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Rapid-onset type 1 diabetes mellitus in middle-aged and older persons

Szybko ujawniająca się cukrzyca typu 1 u osób starszych

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Keywords

type 1 diabetes, elderly, C-peptide, anti-GAD antibodies, LADA

Słowa kluczowe

cukrzyca typu 1, osoby starsze, peptyd C, przeciwciała anty-GAD, cukrzyca LADA

Summary

Introduction. Persons older than 35 years of age are usually diagnosed with type 2 diabetes mellitus and much less frequently with LADA (Latent Autoimmune Diabetes of Adults). According to the definition, initial stages of LADA can be treated with oral medications for 6 months or more. Very seldom, middle-aged or older patients (> 40 years of age) present with type 1 diabetes with characteristic abrupt or rapid onset, like in children or adolescents.

Aim. The aim of the study was to analyze cases of rapid-onset type 1 diabetes mellitus in patients admitted to the Endocrinology Unit within the past 5 years. The analysis was retrospective.

Material and methods. Retrospective analysis of cases of rapid-onset type 1 diabetes mellitus found in our Clinic in the past five years.

Results. We found eight cases of rapid-onset type 1 diabetes mellitus in patients older than 40 years of age in whom it was essential to continue insulin treatment after hospitalization or it was necessary to implement insulin within 2 months after hospitalization.

Conclusions. These cases show that there are no dogmas in diabetes. We should be watchful all the time and be ready to change the initial diagnosis if the course of the disease is atypical. Additional tests that are essential in establishing a diagnosis include C-peptide and, in some cases, anti-GAD autoantibody assays. A low level of C-peptide confirms a diagnosis of type 1 diabetes mellitus only when blood glucose is normalized after insulin therapy. The presented cases indicate that type 1 diabetes mellitus of a typical rapid course can be diagnosed after the age of 40 years and in the elderly and that, apart from insulin dependency, there are no evident features that distinguish type 1 diabetes, even with the rapid onset, from type 2 diabetes. This was a pilot study and that is why the study group was small. Collection of a greater number of data could possibly help find other typical features indicating rapid-onset type 1 diabetes mellitus in middle-aged and older patients.

Streszczenie

Wstęp. U osób po 35. roku życia zazwyczaj rozpoznawana jest cukrzyca typu 2, dużo rzadziej cukrzyca typu LADA (ang. *latent autoimmune diabetes in adults*) – wolno (późno) ujawniająca się cukrzyca typu 1. W tej postaci cukrzycy, zgodnie z definicją, w początkowej fazie choroby przez 6 miesięcy lub dłużej można stosować leku doustne. Rzadko w grupie osób po 40. roku życia zdarza się piorunujący lub bardzo szybki początek cukrzycy typu 1, podobnie jak to często bywa u dzieci.

Cel pracy. Celem pracy była analiza przypadków szybko ujawniającej się cukrzycy typu 1, przyjmowanych do Kliniki w ciągu ostatnich 5 lat. Praca ma charakter opisowy.

Materiał i metody. W ocenie retrospektywnej odnaleziono 8 (osiem) przypadków szybko ujawniającej się cukrzycy typu 1 u osób po 40. roku życia, u których niezbędne było utrzymanie leczenia insuliną na zakończenie hospitalizacji lub niezbędne było wdrożenie insuliny do 2 miesięcy po zakończeniu hospitalizacji.

Nie znaleziono ewidentnych cech charakterystycznych, które mogłyby przepowiadać wczesną insulinozależność pacjentów, poza brakiem wyrównania przy próbie zmiany leczenia z insuliny na leki doustne.

Wnioski. W każdym przypadku chorego na cukrzycę powinniśmy myśleć o różnicowaniu choroby oraz zmieniać wstępnie przyjęte rozpoznanie, gdy przebieg choroby jest nietypowy. Do rozpoznania niezbędne jest wykonanie badań dodatkowych, głównie peptydu C, a w wybranych przypadkach przeciwciał anty-GAD. Niski poziom peptydu C potwierdza rozpoznanie cukrzycy typu 1 pod warunkiem wykonania badania po wstępnym wyrównaniu cukrzycy. Brak lub obecność chorób z autoagresji, zaburzeń lipidowych lub nadwagi nie są czynnikami różnicującymi cukrzycę typu 1 o szybkim początku u osób po 40 roku życia.

Conflict of interest
Konflikt interesów

None
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INTRODUCTION

Persons older than 35 years of age are usually diagnosed with type 2 diabetes mellitus and much less frequently with LADA (Latent Autoimmune Diabetes of Adults). According to the definition, initial stages of LADA can be treated with oral medications for 6 months or more. Very seldom, middle-aged or older patients (> 40 years of age) present with type 1 diabetes with characteristic abrupt or rapid onset, like in children. However, such cases do happen, and delayed diagnosis and improper therapy with oral medications in the early stage result in rapid beta cell exhaustion, C-peptide demise and very unstable disease course preventing effective therapy.

AIM

The aim of the study was to analyze cases of rapid-onset type 1 diabetes mellitus in patients admitted to the Endocrinology Unit within the past 5 years and to attempt to identify factors that can facilitate differential diagnosis.

MATERIAL AND METHODS

The evaluation involved patients admitted to the Endocrinology Unit with newly diagnosed diabetes within the past 5 years. The analysis included patients older than 40 years of age with type 1 diabetes who had to continue insulin therapy after hospitalization due to the impossibility to control diabetes with oral medications or had to start using insulin within 2 months post-hospitalization.

RESULTS

Eight persons met the criteria of rapid-onset type 1 diabetes mellitus. This group included three males and five females. Table 1 presents patient characteristics.

The mean age at diagnosis of diabetes was 58.62 years. The oldest patient was 96 years old, and the youngest was 42.

Four patients (3 females and 1 male) had endocrine comorbidities (a disease of the thyroid gland), but they were diagnosed together with diabetes in only 1 case. In the remaining three patients, autoimmune conditions were identified within 1-5 years after the onset of diabetes. It was hypothyroidism in each case. Apart from hypothyroidism, 1 patient presented with vitamin B_{12} deficiency, and gastroscopy confirmed atrophic gastritis. There are no post-hospitalization data concerning the remaining patients.

The mean body mass index (BMI) amounted to 25.26 kg/m^2. BMI was greater than 30 kg/m^2 (obesity) in only 1 patient. Three patients needed statins to control blood lipid levels. All persons with lipid metabolism disorders had BMI over 25 kg/m^2. The major irregularity in the lipid profile was increased LDL cholesterol level. Furthermore, 4 persons had arterial hypertension.

The typical features of patients with rapid-onset type 1 diabetes mellitus were as follows:

1. Significantly elevated blood glucose levels at admission (over 350 mg/dl) with signs of uncontrolled diabetes mellitus (increased thirst, polyuria, losing weight) and incommensurably only slightly raised HbA1c levels, which indicated a relatively recent onset of considerable hyperglycemia.
2. Very good and rapid reaction to insulin – control obtained within 1-3 days after insulin implementation.
3. An attempt to introduce oral medications ended with a failure – glucose concentration rose rapidly. The only exception was patient 2 who was discharged during an effective oral therapy, but glucose levels increased abruptly 5 weeks post-hospitalization (up to 350 mg/dl) and did not decrease in reaction to restrictive low-carbohydrate diet; the patient was re-admitted, treated with insulin, and had further tests conducted to differentiate the type of diabetes.

Rapid-onset type 1 diabetes mellitus in middle-aged and older persons could not be diagnosed on the basis of:

1. The presence of other autoaggressive conditions. An autoimmune disease was detected together with diabetes in only 1 case. In the remaining patients, autoimmune conditions were identified within 1-5 years after the onset of diabetes. There are no data concerning 2 patients who were not re-hospitalized.
2. The lack of lipid metabolism disorders or hypertension. Their presence did not exclude type 1 diabetes mellitus. The occurrence of lipid disorders and hypertension increases with age. That is why, their presence or absence in patients over 40 years of age does not determine the disease status.

Tab. 1. Characteristics of patients with rapid-onset type 1 diabetes mellitus

No	Initials	Sex	Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)	HbA1c (%)	C-peptide (ng/ml)	Statin use	Arterial hypertension
1	KJ	female	95	78	1.69	27.3	8.0	0.12		yes
2	HJ	male	60	79	1.71	27	8.8	0.31	yes	yes
3	KE*	female	46	82.7	1.59	32.71	9.0	0.4	yes	yes
4	MI	female	61	52	1.61	20.06	9.1	0.52	no	no
5	ŁW	male	48	64	1.69	22.41	8.9	0.4	no	yes
6	PD	male	54	78	1.74	25.76	9.3	0.31	yes	no
7	WZ**	female	63	64	1.56	26.29	8.6	0.6	no	no
8	BA***	female	42	58	1.68	20.55	9.3	0.5	no	no
average			58.62	69.46		25.26	8.88	0.38	3/8	4/8

*2 autoimmune diseases diagnosed after diabetes onset (hypothyroidism, vitamin B_{12} deficiency)
**anti-GAD antibodies > 2,000 IU/ml
***thyroid autoimmune disease diagnosed together with diabetes

3. Weight. Average BMI was higher than 25 kg/m^2; one patient was obese. Healthy weight, particularly with BMI < 25 kg/m^2, should prompt a differential diagnosis of diabetes, but research has shown that type 1 diabetes mellitus can also occur in overweight and obese individuals.
4. Age. The youngest patient that met the criteria was 42 years old, and the oldest – 95.

Cases

The most spectacular case of rapid-onset type 1 diabetes mellitus in individuals older than 40 years of age was a case of a 95-year-old patient admitted to Hospital due to freshly diagnosed diabetes with ketoacidosis and high glucose concentrations (glucose 1,211 mg/dl, with metabolic acidosis (pH 7.271, carbohydrates 16.8 mmol/l), hyperkalemia 5.7 mmol/l, corrected sodium 144 mmol/l, plasma osmolality 372 mOsm/kg H_2O (normal range 280-300 mOsm/kg H_2O)). Chest radiography revealed pneumonia. Additionally, the patient presented with hypertension, had had ischemic stroke 4 years before and had undergone right hip replacement surgery years before. Symptoms of hyperglycemia, in the form of weakness and urinary incontinence developed 4 days before hospitalization and, fortunately, were not ignored by the patient's family. Despite high glucose levels and accompanying pneumonia, the patient's condition was incommensurably good, and intravenous insulin (8 units per kg body weight per hour) led to a rapid normalization of glucose levels and enabled a change of treatment to 4 subcutaneous insulin injections. Initially, high glucose levels and acidosis were associated with newly diagnosed diabetes mellitus and pneumonia. It was assumed that the rapid improvement of the overall condition and quick normalization of blood glucose levels were caused by the simultaneous administration of insulin and antibiotics. Despite a very high glucose concentration at the beginning of inpatient treatment, glycated hemoglobin was relatively low – 8.0%. That is why, as pneumonia subsided, it was attempted to start oral therapy. However, each insulin discontinuation and an attempt to replace it with oral medications resulted in an abrupt increase in glucose levels and it was necessary to return to insulin therapy. In order to verify the type of diabetes, as glucose levels were regulated, blood was collected for C-peptide assay. It yielded the value of 0.12 ng/ml (normal range 1.1-4.4), which indicated type 1 diabetes and entailed the necessity of insulin therapy. Due to the clear clinical picture and an unambiguous C-peptide level that indicated insulin deficiency, anti-GAD antibody testing was deemed unnecessary in this and in the remaining cases. Although a positive result could undoubtedly confirm the autoimmune nature of diabetes in this 95-year-old patient, the negative result would not exclude such a diagnosis. The patient was discharged with insulin therapy of 4 injections.

The second case that drew our attention was rapid-onset type 1 diabetes mellitus in a 58-year-old male admitted due to newly diagnosed diabetes. The medical interview revealed hypertension and hyperlipidemia. The patient had observed increasing polyuria, polydipsia and weakness for several weeks, xerostomia for a week and weight loss of 5 kg in a month. A glucose level at admission was 410 mg/dl with no signs of metabolic acidosis. BMI = 27 kg/m^2. In the initial treatment, the carbohydrate disorders were regulated with basal-bolus insulin. Subsequently, it was attempted to alter the treatment and introduce oral medications (gliclazide 30 mg daily with metformin in gradually increased doses) with good effects – glucose levels were controlled. The hypotensive and hypolipidemic therapies were modified, as recommended by the Polish Diabetes Society. The patient was discharged with the following final diagnosis: "Newly diagnosed type 2 diabetes mellitus, primary hypertension, mixed hyperlipidemia". After 10 weeks, the patient was re-admitted due to increasing glucose levels above 300 mg with concomitant typical symptoms (polyuria, polydipsia, weakness, abrupt weight loss). Medical history: after approximately 5 weeks of relatively good glucose control, the patient observed a rapid increase in blood sugar levels despite using prescribed medications (gliclazide 30 mg daily and metformin 2,000 mg/daily). The patient attempted to intensify diet – he excluded carbohydrates almost completely, yet with no effects. The patient lost about 9 kg, disregarded infections and additional stress. At re-admission, he was in a good overall condition with a glucose level of 359 mg/dl and no signs of metabolic acidosis. On physical examination, BMI was 23.3 kg/m^2, and no abnormalities were noted. Uncontrolled diabetes mellitus was confirmed by an abnormal HbA1C result (9.8%), which was considerably worse than during the previous hospitalization. C-peptide was 0.31 ng/ml (normal range 1.1-4.4), which confirmed type 1 diabetes mellitus. Based on the clinical picture and the result of C-peptide assay, type 1 diabetes mellitus was diagnosed and basal-bolus insulin therapy was implemented.

DISCUSSION

The incidence of diabetes mellitus increases with age. It affects approximately 16% of elderly males and 20% of elderly females. The POLSENIOR study, conducted in 2007-2010 in Poland, which included 4,949 patients aged 65-100 years, revealed carbohydrate metabolism disorders in 42.4% of patients (1).

Old age is not a determinant of type 2 diabetes, but over 90% of elderly patients have this type of diabetes and 95% of newly diagnosed cases are type 2 diabetes. This very large group includes patients in whom the course of the disease and/or efficacy of oral therapy raises concerns from the very beginning despite undertaking liberal goals of metabolic regulation measured with the HbA1C levels (according to the Polish Diabetes Society, target values of HbA1C $\leq$ 8.0% in elderly patients and/or with diabetes mellitus complicated by macroangiopathy and/or with multiple comorbidities (2)). The differential diagnosis of the type of diabetes is rarely undertaken in older patients since the entire situation is additionally complicated by the fact that therapy is not always effective; over 80% of

elderly patients do not achieve the therapeutic goals measured with HbA1C levels (3).

LADA is by definition late-onset autoimmune diabetes in adult patients (usually presenting with positive anti-GAD antibodies$_{65}$ or other islet cell antibodies) that is diagnosed in individuals over 35 years of age who, due to slow beta cell demise, do not require insulin therapy for the first 6 months of treatment (2). LADA is classified as type 1 diabetes mellitus, but slow progression of beta cell exhaustion, at least in certain patients, makes the correct diagnosis challenging.

Based on clinical trials, the incidence of LADA was estimated at approximately 5-10%. In the UKPDS study, 9.4% of type 2 diabetes patients presented with anti-GAD antibodies$_{65}$ and were re-classified to a different group of LADA patients (4). Adult-onset autoimmune diabetes, including LADA, is more common that type 1 diabetes in children. In China, where type 1 diabetes is rare (due to the presence of protective alleles), the incidence of LADA is comparable to that in the European population (5).

Phenotypically, patients with LADA make up a heterogeneous group with the majority of features leading to insulin resistance, but with less advanced changes and fewer metabolic complications compared with type 2 diabetes patients (6). The clinical picture is largely dependent upon age at which diabetes is diagnosed.

GWAS studies (Genome-Wide Association Studies) identified numerous genes predisposing to both type 1 and type 2 diabetes (7). From the genetic point of view, patients with LADA exhibit features typical of both type 1 (HLA, INS VNTR, PTPN22, STAT4, CTLA4, IL2RA) and type 2 diabetes (TCF7L2, FTO) (8, 11). HLA-DQB1 and PTPN22 (type 1 diabetes risk genotypes) were more common in patients with LADA and considerably less frequent in patients with type 1 diabetes diagnosed in childhood (9). The frequency of factor TCLF7L2 was comparable to that in patients with type 2 diabetes (10).

Immunologically, LADA patients present all islet cell antibodies (anti-GAD$_{65}$, IA-A2, ICA, ZnT8A). In long-term observation, temporal fluctuation of antibody levels, with possible demise of previous antibodies and development of antibodies against other factors, draws attention (12, 13).

The system of diabetes classification adopted by the WHO in 1999, which divides this disease into four main types, seems insufficient from the point of view of establishing a correct diagnosis and implementing appropriate treatment in adults with type 1 diabetes or LADA. It is therefore more and more frequently postulated and suggested that a new diabetes classification should be introduced, based on pancreatic beta cell dysfunction and an influence of the interaction between genetic, immune or environmental factors on pancreatic beta cells (14).

The cases presented above do not fall within the current definitions of LADA or type 2 diabetes; these are typical cases of rapid-onset type 1 diabetes.

The case of a 95-year-old patient reported above is special not only due to the age at type 1 diabetes diagnosis. It also shows that, despite common beliefs, not every instance of type 1 diabetes mellitus in adults has a LADA-typical course, with slow beta cell exhaustion and possibility of using sulfonylurea derivatives to control the disease in its initial phase. Also in younger patients (< 19 years of age), not every case of diabetes progresses rapidly. Long-term remissions or only slightly elevated glucose levels that do not require insulin therapy for many months (despite positive antibodies typical of type 1 diabetes) are observed in younger patients, although such situations are rare. This probably happens because glucose levels are very rarely tested in children and adolescents. That is why diabetes mellitus in young individuals is diagnosed usually when blood glucose levels are extreme and produce typical symptoms, such as polyuria, increased thirst and weight loss. The course of the disease in the patient described above was abrupt; only several days had passed from the occurrence of symptoms to hospitalization. The patient had no time to lose weight and her condition was incommensurably good considering extreme glucose levels. Additionally, the level of glycated hemoglobin (HbA1c = 8%) indicated that hyperglycemia had not persisted for a long time before hospitalization. In this case, a diagnosis of LADA cannot be made. Surely, normal glucose levels could not be maintained with oral medications, which is sometimes underlined in the definition of this type of diabetes. A sudden need for insulin and impossibility to regulate glucose levels with oral antidiabetic agents in hospitalized patients over 35 years of age facilitate the correct diagnosis. In certain persons, the lack of efficacy after replacing insulin with oral medications can be observed during hospitalization. In this case, differential diagnosis and a return to insulin therapy are possible.

The other case presents a more difficult situation. Insulin therapy at hospital caused partial remission, which can occur in almost a half of patients with type 1 diabetes. Remission lasted several weeks, which is typical of type 1 diabetes. However, at some point, previously used oral medications occurred to be ineffective. The patient, having been previously instructed about the diet, introduced certain restrictions, but they were ineffective and the patient sought medical assistance at hospital. A repeated inpatient treatment was necessary in order to determine the patient's need for insulin and verify the type of diabetes. The second case demonstrates that the initial diagnosis may not always be correct. In diabetes, one should remain flexible to changes in both the diagnosis concerning the type of diabetes and the type of therapy.

The situation can be even more difficult (both for the patient and doctor) when a patient with type 1 diabetes or LADA is treated on an outpatient basis. In such cases, certain atypical signs of the disease can be overlooked (sudden insulin dependency, low insulin requirement) whilst uncontrolled glucose levels and the lack of efficacy of oral treatment can be blamed on the patient (failure to use medications or follow diet). In these patients, the implementation of insulin can be considerably delayed, which results in unstable course of diabetes and rapid development of complications. First of all, treatment with sulfonylurea leads to complete beta cell demise and glucagon secretion failure (as a secondary reaction). Second,

insulin doses are usually implemented in higher doses (type 2 diabetes means insulin resistance), which causes recurring hypo and hyperglycemia. Early diagnosis of type 1 diabetes or LADA and sufficiently early implementation of insulin treatment enable, at least partial, preservation of C-peptide secretion and greater stabilization of the disease. That is why a re-evaluation of the type of diabetes and potential change of diagnosis must be considered in each case of increasing or persisting hyperglycemia in patients with an initial diagnosis of type 2 diabetes using oral medications. In this case, C-peptide levels must be determined. If they indicate type 1 diabetes (i.e. they are significantly decreased), a change in diagnosis and implementation of adequate therapy become essential. C-peptide assay is possible upon prior regulation of diabetes. Very high glucose concentrations inhibit insulin secretion by beta cells (this action is called "glucotoxicity"). That is why testing for C-peptide when blood glucose levels remain high will always yield low results and may cause an erroneous diagnosis of type 1 diabetes mellitus.

Factors that should draw the diabetologist's attention and make them consider type 1 diabetes include losing weight (it might attest to insulin deficiency and/or considerable hyperglycemia), concomitant autoaggressive diseases or their presence in near family, no obesity or considerable overweight and no other features of metabolic syndrome.

In the cases presented above, certain patients manifested other autoimmune conditions. In other words, these were patients with polyendocrine syndrome. In a large German study, on 151 patients with polyendocrine syndrome, type 1 diabetes mellitus was the first manifestation (mean age of onset 27 years) followed by a thyroid condition that occurred approximately 20 years after the onset of diabetes (15). The situation is similar in all but one cases reported above; diabetes was the first autoimmune disease to be diagnosed. The results of Dittmar's research additionally show that the lack of autoaggressive diseases does not exclude the autoimmune background of diabetes.

CONCLUSIONS

The study has revealed that rapid-onset type 1 diabetes can be diagnosed at any age and that not every instance of type 1 diabetes in middle-aged or elderly patients is LADA which allows initial treatment with oral medications. It seems that each individual with type 1 diabetes mellitus (also with LADA) should be treated with insulin as the therapy of choice from the very beginning since the usage of oral medications, sulfonylurea derivatives in particular, leads to the inhibition of C-peptide secretion and unstable course of the disease. Diabetologists and other doctors attending patients with diabetes should pay attention to atypical features, such as no obesity, history or family history (first-degree relatives) of autoaggressive diseases, losing weight and high glucose levels at the onset of the disease despite a relatively low HbA1c. In these cases, the diagnosis requires verification by C-peptide assay after regulating diabetes and possibly anti-GAD antibody testing, bearing in mind that a low C-peptide concentration supports the diagnosis of type 1 diabetes while a negative anti-GAD antibody result does not rule it out. A proper identification of the type of diabetes is essential for effective treatment. In rapid-onset type 1 diabetes mellitus, the basic therapy involves multiple insulin injections, preferably functional intensive insulin therapy. Each patient requiring initial insulin treatment in inpatient settings, should, upon the determination of the type of diabetes, have the therapy replaced with oral medications during hospital stay. Patients with oral therapy continued after hospitalization should be also informed about the need to periodically control glucose levels and instructed to report to hospital if sugar levels increase abruptly again.

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