What a type of diabetes is having your patient? Challenges in diagnosing diabetes in children and adolescent – case report

Jaki typ cukrzycy ma Twój pacjent? Wyzwania diagnostyczne w cukrzycy u dzieci i młodzieży – opis przypadku

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Abstract

Diabetes mellitus (DM) is due to either defects in not producing enough insulin by the pancreatic $\beta$-cells, or defects in insulin action on peripheral tissues. Type 1 diabetes (T1D) is the most common type in childhood, resulted from the autoimmunity directed at the pancreatic $\beta$-cells. T1D classically presents in lean children with an acute onset of polyuria, polydipsia, weight loss. We describe the case of a 14-year-old girl with acute onset of DM complicated with diabetic ketoacidosis, appendicitis and pancreatitis which was suspected of having T1D. However, regardless a suggestive patient’s phenotype at the disease onset tentative diagnosis of T1D was not confirmed. The case report shows that the overlap of the clinical phenotypes of diabetes displays the diversity of diabetes in young population. Then, diagnostic process must be carefully planned to exclude other diabetes forms and accurately ascertain childhood diabetes type.

Key words: diabetes, diagnostic challenges, children and adolescent.

Streszczenie

Cukrzyca wynika z defektu produkcji insuliny przez komórki $\beta$ trzustki lub niewystarczającego jej działania na tkanki obwodowe. Cukrzyca typu 1 jest najczęstszym typem występującym u dzieci i wynika z autoimmunizacji skierowanej przeciwko komórkom $\beta$ trzustki. Cukrzyca typu 1 klasycznie występuje u szczupłych osób i charakteryzuje się z trzustek białym powstaniem objawów, takich jak: wie-loocz, polidypsja, utrata masy ciała. W pracy opisano przypadek 14-letniej dziewczynki z ostrych początkiem cukrzycy powikłanej cukrzycową kwasicą ketonową, zapaleniem wyrostka robaczkowego oraz zapaleniem trzustki, początkowo podejmowaną o rozwój cukrzyce typu 1. Jednakże, niezależnie od fenotypu prezentowanego przez dziewczynkę na początku choroby, wstępne rozpoznanie cukrzycy typu 1 nie zostało potwierdzone. Opis przypadku pokazuje, że nakładanie się fenotypów klinicznych cukrzycy wskazuje na różnorodność cukrzycy u dzieci. Dlatego proces diagnostyczny powinien być szczegółowo zaplanowany, aby wykluczyć inne rodzaje cukrzycy oraz dokładnie ustalić jej typ.

Słowa kluczowe: cukrzyca, diagnostyka, dzieci i młodzież.
Introduction

Diabetes mellitus (DM) is a metabolic disease of multiple etiology characterised by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. In the clinical practice DM diagnosis is based on blood glucose measurements and the presence of symptoms of marked hyperglycemia such as polyuria, polydipsia, weight loss. According to the etiological classification DM can be divided into following general categories: type 1 diabetes (T1D), type 2 diabetes (T2D), other specific types of diabetes, gestational diabetes (GDM) [1].

Type 1 diabetes is the most common type in children, occurring in 1 in 350 children by age 18 [2], and is resulted from the autoimmunity directed at the pancreatic β-cells which leads to absolute insulin deficiency. Also, there is strong genetic susceptibility to T1D which is associated with human leukocyte antigen (HLA) genotype, with linkage to the DQA and DQB genes. These HLA-DR/DQ alleles can be either predisposing or protective [3]. Type 1 diabetes associated autoantibodies, which are widely used diagnostic markers for β-cell autoimmunity, include islet-cell antibodies (ICA), glutamic acid decarboxylase autoantibodies (GAD-ab), protein tyrosine phosphatase autoantibodies (IA2-ab) and insulin autoantibodies (IAA), autoantibodies against zinc transporter 8 (ZnT8) [1].

While, T2D is caused by insulin resistance, and relative impairment in insulin release due to the pancreatic β-cell dysfunction. Type 2 diabetes can have onset at any age, but typically it occurs in adults older than 40 years of age [1]. However, as obesity has become one of the main health concern in children, recently the prevalence of T2D has rose in that age group. Other types of diabetes, occurring less frequently, comprise genetic defects of β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug or chemical induced diabetes, infections or other genetic syndromes sometimes associated with diabetes [1]. It is noteworthy, monogenic forms of diabetes (MGD) have become more recognizable in the recent years due to greater awareness and wider availability of genetic testing. Those types of diabetes are heterogeneous group of single gene disorders mainly characterized by functional defects of pancreatic β-cells leading to moderate to severe hyperglycemia. MGD comprises neonatal diabetes mellitus, maturity-onset diabetes of the young (MODY), mitochondrial diabetes, and rare diabetes-associated syndromic diseases. The prevalence of MODY accounts for approximately 1–2% of diabetes in children and adolescents [1, 4]. This article aims to show that regardless well-known DM classification in some cases physicians encountered challenges in accurately ascertaining childhood diabetes type.

Case presentation

A 14-year-old girl was admitted to our hospital with 2 days history of polyuria, polydipsia accompanied by symptoms of increasing abdominal girth, nausea and fever. Her past medical history was unremarkable. Family history positive of T2D (father and grandfather). On admission, the girl was drowsy but fully oriented. The patient’s height and weight were 158 cm (25th percentile) and 39.5 kg (5th percentile), respectively, her body mass index (BMI) was 15.8 kg/m² (5th percentile), and she had not experienced any recent changes in weight. Physical examination revealed dehydration, acetone breath, Kussmaul breathing, distended abdomen. Laboratory analysis showed a sever metabolic acidosis, hyperglycemia, urine testing was positive for glucose and ketones, HbA1c of 8.6%, decreased C-peptide level, elevated CRP and triglycerides concentration. Performed abdominal ultrasound was normal. Summary of patient’s laboratory work-up is shown in Table I. Based on these findings, diagnosis of T1D complicated by diabetic ketoacidosis (DKA) was suspected, therefore, insulin and intravenous fluids replacement was started. Initially, her general condition improved. However, her state unexpectedly deteriorated on the second day. Physical examination showed distended stomach with a central abdominal pain at palpation, normal movement of bowels, tachycardia. Blood investigation revealed elevated PCT and pancreatic enzymes. CT scan findings indicated appendicitis with perforation and mild acute pancreatitis. The girl was immediately operated. Within two weeks period her general condition gradually improved. Further examination showed that the autoantibodies to GAD and IA2-ab were negative, while IAA autoantibody was slightly positive. During the course of the next 6 months, her insulin requirement was at 0.7 unit/kg/day, while HbA1c level dropped to 7.1%.

Discussion

The value of defining a type of diabetes is incontestable, because determines appropriate treatment. Despite the fact that the clinical and laboratory features currently used to distinguish a type of diabetes are well recognized, occasionally assigning a type to a patient often depends on the circumstances present at the disease onset, with individuals not necessarily fitting evidently into one category. Commonly, physicians take into consideration the traditional paradigms of diabetes while making an initial diagnosis, such as age at onset (childhood or adult-onset), clinical phenotype (lean or obese) or treatment methods (insulin-dependent or not insulin-dependent). These categories generally describe groups, however, not always are sufficient to classify patients. Then, in defining a type of diabetes not only individual’s phenotype should be considered, but also laboratory tests such as insulin and c-peptide levels, autoantibodies measurement or even genetic testing etc. must be performed. Even though, in some cases, diabetes diagnosis might be imprecise in distinguishing major disease types, using available laboratory tests [1]. It shows the diversity of diabetes in young population as it is presented in this case report.

Patient’s phenotype says type 1 diabetes diagnosis

Firstly, T1D accounts for more than 85% cases of diabetes in individuals below 20 years of age [1]. The girl’s age at the dis-
ease onset was 14 years, which suggested T1D diagnosis. Secondly, the patient was slim and people diagnosed with T1D have traditionally been viewed as lean individuals with lower BMI compared to those, for example, with T2D. Thirdly, she presented the classic symptoms of polyuria and polydipsia, which are noticed in more than 90% of patients with T1D at diagnosis [5]. Fourthly, patient’s initial clinical manifestation was extremely acute, and the girl developed DKA shortly after occurrence of the first symptoms. DKA frequency at T1D varies from 15 to 67% [6]. Finally, in DKA, the deficiency of insulin activates lipolysis in adipose tissue releasing increased free fatty acid (FFA), which accelerates formation of very low density lipoprotein (VLDL) in the liver. Additionally, reduced activity of lipoprotein lipase in peripheral tissue decreases removal of VLDL from the plasma, resulting in hypertriglyceridemia which may lead to acute pancreatitis [7].

On the one hand, her family history was positive for T2D and at least one affected parent is present in one-half to three-quarters of children with T2D, compared to less than 10% of children with T1D [8]. Similarly, maturity-onset diabetes of the young (MODY) has strong association with genetic background and occurs in 69–90% of MODY patients with affected parent. However, positive family history alone cannot be used to distinguish MODY from other forms of diabetes, suspicion for this type of diabetes should be highlighted in children with an affected parent with diabetes, and mainly if there are more than three consecutively affected generations [8].

What says performed laboratory tests?

Table I. Patient’s laboratory work-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycemia [mg/dl] (mmol/l)</td>
<td>426 (23.6)</td>
<td>60–100 (3.3–5.6)</td>
</tr>
<tr>
<td>NGSP A1c [%] (mmol/mol)</td>
<td>8.6 (70)</td>
<td>4.0–5.6</td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.05</td>
<td>7.35–7.45</td>
</tr>
<tr>
<td>HCO₃⁻ [mmol/l]</td>
<td>3</td>
<td>20–26</td>
</tr>
<tr>
<td>BE (mmol/l)</td>
<td>-28</td>
<td>-3.0–3.0</td>
</tr>
<tr>
<td>CRP [mg/l] (mg/dl)</td>
<td>112.8 (11.3)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td>WBC [K/ul]</td>
<td>20.3</td>
<td>4.5–11.0</td>
</tr>
<tr>
<td>Further outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-peptide [nmol/l]</td>
<td>0.45</td>
<td>0.59–1.54</td>
</tr>
<tr>
<td>GAD [U/ml]</td>
<td>0.2</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IAA [%]</td>
<td>6.1</td>
<td>&lt; 5.5</td>
</tr>
<tr>
<td>IA2-AB [U/ml]</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

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fasting C-peptide level was at 0.45 nmol/l, then, it suggested that there was decreased of insulin production, nevertheless, it was not sufficient to classify the girl as T1D patient. Subsequently, the patient was placed at the gray zone in which a longer clinical observation must be conducted to confirm a final diagnosis. The measurements of C-peptide concentration should be repeated in a course of diabetes due to the fact that persistence of C-peptide is a key clinical feature of MODY. Non-fasting C-peptide of 0.2 nmol/l in those with diabetes diagnosed under 30 years of age and > 3 years’ duration has been recommended as a criteria for consideration of MODY testing [10]. The clinical role of C-peptide testing in this context is crucial, mainly to exclude complete insulin deficiency prior to definitive categorized the patient and implemented the treatment. This is particularly relevant in patients with retained substantial C-peptide production which may be strongly indicative that T1D is unlikely, therefore, MODY should be considered [11]. Then, it seems that the girl needs to be tasted for MODY in the future.

Conclusions

Type 1 diabetes is still the most common form of diabetes. Individual’s phenotype alone cannot be used to distinguish between types of diabetes. The first step of diabetes diagnosis in children should aim to confirm or exclude T1D. If there is no evidence of autoimmunity others forms of diabetes must be consider, then, genetic testing might be crucial in defying a type.

References