Novel Insights from Clinical Practice

HORMONE RESEARCH IN PÆDIATRICS

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Severe Pretreatment Cerebral Edema in Newly Diagnosed Type 1 Diabetes

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Established Facts

- Cerebral edema is a rare complication of diabetic ketoacidosis and may occur after the beginning of treatment with fluids and insulin.

Novel Insights

- Patients with severe diabetic ketoacidosis may develop cerebral edema before the beginning of any treatment. Cerebral edema is probably caused by metabolic acidosis, hypocapnia and decreased pCO_2 levels resulting in vasoconstriction of the cerebral vessels.

Key Words
Type 1 diabetes · Rapid progression · Neurological symptoms · Ketoacidosis · Cerebral edema

Abstract
Introduction: Cerebral edema (CE) is a rare and dangerous complication of diabetic ketoacidosis. In typical cases, it may develop during several hours after the beginning of ketoacidosis therapy. Nevertheless, CE sometimes occurs *before* the start of any therapy – as for the patient in this report here. ***Case Report:*** We describe a 12-year-old girl with newly diagnosed type 1 diabetes, presenting with severe headache and disorientation. Diabetes-related symptoms were not reported by the family. Clinical investigation revealed signs of meningeal irritation and Kussmaul breathing. In the laboratory, severe ketoacidosis (pH 6.95) and hyperglycemia (blood glucose 20.9 mmmol/l) were found. Cranial computed tomography showed CE. The patient was treated with a very cautious fluid and insulin therapy and recovered within 3 days. MRI after recovery showed normal findings without residuals of CE. ***Conclusion:*** CE *before* any treatment of ketoacidosis is a very rare complication of type 1 diabetes. Early diagnosis and effective treatment are extremely important for the patient's outcome and prognosis.

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Introduction

Clinically apparent cerebral edema (CE) is a very rare and dangerous complication of diabetic ketoacidosis (DKA). In typical cases, it occurs several hours after the beginning of treatment. Therefore, rapid osmotic changes have been suspected to cause cell swelling and edema [1]. However, recent studies suggest that reductions in cerebral blood flow, hypoperfusion and reperfusion may be more important factors [2, 3]. In a study from the UK, the severity of acidosis was a strong predictor of CE [2]. In another report from Canada, risk for CE was associated with lower initial bicarbonate, higher initial urea nitrogen and higher glucose at presentation. There was a trend towards an association with higher fluid rates and treatment with bicarbonate, but these factors were not independent predictors of CE. In this study, 19% of patients with CE showed this complication already at the initial presentation [3]. Nevertheless, the appearance of CE *before* any treatment of DKA is still a rare complication of type 1 diabetes and hardly known even among pediatric diabetologists. Early diagnosis and therapy are of substantial importance for the patient.

Case Report

A 12-year-old female patient was admitted to our hospital with suspected meningitis. At the time she had been treated with nonsteroidal anti-inflammatory drugs due to a severe headache for 2 days. On admission, the patient was disoriented and in poor general condition (Glasgow Coma Scale 12). Clinical investigation showed dry mucous membranes, signs of meningeal irritation and Kussmaul breathing, while the heart frequency was accelerated (150 beats/min; sinus tachycardia). In the laboratory, severe metabolic acidosis (pH 6.95, pCO_2 10.8 mm Hg, standard bicarbonate 2.4 mmol/l, base excess –27.1 mmol/l), elevated blood glucose (377 mg/dl, i.e. 20.9 mmol/l), mild hyperosmolality (321 mosm/kg; standard 275–300) and an elevated glycosylated hemoglobin (HbA_{1c}; 106.5 mmol/mol, i.e. 11.9%) were found. Serum sodium was 130 mmol/l (standard 136–145), and serum potassium was 3.1 mmol/l (standard 3.5–5.1) at presentation. Further analysis showed positive diabetes-associated autoantibodies against glutamic acid decarboxylase, the protein tyrosine phosphatase IA-2 and against zinc transporter-8. Cranial computed tomography on admission showed CE (fig. 1). After specifically being asked, the family reported that the girl had been drinking a higher amount of fluids in the past days, but neither the exact amount nor the type of fluids could exactly be specified.

The patient was admitted to the intensive care unit and rehydrated intravenously with isotonic saline solution, and insulin was given intravenously. In particular, the girl was given 2.3 units of insulin/kg and 2.570 ml of fluids/m^2 body surface in the first 24 h. Kalium was added to the isotonic saline infusion 2 h after the beginning of treatment. Subsequently, the acidosis slowly improved.

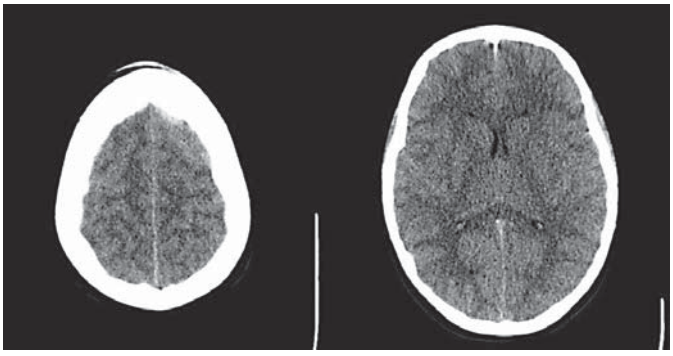

Fig. 1. Cranial computer tomography on admission before the start of rehydration: CE with narrowing of internal and external CSF spaces.

Table 1. Oral glucose tolerance test 3 months before diabetes onset with normal glucose concentration after 2 h and sufficient residual production of C-peptide and insulin

Time	Glucose, mg/dl	C-peptide, nmol/l	Insulin, μU/ml
0 min	83 (4.6)	1.0	14.1
30 min	125 (6.9)	n.d.	103
60 min	194 (10.8)	n.d.	89.8
90 min	230 (12.8)	3.5	61.7
120 min	116 (6.4)	n.d.	62.6

Figures in parentheses indicate glucose concentrations in mmol/l. C-peptide was not determined (n.d.) at 30, 60 and 120 min.

From a blood sugar level below 250 mg/dl (i.e. 13.9 mmol/l), fluid therapy was converted initially to isotonic, after correction of acidosis to half-isotonic infusion of glucose 5% with added 1 mol/l NaCl and 1 mol/l KCl solution and sodium hydrogen phosphate. The patient developed severe hypokalemia with a minimal serum potassium level of 1.7 mmol/l 12 h after the beginning of treatment and hypophosphatemia with a minimal serum phosphate level of 0.27 mmol/l after 18 h, respectively. Then, 24 h after admission, her general condition improved and the disorientation disappeared. After 3 days, therapy was switched to subcutaneous insulin therapy. Eight days after admission, MRI of the brain was performed and showed normal findings without residuals of CE, and the patient was in excellent general condition.

Three months before diabetes onset, an oral glucose tolerance test (OGTT) had been performed due to a unique elevated blood sugar value and had shown normal glucose tolerance (table 1). HbA_{1c} at this time was 42.2 mmol/mol (6.1%). Further analysis revealed type 1 diabetes-associated autoantibodies to glutamic acid decarboxylase and against the protein tyrosine phosphatase IA-2. After the confirmation of positive autoantibodies 3 months

before disease onset, the patient had been educated about the high risk for type 1 diabetes and associated symptoms like polyuria and polydipsia. The family was given a blood glucose meter and advised to get into contact with our diabetes team in case of diabetes-related symptoms or elevated blood sugar levels. The days before presentation with DKA and CE, the patient had been seen in different emergency services. There, the patient had reported severe headache, but had not mentioned and had not been asked about previous medical tests. The further previous medical history was unremarkable except for treatment with gonadotropin-releasing hormone analogues due to precocious puberty. This treatment had been finished 8 months before disease onset.

Discussion

A clinically apparent CE is a very rare and dangerous complication of DKA. The prevalence is about 1% in industrialized nations with a mortality rate of 21–24% [3–5]. In nonindustrialized countries with less sufficient health care systems, the prevalence of CE is probably even higher. In a report from a hospital in India, for example, 14.5% of children with ketoacidosis presented with CE [6]. Subclinical CE occurs more frequently: Glaser et al. [7] showed that radiological changes in the sense of CE occurred in 54% of cases in a cohort of 41 patients with DKA. DKA prevalence at diabetes onset in Germany has been at a constant level of about 21% for the past 15 years. Very young children, pubertal adolescents, girls and individuals with a migration background are at a higher risk for DKA at diagnosis [8]. Clinically significant CE usually develops 4–12 h after treatment has been started. It is believed that some elements of treatment can result in very rapid osmotic changes, which are responsible for the development of cell swelling and edema [1]. An excessive amount of infusion, as well as early and high insulin and bicarbonate doses are considered to be iatrogenic risk factors [2, 5]. However, these findings are based on uncontrolled or only partially controlled studies. The observed risk may therefore be influenced by confounding factors, particularly by the severity of dehydration and acidosis. In a study by Lawrence et al. [3], 21 children with CE were compared to 42 children with uncomplicated DKA. There was a trend towards an association with higher fluid rates and treatment with bicarbonate, but after adjusting for factors reflecting the severity of dehydration, this finding was not identified as an independent risk factor of CE anymore [3]. Four of the 21 patients with CE were reported to have CE at presentation before any treatment of DKA [3]. Although the occurrence of CE *before* treatment has been previously described, it is still very rare and relatively unknown.

Pathophysiological explanations for CE in DKA are predominantly based on animal studies. Yuen et al. [9] performed an experiment by doing MRI in rats with untreated ketoacidosis. Untreated ketoacidosis was associated with reduced cerebral blood flow and low levels of apparent diffusion coefficients, consistent with the existence of cytotoxic edema in untreated DKA [9]. In all likelihood, metabolic acidosis develops first; then, respiratory compensation leads to hypocapnia, and decreased pCO_2 levels result in vasoconstriction of the cerebral vessels. Hyperglycemia may also contribute to this process, as it reduces cerebral blood flow [10, 11]. The reduction of cerebral perfusion leads to ischemic damage of the brain and cytotoxic edema [9]. During treatment, apparent diffusion coefficient values are elevated and cerebral blood flow is increased in human and animal studies. Therefore, hyperemia and the vasogenic edema do probably develop in the course of treatment [9, 10]. Altogether, untreated DKA may lead to cytotoxic edema due to low cerebral blood flow and vasoconstriction following acidosis, while both animal and human studies suggest progression to vasogenic edema and reperfusion injury after the beginning of therapy.

The primary neurological symptoms in our patient are an uncommon presentation of type 1 diabetes manifestation. Diabetes-related symptoms and the diabetes-associated autoantibodies that had already previously been detected were not reported by the family. In addition to the occurrence of CE, the rapid progression to type 1 diabetes was uncommon. Three months before diagnosis, diabetes-associated autoantibodies had already been detected, but a normal 2-hour glucose value had been shown during the OGTT. The time between a normal OGTT and severe manifestation was extremely short. In contrast to the case presented here, subjects in the Diabetes Prevention Trial 1 study had already shown a glucose tolerance disorder at least 6 months before disease onset. In addition, C-peptide levels were much lower in subjects of the Diabetes Prevention Trial 1 study who progressed to diabetes than in the case presented here [12]. Events which may have triggered the rapid progression of the autoimmune process and could explain the fulminant and severe onset of the disease had not happened in the past months. In particular, neither infections nor physical or mental stress or illness had happened in the time period between the first detection of autoantibodies and disease onset. Furthermore, it is remarkable that the patient developed life-threatening ketoacidosis although the family knew about the positive autoantibody results and the risk for

type 1 diabetes. The presented patient and her family had been educated intensively about the risk for type 1 diabetes and symptoms of disease onset, and had been given a blood glucose meter. Possibly, the disease onset was ignored by the family. Although this family had been educated intensively, we would like to emphasize once more the importance of repeated schooling of prescreened patients who are at risk for type 1 diabetes.

Conclusion

In summary, CE is a rare and serious complication of DKA and can occur before any treatment started. In children with sudden onset of severe neurological symptoms, differential diagnostic considerations should include this possibility. Typical symptoms associated with diabetes – polyuria, polydipsia, weight loss – are not always reported. Hyperglycemia may develop extremely quickly when diabetes-associated autoantibodies are present.

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