The Role of Autoimmunity at Diagnosis of Type 1 Diabetes in the Development of Thyroid and Celiac Disease and Microvascular Complications

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OBJECTIVE — The purpose of this study was to explore whether the presence of thyroid and endomysial autoantibodies at diagnosis of type 1 diabetes in children predicts development of thyroid and celiac disease, respectively, and whether diabetes-associated autoantibodies at diagnosis predict development of microvascular complications up to 13 years later.

RESEARCH DESIGN AND METHODS — Autoantibodies were measured at diagnosis of type 1 diabetes in 173 children aged 0–15 years and included thyroperoxidase antibody (TPOA), endomysial antibody (EMA), islet cell autoantibody, GAD antibody (GADA), and insulin autoantibody. Thyroid disease was defined as thyroid stimulating hormone level ≥5 μU/ml. Celiac disease was confirmed by small-bowel biopsy. Assessment of microvascular complications included stereoscopic fundal photography, pupillometry, thermal threshold, and albumin excretion rate (AER).

RESULTS — The incidence rates for thyroid and celiac disease were 0.9 and 0.7 per 100 patient-years, respectively. Within 13 years, 6 of 13 children with positive TPOA tests at diagnosis developed thyroid disease compared with 5 of 139 children with negative TPOA tests ($P < 0.001$). All four patients with positive EMA titers at diagnosis had biopsy-proven celiac disease. Five of 11 patients who developed thyroid disease and 4 of 8 who developed celiac disease had negative TPOA and EMA tests at diagnosis, respectively. Retinopathy was detected in 39% and elevated AER in 36%. The presence of diabetes-associated autoantibodies at diagnosis did not predict microvascular complications though GADA titer levels predicted pupillary abnormality.

CONCLUSIONS — Elevated TPOA and EMA levels at diagnosis of type 1 diabetes predict the development of thyroid and celiac disease, respectively. In children with negative antibody titers at diagnosis, screening at 2-year intervals is recommended.

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Abbreviations: AER, albumin excretion rate; AGA, antigliadin antibody; EMA, endomysial antibody; GADA, GAD antibody; ICA, islet cell autoantibody; IAA, insulin autoantibody; TPOA, thyroperoxidase antibody; TSH, thyroid-stimulating hormone.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetes-associated autoantibodies are often measured at diagnosis and include islet cell autoantibodies (ICAs), antibodies against GAD (GADAs), and insulin autoantibodies (IAAs) (1–3). Clinical onset of type 1 diabetes may also be accompanied by other organ-specific autoantibodies such as thyroperoxidase antibodies (TPOAs) and endomysial antibodies (EMAs) (4–8). They are associated with thyroid and celiac disease, respectively, but could represent nonspecific autoimmunity (9).

Thyroperoxidase is a marker of autoimmune thyroiditis, which is often clinically silent but may progress to either overt or subclinical hypothyroidism (10–14). Thyroid autoantibodies are found in 20–30% of patients with type 1 diabetes, whereas hypothyroidism has a lower prevalence of 5–10% according to most studies (15–18). It may take years for patients with positive autoimmune serology to develop thyroid disease (5,10,16,19–21). However, there is a lack of prospective evidence regarding the predictive role of thyroid autoantibodies for future thyroid disease at the time of diagnosis of diabetes.

The prevalence of celiac disease in patients with type 1 diabetes is between 1 and 8.3% (4,22–34). Celiac disease uncommonly presents with clinical features but is suspected by a positive EMA titer and confirmed by the finding of partial villous atrophy on small-bowel biopsy (32,33,35,36). The EMA titer has a high sensitivity and specificity for identifying patients with type 1 diabetes and celiac disease (22,25) and is superior to other screening tests, such as antigliadin antibodies (AGAs) (37–40). Some patients may develop positive EMA titers and silent celiac disease some years after diagnosis of diabetes (31–34). Consequently, screening every 2–3 years has been recommended (24,31–33). Few studies have used a longitudinal design to examine whether EMAs at diagnosis predicts the

development of celiac disease in patients with type 1 diabetes (31–33).

Measurement of diabetes-associated autoantibodies, such as ICAs, GADAs, and IAAs at presentation with type 1 diabetes is useful for confirming the autoimmune origin of disease (41,42). There is conflicting evidence as to whether diabetes-associated autoantibodies may also be related to long-term development of microvascular complications. Cross-sectional studies have mostly found that diabetes-associated autoantibodies are not related to the presence of complications (41–44). However, higher GADA levels were shown to be more common in patients with peripheral neuropathy and long-standing diabetes (45) and less likely in patients with severe retinopathy and type 1 diabetes (46). Because the prevalence of positivity for GADAs and IAAs declines with diabetes duration (41,43), their measurement at diagnosis of type 1 diabetes may be more relevant to the development of complications than later testing. To date, no study has investigated whether the presence of autoantibodies at diagnosis predicts the later development of microvascular complications.

In this study we investigated whether autoantibodies (TPOAs, EMAs, and diabetes-associated antibodies) found at diagnosis of type 1 diabetes in children were predictive of future development of autoimmune disease and microvascular complications up to 13 years later. We aimed to determine the frequency with which screening for associated disease should be undertaken.

RESEARCH DESIGN AND METHODS

— From a New South Wales population-based incident cohort of children with new-onset type 1 diabetes (diagnosed in 1990–1991), 273 were screened at diagnosis for TPOAs, EMAs, ICAs, GADAs, IAAs, and thyroid-stimulating hormone (TSH) (1). Of these, 173 (63%) were followed longitudinally for up to 13 years (median age at diagnosis 8.2 years, range 0.9–14.9 years, 52% male). Compared with nonparticipants, participants were younger at age of diabetes onset (8.3 vs. 11.6 years, $P < 0.0001$) but were no more likely to come from an urban than a rural area (63 vs. 54%, NS). Informed consent was obtained from all participants and the hospital's ethics committee approved the study.

TPOAs were measured by enzyme-linked immunoassay, EMAs and ICAs by indirect immunofluorescence, GADAs by radioimmunoprecipitation, and IAAs by radioimmunoassay, as previously described (1). Thyroid function was assessed by measuring TSH at diagnosis and then at routine follow-up visits. Diagnosis of thyroid dysfunction was based on elevated TSH levels (>5 μU/ml) and/or documentation of thyroid dysfunction (hypothyroidism or hyperthyroidism) made by a pediatric endocrinologist. After initial screening for celiac disease at diagnosis by measuring EMAs, follow-up screening was accomplished by measuring AGAs from 1992 to 1998 and EMAs thereafter. Celiac disease was confirmed by small-bowel biopsy and was offered to all patients with positive AGA or EMA titers.

Screening for microvascular complications was undertaken 3.1–13.4 years after diagnosis at the Children's Hospital at Westmead and included assessments of retinopathy, nephropathy, and autonomic and peripheral neuropathy (47–50). Retinopathy was defined as the presence of at least one microaneurysm or hemorrhage in at least one eye detected by seven-field stereoscopic fundal photography (48). Albumin was measured using a polyclonal radioimmunoassay (Pharmacia, Uppsala, Sweden). Early elevation of the albumin excretion ratio (AER) was defined as mean AER ≥7.5 μg/min of three urine specimens, whereas microalbuminuria was defined as AER ≥20 μg/min in two of three timed overnight urine collections or an albumin-to-creatinine ratio ≥2.5 mg/mmol. Autonomic neuropathy was assessed by measuring the pupil size before and for 3 s after a light stimulus was delivered, using an infrared pupillometer (Pupilscan; Fairvill Medical Optics). Peripheral neuropathy was assessed by measuring thermal threshold discrimination for hot and cold at the left foot. Patients were required to discriminate between thermal stimuli to progress to a more difficult discrimination task (Thermal Threshold Tester; Medelec, Old Woking, Surrey, U.K.). Pupillary abnormalities and reduced thermal threshold were defined as <5% of the normal range in a nondiabetic adolescent control group previously tested in our laboratory, as previously described (51,52). HbA_{1c} (A1C) was measured at each assessment of complications using the Bio-Rad Diamat analyser (Bio-Rad, Hercules, CA). The nondiabetic range for A1C is 4–6%.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS 11.0.1; SPSS, Chicago, IL). Pearson's χ^2 test or Fisher's exact test was used to compare outcomes between categorical variables. Kaplan-Meier survival curves were generated and the log-rank statistic was used to compare the likelihood of patients with and without positive antibody at diagnosis of diabetes remaining free from thyroid and celiac disease. Cox regression was performed to determine predictors of each microvascular complication over time. Predictor variables included in the model were ICAs, GADAs, and IAAs (continuous or categorical variables), age at diagnosis, and A1C. P values <0.05 were considered significant.

RESULTS

TPOAs and development of thyroid disease

Elevated levels of TPOAs (>100 units/ml) were found in 13 of 166 (7.8%) patients (5 female and 8 male) at diagnosis. There was no difference in sex or age at onset of diabetes between patients with positive compared with negative TPOA. One girl was found to be hypothyroid at diagnosis and commenced thyroxine replacement therapy. Subsequent measurements of TSH were made in the other 12 patients with positive TPOA and in 139 patients (91%) with negative TPOA at diagnosis. The median number of TSH measurements after diagnosis of diabetes was 2 per patient (range 1–10 times) and was available for a median of 7.2 years after diagnosis (range 0.9–13.1 year).

The incidence rate of thyroid disease in the present study was 0.91 (95% CI 0.45–1.62) per 100 patient-years. Sex and age at onset of diabetes had no association with the development of thyroid disease. All patients who developed thyroid disease were asymptomatic at diagnosis. The median time interval between negative to positive screening was 2.8 years. Six of 13 patients (46%) who had positive TPOA at diagnosis developed thyroid abnormalities, whereas 5 of 139 patients (3.6%) who had negative TPOA at diagnosis developed thyroid disease. Patients with positive TPOA at diagnosis were 18 times more likely to develop thyroid disease than those with negative TPOA (5.6–94.0). The mean time to onset of thyroid disease was significantly

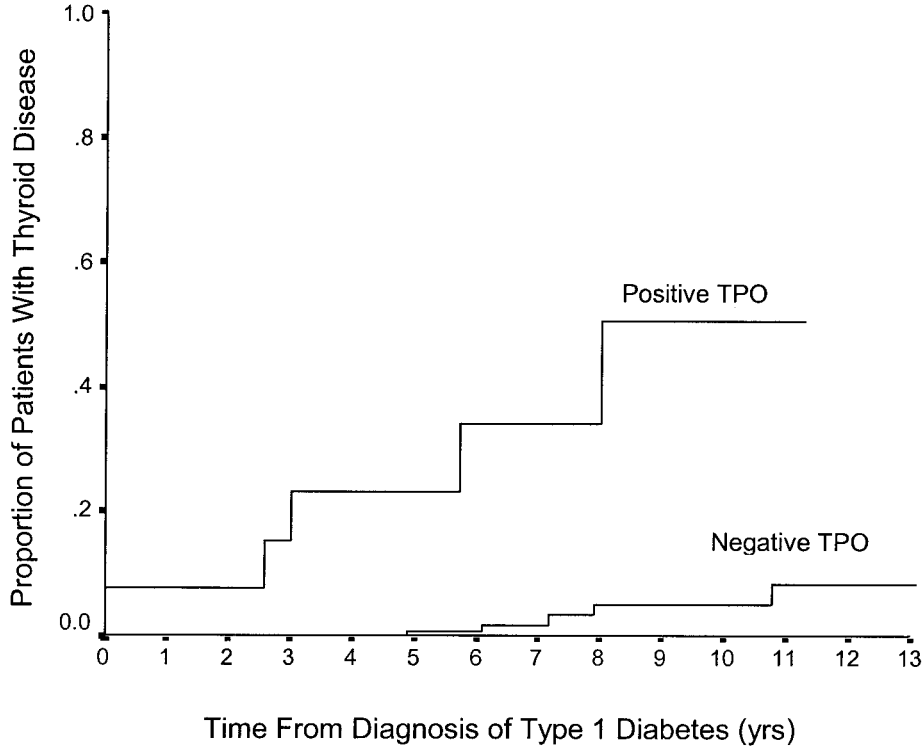

Figure 1—*Kaplan-Meier survival curves show the development of thyroid disease in patients positive and negative for TPOA at diagnosis of diabetes for up to 13 years.*

greater for patients with negative compared with positive TPOA at diagnosis of diabetes (12.7 vs. 8.1 years, $P < 0.0001$) (Fig. 1). However, there was no difference in the median age at onset of thyroid disease (14.9 vs. 15.3 years, NS). Two girls, one with and the other without a positive TPOA titer at diagnosis developed Graves' disease (with positive for thyroid stimulating immunoglobulin) at ages 12 and 14 years, 11 and 8 years after diagnosis of diabetes, respectively. The incidence rate of Graves' disease was 0.16 (0.02–0.59) per 100 patient-years.

EMAs and development of celiac disease

At diagnosis of type 1 diabetes, positive EMA titers (titer >1:160) were found in four patients (2.4%). Celiac disease was confirmed in all four patients by small-bowel biopsy within 1 year of diagnosis, and they subsequently commenced a gluten-free diet. Patients with negative EMA titers at diagnosis were screened for celiac disease a median of twice per patient (range 1–9 times) and for a median of 7.2 years after diagnosis (0.8–13.7 years).

Four of 143 patients (2.8%) had seroconverted between 2.8 and 10.2 years. Patients with negative compared with positive EMA titers at diagnosis were more likely to remain free of celiac disease ($P < 0.00001$). The median time interval between negative to positive titers was 3.6 years. Within 12 months, small-bowel biopsy confirmed celiac disease in all patients, one of whom was also hypothyroid at diagnosis of diabetes. In total, celiac disease was diagnosed by small-bowel biopsy in all 8 patients with positive EMA titers; therefore, the incidence rate was 0.72 (95% CI 0.31–1.41) per 100 patient-years. There were no false-negative EMA tests from initial screening because all patients with biopsy-positive disease had another negative screening test before seroconversion. Sex and age of onset of diabetes did not influence development of celiac disease regardless of EMA status at diagnosis, and no patient was symptomatic when a positive EMA level was detected.

Autoimmunity and development of microvascular complications

At diagnosis of diabetes, positive titers of ICAs were found in 125 of 165 children (76%), GADAs in 112 of 169 (66%), and IAAs in 92 of 143 (64%), and 12 of 170 (6.9%) had no diabetes-associated autoantibodies present at diagnosis. Children with positive IAAs titers were younger at diagnosis ($P = 0.004$) and more likely to be male ($P = 0.02$). Girls were more likely to have positive GADA titers ($P = 0.024$).

Assessment of microvascular complications was made in 171 of 173 (99%) children in the cohort. At least one complication was found in 107 of 171 (63%): retinopathy in 60 of 155 (39%), a pupillary abnormality in 45 of 67 (67%), reduced thermal discrimination thresholds for hot and cold in 23 of 111 (21%) and 9 of 111 (8%), respectively, mean AER ≥7.5 in 58 of 163 (36%) and microalbuminuria in 4 of 159 (3%).

Cox regression demonstrated that the presence of diabetes-associated autoantibodies at diagnosis did not predict the development of microvascular complications. In univariate analysis, IAA and ICA titer levels at diagnosis were associated with the development of retinopathy ($P = 0.021$ and $P = 0.045$, respectively) and GADA titer levels were associated with pupillary abnormalities ($P = 0.007$). However, after adjusting for age at diagnosis, only GADA titer levels remained significant (hazard ratio 1.01 [95% CI 1.00–1.02], $P = 0.026$). The presence of diabetes-associated antibodies did not predict development of thyroid or celiac disease and TPOA or EMA positivity was not associated with any microvascular complication.

CONCLUSIONS — In this population-based incident cohort of 173 children, autoantibody testing at diagnosis was useful in predicting future development of thyroid and celiac disease but not microvascular complications up to 13 years later. Positive TPOA results at diagnosis of type 1 diabetes predicted development of future thyroid disease, and a negative TPOA test was highly predictive of remaining disease free. Positive EMA tests at diagnosis indicated underlying celiac disease.

Patients who were TPOA positive at diagnosis were 18 times more likely to develop thyroid disease than patients who were TPOA negative. Though there is a known association between the presence of TPOAs in patients with type 1 diabetes and thyroid disease (6,8,10,16,17,53–56), only one study previously examined the relationship between thyroid autoimmunity and disease longitudinally from diagnosis (21). As in the present study, their results indicated that more patients with positive compared with negative TPOA titers at diagnosis developed hypothyroidism. In that study, TPOA screening was not performed until 3–10 years after diagnosis, but it was unclear whether TSH screening was also regularly performed (21). Our findings suggest that patients with positive compared with negative TPOA titers at diagnosis are more likely to develop thyroid disease, and they may benefit from annual TSH screening to detect its development. Testing of TPOAs at diagnosis is therefore useful to determine the appropriate frequency of subsequent TSH screening in asymptomatic children. This study does not support a recent recommendation for annual TPOA screening (10).

All four patients in the present study with positive EMA titers at diagnosis of diabetes were found to have celiac disease within 1 year, confirming the high positive predictive value of screening for celiac disease at diagnosis (24,29,32,33). Other studies documenting celiac disease early after diagnosis did not include antibody screening at diagnosis of diabetes, had delayed biopsy, or had limited longitudinal follow-up (24,31–34). Larger cohorts are needed to determine whether positive EMA titers at diagnosis of diabetes is sufficient evidence of celiac disease without the need for biopsy.

Because thyroid and celiac disease can develop several years after diagnosis of diabetes, there is growing consensus that patients with type 1 diabetes should be regularly screened for these diseases (22–27,31–33); current guidelines recommend that this screening should be performed every 2–3 years (57,58). In the current study, children who were initially TPOA and EMA negative at diagnosis did not develop disease for some years after diagnosis of diabetes. In particular, thyroid disease developed at a median of 7.2 years later in patients who were TPOA negative at diagnosis, and EMA seroconversion took place 2.8–10.2 years later in patients initially EMA negative. All patients were asymptomatic at diagnosis. Given the high negative predictive value of TPOAs and EMAs at diagnosis and the low cumulative incidence of disease, screening these children annually is not justifiable. Less frequent screening for thyroid and celiac disease in this subgroup of patients would reduce blood sampling in the first years after diagnosis, which can be traumatic for young children. We recommend screening at 2-year intervals as a safe and cost-effective strategy. Although diagnosis of a small number of cases may be delayed, annual screening would not result in an increase in case detection. Children in whom there is a suspicion of disease, however, should be investigated as clinically indicated.

A limitation of the present study was that screening for TSH, AGAs, and EMAs was not performed annually in all patients. Therefore, irregular screening tests may have identified disease some years after development. Also, before 1998, AGA and not EMA titers were used to screen for celiac disease after diagnosis. Because the AGA titer is known to be a less sensitive screening test for identifying celiac disease than the EMA titer (37–40), it is possible that some cases of celiac disease were missed when AGA titers were used. However, the overall incidence of thyroid and celiac disease is low, and all patients were asymptomatic at diagnosis. Although case ascertainment was 63%, and participants were younger at onset of diabetes than nonparticipants, age of diagnosis was not significant for thyroid or celiac disease. This study used a longitudinal design (up to 13 years follow-up from diagnosis) and found a low incidence of disease in patients with negative antibody tests at diagnosis.

This is the first study to examine the relationship between diabetes-associated autoantibodies at diagnosis of type 1 diabetes and microvascular complications. Although the initial titers for ICAs and IAAs were associated with retinopathy, this was not independent of the effect of age at diagnosis. These results suggest that the presence of ICAs and IAAs at diagnosis does not influence the development of complications. Rather, known predictors of microvascular complications include longer diabetes duration, especially for the prepubertal years with diabetes and health care utilization (47–49). The association of higher GAD titer levels at diagnosis with pupillary abnormalities is consistent with the previous report of higher titers at the time of diagnosis of peripheral neuropathy (45). This autoantibody is not pancreas specific and may be pathogenic for nerve damage.

In this longitudinal study, both TPOAs and EMAs measured at diagnosis were strong predictors of future thyroid and celiac disease, respectively. Disease developed sooner in patients with positive TPOA and EMA tests at diagnosis; however, all patients with type 1 diabetes should be screened both at diagnosis and at regular intervals thereafter. Screening for thyroid and celiac disease at 2-year intervals is appropriate in patients who have negative TPOA and EMA titers at diagnosis of type 1 diabetes. Although measurement of diabetes-associated autoantibodies at diagnosis is mostly not useful for predicting the development of future microvascular complications, higher GADA levels may predict subsequent nerve damage.

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