

Rare disease

Neonatal stroke associated with de novo antiphospholipid antibody and homozygous 1298C/C methylenetetrahydrofolate reductase mutation

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Summary

Antiphospholipid antibodies are a recognised prothrombotic risk factor associated with acute ischaemic infarction. Most autoimmune diseases are rare in infants, and in the neonatal period, autoimmunity is related to transplacental passage of maternal immunoglobulin G autoantibodies. Distinguishing between de novo and acquired autoimmunity has important therapeutic implications and is crucial for determining the prognosis. We present a case of a neonatal thrombotic stroke associated with de novo synthesis of antiphospholipid antibodies, a homozygous 1298C/C methylene-tetrahydrofolate reductase mutation and a double-homozygous plasminogen activator inhibitor 1 polymorphism (PAI-1 844A/A and 675 4G/4G), which may have increased the final thrombotic risk. Her mother was not positive for antiphospholipid antibodies. The authors highlight an unequivocal evidence of a de novo case of paediatric antiphospholipid antibody syndrome and emphasise the need for a thorough investigation in cases of neonatal stroke including molecular thrombophilia study.

BACKGROUND

Antiphospholipid syndrome (aPS) is a multisystem autoimmune disorder characterised by a combination of arterial and venous thrombosis, recurrent fetal loss, thrombocytopenia and the persistence of elevated titres of circulating antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL).^{1 2} aPL are a recognised prothrombotic risk factor associated with acute ischaemic infarction.³ Most autoimmune diseases are rare in infants, and in the neonatal period, autoimmunity is related to transplacental passage of maternal IgG autoantibodies.⁴ The rate of stroke is higher in the primary aPS patients, who are also younger at presentation.³ Distinguishing between de novo and acquired autoimmunity has important therapeutic implications and is crucial for determining the prognosis. The concomitant presence of aPL and prothrombotic gene mutations serve as a 'two-hit' model trigger for the occurrence of stroke.^{2 5} Herein, we present a case of a neonatal thrombotic stroke with de novo synthesis of aPL associated with homozygous 1298C/C methylenetetrahydrofolate reductase (MTHFR) mutation and a double-homozygous 844A/A and 675 4G/4G plasminogen activator inhibitor 1 (PAI-1) polymorphism, which may have increased the final thrombotic risk. Her mother was not positive for aPL.

CASE PRESENTATION

A girl was born at 40 weeks of gestational age by caesarean section after an unremarkable pregnancy with an Apgar index of 9 and 10, in the first and fifth minutes, respectively. There was no family history of precocious stroke, coagulation disorders or autoimmune disease. At 8 h of life, she began multifocal clonic seizures. The neurological examination revealed a left-sided hemiparesis including

face. Cerebral MRI showed an acute ischaemic stroke of the right caudate and lenticular nucleus, with extension to the cerebral peduncle (figure 1). MR angiography was normal. Further investigation revealed a normal echocardiogram and infection was excluded; she presented normal full blood count, coagulation, renal and liver function, and normal serum complement and immunoglobulins.

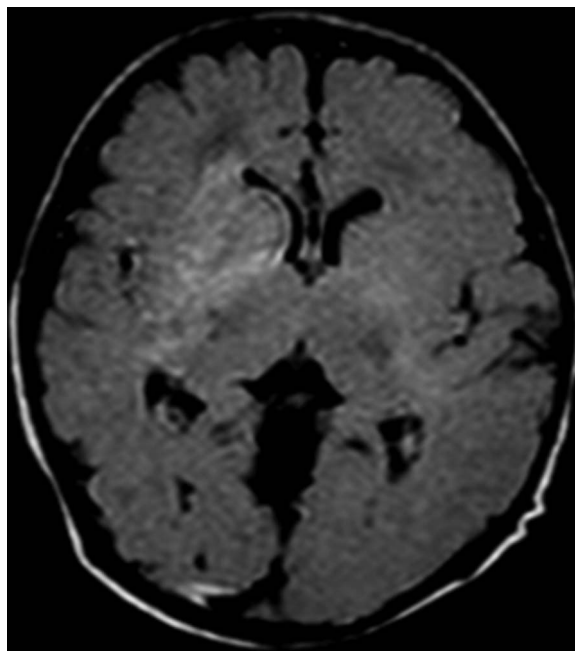


Figure 1 Acute ischaemic stroke of the right caudate and lenticular nucleus, with extension to the right cerebral peduncle.

An extensive investigation of prothrombotic risk factors was performed at the age of 3 months including: protein C, protein S, antithrombin III, homocysteine, LA, aCL, β 2 glycoprotein I (β 2-GPI), antinuclear (ANA) and antidouble-stranded-DNA antibodies (ds-DNA). We also carried out the genotyping for factor V Leiden mutation, MTHFR and PAI-1 polymorphism.

Results of serology for aPL has identified aCL IgG mildly elevated (17.5 GPL/ml); an elevated β 2-GPI IgG (133 U/ml) and a positive LA. aPL IgM for aCL and β 2-GPI were negative. The thrombophilia genotyping array disclosed homozygous 1298C/C MTHFR mutation and a double homozygous PAI-1 844A/A and 675 4G/4G polymorphism. At this point, maternal serum was negative for aPL and other autoantibodies.

Nine months later, the aCL IgG remained elevated (26.9 GPL/ml) and LA continued positive, the β 2-GPI IgG was negative and appeared a positive ds-DNA antibody (23.6 UI/ml).

At the beginning, seizures were managed with anticonvulsant therapy, which have been suspended at 3 months of age, with no new events and with a normal EEG. Antithrombotic treatment was started with aspirin. She was followed through paediatric neurology, paediatric rheumatology and child development consultations with physical therapies.

At 12 months of age, her left-side strength had improved showing only a monoparesis grade 3 of the left upper limb. No further seizures or thrombosis had occurred.

DISCUSSION

This case accomplishes the revised criteria for the primary antiphospholipid antibody syndrome with clinical evidence of arterial vessel thrombosis coexisting with more than one laboratory criteria.¹ Paediatric aPS seems to be rare and its role in paediatric stroke continues to be investigated.⁵ Although there is some clinical evidence of a higher risk for thromboembolic events, an international registry for paediatric aPS, showed that ischaemic stroke was its initial manifestation in 26% of cases.² In another study, ischaemic stroke was also more prevalent in paediatric patients compared with adults (25% vs 13.1%).⁴

Unequivocally, vascular thromboembolism is a major clinical manifestation of aPS. It have been proposed that other comorbid prothrombotic conditions may function as a trigger for the occurrence of ischaemic stroke in paediatric age, like a 'second hit model', explaining the high rate of inherited thrombophilic defects and their combinations in children with aPS.^{2 6} In our case, the homozygous 1298C/C MTHFR mutation and the double homozygous PAI-1 844A/A and 675 4G/4G polymorphism support this concept. The absence of maternal aPL and the results of repeated testing for aPL in our patient corroborate the de novo synthesis of aPL. Authors reported some differences between primary aPS versus secondary aPs showing a statistically significant higher frequency of ischaemic stroke in the group of patients with primary aPS.⁴

In our patient, the presence of various prothrombotic risk factors associated with a de novo primary aPS necessitated an antithrombotic treatment. On this subject, there are no trials evaluating the different efficacy of warfarin, aspirin or heparin treatment in paediatric aPS.

There is still debate in which therapy is the most effective for secondary prevention of stroke with aPS.^{3 7 8} We started antiaggregation with a low dose of aspirin (3 mg/kg/day), without new thrombotic episodes observed.

The detection of ds-DNA antibody put us in alert for the possibility of systemic lupus erythematosus (SLE), knowing that girls with aPS should be monitored for development of SLE,² although to date, the child has not developed other clinical or laboratory manifestations for SLE.

In conclusion, this case emphasises the importance of a complete evaluation of all prothrombotic risk factors in neonatal ischaemic stroke, including thrombophilia genotyping tests for understanding the multifactorial pathogenesis of neonatal ischaemic stroke.

Learning points

- ▶ In neonatal stroke, it is important to clarify all the risk factors and possible causes.
- ▶ Primary antiphospholipid antibody syndrome can be a cause of neonatal stroke, and antiphospholipid antibodies should be re-evaluated at least 12 weeks after the first analysis.
- ▶ In neonatal ischaemic stroke, molecular study for inherited thrombophilic defects should be performed.

Competing interests None.

Patient consent Obtained.

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