ADVANCED ATHEROSCLEROSIS AND STROKE IN A YOUNG PATIENT WITH CUTANEOUS LYMPHOMA

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ABSTRACT

Atherosclerosis might begin in childhood with the development of fatty streaks. However, the advanced lesions of atherosclerosis, which complicate with ischemic events, are frequent rather in the elderly. We report here a case of early severe and symptomatic atheromatosis of large cervical vessels, in a young patient with some risk factors and strong familial history of vascular disease who was diagnosed with Sezary syndrome.

Keywords: atherosclerosis, stroke, cutaneous lymphoma, young adult

INTRODUCTION

Atheroslerosis is considered to be anage dependent process, involving interactions between multiple genetic and environmental factors. It affects medium and large size artheries, characterized by endothelial dysfunction and cronic inflammatory response, leading to the appereance of atherosclerotic plaque. This plaque is formed through the accumulation of lipids, cholesterol and calcium within the intima of the vessel wall. (1) These atherosclerotic plaques cause changes in the vascular wall and as the artery walls thicken a decrease or a block of the blood flow to target organs appear. (2) The progression of atherosclerotic disease appears over decades in most people and often is asymptomatic. However strokes in young adults are uncommon and often a diagnostic challenge, simptomatic atherosclerosis being considered a rare cause.

CASE REPORT

A 34 years old man, smoker, with overweight, at least 3 years history of hypertension without treatment and both parents hypertensive before the age of 30, presented to ER for right upper limb weakness and slurred speech. He has no other comorbidities except pityriasislichenoid. The neurologic examination revealed motor deficit of right upper limb (4/5), brisk symmetric deep tendon reflexes and transcortical motor aphasia. The usual laboratory assessment revealed only mild hypercholesterolemia.

No evidence of inherited prothrombotic states like protein S or protein C deficiency, antithrombin III deficiency, factor V Leiden mutation, prothrombin gene mutation, elevated homocysteine or acquired prothrombotic state like antiphospholipid antibody syndrome was detected.

Both brain CT and MRI (Fig. 1) showed evidence of cerebral small vessel disease with lesions spread in semioval center white matter bilaterally, including a recent left frontal subcortical lesion, probably responsible for the recent clinical symptoms. Cervical and transcranial Doppler ultrasound examination showed severe stenosis of the left middle cerebral artery at the M1 segment (> 80%)

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and of the right internal carotid artery at the bifurcation (> 80%) – Fig. 2. The heart ultrasound examination detected the presence of an aortic annulus calcification.

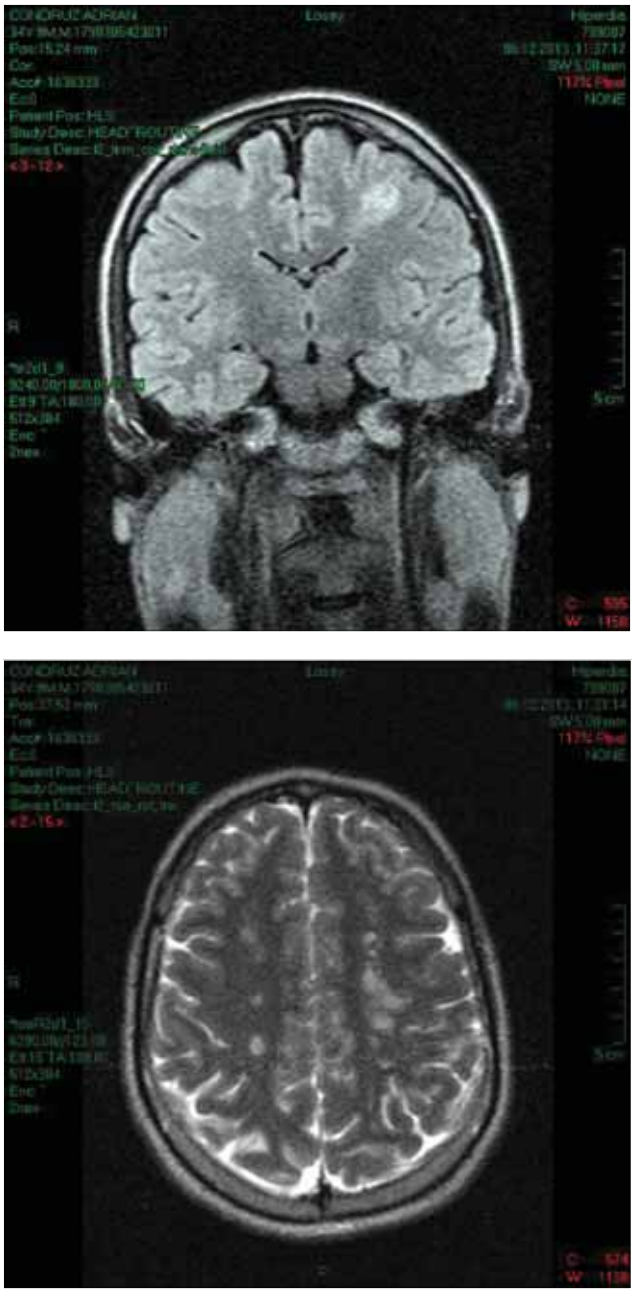

FIGURE 1. *Patient MRI (FLAIR and T2 sequences) showing multiple ischemic lesions in the subcortical white matter*

He received antithrombotic (aspirin 100 mg) and statin (atorvastatin 20 mg) treatment. Neurologically, the patient's condition improved; speaking disorder and right upper limb weakness remitted.

After 4 months his skin lesions have worsened and a skin biopsy was performed. He was diagnosed with mycosis fungoides. However the presence of persistent erytroderma and the appearance of laterocervicallimphadenopathy, with breathing disorders led to hospitalization in the Department of Haematology, where he was diagnosed with Sezary syndrome. The patient succumbed to the illness within 1 week of hospitalization.

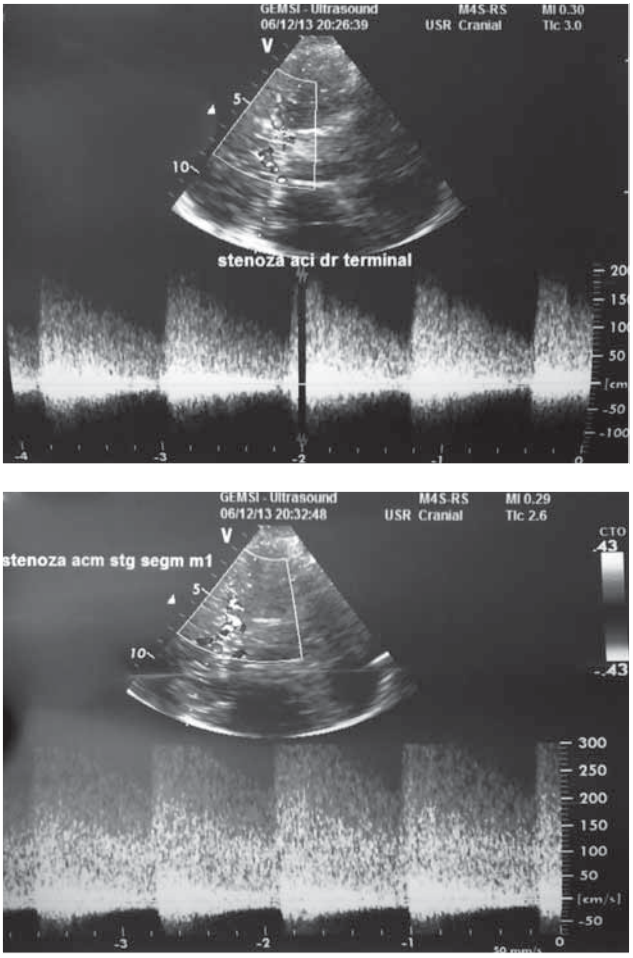

FIGURE 2. *Carotid ultrasound demonstrating stenosis of both internal carotid arteries*

DISSCUSION

Ischemic stroke in young adults presents many and diverse causes. Advanced atherosclerosis represents a rare cause of ischemic stroke at young adults. Although the process of atherosclerosis is known to begin in childhood, usually symptomatic advanced lesions don't appear at young adults.

We report a case of advanced atherosclerosis at a 34 years old male, with some risk factors and strong familial history of vascular disease.

In this case, the presence of severe (> 80%) bilateral stenosis atcervical and transcranial Doppler ultrasound examination (the left middle cerebral artery at the M1 segment and of the right internal carotid artery at the bifurcation) and the presence of

an aortic annulus calcification at the heart ultrasound examination lead us to a premature atherosclerosis etiology.

A major role in the development of atherosclerosis is owned by environmental factors such as diet or smoking and metabolic risk factors such as hypertension, dyslipidemie and diabetes mellitus. Nevertheless these risk factors don't explain the hereditary susceptibility to atherosclerosis. In the recent years, interest in the identification ofgenetic inherited traits grew.

Single gene disorders are the most important evidence of the genetic implication of atherosclerosis. (3) Usually monogenic diseases like familial hipercholesterolemia, mutation in APOB-100 gene, elevates plasma levels of LDL, by affecting the activity of hepatic LDL receptors, which normally had a role in eliminating LDL from plasma. (4,5)

Nevertheless, in majority of cases it is impossible to identify a single gene disorder and probably multiple major genes may be involved. There is a high probability that the existence of such a wide range of atherosclerotic diseases within the population may be determined by polymorphisms within genes in lipid metabolism, inflammation, and thrombogenesis. A good example is apolipoprotein E gene polymorphism, that includes alleles *E2*, *E3*, *E4* and his interaction with hiperlipidemia III. Individuals with hiperlipidemie III are homozygous for E2 allele but not vice versa. (6). Therefore, other genetic or environmental interactions are necessary to produce hyperlipidemia besides homozygosity for the *E2* allele.

In the past several years, the use of genetic models like inbred genetic strains, transgenic animalshelped gain a better understanding of mechanisms and discover a potential therapy. (7)

It had been made experimental studies on inbred mouse strains which differ in their predisposition to atherosclerosis, studies which have pointed whether differences in lipid profiles were influenced by particularly dietary terms or it shows that underlying genetic factors contribute to atherosclerotic susceptibility.

The authors introduced *apoE* – deficient in C57BL/6J mice or strain susceptible to atherosclerosis and C3H/HeJ mice, a prototypical atherosclerosis mouse resistant strain. The study proved that in mice with an *apoE* – deficient background that were fed a chow diet, the level of plasma lipids were approximately the same. The study has also showed that mice with the C3H/HeJ background developed smaller lesions of atherosclerosis than mice with C57BL/6J (B6) background, indicating that differences in atherosclerosis susceptibility are not related to differences in plasma lipid level. (8)

However, at short time after experiencing stroke, our patient was diagnosed with cutaneous lymphoma. It might be possible that this hematologic condition precipitated the cerebrovascular disease, by systemic factors.

CONCLUSIONS

We report here a case of early severe and symptomatic atheromatosis of large cervical vessels, in a young patient with some risk factors and strong familial history of vascular disease.

Unknown genetic inherited traits might be important for atheromatosis in such cases.

We hope that with the use of genetic models will help us understand of the pathogenesis of this process that will lead us to discover a new anti atherosclerosis therapy.

REFERENCES

1. **Weber C., Noels H.** Atherosclerosis: current pathogenesis and therapeutic options. *Nature Medicine*. 2011; 17(11):1410-1422.
2. **Rubin J.B., Borden W.B.** Coronary heart disease in young adults. *Current Atherosclerosis Reports*. In press.
3. **Milewicz D.M., Seidman C.E.** Genetics of cardiovascular disease. *Circulation*. 2000; 102(20):IV103-111.
4. **Bourbon M., Duarte M.A., Alves A.C., Medeiros A.M., Marques L., Soutar A.K.** Genetic diagnosis of familial hypercholesterolaemia: the importance of functional analysis of potential splice-site mutations. *Journal of Medical Genetics*. 2009; 46(5):352-357.
5. **Kane J.P., Havel R.J.** Disorders of the biogenesis and secretion of lipoproteins containing the B apolipoproteins. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The Metabolic & Molecular Bases of Inherited Disease*. 8th edition. Vol. 2. New York, NY, USA: McGraw-Hill; 2001. pp. 2717-2752.
6. **Mahley R.W.** Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science*. 1988; 240(4852):622-630.
7. **Dzau V.J., Gibbons G.H., Kobilka B.K., Lawn R.M., Pratt R.E.** Genetic models of human vascular disease. *Circulation*. 1995; 91(2):521-531.
8. **Shi W., Wang N.J., Shih D.M., Sun V.Z., Wang X., Lusis A.J.** Determinants of atherosclerosis susceptibility in the C3H and C57BL/6 mouse model: evidence for involvement of endothelial cells but not blood cells or cholesterol metabolism. *Circulation Research*. 2000; 86(10):1078-1084.