged ≥3 years, as GAD has been reported by others to show higher prevalence associated with an older age of disease onset.[8] There was no significance between GAD-positivity, DKA and age groups. In a study by Damanhouri *et al.*, it was stated that the prevalence of GAD in patients with diabetes was lower in children aged <3 years than in those who were older.[12] The results presented here show similar findings, whereby GAD was less prevalent in the patients aged <3 years in comparison to those in the three to 12 age group (25.9% [7/27] and 74.1% [20/27], respectively).

Conclusions

The present study showed that islet cell antibodies are more prevalent in younger children (aged less than six years) diagnosed with type 1 diabetes mellitus. In addition, presenting with diabetic ketoacidosis was more common in older children. Although the presence of all three autoantibodies was not shown to correlate with the severity of clinical presentation, the presence of both islet cell antibodies and glutamic acid decarboxylase antibodies in the absence of insulin autoantibodies was associated with a more severe clinical presentation. However, further study on a larger population is recommended to confirm these findings. □

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