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A Dangerous Combination for Stroke in Young Patient: Assimilation of the Atlas and Anti β2-Glycoprotein I Antibodies

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RESUMEN

Hombre de 45 años de edad que acudió a consulta por lateropulsión a la izquierda y mareos. La tomografía de cráneo mostró infarto cerebelar bilateral. En la resonancia magnética se observaron los mismos hallazgos más una zona hipodensa en el tallo cerebral en relación al otro territorio arterial comprometido. En el estudio de laboratorio fue relevante el hallazgo de anticuerpos anti β2-microglobulina I. En la angiografía cerebral se observaron los territorios obstruidos y una rara malformación de la unión vertebrobasilar, la cual se corroboró con una tomografía con reconstrucción tridimensional; el diagnóstico fue asimilación del atlas. Concluimos que debido a la turbulencia creada en el segmento V3 de la arteria vertebral rodeando el atlas, la presencia de anti β2-microglobulina I fue la posible causa de los infartos en el paciente.

SUMMARY

A 45 year old male was admitted to the hospital for unsteady gait and dizziness. The brain CT showed bilateral cerebellar ischemic stroke. The MRI corroborated the stroke in the cerebellum with a third acute ischemic stroke in the pons. The laboratory work up showed a positive anti β2-glycoprotein I antibodies. The cerebral angiogram showed the territories occluded and also a rare malformation of the cranium vertebral junction called assimilation of the atlas. We concluded that due to the turbulence created in the V3 segment of the vertebral artery surrounding the atlas, the presence of the anti β2-glycoprotein was the cause of the infarction in this patient.

A 45 year old man came to the Emergency Room (ER) for dizziness. The symptoms had started 4 days before with light-headedness and disorientation, followed by dizziness, tinnitus and mild occipital headache 2 hours after. The patient attempted to stand up and realized his unsteady gait, went to a primary care physician who ordered a brain CT and then referred the patient to our center for further attention.

The family history was non contributory; he used to be a heavy drinker, last drinking binge 10 years ago. Denied smoking or illicit drug abuse. Upon further questioning, we were told by the relatives that he had a similar episode in the past but had not looked for medical attention. The patient had multiple sexual partners and was never tested for sexual transmitted disorders (STDs).

The neurological exam showed bilaterally rotatory nystagmus, hearing loss of the left ear, intact muscle strength in both extremities, intact sensitivity, proprioception; knee and Achilles reflex 3-, left Babinski with ipsilateral limb ataxia; staggering gait with tendency to fall to the left.

The brain CT showed multiple hypodense, poorly defined lesions in both cerebellar hemispheres with no enhancement; significant perilesional edema with preserved anatomy of the fourth ventricle (figure 1). The brain MRI showed T1 hypodensity on the right cerebellum with acute stroke on the left side plus hypodensities in the occipital lobe on the left side as well as in deep temporal areas (figure 2). The cerebral angiogram showed absence of the left posterior inferior cerebellar artery (PICA) with narrowing of the left vertebral artery in the V3 segment. The anterior circulation was normal (figure 3). The audiometric studies and brain stem evocated potentials showed null response in the left auditives pathways, with bioelectrical conduction from the
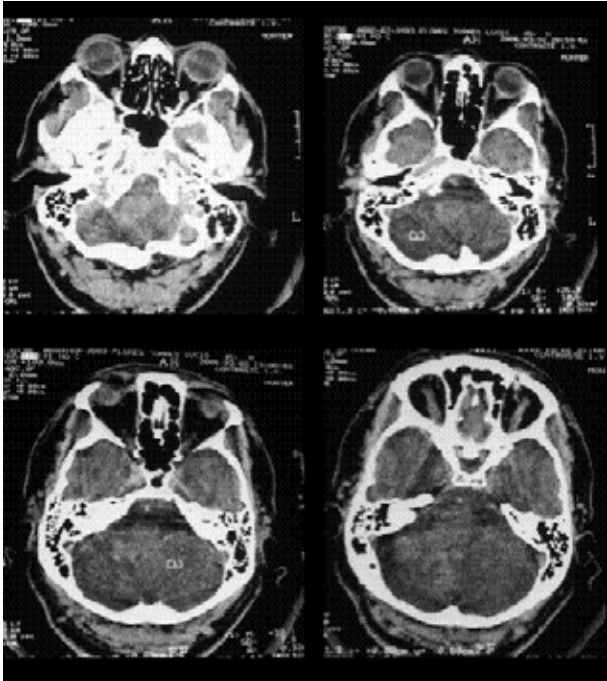
Figure 1. CT scan showing multiple hypodense zones in the left cerebellar hemisphere, ill-defined with perilesional edema without enhancement to the contrast medium
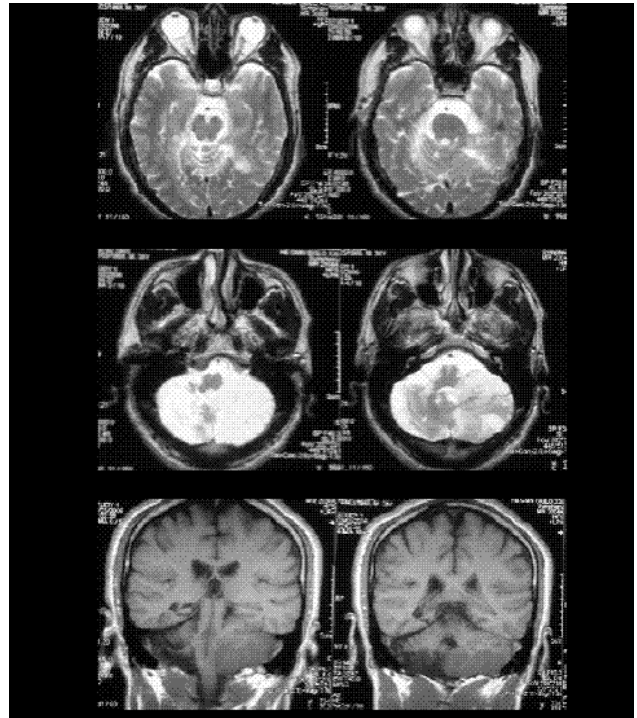

Figure 2. MRI demonstrating infarction areas in both cerebellar hemispheres predominantly in the left and the midline vermix, and another lesion in the left occipital lobe and the thalamic left side with discrete deviation of the brain stem to the right side
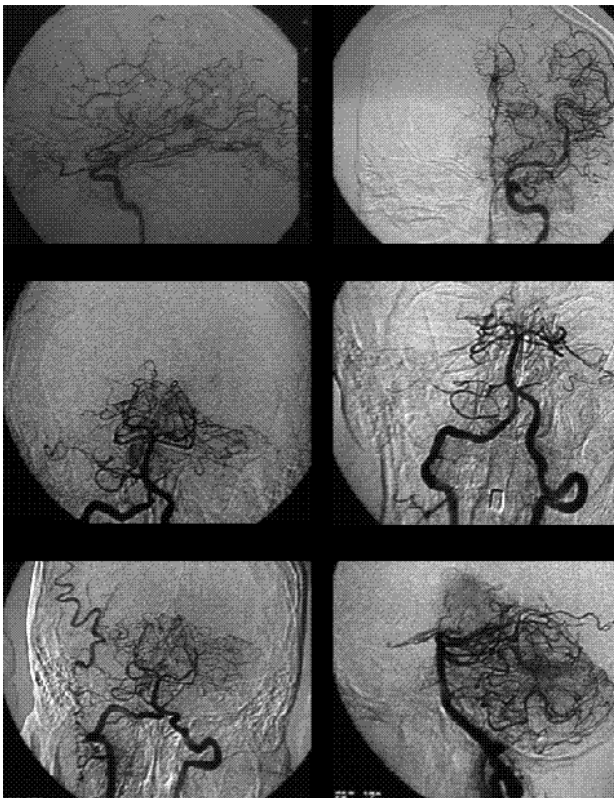

Figure 3. Cerebral angiogram which showed absence of the left Posterior inferior cerebellar artery (PICA) with narrowing of the diameter of the left vertebral artery in the V3 segment
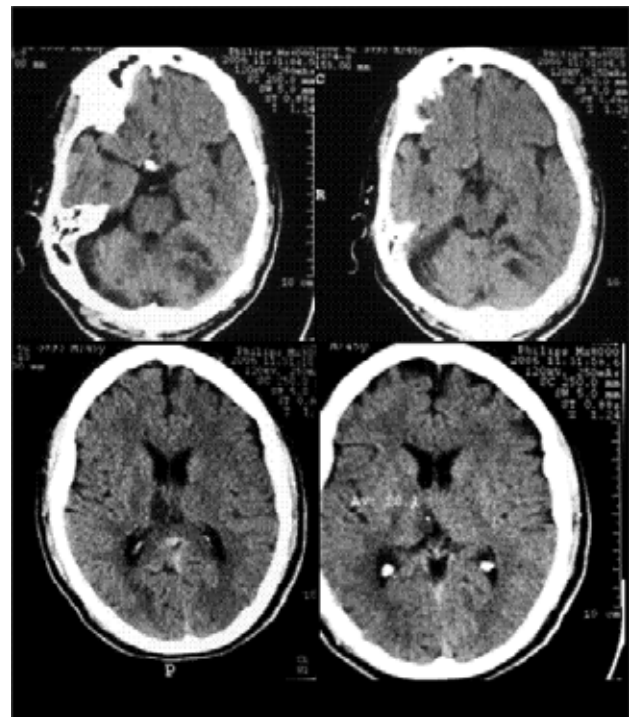

Figure 4. A CT scan with hypodense zone in the diencephalic area without hydrocephalus, and the already seen cerebellar infarctions
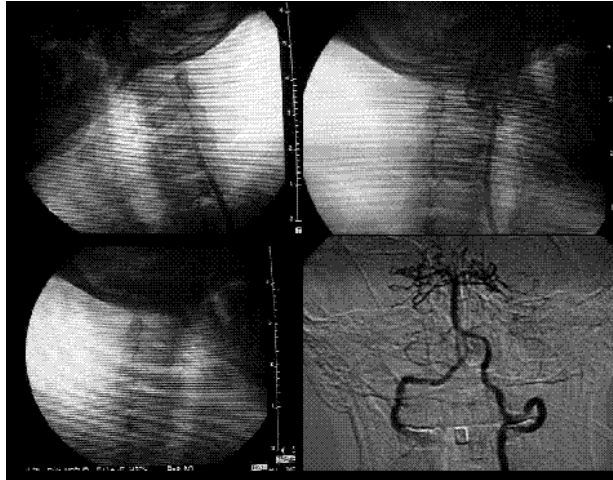
Figure 5. During a second angiogram were identified abnormalities in the bone structure of C1 but the study didn't show them clearly
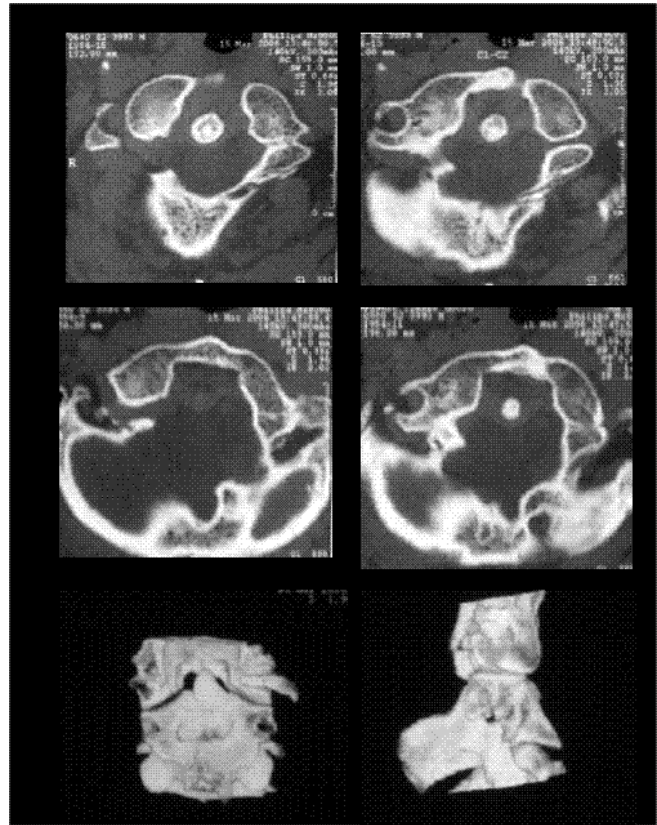

Figure 6. A 3D tomography of the craniovertebral junction showed Assimilation of the Atlas

pontine area to the prethalamic area; hypermetric saccades, and left optokinetic reflex were absent in the left side.

On the ward, the patient developed Parynaud syndrome secondary to another dorsal midbrain stroke (figure 4). He was put on warfarin overlap with heparin thinking the patient was having embolic strokes. The carotid duplex was normal with an intima/media index within normal limits. The transesophageal echocardiogram was normal as well as the Holter monitor. Due to ST changes seen in the EKG and the fact that the patient did not have a traditional cardiovascular risk factors and was having a stroke, a myocardial nuclear stress test was ordered; the results did not show any abnormalities in the cardiac perfusion. The laboratory work up was normal and the hypercoagulable panel is showed in table I, being significant only for a positive anti β2-glycoprotein I (β2GPI) IgM isotype according to the range provided by the laboratory. The Neurovascular Service recommended a radiological examination of the craniovertebral junction as well as a second angiogram with emphasis on the posterior circulation. During the angiogram, the patient involuntarily turned the head to the left and a total occlusion of the vertebral flow on the left V3 seg-

ment was observed, with reopening upon straightening of the head. During the angiogram, abnormalities in the bone structure of C1 were identified but the study did not show them clearly (figure 5). A 3D CT reconstruction of the craniovertebral junction showed assimilation of the atlas (figure 6).

Discussion

The additive effects of vascular insults were most likely the etiology for the repetitive stroke in our patient. There are no cases in the reviewed medical literature with concurrent anti β2GPI antibodies and atlas assimilation. We will review some basic concepts needed to justify our approach and diagnosis in this case.

In general, the vertebral artery arises from the subclavian artery. This has been classically divided in 4 segments: V1 to V4; V1 goes from its origin to the C6 vertebra, V2 segment runs from C6 until C2, ascending through the foramen transversarium, then leaving it to encircle the axis in the outside surface to enter again at the first cervical vertebra; V3 segment refers to the artery portion leaving C2 until the entering the cranial dura mater following a sharp curve to the surface of the atlanto-occipital joint and finally the V4 segment follows the interior surface of the dura matter, advancing through the foramen magnus.[1] The intracranial branches of the vertebral arteries are the anterior spinal artery, the posterior spinal artery, the perforating branches for the bulbar olives and the posterior inferior cerebelar artery (PICA), which is the most important and the biggest branch of the vertebral artery.[2] The vertebral artery, due to its tortuous course can be compressed at different levels, but even if compressed, only few entities have been reported to cause vertebrobasilar insufficiency.

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Table I
Special laboratory work up

VDRL	Negative
ELISA HIV	Negative twice
HCV	Negative twice
HBsAg	Negative twice
HBcAb	Negative twice
Anti β2GPI IgM (U/mL)	13.5 (Normal below 10)
Anti β2GPI IgG (U/mL)	11.8 (Normal below 20)
Anti aCL IgM (UMPL/mL)	6.8 (Normal below 10)
Anti aCL IgG (UGPL/mL)	2.5 (Normal below 11)
CSF analysis	Colorless, negative coagulation, 1 WBC per mm^3, 844 erythrocyte, glucose 71 mg/dL, chloride 127 mEq/L, protein 39 mg/dL, negative gram stain, dark field negative stain

Vertebrobasilar insufficiency can be either extrinsic or intrinsic.[3] The intrinsic compression is mainly due to atherosclerotic lesions,[3-5] and the extrinsic compression is related to tumors, osteophytes, myofascial bands, disk herniation and craniovertebral joint malformations, among these the assimilation is the most common.[6] There are two cases reports of two patients with transient rotational compression of the vertebral artery caused by herniated cervical disk,[7] resembling the occlusive phenomena that we witnessed in our patient except for the absence of hypercoagulable state in the reported case.

The most common sites of vertebral artery compression are at its origin, i.e. the V1 segment; close to the transverse foramina of C6, during its ascending pathway through the other vertebrae and finally where the vertebral artery turns around the lateral mass of the axis.[8,9]

The assimilation of the atlas is certainly a common malformation (about 2.7 % of the general population) but due to the extensive damage already present in the areas of the posterior circulation, the patient was not considered a surgical candidate. This malformation is more common in men,[10-12] consisting of continuity between the occipital bone and the atlas, more specifically, between the anterior arch of the atlas and the bone cortex, or bone marrow reaching posteriorly the lateral masses or the less prominent posterior arch. It is rare to have symptoms due to this malformation, but when they are present, is usually reported as dizziness, ataxia, cervical pain and sometimes long descending pyramidal

tract symptoms due to compression of the spinal cord for the posterior displacement of the odontoid apophysis.[12]

The indications for revascularization of the posterior circulation are mainly in patients with intraarterial occlusive lesions and extrinsic compression. The procedures are two: reimplantation of the vertebral artery and intracranial by-pass;[13,14] being the latter the eariest and most useful for its brief operation time and better access.[9] Unfortunately, this technique was not an option in our patient because the damage was already done and there is no evidence to support these interventions because we account for a good medical therapy.[15,16]

Is there a place for the anti β2-glycoprotein I antibody in this patient? The first observation regarding the lupus anticoagulant (LA) was that it caused thrombosis instead of bleeding in patients with systemic lupus erythematosus; later a cascade of studies have been done to identify the antiphospholipid antibodies (aPL) in several clinical scenarios.[17] This family of antibodies includes the original LA, which is a prothrombotic antibody binding phospholipids; in vitro showed a prolonged partial prothrombin time (ppt).[18] The other predominant antibody is the anticardiolipin antibody (aCL). This aCL is reported as a titer specific for the isotype IgG, IgM or IgA,[18] and binds the surface of the endothelial cells with many epitopes. There are recent data involving other proteins as more specific antigenic targets for aCL. The β2GPI is a plasma protein expressed on the cells involved in anti-phospholipid syndrome-related tissue damage[19] and believed to be a natural anticoagulant[20] and is considered the predominant target of autoimmune aPL and even more specific for antiphospholipid syndrome (ALS)[20,21] although other proteins like prothrombin, protein C, protein S and annexin V could play a minor role on the physiopathology.[22]

The pathogenic mechanism in ALS is a very complex and yet not fully understood issue. First, these antibodies could interfere with the function of the coagulation cascade proteins leading to a procoagulant state.[23] The direct binding of β2GPI to the endothelial cell surface is facilitated by the constitutive negative charge of the endothelial surface, enhanced surface expression of negatively charged phophatidyl serine during endothelial cells apoptosis after an injury[24] and for the annexin II that acts as a receptor for β2GPI to activate endothelial cells.[25,26] The binding of anti β2GPI to the already attached protein creates a neoprotein (when combined with the membrane antiphospholipids) that activates endothelial cells, inducing the adhesion molecules expression and

cytokines production potentiating a prothrombotic endothelium.[23,27] There is also evidence of platelet activation by aPL, activation of mononuclear cells by native human β2GPI and the secondary release of interferon-γ (INF-γ) that activates the endothelial cell;[14,28] also there is an increasing data trying to link this nouvelle protein to thrombosis.

Finally, since the prevalence in overall populations of aPL for LA is 8 %, IgG a CL 6.5 % and IgM aCL 9.4 %[29,30] and the clinical syndrome is less frequent, there are speculations that a "second hit" could be involved in the clinical expression of ALS. This could include traumatic injury to the vascular bed (e. g. flow turbulence), non immunologic procoagulant factors or the presence of infection leading to cytokine production and endothelial cell activation.[31]

The Sapporo criteria for ALS are not met in our case.[32] These criteria have a sensitivity of 71 % and a specificity of 98 %,[33] which leaves some room to include patients with other prothrombotic proteins and stroke. The presence of circulating anti β2GPI created a prothrombotic environment with the resulting the turbulence of the tortuous course of the vertebral artery trying to accommodate to the atlas assimilation and triggering the stroke. This can be the second hit needed for all these group of proteins to activate the endothelial cell. This case is unique because this combination, but the most important goal is not to look an atlas assimilation in young people with stroke, but to make the point that a thorough investigation is needed when the cardiovascular risk factors are not present.

Sometimes the etiology of stroke in patients with diabetes, hypertension, dyslipidemia, smoking in old population with widespread intra or extracranial atherosclerosis and cardiomegaly with atrial fibrillation, is very obvious, but there are other subgroups of people in the middle-age who might have some of this classical risk factor for stroke but it is not enough to explain such a repetitive and wide damage. Even in older patients with all the possible vascular comorbidities, they can also have other factors that increase the risk of stroke. It is of paramount importance to investigate the etiology of stroke in all ages, like atherosclerosis, arrhythmias, dissection, vascular malformations, infections or hypercoagulable states with their diverse and broad etiologies.

In our case, the presence of the atlas assimilation was most likely congenital, which means the left VA was malformed for years and it caused the stroke until the patient was in his forties. Is there any explanation for this? We do not know for sure, but it could be that the tear and wear of the vessels over the years by endlessly turbulent flow might have finally triggered the attachment of the antibody to the endothelium and caused the acute stroke. These are speculations and further research is needed to clarily this point.

The patient was discharged on oral anticoagulants and was followed up by neurosurgery service to evaluate instrumented occipitovertebral fusion but the patient refused the procedure and decided to go back to his primary physician to follow the INR as recommended. A neurological consultation in the future was indicated.[34]

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