Clinical commentary

Epileptic Disord 2012; 14 (3): 329-33

Seizure heralding tuberculous meningitis

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Received December 27, 2011; Accepted March 26, 2012

ABSTRACT – Seizures may frequently occur during tuberculous meningitis. We describe a patient with an apparent generalised tonic-clonic seizure, initially not associated with any magnetic resonance imaging (MRI) abnormality, which was the presenting symptom of tuberculous meningitis. Follow-up MRI, performed after gadolinium administration, showed signs of meningeal involvement. Seizures may be the presenting symptoms of tuberculous meningitis even in the absence of evident intracerebral lesions on MRI. Therefore, contrast-enhanced brain MRI should be performed in the diagnostic workup for each first seizure, especially in patients with a clinical suspicion of CNS infectious disease. The term "heraldic seizure", indicating a subset of acute symptomatic seizures presenting at the onset of a brain/systemic injury or preceding the full clinical manifestation of a cerebral insult, may be helpful to classify these seizures retrospectively, based initially on unknown aetiology.

Key words: acute symptomatic seizure, EEG, heraldic seizure, magnetic resonance imaging, tuberculous meningitis

Tuberculous meningitis (TBM) is one of the common infections of the central nervous system (CNS) representing a serious problem, not only in developing countries endemic to tuberculosis, but also worldwide, due to increased immigration. It is characterised by fever, headache, alterations of consciousness, vomiting, focal neurological deficits, and seizures.

Seizures have been reported to occur in TBM with variable incidence, ranging from 17 to 93% (Patwari *et al*., 1996). The aetiology of seizures is multifactorial, as they may result from increased intracranial pressure, cerebral oedema, hydrocephalus, meningeal irritation, tuberculomas, and cerebral ischaemic lesions (Patwari *et al*., 1996). All types of seizures may occur, especially motor focal or generalised tonic-clonic seizures (Patwari *et al*., 1996). Sporadic cases of TBM accompanied by non-convulsive status epilepticus have also been reported (Narayanan and Murthy, 2007; Arman *et al*., 2011).

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doi:10.1684/epd.2012.0516

We describe a patient with an apparent generalised tonic-clonic seizure, initially not associated with any magnetic resonance imaging (MRI) abnormality, which was the presenting symptom of TBM. To our knowledge, this is the first case of a seizure being the initial symptom of TBM in the absence of any intracerebral lesion documented by MRI.

Case report

A 42-year-old male, who recently emigrated from India to Italy, was admitted to our neurology clinic with complaints of confusion, apathy, malaise, fever, and long-lasting headache that had developed insidiously over a two-week period. Three weeks before, he had already been admitted to the neurology clinic for a diagnostic evaluation of an apparently generalised tonic-clonic seizure occurring after sleep deprivation. On that occasion, neurological examination, laboratory data (apart from increased creatine kinase), standard EEG, CT, and non-contrast enhanced brain MRI were normal. Physical examination revealed a thoracic subcutaneous lesion which was interpreted as an abscess and antibiotic treatment with clarithromycin (500 mg/day for 5 days) was started. Previous medical history was unremarkable and he denied alcohol consumption and did not take any drugs. The patient was discharged with a diagnosis of an apparent generalised tonic-clonic seizure (unprovoked seizure) and no antiepileptic treatment was started.

On his second admission to our neurological clinic, the examination revealed signs of mental alterations in the form of spatial and temporal disorientation. Neither sensory-motor deficits nor signs of meningeal irritation were evident, tandem gait was impaired, deep tendon reflexes could be elicited, and plantar reflexes were flexor. The thoracic subcutaneous lesion noted during the previous admission was still present.

Routine blood tests revealed an elevated white blood cell count of 12,000/mm^3, low erythrocyte count of 4,180,000/mm^3, high C-reactive protein level of 1.09 mg/dl, and low potassium level of 2.8 mmol/L. Cerebrospinal fluid (CSF) examination revealed a high protein level of 237.2 mg/dL (normal: 15-45), a low chloride level of 98 meq/l (normal: 120-130), a high lactate level of 6.9 mmol/L (normal: 1.1-2.4), and low CSF/serum glucose ratio of 0.17 (normal: >0.5); a marked pleocytosis (198 white blood cells/mm^3 [10% neutrophil granulocytes, 90% lymphocytes] and 26 red blood cells/mm^3) was present. A blood smear ruled out a diagnosis of malaria. CSF DNA polymerase chain reaction (PCR) was negative for adenovirus, cytomegalovirus, Epstein-Barr virus, herpes-simplex 1 and 2, and enterovirus. PCR resulted positive for Mycobacterium tuberculosis. A biopsy of the thoracic skin lesion was performed, revealing cutaneous tuberculosis. HIV serology resulted negative.

Direct thoracic radiography was normal. The low potassium level was not associated with ECG changes (ECG was normal). Follow-up comparison MRI showed a triventricular enlargement, without evident aqueductal stenosis, together with subependymal oedema and flattened cortical sulci. After gadolinium administration, a meningeal thickening and enhancement of the subarachnoid spaces and dura mater in the left temporal lobe were revealed (*figure 1*).

The EEG showed a pattern of diffuse slow waves without clear lateralisation or evident epileptiform abnormalities (*figure 2*).

During clinical follow-up of the patient, a diplopia due to a left abducens nerve palsy appeared. Based on the overall clinical picture of MRI, EEG, and CSF data, a diagnosis of TBM was made, and antibiotic treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol was started. Antiepileptic treatment with levetiracetam at 1,000 mg/day was also initiated. The patient's clinical picture progressively

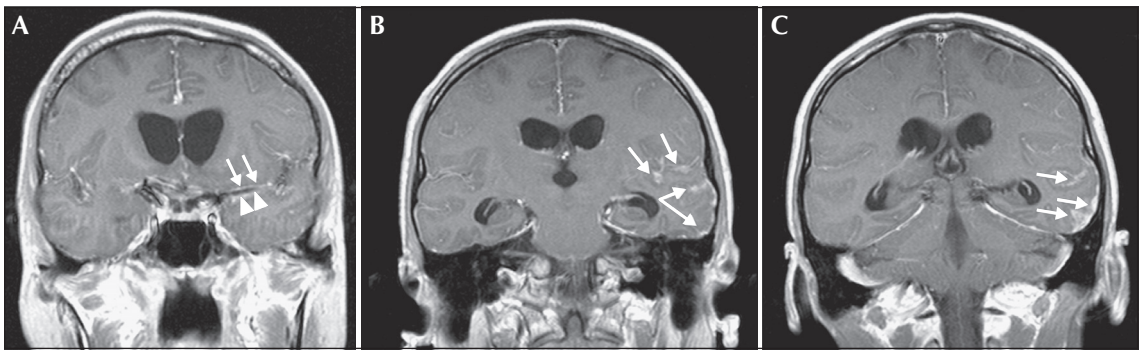

Figure 1. (A) Enhancement of the wall of the left middle cerebral artery (arrows) and upper surface of the left temporal pole (arrowheads) are noted (B) Thickening and enhancement of the subarachnoid spaces and >dura mater are noted in the left temporal lobe (arrows) Enhancement extends into the left Sylvian fissure (C) Irregular thickening of the dura mater and enhancement of the sulci in the left posterior temporal lobe are noted (arrows).

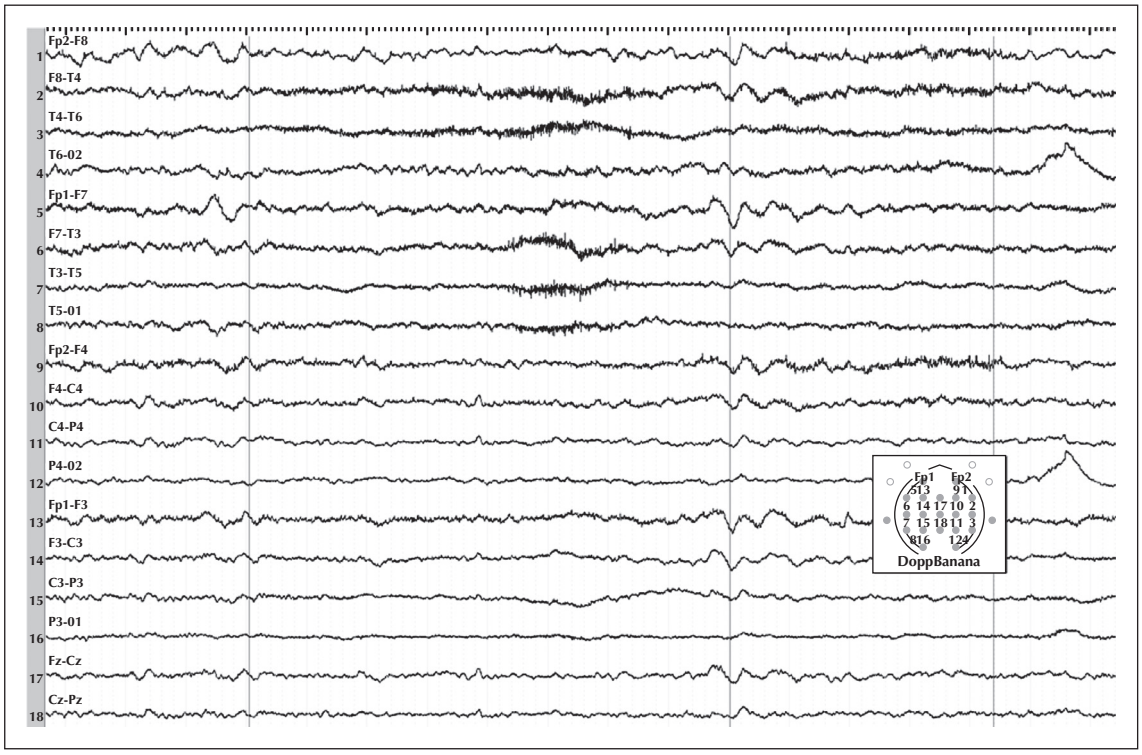

Figure 2. Pattern of diffuse EEG slow waves without clear lateralisation or evident epileptiform abnormalities. Sensitivity: 7 μV/mm; low filter: 0.53 Hz; high filter: 70.0 Hz; paper speed: 20 sec/page; each vertical bar: 1 sec.

improved, although mild residual cognitive deficit with psychomotor slowing, as well as the diplopia, still persisted at discharge. Since then (at one year of follow-up), he has had no more seizures.

Discussion

Seizures are a common clinical feature of TBM, occurring at any stage of the infection, with an estimated incidence ranging from 17 to 93% (Patwari *et al*., 1996), being lower in adults than in children (Arman *et al*., 2011). They cause an additional burden of disability, producing neurological deficits which are a significant predictor of mortality (Paganini *et al*., 2000), often requiring long-term, antiepileptic therapy. The aetiology of seizures in TBM is multifactorial and is related to pathophysiological changes occurring during the disease process. Cerebral oedema, meningeal irritation, and raised intracerebral pressure are thought to represent the most probable cause of seizure in the early phase of TBM, and hydrocephalus and arteritis in the later stage (Patwari *et al*., 1996). Other factors which are responsible for seizure activity are tuberculomas (single or multiple) and cerebral infarctions.

Epilepsy is relatively common in CNS tuberculosis, but its natural course is unclear. Although definite data on prognosis of epilepsy in patients with seizures related to TBM are not available, a recent study has demonstrated that seizures associated with tuberculomas most often resolve after successful treatment of the underlying CNS tuberculosis (Alsemari *et al*., 2012). It is also noteworthy to consider the epileptogenic potential of isoniazid, one of the most widely used anti-tuberculosis drugs. An acute overdose of this drug is potentially fatal and is characterised by the clinical triad of: repetitive seizures unresponsive to the usual anticonvulsants, metabolic acidosis, and coma (Temmerman *et al*., 1999). However, seizures occurring after single conventional doses of isoniazide have also been reported (Gupta *et al*., 1984).

Seizures can be the presenting feature of TBM, especially in children (Arman *et al*., 2011). To our knowledge, there is no previously reported case of a seizure as the initial symptom of TBM in the absence of any intracerebral lesion documented by MRI. In fact, the absence of cerebral abnormalities on initial MRI (as well as the absence of relevant EEG abnormalities) ruled out any possible association between the seizure and intracranial lesions, such as tuberculomas, hydrocephalus and infarctions. However, it should be considered that the initial MRI was performed without contrast and we could not definitively confirm the presence of leptomeningeal enhancement as the

possible cause of seizure in our patient. The full development of the typical clinical picture within a few days, together with neurological and CSF findings strongly supporting the diagnosis of meningitis, argued in favour of a correlation between the seizure experienced by the patient and the infectious process. Indeed, follow-up cerebral MRI, performed after gadolinium administration, showed thickening and enhancement of the subarachnoid spaces and *dura mater* in the left temporal lobe. Despite a more prominent involvement of the left temporal lobe, the EEG features of the patient revealed a pattern of diffuse slowing, which is the usual pattern encountered in TBM (Kalita and Misra, 1998). The absence of clear-cut lateralisation is an additional feature pointing to a widespread meningeal irritation as the most likely cause of the seizure experienced by the patient.

It is reasonable to hypothesize that the initial meningeal irritation, occurring in the first stage of the infectious process, was most likely responsible for the seizure, also considering the fact that there were no other reasons which could potentially explain the trigger of epileptic activity or decrease of seizure threshold. As a consequence, it could be argued that our first diagnosis of unprovoked seizure was not completely correct, considering the subsequent clinical evolution. The patient probably had an acute symptomatic seizure (Hauser and Beghi, 2008) preceding the full clinical manifestation of the infectious disease.

Although tuberculosis may frequently occur in subjects with immunodepression, such as AIDS patients (Chamie *et al*., 2010), in our case we did not find any cause of immunodeficiency (HIV infection, granulocytopenia, or T-cell deficiency).

We believe the term "heraldic seizure" may be appropriate to define the seizure experienced by our patient, since the full clinical manifestation of the infectious process was "heralded" several days later. This term, which is not included in the ILAE seizure classification (Commission, 1981), has been used to define epileptic seizures caused by cerebrovascular disease, occurring immediately before, and thus "heralding", a stroke (Garcìa-Garcìa *et al*., 2004; Brigo *et al*., 2011). Heraldic seizures may therefore represent a subset of acute symptomatic seizures (currently defined as those events presumed to be an acute manifestation of a brain insult, occurring at the time of, or in close temporal association with, a cerebral or systemic injury) (Hauser and Beghi, 2008; Commission, 1993). We propose to use this term with regards to: 1) seizures as the first sign of a cerebral or systemic insult; and 2) seizures preceding the full clinical manifestation of a cerebral insult, which at the time of the epileptic event is not definitively demonstrated. Unlike the term "acute symptomatic seizure", which by itself does not provide any chronological specification, the term "heraldic seizure" should be reserved for those seizures occurring *before* a diagnosis of brain/systemic insult, underlying and causing the epileptic events, is definitively made. The diagnosis of "heraldic seizures" should therefore be retrospective and made when a direct/indirect causal association between seizures and systemic/cerebral insult has been demonstrated, according to the widely accepted Bradford Hill's criteria for causation (which include, among others, temporal relationship, plausibility, and consideration of alternative explanations) (Hill, 1965). When used with regards to seizures preceding the full clinical manifestation of a cerebral insult, which is not definitively demonstrated at the time of the epileptic event, the term "heraldic" may be helpful to classify these seizures retrospectively, based initially on unknown aetiology.

In conclusion, this case study suggests that seizures may be the presenting symptom of TBM, even in the absence of evident intracerebral lesions on MRI. Contrast-enhanced brain MRI should therefore be performed in the diagnostic workup for each first seizure, especially in patients with a clinical suspicion of CNS infectious disease. The term "heraldic seizure", indicating a subset of acute symptomatic seizures presenting at the onset of a brain/systemic injury, or preceding the full clinical manifestation of a cerebral insult, may be helpful to classify these seizures retrospectively, based initially on unknown aetiology. □

Disclosures.
None of the authors has any conflict of interest to disclose.

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