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Case Report

Seizure freedom following surgery for multi-focal epilepsy due to cerebral malaria

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1. Introduction

Nearly 50% of the world's population, mostly from sub-Saharan Africa, is at risk of malaria, according to the World Health Organization [1]. In Thailand, malaria is still endemic in some parts of the country. Evidence has shown predilection for brain involvement in the acute phase of cerebral malaria (CM). Cerebral dysfunction of selective brain regions may account for long-term neurological deficits including epilepsy. Hippocampal sclerosis (HS) secondary to CM has been rarely reported [2]. The clinical course including response to treatment of HS in this setting is therefore unknown.

This report presents another case of chronic epilepsy with HS secondary to CM. Detailed clinical course, electrographic and imaging findings, and response to treatment including epilepsy surgery are described.

2. Case Report

A 44-year-old left-handed male began having seizures since the age of 21. At the time, he lived in the Chumphon Province in the south of Thailand, known as a malaria endemic area, according to the World Malaria Map [3]. Six months prior, he had two episodes of malarial infection. The first episode was uncomplicated malaria where he developed only fever and diffuse headache. One month later, he moved to Kanchanaburi Province, another malaria endemic area, as shown in Fig. 1. While being there, he worked with his friends as a harvester in the forest. They all developed high-grade fever and headache. However, he was the only one who became unresponsive and required hospitalization. He was intubated and transferred to the Hospital for Tropical Diseases in Bangkok. He was completely unconscious for 3 days and then gradually recovered over two weeks. His current seizure consists of a cephalic aura described as "a weird feeling in his head", at times followed by loss of awareness associated with oroalimentary automatisms seizure. On rare occasions, he would develop, either left- and right-sided focal onset evolving to a generalized tonic-clonic (GTC) seizure. His seizures were resistant to several anti-seizure drugs (ASDs) including phenytoin, phenobarbital, clonazepam, valproic acid, levetiracetam, and lamotrigine. He still suffered from an average of seven focal seizures per month. He had no family history of epilepsy. His birth history was uneventful. There was neither history of febrile seizures nor central nervous system (CNS) infection at young age. No history of head injury was noted.

He has normal intelligence and his neurological examination was unremarkable. Magnetic resonance imaging (MRI) revealed left hippocampal sclerosis and non-specific subcortical white matter changes in bilateral frontal lobes, as shown in Fig. 2.

He underwent a video-electroencephalography (EEG) monitoring (VEM) as part of a presurgical evaluation where seven typical seizures were captured. Semiologically, three different types of seizures were recorded. One was a typical cephalic aura followed by minimal oral automatism (seizure # 1–3, 6, 7); another was a focal impaired awareness seizure (without aura) followed by right-sided dystonic posturing (seizure # 4), and the last was a cephalic aura followed by left hand dystonic posturing with subsequent left hand automatism/right hand dystonic posturing (seizure # 5). Contradictory semiological lateralization was observed between seizure # 4 and # 5. Electrophysiologically, either voltage attenuation or rhythmic theta activity over left temporal region at ictal EEG onset was observed during six seizures, as shown in Fig. 2. The one remaining seizure (seizure # 5), had EEG onset starting with rhythmic theta activity over right temporal region, corresponding with the seizure semiology of initial left hand dystonic posturing. Interictally, multiple independent spike foci (MISF) were noted at O2, T5O1, F8FT10, and F7FT9. Most pronounced interical epileptiform discharges (IEDs) were appreciated at O2 (50%), followed by T5O1 (20%), shown in Fig. 2.

Standard anterior temporal lobectomy (ATL) with amygdalohippocampectomy (AHC) was performed. Pathology revealed HS, International League Against Epilepsy (ILAE) type I. At the present, it has been 16 months since the patient underwent surgery. He was completely free from any types of seizure for 10 months and then developed two minor seizures over the past 6 months.

3. Discussion

Nearly one-third of CM survivors develop epilepsy or other neurological conditions soon after recovery [4,5]. Among children who

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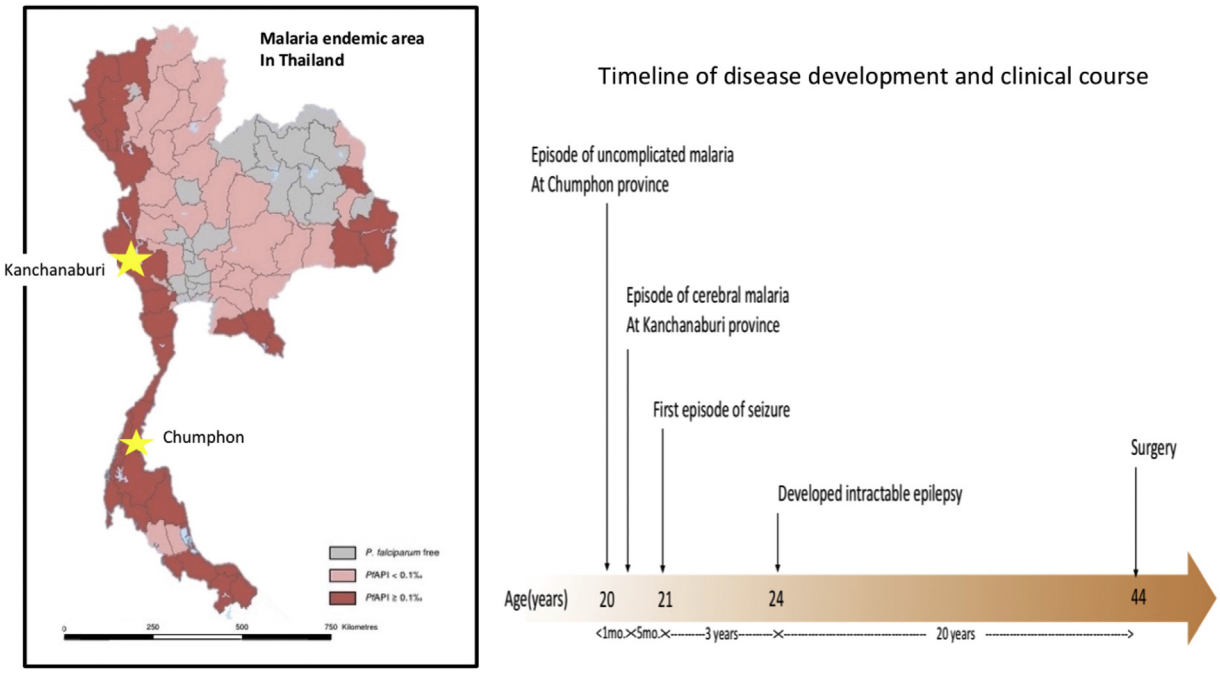

Fig. 1. Left side of the picture shows malaria endemic areas in Thailand (adapted from Malaria Atlas Project: http://www.map.ox.ac.uk/browse-resources/transmission-limits/Pf_limits/THA/). Yellow stars represent areas where the present case lived at the time of being infected with malaria. Areas in red have annual case incidence of malaria to likely exceed 1 per 10,000. Right side of the picture shows a timeline of disease development and clinical course of chronic epilepsy after cerebral malaria.

survive from CM, 10% developed epilepsy within 3 years [5]. In the present case, a temporal association between CM and epilepsy with interval of 5 months strongly points towards causality. HS and nonspecific subcortical white matter lesions in frontal lobes are structural sequelae of CM in this case. Previous autopsy studies indicated axonal injury as a key feature of CM [4]. The subcortical white matter changes identified

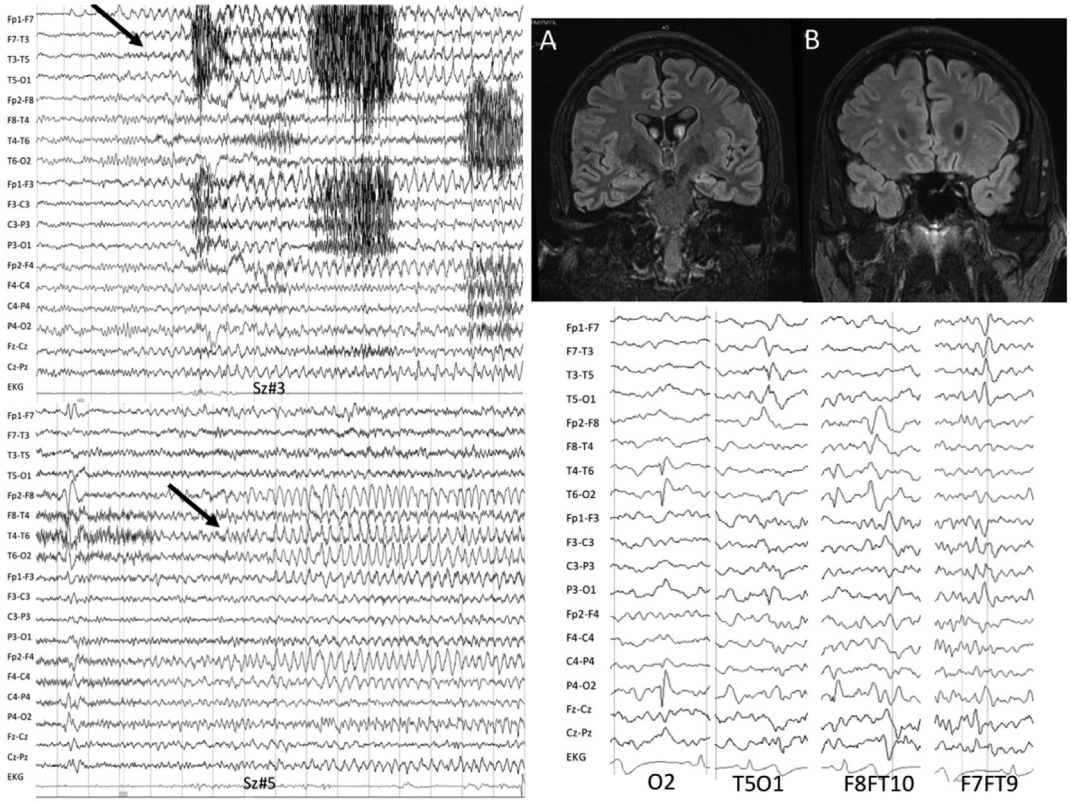

Fig. 2. Top right pictures are Fluid Attenuation Inversion Recovery (FLAIR) sequence MRIs in coronal views showing definite left hippocampal sclerosis and few tiny areas of increased signal intensity in subcortical white matter of bilateral frontal lobes. Bottom right pictures reveals interictal epileptiform discharges (IEDs) noted at O2, T5-O1, F8-FT10, and F7-FT9. Most pronounced IEDs are noted at O2, followed by T5-O1. Top left picture represents the majority (six out of seven recorded seizures) of the ictal EEG onset (antero-posterior bipolar montage, low-frequency filter 1 Hz, high-frequency filter 70 Hz, paper speed 15 mm/s, sensitivity 15 μV/mm) where they arise from left temporal region in the form of medium-amplitude rhythmic theta activity. Bottom left picture shows contradictory ictal EEG onset over right temporal region during one seizure (seizure # 5).

in CM survivors with sequelae may represent axonal injury caused by a broad range of cerebral insults that occur during CM including raised intracranial pressure (ICP) [5].

Drug-resistant multifocal epilepsy with temporo-occipital predominance was observed in the present case. Few reports of EEG features in acute phase of CM suggested that ictal and interictal discharges consistently arose from posterior temporo-parietal regions given that these areas are watershed zones, between the carotid and vertebra-basilar territories, which were compromised in blood supply secondary to ICP during acute phase of CM [6]. Despite the presence of multiple potential epileptic foci as a result of CM, a standard ATL with AHC can provide good seizure control with almost complete seizure freedom. Such successful outcome after a surgery in patients with multiple potential epileptic foci can also be seen in other conditions, for instance in patients with tuberous sclerosis complex [7]. In addition, seizure relief after ATL in a patient with posterior temporal lesion was also previously reported by Sperling et al. [8]. Some hypothetical reasons for being seizure-free after surgery even with multifocal spikes are 1) epileptic foci outside area of resection are related to epileptogenic tissue, but are still lacking capacity to spread due to interruption pathways necessary for it [9]; 2) these activities will undergo "running down" phenomenon over time [10]; or 3) some of these spikes are inhibitory spikes located outside the limits of epileptic foci [11]. One previous study showed that residual spikes outside the area of resection could be detected in 47% of patients with no seizures after ATL [12].

To the best of our knowledge, until now, there has been only one case report by Schijns [2] who described a 50-year-old male patient with mesial temporal sclerosis after CM. The patient achieved seizure freedom after ATL with AHC. He developed epilepsy with interval of 6 months after acute phase of CM. In contrast to our case, the patient had restricted epileptic focus limited to only anterior temporal region, although there was ictal spread to involve postero-temporal region during some seizures. Pathophysiology of HS development after CM in human is still unknown. In animals, however, there is evidence of compression of capillaries and ischemic demyelination, particularly in and around the hippocampal area identified in *Plasmodium berghei* infected mice [5]. Another case report of a 38-year-old male with epilepsy and CM had neuropsychological evidence of delayed memory deficit suggestive of temporal/hippocampal dysfunction, but brain MRI was remarkable [13]. Limited information about clinical characteristics of epilepsy after CM in 12 children was shown in the study of Birbeck [14]; however, no information in adults has been reported. This is likely due to under-investigated medical practices and treatment gaps for epilepsy in countries affected by malaria [15].

The Pathophysiology of CM-associated neurological impairment remains unclear. Possible mechanisms are sequestration of parasitized erythrocytes in the cerebral vasculature leading to brain hypoxia with resultant neuronal injury [16] and infection-induced fever inducing a release of proinflammatory and proconvulsant cytokines which possibly mediate a release of nitric oxide and neurotoxic glutamate [17].

4. Conclusion

In summary, there have been few reports of the clinical course of chronic epilepsy after CM. This report demonstrates a drug-resistant case of CM-induced HS. In addition, the present case demonstrates that even with multifocal potential epileptic foci in this condition, a successful surgical outcome after a standard ATL can be achieved.

Conflict of interest statement

The authors declare no conflict of interest.

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