Hemorrhagic Cerebrovascular Disease: An Unusual Presentation of Hyperhomocysteinemia

Accidente cerebrovascular hemorrágico: una inusual presentación de hiperhomocisteinemia

Acidente vascular cerebral hemorrágico: uma apresentação incomum da hiper-homocisteinemia

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Abstract

Introduction: Stroke is a major cause of morbidity and mortality worldwide, with hemorrhagic stroke being the deadliest form of acute stroke. Therefore, the cause of the event should be determined to direct the associated therapy and take preventive measures. Hyperhomocysteinemia has been described as a rare

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etiology of stroke. Although hyperhomocysteinemia has been associated with venous thrombotic events, altered endothelial function, and procoagulant states, its clinical role in stroke remains controversial. *Case description:* We present a case of a 60-year-old male patient with primary autoimmune hypothyroidism who presented with dysarthria, facial paresis, and left upper-limb monoparesis after sexual intercourse. A simple skull computed tomography scan showed hyperintensity in the right basal ganglion, indicating an acute hemorrhagic event. Etiological studies were performed, including ambulatory blood pressure monitoring, cerebral angiography, and transthoracic echocardiogram, which ruled out underlying vascular pathology. During follow-up, vitamin B12 deficiency and hyperhomocysteinemia were detected, without other blood biochemical profile alterations. Supplementation was initiated, and homocysteine levels gradually decreased, without new neurological deficits observed during follow-up. *Conclusion*: Quantification of homocysteine should be considered in patients with a cerebrovascular disease without apparent cause, as documenting hyperhomocysteinemia and correcting its underlying etiology are essential not only for providing appropriate management but also for preventing future events.

Keywords: Cerebrovascular disorders; stroke; hyperhomocysteinemia; vitamin B12 deficiency; cerebral hemorrhage.

Resumen

Introducción: el accidente cerebrovascular es una causa importante de morbilidad y mortalidad en todo el mundo, y el accidente cerebrovascular hemorrágico es la forma más mortífera de accidente cerebrovascular agudo. La determinación de la causa del evento es esencial para dirigir la terapia asociada y poder tomar medidas preventivas. La hiperhomocisteinemia se ha descrito como una etiología poco frecuente de accidente cerebrovascular. Aunque esta se ha asociado con eventos trombóticos venosos, disfunción endotelial alterada y estados procoagulantes, sigue siendo controvertido su papel clínico en el accidente cerebrovascular. *Descripción del caso*: se presenta el caso de un hombre de 60 años con hipotiroidismo autoinmune primario que presentó disartria, paresia facial y monoparesia del miembro superior izquierdo después de un encuentro sexual. Una simple tomografía computarizada de cráneo mostró hipointensidad en la región del ganglio basal derecho, que indicaba un evento hemorrágico agudo. Se realizaron estudios etiológicos, incluyendo monitorización ambulatoria de la presión arterial, angiografía cerebral y ecocardiograma transtorácico, que descartaron patología vascular subyacente. Durante el seguimiento, se detectó deficiencia de vitamina B12 e hiperhomocisteinemia, sin otras alteraciones en el perfil bioquímico sanguíneo. Se inició la suplementación y los niveles de homocisteína disminuyeron gradualmente, sin observar nuevos déficits neurológicos durante el seguimiento. *Conclusión:* la cuantificación de homocisteína debe ser considerada en casos de enfermedad cerebrovascular sin causa aparente, dado que documentar la hiperhomocisteinemia y corregir su etiología subyacente es esencial no solo para proporcionar un manejo adecuado, sino también para prevenir eventos futuros.

Palabras clave: enfermedad cerebrovascular; hiperhomocisteinemia; déficit de vitamina B 12; hemorragia intracerebral.

Resumo

Introdução: o acidente vascular cerebral (AVC) é uma das principais causas de morbidade e mortalidade em todo o mundo, sendo o AVC hemorrágico a forma mais letal de AVC agudo. A determinação da causa do evento é essencial para direcionar a terapia associada e poder tomar medidas preventivas. A hiper-homocisteinemia tem sido descrita como uma etiologia rara de acidente vascular cerebral. Embora a hiper-homocisteinemia tenha sido associada a eventos trombóticos venosos, disfunção endotelial alterada e estados pró-coagulantes, seu papel clínico no AVC permanece controverso. *Descrição do caso:* apresentamos o caso de um homem de 60 anos com hipotireoidismo autoimune primário que apresentou disartria, paresia facial e monoparesia do membro superior esquerdo após relação sexual. A tomografia computadorizada de crânio mostrou hipointensidade na região do gânglio da base direito, indicando

evento hemorrágico agudo. Foram realizados estudos etiológicos, incluindo monitorização ambulatorial da pressão arterial, angiografia cerebral e ecocardiograma transtorácico, que descartaram patologia vascular subjacente. Durante o acompanhamento, foram detectados deficiência de vitamina B12 e hiper-homocisteinemia, sem outras alterações no perfil bioquímico sanguíneo. A suplementação foi iniciada e os níveis de homocisteína diminuíram gradualmente, sem novos déficits neurológicos observados durante o acompanhamento. *Conclusão:* a quantificação da homocisteína deve ser considerada em casos de doença vascular cerebral sem causa aparente, pois documentar a hiper-homocisteinemia e corrigir sua etiologia subjacente é essencial não apenas para fornecer manejo adequado, mas também para prevenir eventos futuros.

Palavras-chave: doença cerebrovascular; hiper-homocisteinemia; deficiência de vitamina B 12; hemorragia intracerebral.

Introduction

Stroke is defined as a global or focal alteration in brain function with a rapid onset lasting longer than 24 h or leading to death without any other apparent cause (1). The latest Global Burden of Disease study (Global Burden of Disease) in 2017 estimated that nearly 24.1 million new stroke cases and 700.000 more stroke-related deaths occurred compared to previous years, and 10% of these events are secondary to intracerebral hemorrhages (ICHS), where blood extravasation causes damage into the cerebral parenchyma (2,3). Hemorrhagic stroke generates a more significant disease burden, resulting in higher mortality and disability-adjusted life years (DALYS). In developing countries, mortality can reach 80% in moderate- to low-income countries, like Colombia, making it the deadliest form of acute stroke, with no or minimal trend toward improvement over time. In Colombia, of the 32.557 stroke-related deaths between 2011 and 2015, up to 83% were caused by a hemorrhagic stroke (4,5).

Therefore, the cause of the event should be determined to direct the associated therapy and take preventive measures. Among the rare etiologies, hyperhomocysteinemia has been described as an entity with a prevalence of 1% in the general population and has been associated with some venous thrombotic events, procoagulant states, and altered endothelial function (6,7). Hyperhomocysteinemia is characterized by increased plasma levels of homocysteine and related metabolites; previous studies reported that elevated plasma homocysteine level is an important modifiable risk factor and is associated with higher mortality rates from ischemic stroke, cardiovascular diseases, and peripheral artery disease by contributing to increased oxidative stress, endothelial dysfunction, and atherosclerosis (8-10,9-11). However, the clinical role of hyperhomocysteinemia in stroke is still controversial. We present a 60-year-old patient without major cardiovascular risk factors presenting with an acute hemorrhagic brain event and vitamin B12 deficiency associated with hyperhomocysteinemia that was documented as the only alteration and possible cause of stroke. This case made us realize a possible strong

association between hyperhomocysteinemia and not only procoagulant events but also possible hemorrhagic ones that can occur if this condition is not appropriately treated.

Case report

A 60-year-old male patient from Cali (Colombia) with a significant medical background for primary autoimmune hypothyroidism visited the emergency department with complaints of dysarthria, facial paresis, and left upper-limb monoparesis without other associated symptoms lasting for 3 h, which began 5 min after engaging in sexual intercourse. Upon admission, his blood pressure, heart rate, respiratory rate, and saturation were 134/84 mmHg, 78 bpm, 19 rpm, and 94% without supplemental oxygen, respectively, and he was afebrile. His physical examination revealed dysarthria with left central facial paralysis, ipsilateral hemiparesis, 4/5 strength in the upper and lower limbs, and a National Institutes of Health Stroke Scale score of 6.

The stoke code was activated in the institution, and a simple skull CT scan was performed (Figure 1), which showed hyperintensity in the right basal ganglion region consistent with an acute hemorrhagic event in this area.

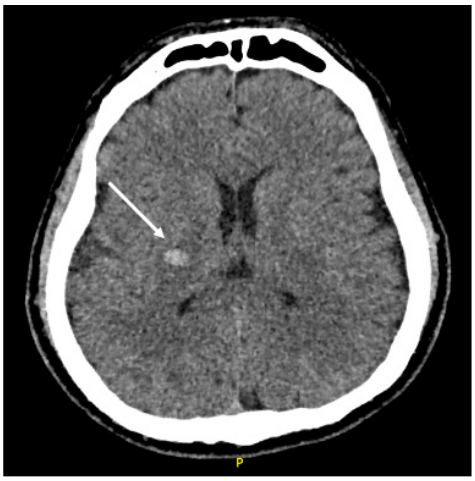

Figure 1. Simple CT: Coronal section. An intraparenchymal hematoma of the right basal ganglion is observed in the topography of the putamen and the internal capsule of the patient (arrow)

Thus, invasive pressure monitoring with an arterial line was indicated, and the patient was transferred to the intensive care unit for neurological and blood pressure monitoring. Paraclinical tests were performed (see Table 1), which showed no alterations in blood parameters, electrolyte levels, or kidney or thyroid function. For the etiological examination, ambulatory blood pressure monitoring was performed, which eliminated arterial hypertension. Cerebral angiography was performed without any abnormal findings, except for right gangliobasal hematoma,

which eliminated vascular pathology as a cause of a stroke as aneurysms, arteriovenous malformations, and neoplasia were also ruled out. In addition, a transthoracic echocardiogram was performed, which showed negative findings for ischemia. The evolution findings were favorable, with gradual improvement of the deficit. No further complications occurred during hospitalization, and thus, no intravenous vasodilators were administered.

Table 1. Results of paraclinical studies of hospitalization and consultation

Laboratory	Patient	Reference value
Hemoglobin (g/dL)	12.6	13.7-17.5
Hematocrit (%)	36.1	40.1-51
Mean body volume (fl)	109	79-92.2
Mean body hemoglobin (pg)	38.2	25.7-32.2
Red cell distribution width (%)	13.9	11.6-14.4
Leukocytes (uL) (%)	4490	4230-9070
Neutrophils (uL) (%)	2170	1780-5380
Lymphocytes (uL) (%)	1880	1320-3570
Monocytes (uL) (%)	280	30-820
Eosinophils (uL) (%)	140	40-540
Platelets (uL)	185000	163000-337000
IgA gliadin (UR/mL)	24.71 (negative)	0-25
IgG gliadin (UR/mL)	1.68 (negative)	0-25
Vitamin B12 (pg/mL)	100 (at the emergency visit)	279-996
B2 microglobulin (pg/mL)	1.9 (normal)	1.1-2.4
IgG cardiolipin (GPL, U/mL)	1.2	0-15
IgM cardiolipin (MPL, U/mL)	0.3	0-15
Protein electrophoresis	Albumin: 57.8 Alfa: 3.4 Alfa 2: 8.1 Beta 1: 6.9 Beta 2: 7.7 Gamma: 16.1 Slight increase in beta 2 and doble migration in alfa 2 region. No monoclonal spike.	Albumin: 55.8-66.1 Alfa 1: 2.9-4.9 Alfa 2: 7.1-11.8 Beta 1: 4.7-7.2 Beta 2: 3.2-6.5 Gamma 1: 1.1-18.8
Homocysteine (umol/L)	>50	4.4-10.8
Folic acid (ng/mL)	11.8	5.4-18
HbA1C (%)	5.8	<6.2
Total cholesterol (mg/dL)	161	<200
HDL (mg/dL)	40	>60
LDL (mg/dL)	205	<70
Triglycerides (mg/dL)	132	<150
TSH (uUI/mL)	3.4	0.34-4.25
Free T4 (ng/dL)	1.09	0.7-1.24
Acs intrinsic factor (AU/mL)	87.05	1.21-1.52

The patient was discharged after 3 days with indications for an outpatient follow-up at the internal medicine and neurology departments. During a neurology consultation, his vitamin B12 levels were evaluated due to the high prevalence of neuropsychiatric symptoms associated with vitamin B12 deficiency in our population. Therefore, it is common practice to routinely measure these levels from hospitalized patients as a preventive measure, even in the absence of symptoms. The serologic vitamin B12 levels were <100 pg/mL, and homocysteine testing was requested, which showed levels of >50 pg/mL. In this context, the supplementation was started, which gradually decreased the homocysteine levels. During follow-up, the patient did not present new neurological deficits. When malabsorption was considered a cause of vitamin B12 deficiency, celiac disease was ruled out, IgA and IgG anti-gliadin were negative, and a paraneoplastic compromise was excluded by normal protein electrophoresis. Finally, positive antibodies against intrinsic factors were found, suggesting that vitamin B12 deficiency was caused by pernicious anemia.

Discussion

Stroke is a highly prevalent pathology nowadays, with important implications for the quality of life and high morbidity and mortality (12). The advances in treatment and management affected the prognosis and rehabilitation of stroke patients (13). Hemorrhagic stroke accounts for 20% of bleeding episodes (10) and is divided into ICH and subarachnoid hemorrhage (SAH). Although less common than ischemic events, hemorrhagic events result in higher morbidity and 30-day mortality rates ranging between 35% and 52%, which is 5 times higher than the rate associated with ischemic stroke.

The most common primary cause of ICH is hypertension, given its deleterious effect on small penetrating arteries originating from the large intracerebral vessels. Most lesions are found in the putamen, internal capsule, thalamus, and pons. Another primary cause of ICH is cerebral amyloid angiopathy (AA). Among the secondary causes, vascular malformations, neoplasms, and hemorrhagic transformation of ischemic infarcts were identified (10). Here, we report the case of an adult Caucasian man with a compensated autoimmune hypothyroidism as the only important medical antecedent who presented with onset neurological deterioration caused by an acute gangliobasal hemorrhagic event with the most frequent causes being ruled out. His ambulatory blood pressure monitoring was normal, and during hospitalization blood pressure values were normal; however, cerebral angiotomography revealed vascular malformations and malignancy. Moreover, AA is a pathology that more commonly occurs in elderly people, women, and patients with a history of Alzheimer's disease, and thereby, the age range of our patient was ruled out to be much lower than those who commonly presented AA (14). Furthermore, intracranial hemorrhage did not compromise the lobe that is classically affected

in AA, and no radiologic signs of previous microhemorrhages (15,16). Additionally, the images are not suggestive of cerebral amyloid angiopathy (CAA). The modified Boston criteria require that CAA can be suspected if multiple hemorrhages in the lobar, cortical, or cortico-subcortical region and cortical superficial siderosis occur; thus, this patient is unlikely diagnosed with CAA (16). Finally, vitamin B12 deficiency with secondary hyperhomocysteinemia was observed and considered as the possible primary cause of the event as it is the only abnormal parameter of this patient's blood tests. The reviews conducted to date revealed that hyperhomocysteinemia has been documented as a risk factor for hemorrhagic events; however, vitamin B12 and folic acid levels were not measured (17,18). Moreover, the reviews conducted by Li et al. and Zhou included only the Asian population, and only one study included the Caucasian population. Thus, this is the first report on a Latin population.

Homocysteine is a thiol found between two metabolic pathways: the methionine cycle and the transsulfuration sequence that converts methionine into cysteine. The second cycle requires pyridoxine phosphate (19). Homocysteine has four clear functions: a precursor of cystathionine and cysteine, among other metabolites; a medium for methionine conservation; a methyl receptor in choline catabolism; and a substrate for folate recycling. Regarding the last function, homocysteine within the cellular economy is a key factor in forming tetrahydrofolate, a reaction carried out by methionine synthase that requires vitamin B12 (20). If methionine synthase or vitamin B12, its cofactor, is deficient, then homocysteine accumulates. Therefore, hyperhomocysteinemia is often diagnosed as megaloblastic anemia, which is another form of vitamin B12 deficiency (21). Pernicious anemia is a common cause of vitamin B12 and folic acid deficiencies.

Hyperhomocysteinemia has been defined as an independent risk factor for cardiovascular and cerebrovascular diseases and poor outcomes in severe head trauma (22). In addition, in different Asian populations presenting SAH, homocysteinemia higher than those in the average population has been reported, which is associated with a higher prevalence of mutation in methylenetetrahydrofolate reductase, an enzyme responsible for metabolism (22). Homocysteine levels have also been determined as a risk factor for hemorrhagic cerebrovascular events, probably due to greater activity of metalloproteinase 9, which generates greater instability in atherosclerotic plaques, affects the vascular basement membrane, and favors greater expansion of hematomas in cases of subarachnoid bleeding (23,24).

Some studies have shown that B12 and folic acid administration can prevent ischemic stroke (21). One of them found that low B12 levels in ischemic stroke and low folic acid levels in hemorrhagic stroke were associated with lower Glasgow scale scores (25). However, the association between B12 levels, homocysteine levels, and hemorrhagic stroke is rarely reported. Further, hyperhomocysteinemia is related to atherosclerotic small-vessel disease and cardiac ischemic events. However, no strong evidence, large randomized study, or clear proportional relationship was observed between the severity of brain events and

hyperhomocysteinemia. Thus, hyperhomocysteinemia is accepted as an independent risk factor for cardio-cerebrovascular, coronary heart, and peripheral arterial diseases (19). Its exact quantification is difficult due to the properties of homocysteine, which exists in three forms that require quantification: proteins, sulfhydryl groups, or disulfide groups. An increase of 12–30, 31–100, and >100 has been described, corresponding to mild, moderate, and severe elevations, respectively (19). The patient described here exhibited moderate elevation, a clinically significant finding in a case where high cardiovascular risk is unclear and non-cardiovascular risk factors are not yet determined. If the patient had no diabetes, obesity, or hypertension, the homocysteine blood level would not even have been evaluated.

Elevated homocysteine levels lead to endothelial dysfunction, which prevents effective vasodilation. Moreover, platelet and leukocyte activations are altered, resulting in prothrombotic and antithrombotic imbalances (19). Elevated homocysteine levels lead to a clear thrombotic predisposition due to platelet aggregation, an increased low-density lipoprotein level and oxidation, abnormal fibrinolysis including decreased antithrombin III and protein C activities, increased smooth muscle cell proliferation, and activated inflammatory cascades (6). The oxidative stress is increased because homocysteine auto-oxidizes in the plasma and consumes nitric oxide. Additionally, glutathione peroxidase expression is decreased, and an inversely proportional relationship has been found between its levels and cardiovascular risk (19). The pathophysiology of hyperhomocysteinemia in stroke occurrence remains elusive. However, its effects on the arterial walls, such as endothelial dysfunction, increased oxidative stress, procoagulant states, and inflammation induction, can accelerate the progression of atherosclerosis (18). As a result, the incidence of ICH may be elevated, leading to vascular endothelial damage and vessel wall necrosis. These changes ultimately increase the risk of both ischemic and hemorrhagic cerebrovascular events, which can cause significantly higher morbidity and mortality in affected individuals (18,26).

Diet is rarely mentioned as a direct risk factor for hemorrhagic cerebrovascular disease; however, it has been found to indirectly play a role in the pathogenesis of brain aneurysms and may affect other risk factors. The results of studies on the benefit of lowering the serum homocysteine level for cardiovascular disease and mortality are inconclusive; however, adequate vitamin B12 intake may protect against intracranial aneurysm formation (27,28).

Conclusion

To date, only a few reports discussed elevated homocysteine levels as a risk factor for hemorrhagic stroke. Whether elevated homocysteine level in association with other risk factors explains the vascular injury that led to this event is not yet clear. Hence, further research is required to determine the extent of the association between homocysteinemia

and B12 and folic acid deficiencies as risk factors for stroke and identify patients who should be included in cerebrovascular disease screening.

Limitations

The present retrospective study can only obtain information from the patient's medical chart and the recall of the attending physicians who managed the case. Moreover, the methods used to measure the homocysteine blood levels can have sensitivity and relativity issues, and the patient's levels before the onset of stroke.

One of the limitations is that the patient did not undergo brain magnetic resonance imaging, which could have evaluated other etiologies, such as cavernous malformations or AA.

Data availability

The data used to support the study findings are restricted by Fundación Valle del Lili Ethics Committee to protect patient privacy. Data are available from Dr. Guillermo E. Guzmán for researchers who meet the criteria to access confidential data.

Consent

The planning, conduct, and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013. The study was approved by Fundación Valle del Lili Ethics Committee. Informed consent has been obtained and is retained by the authors and made available to Hindawi only on request.

Authors' contribution

Veline Martínez: Conceptualization, research, supervision, validation - verification, visualization - data presentation, writing - original document, writing - proofreading & editing.

Esteban Echeverri: Conceptualization, data curation, formal analysis, research - methodology - design and development, validation - verification, visualization, writing - proofreading and editing.

María Alejandra Urbano: Conceptualization, data curation, formal analysis, research - methodology - design and development, validation - verification, visualization, writing - proofreading and editing resources - supply of study materials, software.

Laura Juliana Ballen: Conceptualization, data curation, formal analysis, research - methodology - design and development, validation - verification, visualization, writing - proofreading and editing resources - supply of study materials, software.

Guillermo Edinson Guzmán: Conceptualization, research, supervision, validation - verification, visualization - data presentation, writing - original document, writing - review and editing.

Disclosure

There was no sponsorship, and the production of the study was under the own dedication of the authors.

Conflicts of interest

The authors have no conflicts of interest to declare.

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