Myocardial Infarction as Debut of Catastrophic Antiphospholipid Syndrome in an Adolescent

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by thrombosis (venous, arterial, and/or microvascular events), and obstetric morbidity. It appears in the presence of one or more of these antiphospholipid antibodies: lupus anticoagulant, anticardiolipin antibodies (immunoglobulin G or immunoglobulin M), anti-β2-glycoprotein 1 antibodies (immunoglobulin G or immunoglobulin M). The APS may occur on its own (primary APS) or together with other both autoimmune and infectious diseases (secondary APS). (1)

Sixty to 80% of APS patients are female. While the pathophysiology is still unclear, it might be due to the presence of antibodies targeted against vascular endothelial cell surface proteins or platelets, which could be associated with the thrombotic events resulting from this syndrome. (1)

Catastrophic APS is a severe form of this disorder characterized by rapid involvement of 3 or more organs and associated with high mortality rates. (2) The most commonly affected organs are the kidneys, followed by the lungs and the brain. Fewer patients experience cardiac consequences.

According to Euro-Phospholipid, (3) catastrophic APS represented just 0.8% of the entire cohort. In terms of cardiac occurrences, the most common was valve dysfunction (11%), followed by acute myocardial infarction in 5.5% of patients, although the latter was the initial outcome in just 2.8% of cases.

Our clinical case involved a young female patient diagnosed with catastrophic APS, with ST-elevation acute coronary syndrome as the form of presentation.

This 17-year-old female patient, with no risk factors or cardiovascular history, came to the Emergency Department with sharp precordial pain lasting an hour, in association with a syncope with *restitutio ad integrum*. She had recently started oral contraception with drospirenone and ethynyl estradiol. Upon admission, she had precordial pain, normal blood pressure, tachycardia (120 beats/minute),, and generalized paleness. Lab tests upon admission showed serious anemia and thrombocytopenia, 17% hematocrit, 5.9 g/dL hemoglobin, and 14,100/mm^3 platelet count. She had impaired renal function, with serum creatinine 1.45 mg/dL (normal value: 0.5-1.2 mg/dL) associated with proteinuria and granular hyaline casts. The high-sensitivity troponin dosage was 227.7 pg/mL (normal value: up to 14 pg/mL). The electrocardiogram showed sinus tachycardia with ST-segment elevation on the inferolateral dorsal leads, associated with ST-segment specular depression in anterior leads (Figures 1A and 1B). A Doppler transthoracic echocardiogram was performed which showed akinesia of all lower segments and moderate mitral regurgitation, with eccentric regurgitant jet to the posterior leaflet, secondary to retraction of the posterolateral papillary muscle. The left ventricular ejection fraction was estimated at 40%.

Due to the complexity of the condition and serious blood count results, there was an emergency referral to Hematology and Rheumatology Departments. A peripheral blood smear showed anisocytosis, microcytosis, and hypochromia, with a 1% schistocytes count associated with thrombocytopenia. The emergency immune and hematological study reported autoimmune hemolytic anemia mediated by warm and cold antibodies, immunoglobulin G (IgG), and complement. As a result of severe bicytopenia and a history of syncope leading to traumatic brain injury, a brain, chest, and abdomen computerized tomography (CT) was performed to rule out brain bleeding. The CT showed multiple acute splenic infarctions.

Transient complete AV block occurred intercurrently during her stay at the Emergency Department; therefore, an emergency coronary cineangiography was requested. It showed occlusion of the atrioventricular branch of the dominant circumflex artery, with an angiographic image consistent with abundant endoluminal thrombotic material (Figure 2A). The attempts of mechanical thrombectomy with balloon, manual endoluminal thrombus aspiration, aspiration through guide catheter extension and Sophia catheter failed. Then, atrioventricular branch occlusion was observed consistent with coronary artery dissection. As a result, a drug-eluting stent was placed in this vessel with good angiographic results (Figure 2B). A temporary transjugular pacemaker was implanted during the same procedure with semi-permanent vascular access. In addition, 1 g methylprednisolone was administered intravenously as initial immunosuppressive therapy.

Within 24 hours after admission, the laboratory tests showed positive lupus anticoagulant (LAC), and high anticardiolipin and anti-β2-glycoprotein 1 antibodies levels, so the condition was considered to be a catastrophic APS with coronary, splenic, and microvascular renal involvement. Anticoagulation with heparin was administered by continuous infusion

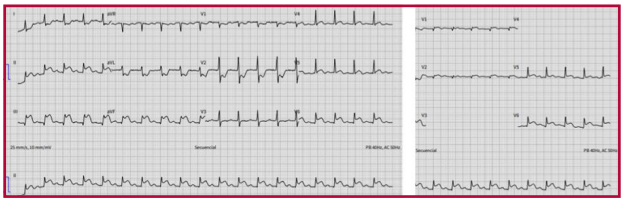

Fig. 1. A) 12-lead ECG showing sinus tachycardia with ST-elevation on the inferior and lower lateral wall (DII, DIII, aVF; V5 and V6 leads) **B)** Right and posterior leads ECG showing ST-elevation both in right and posterior leads (V3R, V4R; V7 and V8)

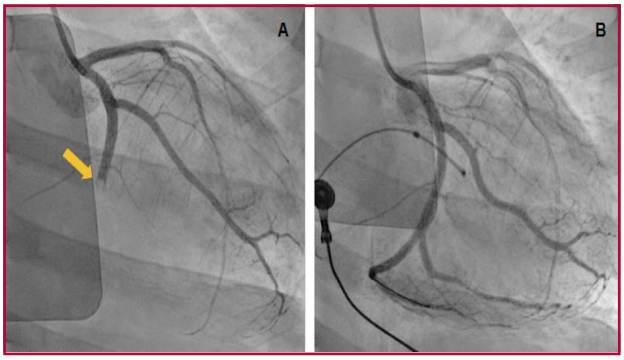

Fig. 1. Coronary cineangiography images. **A)** Right caudal oblique view. The yellow arrow shows the site of occlusion of the AV branch of the circumflex artery, with angiography images consistent with abundant endoluminal thrombotic material. **B)** The same view shows the final angiography result after placement of a drug-eluting stent in the AV branch of the circumflex artery. There is also embolization of thrombotic material in the distal part of the posterior descending branch.

pump. Intravenous methylprednisolone pulses, 3 plasmapheresis cycles, and 1 g rituximab were also prescribed. The patient showed favorable clinical progress and was discharged after 8 days of hospitalization under oral corticosteroids. A triple antithrombotic therapy was selected, including one-month anticoagulation with warfarin and dual antiplatelet therapy with aspirin and clopidogrel, followed by warfarin and clopidogrel. Subsequent cardiology follow-up included cardiac magnetic resonance imaging (MRI) to assess the ventricular function, showing a 49% left ventricular ejection fraction with moderate mitral regurgitation and extensive late enhancement, as well as evidence of extensive necrosis in the inferior and inferolateral segments.

While the incidence of catastrophic APS is low according to literature, this case shows the importance of considering this condition due to the severity and systemic consequences involved.

In our patient, the main target organ was the heart, with ST-elevation acute coronary syndrome (STEACS) secondary to acute occlusion of the circumflex artery. As described above, cardiac occurrences are not the most common, with acute coronary syndrome representing a minority of cases.

This case reflects the importance of considering this diagnosis in young patients with STEACS, together with blood count variations. In addition, the difficulty of interdisciplinary management and rapid decision-making is highlighted. Although thrombus aspiration failed, this strategy might be the most suitable to treat coronary occlusion by limiting the use of antiplatelet agents, and thus, reducing the risk of bleeding.

Besides, a long-term antithrombotic scheme is controversial. While clinical practice guidelines (4,5) recommend only one week of triple therapy for patients with a high risk of bleeding, in this case, the high risk of thrombus led to one-month triple therapy. Warfarin was selected as the anticoagulant, since current literature shows that vitamin K antagonists continue to be better than new oral anticoagulants. (6) Finally, and most importantly, this case proves the relevance of a multidisciplinary and early approach by all the departments involved (Cardiology, Interventionist Cardiology, Emergency, Nephrology, Rheumatology, and Hematology) for the decision-making process in a condition entailing both diagnostic and therapeutic challenges.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web)

Funding

No funding was received.

Acknowledgements

We would like to thank other specialists that contributed to the diagnosis and treatment of our patient: Dr. Nicolás Alvarado (Rheumatology Department), Dr. Verónica Privitera (Hematology Department), and Dr. Federico Varela (Nephrology Department). Hospital Italiano de Buenos Aires.

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This work received the Best Clinical Case Award "Al Cardiólogo Joven" at the 49th Argentine Congress of Cardiology.

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Brugada Syndrome in Children. The Tip of an Uncommon and Fatal Iceberg. First Unusual Case Report in a Child and Her Family Members in Argentina

A 9-month female baby was referred to our hospital following admission in another institution with poor general condition, tachycardia, and fever resulting from the usual immunization schedule. Upon admission, she was under mechanical ventilation, with signs of hemodynamic instability. The ECG showed regular monomorphic ventricular tachycardia (VT), heart rate (HR) >200 bpm, and wide QRS with complete right bundle branch block (CRBBB) (Figure 1a). She was under regular doses of intravenous (IV) amiodarone and propranolol. The patient was unresponsive to adenosine and electrical cardioversion (ECV), and after confirming severe left ventricular systolic function (LVSF) impairment, she received peripheral extracorporeal membrane oxygenation (ECMO) and IV milrinone. After a few hours, the ECG showed sinus rhythm, HR 80 bpm, AV conduction 1:1, PR interval 220 msec, CRBBB, QRS 240 msec, with probable late potentials after the QRS complex, particularly in right precordial leads (Figure 1b). The color Doppler imaging showed absence of structural heart disease, normal coronary arteries at their origin, normal LV diameters with improved LVSF, and moderate dilatation in the right chambers.

Our differential diagnosis was Brugada syndrome (BrS), a sodium channelopathy that might lead to arrhythmia and myocardial involvement, vs giant cell myocarditis, vs arrhythmogenic cardiomyopathy. As a result, a gadolinium enhanced nuclear magnetic resonance was required, which was normal, and allowed us to rule out myocarditis (1) and any mediastinal tumors (2) that may appear with a "Brugada-like pattern" on the ECG. The laboratory infection and toxicology screens were negative. A thorough interview with the parents revealed that the baby was the first child of non-consanguineous parents, the pregnancy was spontaneous and uncomplicated and the delivery was natural. According to the parents, when the child was 6 months old, she had generalized paroxysmal events of tonic-clonic type due to post-immunization fever, which were considered unsignificant by her pediatrician. Her 34-year-old mother claimed to have experienced two syncope events 15 years before, which were preceded by palpitations during physical exercise. Her maternal grandfather experienced sudden death at 22, as well as some of his siblings (Figure 2a). The mother's ECG showed a spontaneous type 1 Brugada pattern (Figure 2b). The Holter showed symptomatic atrial tachycardia (AT) events (Figure 2c) that improved under oral ivabradine.

A genetic test (GT) was requested considering our patient as an index case and using a next-generation sequencing (NGS) panel in accordance with present guidelines. (3) Amiodarone was discontinued, and oral quinidine was administered; the adult dose was adjusted based on the patient's weight and body surface. The patient was stabilized and discharged under home monitor and automated external defibrillator. However, she was readmitted only 12 hours later with HR 270 bpm, wide QRS and CRBBB, but this time responsive to ECV. Atrial tachycardia was assumed, and therapy with oral ivabradine and cilostazol was added; however, she showed torpid evolution with subintrant tachycardias that resulted in readmission and peripheral ECMO. As it became difficult to control her high HR, IV esmolol was given with good response; quinidine and cilostazol were discontinued, and milrinone and sotalol were administered. While the patient was under ECMO we performed an electrophysiology test. No arrhythmia could be induced; thus, an AV node ablation procedure was conducted with placement of a dual chamber epicardial implantable cardioverter-defibrillator (ICD), which revealed failure to capture and high epicardial thresholds in both ventricles. Consequently, the defibrillator lead was replaced in the endocardial right ventricle by a transatrial approach and was programmed to operate in DDD mode. When the patient was no longer under ECMO, she experienced constant VT with a HR 170 bpm, both properly censored and reverted using antitachycardia therapy, reinduction after a few minutes,

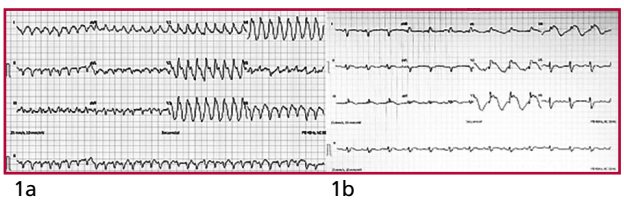

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Fig. 1.

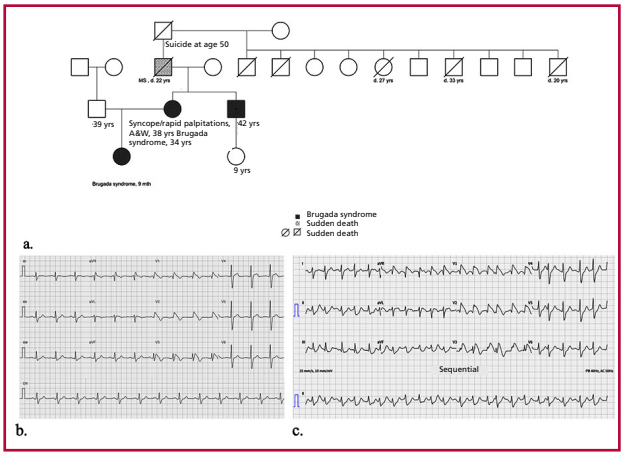

Fig. 2. a) Family history; b) Maternal ECG; c) Maternal ECG, atrial tachycardia

and appropriate shock. As VT became more frequent in DDD and/or VVI mode with HR 90 bpm, we decided to reset the ICD to VVI 60 bpm and managed to fully control tachycardia.

The GT revealed a heterozygous pathogenic variant in SCN5A gene c.535C>T (p.Arg179*). We know that this genetic change leads to early protein truncation, resulting in absent or abnormal protein, and subsequent loss of cardiac sodium channel function, a genetic mechanism considered to be the cause of BrS. The patient's mother and mother's brother (i.e., the patient's uncle) are both carriers of the same pathogenic variant in SCN5A gene. Fortunately, her uncle's daughter is negative, i.e., she has not inherited her father's pathogenic variant (Figure 2 a). As with other genetic disorders with an autosomal dominant inheritance pattern, although our patient inherited her mother's mutation, and her mother, in turn, inherited the variant from her own father, there is still no explanation why the patient had such a severe phenotype, while her mother barely experienced any symptoms and her uncle had none (and even had a normal ECG). Cascade testing was performed for the rest of the family, those with negative results were exempted from longitudinal follow-up, and prevention and monitoring actions were taken in those with a positive GT.

In addition, epilepsy was confirmed in the baby, and she was prescribed levetiracetam with optimal response. The pathophysiology shared by idiopathic epilepsy and BrS is an impaired transmembrane ion current caused by mutations in genes that encode the subunits of several ion channels. Sodium channel dysfunction is a common pathogenic route for these two clinical conditions, suggesting that it might be the cause of heart and brain manifestations in this group of patients. (4)

In 1987 doctors Brugada treated a 3-year-old patient who recovered from cardiac arrests and had a structurally normal heart, whose sister experienced sudden death at the same age. Both children had a distinct ECG pattern that is now known as BrS. (5) Research then focused on young adults with no evident heart disease, recognized as a major cause of sudden death (SD). While several studies estimate that BrS represents up to 20% of SD cases in infants and young individuals, little is known about the prevalence, diagnostic criteria, natural course, and treatment of this disease in pediatric patients. (6)

This very young patient with BrS first experienced monomorphic ventricular arrhythmias with CRBBB from the left ventricle, and severe atrial arrhythmias requiring exceptional therapy, and finally received a drug treatment uncommon for patients with BrS. In this case, arrhythmias were later controlled using betablockers and maintaining a very low HR for her age.

The SCN5A mutation results in absence of a protein, which is associated with severe phenotypes. Her mother and other family members were diagnosed after the child's diagnosis, and both follow-up and counseling was arranged for family planning. The latter highlights the importance of careful symptom assessment, detailed family history, and thorough ECG review.

This case is intended to raise awareness on the importance of BrS identification in pediatric patients, in an attempt to understand the pathophysiology of this complex, heterogeneous and life-threatening condition. We also emphasize the need for further studies and exchanges in order to build consensus in terms of Brugada syndrome management both in children and adults.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website).

Funding

No funding was received.

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Harlequin Syndrome as an Unusual Presentation of Carotid Artery Dissection

This is the case of a 40-year-old male patient with no relevant medical history.

In February 2022, the patient presented to the Emergency Department, with headache and acute right palpebral ptosis after playing football. A magnetic resonance angiography (MRA) of the neck and intracranial vessels was performed, which resulted in right internal carotid artery dissection (ICAD) diagnosis (Figure 1 A & C).

The patient was treated with low molecular weight heparin and then aspirin.

He progressed with improvement of his Horner syndrome (palpebral ptosis, miosis), so he was discharged 4 days later.

The MRA was repeated after 30 days, and it revealed, as the previous imaging test though to a lesser extent, a reduction in the diameter size and irregularity of the right internal carotid artery from the visible extracranial area to the bifurcation, with no apparent involvement of the ipsilateral middle cerebral artery. It also revealed a larger luminal diameter of the postbulbar segment of the right internal carotid artery compared to the previous imaging test (Figure 1 B & D).

The patient continued with milder palpebral ptosis. Anisocoria improved as well.

Three months later, while monitoring his condition, the patient claimed to notice flushing and sweating on the left side of the face during strenuous physical activity, with the right side remaining pale and non-sweaty (Figure 2).

These symptoms remitted after a few minutes of rest.

ICAD clinical findings may include local signs and symptoms such as unilateral headache (periorbital and frontotemporal pain in the face or anterior part of the neck), Horner syndrome (miosis, ptosis, and anhidrosis), and cranial nerve paralysis. Horner and Harlequin syndromes result from compression, stretching, or hypoperfusion of the sympathetic nerve fibers (vasomotor and sudomotor fibers) within the carotid wall. (1)

Acute onset painful Horner syndrome is almost a pathognomonic sign of ICAD. Asymmetrical flushing (Harlequin syndrome) is an uncommon finding in ICAD, as both vasomotor and sudomotor fibers innervating the face are mostly adjacent to the external carotid artery wall. (2)

The MRA is currently the preferred technique to confirm ICAD diagnosis.

Awareness of this cosmetically striking syndrome following ICAD is useful to avoid unnecessary additional tests, as it spontaneously disappears over time. (3)

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website).

Ethical considerations

The patient signed informed consent form for the publication of his photograph.

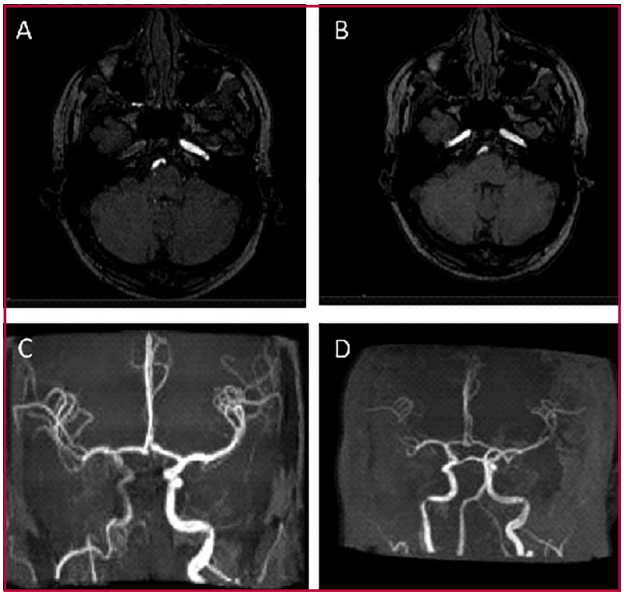

Fig. 2. A & C. Magnetic resonance angiography of neck vessels upon admission **B & D.** Magnetic resonance angiography after 30 days

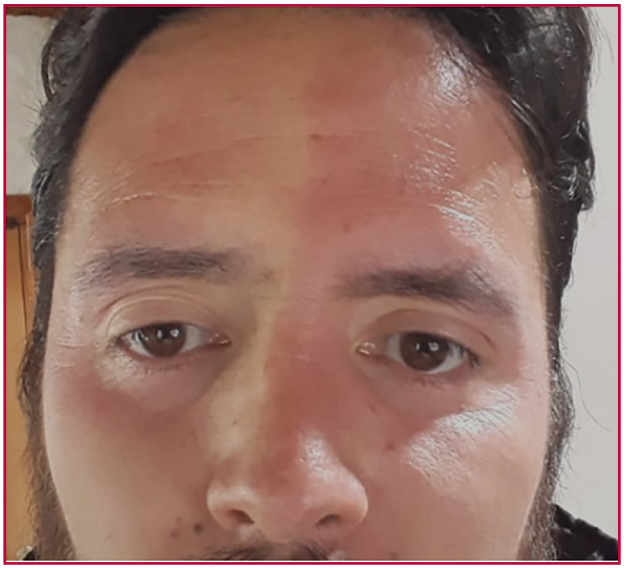

Fig. 1. Paleness and anhidrosis on the right side of the face after strenuous physical activity. Ipsilateral palpebral ptosis is also observed.

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