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A case of post-leptospirosis autoimmune epilepsy presenting with sleep-related hypermotor seizures

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ABSTRACT – This video-illustrated case report concerns a 49-year-old woman who presented with sleep-related hypermotor seizures. The antecedent history of leptospirosis, high frequency of new-onset seizures, presence of an unclassified anti-neuronal antibody, and dramatic response to steroids strongly supported post-infectious immune-mediated pathogenesis in our patient. To the best of our knowledge, post-leptospirosis autoimmune epilepsy presenting as sleep-related hypermotor seizures has not hitherto been reported. [*Published with video sequence on www.epilepticdisorders.com*].

Key words: autoimmune encephalitis, autoimmune epilepsy, leptospirosis, sleep-related hypermotor seizures

Leptospirosis is a zoonosis with worldwide distribution (Bharti *et al*., 2003). The disease results from infection caused by spirochetes belonging to the genus *Leptospira* (Levett, 2001). The clinical presentation may vary from a subclinical infection or a self-resolving febrile illness, to a fulminant illness with multisystem involvement (Bharti *et al*., 2003). Neurological manifestations, though uncommon, have been reported in the post-leptospiremic phase of the illness (Bharti *et al*., 2003). The pathogenesis of neurological manifestations is considered to be immune-mediated (Bharti *et al*., 2003). Additional direct invasion of the central nervous system by the spirochete has only rarely been reported (Schiefecker *et al*., 2015).

Epilepsy with sleep-related hypermotor seizures is a rare form of focal epilepsy (Tinuper *et al*., 2016). Aetiology is heterogeneous with genetic, lesional, and cryptogenetic forms described (Nobili *et al*., 2014). Autoimmune epilepsy (AE), as a cause of sleep-related hypermotor seizures, has not yet been described, to the best of our knowledge. Here, we report a unique case of post-leptospirosis autoimmune epilepsy with sleep-related hypermotor seizures.

VIDEO ONLINE

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Case study

A 49-year-old woman on thyroid replacement therapy (Eltroxin at 50 μg) for the last two years was hospitalized and treated for leptospirosis six weeks prior to admission. She presented to us with frequent episodes of paresthesia involving one half of the face which occurred in the previous 10 days. The patient described the episodes as an electric shock-like sensation, which initially involved the right half of the face and extended up to the neck, lasting for a few seconds and recurring every two to three hours. After four days from the onset, she developed similar complaints involving the left side, which would occasionally extend up to the left side of the trunk or the entire left half of the body. These episodes occurred exclusively while she was asleep and were witnessed by her husband who also noticed her suddenly waking from sleep with jerk-like movements of the right upper extremity during these episodes. There were no other associated symptoms. Her neurological examination was unremarkable, including intact higher mental functions and cortical sensations. She was initially treated at a peripheral hospital with three antiepileptic drugs (AEDs) (levetriacetam at 750 mg/day, clobazam at 5 mg/day, and phenytoin at 200 mg/day) without significant benefit.

The patient was admitted to our centre for video-EEG (VEEG) monitoring to capture the events. She had 60 stereotyped events during a 24-hour monitoring period. All the events occurred out of sleep, were very brief, and lasted for less than 10 seconds. Clinically, they were characterized by sudden hypermotor movements of the right upper and lower limbs, and turning of the face to the right side with abnormal posturing of the right hand. In some of the events, the left upper limb was also involved. The interictal EEG was normal and the ictal EEG consisted of diffuse attenuation of background activity after which the EEG was obscured by myogenic artefacts (*figure 1; video sequences*).

The patient was further investigated to identify an underlying aetiology. Her routine haemogram, biochemical parameters, gynaecological examination, and pelvic ultrasonogram were normal. She was euthyroid (TSH: 2.0459 μIU/ml) and thyroid antibody levels were normal (thyroglobulin antibody: 3.59 IU/ml; anti-TPO: 1.11 U/ml). Her CSF examination showed 2 cells/mm3, all lymphocytes, with glucose at 61 mg/dl (corresponding blood glucose was 90 mg/dl) and protein at 44.1 mg/dl. Her brain MRI was normal (*figure 2*). In view of the recent history of leptospirosis (IgM ELISA positive: 18.888 PB units) and very high frequency of new-onset seizures, an autoimmune aetiology was investigated. Tests with antibodies against N-methyl-D-aspartate (NMDA), gamma amino butyric acid (GABA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA 1 and 2),

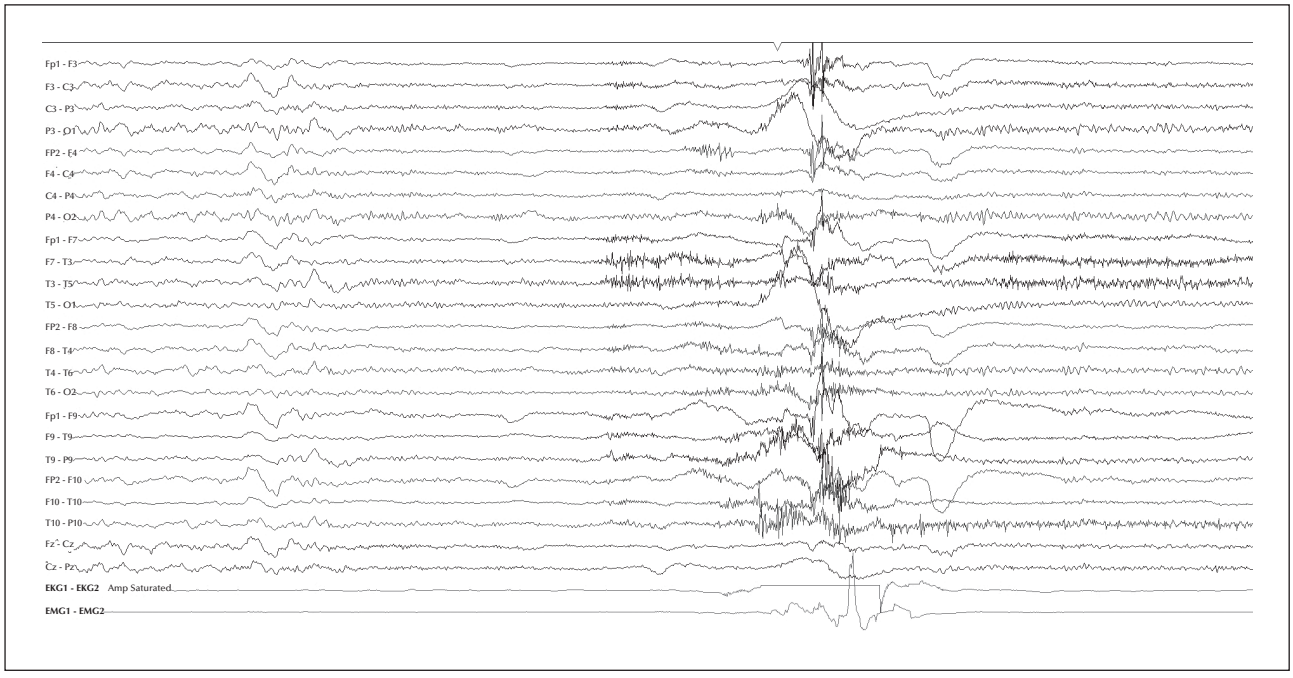

Figure 1. The initial part of the EEG shows a recording during sleep with a subsequent attenuation of background as the patient is aroused; the background is subsequently obscured by myogenic artefacts associated with a hypermotor event.

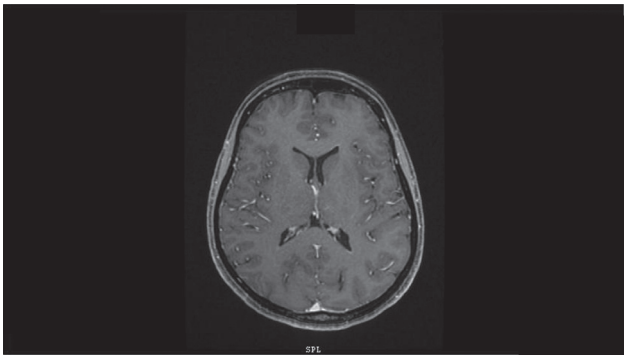

Figure 2. Normal axial T1 with contrast MRI of the patient.

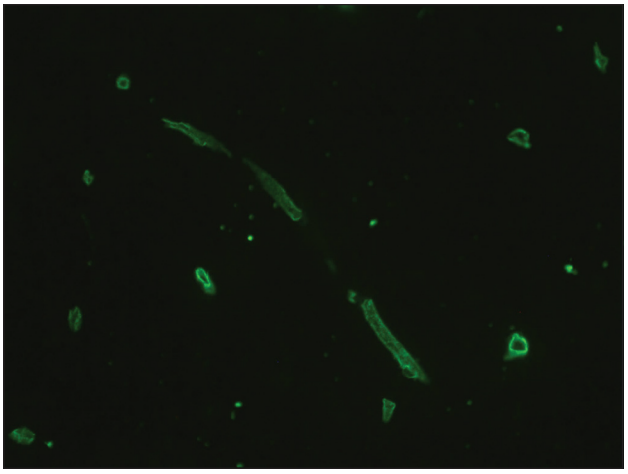

Figure 3. Indirect immunofluorescence of monkey cerebellum (x40) showing antibodies binding to cerebellar capillaries.

voltage-gated potassium channel (leucine-rich glioma associated protein [LGI]1/contactin-2 associated protein [CASPR 2]), and glutamic acid decarboxylase (GAD), as well as known paraneoplastic antibodies (anti-neuronal nuclear antibody [ANNA] 1, 2 and 3, anti-glial nuclear antibody [AGNA] 1, purkinje cell cytoplasmic antibody [PCA] 1, 2 and Tr, amphiphysin antibody, anti-collapsin response mediator protein [CRMP]-5, and anti-Ma/Ta antibody) were all negative. However, she tested positive for an unclassified anti-neuronal antibody binding to the cerebellar capillaries (*figure 3*).

We considered our patient to have an AE in view of the recent leptospiral infection (post-infectious), the explosive onset of seizures, and the presence of an unclassified neuronal antibody. She was managed with intravenous methylprednisolone at 1 g daily for five days, followed by oral steroids (prednisolone at 1 mg/kg), along with oxcarbazepine monotherapy (300 mg twice a day). She showed a dramatic response to the above therapy and her seizures completely resolved within a week. She was discharged on oral steroids and oxcarbazepine. She has received regular follow-up visits for the last 11 months and has remained completely seizure-free. She has also been off steroids for the last seven months and off oxcarbazepine for the last five months.

Discussion

Leptospirosis is an emerging global zoonotic disease, more commonly seen in the tropics (Bharti *et al*., 2003). Human infection results from contact with urine from an infected animal, with the pathogenic organism gaining access through mucosa or abraded skin (Levett, 2001). The pathogenic organism belonging to the genus *Leptospira*, is a spirochete, a highly motile, coiled organism. Currently, the genus includes 20 named species, nine of which are pathogenic and five are intermediately pathogenic (Levett, 2001).

The clinical manifestations of leptospirosis are diverse. While most infections are subclinical or present as undifferentiated febrile illness, others may present with a fulminant form of the illness resulting in jaundice, renal failure, and sometimes fatal pulmonary haemorrhage. The reason behind this varied clinical presentation is unknown, but may be related to a combination of host immunity, as well as virulence of the strain (Bharti *et al*., 2003).

Neurological involvement is seen in 10-15% of patients with leptospirosis (Mathew *et al*., 2006). The pathogenesis of neurological involvement is considered to be immune-mediated (Bharti *et al*., 2003), though rare primary neurological involvement is also reported (Schiefecker *et al*., 2015). The spectrum of neurological involvement includes aseptic meningitis, polyneuritis, meningoencephalitis, myelopathy, and intracranial haemorrhage (Panicker *et al*., 2001; Mathew *et al*., 2006). Epilepsy as a neurological manifestation of leptospirosis has not yet been fully elucidated. Extensive work-up for epilepsy was performed for our patient and was negative, except for positive leptospiral antibodies and an unclassified neuronal antibody. Neuronal antibodies that do not fall into the category of known antibodies are frequently encountered in neuroimmunological laboratory practice (Kannoth *et al*., 2016). Although their aetiological role at present is uncertain, the presence of unclassified neuron-specific antibodies in our patient may be a pointer to nervous system autoimmunity. Hypothyroidism has been reported to have a significant association with other autoimmune diseases (Boelaert *et al*., 2010). Although it could be speculated that hypothyroidism would have predisposed our patient to a post-infectious autoimmune process, this association is probably coincidental.

Autoimmune encephalitis includes a group of antibody-associated syndromes characterized by immune-mediated encephalopathy (Pruitt, 2011). The classic presentation consists of a subacute course with fluctuating cognition, associated with psychiatric symptoms, seizures, and movement disorders (Lancaster, 2016). The antibodies that are particularly associated with seizures include anti-NMDAR, anti-GABA-A and B, anti-GAD65, and anti-LGI1 (Lancaster, 2016).

However, AE is an ill-defined entity with no universally applicable criteria. Current literature, including the criteria proposed for AE, places overemphasis on antibodies while giving less weight to post-infectious autoimmunity and the response to immunotherapy (Suleiman *et al*., 2013). However, our case exemplifies an opportunity to treat refractory focal epilepsy with immunotherapy despite an absence of defined antibodies.

Epilepsy with sleep-related hypermotor seizures is a rare form of focal epilepsy with an estimated prevalence of 1.8/100,000 individuals (Tinuper *et al*., 2016). The aetiology is heterogeneous with genetic, lesional, and cryptogenic forms described. Among the symptomatic drug-resistant cases, focal cortical dysplasia (FCD) type II is the most common aetiology (Nobili *et al*., 2014), particularly of the FCD IIb type. Typically, the seizures are abrupt at onset and termination, brief (<2 minutes), and stereotyped (Tinuper *et al*., 2016). The clinical expression includes hypermotor events associated with hyperkinetic features, vocalization, and emotional facial expression (Tinuper *et al*., 2016). Clustering is commonly observed, but not necessary (Tinuper *et al*., 2016). In many cases, interictal EEG, and sometimes even the ictal EEG, may be uninformative (Provini *et al*., 1999).

Our patient presented to us in post-leptospiremic immune phase. In contrast to our case, autoimmune encephalitis usually has a subacute course with neurocognitive impairment, seizures, and movement disorders. The sleep-related hypermotor seizures in our patient responded dramatically to steroids and the AED could be tapered off and stopped, with the patient continuing in remission for nearly one year during follow-up. Autoimmune encephalitis presenting with isolated seizures that occur exclusively during sleep is atypical and has not previously been reported to the best of our knowledge. The antecedent history of leptospirosis, high frequency of new-onset seizures, presence of an unclassified anti-neuronal antibody, and dramatic response to steroids supports an immune-mediated pathogenesis in our case. A micro-agglutination test was not performed and is a limitation in the present case report, however, IgM ELISA which was used in this case has been reported to exhibit high sensitivity and specificity; in the study of Mulla *et al*. (2006), IgM ELISA was reported to show a sensitivity of 88% and specificity of 91%. Moreover, IgM ELISA has been recommended by the WHO as a diagnostic test for the serodiagnosis of leptospirosis in resource-poor settings (Desakorn *et al*., 2012).

Conclusions

Our patient highlights the varied and atypical presentation of neuroleptospirosis. Although autoimmune encephalitis has been classically described as a cluster of cognitive and behavioural symptoms, epilepsy, and movement disorders, our patient demonstrated a presentation similar to that of a pure epilepsy syndrome. While the aetiology of epilepsy with sleep-related hypermotor seizures is often genetic or related to the presence of a FCD, our patient stands out as a unique example with a post-infectious autoimmune aetiology. This case report also underscores the need for diagnosing AE based on clinical criteria and response to immunotherapy without overdependence on the presence of classically described antibodies. To the best of our knowledge, this case is the first report of neuroleptospirosis presenting as AE with a dramatic and sustained response to immunotherapy. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

Legend for video sequence

Clinical: The event occurs out of sleep and is abrupt at onset; the patient awakens from sleep, with asymmetric dystonic posturing of the upper extremities and jerking (more pronounced on the right than left). The event is brief, and the patient is immediately responsive after the event and also able to move her limbs when asked to do so.
EEG: Background activity attenuates, and the EEG is subsequently obscured by myogenic artefacts.

Key words for video research on www.epilepticdisorders.com

Phenomenology: brief hypermotor events, hypermotor seizures
Localisation: left hemispheric, extra-temporal, probably frontal
Syndrome: epilepsy with sleep-related hypermotor seizures
Aetiology: autoimmune

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TEST YOURSELF

(1) Which of the following is not a characteristic feature of sleep-related hypermotor epilepsy?
A. Brief (<2-min) stereotyped motor events with abrupt onset and offset
B. Automotor seizures
C. Can occur during an awake state
D. Mostly frontal in origin

(2) Which of the following is not diagnostic of autoimmune epilepsy?
A. Recent and explosive onset of seizures (<3 months)
B. Associated neurocognitive deficits and movement disorders
C. Good response to immune therapy
D. Good response to antiepileptic drugs

(3) Which of the following is not a common neurological manifestation of leptospirosis?
A. Aseptic meningitis
B. Meningoencephalitis and myelitis
C. Trigeminal neuralgia
D. Guillain-Barre syndrome
E. Mononeuritis multiplex

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".