Case Report

Hemorrhagic stroke: Uncommon complication of diabetic ketoacidosis in pediatric patients ☆

Fathi Hilal, MD[a], Eman Mahdi, MD[b], Ayman Nada, MD, PhD[a],*

[a] *Department of Radiology, University of Missouri, One Hospital Dr, Columbia, MO 65212, USA*
[b] *Department of Radiology, Virginia Commonwealth University, Richmond, VA, USA*

ARTICLE INFO

ABSTRACT

Diabetic ketoacidosis (DKA) is a well-known complication of type 1 diabetes mellitus. Diabetic ketoacidosis predisposes patients into devastating neurological complications. The most common neurologic complication is cerebral edema. Stroke either ischemic or hemorrhagic are uncommon complications of DKA with worse patient's outcome. Hemorrhagic stroke can manifest as subarachnoid or intraparenchymal hemorrhage. We present a 14-year-girl presented with DKA and complicated with both subarachnoid and intraparenchymal hemorrhages. Owing to early diagnosis and prompt treatment the patient had good outcome.

Introduction

Diabetic ketoacidosis (DKA) is a well-known complication of type 1 diabetes mellitus which is an autoimmune disease. The prevalence of type 1 diabetes mellitus in children and teenagers has increased from 1.48 per 1000 in 2001 to a rate of 2.15 per 1000 in 2017 [1]. DKA can be the presenting manifestation in up to 33% of patients with type 1 diabetes mellitus and it is the leading cause of mortality in this population [2]. The mortality rate of DKA in the United States is 0.15% [3].

Neurological complications occur in 0.3%-1% of cases with DKA and they present with sudden neurological deterioration and it is associated with 24% mortality [4,5]. This sudden deterioration usually occurs within 24 hours of DKA presentation,

often when patients start to improve [6]. These complications are more common in children under 5 and who are newly diagnosed with type 1 DM. Cerebral edema accounts for most of DKA mortalities (57%-87%) [7]. Cerebral edema can be severe to the extent of causing brain herniation which carries a very big risk of mortality [8]. Cerebral edema accounts for 90% of these complications. Stroke, both hemorrhagic and ischemic, causes the remaining 10% of complications [9].

Dural venous sinus thrombosis, ischemic and hemorrhagic strokes account for minority of neurological manifestations in DKA [5,10]. Hemorrhagic strokes (HS) carry a higher risk of mortality compared to ischemic strokes [11]. Hemorrhagic stroke may present as punctate hemorrhages, hematoma or subarachnoid hemorrhage (SAH) and it is a very rare complication [10,12–14]. SAH presents clinically with sudden severe

---

headache, nausea and vomiting, disturbed conscious level, seizures, nuchal rigidity and focal neurological deficits [15–17].

In this report we will describe an uncommon complication of DKA in pediatric patient who presented with subarachnoid and intraparenchymal hemorrhage.

Case report

A 14-year-old female with a 4-year history of uncontrolled type 1 DM complicated with 4-5 episodes of DKA and a history of depression presented to the ER after being found unresponsive at home. Physical examination revealed a teenage girl in distress with a GCS of 11, hyperglycemia (826 mg/dl), temperature of 36.8°C, HR of 140/ min, RR of 28/min, BP of 142/91 mmHg, intact distal pulses and SpO2 of 97%. Her respiration was rapid and deep (Kaussmaul breathing), and lungs were clear on auscultation. Neurological examination revealed altered mental status with no focal deficits. She had a perianal abscess with fluctuance and punctum draining purulent fluid. The rest of her examination was normal except for dry oral mucous membranes for which the patient has been given 2 L of normal saline. Post-abscess drainage contrast-enhanced CT of abdomen and pelvis showed small residual subcutaneous abscess without deep extension into the rectum. The patient's labs showed leukocytosis (WBCs 42,000/mm^3), pH of 6.7, HCO$_3$ of 3 mEq/L, K of 5 mEq/L and elevated lactic acid (3.4 mmol/L) which was consistent with DKA. She was stated on insulin regimen according to DKA treatment recommendations.

Following the management of the abscess, the patient experienced a 2-minute seizure and was given 2 doses of 1mg Ativan and 250 mL of 3% normal saline. A noncontrast head CT scan showed diffuse bilateral frontotemporal and occipital sulcal hyperdensities more appreciated within the sylvian fissures (Fig. 1). Few punctate hyperdensities in the splenium of the corpus collosum and right parietal lobe were observed and consistent with intraparenchymal hemorrhage (Fig. 1). Follow-up noncontrast brain MRI scan showed interval resolution of extensive subarachnoid hemorrhage with minimal residual SAH within the right frontal superior sulcus (Fig. 2). Scattered intraparenchymal hematomas within the splenium of the corpus callosum, and right frontoparietal lobes were confirmed (Fig. 2).

The patient was transferred to PICU where she started to improve clinically and discharged uneventfully 5 days later.

Discussion

This report emphasized the imperative role of prompt neuroimaging in the management of suspected neurological dysfunction in patients presented with DKA. Critical timely appropriate management improved the patient's outcome despite significant patient presentation. The patient developed DKA secondary to neglected perianal abscess which is further complicated with hemorrhagic stroke i.e., subarachnoid and intraparenchymal hemorrhages.
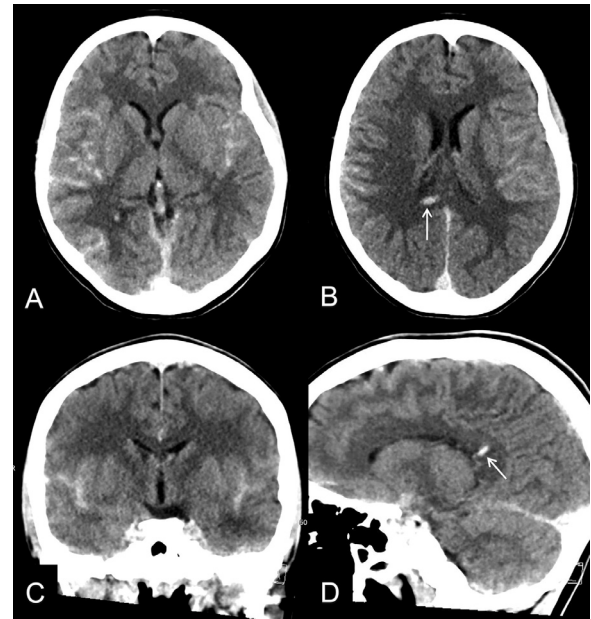

Fig. 1 – 14-year-old female presented with seizure following DKA. Axial CT head with brain algorithm at the level of frontal horns of the lateral ventricles (A, and B) demonstrate bilateral hyperdensities within the frontotemporal and occipital sulci, consistent with SAH. Small hyperdense focus within the right splenium of corpus callosum (arrow) was consistent with IPH. Coronal (C) and sagittal (D) CT images of the head with brain algorithm show extensive hyperdensities within the sylvian fissures and fronto-temporal sulci, consistent with SAH, and small focal hyperdensity at the right splenium of corpus callosum (arrow), consistent with IPH. IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage.
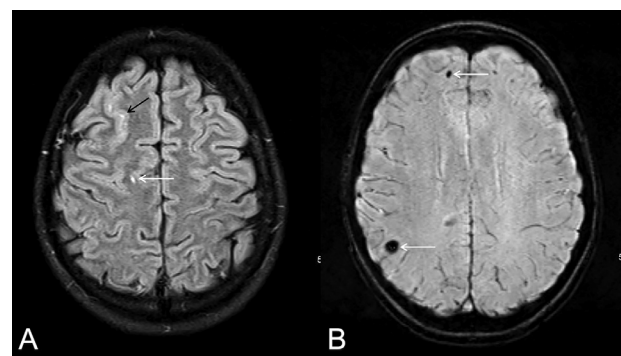

Fig. 2 – 14-year-old female presented with seizure following DKA. Axial FLAIR (A), and SWI (B) follow-up MR images show minimal residual SAH within the right superior frontal sulcus (black arrow) and scattered foci of IPH (white arrows), more conspicuous in SWI. FLAIR, fluid attenuated inversion recovery; IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage; SWI, susceptibility-weighted image.
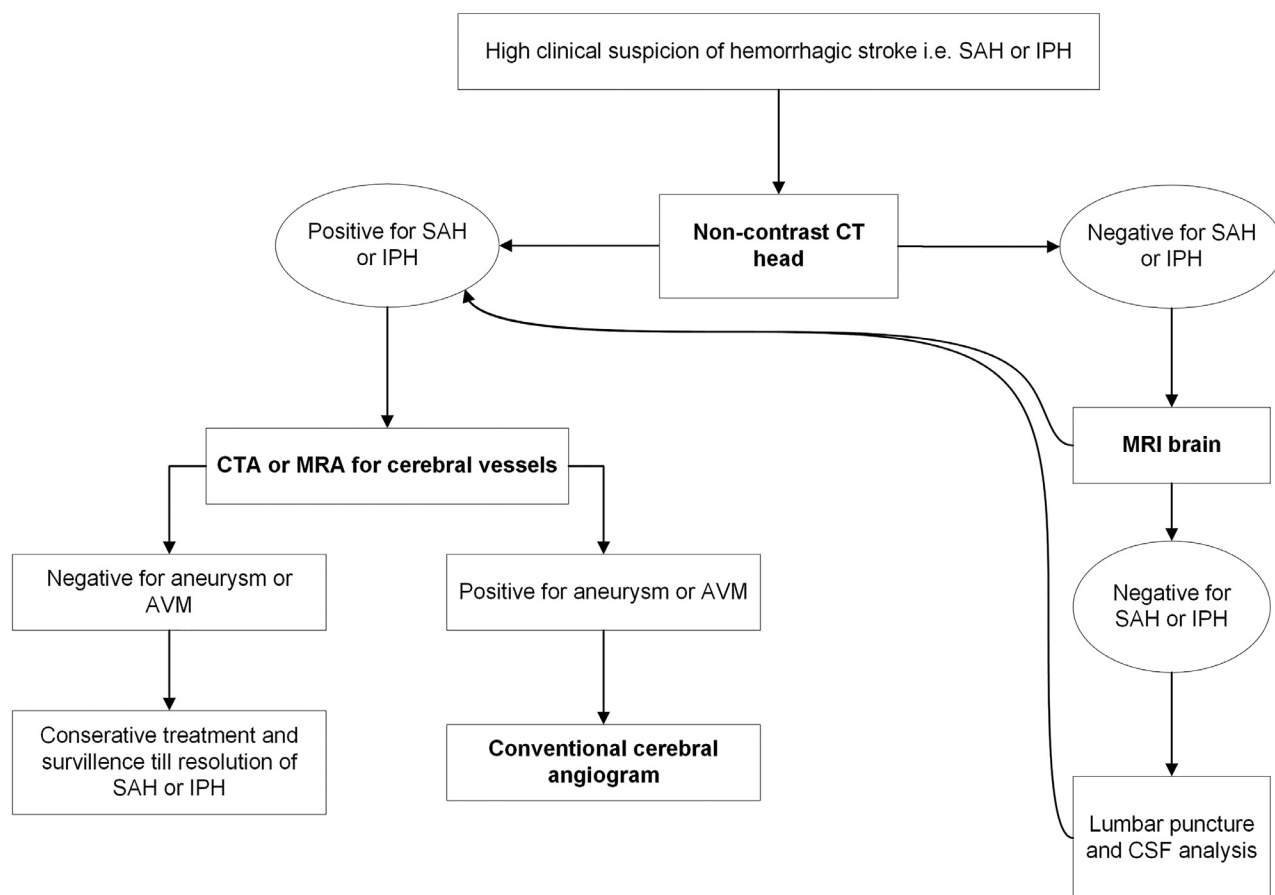
Fig. 3 – Flow chart for imaging evaluation of suspected subarachnoid (SAH) or intraparenchymal (IPH) hemorrhages.

DKA is a devastating clinical metabolic complication, most common in patients with type 1 diabetes mellitus [18]. Furthermore, neurologic complications in patients presented with DKA such as cerebral edema and ischemic-hemorrhagic stroke entail high risk of morbidity and mortality [19]. Hemorrhagic stroke includes intraparenchymal and subarachnoid hemorrhage in most of cases [4,5].

The overall annual incidence of stroke in children is 2.3 per 10,000. Ischemic stroke rate is 1.2/10,000 and HS rate is 1.2/10,000. [20] The incidence of stoke in children with DKA is undetermined due to lack of randomized clinical trials. Pediatric strokes have a morbidity rate of 66% and mortality rate of 7%-28% [5]. Most HS in children in general are intraparenchymal and supratentorial. About 80% are cortical in origin. Involvement of basal ganglia is less than 10%. Subarachnoid and intraventricular hemorrhages are less common [16].

The association between DKA and HS is not well-known. However, there are several possible etiologies that might explain these HS. A hypotensive episode happening in watershed areas resulting in vascular injury and softening of tissues with subsequent hemorrhage [13,19]. Hyper-ketonemic state and decreased level of glutathione resulting in lipid peroxidation result in oxidative injury [21]. Endothelial perturbation caused by increased levels of pro-inflammatory markers, for example, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) [22]. Disseminated intravascular coagu-

lation (DIC) that is confined to cerebral vessels was observed in some cases [23]. All of the above could play a role in the occurrence of vascular injury which can lead into SAH. Our case presented with extensive subarachnoid hemorrhage that could be attributed to disrupted blood brain barrier.

Acute severe headache and seizure are the major presenting symptoms for subarachnoid and intraparenchymal hemorrhage [24]. Patients should be promptly investigated with non-contrast head CT. The imaging findings include curvilinear hyperdensities in the subarachnoid spaces, for example, basal cisterns and cortical sulci. Cerebral intraparenchymal hematomas will usually manifest as punctate hyperdense foci at the cortical-subcortical interface, within the corpus callosum and basal ganglia [12]. Large intraparenchymal hematomas are rare and if occurs usually will be associated with surrounding vasogenic edema and cause significant mass on adjacent vital structures [13,14]. Further evaluation with CT cerebral angiogram should be performed to reveal the underlying etiology of SAH or IPH [25]. For patients who cannot undergo CTA due to contrast allergy or renal impairment, magnetic resonance imaging of the brain and magnetic resonance angiography of the cerebral vessels are good alternatives [17,26,27]. MRI studies also better evaluate for ischemic cerebral infarct especially small ischemic lesions, dural venous sinus thrombosis or underlying vascular malformation since it has more soft tissue contrast compared to CT [28–30].

If the non-contrast CT head is nondiagnostic with high clinical suspicion of SAH, lumber puncture should be performed for cerebrospinal fluid (CSF) analysis for xanthochromia in case of radiologically occult SAH. The typical findings on CSF analysis include yellowish discoloration of CSF, red blood cell count (RBCs) and bilirubin and oxyhemoglobin pigments (Fig. 3) [31].

Several prior reports of HS with DKA emphasized higher sensitivity of MRI for detecting subtle subcortical white matter petechial hemorrhage which are occult on head CT. These petechial hemorrhages appear as hyperintense foci on T2 and FLAIR images. They can also appear as ring-and-ball due to small artery occlusions on postmortem histology 12 or hematomas affecting deep nuclei, for example, thalamus [13,14] Susceptibility-weighted images and gradient-weighted images are the most sensitive MR sequences to detect subtle petechial hemorrhages [32].

Management of HS depends on early recognition with prompt neuroimaging. There should be a high index of susception for any sudden or severe deterioration of the level of consciousness of patients despite correction of the metabolic derangement. Clinical manifestations that raise suspicion of increased intracranial pressure (ICP) which include sudden severe headache or projectile vomiting should be promptly investigated with noncontrast head CT scan. Additional imaging depends on the findings on the head CT and patient characteristics, for example, young normotensive patient who is a candidate of surgical intervention should be further investigated with angiograph or MRI [27]. Ruptured preexisting cerebral aneurysms are the most common cause of SAH (85%), AVMs and other vascular malformations cause 5%. In about 10% of cases, imaging does not reveal the source of bleeding [26].

Primary management of SAH is transferring the patient to a comprehensive hospital with experienced staff and close monitoring of the patient's blood pressure to keep systolic blood pressure (SBP) at 160-130 mmHg using calcium channel blockers (CCB) or beta blockers (BB). Hyperglycemia and hypoglycemia may worsen the prognosis, but aggressive control of hyperglycemia is not associated with better outcomes [17].

To prevent rebleeding, oral or intravenous (IV) nimodipine is recommended after SAH onset. Aneurysmal SAH should be treated with endovascular or surgical treatment (eg, clipping) within 72 hours. For nonaneurysmal SAH, medical treatment is preferred (eg, nimodipine). Antifibrinolytics (eg, tranexamic acid) can also be added for <72 hours only [17].

ICP is 1.5-6 mmHg in infants, 3-7 mmHg in young children and 10-15 mmHg in older children and adults. Keeping ICP below 20 mmHg is suggested. Device monitoring of ICP is advised if the GCS is 3-8. Cerebral perfusion pressure (CPP) which equals mean arterial pressure (MAP) minus ICP should be kept at 40-6- mmHg and hypotension should be avoided. CPP = MAP-ICP [33].

Treatment options for increased ICP include head raising at 30° but not more than 40° as it may decrease CPP. Mannitol, however, it could cause hypovolemia and electrolyte disturbance. Hypertonic saline (3%) is a better option. Analgesia and avoiding secondary brain injury (eg, hypo/hyperglycemia, seizures, hyperthermia and electrolyte imbalance) are also important measures [34]. Additional treatment with CSF drainage via ventriculostomy could also be used if needed [17].

Conclusion

Hemorrhagic complications are rare devastating complications in patients presented with DKA, secondary to disruption of the blood brain barrier. Clinical deterioration of the patients' neurologic functions can be subtle and even present despite corrected metabolic derangement. Evaluation of these patients with neuroimaging allows for early detection of these hemorrhagic complications and excludes other possibilities. The radiologists should be aware of the wide spectrum of neurologic complications in patients with DKA to allow for prompt management which improve patients' outcome.

Patient consent

The patient gave a consent for publication.

REFERENCES

[1] Lawrence JM, Divers J, Isom S, Saydah S, Imperatore G, et al. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001-2017. JAMA 2021;326:717–27. doi:10.1001/jama.2021.11165.

[2] Bialo SR, Agrawal S, Boney CM, Quintos J. Rare complications of pediatric diabetic ketoacidosis. World J Diabetes 2015;6:167–74. doi:10.4239/wjd.v6.i1.167.

[3] Dunger DB, Sperling MA, Acerini CL, Bohn D J, Daneman D, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004;89:188–94. doi:10.1136/adc.2003.044875.

[4] Edge JA, Hawkins MM, Winter DL, Dunger D B. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 2001;85:16–22. doi:10.1136/adc.85.1.16.

[5] Ho J, Pacaud D, Hill MD, Ross C, Hamiwka L, et al. Diabetic ketoacidosis and pediatric stroke. Can Med Assoc J 2005;172:327–8. doi:10.1503/cmaj.1032013.

[6] Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001;344:264–9. doi:10.1056/nejm200101253440404.

[7] Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264–9.

[8] Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988;113:10–14. doi:10.1016/s0022-3476(88)80521-3.

[9] Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13:22–33. doi:10.2337/diacare.13.1.22.

[10] Finn BP, Power C, McSweeney N, Breen D, Wyse G, et al. Subarachnoid and parenchymal haemorrhages as a complication of severe diabetic ketoacidosis in a

preadolescent with new onset type 1 diabetes. Pediatr Diabetes 2018;19:1487–91. doi:10.1111/pedi.12760.

[11] Goeggel Simonetti B, Cavelti A, Arnold M, Bigi S, Regényi M, et al. Long-term outcome after arterial ischemic stroke in children and young adults. Neurology 2015;84:1941–7. doi:10.1212/wnl.0000000000001555.

[12] Mahmud FH, Ramsay DA, Levin SD, Singh R N, Kotylak T, et al. Coma with diffuse white matter hemorrhages in juvenile diabetic ketoacidosis. Pediatrics 2007;120:e1540–6. doi:10.1542/peds.2007-0366.

[13] Atluru VL. Spontaneous intracerebral hematomas in juvenile diabetic ketoacidosis. Pediatr Neurol 1986;2:167–9. doi:10.1016/0887-8994(86)90011-1.

[14] Lin JJ, Lin KL, Wang HS, Wong A M, Hsia S H. Occult infarct with acute hemorrhagic stroke in juvenile diabetic ketoacidosis. Brain Dev 2008;30:91–3. doi:10.1016/j.braindev.2007.06.001.

[15] Meyer-Heim AD, Boltshauser E. Spontaneous intracranial haemorrhage in children: aetiology, presentation and outcome. Brain Dev 2003;25:416–21. doi:10.1016/s0387-7604(03)00029-9.

[16] Lynch JK. Cerebrovascular disorders in children. Curr Neurol Neurosci Rep 2004;4:129–38. doi:10.1007/s11910-004-0027-3.

[17] Dong Y, Guo ZN, Li Q, Ni W, Gu H, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of spontaneous subarachnoid haemorrhage. Stroke Vasc Neurol 2019;4:176–81. doi:10.1136/svn-2019-000296.

[18] Zaher FZ, Boubagura I, Rafi S, Elmghari G, Elansari N. Diabetic ketoacidosis revealing a severe hypertriglyceridemia and acute pancreatitis in type 1 diabetes mellitus. Case Rep Endocrinol 2019;2019:8974619. doi:10.1155/2019/8974619.

[19] Foster JR, Morrison G, Fraser DD. Diabetic ketoacidosis-associated stroke in children and youth. Stroke Res Treat 2011;2011:219706. doi:10.4061/2011/219706.

[20] Fullerton HJ, Wu YW, Zhao S, Johnston S C. Risk of stroke in children: ethnic and gender disparities. Neurology 2003;61:189–94. doi:10.1212/01.wnl.0000078894.79866.95.

[21] Jain SK, McVie R, Bocchini JA. Hyperketonemia (ketosis), oxidative stress and type 1 diabetes. Pathophysiology 2006;13:163–70. doi:10.1016/j.pathophys.2006.05.005.

[22] Romano M, Pomilio M, Vigneri S, Falco A, Chiesa P L, et al. Endothelial perturbation in children and adolescents with type 1 diabetes: association with markers of the inflammatory reaction. Diabetes Care 2001;24:1674–8. doi:10.2337/diacare.24.9.1674.

[23] Timperley WR, Preston FE, Ward JD. Cerebral intravascular coagulation in diabetic ketoacidosis. Lancet 1974;1:952–6. doi:10.1016/s0140-6736(74)91261-6.

[24] Patel S, Parikh A, Okorie ON. Subarachnoid hemorrhage in the emergency department. Int J Emerg Med 2021;14:31. doi:10.1186/s12245-021-00353-w.

[25] Heit JJ, Iv M, Wintermark M. Imaging of intracranial hemorrhage. J Stroke 2017;19:11–27. doi:10.5853/jos.2016.00563.

[26] Muehlschlegel S. Subarachnoid hemorrhage. Continuum (Minneapolis, Minn) 2018;24:1623–57. doi:10.1212/con.0000000000000679.

[27] Broderick JP, Adams HP Jr, Barsan W, Feinberg W, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 1999;30:905–15. doi:10.1161/01.str.30.4.905.

[28] Moreau F, Asdaghi N, Modi J, Goyal M, Coutts S B. Magnetic resonance imaging versus computed tomography in transient ischemic attack and minor stroke: the more you see the more you know. Cerebrovasc Dis Extra 2013;3:130–6. doi:10.1159/000355024.

[29] Bonneville F. Imaging of cerebral venous thrombosis. Diagn Interv Imaging 2014;95:1145–50. doi:10.1016/j.diii.2014.10.006.

[30] Bashir U, Shah S, Jeph S, O'Keeffe M, Khosa F. Magnetic resonance (MR) imaging of vascular malformations. Pol J Radiol 2017;82:731–41. doi:10.12659/PJR.903491.

[31] Nagy K, Skagervik I, Tumani H, Petzold A, Wick M, et al. Cerebrospinal fluid analyses for the diagnosis of subarachnoid haemorrhage and experience from a Swedish study. What method is preferable when diagnosing a subarachnoid haemorrhage? Clin Chem Lab Med 2013;51:2073–86. doi:10.1515/cclm-2012-0783.

[32] Halefoglu AM, Yousem DM. Susceptibility weighted imaging: clinical applications and future directions. World J Radiol 2018;10:30–45. doi:10.4329/wjr.v10.i4.30.

[33] Palmer J. Management of raised intracranial pressure in children. Intensive Crit Care Nurs 2000;16:319–27. doi:10.1054/iccn.2000.1511.

[34] Kukreti V, Mohseni-Bod H, Drake J. Management of raised intracranial pressure in children with traumatic brain injury. J Pediatr Neurosci 2014;9:207–15. doi:10.4103/1817-1745.147572.