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Ischemic stroke of hematological origin, a more common cause than we think? A study of two cases EHU Oran

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Abstract :
Hematological disorders are a rare cause of stroke, and they are the subject of publications, but they are rarely investigated after a stroke due to the high cost of paraclinical investigations, the cost-effectiveness of which remains to be defined.
They account for less than one percent of ischemic stroke etiologies.
The most commonly implicated mechanism is hyperviscosity, usually associated with polycythemia, thrombocytosis, or paraproteinemia.
In this article, we present two cases of patients in whom an underlying hematological disorder was identified as a predisposing factor for ischemic stroke.
Keywords*: Ischemic stroke • Hematological pathology • Sickle cell disease • Paroxysmal nocturnal hemoglobinuria • Hyperhomocysteinemia.*

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I. Introduction:

Sickle cell disease is a genetic disorder of hemoglobin (Hb) that is inherited in an autosomal recessive manner. The disease results from a single point mutation in the sixth codon of the ß-globin gene, causing the synthesis of an abnormal Hb, HbS[1,2].

The pathophysiology of ischemic stroke in sickle cell disease is complex, involving intimal hyperplasia of intracranial vessels, thrombosis, and very rarely, fat embolism from areas of bone necrosis[1,2].

Paroxysmal nocturnal hemoglobinuria (PNH), also known as Marchiafava-Micheli disease, is a rare disorder of the hematopoietic stem cell, caused by an acquired somatic mutation in the PIG-A gene. This results in a blockade of the synthesis of glycosylphosphatidylinositol (GPI) anchor molecules, which are responsible for attaching numerous proteins to the cell surface. Among these proteins are CD59 and CD55, complement inhibitory proteins that normally prevent the final assembly of the membrane attack complex (MAC) [3,4,5]

It has been known for several years that even moderate hyperhomocysteinemia is a risk factor for venous thrombosis (with a risk multiplied by 2.5-3.4) and a cardiovascular risk factor (as atherosclerotic disease can in turn lead to the occurrence of stroke)[6]

In this article, we present two cases of ischemic stroke with hematological origins, which require a comprehensive investigation to identify them, especially in young patients.

II. OBSERVATIONS:

1/Observation n° 1:

A 67-year-old right-handed woman, married with two children (G2P2), and a medical history of hypertension, presents with a confusional state (global amnesia and temporal-spatial disorientation) and acute-onset tetraplegia for the past 10 days, preceded by akinetic mutism.

Brain CT scan shows bilateral hypodensities in the frontal region within the territory of the anterior cerebral artery, and brain MRI reveals symmetric bilateral lesions in the centrum semiovale, suggestive of metabolic encephalopathy or fat embolism (Figure 1), as reported by the radiologists.

Cardiac evaluation (trans-thoracic echocardiography, Doppler ultrasound of the supra-aortic trunks, Holter ECG) is normal.

Abdominal CT scan reveals stage A acute pancreatitis complicated by splenic infarction.

Fundoscopy shows non-proliferative stage 1 sickle cell retinopathy.

Laboratory findings include:

Normochromic normocytic regenerative anemia with a hemoglobin level of 8 g/dL, associated with the presence of sickle cells on peripheral blood smear.

Biochemical cholestasis syndrome: total and direct hyperbilirubinemia (32 mg/dL, 4 mg/dL, 27 mg/dL, respectively); alkaline phosphatase at 114 U/L; and gamma-glutamyl transferase at 133 IU/L, indicating an obstruction in the main bile duct without specifying its nature.
Lipase levels are three times higher than the normal range.
Hemoglobin electrophoresis shows a heterozygote S and C double profile.

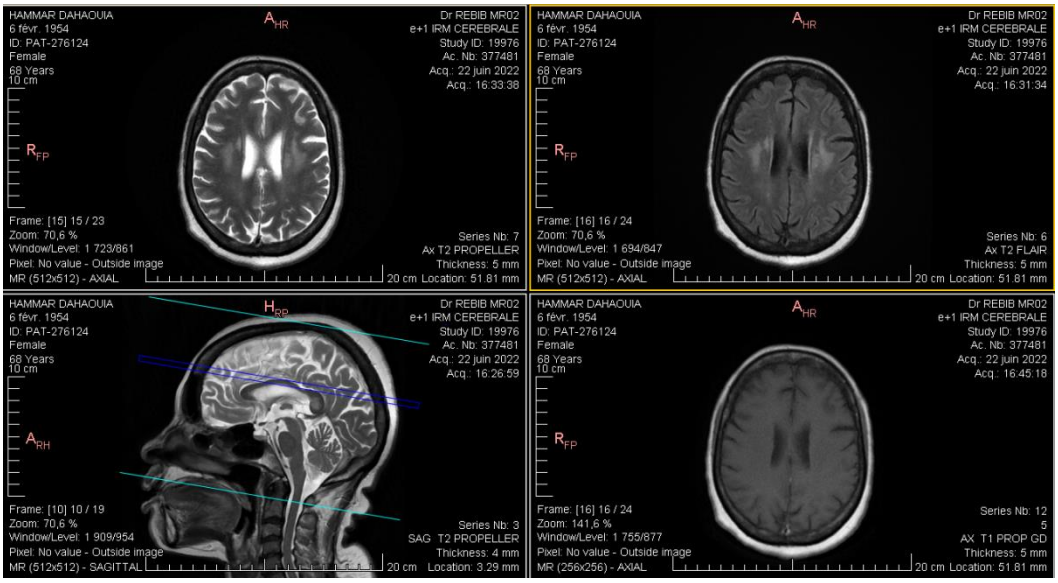

FIGURE 01: Bilateral and symmetrical lesions in the centrum semiovale, suggestive of metabolic encephalopathy; however, the appearance of the lesions is consistent with fat embolism.

Based on the clinical symptoms, imaging results, and laboratory findings, a diagnosis of underlying heterozygous sickle cell disease was made.

Management options including hydration, body warming, antiplatelet therapy,

Antibiotic treatment, and vaccination against encapsulated organisms were suggested, and the patient showed a favorable outcome.

2/Observation n° 2:

A 40-year-old married woman with 3 children (G5P3) and a medical history of hypertension and hypothyroidism was admitted with a decreased level of consciousness (Glasgow Coma Scale score of 9/15) and right hemiparetic syndrome (NIH Stroke Scale score of 14).

The initial brain CT scan was normal, but brain MRI showed multiple hyperintense signals on T2 FLAIR sequences, restricted diffusion with concurrent decreased apparent diffusion coefficient (ADC) values, and some areas of hemorrhagic transformation, suggestive of a thromboembolic origin (Figure 2).

Cardiac evaluation (transthoracic echocardiography, Doppler ultrasound of the supra-aortic trunks, Holter ECG) was normal, except for pericardial effusion related to hypothyroidism.

Laboratory tests revealed a regenerative microcytic hypochromic anemia with a hemoglobin level of 8 g/dL, anisopoikilocytosis, and the presence of schistocytes on peripheral blood smear.
Testing for anti-SAPL antibodies was negative.
Hyperhomocysteinemia was observed with a level of 17.21 umol/L.

Flow cytometry revealed the presence of a large paroxysmal nocturnal hemoglobinuria (PNH) clone on red blood cells, accounting for 90.95% of the cells.

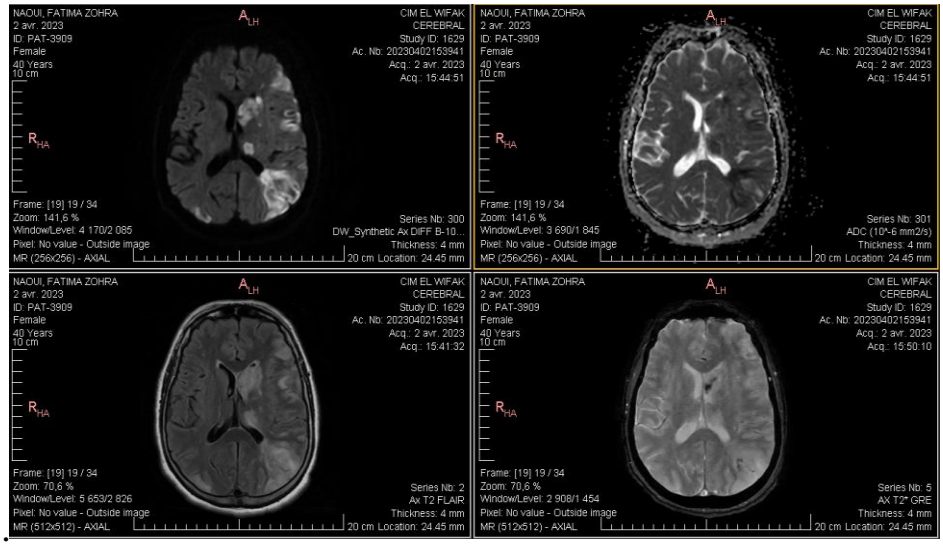

FIGURE 02: Multiple hyperintense signals on T2 FLAIR sequence with restricted diffusion and decreased ADC values, not systematically distributed, with some areas showing hemorrhagic transformation.

The patient was started on therapeutic anticoagulation treatment along with statins. Additionally, she received supplementation with folic acid and her hypothyroidism was corrected, as it was identified as an aggravating factor. She showed improvement with regained consciousness, and her NIH Stroke Scale score at discharge was 4.

A myelogram was scheduled to determine whether the patient had the classic or aplastic form of paroxysmal nocturnal hemoglobinuria (PNH).

A discussion with the hematology team was initiated to consider initiating a long-term treatment regimen with eculizumab infusions.

III. Discussion :

These two cases demonstrate hematological origins of ischemic stroke, sometimes even multiple causes in the same individual.

In the first case, the ischemic stroke is secondary to double heterozygous S and C sickle cell disease. Hemolysis events can lead to the formation of brown pigment stones that obstruct the main bile duct, resulting in cholestasis syndrome and obstruction of the Vater's ampulla, leading to acute pancreatitis as presented in this case[7].

Pancreatic encephalopathy is a rare complication of severe acute pancreatitis. Inflammation and necrosis of the pancreas result in the release of proteases and lipases into the bloodstream. Their action on the cerebral parenchyma, after the blood-brain barrier becomes compromised, leads to diffuse inflammatory edema and cellular necrosis [8,9].

The involvement can be microvascular and/or macrovascular, and several factors are implicated:

Microvascular occlusion: retinal vessels, which caused non-proliferative stage 1 sickle cell retinopathy in this case.

Factors related to red blood cells: polymerization of HbS, global rheological abnormalities (dehydration, mechanical fragility, decreased deformability, increased blood viscosity, presence of dense cells).

Macrovascular occlusion: intimal hyperplasia of cerebral vessels (vasculopathy), as well as other vessels (pulmonary, splenic, renal, penile, etc.). Macrovascular occlusion is thought to be the determining factor in cerebrovascular accidents (strokes) due to intimal hyperplasia and may also affect other organs (lung, spleen leading to splenic infarcts, kidneys, etc.) [10].

In the second case, there is an association of two hematological causes responsible for the occurrence of stroke: hyperhomocysteinemia and paroxysmal nocturnal hemoglobinuria (PNH).

The occurrence of venous and arterial thrombosis in PNH is thought to be related to two mechanisms:

1-Plasma nitric oxide deficiency (which binds to free Hb during hemolysis) causing endothelial and platelet activation, thrombin generation, and vasoconstriction.

2-Formation of phospholipid-rich microparticles[11,12,13]..

Thromboembolic complications are more frequent in the classic form of PNH than in the aplastic form. Moderate hyperhomocysteinemia (15-100 micromol/L) is a common condition, affecting 5 to 8% of the population. It can have genetic origins, most commonly associated with a thermolabile variant of MTHFR, or it can be acquired, often due to nutritional deficiencies (vitamin B12, folate, vitamin B6). It can also occur in cases of renal or hepatic insufficiency or as a side effect of certain medications[11,12,13].

IV. Conclusion:

In our experience, the clinical presentation does not typically raise suspicion of a hematological origin of stroke, except in cases of multiple infarcts that warrant investigation for antiphospholipid antibody syndrome. The involvement of hematological factors in the development of arterial thrombosis is likely, although rarely in isolation, but rather as contributing factors. However, it is uncommon for secondary prevention after a stroke to be altered by the discovery of a blood abnormality, such that the absence of therapeutic implications does not justify systematic investigation. Nevertheless, it is important to keep in mind that a cerebral infarction can sometimes reveal an undiagnosed hematological disorder.

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