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REMISSION PERIOD IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

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Abstract

Type 1 diabetes mellitus (DM) is characterized by a progressive autoimmune destruction of pancreatic beta cells, process that can be influenced by clinical and metabolic factors. The objective was to identify those factors that might influence residual pancreatic beta cell function and installation of remission period.

The study was performed on a group of 56 cases, aged between 2 and 18 years, who were evaluated for their clinical characteristics, frequency and duration of remission, factors that influence remission phase. Remission period was defined as a requirement of insulin < 0.5 U/kg/day. There was partial remission in 25 cases (44.6%), gender repartition was 11 boys: 14 girls. Remission was present in 17 cases (68%) within the first 3 months after the diagnosis of DM was established. Duration of remission ranged from 2 to 24 months. Young children aged between 2 and 5 years have shown partial remission periods in a much lower percentage (28%) than school-age children between 6 and 12 years (72%). At the onset of diabetes, 13 cases (52%) had mild form of diabetic ketoacidosis (DKA) and 10 cases (40%) had moderate form of DKA. The results have shown that both age and severe symptoms at onset were associated with a greater destruction of pancreatic beta cells and a low rate of remission phase.

keywords*: partial remission, type 1 diabetes mellitus, children and adolescents.*

Background

Progressive autoimmune destruction of pancreatic beta cells in type 1 DM starts several years before the appearance of clinical manifestations that are characteristic for diabetes.

Evolution of patients diagnosed with type 1 DM is often characterized by a transient improvement in beta-cell function after initiation of insulin therapy.

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In general, remission phase is characterized by a significant decrease in exogenous insulin requirements (<0.5 U/kg/day), maintaining a good metabolic control. Other authors consider more relevant the use of two criteria for defining the remission phase: the need for insulin <0.5 U/kg/day and glycated hemoglobin values under 7.5% [1, 2, 3].

Usually, in most cases involving children there is partial remission; during this period the patient usually has near-normal blood glucose values in combination with a low insulin requirement and with no clinical manifestations. The literature describes only a few cases of complete remission which did not require any insulin treatment for a variable period of time.

In the pathogenesis of remission there are involved two factors: partial restoration of pancreatic beta cells with improvement in insulin secretion and peripheral insulin sensitivity [4, 5].

The clinical significance of the remission period lies in the possibility of therapeutic intervention in order to stop the destruction of pancreatic beta cells and the preservation of endogenous insulin secretion.

Study Purpose

The purpose of this study was to identify factors that may influence the function of residual pancreatic beta cells and installation of the remission period, and also remission duration in the first year after the diagnosis of type 1 DM was made.

Material and method

The study included 56 children, newly diagnosed with type 1 DM, aged between 2 and 18 years, who were admitted to the Emergency County Hospital Craiova from January 2000 to December 2009.

In these cases the following aspects were evaluated: the frequency and duration of the remission period, clinical features, presence of ketoacidosis and its clinical forms, glucose values at the time of diagnosis. After discharge, the cases were monitored monthly in the first year after onset. During this time events such as hypoglycemia and hyperglycemia were analyzed, insulin doses were adjusted according to daily blood glucose self-monitoring conducted at home. The daily insulin requirement was evaluated.

Partial remission was defined as the period in which the need for insulin was less than 0.5 U/kg/day, and this way glycemic levels were close to normal values. Glucose levels were determined from capillary blood, and for the determination of Hb A1c an assay based on latex immunoagglutination inhibition methodology was used.

Student test and Chi-square test were used to evaluate the statistical significance and p value <0.05 was accepted as significant.

Results

In the studied period there were 56 newly diagnosed type 1 DM cases, which were included in this study. In Table 1 there are presented clinical and biological characteristics of type 1 DM cases, including those who experienced the remission period and also those who did not presented remission period.

In the whole group, which includes all cases of diabetes from the study, there is a clear predominance of female cases (60.7%),

and also a greater concentration of those who live in urban areas (55.3%).

Table 1. Clinical and biological characteristics of type 1 DM at onset (N = 56)

Clinical and biological characteristics	Remission (N = 25)		No remission (N = 31)		p
	Nr.	%	Nr.	%	
Gender					
Male	11	44%	11	35,48%	p= 0,70
Female	14	56%	20	64,52%	
Age at onset					
2 -5 years	7	28%	8	25,8%	
6 – 12 years	18	72%	15	48,4%	p = 0,02
13 – 18 years	0	0%	8	25,8%	
Diabetic Ketoacidosis					
No DKA	2	8%	0	0%	
Mild	13	52%	4	12,9%	p <0,001
Moderate	10	40%	20	64,5%	
Severe	0	0%	7	22,6%	
Glycemic level at onset					
180 – 300 mg%	8	32%	3	9,7%	
300 – 500 mg%	12	48%	25	80,6%	p = 0,03
> 500 mg%	5	20%	3	9,7%	
History of diabetes					
Yes	14	56%	18	58,1%	p= 0,90
No	11	44%	13	41,9%	

Studying the age distribution of cases we have found that age group 6-12 years was the most common (58.9%), followed by age group 2-5 years with a rate of 22.7%.

DKA incidence was 96.4% (54 cases), moderate form of DKA was predominant in 30 cases (53.5%), mild in 17 cases (30.3%) and severe in 7 cases (12.5%).

It was found that inaugural DKA was present in all age groups, but with increased frequency, especially of moderate and severe form, in preschoolers and school age children.

Glycemic levels on admission ranged between 180-300 mg% in 11 cases (19.6%), between 300-500 mg% in 37 cases (66.1%), while values above 500 mg% were present in 8 cases (14.3%).

Partial remission was seen in 25 cases: the incidence of partial remission period was 44.6% (Figure 1); 14 girls (56%) and 11 boys (44%) (Figure 2).

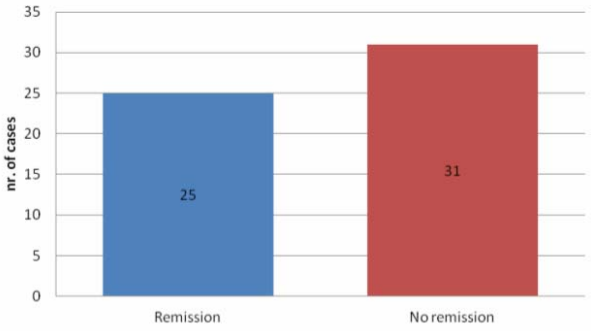

Figure 1. Incidence of partial remission period.

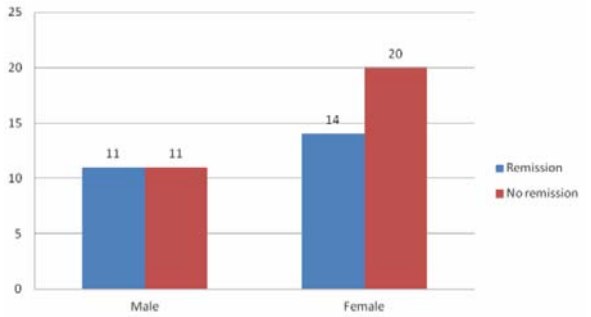

Figure 2. Gender distribution.Positive family history of diabetes was found in 14 cases with remission (56%) (Figure 3).

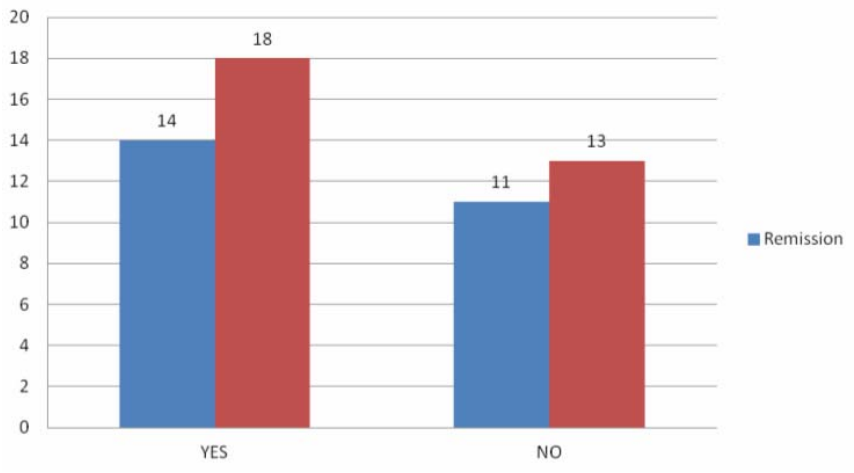

Figure 3. Family history of diabetes.

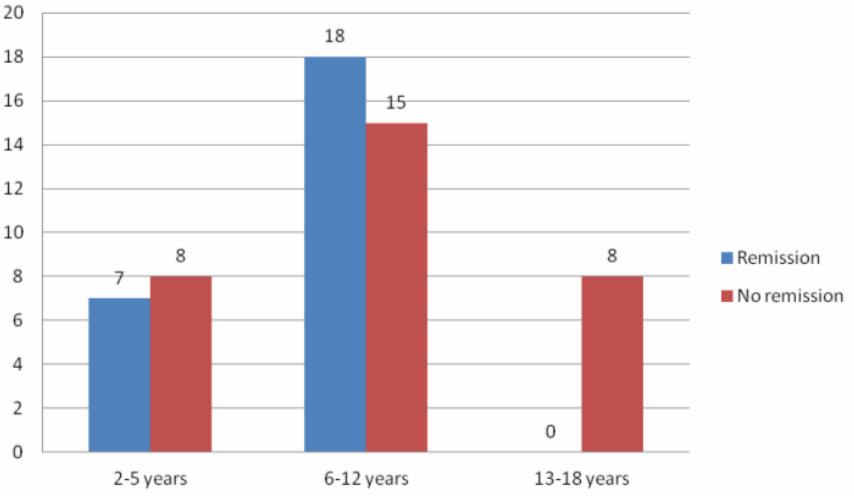

Figure 4. Age distribution.

In a single case, a 10 years old girl, presented a complete remission for over a year, with no ketoacidosis at onset and after one month from the onset the insulin treatment was interrupted, glycemic control was good, with Hb A1c levels between 6-7%. But in this case the evolution in time was not favorable, the parents did not accept the constant monitoring of glycemic levels, they did not maintain any contact with medical personnel and after one year and six months the child has returned to hospital with severe ketoacidosis.

We have found that partial remission was more common in the age group 6-12 years (72%), between 2 and 5 years the frequency of remission was 28% and in the age group 13-18 years, none of the cases presented remission (Figure 4).

DKA incidence was 92% (23 cases), mild DKA was predominant in 13 cases (52%) and a moderate form was present in 10 cases (40%), none of the cases with remission has presented a severe DKA at onset (Figure 5).

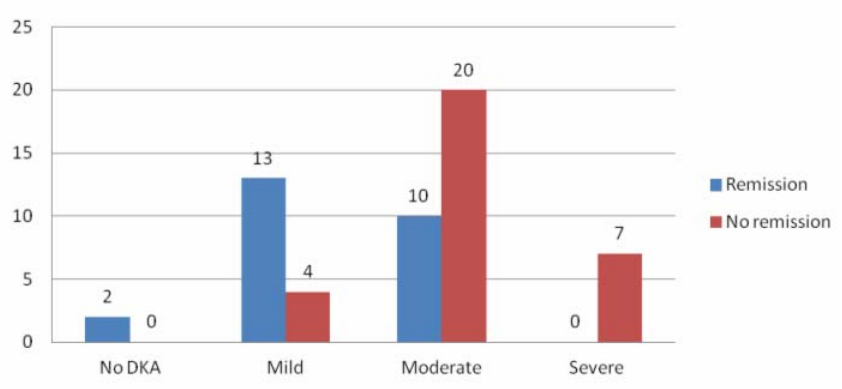

Figure 5. Incidence of diabetic ketoacidosis (DKA).

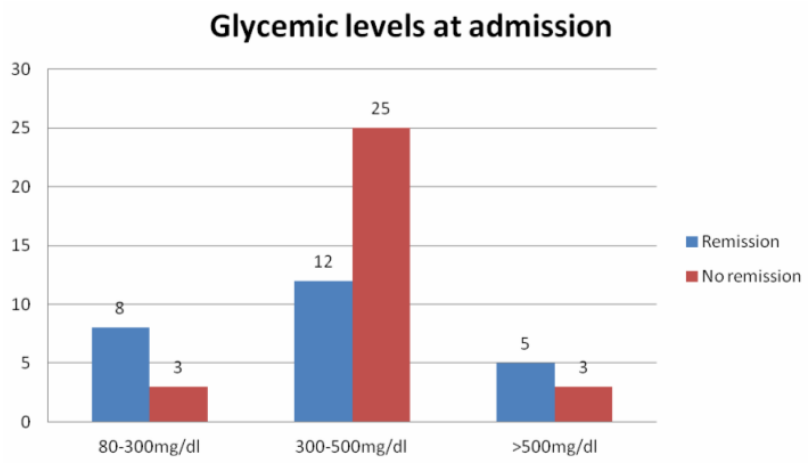

Figure 6. Glycemic levels at admission.

We have tried to correlate the incidence of the remission period with clinical form of ketoacidosis and we have found that from 15 cases with mild DKA, 11 cases went into remission, and from 30 cases with moderate DKA only 10 cases went into remission, and none of the cases with severe DKA presented any remission. Comparing the two subgroups, we have found that DKA at onset correlates with a lower incidence of the remission period ($p < 0.001$).

Remission was installed in most cases (68%) within 3 months after diagnosis of type 1 DM was established.

The duration of remission ranged from 2 to 24 months; in 9 cases (36%) remission lasted between 2 and 6 months, in 10 cases (40%) between 6 and 12 months and in 6 cases (24%) over 12 months.

Mean blood glucose levels on admission in children with remission ranged from 300-500 mg% in most cases (48%), 8 cases (32%) had glucose levels between 180-300 mg%, and 5 cases (20%) had glucose levels above 500 mg% (Figure 6).

HbA1c values were not available, in evolution, in all cases, so it was not possible to establish correlations based on this parameter.

Discussion

According to literature data, the period of complete remission is rare in children with type 1 DM [6, 7]; some authors [8] reported an incidence between 0 - 3.2%. No factor with an

obvious influence in installing the complete remission period could be found. In our study we have found only one case that presented a complete remission.

On the other hand, the period of partial remission is commonly found in children with type 1 DM, as it is reported in many published studies [6, 9].

In our study partial remission was seen in 44.6% of the cases, the percentage of cases being lower than that one found in the literature. This finding could be correlated with the later establishment of the diagnosis and may explain the relatively high frequency of cases of type 1 DM in children who were diagnosed with various forms of ketoacidosis at onset.

It should be mentioned that the incidence of the remission period in literature data varies according to several criteria used to define it. Some studies define the remission period based only on the need for insulin [10, 11] being below 0.5 U/kg/day; other studies include Hb A1c levels ranging between 6-8% [2, 3] in the definition of the remission period. In a study by Drash et al. [14] the incidence of partial remission was 70%, and in a study by Agner et al. [15] the remission period was interpreted as an insulin need that was less than or equal to 50% of the insulin dose at discharge from the hospital, incidence of remission being 30%.

As we mentioned in our study, the presence of ketoacidosis at onset was found with higher frequency compared to other studies in the literature [6, 7, 9]. The degree of metabolic decompensation at the onset of the disease is considered by most authors an important factor that influences the occurrence and duration of remission. Ketoacidosis at onset was correlated with low residual endogenous insulin secretion and poor metabolic control in the first 2 years after diagnosis.

Therefore it is very important to do everything possible to inform both health professionals and the general population about major clinical manifestations of type 1 DM at onset in children.

Regarding the correlation between the remission period and the age group in our study most cases were included in the age group of 6 to 12 years, similar to literature data. Several studies [15, 16, 17, 18] have shown a low incidence of remission periods in children aged less than 5 years due to increased frequency of DKA at onset, with rapid and progressive destruction of pancreatic beta cells. Some authors [9] found a higher incidence of remission in children aged between 2 and 5 years in contrast with age group 6 to 12 years; the authors explained that these differences are due to role of ethnic factor and HLA type.

On the subject of the distribution of cases with remission according to gender, we found a slightly higher frequency in female gender (%). Some authors [19] reported an incidence and duration of remission periods higher in boys than in girls, but most authors [10, 19, 20, 21] considered that the remission period, in general, is not influenced by male or female gender.

Other factors described by many authors, that correlate with the occurrence and duration of remission period, such as C-peptide levels and HbA1c, could not be followed in this study. Most authors [11, 15] showed a close correlation between C-peptide levels on one side and the incidence, and remission duration,

on the other side. It is considered that in order to assess the dynamic of residual pancreatic beta cell function it is necessary to repeat measurements of stimulated C-peptide, reflecting endogenous insulin secretion, but for now the stimulated C-peptide values were not proposed for defining the partial remission period [22, 23]. In addition, stimulated C-peptide determination method is too laborious, expensive and difficult to perform in children.

Conclusions

In the study group, the incidence of the remission period (44.6%) was lower compared with the data from the literature. The importance of the remission period lies in the possibility of therapeutic intervention to stop destruction of pancreatic beta cells and preserve endogenous insulin secretion.

Factors that influenced the period of partial remission were: prepubertal age between 6 to 12 years old (72%), female gender (56%) and establishment of early diagnosis in the absence of ketoacidosis or presence of mild and moderate forms of it.

Early diagnosis of the disease and maintaining a strict metabolic control in the first year after onset could influence both the installation and extension of remission period. In addition, it is very important to monitor the glycemic control during the entire period of remission, avoiding the deterioration of the control at the end of remission.

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