Case Report

Beta-cell dysfunction complicating haemolytic uraemic syndrome

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Introduction

Although the kidney is the main target organ of the microangiopathic process underlying the haemolytic uraemic syndrome (HUS), several reports have focused interest on the increasing number of extrarenal manifestations, which complicate the disease and enhance its morbidity and mortality [1,2]. This case report concerns a 6-year-old boy, who presented with a classic HUS and developed hyperglycaemia, which required insulin treatment for 4 months despite a rapid recovery of the renal impairment.

Case report

A 6-year-old boy was admitted to the hospital because of severe gastroenteritis, epistaxis, seizures, and anuria. There was no family history of diabetes. The patient was negative for HLA DR3/DR4, insulin autoantibodies (IAA), islet cell (ICA), glutamic acid decarboxylase (GADA) and IA2 antibodies. These diabetes-specific autoantibodies remained negative during the whole follow-up period. Glycated haemoglobin A₁c was 4.7% three weeks after the onset of HUS (normal range: 5.0 ± 1.0%, mean ± 2 standard deviation). At cessation of dialysis the serum creatinine was 500 μmol/l, the BUN 48 mmol/l.

Ten days after admission the blood glucose concentration rose to 13.0 mmol/l; there was no ketoacidosis. The patient was treated with a continuous intravenous insulin infusion (0.1 IU/kg body weight/h) until hyperglycaemia was corrected. A subcutaneous insulin regimen was then initiated with two daily injections of an intermediate-acting insulin (1 IU/kg body weight/day). Attempts to discontinue the insulin treatment during the hospitalization period led to hyperglycaemia. The patient was discharged after 33 days with a serum creatinine of 64 μmol/l; antihypertensive treatment was no more necessary. Further insulin treatment was required in decreasing doses (0.3–0.1 IU/kg body weight/day) for 4 months. After the cessation of insulin treatment the boy remained normoglycaemic.

Intravenous glucose tolerance tests (ivGTT) were performed 10 weeks, 1 and 3 years after the onset of HUS. The first phase insulin responses (FPIR = 1’+ 3’ insulin response) as well as the glucose assimilation coefficients (K-value) are demonstrated on Table 1.

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Table 1. Results of intravenous glucose tolerance tests (ivGTT)

<table>
<thead>
<tr>
<th></th>
<th>FPIR</th>
<th>K-value</th>
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<tbody>
<tr>
<td>ivGTT after 10 weeks</td>
<td>54.5 μU/ml (5th–10th centile)*</td>
<td>2.2 (normal)</td>
</tr>
<tr>
<td>ivGTT after 1 year</td>
<td>30.6 μU/ml (&lt; 1st centile)*</td>
<td>3.8 (normal)</td>
</tr>
<tr>
<td>ivGTT after 3 years</td>
<td>117.8 μU/ml (30th–50th centile)*</td>
<td>4.3 (normal)</td>
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</tbody>
</table>

*According to Kuglin et al. [10]

FPIR = first phase insulin response, 1’+ 3’ value; K-value = glucose assimilation coefficient.

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deviations) and remained normal after insulin cessation (after 12 weeks: 5.3%, 1 year: 5.6%, 3 years 5.5%).

During the acute phase of HUS an increase of lipase activity was found (103 IU/l, normal range 7–60). Amylase activity was 72 IU/l on admission (normal range 25–115 IU/l) and dropped to 25 IU/l after 2 weeks.

Discussion

The haemolytic uraemic syndrome is characterized by acute haemolytic anaemia, thrombocytopenia, and renal failure. However, an increasing number of extrarenal manifestations have been reported recently, indicating a multorgan involvement during the course of this disease [1,2].

Hyperglycaemia and the development of insulin-dependent diabetes mellitus belong to the rare, but severe complications of HUS [3,4]. A wide spectrum of disturbances of glucose metabolism has been described, ranging from a severe glucose intolerance and ketoacidosis during the acute phase of HUS to permanent diabetes mellitus. This report deals with a young child with HUS, who developed an insulin-dependent glucose intolerance during the acute phase and remained insulin-dependent for 4 months despite a rapid renal and haematological recovery.

The precise cause of β-cell dysfunction during HUS remains unclear. Hyperglycaemia during peritoneal dialysis could be due at least partly to a glucose overload, especially if fluids containing high dextrose concentrations are required [5]. The present patient, however, did not receive such fluids during dialysis. Moreover, glucose intolerance only started 5 days after the cessation of peritoneal dialysis. Stress may be the major cause of hyperglycaemia during the acute stage of the syndrome, particularly in those patients being genetically susceptible to diabetes mellitus [6]. Such considerations seemed unlikely in this patient, since there was no genetic or immunological parameter indicating a predisposition to diabetes. Anti hypertensive drugs used in hypertensive haemolytic uraemic syndrome have been implicated to contribute to the hyperglycaemia. The young boy was treated with nifedipine for 30 days. Although this drug has been occasionally implicated to cause reversible hyperglycaemia in certain animal models and type II diabetes patients, recent studies showed that short-term therapy with nifedipine in non diabetic and diabetic individuals did not change glucose homeostasis [7].

Finally, thrombotic and haemorrhagic necrosis of the pancreas may cause diabetes. Such histopathological alterations have been occasionally documented in patients with the haemolytic uraemic syndrome [8]. Upadhyayya et al., however, could not associate the histological findings with the clinical course of HUS in one patient [1]. On the other hand, laboratory evidence of pancreatitis during HUS existed in a young girl, who developed diabetes mellitus, but the autopsy did not confirm this diagnosis [3]. Despite these controversial references, we postulate that the cause of the disturbance in carbohydrate metabolism in the present patient may have been the involvement of both the endocrine and exocrine pancreas in the microangiopathic lesions underlying the HUS, since (i) a transient increase of serum lipase activity was observed, (ii) the normal HbA1c value 3 weeks after the onset of the disease indicated that no disturbance of glucose metabolism preceded the HUS onset, and (iii) a transiently impaired insulin secretion was observed.

Why β-cell dysfunction complicating HUS develops into a persistent diabetes mellitus in some patients and remains transient in others is not clear. The extent of the underlying pancreatic injury may be an important factor, but there is no clinical marker, which allows prognosis. Robson and Leung postulated that female gender, high white blood cell count and anuria during the acute phase of HUS may be risk factors for the development of hyperglycaemia in this renal disease [9]. These criteria were not relevant for the present patient. On the other hand, the co-existence of additional genetic or immunologic markers may enhance the risk of development of a persistent diabetes mellitus [6]. In any case, a close long-term follow-up of these patients is recommended.

In conclusion, the haemolytic uraemic syndrome may be complicated by islet-cell dysfunction as a result of pancreas involvement in the microangiopathic process. An early recognition of the acute insulin deficiency during HUS could then prevent the development of ketoacidosis in this critical phase of the disease and diminish the danger of an unfavourable prognosis in these patients.

References


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