

BRIEF COMMUNICATION

Acute cerebral microbleeds in refractory status epilepticus

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SUMMARY

Cerebral microbleeds (CMBs) are commonly found in patients with stroke and cerebral amyloid angiopathy. However, there have been no reports of CMBs or their acute appearance in patients with status epilepticus. Herein we describe two patients with refractory status epilepticus of uncertain origin. Both patients were previously healthy, and their initial imaging showed no underlying CMBs. One patient's follow-up susceptibility-weighted

imaging 29 days after initial imaging showed 63 new CMBs. The other patient's follow-up susceptibility-weighted imaging 41 days after initial imaging showed 14 new CMBs. Multimodal neuromonitoring revealed increase in lactate–pyruvate ratio, decrease in partial brain tissue oxygen tension, increase in pressure reactivity index, and fluctuations of blood pressure and cerebral perfusion pressure. This report demonstrates that multiple new CMBs may develop in patients with refractory status epilepticus (SE).

Cerebral microbleeds (CMBs) are commonly found in patients with small vessel diseases, such as intracerebral hemorrhage, ischemic stroke, and cerebral amyloid angiopathy (Charidimou & Werring, 2012). To our knowledge, however, the acute appearance of CMBs in status epilepticus (SE) has not been reported.

We describe two patients who (1) were treated for refractory SE of uncertain origin, (2) did not have evidence of underlying small vessel diseases including CMBs on initial magnetic resonance imaging (MRI), and (3) showed multiple new CMBs on follow-up susceptibility-weighted imaging (SWI).

CASE REPORT

Case 1

A 63-year-old woman presented with a generalized tonic–clonic seizure, which was controlled with intravenous lorazepam and phenytoin. Her workup including serum and cerebrospinal fluid (CSF) studies (neurotropic virus and bacteria, cytology, paraneoplastic antibody, autoimmune antibody, and 14-3-3 protein) and MRI

(GE 3.0 Tesla, General Electric, Fairfield, CT, U.S.A.) were unrevealing except for a mild pleocytosis (7/μl). She was treated for encephalitis of unknown etiology. Two days after admission, her mental status deteriorated, and she developed rhythmic eye blinking. Continuous video-electroencephalography (EEG) (XLTEK, Excel-Tech Ltd., Oakville, ON, Canada) showed generalized epileptiform discharges (see Fig. S1). Seizures continued for 3 weeks despite multiple antiepileptic drugs (AEDs) including phenytoin, valproic acid, topiramate, clonazepam, pregabalin, lacosamide, phenobarbital, and continuous infusions of midazolam and ketamine. Her course was complicated by thrombocytopenia, pneumonia, urinary tract infection, and fluctuations of blood pressure. Follow-up imaging was obtained 29 days after the initial MRI and revealed 63 new CMBs on SWI: 44 lobar (9 frontal, 12 parietal, 19 temporal, 2 occipital and 2 insular); 13 deep (3 corpus callosum and 10 white matter); and 6 infratentorial (5 brainstem and 1 cerebellum) (Fig. 1A) (Gregoire et al., 2009). She recovered from SE with severe disability (following simple commands and quadriplegia) at discharge after 3 months.

Case 2

A 27-year-old man presented with a generalized tonic–clonic SE. Initial laboratory tests including an extensive encephalitis panel were unremarkable except mild pleocytosis (10/μl). Brain MRI was unremarkable and showed no evidence of small vessel disease. His seizures were intractable despite multiple AEDs including

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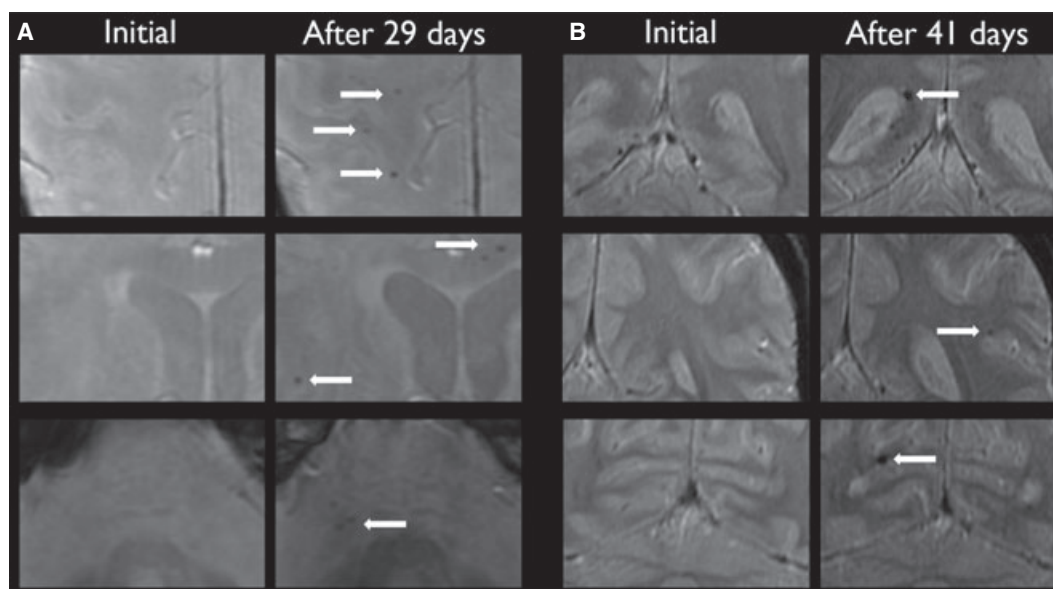


Figure 1.

Multiple new CMBs detected on follow-up SWI. **(A)** Patient 1. **(B)** Patient 2. Both initial and follow-up images were acquired using the same 3.0-T MRI system and protocol (please see Data S1) in each patient. Initial images were coregistered to the follow-up images using the MIPAV software (ver. 5.4.1; National Institutes of Health, Bethesda, MD, U.S.A.). Arrows indicate new CMBs that were not seen initially. Ventricles were enlarged due to atrophy on follow-up imaging.

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phenytoin, valproic acid, carbamazepine, topiramate, clonazepam, lacosamide, phenobarbital, and levetiracetam, continuous infusions of midazolam, pentobarbital, and ketamine, and electroconvulsive therapies (see Fig. S2). Multimodal neuromonitoring was performed to detect secondary brain injury, and showed metabolic distress (lactate–pyruvate ratio >40), cerebrovascular dysautoregulation (pressure reactivity index >0.2), brain tissue hypoxia (partial brain tissue oxygenation <15 mm Hg), and fluctuations of blood pressure and cerebral perfusion pressure (see Fig. S3) (Helbok et al., 2011). These monitoring results were used to optimize cerebral metabolism, perfusion, and oxygenation. Follow-up imaging 41 days after the initial study showed 14 new CMBs: 11 lobar (3 frontal, 4 parietal, 2 temporal, and 2 occipital); and 3 deep (1 corpus callosum and 2 white matter) (Fig. 1B) (Gregoire et al., 2009). The hospital course was complicated by thrombocytopenia, pneumonia, acute respiratory distress syndrome, septic shock, and multi-organ failure. Five months after admission, he was still in a vegetative state and died of sepsis.

DISCUSSION

CMBs have long been regarded as markers of chronic small vessel diseases (Charidimou & Werring, 2012). Postulated mechanisms for the presence of CMBs include accumulation of old microscopic bleeding and

hemosiderin-laden macrophages nearby chronically diseased small vessels. However, recent reports suggest that CMBs may appear rapidly (within days) during the acute ischemic stroke and after carotid artery stenting or cardiac valve surgery (Jeon et al., 2009, 2010; Kakumoto et al., 2012). Mechanisms for the acute development of CMBs may differ from those implicated for chronic CMB development. Leakage of blood products through increased capillary permeability due to blood–brain barrier (BBB) breakdown has been hypothesized as the mechanism (Jeon et al., 2009, 2010). A recent report showed that serum levels of vascular endothelial growth factor in stroke patients with CMBs were higher than those without CMBs, suggesting a role of increased permeability (Dassan et al., 2012). Our findings further support this theory. BBB compromise occurs due to seizure itself and from angiogenesis or inflammation associated with long-lasting seizures, which may cause CMBs in SE (Ransohoff, 2009). In our patients, the causes for increase in vascular permeability and subsequent emergence of new CMBs may be multifactorial including cerebral or systematic inflammation and increased metabolic distress (Ransohoff, 2009). CMBs have been observed in more than one half of patients with infective endocarditis, although systematic studies on CMBs in sepsis or cerebral inflammation are scarce (Klein et al., 2009; Okazaki et al., 2011). Elevated blood pressure and cerebral perfusion pressure in the setting of cerebrovascular dysautoregulation may have further accelerated leakage of blood

products through a disrupted BBB. A recent study showed that blood pressure variability was related to the development of new CMBs over a median of 14 months in patients with ischemic stroke and underlying CMBs (Liu et al., 2012). Moreover, bleeding-prone states such as thrombocytopenia may further aid leakage of blood products through an impaired BBB. Twelve percent of young, nonhypertensive patients with thrombocytopenia (a median of platelet counts = 17,500/ μ l) due to aplastic anemia have shown asymptomatic CMBs (Sharma et al., 2012). It is also plausible that anticoagulation for deep vein thrombosis prophylaxis contributed to the acute development of CMBs in our patients, but previous studies did not show the associations between anticoagulation and new CMBs (Jeon et al., 2009, 2010).

CMBs have been associated with cognitive impairment, depression, gait instability, and poor quality of life in other populations (Tang et al., 2011; Charidimou & Werring, 2012; Choi et al., 2012; Choi-Kwon et al., 2012). The mechanisms by which CMBs are related to neurologic symptoms have been hypothesized as direct structural damage or functional disturbance to surrounding brain tissue, indirect effects such as arteriolar narrowing causing hypoperfusion, and general markers for the severity of brain injury (Charidimou & Werring, 2012). At present, it is uncertain that our patients' CMBs contributed to poor neurologic outcomes. However, given that SE survivors also have cognitive and emotional sequelae, CMBs' contribution to poor neurologic outcome after SE should be investigated further (Sayin et al., 2004; Legriél et al., 2010). Prospective studies are warranted to validate our novel observation and demonstrate CMBs' epidemiology and clinical implications, including prognostication, in patients with SE.

DISCLOSURE

The authors report no disclosures. Standard protocol approvals and patient consents: This study was approved by the institutional review board at our center. Informed consents for this study were obtained from patients' family members. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplemental methods.

Figure S1. [Patient1] Surface electroencephalography (EEG) and physiologic variables.

Figure S2. [Patient2] Surface and depth electroencephalography (EEG).

Figure S3. [Patient 2] Multimodal neuromonitoring.

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