Our patient was diagnosed with PNS due to the symptom improvement observed after one year of follow-up. Unlike the other 5 patients, in our patient the diagnosis of prostate cancer was established 2 years after onset of OMS and, as in the case reported by Nasri,[6] he presented 2 tumours.

We would like to highlight that OMS is considered a classical PNS, although it is rarely associated with prostate cancer; however, it should be considered in cancer screening studies, even years later. Furthermore, even in the case of periodic treatment with immunoglobulins, only treatment of the underlying tumour may help improve symptoms.

References

1. Berger JR, Bensalem M, Dalmau J. A brainstem paraneoplastic syndrome associated with prostate cancer. J Neurol Neurosurg Psychiatry. 2009;80:934—5, http://dx.doi.org/10.1136/jnnp.2008.153015.
2. Cuenca Hernández R, Esquivel Lopez A, Gordo Mañas R, Hípola González D. Síndrome opsoclonus mioclonus de evolución benigna y cáncer de próstata. Neurología. 2020;35:64—5, http://dx.doi.org/10.1016/j.nrl.2017.07.015.
3. Storstein A, Raspotnig M, Vitaliani R, Giometto B, Graus F, Grisold W, et al. Prostate cancer. Hu antibodies and paraneoplastic neurological syndromes. J Neurol. 2016;263:1001—7, http://dx.doi.org/10.1007/s00415-016-8090-7.
4. Baloh RW, DeRossett SE, Cloughesy TF, Kuncl RW, Miller NR, Merrill J, et al. Novel brainstem syndrome associated with prostate carcinoma. Neurology. 1993;43:2591—6 https://pubmed.ncbi.nlm.nih.gov/8255462/
5. Armangue T, Sabater L, Torres-Vega E, Martinez-Hernandez E, Arino H, Petit-Pedrol M, et al. Clinical and immunological features of opsoclonus-myoclonus syndrome in the era of neuronal cell surface antibodies. JAMA Neurol. 2016;73:417—24, http://dx.doi.org/10.1001/jamaneurol.2015.4607.
6. Nasri A, Kacem I, Jerdak F, Djebara MB, Mejri N, Sidhom Y, et al. Paraneoplastic opsoclonus-myoclonus-ataxia syndrome revealing dual malignancy. Neurol Sci. 2016;37:1723—5, http://dx.doi.org/10.1007/s10072-016-2632-8.

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Mutations in the type IV collagen gen (*COL4A1*) as an unusual etiology of cerebrovascular disease in young adults

Mutaciones en el gen del colágeno tipo IV (*COL4A1*) como etiología infrecuente de enfermedad cerebrovascular en el adulto joven

Dear Editor,

Mutations in type IV collagen genes (*COL4A1* and *COL4A2*) constitute an extremely rare cause of cerebrovascular disease. The first descriptions of the clinical spectrum of this association report the frequent presence of porencephalic lesions with neurological symptoms of highly variable severity, including intellectual disability, ischaemic and haemorrhagic stroke, and epilepsy. In 2005, Plaisier et al.[1] reported a subgroup of patients with well-defined clinical characteristics, showing a frequent combination of both large- and small-vessel disease, especially intracranial aneurysms, as well as ophthalmological defects and non-neurological systemic symptoms. The authors called this constellation of symptoms hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome.

We present the case of a 23-year-old woman who attended the emergency department due to a 3-day history of intense holocranial headache that did not improve with usual analgesia. She did not report phono- or photophobia, focal neurological symptoms, or intracranial hypertension. Results from the neurological examination, including evaluation of meningeal signs, were completely normal. A head contrast CT scan showed a carotid aneurysm with no signs of intracranial haemorrhage; a lumbar puncture revealed absence of xanthochromia or elevated protein levels. A brain MRI study confirmed the presence of an aneurysm and showed extensive leukoencephalopathy mainly affecting the deep white matter. A porencephalic cystic cavity was observed at the level of the anterior horn of the lateral ventricle (Fig. 1). A diagnostic cerebral angiography study was also performed (Fig. 2).

The patient was born in Argentina, and her medical history is not available. The patient's mother reported history of mild psychomotor retardation attributed to prolonged childbirth, and cataract surgery at an early age. She has no known family history, although she has no contact with her father's family. A comprehensive blood analysis including kidney function and creatine kinase (CK) delivered normal results. An ophthalmological examination revealed bilateral

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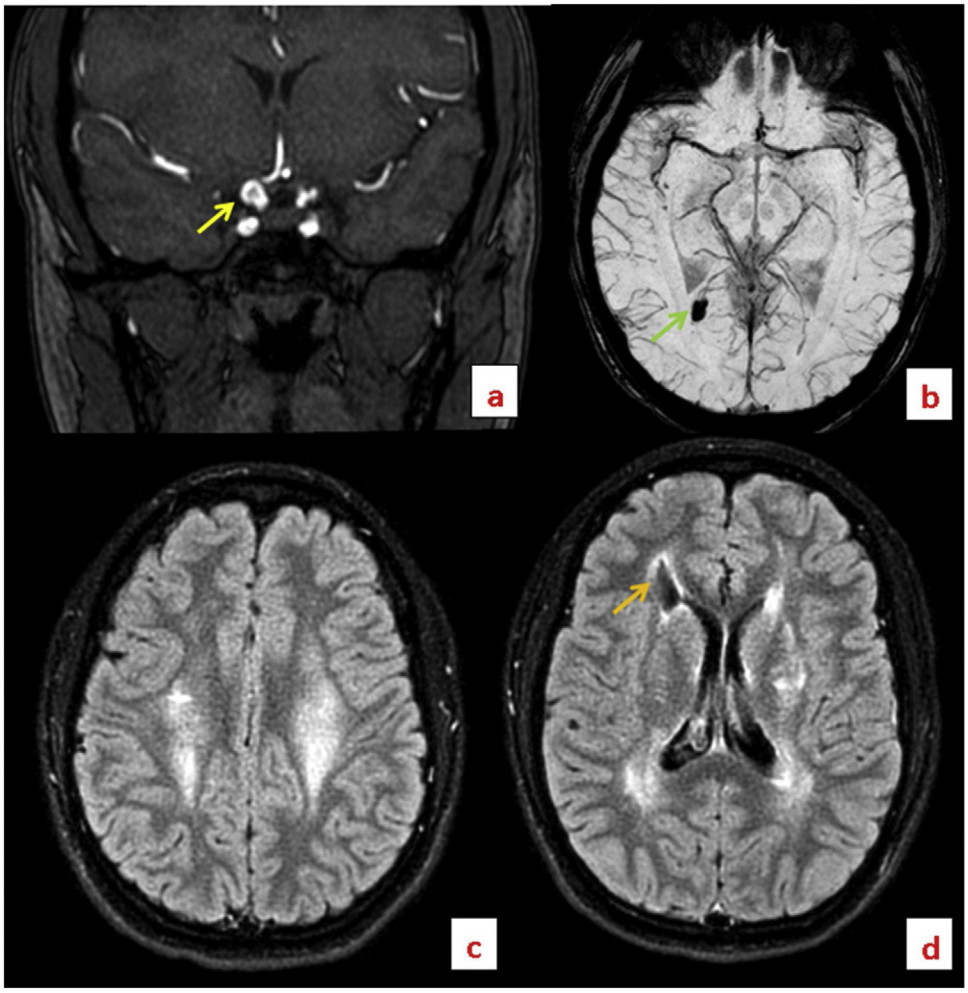

Figure 1 MRI scans. a) Coronal 3D time-of-flight sequence showing a saccular aneurysm (yellow arrow) on the terminal segment of the right intracranial internal carotid artery. b) Axial SWI sequence showing a focus of paramagnetic susceptibility (green arrow) in the right peritrigonal region, corresponding to a chronic-subchronic haemorrhagic focus. c) Axial FLAIR sequence showing hyperintense lesions in both corona radiata, in association with leukoencephalopathy. d) FLAIR sequence showing hyperintense lesions in periventricular areas, as well as in the adjacent deep subcortical white matter, compatible with leukoencephalopathy. A porencephalic cyst (orange arrow) is also present.

microcornea and mild vessel tortuosity in the right retina. Results of the genetic study were positive for *COL4A1* mutation c.2317G>A (p. Gly773Arg), in heterozygosis. Results of the study of genes involved in such other hereditary diseases as CADASIL or Fabry disease were negative.

The patient was diagnosed with a cerebral microangiopathy associated with the *COL4A1* gene, with some symptoms of HANAC syndrome. The aneurysm was treated with an endovascular procedure and genetic counselling was provided. To date, the patient has not presented other symptoms, such as nephropathy or muscle cramps. Results from such diagnostic tests as kidney ultrasound and 24-hour urine protein test were negative. Headache was controlled with low doses of amitriptyline as a preventive treatment. The family segregation study yielded negative results.

Discussion

The differential diagnosis of cerebrovascular disease in young patients is challenging. Our patient presents some clinical and radiological data that may suggest type IV collagen diseases and related syndromes.

A) Cerebral microangiopathies in young adults may be due to genetic or acquired causes.
B) In the event that cerebral aneurysms are detected, especially if they are hereditary, it is essential to screen for connective tissue diseases and such cellular matrix diseases as polycystic kidney disease or collagen diseases.[2]
C) Type IV collagen diseases (*COL4A1* and *COL4A2*) should be suspected in case of small- and large-vessel disease. Leukoencephalopathy is predominantly frontal and temporal, mainly

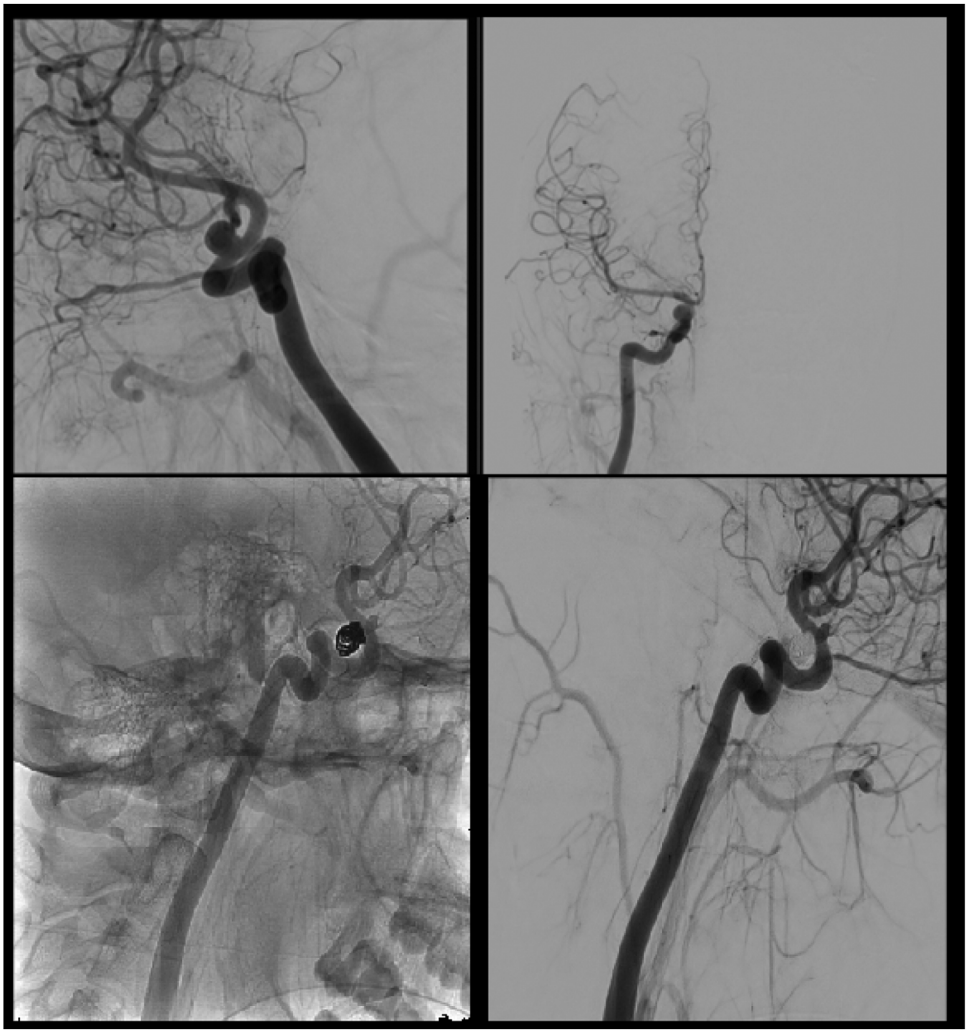

Figure 2 Cerebral angiography study. The top images are from the diagnostic arteriography in the late arterial phase: oblique view (first image) and anteroposterior view (second image). The third and fourth images show the embolisation of the aneurysm with coils.

affecting the centrum semiovale. Presence of porencephalic cavities is variable; these lesions are more frequent in more aggressive phenotypes of the disease and are usually misinterpreted as perinatal insults.

D) Within the spectrum of symptoms associated with *COL4A1*, HANAC syndrome may be considered a mild phenotypic expression with well-defined clinical characteristics. Cerebral aneurysms are located in the internal carotid artery, especially at the level of the siphon. The copresence of non-neurological symptoms is frequent, and they should be directly sought. Eye anomalies include the presence of microcornea, cataract, and retinal vascular anomalies; therefore, an ophthalmological examination is required. Nephropathy may be subtle, manifesting as renal cysts or microhaematuria. Myalgia is the least frequent symptom; slight elevations in serum CK levels are occasionally the only sign.[1,3]

Therefore, we should highlight the fact that although hereditary diseases are extremely infrequent individually, as a group they constitute a significant cause of cerebrovascular disease in young patients. Early diagnosis of patients enables appropriate genetic counselling.

References

1. Plaisier E, Gribouval O, Alamowitch S, Mougenot B, Prost C, Verpont MC, et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. N Engl J Med. 2007;357:2687—95, http://dx.doi.org/10.1056/NEJMoa071906. PMID: 18160688.
2. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. Neurology. 2018;91:e2078—88, http://dx.doi.org/10.1212/WNL.0000000000006567. Erratum in: Neurology. 2020 Feb 18;94(7):332. PMID: 30413629; PMCID: PMC6282239.
3. Alamowitch S, Plaisier E, Favrole P, Prost C, Chen Z, van Agtmael T, et al. Cerebrovascular disease related to COL4A1 mutations in HANAC syndrome. Neurology. 2009;73:1873—82, http://dx.doi.org/10.1212/WNL.0b013e3181c3fd12. PMID: 19949034; PMCID: PMC2881859.

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