

Fitting and flailing: recognition of paediatric antiphospholipid syndrome

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2012-302404>).

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Received 31 October 2012

Revised 4 September 2013

Accepted 10 September 2013

Published Online First

10 March 2013

ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune condition where the presence of antiphospholipid antibodies is thought to predispose to thrombotic events. It is uncommon in the paediatric population, but current diagnostic criteria are based on adult population studies, making assessment of its true paediatric prevalence difficult. We present two cases of paediatric APS, who presented with primary neurological events, and discuss approaches to diagnosis, interpretation of screening investigations, including antinuclear antibodies (ANA), anti-extractable nuclear antigen (ENA) antibodies and lupus anticoagulant. Possible approaches to the management of paediatric APS are discussed.

CLINICAL PRESENTATION

Case 1

A 13-year-old girl attended her local hospital with a 3-week history of weakness of her right arm and leg and recurrent episodes of involuntary movements of her right shoulder, arm and hand. She described difficulty in holding a fork, dropping cups and unsteadiness in walking, with a history of falling to either side. She also described intermittent episodes of the sensation of burning or pain in her fingers and toes over the previous 6 months or more. She described extreme fatigue and occasional episodes of dizziness. There was no history of headache or bladder or bowel symptoms. Past medical history revealed mild atopy. Examination was unremarkable with no consistent pattern of muscle weakness and symmetrical deep tendon reflexes.

Comment: assessment of weakness and abnormal movements

History of acute onset unilateral motor symptoms that is, weakness and involuntary movements makes a central neurological cause for her symptoms more likely than a primary muscle problem. It

is important to qualify what the history of weakness actually means as it is often confused with paucity of use of a particular limb, which may be due to actual loss of power (true weakness) or a functional problem due to apraxia, involuntary movements, hemineglect or hypotonia. Myasthenia gravis, an autoimmune condition leading to muscle weakness and fatigue due, in the majority of patients, to antibodies against acetyl choline receptors at postsynaptic neuromuscular junction, or muscle-specific kinase can cause fluctuating episodes of muscle weakness and should be considered in patients presenting with intermittent muscle weakness.¹ The weakness may affect extraocular muscles, bulbar or limb muscles, becoming generalised over time in the majority of patients. The pattern of weakness fluctuates but often worsens later in the day or after activity and improves with rest.² It is not associated with involuntary movements. In this patient, formal examination did not reveal any objective weakness or fatigability in which case the symptoms of fall, dropping cups and unsteadiness could be attributed to intermittent involuntary movements thus raising the suspicion of an acute onset movement disorder in her.

Characterising the phenomenology of involuntary movements is a key step to the diagnosis. A very useful tool is to obtain a home video as the abnormal movements may not be apparent on clinic/ED visits. Movement disorders may be hyperkinetic (excessive movements) or hypokinetic (paucity of movements) and are also known as dyskinesias and akinetic/rigid disorders, respectively. Dyskinesias include most of the movement disorders in children including tics, stereotypies, chorea, ballismus, dystonia, myoclonus and tremors. Table 1 gives a brief description of these dyskinesias.

A full history should include details regarding onset, duration and progress of the involuntary movements, any preceding

To cite: Freeman H, Patel J, Fernandez D, et al. *Arch Dis Child Educ Pract Ed* 2014;**99**:28–36.

Table 1 Dyskinesias (adapted from Singer *et al*³)

Dyskinesia	Description
Dystonia	Intermittent and sustained involuntary muscle contractions that produce abnormal (twisting) postures
Chorea	Involuntary, continual, irregular, movement which fragments at variable rate and direction and occur randomly and unpredictably
Ballismus	Involuntary, high amplitude flinging movements occurring more proximally. May coexist with chorea and is likely to be a spectrum of chorea
Myoclonus	Sudden, quick, involuntary muscle jerks caused by muscle contractions
Tics	Involuntary sudden, rapid, repetitive, non-rhythmic, simple or complex movements or vocal activity preceded by an urge
Stereotypies	Involuntary patterned and coordinated, repetitive, non-reflexive movements. Often rhythmic
Tremors	Oscillating, rhythmic movements about a fixed point, axis or plane due to alternate contractions of antagonist muscles

infections (especially sore throat), effect on voluntary function, diurnal variation, exacerbating and relieving factors, and the presence of urge, volition or suppressibility. In addition, the presence of any cognitive, psychiatric or emotional symptoms, any other systemic symptoms and family history, perinatal history and drug history should be detailed. It is also important to determine the topographical distribution of the involuntary movements.⁴ Here the unilateral involvement raises the possibility of hemiballismus, hemichorea or hemidystonia.

Aetiologies of dyskinesia with onset in children where chorea is a predominant feature are shown in table 2.

A list of all potential causes of dyskinesia is exhaustive but fortunately a large majority of children with acute/subacute onset chorea turn out to have acquired causes and, among these, postinfectious (Sydenham's chorea) or autoimmune (SLE and APS) and psychogenic aetiologies predominate. Thus, MRI scan with diffusion-weighted images, full blood count (FBC), clotting, liver function, electrolytes, bone profile, C-reactive protein (CRP), autoimmune profile including ANA, anti-dsDNA antibodies and complements, thyroid function (TFTs), copper, ceruloplasmin, slit lamp examination to look for Kayser–Fleischer rings, antistreptolysin titre (ASOT) and anti-DNAse B antibodies would form a good first-line investigation panel that will capture the common aetiologies and not miss the rare but treatable conditions. Further investigations should be dictated by the results of these first-line investigations and presence of any clues on history and examination.

Investigation

MRI brain was reported as normal and bloods including full blood count, liver function, electrolytes, lactate dehydrogenase (LDH) and CRP were all within normal limits. Her activated partial thromboplastin time ratio (APTR) was mildly elevated at 1.8 and lupus anticoagulant was noted to be positive but this was felt to reflect a recent viral illness. Bloods were also sent for ANA, anti-dsDNA and anti-ENA antibodies at this time.

Table 2 Aetiologies of dyskinesia

Category	Disease
Autoimmune	Systemic lupus erythematosus (SLE) Antiphospholipid syndrome (APS) Poststreptococcal—Sydenham's chorea Anti-NMDA receptor encephalitis Acute demyelination—Acute disseminated encephalomyelitis (ADEM)
Drug	Anticonvulsant Neuroleptics CNS stimulants
Infections	Lyme disease Mycoplasma Tuberculous meningitis HIV Viral encephalitis Parasitic and protozoal
Endocrinopathy	Hyperthyroidism Hypoparathyroidism Pseudohypoparathyroidism
Vascular and hypoxic	Stroke Cardiopulmonary bypass
Genetic, metabolic and hereditary degenerative	Familial paroxysmal choreoathetosis Wilson's disease Mitochondrial (eg, Leighs) Abetalipoproteinaemia Glutaric aciduria Lesch–Nyhan syndrome Ataxia telangiectasia Huntington's disease
Others	Tumours Trauma Psychogenic

CNS, central nervous syndrome; NMDA, N-methyl-D-aspartate.

Comment: lupus anticoagulant

This patient was found to have an elevated APTR, and subsequent positive lupus anticoagulant (LA). LA is a functional test used to detect the presence of IgM or IgG antibodies directed against phospholipid components of plasma, and a positive result is one of the inclusion criteria for the diagnosis of antiphospholipid syndrome (APS).⁵ While the *in vitro* effect of these antibodies is to delay clotting, the *in vivo* clinical impact is a prothrombotic predisposition.

The prolonged APTR and positive lupus anticoagulant in this case was thought to reflect a recent viral illness rather than APS. This highlights one of the difficulties in assessing paediatric APS, as antiphospholipid antibodies are reported to be positive in up to 25% of apparently healthy children.⁶ Male noted that in a population of 95 children with positive LA, this was an incidental finding with no clinical findings.⁷ Furthermore, of 83 children followed up over an average of 1.9 years, 58% normalised their activated partial thromboplastin time (APTT) suggesting that lupus anticoagulants can be a transient phenomenon in young children. Many childhood infections are thought to induce antiphospholipid antibodies.⁸

It is recommended that lupus anticoagulant should only be checked in patients who have a high clinical

probability of having antiphospholipid syndrome, or who have a persistent unexplained prolonged APTT on routine testing.⁹ If positive, the lupus anticoagulant should be repeated after a period of 12 weeks to confirm its persistence.

In the light of the normal MRI report, and reported inconsistencies in clinical examination findings, functional or fabricated illness was considered among the wide list of differential diagnoses.

Comment: functional illness

Difficulties in elucidating examination findings consistent with the history of weakness and involuntary movements led to the differential of functional illness being considered. While movement disorders can be a manifestation of functional illness, indicators of organic disease should not be missed. In cases of functional illness, patients are more likely to be female, especially in adolescence, and to have tremor, myoclonus or dystonia. Diagnostic criteria for psychogenic movement disorders in adults have been published and include abrupt onset, inconsistency, incongruity and distractibility, false weakness and false sensory signs.¹⁰ It has been suggested that these criteria apply to paediatric cases as well.¹¹ In this case, the younger age, the consistent pattern of unilateral disease, persistent fatigue with positive lupus anticoagulant all point to a possible organic pathology. Although a normal MRI scan is expected in functional dyskinesias, it does not rule out secondary dyskinesias due to autoimmune mechanisms for example, Sydenham's chorea, endocrinopathy, drug-induced dyskinesias or a primary genetic dyskinesia.

Over subsequent months her symptoms progressed with increased weakness of the right side making walking difficult. She described her right hand and leg feeling numb, cold and heavy. She had increased frequency of involuntary movements of the right side, with splaying movements of the fingers of the right hand and 'jerking' of the right arm. These movements were noted by parents even during periods of sleep. She also described worsening fatigue and daily episodes of dizziness. She developed slurring of her speech which was more pronounced when tired.

Comment: fatigue

Fatigue can be a difficult symptom to assess, being commonly described. Assessment of fatigue requires enquiry regarding sleep pattern, daily activities, appetite and intake, infectious episodes and daily activity episodes. Abnormal movements or underlying pain can contribute to muscle fatigue, while anaemia may also be a contributing factor. Persistent or disabling fatigue can be a presenting feature of autoinflammatory conditions and should indicate a need to enquire after other features of these diseases including fever, mouth ulcers, hair loss, joint problems and rash.

She was then referred to the tertiary neurology team, where on further examination she was noted to have slight reduction of muscle power in the right arm with hypotonia, and choreiform movements on the right

side affecting the upper limb and face (hemichorea), with a 'milkmaid grasp' noted on the right. Movements were present at rest and in sleep but worse on activity. There was no obvious dysarthria but detailed speech and language assessment noted decreased coordination of tongue and facial muscles in continuous speech.

Comment: chorea

A milkmaid grasp is typically noted with abrupt waxing and waning of the grip due to inability to maintain muscular contraction and is classically described in Sydenham's chorea associated with Rheumatic fever but may be seen with other causes of chorea as well. The speech difficulty described is due to the chorea affecting tongue muscles and can be demonstrated by asking the child to protrude the tongue which will abruptly go back in the mouth (darting tongue). Other classical signs noted in chorea include the pronator sign: when the patient holds the arms above the head the palms turn outward, and a choreic hand: arms when extended in front of the body results in flexion of the wrist and overextension of the metacarpophalangeal joints. Both these signs result from hypotonia.¹²

Further investigations included a repeat MRI which was normal. Results of the ANA previously sent were now reported as positive with a titre of 1/160 with a homogeneous and speckled pattern. The anti-ENA antibodies were negative and anti-dsDNA elevated at 60 IU/mL (normal <20). Further and repeat bloods as listed in table 3 were sent, and results are also shown in the table. Please note plasma viscosity (PV) is presented as the hospital laboratory had replaced erythrocyte sedimentation rate (ESR) with PV. Urinary organic acids were normal and urine protein creatinine ratio was normal at 8 mg/mmol.

Comment: ANA

An autoimmune screen was requested including ANA (antinuclear antibodies) and anti-ENA (extractable nuclear antigen) antibodies for this patient. ANA are often requested as a screening test, but it is important to be clear why these are required, and what results such as homogeneous and speckled actually indicate.

The ANA can be tested by ELISA or immunofluorescence (IF) methods. The basic premise of the test is to look at the reactivity of antibodies in patients' blood with antigens expressed by human cells and more specifically by cell nuclei. Two factors are important in interpretation of ANA—the dilutional titre of the patients serum and the pattern of fluorescence, for example homogeneous, speckled, nucleolar or centromere.

A low titre ANA, that is 1/40 in an asymptomatic individual is of dubious significance: up to 32% of healthy adults are reported to be ANA positive at 1:40 serum dilution.¹³ This drops to 5% at a dilution of 1:160. It is suggested that titres $\leq 1:80$ are considered low, 1:160–1:640 medium, and high titres are those $\geq 1:1280$.¹⁴ An approach to interpretation of ANA must therefore include clinical history and examination to assess for symptoms and signs of

Table 3 Results for patient 1 (abnormal results are highlighted in bold)

Hb	13.7 g/dL (11.7–15.3)	Ammonia	46 (<40) μ mol/L
WCC	11.01×10^9 /L (4.5–13)	Lymphocytes	1.4×10^9/L (1.5–4.5)
Plts	169×10^9 /L (150–400)	amino acids	Normal
CRP	0.6 mg/L (<5)	ANA	Positive
ALT	11 IU/L (10–50)	Anti-dsDNA	232 IU/mL (<25)
PV	1.62 (1.5–1.7)	Anti-ENA antibodies	Negative
Ceruloplasmin	0.25 g/L (0.2–0.5)	C3	1.24 g/L (0.8–2.1)
Ferritin	44 μ g/L (15–150)	C4	0.11 g/L (0.15–0.5)
D-dimer	1434 ng/mL (<500)	Anticardiolipin IgG	51.9u/mL (<10)
Lactate	1.5 mmol/L (0.5–2.2)	Anticardiolipin IgM	4.2 u/mL (<10)
Direct antiglobulin test	Positive	Lupus anticoagulant	Positive

ALT, alanine transaminase; ANA, antinuclear antibodies; ENA, extractable nuclear antigen; CRP, C-reactive protein; Hb, haemoglobin; Plts, platelets; WCC, white cell count.

autoinflammatory disease coupled with titre and appearance of a positive ANA. Diseases which are associated with a positive ANA include SLE and systemic sclerosis among others, and further detail including the relative sensitivities and specificities of ANA for these conditions are shown in table 4.

Nuclear fluorescence may be further described as homogeneous, speckled, peripheral or centromere specific in staining appearance. Homogeneous may reflect the presence of anti-dsDNA antibodies, antichromatin, antihistone and anti-Scl70 antibodies. Anti-dsDNA is considered specific for SLE, and anti-Scl70 for scleroderma, thus a homogeneous appearance immediately leads to consideration of these diseases and the need for more detailed ENA analysis.

Further associations of the immunofluorescence staining patterns are shown in table 5.

Diagnosis

In view of the positive lupus anticoagulant and raised anticardiolipin antibodies with choreiform movements, the diagnosis of APS was considered. Review of family history did not reveal any previous family members with APS, miscarriage or thrombotic event. The further laboratory features of raised anti-dsDNA antibodies and positive ANA with documented lymphopaenia (on two occasions) met three of the 11 American Academy of Rheumatology (ACR) diagnostic criteria for systemic lupus erythematosus (SLE).¹⁷ Further supporting features included her profound

fatigue and choreiform movements in the absence of an infectious cause, a positive direct antiglobulin test and low C4. These combined features would meet the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE.¹⁸ Therefore, she was diagnosed with probable SLE with secondary antiphospholipid syndrome. She was commenced on immunosuppressive therapy with pulsed methylprednisolone, subsequent oral prednisolone, mycophenolate mofetil (MMF) and hydroxychloroquine. In the context of probable antiphospholipid syndrome, anticoagulant therapy was discussed with the family and initiated. Her symptoms rapidly resolved following steroid therapy and MMF, and after a period of 6 months her anticoagulation was stopped.

Case 2

A 9-year-old girl was brought in by ambulance to the emergency department with generalised tonic-clonic seizure. The seizure terminated but she had further left sided focal seizures which secondarily generalised. On termination of the seizures, she was left with a dense left hemiparesis and slurred speech, but was alert and responsive without confusion or disorientation.

Table 5 Immunofluorescence patterns and associations (adapted from¹⁶)

Immunofluorescence	Antibody	Disease
Homogeneous	Anti-dsDNA Anti-Scl70	SLE Scleroderma
Speckled	Anti-RNAP II Anti-La Anti-Sm	SLE/scleroderma Sicca symptoms SLE
Peripheral	Lamins A,B,C Nuclear pore complexes	SLE Primary biliary cirrhosis (PBC)
Centromere	CENP-A, B,C	Scleroderma/CREST
Nucleolar	Anti-RNAP I/III, U3RNP	Scleroderma
Cytoplasmic	Anti-Ro, antiribosomal P Antimitochondrial	SLE PBC

CREST, calcinosis, raynauds, oesophageal dysmotility, scleroderma, telangiectasia; the limited cutaneous form of systemic sclerosis; SLE, systemic lupus erythematosus.

Table 4 Autoinflammatory diseases associated with a positive ANA^{14 15}

Disease	Sensitivity %	Specificity %
SLE	93–95	57
Sjogren syndrome	48	52
Systemic sclerosis	85	54
Juvenile idiopathic arthritis (JIA)	57	39
JIA with uveitis	80	53
Polymyositis/dermatomyositis	61	63

ANA, antinuclear antibodies; SLE, systemic lupus erythematosus.

Comment: seizure and paresis

As per NICE guidelines (ref CG137 issued January 2012) with the acute presentation of prolonged seizures the first step of management in the emergency department is to assess and secure the airway, breathing and circulation and commence high flow oxygen.¹⁹ Confirm clinically that it is an epileptic seizure, check for blood glucose to rule out hypoglycaemia as a treatable cause of seizure, and then administer intravenous lorazepam or buccal midazolam/rectal diazepam if intravenous access is not available. Ten minutes later a second dose of lorazepam can be given intravenously if the seizure continues. The next step will be to administer a loading dose of phenytoin (or phenobarbitone if already on phenytoin) if the seizure persists. Rectal paraldehyde may also be considered at this stage. Intensive care or senior anaesthetic colleagues should be advised of patients requiring phenytoin or phenobarbitone to allow preparations for rapid sequence induction of anaesthesia with thiopental sodium should the seizure persist. Patients will then require transfer to paediatric intensive care for further management in case of refractory seizure.

Postictal paresis (Todd's paresis) can last for anywhere between a few minutes to 36 h. Todd's paresis is of good lateralising value as more than 90% of time it points to a seizure origin in the opposite frontal lobe involving the sensory-motor cortex. When present it is thus a good clinical clue to help distinguish between a primarily generalised seizure and a focal onset seizure with secondary generalisation. It is often lesion associated and should encourage neuroimaging, particularly in new onset seizures.²⁰ Further management upon termination of seizures requires assessment of the possible cause of new onset focal seizure, and possible causes as listed in box 1 should be considered. Evaluation will include a detailed history, physical examination including full neurology assessment; and investigations including infection and metabolic screens, neuroimaging and EEG. MRI scan of brain is the neuroimaging investigation of choice but a CT scan of the brain may be organised, especially in the acute setting, if the MRI scan is not available or contraindicated.

Neuroimaging, in particular an MRI scan, will help detect many of the above aetiologies. In addition to FBC, electrolytes, CRP, blood culture, calcium, magnesium and blood gas, cerebrospinal fluid (CSF) microscopy and culture, protein and glucose (provided raised intracranial pressure is ruled out and MRI shows no focal mass lesion) should be considered in a child with prolonged seizure, especially without complete recovery. Intravenous antibiotics and antivirals should be considered promptly if meningitis or encephalitis is suspected.

She was commenced on intravenous antibiotics and aciclovir and underwent urgent CT head which was reported as normal. Further history obtained from the parents suggested a 1-week history of intermittent headaches and twitching of the left arm in the 2 days prior to presentation. Past medical history revealed frequent episodes of epistaxis and a previous admission 14 months

Box 1 Possible causes of new focal seizure

Idiopathic focal epilepsies
Infection (meningitis, encephalitis, cerebral abscess)
Cerebrovascular events
Trauma
Tumour
Developmental abnormalities (including focal cortical dysplasia)
Central nervous syndrome inflammation (acute disseminated encephalomyelitis (ADEM), vasculitis)
Metabolic (hypoglycaemia, hypocalcaemia, hypomagnesaemia, electrolyte derangements)
Mitochondrial

earlier with glomerulonephritis, thought to be post-streptococcal infection. Family history was unremarkable with no history of APS, miscarriage or thrombosis.

Comment: neuroimaging

A normal CT scan done early in the course of events does not rule out the possibility of stroke, and further neuroimaging should be considered in the context of focal neurological deficit. Abend *et al* showed that 22% of their cohort of children with stroke presented with seizure and all of them had focal neurological deficit.²¹ The authors recommended prompt neuroimaging to avoid misdiagnosis of stroke in children.

In view of the persistent hemiparesis, she went on to have a MRI/MRA brain which showed a diffuse increase in signal of the superior right frontal and anterior parietal lobes possibly reflecting an encephalitic process. No mass/haemorrhage, vascular or diffusion abnormality was noted, ruling out stroke. EEG showed diffuse delta and theta activity of the right hemisphere suggestive of an acute hemispheric insult. Blood and CSF were taken for an infection and autoimmune screen—and results are shown in table 6. ECG and echo were both reported as normal.

Comment: antistreptolysin titre (ASOT)

Despite extensive investigations, an infectious aetiology for the possible encephalitic process could not be identified. It can be seen that at the time of this presentation, this patient had elevated ASOT and anti-DNAse B titres suggesting a recent streptococcal infection. These titres tend to elevate 3–4 weeks postinfection, and a paired titre is most useful in evaluating the time frame of acute infection; however, it is recognised that titres can remain elevated for up to 12 months, making an isolated elevated result difficult to interpret.

The hemiparesis gradually resolved over 4 days but she continued to have left sided Jacksonian seizures to day 7 postadmission, requiring anticonvulsant therapy. She then developed fever and maculopapular rash with petechiae.

Table 6 Results for patient 2 (abnormal results are highlighted in bold)

WCC	5.89×10 ⁹ /L (4.5–13)	Globulin	43 g/L (22–36)
ESR	39 mm/h	EBNA	Negative
CRP	47 mg/L (<5)	EBVCA	Positive
ANA	Negative	EBV capsid IgM	Negative
Anti-ENA antibodies	Negative	Direct antiglobulin test	Negative
Lupus anticoagulant	Positive	Mycoplasma and influenza CFT	Negative
IgA	2.2 g/L (0.7–2.5)	CMV serology	Negative
IgG	15.5 g/L (5.4–16.1)	CSF oligoclonal studies	Not oligoclonal
IgM	3.0 g/L (0.5–1.8)	CSF gram stain	WC12, RBC 1520, no organisms or growth
Anti-dsDNA	6 (<30) IU/mL	C3	1.47 g/L (0.8–2.1)
ANCA	Negative	C4	0.31 g/L (0.15–0.5)
Anticardiolipin IgM	2.5u/mL (<10)	Anticardiolipin IgG	3.6u/mL (<10)
Antistreptolysin titre	800 (<400)	CSF pneumococcal PCR	Negative
Anti-DNAse B	600 (<200)	CSF meningococcal PCR	Negative
HIV Ag/Ab	Negative	CSF viral PCR	Negative for enterovirus, HSV, VZV, CMV, EBV, HHV-6

ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibody; CFT, complement fixation test; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; EBNA, Epstein Barr nuclear antigen; EBV, Epstein Barr virus; Epstein Barr virus capsid antigen; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; HHV-6, human herpes virus-6; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, Varicella Zoster Virus; WCC, white cell count.

Comment: differentials to consider in context of fever, rash and seizures

A wide number of potential diagnoses should be considered in patients presenting with new onset seizures, fever and rash. Infectious causes are essential to exclude and serology and CSF investigations as listed above should be performed. It is important to also consider other potential causes as listed in table 7 to ensure rare causes such as haemophagocytic lymphohistiocytosis (HLH) are not missed.

On dermatology review, the rash was felt to be drug related and anticonvulsant medication was discontinued, with subsequent improvement in rash.

By day 10, she had made a full recovery with no further seizure activity or detectable weakness. A repeat MRI showed a subtle hyperintensity of the right frontoparietal cortex consistent with resolving encephalitis. Following discharge she remained asymptomatic on continued follow-up.

Further information

Following discharge, a delayed result was reported: lupus anticoagulant positive. This was repeated on several occasions—and remained positive over a 12-month period. On repeat bloods, she was also found to have persistently raised IgM, and plasma viscosity (1.87 normal value 1.5–1.72). The combination of presentation with seizures, hemiparesis, changes on MRI brain and raised globulin with positive lupus anticoagulant led to the diagnosis of antiphospholipid syndrome and anticoagulation therapy has been commenced.

Comment

The prior history of acute poststreptococcal glomerulonephritis raises the question of predisposition to

vasculitic disease, but also in the absence of previous renal biopsy whether the glomerulonephritic episode may have represented an early manifestation of the current disease process. It is recognised that infections including streptococcal infections can induce production of antiphospholipid antibodies, and while these induced antibodies have often been considered to be non-pathogenic, there is increasing recognition that this is not always the case.⁸ The particular significance of a possible recent streptococcal infection in this patient is not known, but it is possible that it effectively precipitated the onset of her condition. Renal manifestations of paediatric APS include thrombotic glomerular

Table 7 Differentials to consider in context of rash, fever and seizures

Differentials	
Haematological	Haemophagocytic lymphohistiocytosis (HLH) Leukaemia
Infection	Febrile seizure Meningococcal infection Measles Varicella Human herpes virus-6 (HHV-6) Herpes simplex virus (HSV) Adenovirus Enterovirus
Autoinflammatory	Neuropsychiatric SLE APS Kawasaki disease Henoch-Schonlein purpura
Drug-induced	Antibiotic-induced fever/rash Anticonvulsant-induced

APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Table 8 Clinical manifestations of antiphospholipid syndrome adapted from Ruiz Irastorza²⁶

Frequent	Less common	Unusual	Rare
Venous thromboembolism	Preterm delivery	Epilepsy	Budd-Chiari syndrome
Thrombocytopenia	Pre-eclampsia	Chorea	Transverse myelitis
Fetal loss	Haemolytic anaemia	Retinal vessel thrombosis	Adrenal haemorrhage
CVA	Coronary artery disease	Mesenteric ischaemia	
Migraine		APS nephropathy	
Livedo reticularis		Digital gangrene	
		Amaurosis fugax	
		Pulmonary hypertension	
		Osteonecrosis	
		Vascular dementia	

APS, antiphospholipid syndrome; cerebrovascular accident.

microangiopathy which manifests with haematuria and hypertension, with or without proteinuria.²²

DISCUSSION

Paediatric antiphospholipid syndrome

Both these cases highlight potential neurological presentations of paediatric antiphospholipid syndrome and some of the difficulties in reaching a diagnosis. Antiphospholipid syndrome is a systemic autoimmune condition where the presence of antiphospholipid antibodies are thought to predispose to thrombotic events, including arterial and venous thromboses and fetal losses through complex effects on endothelia, platelets and monocytes.²³ The clinical presentation can be varied, affecting most organs through effects on their vascular beds.²⁴ Table 8 lists the most common clinical manifestations of APS and their relative frequencies. A rare and

serious presentation of APS is catastrophic antiphospholipid syndrome (CAPS): catastrophic antiphospholipid syndrome with widespread small vessel thrombosis, resultant multi-organ failure and a mortality of greater than 30%.^{25 26} Data from the international paediatric APS registry suggests that at first presentation 60% of their cohort had evidence of venous thromboses, 32% had arterial thromboses, 6% small vessel thrombosis and 2% mixed arterial and venous thrombosis.²⁷ Ischaemic stroke was the initial manifestation in 26% of subjects in this cohort, and so APS needs to be considered in any child presenting with sudden onset weakness or ischaemic change noted on neuroimaging.

Pitfalls of APS definition in paediatrics

A problem with interpretation of the registry data is that all children entered into the international registry must meet the international consensus guidelines for APS as listed in table 9. A potential pitfall of these guidelines is that they require clinical evidence of thrombosis (or pregnancy loss—which is uncommon in the paediatric population) and laboratory evidence of antiphospholipid antibodies. As discussed previously, antiphospholipid antibodies have been documented in healthy populations and found to occur transiently following infections. Thrombotic episodes are, however, uncommon in children, probably reflecting healthier baseline endothelium, fewer additional prothrombotic risk factors such as smoking, combined oral contraceptive use, hypertension and hyperlipidaemia, but also developmental differences in the coagulation and fibrinolytic systems.²⁸

Neurological manifestations of paediatric APS

As previously mentioned, over a quarter of patients entered into the paediatric APS registry had ischaemic stroke as the first recognised manifestation of disease. Interestingly, 72% of patients entered into this registry

Table 9 Research criteria for diagnosis of APS (adapted from²⁹)

Clinical criteria	Laboratory criteria	
Vascular thrombosis	Pregnancy morbidity	
1 or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ	1 or more unexplained deaths of a morphologically healthy fetus at or beyond the 10th week of gestation, with healthy fetal morphology documented by ultrasound or direct examination of the fetus	Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
Thrombosis should be supported by objective validated criteria—that is, unequivocal findings of appropriate imaging studies or histopathology	1 or more premature births of a morphologically healthy newborn before the 34th week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions or recognised features of placental failure	Anticardiolipin antibody of IgG or IgM isotype, or both, in serum or plasma, present in medium or high titres on two or more occasions at least 12 weeks apart, measured by a standardised ELISA
	3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded	Anti-β2-glycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma, present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA according to recommended procedures

APS is present if at least one clinical and one laboratory criteria are present.

APS, antiphospholipid syndrome.

had non-thrombotic features at presentation, including skin, haematologic and non-thrombotic neurological disorders.²⁷ Reported skin manifestations included livedo reticularis, Raynaud phenomenon, ulceration, pseudovasculitic lesions and chronic urticaria, while haematological manifestations included Evans syndrome, leucopaenia and haemolytic anaemia.²⁷ Migraine, chorea and epilepsy were the most common non-thrombotic neurological disorders in this cohort.³⁰ Other reported neurological presentations of APS include acute encephalopathy, multi-infarct dementia, transient amnesia, transverse myelitis, dystonias, hemiballismus and tics.^{31–34} Chorea has been described as an early symptom in APS, occurring before thrombosis; and it is well recognised as a rare feature of neuropsychiatric lupus.³⁵ It may be difficult to distinguish APS-related chorea from other primary or secondary choreas but in APS chorea is noted to be aggravated by anxiety and stress, and to subside during sleep. Patients will often try to hide abnormal movements by attempting to restrain the limb or try to mask movements with a purposeful gesture, and this was evident in our patient.

The mechanism of neurological dysfunction in APS remains to be elucidated, but possible causes include antiphospholipid antibodies binding to brain endothelium with resultant endothelial dysfunction, microthrombosis and vasculitis.^{36–37} Direct binding of antiphospholipid antibodies to neural cell surfaces has also been demonstrated and may modulate neuronal function.^{38–39}

Management of paediatric APS

A potential challenge in the paediatric patient is managing patients with non-thrombotic neurological events combined with positive laboratory markers, as technically they fail to meet the diagnostic criteria for APS. Our two patients both presented with neurological events, persistently positive lupus anticoagulant and subtle changes on neuroimaging, which may represent small thrombotic lesions poorly defined by the scanning techniques. Other studies have also reported chorea and abnormal movements in the absence of changes on central nervous syndrome (CNS) imaging, and it has been suggested that this may represent poor visualisation of subtle changes or that the clinical features are mediated by direct neuronal binding of antiphospholipid antibodies.³⁸ This raises the question whether therapy of movement disorders in APS should be managed by anticoagulation therapy or by primary immunosuppression, with the aim of reducing pathogenic antibodies. Evidence-based recommendations for therapy of APS have been published based primarily on adult data⁴⁰ and require cautious interpretation for the paediatric population, considering the different baseline endothelial risk factors as discussed above.

The recommendations are for general measures designed to minimise cardiovascular risk factors, mainly lifestyle, and use of low molecular weight heparin

prophylaxis in high risk situations such as surgery. Patients with SLE are recognised to be at increased risk of thrombotic events and use of hydroxychloroquine and aspirin as primary prophylaxis is recommended. Secondary thromboprophylaxis is recommended for patients with definite APS and previous arterial or venous thrombosis. One consideration is the management of accompanying inflammatory disease, which may increase prothrombotic risk if poorly controlled.

Our approach has been to institute anticoagulation therapy in our patient with associated SLE, closely monitored, combined with general advice regarding healthy lifestyle and minimising additional prothrombotic risk factors, while additional immunomodulatory therapy was initiated. When good control of SLE was achieved, and inflammatory markers and neurological symptoms normalised, anticoagulation was discontinued. However, patient 2 had persisting changes on MRI suggesting a possible ischaemic event representative of primary APS and so after discussion regarding risks and benefits with the family, anticoagulation therapy continues. Questions regarding type and duration of therapy—whether to continue with warfarin anticoagulation, antiaggregation therapy or hydroxychloroquine and whether to continue lifelong—remain. It is these questions which make the paediatric APS registry so valuable as only by gathering international data on this rare condition will these questions be answered.

In summary

We present two cases of children who presented with abnormal movements and seizures, respectively, and were found on subsequent testing to have positive lupus anticoagulant. While the differentials for patients presenting with seizure or movement disorder are wide, unless APS is considered and baseline investigations obtained, the potential to intervene to prevent possible subsequent thrombotic events may be missed. We have tried to highlight some of the difficulties surrounding recognition and management of paediatric APS and to explain the relevance of appropriate investigations.

Contributors AVR and HF conceived the idea and prepared the manuscript through several drafts. JP, DF and PS contributed to manuscript and reviewed the final version.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Commissioned; externally peer reviewed.

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Fitting and flailing: recognition of paediatric antiphospholipid syndrome

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Arch Dis Child Educ Pract Ed 2014 99: 28-36 originally published online October 3, 2013

doi: 10.1136/archdischild-2012-302404

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Freeman H, Patel J, Fernandez D, *et al.* Fitting and flailing: recognition of paediatric antiphospholipid syndrome (*Arch Dis Child Educ Pract Ed* 2014;99:28–36). There are two errors in this paper which were not corrected by the production department and we would like to apologise for this oversight. In the title of table 4, page 31, it should read “Autoimmune diseases associated with a positive ANA”. On the same page, top of the left hand column “autoinflammatory” should be “autoimmune”.