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Case Report

Unusual Presentation for Diabetic Ketoacidosis, Moya-Moya Disease Resulted From DKA-Associated Stroke in Children

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Introduction

Diabetic Ketoacidosis in children (DKA) remained to be a life-threatening condition. Despite the significant international efforts to develop different protocols for management in order to decrease the associated mortalities and morbidities, the incident rate of catastrophic neurological complications, namely cerebral edema, continues to be static in the range between 0.3 to 0.9 per cent with Overall mortality rate in children and adolescents from 0.15 to 0.51 [1-4]. Studies have found that 50 to 80 percent of mortality in children with DKA is attributed to cerebral injury [1-3, 5, 6].

As far as stroke in children is a concern, the overall incidence of pediatric stroke is estimated to be at the range between 2-13 per 100000 children [7]. The risk of acute ischemic or hemorrhagic stroke during the acute DKA episode is unknown. A case series found that approximately 10% of intracerebral complications of DKA are due to hemorrhagic or ischemic brain infarction [8], which, surprisingly, was not always associated with cerebral edema [9].

There is a paucity in literature dealing with DKA associated stroke. The clinical presentation and the diagnosis approach is quite challenging in pediatrics giving the communication challenges and the overlapping of signs and symptoms which could be attributed to other concurrent entities such as brain edema, acidosis, and electrolytes imbalance [8, 10, 11, 12].

We are reporting a case of DKA associated stroke in a 12-year-old boy and discussing the course and neurological outcome followed by a literature review of the presentation, pathophysiology and management options found in the literature

Case Presentation

A 12-year-old boy has a 5-year history of diabetes mellitus type 1, for which he was treated with Glargine 18 units at night and as part 3 units three times a day pre-meal. Despite being poorly controlled and having had a significantly elevated level of HbA1c at 11.7, this was his first Diabetes Ketoacidosis presentation. The patient anthropometric measurements are shown in Table 1.

BSA(m2)	BMI	Weight (KG)	Height(cm)	Age(year)
1.00	15.7	27.5	132	12

Table 1: patient anthropometric measurements.

He attended a primary health center with a 2-day history of epigastric pain and vomiting associated with poor oral intake and lethargies. At that time, blood gas showed mild acidosis with PH of 7.19, pco2 of 34 and HCO3 of 13, therefore He had received 30 ml/kg normal saline in subsequent boluses in addition to 0.1 Unit/kg of rapid acting insulin subcutaneously, and he was referred to our tertiary ER. Upon arrival, he was found to be awake and mildly dehydrated with HR of 111 beat/min and normal blood pressure.

The initial blood test results revealed the following findings: glucose level was 27 mmol/dl, PH 7.19, pco2 34 and HCO3 13 which was consistent with mild DKA.

He was admitted to the High Dependency Unit (HDU) where DKA management has been established according to our local DKA management protocol. Fluid replacement was calculated based on maintenance + 5% dehydration correction over 48 hours which was equal to 110 ml/h and the insulin was infused at a rate

of 0.1unit/kg/hour. Over the following 5 hours, blood glucose level decreased gradually (27-23-16-14-9) with stable Sodium level at 134. PH and HCO3 levels have improved from 7.25 to 7.34 and from 10 to 16, respectively. Creatinine levels decreased gradually until they reached normal levels. The lab's changes over time are shown in Table 2.

Time(hours)	Fluid(ml/h)	Insulin(u/h)	Glucose (mmol/liter)	PH	Hco3	Pco2	Crea	NA
1	110	0.1	27	7.25	10	25	100	134
2	110	0.1	23					
3	110	0.1	16					
4	110	0.1	14	7.34	16	30	88	
5	110	0.1	9				71	
6	60	0	8	7.34	18	34	60	137

Table 2: Serum biochemical changes over the first 6 hours.

Five hours later, Patient became unresponsive to oral stimulation, not oriented to the surroundings and aphasic. Pupils, HR, and BP were not altered, and no clinical sign of seizure was evident. He was clinically diagnosed with cerebral edema for which a stat dose of mannitol 0.5g/kg along with NaCl 3% 4ml/kg were delivered and the IVF was decreased by 50% to 60ml/h. At this stage we ceased the insulin infusion as the patient was out of DKA and blood glucose level was 8 mmol/liter.

Brain CT scan showed left basal ganglia Hypodensities seen in the caudate nucleus and lentiform nucleus. With No other focal parenchymal abnormal density Figure 1.

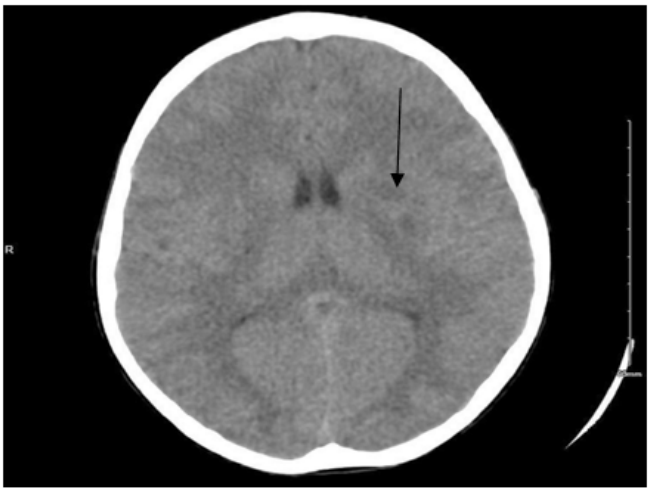

Figure 1: Brain CT.

Left basal ganglia Hypodensities seen in the caudate nucleus and lentiform nucleus (black arrow). With No other focal parenchymal abnormal density

Over that night, the patient continued to be drowsy and sleepy with poor speech output and impaired recognition. However, while he was maintaining his airway, no cranial nerve or focal neurological deficits were observed. 4 hours later, we resumed the insulin infusion at a rate of 0.03 u/kg/h. By that time, he developed a new right upper limb paresis. Apart from this, he showed significant improvement in his neurological condition therefore, he was transferred to HDU for further management.

Over the following days in HDU, he suffered from a second attack of slurred speech and disorientation, as well his right side became weaker with upper limb power of 3/5 and a lower limb power of 4/5 along with weak reflexes in both sides.

Brain MRI with angiogram showed: left Middle Cerebral Artery (MCA) territory showering acute ischemic insults, Moderate to marked stenosis of the left M1 and A1 with irregularity as well mild irregularity of the right M1 without significant stenosis Figure 2 and 3.

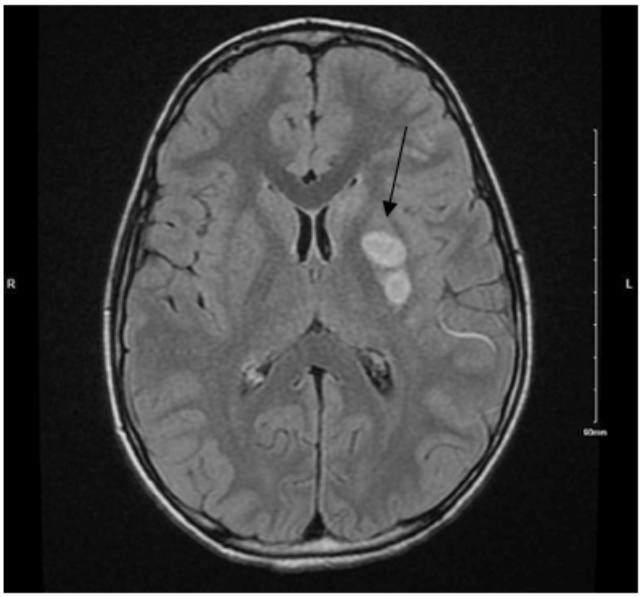

Figure 2: Brain MRI T2.

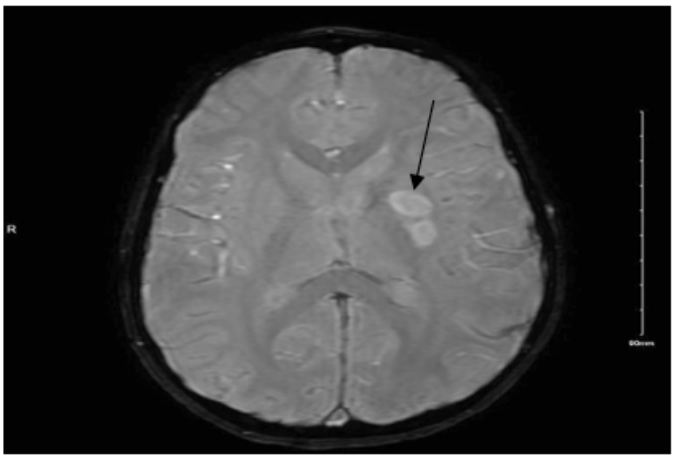

Figure 3: Brain MRI T2 Multiple left cerebral hemisphere lesions with abnormal signal intensity are noted in the left basal ganglia at putamen and caudate nucleus (black arrow).

The following studies were performed and resulted normal:

parameter	value	range
White Blood Cells WBC	14	4.5–11 x 109 cells/L
Hgb mg/dL	142	30–200
Platelet	326	150–350 x 109/L
PT	10.6	
Activated partial thromboplastin time (aPTT) (seconds)	23.4	30-40
INR	1	
FACTOR VIII: IU/mL	> 1.5	>0.4
vWF IU/dL	191.4	50-200
Anti-RNP unit	11.9,	<20
Antinuclear antibodies (ANA) IU/ml	8.38	<10
Anti–double-stranded DNA (dsDNA) antibodies, IgG (IU)	27.13	< 25
C3 g/L	0.9	0.9-1.8
C4 g/L	0.17	0.10-0.4
CRP mg/L	2	< 8.0
Lupus Anticoag:	negative	
Quantiferon-TB:	negative	

Anticardiolipin Antibodies ACA IgM U/ml	5.9	<10
ACA IgA U/ml	1.9	<10
ACA IgG: U/ml	1.9	<10
anti–Sjögren's-syndrome-related antigen A Anti-SS-A: U/ml	1.45	<7
anti–Sjögren's-syndrome-related antigen B Anti-SS-B:	2.1,	<7
Factor 5 Liden:	normal	
Sickle cell:	negative	
CSF analysis		
Protein: mg/dL	2.25,	<45
Glucose: mmol/L	4.6	2.5-4.5
WBC: cells/µL	<1,	0-5

Renal and liver function tests were normal, Echocardiography and ECG were normal on the 11th day admission. He developed a right facial nerve palsy. Brain CT showed: Re demonstration of the left frontal white matter and basal ganglia hypodense areas suggestive of the ischemic insult. Fundoscopy was normal Hematology and rheumatology service's initial opinion was consistent with large VS medium vasculitis, which was ruled out later after the full workup had completed. Therefore, the patient was commenced on aspirin 81 mg daily 44 days from admission, Repeat MRI showed: Circumferential enhancement of the left M1 and A1 with luminal narrowing suggesting vasculitis Figure 4.

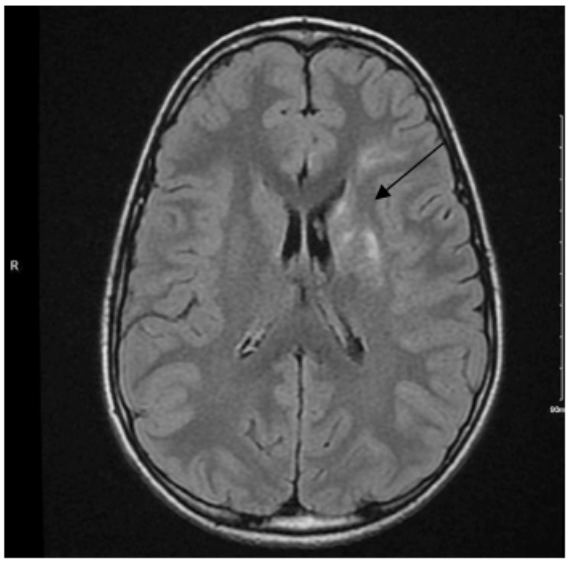

Figure 4: Brain MRI Newly seen focal left frontal periventricular white matter acute infarct (black arrow). Partial evolution of the prior multifocal left frontal and basal ganglia infarcts. - Marginal worsening of the left proximal M1 stenosis with still seen enhancement suggesting vasculitis. - The left subarachnoid ICA and A1 stenosis did not change. The right M1 irregularity is less apparent now.

The patient was discharged home with a diagnosis of left MCA stroke and early Moya-Moya disease.

One month later at neurology clinic: he presented with a 1-week history of bifrontal headaches, lasting for 30 minutes without weakness, photophobia, nausea, or vomiting. They did not affect his daily activities and were controlled by acetaminophen.

Over the following months, he has another episode of facial weakness which lasted for several hours and resolved spontaneously without any medical intervention.

Repeat neurological studies after 3 months revealed unremarkable Carotid artery findings by Doppler. Brain angiogram suggested probable Moya-Moya like syndrome 5 months following the initial presentation, he presented to ER with Transient Ischemic Accident (TIA) episode consisted of headache and slurred speech lasted for several hours and resolved spontaneously. Brain CT revealed old left basal ganglia and left periventricular hypodensities related to the previous infarction.

Repeat brain MRI revealed encephalomalacia at the site of the previous insult in the left centrum semi oval highly and basal ganglia. MRA shows stable narrowing in the left side as described with probable new mild narrowing in the A1 segment of the right ACA. Figure 5 and 6.

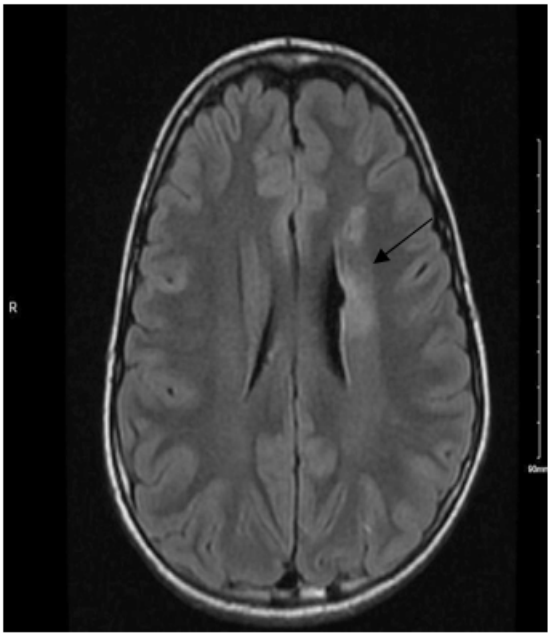

Figure 5: Brain MRI FLAIR.

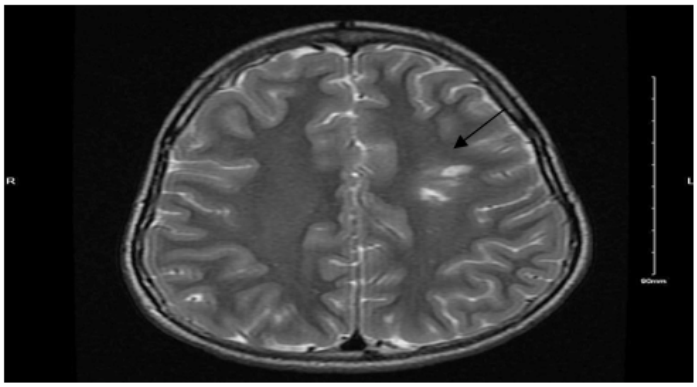

Figure 6: Brain MRI T2.

There are multiple foci of high T2, and low T1 signal intensity seen at the left centrum semi oval and basal ganglia following the distribution of the previous insult consistent with gliosis. Mild ex vacuo dilatation of the adjacent part of the left lateral ventricles identified. There is no acute brain insult. There is no intra extra-axial hemorrhage.

As described above, encephalomalacia at the site of the previous insult in the left centrum semi oval highly and basal ganglia. There is no acute brain insult. MRA shows stable narrowing in the left side as described with probable new mild narrowing in the A1 segment of the right ACA.

Last follow-up on 27/5/2021:

The clinical exam revealed mild right-sided upper limb weakness of 4/5. Mild mouth deviation to the left with absence of the right nasolabial fold. Sensory is intact. The rest of the exam is unremarkable Final diagnosis Type1 DM Left MCA infarction with subsequent encephalomalacia and early Moya-Moya disease.

Discussion

The early signs of stroke in children presenting with DKA are nonspecific and include headache, lethargy, confusion and changes in vital signs readings such as heart rate, blood pressure and respiratory rate [10], the presence of new behavioral changes, new-onset seizure and altered level of consciousness were found to be the dominant features in children diagnosed with DKA-associated stroke in one study [11] Nevertheless, less than30% of children with DKA-associated stroke would have focal neurological findings guiding the physician reaching the diagnosis clinically [8]. It is quite challenging for the physician to ascertain the overlapped clinical findings.

Whether they are related to brain edema, stroke or accompanied metabolic changes related to DKA. In addition, the presence of cerebral edema could not certainly solve the dilemma of which one cause the other, as cerebral edema could cause cerebral infarction and vice versa.

Children diagnosed with DKA-associated stroke may have arterial ischemic and hemorrhagic strokes located in a wide variety of cerebral areas which could be single or multiple thrombi distributed unilaterally or bilaterally. The pathologic tissue findings of acute cerebral infarction related to DKA are not expected to be different from those of a non-diabetic child who had suffered a stroke [12].

Stroke Pathophysiology

The risk of stroke in DKA could be attributed to endothelial damage due to Systemic inflammation that is present in DKA, which might be responsible for the associated coagulopathy.

Abnormalities in coagulation factors, platelet activation, blood volume and flow, and vascular reactivity may play a role in risk increase of Thrombotic stroke in children with DKA. DKA-associated cerebral edema may also cause ischemic injury and hemorrhage, although, reports of stroke cases not associated with cerebral edema have been present [8]. Evidence of the inflammatory response during DKA is shown by elevated levels of inflammatory markers (CRP), cytokines (IL6, IL1β, TNFα), and complement activation [13]. Complement activation found to have role in developing cerebral edema in patient with DKA, brain autopsies of 2 patients died from brain edema suggested activation of complement and C5b-9 which may have contributed to the mechanism of brain edema of DKA [14].some Studies determined intravascular coagulopathy within the brain to play a key role in the production of coma and the following mortality in those patients [15, 16].

Deep Venous Thrombosis (DVT) rate following Central Venous Catheter Insertion (CVC) in children with DKA are way much higher in comparison to that found in children without DKA. Therefore, Femoral CVCs should be avoided in DKA patients or removed as soon as possible, and DVT prophylaxis should be considered if a CVC is required [17, 18]. This could be related to elevated levels of von Willebrand Factor (vWF) and tissue plasminogen activator (tPA) which was found to be more than 2 standard deviations than control in one study [8]. Another cause could be related to protein C activity which was found to be significantly decreased by DKA in one study, however, it was normalized slowly following treatment. the same study reported that Free protein S was low, Protein C antigen and protein S levels remained normal within the first 24 hours, von Willebrand factor (vWF) antigen and vWF activity were both significantly increased prior to treatment but decreased with treatment. However, vWF activity remained elevated at 120 hours. Fibrinogen concentrations showed no significant changes.

Homocysteine was significantly decreased prior to treatment and increased with the initiation of treatment. Folate was significantly increased prior to treatment and decreased to high normal levels. The study concluded that increased vWF and the decreased levels of protein C activity and of free protein S support the hypothesis that DKA and its treatment results in a prothrombotic state and activation of the vascular endothelium, which, in turn, predispose to cerebrovascular accidents [19, 20].

Another study found that ketoacidosis was associated with significantly higher levels of factor VIII coagulant activity, factor VIII-related antigen and fibrin degradation products, a shorter partial thromboplastin time and reduced concentrations of antithrombin III [21]. Additionally, platelets aggregability has been shown to increase following acute hyperglycemia in one study in adult volunteers [22].

Diagnosis

In acute cases, brain CT scan is considered the most feasible investigation of choice to rule out other intracranial emergencies such as bleeding and herniation. Studies have found that CT scan had high sensitivity (99.1%) for 'high cerebral pressure' but a much lower specificity (78 1%) [23] CT scan sensitivity for identification of ischemic infarction in the acute phase is only 50% [24]. On the other hand, the best modality for detecting the early signs of stroke is magnetic resonance imaging (MRI) with perfusion- and/or diffusion-weighted imaging which has a sensitivity reaching 100% [24]. The gold standard for assessment and diagnosis of cerebral vasculature remains cerebral angiography. Being non-invasive, MR angiography (MRA) is considered beneficial in detecting large vascular lesions [25]. Another less invasive option could be CT angiography, which requires contrast injection, however, it may be used to evaluate the cerebral circulation in the early phases of acute stroke [25].

Management Fully evidence-based management guidelines for children experiencing acute ischemic or hemorrhagic infarction do not exist and have been extrapolated from adult data. Prevention of DKA is the most effective method of preventing complications [4].

Patients suspected of having central nervous system (CNS) complications should be treated in a pediatric intensive care unit, with prompt neurological imaging studies (cranial CT or MRI, or both) to look for evidence of cerebral edema or other intracranial pathologies [11]. The priority in PICU is to treat a suspected cerebral edema unless it is absolutely excluded, and other clear causes are evident. There may be some alternative management options for thrombus causing stroke [4]. Treatment options include conservative and symptomatic management such as controlling temperature, maintaining normal oxygenation and blood pressure and normalizing blood glucose levels. Recommendations advise to use enoxaparin or warfarin for the high-risk patients to prevent a future recurrence, whereas aspirin is considered a good long-term prophylaxis for those with minimal risk of recurrent stroke. No rule for Tpa in management of ischemic stroke in children. A detailed recommendation is published by American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young [26].

Conclusion

DKA associated stroke is not a rare presentation and could be misdiagnosed for other entities such as cerebral edema. High level of suspicious is warranted for correct detection and management. Aspirin for low-risk patient and enoxaparin or warfarin for high-risk patient is the only recommended long term management for children post ischemic stroke

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