Introduction. Stress is one of factors seen as contributing to type 1 diabetes (T1DM) development. The reason of the highest increase in T1DM among children under 5 years of age has been not explained. The aim of this study was to assess incidence rate of serious life events (SE) prior to diabetes diagnosis and examine if there is a difference in occurrence of such events between families of children with T1DM recognized at the age < 5 years and > 5 years.

Material and methods. There were included 347 parents of children with T1DM and 475 parents of children without diabetes. Participants were divided into two groups with T1DM recognized at the age < 5 ys and > 5 ys. Parents completed a questionnaire especially constructed for the purpose of this study, included questions about experience of SE which can cause chronic stress (as seen in Posttraumatic Stress Disorder).

Results. Families of children with T1DM onset < 5 ys had experienced SE before diabetes recognition significantly more often than control subjects 57/66 vs 38/86 respectively, OR 1,95, p=0.011. There was no difference in the number of families of children with T1DM recognized < 5 ys and > 5 ys 57/66 vs 16/108 respectively, OR 0,8, p= 0.369, and between children with T1DM recognizes > 5 ys and controls 116/108 vs 173/177 respectively, OR 1.1 p = 0.608. In both groups with T1DM divorce was the most common SE and affected more often families of children with T1DM than controls, p < 0.05.


Wstęp. Stres jest jednym z czynników przyczyniających się do rozwoju cukrzycy typu 1 (T1DM). Przyczyna największego wzrostu zachorowań na T1DM u dzieci < 5 r.ż. nie została jak dotąd wyjaśniona. Celem badania była oce- na częstości wydarzeń traumatycznych (SE), które wystąpiły w okresie przed rozpoznanie cukrzycy typu 1 (T1DM). Jednocześnie analizowano czy była różnica w występowaniu wydarzeń stresowych pomiędzy rodzinami dzieci, u któ- rych rozpoznano T1DM < 5 r.ż., i > 5 r.ż. Material i metody. Do badania włączono 347 rodziców dzieci z cukrzycą typu 1 i 475 rodziców dzieci bez cukrzycy. Rodziny dzieci z T1DM zostały podzielone na dwie grupy w zależności
Introduction

Diabetes is a chronic disease which affects both adults and children. Diabetes type 1 is customarily associated with children and adolescents with the peak incidence at 12–13 years of age for boys and 9–12 years for girls [1]. The increase in incidence of diabetes has been noticed worldwide. What calls for particular attention is the greatest increase seen in children under the 5 years of age in countries with both low and high prevalence of diabetes [2–6]. Whereas in European countries an overall rate in incidence of T1DM is 3% the rate of increase in the 0 to 4 year-old-age group is 4.8% as the large international study EURODIAB demonstrated [3]. The same study shows that Poland is on the top of the list of the countries with highest increase in incidence of T1DM.

Although diabetes as illness has been known for centuries and many studies were carried out pathogenesis of this disease is not fully understood. There are many hypotheses explaining the pathway of diabetes development. Genetic factors are considered to be the most important cause of T1DM. However, the European population is genetically stable therefore the rise in T1DM over the past decades cannot be explained only by the significant and rapid transmission of diabetes genes. Data from different migration studies implicate environmental factors in the cause of the increased T1DM incidences [7, 8]. Higher rates of T1DM in more industrialized countries with higher standards of living are explained by another hypothesis: increased hygiene which may cause the development of a more sensitive immune defense with an increased risk of deviation [9], insulin resistance due to excessive weight gain, which further increases the rate of beta-cell apoptosis [10], certain dietary factors [11], viruses [12] or psychological stress [13, 14].

Stress through its effect on the sympathetic nervous system can have an influence on glucoregulatory system: increase of adrenaline and testosterone raises insulin resistance while cortisol production decreases insulin sensitivity. It is speculated that elevated pressure on insulin-producing beta-cells increases their presentation to autoantigens and this way may activate autoantibodies, resulting in autoimmune destruction of beta cells particularly in people with genetic predisposition to autoimmunity [15–17]. Due to the suppression of the immune defense psychological stress increases vulnerability to viral infections which might cause diabetes in humans [18]. Stressful life events have been suggested to be involved in diabetes related autoimmunity in young children [19, 20].

The aim

The aim of the current study was to investigate whether psychological stress measured as incidence rate of serious life events in families occurred more often in families of children with diabetes before illness diagnosis in comparison with families in general population. We were also interested if such stress affected more often families of children with T1DM recognized at the age below 5 years compared to families of children with diabetes recognized at older age. As it is a retrospective study we concentrated only on the number of events which occurred in families, reported by parents themselves. We may assume that due to the immaturity of nervous and immunological systems response to the stress is different in younger children, probably more severe but it is difficult to assess the impact and the ways of coping from the perspective and with the use of only a questionnaire.

Patients and methods

The study was performed from November 2008 to March 2010. There were invited to participate in
this study parents of 347 children with type 1 diabetes treated in the Department of Paediatrics Medical University of Warsaw. Control subjects included parents of 475 children without diabetes, who were enrolled from 6 kindergartens and 4 schools in Warsaw and its surrounding. Families of children with diabetes participating in this study were divided into two groups depending on the age at diabetes recognition.

All participants anonymously completed an inventory on the stressful events in family. Parents of children with diabetes filled it in during a routine visit in the outpatient clinic while parents from the control group received an inventory during a school meeting or at the moment of collecting a child from the kindergarten. During the pilot study parents evaluated questions as not difficult to answer, the anonymity of participants and the understanding of the importance of finding the cause of diabetes helped in participation in the study. The inventory (Stressful Life Events List) – a type of self-reported questionnaire, especially constructed for the purpose of this study, included questions about experiences of serious life events which can cause chronic stress (as seen in Posttraumatic Stress Disorder) to survey the number of such happenings in families. It consisted of questions about events set in hierarchical order from relatively mild happenings to severe ones. The specific types of serious life events were covered: job loss, being subjected to violence, separation, divorce, medical problems during pregnancy, miscarriage, a serious accident in the family, a serious disease in the family, death of a close relative. Economic status was assessed with the question about parents’ unemployment; we did not ask parents about education because in our country low education is not a marker of economic status. It is important to stress that children in Poland have free medical care independent of parents’ health insurance. All experiences of serious life events were assessed as dichotomous (yes/no) questions. If the answer was positive participants were asked to write the year of event. There were calculated all numbers of serious life events in the families from the birth of the child to diabetes recognition. Stressful situations after the diabetes onset were not taken into consideration in data analysis. Each family might be affected by one or more serious life events. In the control group there were evaluated the numbers of serious life events from the birth of the child. Serious life events as prolonged disease of parents which was recognized before the birth of the child were counted as started at the birth. Besides, the questionnaire included questions about the demographic data such as sex and the year of parents and children birth.

Diabetes type 1 was diagnosed according to ISPAD criteria [21]. All diabetic children were treated with insulin. The study has been approved by a local ethics committee.

**Statistical analysis.** The assumption that data was sampled from the population that follows Gaussian distributions was tested using the method Kolmogorov and Smirnov. Between-group comparison was made using Student t-test (unpaired, 2-tailed) or Mann–Whitney U-test. Results were given as mean values with standard deviations (SD). The differences in the number of serious life events between groups with diabetes recognized at different age were evaluated using Chi-Square Test or Fisher’s Exact Test. To determine the effects of serious life events on diabetes recognition, we conducted a multiple logistic regression analysis. The adjusted odds ratio (OR) was reported with 95% confidence intervals [CI]. *P* values < 0.05 were considered as statistically significant.

**Results**

The I group consisted of parents of 123 children (67 girls, 56 boys) with diabetes onset at the age 0–5 years. The II group included parents of 224 children (108 girls, 116 boys) with diabetes onset at the age 6–17 years. Similarly, the control group was divided into 2 subgroups depending on the age of the child. The control group I consisted of parents of 124 children, at the age 0–5 years, and the II group – parents of 350 children at the age 6–17 years.

There was no difference in the mean age of children at diabetes recognition and control subjects in the group I (3.1 ± 1.4 *vs* 2.8 ± 2.0 years respectively, *p* = 0.100) and in the II group (9.9 ± 2.8 *vs* 9.5 ± 3.4 years respectively, *p* = 0.210). The diabetes duration was longer in the I group 6.2 ± 4.1 years than in the II group 3.6 ± 2.8 years *p* < 0.0001. There were no significant differences regarding the age of parents at the time of the birth of the child in diabetic patients *versus* control subjects in the II group (fathers median age values 28 *vs* 29 years respectively, *p* = 0.549, mothers median age values 26 *vs* 27 years respectively, *p* = 0.343). In the group I parents were younger than controls (fathers median values 29 *vs* 31 years respectively,
In the I group the number of families who had experienced at least one serious life event before diabetes recognition was significantly higher than the number of families in the control group 57/66 vs 38/86 respectively, $\chi^2 = 6.43$, OR 1.95 95% CI: 1.2 to 3.3, $p = 0.011$. The most often serious life event in the I group was divorce. The multiple logistic regression analysis showed that divorce and serious accidents in the family were significantly associated with diabetes (Table 1).

In the II group there was no difference in the number of families of children with T1DM affected with at least one serious life event and controls 116/108 vs 173/177 respectively, $\chi^2 = 0.303$, OR 1.1 95% CI 0.7 to 1.5, $p = 0.608$. The multiple logistic regression analysis showed that divorce and death in the family were significantly associated with diabetes (Table 2).

When we looked at the families of children with diabetes there was no difference in the number of families in the I and II groups affected with at least one serious life event 57/66 vs 116/108 respectively ($\chi^2 = 0.94$, OR 0.8 95% CI 0.52 to 1.25, $p = 0.369$). There was no difference between the groups in the number of specific types of serious life events except grandparents death (Table 3).

There was no difference between both groups in the number of families with newly recognized diabetes in another member of family. Diabetes occurred in 5 families of children with T1DM recognized before 5 years and in 6 families of children with T1DM recognition after 5 years of age ($p = 0.3$).

**Discussion**

Our study showed that serious life events affected more often children with diabetes recognized in younger age below 5 years than control subjects. We didn’t observe such a tendency in children with diabetes recognized at the older age. In this group we did not find any difference in the number of families affected with serious life events in comparison with the control subjects. Moreover, despite the shorter life period from the birth to diabetes recognition children with diabetes onset at the age below 5 years were affected with the same number of negative life events as their peers with diabetes recognized at the age over 5 years.

In recent years it has been noted high increase in incidence rate of type 1 diabetes mellitus in Poland, above 260% since 1989. Analysis of age subgroups showed the greatest increase in the incidence rate among the youngest children, 3.59 times for children aged 0–4, 3.40 times for children aged 5–9 and 2.08 times for children aged 10–14 [3]. Both genetic and environmental factors are considered in the etiology of type 1 diabetes. However, such a high increase in the diabetes onset converting Poland from the country with one the lowest incidence rates in Europe to the country with the highest incidence rate should be considered triggered off rather by environmental factors than by genetic ones.

Prolonged persisting psychological stressors can lead to the pathogenic state that can cause organic disease [22]. Increased levels of stress hormones, notably the glucocorticoids, catecholamines, cortisol can promote among different chronic illnesses the development of type 1 diabetes mellitus. Animal studies showed that individual differences in parental care are related to the health of the offspring. Variations in maternal care in early postnatal life are associated with the development of neural system that underlines the expression of individual differences in behavioral and the limbic hypothalamic–pituitary–adrenal (L–HPA) responses to stress in rats [17]. Human studies showed that caregivers play important roles in regulating activity of the L–HPA system during the development. When young children were exposed to moderately less sensitive and responsive care, increases in cortisol were observed [20]. Essex et al. [19] showed that preschoolers exposed to high levels of concurrent maternal stress and high maternal stress in infancy had elevated cortisol levels.

Considering young children, stressors such as caregiver insensitivity (often leading to an insecure attachment relationship with the caregiver) and negative parental moods (e.g. due to parental stress and serious life events, depression) might be important stressors in early childhood [18]. Similarly to our observation that negative life events affected more frequently families of children with diabetes recognized at younger age in comparison with healthy controls Thernlund et al. [23] noted that experiences of negative life events (e.g., separation of the parents, serious illness, or death in the family) during the first 2 years of life were more common in newly diagnosed diabetic children than in control subjects. Sepa et al. [16] found in 1-year-old children that psychosocial factors (e.g., high parenting stress, experiences of a serious life event, foreign origin of the mother) were associated
with diabetes-related autoimmunity in the child, independent of family history of diabetes.

We did not find any differences in the number of families affected with negative life events in children with diabetes recognized at the age over 5 years comparing to controls. Similar observation noted Littotin et al. [24] who examined young adults with newly recognized diabetes and Hägglöf et al. [25] who found that the number of life events during the year prior to the onset of diabetes in children aged 0–14 was the same as in the controls.

Our study showed that some kinds of stressful life events as divorce, serious accidents or death in the family were associated with diabetes. However, only divorce was significantly associated with diabetes in both groups of diabetic children and was the most common serious life event in their families. The role of divorce as negative life event predisposing to T1DM reported Sepa et al. [15], who found that that the risk of having developed diabetes-related autoimmunity at 2.5 years of age was 3-fold higher after having been exposed to parental divorce or having a mother who had experienced violence during the child’s lifetime.

The limitation of our study is the lack of the control group formed from the population registry, unfortunately in our country there is no such an official children registry. Therefore we decided to include randomly in the control group parents of children from some schools and kindergartens from the area of Warsaw. Our study is an analysis using only quantitative data; we didn’t assess the emotional burden for the family the stress might have brought on or the length of the experienced event. It is possible that stress factors might affect the family for a long period of time before the event, for instance, the stressful situation at home can occur long before divorce. Such factors may be responsible for differences in individual responses to stress. We used a self-report inventory to assess the number of events. The problem with such tools is they relay on memory of participants and their honesty. The difficulty to admit for example to family aggression may affect results. Another bias may lay in the way of data analysis. It is a retrospective study, data was collected in the different time from diabetes onset for each participant, also in comparison with control group. With fast changes in life style, loosening family ties and difficulties in psychological adaptation to a new way of living reported by patients in clinical contact it is necessary to look closely at biological response of organism to stressful events. As stress is more and more often reported to be a factor involved both in pathogenesis and treatment of many diseases such knowledge would allow us to devise intervention strategies to minimize its effect.

**Conclusions**

The results of our study confirm previous reports and highlight the possible association between negative life events in families and development of type 1 diabetes in the youngest children. Children under 5 years of age despite shorter life period from birth to diabetes recognition were affected with the same number of stressor as their peers with diabetes recognized at elder age. Moreover, the number of stressful life events in the youngest age group was significantly higher than in families of children without diabetes. Especially parental loss due to divorce may be a factor in the development of diabetes. Further prospective studies should be encouraged to prove an etiological link between stress and type 1 diabetes and to expand understanding of involved mechanisms.
Szewczyk L. i inni: Interakcje pomiędzy układem adrenergicznym a układem endokrynnym

PIŚMIENNICTWO/REFERENCES