

# Primary antiphospholipid syndrome manifesting as partial status epilepticus

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### ABSTRACT

تعد متلازمة مضادات الدهون الفسفورية مرض مناعي عرف بتخثر الأوعية ومضاعفات الحمل واستخدام مضادات الدهون الفسفورية المستمرة. أما الأعراض العصبية فتشمل الجلطة، والرجفة والتشنج من بين الأعراض الأخرى. تساعد الحالة الإقفارية في ظهور التشنجات التي تظهر من حين لآخر. نستعرض في هذا التقرير حالة مريض يبلغ من العمر 61 عام والذي تطور لديه تشنج جزئي تطور إلى حالة صرع. كانت هذه التشنجات مقاومة للأدوية وإحتاج إلى خطة علاجية قوية مع أدوية عديدة مضادة للصرع. تم تشخيصه بمتلازمة مضادات الدهون الفسفورية وتم علاجه بمضادات التخثر. لم تظهر إي حالة إقفارية في تصوير الرأس. أظهر هذا التقرير أن متلازمة مضادات الدهون الفسفورية الأولية تعكس حالة صرع غير مرتبط بإقفار الدماغ الحاد.

Primary antiphospholipid syndrome (APS) is an autoimmune disease defined by vascular thrombosis, pregnancy complications, and persistent antiphospholipid antibodies. Neurological manifestations include stroke, seizures, and chorea among others. Seizures are often precipitated by an acute ischemic event, but occasionally, structural abnormalities are absent. We present a 61-year-old man who developed partial seizures that progressed into partial status epilepticus. His seizures were intractable and required aggressive treatment with multiple anti-epileptic medications. He was diagnosed with primary APS and treated with anticoagulation. Head imaging did not reveal any acute ischemic events. This case demonstrates that primary APS may present as a refractory status epilepticus unrelated to acute cerebral ischemia.

*Neurosciences 2013; Vol. 18 (2): 160-162*

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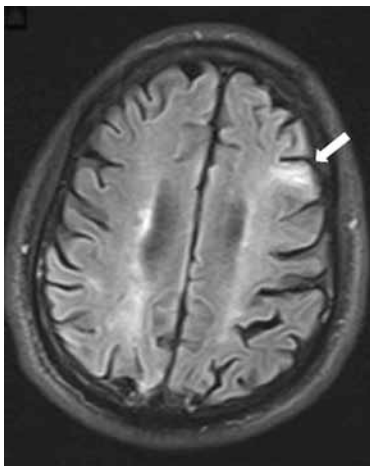
*Received 6th September 2012. Accepted 23rd December 2012.*

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Antiphospholipid syndrome (APS) is a systemic autoimmune disease that usually affects young adults before the fifth decade of life. It is defined by the presence of vascular thrombosis or pregnancy morbidity and positive antiphospholipid antibodies (APA) including lupus anticoagulant, anticardiolipin antibody, and anti- $\beta$ 2 glycoprotein-I antibody, on 2 or more occasions at least 12 weeks apart.<sup>1</sup> We recently encountered a 61-year-old man with partial status epilepticus (PSE). Brain imaging failed to reveal an underlying structural lesion. Extensive work up was consistent with primary APS. We hypothesize that APS causes PSE, probably via an immunological mechanism. Our objective in presenting this case is to highlight the role of auto-immunity in the differential diagnosis of seizures with unknown etiology.

**Case Report.** A 61-year-old man with hypertension and eosinophilia presented with brief jerking episodes of the right lower extremity. A head and spine MRI with head and neck magnetic resonance angiography (MRA) were unrevealing except for a remote infarct in the watershed between the left anterior and middle cerebral arteries (Figure 1). Work up revealed elevated APA including lupus anticoagulant (71.4 sec [normal 28.8-37.6 sec]), and anticardiolipin (104 IgG phospholipid units [GPL] [normal 0-14 GPL]). An EEG did not record epileptiform discharges concurrent with these jerks and these movements were considered psychogenic in origin. He was readmitted a few months later with similar jerks now affecting the left lower extremity. The head MRI was unchanged. Lumbar puncture yielded clear CSF, 24 white blood cells, with normal glucose and protein content. Bacterial and fungal cultures, cryptococcal antigen, and cytology were all negative. The APA levels remained elevated (lupus anticoagulant > 200 sec, anticardiolipin 101 GPL, anti- $\beta$ 2 glycoprotein-I antibodies >150 standard G units [SGU] [normal 0-20 SGU]). Antiphospholipid syndrome was diagnosed and warfarin started. He continued to have episodic left arm and leg jerks with

head turning to the left. Multiple intravenous doses of lorazepam (1-2mg) and a loading dose of fosphenytoin (20 mg/kg) limited the jerks to the left leg, but they became persistent. Continuous EEG showed right parieto-occipital semi-periodic spike and slow waves occurring every 1-2 seconds (Figure 2), so PSE was diagnosed. Over the following few days, levetiracetam 2g intravenously twice daily, valproate 1g intravenously twice daily, and phenobarbital 60mg twice daily were added, but only suppressed the seizures partially. He was intubated and given midazolam continuous infusion that aborted the clinical and electrographic seizures. A third head MRI was unchanged. Midazolam was tapered off gradually over the following 3 days with persistent control of the seizures, and eventually he was extubated. He was discharged to a rehabilitation facility with residual left hemiparesis on oral phenytoin 300mg daily, levetiracetam 2g daily, and warfarin 5mg daily. Three weeks after discharge, he presented again with unremitting left lower extremity myoclonic jerks for 2 hours, aborted temporarily with 4mg of intravenous lorazepam. An EEG showed frequent ictal discharges of the right posterior quadrant onset, with subsequent spread in the right hemisphere that correlated with recurrent clinical partial seizures. The phenytoin level was sub-therapeutic, so the dosage was increased, and phenobarbital was restarted. His seizures subsided 4 days later. Two weeks following discharge he was started on Plaquenil 400mg daily when evaluated by the rheumatology service. Upon follow up by neurology 2 months later, he remained seizure free.



**Figure 1** - Head MRI axial view, fluid-attenuated inversion recovery (FLAIR) sequence, performed during the first admission, showed FLAIR hyperintensity (arrow) in the watershed between the left anterior and middle cerebral arteries suggestive of a remote infarct.

**Discussion.** In addition to vascular thrombosis and pregnancy morbidity (fetal loss, fetal growth restriction, or preeclampsia), other clinical manifestations of APS include valvular heart disease, renal thrombotic microangiopathy, thrombocytopenia, hemolytic anemia, and livedo reticularis.<sup>2</sup> Common neurological manifestations are cerebrovascular, but also include migraine, epilepsy, and chorea.<sup>3</sup> Patients with APS and arterial thrombosis are treated with warfarin for life.<sup>4</sup> Antiphospholipid syndrome vasculopathy is hypothesized to occur via activation of endothelial cells, monocytes, and platelets, resulting in overproduction of tissue factors and thromboxane A2. Associated seizures are often caused by ischemia, but occasionally, structural abnormalities are absent. In these cases, it is hypothesized that seizures occur secondary to microvascular ischemia, which increases blood-brain-barrier permeability, leading to neurotoxicity from an influx of autoantibodies and cytokines.<sup>3</sup> In our patient, the ischemic changes in the left hemisphere were old and topographically unrelated to the seizures; thus, inconsistent with an ischemic stroke as the underlying cause. Based on an unrevealing extensive MEDLINE literature search, we were unable to identify a previous case of nonstructural related PSE in a patient with primary APS.

Simple partial seizures are often not associated with scalp EEG ictal discharges. Unfamiliarity with this fact might have contributed to the initial misdiagnosis of non-epileptic events in our patient. Because response to treatment is usually poor, and in inexperienced hands,



**Figure 2** - Ictal EEG showing right parieto-occipital semi-periodic spike and slow waves occurring at 1-2 seconds intervals (arrows).

aggressive management could result in complications that are more serious than the disease itself, early diagnosis, and treatment of the underlying cause are important.

Autoimmune neurologic disorders, particularly limbic encephalitis and paraneoplastic diseases, can manifest as seizures. Associated autoantibodies include antineuronal nuclear antibody type 1, collapsin response-mediator protein 5 (CRMP-5), Ma2, voltage-gated potassium channel complex, glutamic acid decarboxylase 65, N-methyl-D-aspartate,  $\gamma$ -aminobutyric acid B, and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.<sup>5</sup> In recent years, there has been growing evidence supporting an autoimmune etiology underlying drug-resistant seizures.<sup>5</sup> Such seizures may benefit from immunotherapy in addition to anti-epileptic medications.<sup>5</sup>

In conclusion, we suggest that APS should be considered in patients with PSE lacking causal structural brain abnormalities. Although immunotherapy was not required to control our patient's seizures in the acute

setting, we advocate that it should be considered in cases of intractable seizures secondary to APS, especially when anti-epileptic drugs fail to achieve complete seizure control.

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