Title: Antiphospholipid-related chorea

Authors: Mena Farag¹, Beverley J Hunt², Thomasin C Andrews¹

Dr Mena Farag¹ BSc (Hons), MBBS, MRCP (UK), PGCert (Dist)

Professor Beverley J Hunt² MD, FRCP, FRCPath

Dr Thomasin C Andrews¹ MD, BSc, FRCP

Affiliations:

¹ Department of Neurology, Guy’s and St Thomas’ NHS Foundation Trust, St Thomas’ Hospital, Westminster Bridge Road, London, SE1 7EH

² Thrombosis & Haemophilia Centre, Guy’s and St Thomas’ NHS Foundation Trust, St Thomas’ Hospital, Westminster Bridge Road, London, SE1 7EH

Correspondence to:

Dr Mena Farag

Department of Neurology

Guy’s and St Thomas’ NHS Foundation Trust

St Thomas’ Hospital

Westminster Bridge Road

London, SE1 7EH

E-mail: mena.farag@nhs.net

Mena Farag https://orcid.org/0000-0002-0679-0117

Keywords: CLINICAL NEUROLOGY; MOVEMENT DISORDERS; PET, FUNCTIONAL IMAGING
Disclosures:

All authors satisfy the ICMJE criteria for authorship.

The authors declare that there are no conflicts of interest relevant to this work. The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

The authors declare that there are no additional disclosures to report.

Ethical Compliance Statement:

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Written informed patient consent has been obtained to publish.
Abstract:

Chorea can be associated with autoimmune diseases such as antiphospholipid syndrome and has been associated with the isolated presence of antiphospholipid antibodies (aPL). Chorea is a rare neurological manifestation of antiphospholipid syndrome. The pathophysiological mechanisms underlying aPL-related chorea are still debated. One postulated mechanism is aPL or other autoantibody binding to brain-blood vessel endothelium, resulting in endothelial dysfunction secondary to a proinflammatory cascade, with sequelae of inflammation and local microthrombosis. Another postulated mechanism considers immune-mediated attack (aPL or antibasal ganglia antibodies) against specific basal ganglia epitopes. Here, we report a patient with isolated aPL-related chorea that followed a relapsing-remitting course. We highlight the role of brain metabolic imaging with fluorodeoxy glucose positron-emission tomography in the diagnostic workup of chorea and the challenges in the practical management of aPL-related chorea with symptomatic treatments.
Introduction:

Chorea is a hyperkinetic movement disorder that has a wide differential diagnosis, including inherited/degenerative, autoimmune (including post-infectious), metabolic, structural and drug-related causes. Chorea can be associated with autoimmune diseases such as antiphospholipid syndrome (APS) and has been associated with the isolated presence of antiphospholipid antibodies (aPL). Chorea is a rare neurological manifestation of APS with a prevalence of 1.3% reported in one cohort of one thousand APS patients in Europe. Chorea of subacute onset is a movement disorder that typically has a monophasic course. 80% of chorea presenting in pregnancy as chorea gravidarum occur during the first trimester and typically affects young primigravids. In the literature of patients with systemic lupus erythematosus and chorea, the duration of chorea is typically short-lived with a mean duration of approximately eight weeks, similar to Sydenham’s chorea, but with the tendency to relapse being only occasional. Here, we report the case of a patient with isolated aPL-related chorea that followed a relapsing-remitting course.

Case Report:

A forty-two-year-old woman with a background of migraine with aura developed chorea gravidarum within the first week post-partum during her first pregnancy, aged thirty-three, and again fourteen weeks into her second pregnancy aged thirty-five (Figure 1: 1-2). She presented with asymmetric hyperkinetic choreiform movements of the limbs and oromandibular area. Family history was remarkable for pulmonary embolism (father) and rheumatoid arthritis (aunt). There was no prior history of combined oral contraceptive use or exposure to dopamine-receptor blocking drugs.

Investigations were remarkable for high titre triple positivity of aPL (anti-cardiolipin antibodies, anti-β-2-glycoprotein-I (anti-β-2-GPI) antibodies and positive lupus anticoagulant) and intermittently raised antistreptolysin O titre (400 IU/ml (reference: 0-200 IU/ml). Recent aPL titre levels remained persistently raised: anti-cardiolipin 1160.9 u/mL (reference: 0.0-12.1 U/mL), IgG anti-β-2-GPI 3298.5 U/mL (reference: 0.0-10.0 U/mL), dilute Russell’s viper venom time (dRVVT) 1.73 ratio (reference: 0.85-1.17 ratio) with persistence presence of lupus anticoagulant by dRVVT and dilute activated partial thromboplastin time analysis. Blood tests were normal or negative for TSH, calcium, copper, caeruloplasmin, anti-DNAase B, basal ganglia antibodies, ANA, anti-dsDNA, Caspr2/LGi1/NMDAR antibodies.

MRI brain showed an incidental pineal cyst and no basal ganglia lesion or signal change with serial imaging showing stable appearances with no cause for chorea identified. Brain FDG-PET-CT raised the possibility of hypermetabolism in the left basal ganglia and mild temporal hypometabolism bilaterally (Figure 2).
The chorea remitted within nine months of her first delivery, noting she took only aspirin during her first pregnancy. In the last trimester of her second pregnancy the choreiform movements were not particularly marked. Around seven weeks post-partum, she developed very marked choreiform movements and became clumsy and somewhat impulsive and repetitive. She received treatment with low-molecular-weight-heparin (for six weeks for thromboprophylaxis), prednisolone and intravenous immunoglobulin, while breastfeeding. Tetrabenazine was trialled, as the involuntary movements were troublesome, and this helped to suppress chorea, though lowered her mood. The chorea remitted within twenty-four months. She developed a recurrence of unprovoked chorea three years later (Figure 1: 3), when she was not pregnant or taking hormone therapy. Olanzapine was trialled with benefit and her movements and mood symptoms of hypomania improved. She relapsed with a fourth recurrence of chorea two years later (Figure 1: 4) and recommenced olanzapine. She received pulsed oral methylprednisolone 500mg for five days, commenced immunotherapy with azathioprine then weaned off olanzapine. On last review she reached a dose of azathioprine 150mg daily with minor symptomatic improvement in the chorea, though reported possibly better control of choreic involuntary movements when taking olanzapine. She discontinued azathioprine in May and reported no discernible change or difference in the chorea since coming off this medication.

Discussion:

The pathophysiological mechanisms underlying antiphospholipid-related chorea are still debated. One postulated mechanism is aPL or other autoantibody binding to brain blood vessel endothelium resulting in endothelial dysfunction secondary to a proinflammatory cascade, with sequelae of inflammation and local microthrombosis; this would be expected to cause irreversible changes. Another postulated mechanism considers immune-mediated attack (aPL or anti-basal ganglia antibodies) against specific basal ganglia epitopes.

One case series of six paediatric patients (four with chorea who had aPL) examined this autoantibody hypothesis. The serum from the paediatric APS patients with chorea demonstrated elevated binding of IgG to neuronal cell-surface antigens of cultured neuronal cells with dopaminergic characteristics.

The role of brain metabolic imaging with FDG-PET in the diagnostic work-up of chorea of unknown aetiology has recently been advocated in the literature. FDG-PET may be helpful in distinguishing reversible causes of chorea (e.g. aPL-related chorea) from neurodegenerative causes, particularly in the presence of striatal hypermetabolism. Striatal hypermetabolism on FDG-PET cerebral imaging has been reported in cases of aPL-related chorea, as in our patient.
No standard treatment exists for aPL-related chorea. Current evidence derives from retrospective non-randomised trials, case reports or series, including for symptomatic treatment with tetrabenazine, dopamine antagonists, steroids and immunosuppressants.

**Key Points:**

- Chorea can be associated with autoimmune diseases such as antiphospholipid syndrome and has been associated with the isolated presence of antiphospholipid antibodies (aPL).
- Chorea of subacute onset is a movement disorder that typically has a monophasic course.
- Fluorodeoxy glucose positron-emission tomography may help in distinguishing reversible causes of chorea such as aPL-related chorea from neurodegenerative causes, particularly in the presence of striatal hypermetabolism.
- Current evidence for the treatment of aPL-related chorea derives from retrospective non-randomised trials, case reports or series, including for symptomatic treatment with tetrabenazine, dopamine antagonists, corticosteroids and immunosuppressants.

**References:**


Figure 1. Timeline illustrating the course of relapsing-remitting chorea and trials of treatment.
Figure 2. FDG-PET-CT [(A) coronal, (B) axial] showing hypermetabolism (A, B) in the left basal ganglia (increased tracer uptake in the left caudate and left lentiform nucleus) and very mild temporal hypometabolism (A) bilaterally.
Author Roles:

MF was involved in conception, data analysis, design and drafting the manuscript. MF, BJH and TCA were involved in the clinical care of the patient. BJH and TCA were involved in critical review and final approval of the manuscript.