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Letter to the Editor

Pediatric critical illness associated cerebral microhemorrhages

Dear Editor,

Cerebral microhemorrhages or CMBs are small, hypointense foci occurring in the brain parenchyma, with a maximum size of 5 mm, or even up to 10 mm on haemorrhage sensitive MRI sequences. Traditionally, this clinical entity is seen in conditions such as cerebral amyloid angiopathy (CAA), chronic hypertension (termed hypertensive microangiopathy), and diffuse axonal injury (seen especially in a history of trauma) – with their own specific patterns on MRI. The advent of technology in MRI has allowed increased utilization of haemorrhage sensitive sequences, namely gradient echo (GRE) and susceptibility weighted imaging (SWI) in routine brain scans. On histopathological examination, these microhemorrhages are due to hemosiderin accumulation in macrophages [1]. The presence of hemosiderin causes the signal loss, or hypointense appearance on GRE/SWI sequences. Despite the increased detection, the clinical significance of microhemorrhages remains controversial – complicating patient management. There is increasing literature available attributing the occurrence of cerebral microhemorrhages to other, less well known causes, such as high-altitude exposure, acute respiratory distress syndrome (ARDS), infective endocarditis, or critical illnesses/sepsis; even so, most of the literature discusses this entity in the adult population. Scarce literature is available describing its occurrence in the pediatric population. Herein, we discuss the occurrence of cerebral microhemorrhages in a pediatric patient with critical illness, in our institution.

A 2-year-old, otherwise healthy boy presented with fever, upper respiratory tract symptoms, and rapid breathing for 3 days. No history of trauma was notable. He was born full term, with no significant antenatal or postnatal history. Delivery was via spontaneous vaginal delivery. His immunization was up to date. On examination, he was lethargic looking, with a recorded temperature of 40 °C. He was sitting in a leaning forward position, and was noted to be tachypneic, with a respiratory rate of 50 breaths per minute. Saturation on room air was 94%. Subcostal, as well as intercostal recessions were present. Stridor was evident. His peripheries were cold, however, pulse volume was still good. Blood pressure was 108/84 mmHg. Auscultation of the lungs noted generalized rhonchi and crepitations; the remaining systemic examination was unremarkable. A preliminary diagnosis of epiglottitis was made, with possible airway compromise. The otorhinolaryngology (ORL) and anaesthetic teams were consulted, anticipating the possibility of epiglottitis with difficulty in intubation for airway protection. Direct laryngoscopy revealed an inflamed and swollen epiglottis; the child was subsequently intubated and admitted to the intensive care unit (ICU), for further management. While in the ICU, he developed nosocomial pneumonia and a few episodes of tachycardia and desaturation, requiring multiple rounds of nebulization as well as subcutaneous bricanyl. Intravenous antibiotics were initiated. Cultures were negative, while the blood investigations did not suggest presence of disseminated intravascular coagulopathy. After 1 week of ICU admission, attempts were made to extubate; however, child did not show full Glasgow Coma Scale (GCS) recovery. An urgent cranial computed tomography (CT) was pursued, revealing small, punctate hemorrhages at the left frontal and parietal regions. His clinical condition eventually improved, and was transferred to the general paediatrics ward. Neurological assessment while in the ward noted presence of upper motor neuron signs, which were previously absent. The child had increased deep tendon reflexes, positive Babinski's sign, but absence of superficial reflexes, fasciculations, and atrophy. Daily assessment noted resolution of these signs. He was then discharged well, after a total of 4 weeks of admission, and arranged for a follow up magnetic resonance imaging (MRI) of the brain on an outpatient basis, 6-months post discharge. The brain MRI revealed hypointense foci at the previously noted areas of punctate hemorrhages on CT, as well as numerous other small similar signal foci measuring < 5 mm, distributed juxta- and subcortically, as well as concentrated at the splenium of the corpus callosum [Fig. 1]. These abnormal signals spared the thalami, deep gray matter, and cortex, and were only seen on the GRE sequence. Based on the MRI appearance and pattern, a diagnosis of sepsis/critical illness associated microhemorrhages was made. The child remains under the paediatrics clinic follow up, and shows no recurrence of the upper motor neuron signs seen while he was admitted.

1. Discussion

The prevalence of cerebral microhemorrhages, or CMBs, increases with increasing age. Population studies have cited a prevalence of 6% (age 45–50 years) to 36% (age 80 years or more) [2]. Those with no known vascular disease or risk factors, expectedly, have a lower prevalence of microhemorrhages (2.3%) [3]. These figures are generated from the adult population; the prevalence of cerebral microhemorrhages in the pediatric population is unknown. Some studies have looked at specific groups of pediatric patients, to determine the prevalence of cerebral microhemorrhages. In 1 study, CMBs were found to be more prevalent in heart disease patients undergoing cardiopulmonary bypass [4], while another study looked at the prevalence of CMBs in patients with Down's syndrome – revealing a higher prevalence in those with Down's syndrome compared to age matched controls, presumably due to an extra copy of the amyloid precursor protein gene, found on chromosome 21; a marker for early onset cerebral amyloid angiopathy [5].

Traditionally, the common causes of CMBs include cerebral amyloid angiopathy, chronic hypertension (hypertensive microangiopathy), and diffuse axonal injury (DAI) in trauma patients. Uncommonly, they may also be found in neurovasculitis, cerebral cavernous malformations, as hemorrhagic micrometastasis in patients with melanoma or renal cell carcinoma, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), as well as in Parry-Romberg syndrome [6]. CMBs due to critical illnesses or sepsis have not

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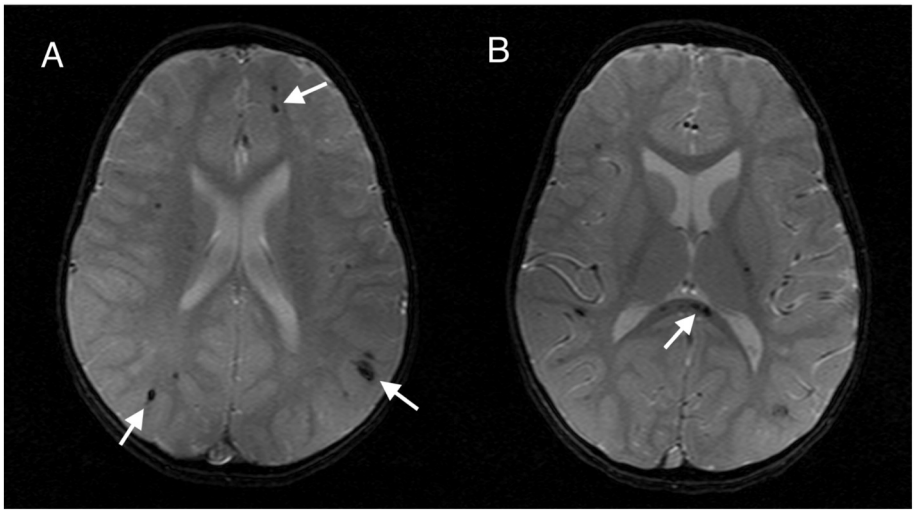

Fig. 1. Magnetic resonance images (MRI) of the brain, in axial section, on the gradient echo (GRE) sequence, showing;
A Multiple, small, hypointense foci are seen distributed juxta- and subcortically (white arrows).
B A focal area of hypointense foci, in keeping with microhemorrhages, is seen at the splenium of the corpus callosum (white arrow).

been reported and discussed widely in the literature. This may have led to its under-diagnosis.

The largest of the few studies that have looked at critical illness or sepsis associated CMBs [7–9] is by Mandell et al. [7], where 12 adult patients admitted to the ICU due to various causes were assessed via brain MRI. Of these 12 patients, 11 received mechanical ventilation, while 3 out of 12 were on extracorporeal life support. The brain MRI findings were extensive cerebral microhemorrhages, diffusely involving the juxtaxortical white matter and corpus callosum, but sparing the cortex, deep and periventricular white matter, basal ganglia, and thalami. To our knowledge, only 2 cases of pediatric patients with sepsis/critical illness have been reported with similar neuroimaging findings so far [8,9], apart from the patient at our institution.

Mandell et al. hypothesized a common pathogenesis between the CMBs pattern in patients with critical illness/sepsis to those with high altitude exposure and acute respiratory distress syndrome (ARDS). Patients with high altitude exposure have been reported to have corpus callosum predominant microhemorrhages [10,11], whereas in ARDS, a similar CMBs predominance has been observed [12]. After reviewing the published images in these studies, they noticed that these patients also had juxtacortical white matter CMBs. Due to the marked similarity in the pattern of CMBs, hypoxemia has been put forth as a possible cause – causing hydrostatic or chemical effects on the blood brain barrier, potentially accounting for extravasation of erythrocytes [12,13]. A similar pattern of CMBs was seen in our case, as well as the other 2 pediatric cases reported in the literature, supporting this theory.

The advent of MRI technology has allowed better depiction of cerebral microhemorrhages in patients coming for brain MRI. The utilization of haemorrhage sensitive sequences, namely gradient echo (GRE) and susceptibility weighted imaging (SWI) translates to an increased true positive detection rate, ranging from 48 to 89%. However, one needs to bear in mind the possible mimics or false positives, when interpreting the MRI images, which occur at a rate of 11–24% – causes which include microaneurysms, microdissections, and microcalcifications [9]. Phase images can then be used to rule out these potential mimics.

The clinical significance of cerebral microhemorrhages, when present, is till this day debatable. Previously thought to be incidental, some studies have shown that cerebral microhemorrhages are predictive of cognitive decline, ischemic stroke, and serve as risk factors for intracerebral haemorrhage [14]. What happened in our patient was the manifestation of upper motor neuron signs previously absent – which improved gradually prior to discharge. Whether or not there is an association between these clinical signs and the cerebral microhemorrhages seen on the follow up MRI, remains speculative.

Cerebral microhemorrhages, or CMBs, are increasingly detected in clinical practice, due to the advent of MRI technology. Previously thought to be exclusively a disease affecting the elderly, increasing studies have shown that it is also seen in the younger population – even in the pediatric age group. There are a multitude of causes, some are well known, while others are not. In patients with critical illness or sepsis manifesting with neurological signs and symptoms, neuroimaging via MRI with haemorrhage sensitive sequences may be useful for diagnosis, prognostication, and management.

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Authors' contributions

All authors contributed significantly to the preparation of this manuscript.

Ethical standards

Informed written consent was obtained from the patient's parents. This work was prepared in accordance to our institution's guidelines.

Declaration of Competing Interest

None.

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Nil.

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