Case Report -3

Pleiotropy of APLA - Antiphospholipid Syndrome

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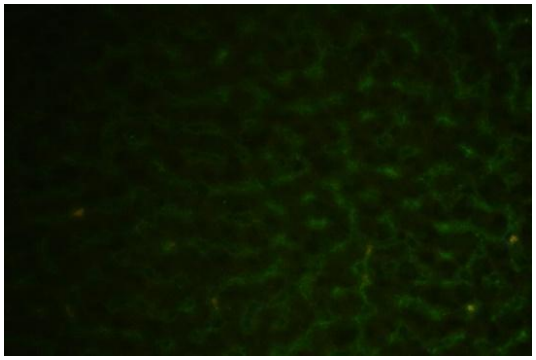
An 8-year-old male, presented to the outpatient clinic, with cough for four weeks and multiple episodes of vomiting that were non-bilious, non-projectile but post-tussive. He had symptomatic management with homoeopathic medication but had become lethargic, and dehydrated, experienced headaches over the back of his head, with occasional dizziness, and swayed while walking on these days. There was no weakness, fever, loose stools, altered sensorium, seizures, drooling of saliva, deviation of angle of mouth, or nasal regurgitation of feeds. The cough was moist with a mucoid expectorate, but not associated with any disturbance of sleep or school day. He had poor intake and loss of appetite. He denied any sick contacts, migraine, or syncope.

Past history

The only child born to non-consanguineous parents, as a preterm at 28 weeks, by LSCS, with a birth weight of 1200 grams. No intervention or respiratory support was needed and was discharged after a week in the nursery. Breastfed till the age of two years, he had normal motor development, except that he started speaking well only by the age of four. Currently, his scholastic performance is good and up-to-date for vaccinations, and lives near a flood-prone semi-rural area. He has no allergies to food or medications nor did he undergo surgeries or have similar symptoms in the past.

Family history

His father was a blue-collar worker who did not have a habit of smoking. His mother was employed, with family-related stress and reactive airways kept under control with inhalers. A Gravida 3 Para 1, had two previous abortions before this child. The first pregnancy terminated as an abruptio placenta at 7 months. The second pregnancy culminated in a missed abortion at three months. The third pregnancy was investigated to be Anti Phospholipid antibody positive (APLA) positive. Her periods were irregular, and she had non scarring chronic falls of hair. A photosensitive rash was suspected on one occasion but had no arthralgia or ocular symptoms. She was detected as Anti-Nuclear Antibody (ANA) positive 1 in 100



with a speckled pattern. (Figure 1)

Figure 1: Speckled Anti-Nuclear Antibody Pattern

The mother's grand uncle had been APLA positive and had commenced on blood thinner after a stroke-like episode who subsequently expired.

Course of illness

The boy was triaged to find a normal cardiorespiratory status, but was sick-looking with some dehydration and features of an upper respiratory infection. There was no squint, seizures, or signs of meningeal irritation. Though he consumed meals normally, he was reluctant to sit up in bed, or walk to the toilet. When examined, he had an unsteady gait, but there was no abnormality of speech, nystagmus, or tremor. After admission, he continued to experience headaches even after intravenous fluids.

Investigations: Normal peripheral smear, coagulation profile, and hepatic and renal functions.

Figure 2: CT BRAIN PLAIN:
An ill-defined hypodense involving the left cerebellar hemisphere and cerebellar vermis on the left side suggests an infarct. There is minimal compression of the fourth ventricle on the left side, however, no evidence of any dilatation of the third or bilateral lateral ventricle is noted. The note is also made of pan sinusitis

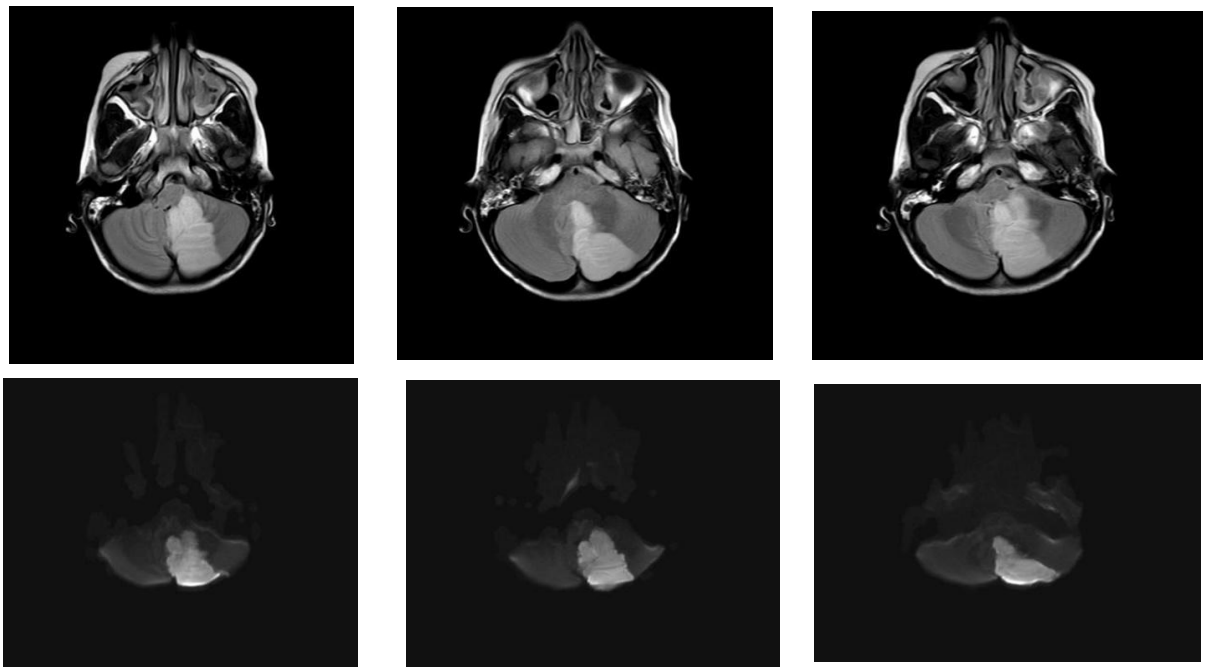


Figure 3: MRI BRAIN SCREENING: Large irregular T2 W flair hyperintensity with diffusion restriction and reduced ADC values involving the cerebellar vermis and left half of the cerebellum, suggestive of acute infarct. There is no evidence of bleeding. Mild effacement of the fourth ventricle. The mass effect is over the left half of the medulla

Imaging Studies:

A CT Brain (Figure 2) performed showed an ill-defined hypodense area involving the left cerebellar hemisphere and cerebellar vermis on the left side, suggesting an infarct. There is minimal compression of the fourth ventricle on the left side, but no evidence of any dilatation of the third or bilateral lateral ventricle was noted. A note was made of pan sinusitis.

An MRI Brain (Figure 3) showed a large irregular T2 W flair hyperintensity with diffusion restriction and reduced ADC values involving cerebellar vermis and the left half of the cerebellum suggestive of an acute infarct. There is no evidence of bleeding. Mild effacement of the fourth ventricle. A mass effect was present over the left half of the medulla.

MRI Angiography Brain and Neck (Figure 4) showed no significant stenosis or occlusion.

Figure 4: Normal Carotid Angiogram

ECHO was normal.

Stroke Panel Workup: Coagulation profile, Sickledex negative, Protein C and S Normal, Auto antibodies including APLA were negative.

Genetic studies were non-contributory: No genetic variant related to phenotype was reported.

Problem List included an acute febrile illness associated with gastritis, pan sinusitis with middle ear effusion with an underlying aetiology hypothesised as **Anti Phospholipid Syndrome with Stroke.**

Acute Posterior Cerebellar Circulation Stroke with revascularisation by collateral circulation to the cerebellum. A total clinical resolution sans blood thinners and adequate hydration without a residual deficit was noted in a few days.

DISCUSSION

Antiphospholipid syndrome (APS) is a rare multisystem autoimmune disorder with an incidence of 2.1 in 100,000 individuals reported in the United States.(1)

The grand uncle of the patient had suffered a stroke, who was put on blood thinners, and had expired. The child's mother was positive for APL antibodies and experienced foetal wastage. She was put on aspirin and an elective Cesarean Section was performed at 28 weeks of her precious pregnancy. Her APL antibodies disappeared a few months after her delivery while she remained asymptomatic. The mother was later identified to be ANA positive but remained APL negative later when investigated for chronic hair loss. Cutaneous facial erythema was once noted without associations like arthritis or uveitis as she has remained asymptomatic over a year follow-up.

The child was admitted after a febrile illness with multiple episodes of vomiting causing dehydration. This led to thrombosis of his posterior cerebellar vessels as viewed by imaging studies. An

exhaustive battery of tests to identify an underlying cause was non-contributory.

The child has been followed up for almost one year with good weight gain and good scholastic performance with no residual or recurrence of clinical features experienced earlier.

Antiphospholipid syndrome

Definition: Anti-phospholipid syndrome is the presence of Antiphospholipid (APL) antibodies in a person who has suffered pregnancy loss or organ thrombosis.(1)
There are three types of clinical presentations of stroke:

A. Thrombotic type: Diagnosis is based on the presence of a clinical picture of arterial or venous thrombosis along with a persistent laboratory marker for APLA like in Deep Vein Thrombosis.

B. Obstetric type of APS: Patients are diagnosed based on the presence of APL antibodies during pregnancy together with premature birth, foetal death after 10 weeks, multiple embryonic losses before 10 weeks of gestation or placental insufficiency.

C. Catastrophic APS: Rare, life-threatening form of APS with micro and macrovascular involvement of multiple organs.
These APL antibodies are directed against phospholipid-binding proteins.(2)

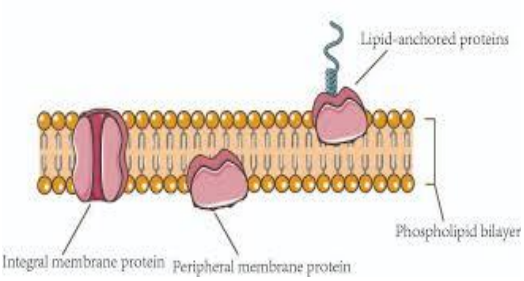


Figure 5: Antibodies Directed Against Phospholipid Binding Proteins

APS can be primary when there is no evidence of autoimmune disease or secondary to autoimmune processes, such as systemic lupus erythematosus (SLE), in 40% of cases. Literature review shows that there are three types of APL antibodies:(3)

1. Anticardiolipin antibodies IgG or IgM (ELISA)
2. Anti-beta-2-glycoprotein-I (anti-β2GPI) antibodies IgG or IgM (ELISA)
3. Lupus anticoagulants (functional clotting assays)

A study found positive APLAs in 6% of all pregnant patients, 13.5% of stroke patients, and 9.5% of patients with deep venous thrombosis (DVTs). Coagulation factor mutations detected by genetic studies increase the risk of thrombosis in people who have APL antibodies.(2)

The antibody profile, including type, titer, and underlying comorbidities, may determine the likelihood of developing clinical APS.

APL antibody titer is elevated during viral infections more than in bacterial infections. One large meta-analysis found that almost 50% of patients diagnosed with COVID-19 had positive APS, most commonly lupus anticoagulant. However, this analysis found no increased thrombotic risk in APLA-positive COVID-19 patients.(3)

A biochemistry panel, including renal function tests, and a complete blood count is used to monitor patients. Repeated APLA testing is not indicated unless required for future treatment decisions.

Low levels of APLAs may also be normally present and may be transient, leading to the requirement of positive antibodies at least 12 weeks apart for diagnosis.

Anticoagulation is not recommended in non-criteria manifestations of APS.(4)

Thrombocytopenia below 50,000/mL(3) may need treatment with corticosteroids with or without IVIG or rituximab can be used.

Take home Message: Children admitted with viral infection have to be treated for their dehydration with an eye for thrombotic complications in the recovery phase of their viral illness as in this case report. A meticulous history of daily intake output and a gait examination on rounds daily in the case of slow recovery is mandatory to detect cerebellar dysfunctions. Prompt clinico-radiological correlation is needed to identify thrombotic episodes in families with a history of stroke as this child. Every child is precious, and every life is precious. The onus is on the clinician: the eye does not see what the mind does not know, hence the significance of this Case Report.

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Consent for Publication was obtained from the parents

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