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Islet GAD autoantibodies in elderly patients with type 2 diabetes

Diabetes is an important health problem in the elderly. In the last years there has been growth in the number of elderly people affected by type 2 diabetes. The presence of islet cell autoantibodies (ICA), and especially of glutamic acid decarboxylase autoantibodies (GADA), in patients with non-insulin-dependent diabetes mellitus characterizes the so-called latent autoimmune diabetes in adults (LADA). Little is known about the frequency and significance of islet cell immunity in elderly patients with type 2 diabetes (1–3).

Circulating antibodies to the islet autoantigen GAD are detected in 6–50% of subjects clinically diagnosed with type 2 diabetes in various populations (3).

It has been noted that the frequency of autoreactive antibodies is generally higher in older individuals. With advancing age, the immune system undergoes changes which predispose to autoimmune reactivity. Ageing reduces the efficiency of physical barriers, decreasing protection against invasive pathogens, and exposing previously hidden antigens in the body's own tissues (4, 5).

Ageing is also associated with increased levels of chronic inflammation. Elderly patients with diabetes seem to have a marked activation of the acute phase response (1, 2). Within the inflamed tissue, inflammatory cytokines and autoantigens provide activation signals that promote plasma cell differentiation and survival. The autoantibodies produced locally by these plasma cells contribute to the severity of inflammation. These persisting autoantibody titers, though often low and not causing acute clinical symptoms, are likely to maintain a low level of chronic inflammation and progressive tissue destruction, which reduces the threshold for another break of immunological tolerance (5–7).

Increasing age is associated with a decreasing ability to mediate effective immune responses especially to newly encountered antigens. Woodland et al. (7) proposed that the majority, if not all, of the response to newly encountered antigens in the elderly is mediated by cross-reactive memory T cells. There is a possibility that memory immune responses, first generated when the individual is young, may play a critical role in the appearance of serum autoantibodies by reactivation later in life (recall memory), which induces an autoimmune memory response through molecular mimicry (5–7).

Recent studies indicate that type 2 diabetes may be a disease of the innate immune system (1, 2). Pietropaolo et al. (1) found more pronounced activation of the acute phase response in patients with GADA evidence and suggested that the inflammation may be part of the autoimmune reaction against beta-cells.

The aim of the study was to evaluate the clinical significance of the occurrence of islet cell antibodies and to assess the changing frequency and titers of GADA in groups of elderly patients with type 2 diabetes.

CLINICAL CHARACTERISTICS OF STUDIED PATIENTS

In the whole group there were 74 (50 F; 24 M) patients with diagnosed type 2 diabetes, aged 60–91 y, mean age 69.5±8.3 years. Duration of diabetes was 0.5 to 23, mean 5.6±6.4 years. The duration of diabetes in 50 subjects was below 5 years; there were 24 patients with newly (0.5–1.0 y) diagnosed diabetes (19 in group 1, 3 in group 2 and 2 in group 3). The patients were divided into three age-related groups. Group 1 covered 47 (31 F; 16 M) patients aged 60–69 y, mean age 64.2±3.0 years. Group 2 was composed of 14 subjects (9F; 5 M) aged 70–79, mean age 74.0±2.6 years and group 3 included 13 patients (10 F; 3 M) aged 80–91, mean age 83.8±4.3 years.

In 23 patients in the entire group diabetes co-occurred with autoagression diseases such as thyroid disease (most frequent), albinism, bronchial asthma, psoriasis, Addison's disease and Addison-Biermer anaemia. The greatest number of patients with autoagression disease was in the group aged 60–69 y (19 patients, i.e. 40% of patients in that group) and the smallest number (One patient) was found in the group of patients over 80 years old.

METHODS

GADA were determined by radioimmunometric assay (RIA) [GAD-AB kits] with CIS reagents. The positive GADA titers were over 1 U/ml. The smallest detectable GADA concentration was 0.3 U/ml.

The patients were divided into two groups according to GADA titers: 1) patients with positive GADA (>1.0 U/ml) and 2) patients with GADA below 1.0 U/ml (0.3–0.99 U/ml), i.e. sublimited values below the borderline. The group of GADA positive patients was further divided into two subgroups: patients with GADA titers ranging from 1.0 to 2.0 U/ml (medium titers) and patients with titers >2 U/ml (high titers).

RESULTS

The results of the study are shown in Table 1 and Figure 1. Twenty (27%) patients of the entire group had GADA with titers >1.0 U/ml, including 8 (10.8%) patients with GADA titers > 2 U/ml and 16.2% with titers ranging from 1.0 to 2.0 U/ml. Patients with GADA titers < 1.0 U/ml were the most numerous and they constituted more than 30% of all the subjects. In group 1 positive GADA (>1 U/ml) were found in 13 (27.7%) out of 47 assays performed, i.e. in 6 (12.8%) patients the GADA level was in the range between 7.1 and 64.5 U/ml and in 7 (14.9%) subjects between 1.02 and 2.1 U/ml. Most frequently, in as many as 11 (23.4%) patients, GADA titers between 0.38 and 0.98 U/ml were found (method sensitivity > 0.3 U/ml). In the second group – 3 (21.4%) patients were GADA positive (> 1.0 U/ml). In two patients (14.3%), the GADA titres were 38.5 and 68.5 U/ml respectively, and in 1 (7.1%) they were 1.63 U/ml. In 5 (35.7%) patients the GADA level ranged between 0.4 and 0.99 U/ml. In group 3 there were positive GADA (>1.0 U/ml) in 4 (30.8%) assays (1.3–12.1 U/ml). In 1 (7.7%) patient the level was 12.1 U/ml, in 3 (23.1%) the level ranged between 1.3 and 1.42 U/ml. GADA titres between 0.61 and 0.94 U/ml were found in 8 (61.5%) patients. Group 3 was characterized by the highest percentage of patients with both medium and sublimited GADA titers and the lowest percentage of patients with no GADA found. The percentage of patients with high GADA titers was the highest in group 1 and did not significantly change with the age of the patients. In the older patients the frequency of low GADA titers (close to 1 U/ml) clearly increased.

Table 1. The frequency of different GADA titers in particular subject groups

Parameter	Whole studied group No of pts	Group 1 (60–69 y) No of pts	Group 2 (70–79 y) No of pts	Group 3 (80–91 y) No of pts
Number of all assays	74 (100%)	47 (100%)	14 (100%)	13 (100%)
All assays GADA positive >1 U/ml	20 (27.0%)	13 (27.7%)	3 (21.4%)	4 (30.8%)
GADA >2.0 U/ml, high titer	8 (10.8%)	6 (12.8%)	1 (7.1%)	1 (7.7%)
GADA >1.0 to 1.9 U/ml, medium titer	12 (16.2%)	7 (14.9%)	2 (14.3%)	3 (23.1%)
GADA >0.3 U/ml to <1 U/ml, low titer	24 (32.4%)	11 (23.4%)	5 (35.7%)	8 (61.5%)
GADA < 0.3 U/ml	30 (40.6%)	23 (48.9%)	6 (42.9%)	1 (7.7%)

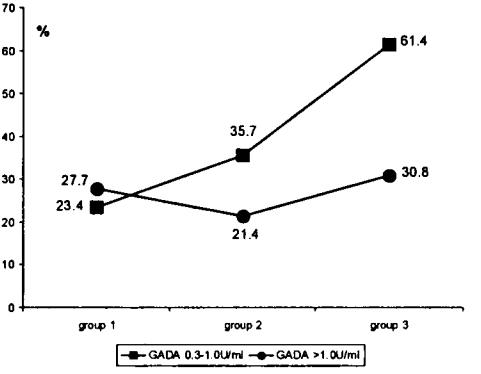

Fig. 1. The comparison of the percentage of GADA-positive patients with low titers with the whole group of titers >1 U/ml, in particular age groups

DISCUSSION

The prevalence of GADA in our subjects is comparable to the data provided by other authors (3). The fact that the percentage of GADA positive patients (27%) in the subject group is higher than usual (10–12%) may result from its characteristics, i.e. there were twice as many women as there were men and there was a high percentage of patients with co-occurring autoaggression disease (1, 8). The high frequency of low titer antibodies in group 1 patients can be explained as Schranz et al. did (9): many subjects had had diabetes for a short time. The ageing process of the autoimmune system as a risk factor for autoimmunity (4–7) seems to be the most convincing reason why the percentage of patients with low and sublimited antibody titers increased with age, as there are few patients with co-occurring autoaggression disease and short-lasting diabetes in groups aged ≥70 years. The observed GADA titers indicate a slight intensification of autoaggression processes. Clinical studies of Carlsson et al. (10) additionally emphasized that increased age is as strong a risk factor for LADA as it is for type 2 diabetes.

CONCLUSIONS

Elderly diabetic patients are characterized by an increasing frequency of sublimited GADA titers as they aged. The low autoantibody levels may signify a less aggressive beta-cell auto-immunity as well as instability of the immunological system related to ageing or both.

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SUMMARY

Little is known about the prevalence and significance of islet cell immunity in elderly patients with type 2 diabetes. The objective of the paper was to establish the changing frequency and titers of GADA in elderly diabetics. 74 (50 F; 24 M) diabetic patients (60–91 y) divided into age-related groups. Group 1: 47 (31 F; 16 M) patients (60–69 y). Group 2: 14 (9 F; 5 M) pts (70–79). Group 3: 13 (10 F; 3 M) pts (80–91). GADA were determined by RIA (GAD-AB kits), (CIS). The positivity threshold of GADA titers was over 1 U/ml. 20 (27%) patients of the entire group had GADA with titers >1.0 U/ml. Patients with GADA titers <1.0 U/ml were the most numerous and they constituted more than 30% of all subjects. Group 1: Positive GADA were found in 13 (27.7%) assays (1.02–64.5 U/ml). In 11 (22.9%) patients GADA titers 0.38–0.98 U/ml were found (method sensitivity>0.3 U/ml). Group 2: In 3 (21.5%) patients, GADA were >1 U/ml; in 4 (28.6%) patients GADA ranged from 0.93 to 0.99 U/ml. Group 3: There were positive GADA in 4 (30.8%) assays (1.3–12.1 U/ml). In 8 (61.5%) patients GADA ranged from 0.61 to 1.42 U/ml. The percentage of

patients with high GADA titers did not change significantly with age. The frequency of low GADA titers (<1 U/ml) clearly increased in the older patients. Elderly diabetic patients are characterized by increasing frequency of sublimited GADA titers. The low level of autoantibodies may signify a less aggressive beta-cell autoimmunity as well as the instability of the immunological system related to ageing or both.

Przeciwciała przeciwwyspowe anty-GAD u chorych na cukrzycę typu 2 w wieku podeszłym

W literaturze mało jest danych dotyczących znaczenia oraz częstości występowania przeciwciał przeciwwyspowych u chorych z cukrzycą typu 2 w wieku podeszłym. Celem pracy była ocena stężeń oraz częstości występowania przeciwciał anty-GAD u chorych na cukrzycę typu 2 w takim wieku. 74 (50 K; 24 M) chorych (wiek 60–91 lat) podzielono na trzy grupy: grupa 1 liczyła 47 (31 K; 16 M) osób (wiek 60–69 lat); grupa 2 – 14 (9 K; 5 M) (wiek 70–79 lat); grupa 3 – 13 (10 K; 3 M) osób (wiek 80–91 lat). GADA oznaczano metodą RIA (Anti-GAD-AB), (CIS). Za dodatnie przyjmowano miano GADA >1U/ml. GADA >1 U/ml w całej badanej grupie stwierdzono u 20 (27%) chorych. Chorzy, u których stwierdzono GADA <1 U/ml, stanowili 32,4% (24 osoby). W grupie 1 GADA >1U/ml stwierdzono w 13 (27,7%) oznaczeniach (1,02-64,5 U/ml). U 11 (22,9%) chorych wykryto GADA w mianie 0,38–0,98 U/ml (czułość metody>0,3 U/ml). Grupa 2: GADA>1 U/ml wykryto u 3 (21,5%) osób; u 4 (28,6%) badanych miana GADA zawierały się między 0,93 a 0,99 U/ml. Grupa 3: GADA>1 U/ml stwierdzono w 4 (30,8%) oznaczeniach (1,3–12,1 U/ml). U 8 (61,5%) badanych miana GADA wynosiły 0,61–1,42 U/ml. Odsetek pacjentów z GADA>1 U/ml nie zmieniał się istotnie w grupach wiekowych, natomiast wśród starszych chorych wyraźnie wzrastała częstość GADA w niskim (<1 U/ml) mianie. Chorych na cukrzycę w wieku podeszłym charakteryzuje rosnąca wraz z wiekiem częstość występowania GADA w niskich mianach. Może to wskazywać na mniejsze nasilenie procesu z autoagresji lub spowodowaną wiekiem niestabilność układu immunologicznego, albo na obie przyczyny jednocześnie.