Rare but not to be missed : acute focal cerebral lesions in two children with new-onset diabetes mellitus

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Abstract

Type 1 diabetes mellitus can present with ketoacidosis, a severe condition responsible for most of the morbidity and mortality. Neurological complications arise in approximately 1% of cases, essentially in the form of cerebral edema, and less frequently ischemic or hemorrhagic stroke. Here we report two cases; both children had severe ketoacidosis at onset of the disease and were admitted with altered consciousness. The first child presented with cerebral edema rapidly diagnosed and treated; he developed left hemiparesis with evidence of ischemic sequelae on the brain MRI. The second child presented a Parinaud syndrome which led to diagnosis of ischemic stroke.

Introduction

Type 1 diabetes Mellitus (T1DM) is a leading cause of chronic disease in children, often presenting with ketoacidosis. In the context of ketoacidosis (often with severe metabolic disruption), children may present with an altered level of consciousness and require intensive resuscitation and care. Although most patients rapidly recover with fluid and insulin therapy, neurological complications may occur. We describe two cases illustrating these unfortunate outcomes.

Case 1

A 5-year-old boy with an altered level of consciousness was admitted to a general hospital. The child had been examined twice the previous day (firstly by his family doctor and secondly by a pediatric fellow in the emergency department), with symptoms of vomiting, abdominal pain and weight loss, On both occasions, he had been discharged with the diagnosis of viral gastroenteritis.

On his third presentation, and then admission in the emergency department, vital signs were within normal range except for a raised respiratory rate for age (tachypnea). Investigations revealed severe hyperglycemia (697 mg/dL[NL 60-100]) and ketoacidosis (pH 6,95 [NL 7.35-7.45], undetectable HCO3, PCO2 14 mmHg [NL 32-48], ketonemia 7 mmol/L), leading to the diagnosis of new-onset T1DM and diabetic ketoacidosis (DKA).

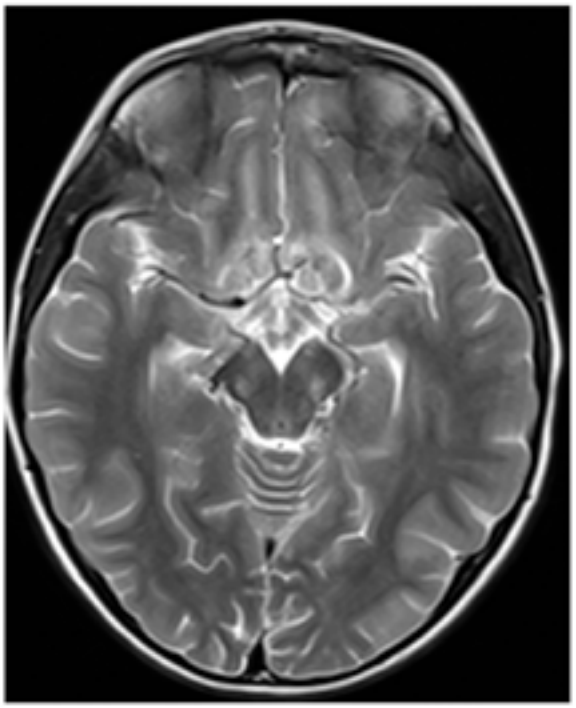
His Glasgow coma scale (GCS) was 13/15 at that time, and the child received one bolus of 20 ml/kg of NaCl 0,9%, followed by a second bolus of 10 ml/kg after 1 hour. At that time, insulin was started at a rate of 0,1 U/kg/hour. This precipitated his blood glucose to drop to 276 mg/dL, 4 hours after admission. He was transferred to the pediatric intensive care unit (PICU) in a referral hospital, where the GCS progressively deteriorated to 4/15. A head CT-scan revealed global cerebral edema with subfalcine and tonsillar herniation. Hypertonic therapy using mannitol, followed by hypertonic saline (NaCl 3%) improved his clinical signs over a few hours. Over the next 24 hours, the patient returned to a normal neurological status. He was transferred back to the general hospital after 48 hours, where he was switched to subcutaneous insulin therapy and diabetes education started. Three days later, the child developed a left hemiparesis with steppage and pyramidal signs. Additionally, sleep-related bradycardia and hypotension developed. The child was readmitted to the intensive care unit for 48 hours where cerebral MRI revealed extensive ischemic lesions suggestive of post-herniation ischemia due to cerebral oedema (Fig. 1 A-D). A week later, the child presented with short episodes of hypotonia and pallor, which led us to suspect seizures. Prolonged EEG showed no signs of epileptic activity and he did not require any anti-seizure treatment. No further episodes were observed. He was discharged home with rehabilitation for his hemiparesis and ongoing diabetic management.

Case 2

A 6-year-old boy with no relevant medical history presented to the emergency department with abdominal pain and vomiting for the preceding 48 hours, and on history revealed 2 months of symptomatic polydipsia. Vital signs showed a raised respiratory rate for age, tachypnoea (27 breaths/minute), fever (38°c) and tachycardia (127 beats/minute). On initial clinical examination, he was found not only to have signs of acute weight loss (estimated 3kg weight loss) but examination revealed a confused and stuporous patient with a response to verbal stimuli (GCS 14/15). Investigations showed a severe acidosis (pH 6.9, HCO3 3.6 mmol/L [NL20-28], PCO2 23 mmHg) and hyperglycemia (406 mg/dl), leading to the diagnosis of new-onset T1DM with severe DKA. Additionally, he had hypokalemia (2.3 mmol/L [NL 3.4-4.7]), prior to the commencement of insulin therapy. Screening for Covid-19 (PCR) was positive, with the child demonstrating mild covid manifestations (cough and one temperature spike).

Treatment was started in the emergency room with a 10 ml/kg bolus of NaCl 0,9% followed by an IV insulin infusion at a rate of 0,1 U/kg/hour. The child was admitted to the PICU, where IV insulin was continued, and fluid management for his maintenance, rehydration and ongoing losses carefully corrected over 48 hours. Supplemental potassium was also administered. His vital signs rapidly normalized and his neurological condition improved over the next 48 hours, at which time he was transferred to the pediatric diabetic ward. Subcutaneous insulin was started, within the context of a multidisciplinary education protocol for new diabetic patients and their families. At this stage the little boy's level of consciousness was fully restored, enabling a thorough neurological examination. On examination a vertical gaze palsy was revealed (Parinaud syndrome). A cerebral MRI confirmed an ischemic lesion of the left thalamus extending to the left cerebral peduncle (Fig. 2 A-C). Over the following weeks, repeated neurological examination highlighted an almost complete resolution of the Parinaud syndrome. The child developed no other symptoms from the SARS-CoV2 infection.

Figure 1 A-D: T2 (A) and FLAIR (B-C) axial MRI of the brain of a 5 year-old-boy (patient 1) obtained nine days after onset of symptoms showing several ischemic lesions : basifrontal bilateral (A-B) and in the posterior arm of the right internal capsule (C). Figure D shows diffusion sequences of the basifrontal lesions.



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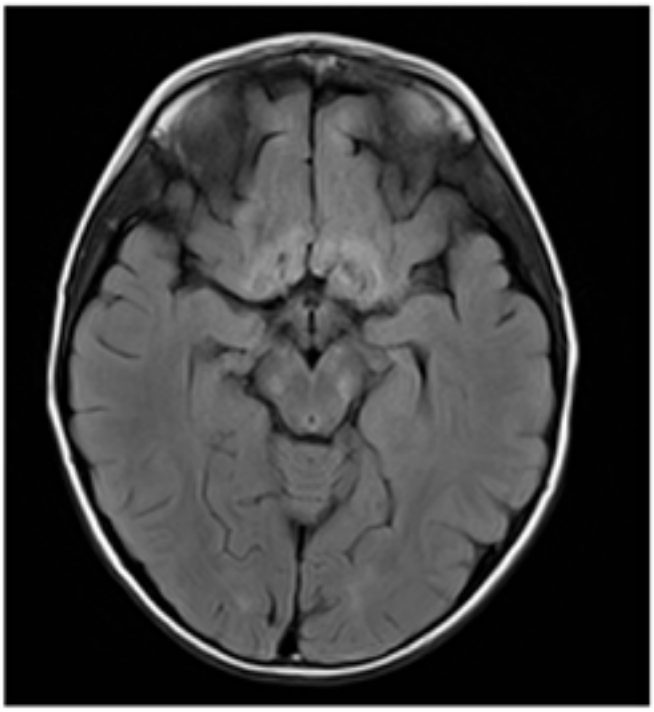

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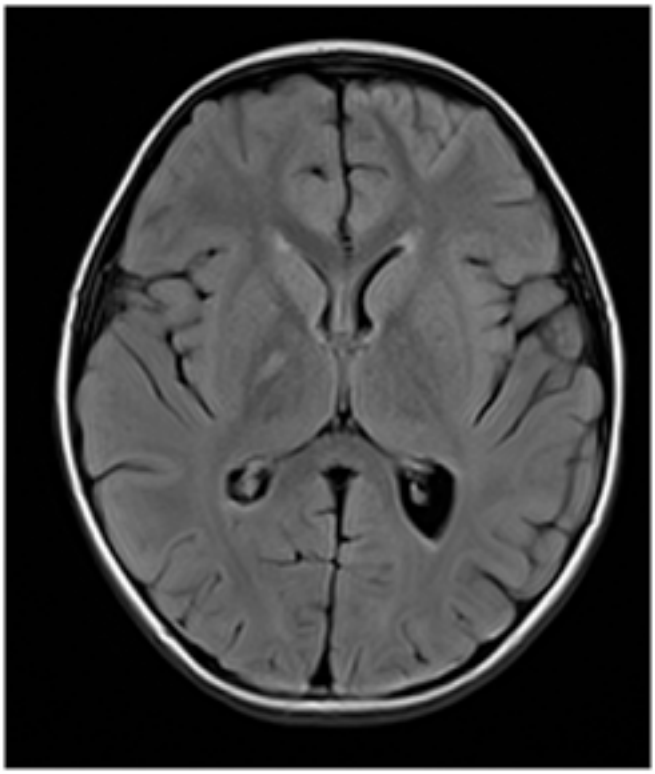

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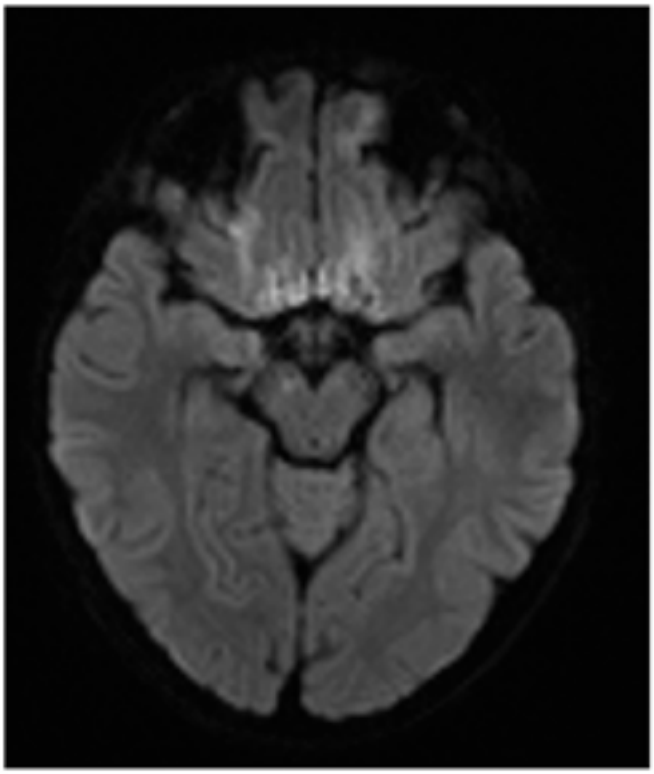

D

Discussion

T1DM is a well-known condition in children and one of the most frequent causes of chronic disease (1). Approximately one-third of children present with diabetic ketoacidosis (DKA) at diagnosis, which significantly impacts on the morbidity and mortality. Ketoacidosis is a state of insulin deficiency leading to catabolism and lipolysis, resulting in hyperglycemia and ketonemia. This results in hyperosmolality, metabolic acidosis and dehydration due to osmotic diuresis. Ketoacidosis is defined by hyperglycemia (glucose >200 mg/dl), ketonemia (blood ß-hydroxybutyrate ≥3 mmol/L) and/or ketonuria, and acidosis (pH <7,3 and/or HCO3 <15 mmol/L).

Neurological complications of DKA are rare but potentially severe and life threatening. The most frequent complication is cerebral edema (CE), observed in less than 1% of patients but estimated to be present in 10% of those presenting with severe ketoacidosis (pH <7.1) (2). Furthermore, evidence of subclinical edema on imaging suggests that there is a clinical spectrum in CE, with only the most severe cases being clinically detected (3). The diagnosis of CE remains challenging, especially in younger children. The Cushing's triad (bradycardia, irregular respirations, and a widened pulse pressure) is seen only late in the evolution of CE and physicians should be alert even in cases where these parameters are within normal range. Furthermore, imaging can be falsely negative in the early first few hours. Another diagnostic challenge arises from the fact that CE has long been thought to be a complication of mis-managed fluid resuscitation, with the quantity of fluids administration and the use of hypotonic solutions being pinpointed as causing or aggravating CE. The PECARN FLUID trial, published in 2018 and the first randomized control trial to evaluate this risk, has not confirmed this belief (4). In response, current guidelines have been recently reviewed and advocate for an IV fluid replacement adapted to the degree of dehydration (1). Use of sodium bicarbonate is still discouraged, with current evidence suggesting it may increase risk of CE.

Knowledge of risk factors for developing CE is incomplete. Low PCO2 on admission, higher blood urea nitrogen and more severe acidosis are current presented risk factors (5). Younger age and new-onset diabetes are also considered risk factors as smaller children's brains are more susceptible to hypoxia and reduced cerebral perfusion. This is supported by the growing research on the pathogenesis of CE which hypothesizes that CE could be due to a defect of cerebral autoregulation leading to hyperemia and vasogenic edema, as well as brain hypoperfusion and reperfusion injury (6,7).

Other neurological complications of DKA that may be observed include: cerebral vein thrombosis, arterial ischemic stroke and hemorrhagic stroke. In children, stroke accounts for 10% of intracerebral complications from DKA and although rare, they are responsible for severe morbidity.

Whilst stroke can be a consequence of CE due to vascular compression, it can also occur independently. The pathogenesis can be linked to several mechanisms well demonstrated in a state of acidosis and hyperglycemia. These mechanisms include (a) a systemic inflammatory state with high levels of cytokines and complement activation, resulting in vascular injury; (b) a disruption in the normal coagulation pathway which is not well understood (some studies showing enhanced platelet activation and higher levels of procoagulant factors during DKA); and (c) impaired cerebral autoregulation, with studies suggesting it could be specifically due to DKA (8,9,10). Furthermore, studies in the adult population show a link between stroke and hyperglycemia, with a well-known higher risk of stroke in patients with T1DM. Such evidence in children is still lacking. Bharill et al. recently reported a pediatric case of stroke associated to T1DM without DKA, suggesting this association could also exist in children (11).

Clinical focal signs are found in less than 30% of cases of stroke, with children having largely non-specific symptoms and signs (lethargy, behavioral changes, confusion, blood pressure and/or heart rate changes). This makes the differentiation between acute stroke from CE difficult. Prompt diagnosis using neuroimaging techniques (preferably MRI) is essential, especially if focal signs are present. Imaging should also be considered in cases of a change in neurological examination or a slower than normal improvement of neurological symptoms with normalizing blood parameters. CT is less efficient in diagnosing strokes and can be falsely negative in the first hours of CE (12).

Our two cases illustrate the overlap between the two clinical entities of CE and stroke. In the first case, MRI showed post-herniation lesions as well as asymmetric ischemic lesions accounting for the hemiparesis. In this case, CE was diagnosed during the acute phase incorrectly accounting for both lesions. Our second case raises other clinical learning points. Firstly, the delay of imaging does not allow us to discriminate a stroke from vascular compression caused by early undetected cerebral edema and secondly, Covid-19 infection could be considered a confounding factor, as cases exist demonstrating associations between strokes and a severe form of the infection (13,14). In this case however, the Covid-19 related symptoms were mild, supporting DKA as the most likely etiology.

Conclusion

DKA is a frequent and severe condition in children, which every clinician is susceptible to encounter. Acute and patient tailored treatment is essential in managing those children. The knowledge that neurological complications may appear should induce clinicians to monitor neurological status for at least 48h after starting the treatment, even if DKA symptoms are resolved. The higher risk of stroke in these patients should be remembered and motivate imaging in case of focal signs, or lack of improvement of neurological status.

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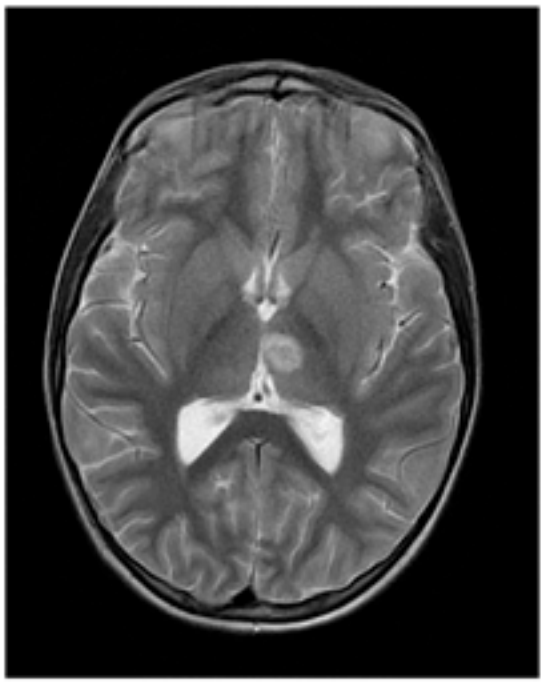
Figure 2 A-C: T2 (A), FLAIR (B) and diffusion sequence (C) MRI of the brain of a 6 year-old-boy (patient 2) obtained 1 week after DKA treatment showing an infarction of the left thalamus extending to the left cerebral peduncle.



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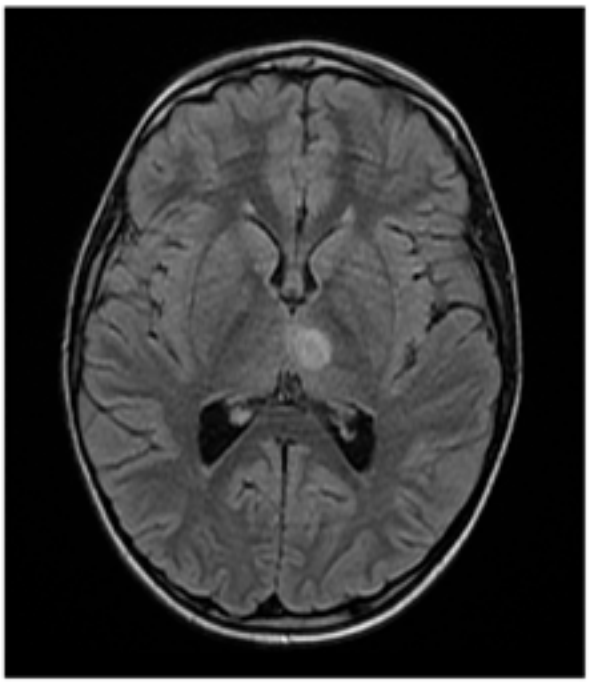

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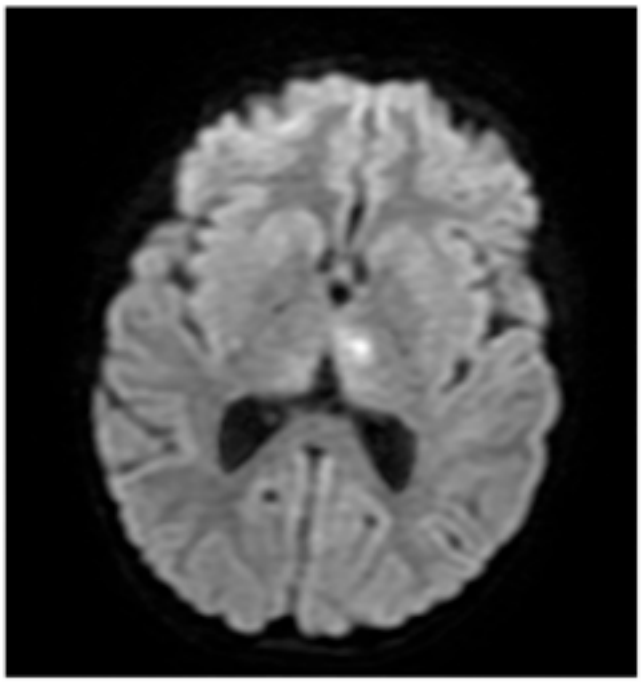

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