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Coincident Presence of Thyro-gastric Autoimmunity at Onset of Type 1 (Insulin-Dependent) Diabetes

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Summary. We have determined thyroid microsomal and gastric parietal cell autoantibodies in 972 patients with onset of Type 1 (insulin-dependent) diabetes before age 20 years. In a cross sectional study, the frequencies of these autoantibodies did not change significantly over the ensuing 20 years following diagnosis of diabetes. In a longitudinal study of 424 patients with Type 1 diabetes followed up to 5.3 years, few new patients with thyro-gastric autoantibodies were identified. Whereas the frequencies of these autoantibodies among the diabetic patients were more than fivefold greater than for age, sex and race matched controls, they resembled those seen in the non-diabetic general population ($n=1524$) for the over 60 year age group. We conclude that in patients with thyro-gastric autoantibodies and Type 1 diabetes, the onset of autoimmune processes affecting the thyroid, gastric mucosa and pancreatic islets tend to be simultaneous, although the resultant diseases have different natural histories.

Key words: Thyroid microsomal autoantibody, gastric parietal cell autoantibodies, Type 1 diabetes, indirect immunofluorescence.

A number of aetiologies have been proposed for Type 1 diabetes as reviewed recently by Cahill and McDevitt [1]. We, like others, have been impressed by the increased frequencies of other putative autoimmune diseases, such as those involving the gastric mucosa, thyroid and adrenal cortex in patients with Type 1 disease [2–6]. We report here the appearance of thyro-gastric autoantibodies in relation to the onset of diabetes among young patients with Type 1 diabetes.

Patients and Methods

Patients

Sera were obtained from 826 Caucasoid and 146 Black patients attending the Universities of Florida or Missouri, or the Florida Camp for Children and Youth with Diabetes with onset of Type 1 diabetes at less than 20 years of age. The mean age of onset was 8.5 ± 0.3 years and the mean duration of Type 1 diabetes at the time of the first observation was 4.2 ± 0.3 years. The mean age of the patients at the time of study was 12.8 ± 0.2 years (range: 0.5–40 years). Of the 972 patients, we also collected serial serum samples annually from 424 for 1–5 years.

Control sera from 1524 patients of all ages were obtained from the Gainesville Civitan Regional Blood Center or from non-endocrine clinics at the University of Florida. None of the control patients had diabetes or other endocrine disorders or an immediate family member with these diseases. In each age class, the number of male and female patients was equal. The studies were conducted in compliance with the University of Florida requirements for informed consent.

Methods

An indirect immunofluorescent technique using goat anti-human IgG fluorescein isothiocyanate conjugates (Kallested, Austin, Texas, USA) was used to determine the presence of autoantibodies to the thyroid gland (thyroid microsomal antibodies) and to the gastric parietal cells of stomach. Human blood group 0 tissues were obtained surgically, snap frozen and used unfixed as tissue substrates [10]. Thyroid tissue used was from a patient with Graves' disease. Gastric fundus was from a patient undergoing gastrectomy because of neoplasia. All serum samples were diluted to 1:4 and were evaluated blindly, with positive and negative controls included in each assay batch for thyro-gastric autoantibodies. Thyroglobulin autoantibodies were not determined as we have previously shown that these antibodies were not more frequent in young patients with Type 1 diabetes [3].

A multiway table of independence using the G test was used for statistical analyses [7]. The results are expressed as mean ± SEM.

Two studies were undertaken. A cross-sectional study was carried out to determine the frequency of autoantibodies in the first serum samples obtained from all 972 patients with Type 1 diabetes in respect to duration of the disease. A longitudinal study was also performed to determine the rate of change in autoantibody status at 6-month to yearly intervals from the time of the first serum sample in 424 of the 972 patients with Type 1 diabetes.

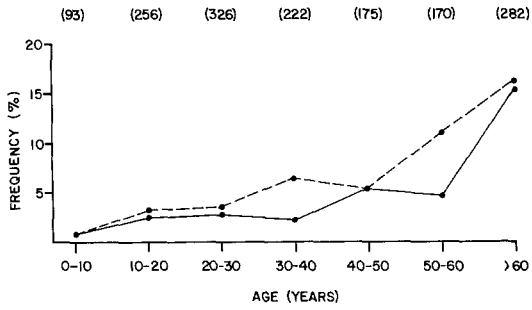

Fig. 1. Frequency of thyroid microsomal (broken line) and gastric parietal cell autoantibodies (solid line) per decade of age in 1 524 control patients. The figures in parentheses represent the number of people in each decade of age

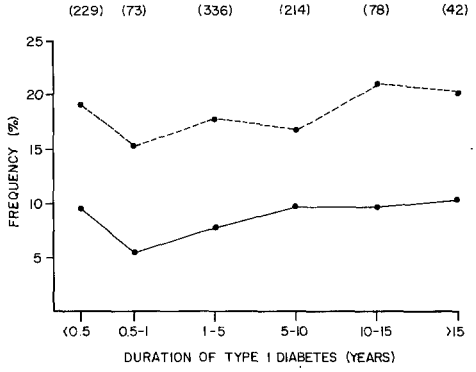

Fig. 2. Frequency of thyroid microsomal (broken line) and gastric parietal cell autoantibodies (solid line) in patients with Type 1 diabetes grouped by duration of disease. Figures in parentheses represent the number of patients in each duration group

Table 1. Frequency of thyroid microsomal autoantibodies in patients with Type 1 diabetes who have islet cell autoantibodies

	Frequency of thyroid microsomal autoantibodies (%)	
	< 3 years	> 3 years
Male	18.5	14.4
Female	26	27.6

The mean duration of the group with duration of disease > 3 years was 8.1 ± 6.2 years

Results

Control Population

The frequencies of thyroid microsomal antibodies and gastric parietal cell antibodies for the control population are shown in Figure 1. There was a gradual increase in the frequencies of these autoantibodies with age with an abrupt rise during the sixth decade of life.

Frequency of Autoantibodies with Duration of Type 1 Diabetes

In the cross-sectional study, the frequencies of thyroid microsomal antibodies and gastric parietal cell antibodies were not statistically different with respect to duration of disease ($p = 0.9$; Fig. 2). Significant differences in the frequencies of thyroid microsomal antibodies and gastric parietal cell antibodies in females over males with Type 1 diabetes, as previously reported [2–5], were found ($p < 0.001$ and $p < 0.01$ respectively). There was no increase nor difference in the frequencies of thyroid microsomal autoantibodies and gastric parietal autoantibodies with duration when the data was analyzed by sex. The proportions of male to female patients with Type 1 diabetes in each duration group were not significantly different. The frequency of either thyroid microsomal antibodies and/or gastric parietal cell antibodies (i. e., any thyro-gastric antibody) in patients at the onset of Type 1 diabetes was 26.1%.

Furthermore, when patients with Type 1 diabetes with islet cell autoantibodies were examined with respect to duration of disease, the frequencies of thyroid microsomal autoantibodies were not different in patients with duration of disease < 3 years compared to those with duration > 3 years (Table 1).

Since the findings of constant frequencies of thyroid microsomal antibodies and gastric parietal cell antibodies from onset of Type 1 diabetes above could be explained by a balanced loss of patients with positive antibodies coincident with a similar number that had developed autoantibodies over the period of observation, we examined this possibility in a longitudinal study.

Longitudinal Study

Four hundred and twenty four patients were followed for up to 5.3 years with annual determinations of autoantibodies. Only two patients converted from negative to positive with respect to thyroid microsomal antibodies. Six 'new' patients developed gastric parietal cell antibodies during the period of observation; however, four of these patients had been identified previously to have thyroid microsomal antibodies and continued to have these antibodies in their sera over the period of observation. Only one patient lost thyroid microsomal antibodies with time. She had undergone thyroidectomy, which is known to be associated with loss of thyroid autoantibodies.

The mean length of follow up was 2.8 ± 0.1 years. The total follow up was 1 187 patient years. Thus one patient per 148 follow up years developed autoantibodies on follow up. Also, if one considers thyroid microsomal antibodies and gastric parietal cell antibodies as a single entity, which have been labelled previously by others as thyro-gastric autoantibodies, then only one patient per 396 years of follow-up developed thyro-gastric autoantibodies.

Discussion

Our results demonstrate that the frequency of autoantibodies in young patients with the onset on Type 1 dia-

betes before 20 years of age, such as thyroid microsomal antibodies and gastric parietal cell antibodies, do not increase appreciably with duration of the disease. That is, the frequency of these antibodies are not significantly different at the onset of Type 1 diabetes or up to 30 years duration of Type 1 diabetes. Furthermore, only one patient per 148 follow-up years developed an autoantibody not present at a previous examination. Most of these patients had had either thyroid microsomal antibodies or gastric parietal cell antibodies previously determined. Thus, if we consider thyro-gastric autoimmunity as a single entity, only three new patients per 1187 follow-up years (one per 396 years) developed thyro-gastric autoantibodies.

Previous reports have found either an increase, decrease or no clear relation in the frequencies of thyro-gastric autoantibodies with duration of Type 1 diabetes [8–10]. These studies dealt mainly with older patients (> 20 years of age), whereas our study consisted of patients who developed Type 1 diabetes before the age of 20 years and who were usually less than 40 years of age at the time of study. Most were considerably younger. Whittingham et al. [10] showed increasing frequencies of thyro-gastric autoantibodies in patients with Type 1 diabetes of less than 10 years duration, constant frequencies in patients with Type 1 diabetes for 10 to 20 years and a decline in frequencies in patients with Type 1 diabetes for more than 20 years. They suggested that survival with Type 1 diabetes might be adversely affected in patients with other autoimmune diseases [10].

As shown in Figure 1, there is a gradual increase in the frequencies of thyro-gastric autoantibodies in a normal control population with ageing, with an abrupt rise during the fifth and sixth decades. Thus older patients with Type 1 diabetes might develop thyro-gastric autoantibodies as part of the 'normal' process of ageing. Clearly among our younger patients with Type 1 diabetes, thyro-gastric autoantibody frequencies were more similar to control subjects in the sixth decade than to age matched controls.

We, as well as others, have proposed that the genetic predisposition to thyro-gastric autoimmune disease is an additional risk factor for the development of Type 1 diabetes unrelated to the risk with certain HLA-DR genotypes [11–12]. Our data suggest that thyro-gastric autoantibodies are expressed at a younger age and are more penetrant in individuals with Type 1 diabetes. However, there may be a difference in the frequency of thyro-gastric autoantibodies dependent on the age of onset of Type 1 diabetes [13]. This may explain our differences with studies in which primarily older patients have been studied [9]. Irvine et al. have shown a rise in the incidence of thyroid microsomal autoantibodies in female patients with Type 1 diabetes over the age range 20–50 years [14]. Males did not show this rise. We found no such difference between the sexes. Bottazzo et al. have shown that in 116 patients with duration of Type 1 diabetes between 3 and 16 years, 70% of patient with islet cell autoantibodies have thyro-gastric autoantibodies [14]. Our data do not confirm this finding but show a slight decrease in males and no change in females of the frequency of thyroid microsomal autoantibodies in patients with islet cell autoantibodies.

The follow-up is relatively short (2.8 years per patient) and obviously longer follow-up is needed for a definitive answer. However, if for example, only 5% of children with Type 1 diabetes are not identified at an initial screening, the determination of these organ-specific autoantibodies at one point in time would still identify the majority of patients at risk for other autoimmune diseases. Our studies with thyroid microsomal autoantibodies suggest that these antibodies are excellent predictors of thyroid disease in children with Type 1 diabetes [6]. The negative predictive value has remained at 100% but the positive predictive value has increased from 40% to 55% in a 3-year follow-up study of patients with thyroid microsomal autoantibodies [6]. Our experience with adrenal and gastric parietal cell autoantibodies has been similar although less extensive than with thyroid microsomal autoantibodies [2, 4].

This study demonstrates that many young patients with Type 1 diabetes have other autoimmune processes, as identified by positive autoantibodies, which are present by the time that clinical diabetes has been diagnosed. In the spontaneously diabetic BB rat, we have also demonstrated similarly that gastric parietal cell autoantibodies were detectable before or near the age of onset of diabetes with little increase in the frequency of gastric parietal cell autoantibodies thereafter [15]. These results raise the possibility that both Type 1 diabetes and other associated autoimmune diseases result from a common process. Whether patients with Type 1 diabetes and other endocrinopathies have a different aetiology or inheritance than patients with only Type 1 diabetes is not known. Future epidemiological studies should consider separately the diabetic patient with multiple endocrinopathies.

In summary, we would conclude that 26% of young children with Type 1 diabetes have a polyglandular autoimmune syndrome which affects the endocrine pancreas, the thyroid, and the gastric mucosa at a similar initial point in time. Routine initial screening of patients with Type 1 diabetes for the presence of thyroid microsomal and gastric parietal cell autoantibodies would identify the majority of patients at risk for clinical disease of those organs. However, progression to clinical disease of the thyroid gland, gastric parietal cells and pancreatic islets in such patients occurs at different rates.

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