Popcorn Brain: Familial Multiple Cerebral Cavernomatosis

Case Report

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Abstract—Popcorn Brain: Familial Multiple Cerebral Cavernomatosis

Introduction. Cerebral vascular malformations are a heterogeneous group of disorders with several clinical manifestations. Cerebral Cavernous Malformations (CCM) are defined by dilated vascular spaces, with a single layer of endothelium, no mature vessel wall, and no intervening brain parenchyma. CCM may be sporadic or have an autosomal dominant hereditary pattern. **Case Report.** Here we present the case of a 31-year-old male with a medical history of multiple vascular malformations, difficult to treat epilepsy, and multiple hemorrhagic strokes. At initial evaluation the patient revealed mild dysarthria, left hemiparesis 4/5, hyperreflexia, left dysdiadochokinesia and dysmetria with a modified Rankin scale (mRS) score of 1. Magnetic Resonance Imaging (MRI) of the brain showed multiple supra and infratentorial parenchymal lesions with heterogeneous components on T1-weighted and T2-weighted sequences, surrounded by a rim of signal loss, demonstrating a "popcorn" appearance on Susceptibility-Weighted Angiography (SWAN) MRI. Molecular testing reported a heterozygous KRIT1 c.1099dup (p. His367Profs*3). Screening of fist degree relatives was performed, and antiepileptic treatment was adjusted. As of today, our patient has a mRS of 3, with refractary epileptic seizures. **Conclusion.** Symptomatic CCM must receive targeted medical treatment with a multidisciplinary approach. If a patient presents with more than one lesion, a familial case should be suspected, molecular testing and a screening head computed tomography (CT) should be done in first degree relatives. It is important to follow-up any patient with CCM with an annual MRI to monitor the size and number of lesions, symptomatic medical treatment is indicated, and surgical treatment should also be assessed. **Ictus 2022;3(1):e14012203002**

Keywords—Cavernoma, Familial Cavernomatosis, Magnetic Resonance Imaging, Structural Epilepsy.

Resumen— Cerebro en Palomita de Maíz. Cavernomatosis Cerebral Múltiple Familiar

Introducción. Las malformaciones vasculares del cerebro son un grupo heterogéneo de trastornos con manifestaciones clínicas diversas. Las Malformaciones Cavernosas del Cerebro (MCC) son definidas como espacios vasculares dilatados, con una capa única de endotelio sin pared madura del vaso, y sin involucro de parénquima cerebral. Las MCC pueden ser esporádicas o tener un patrón autosómico dominante. **Reporte de Caso.** Presentamos el caso de un hombre de 31 años con historia de múltiples malformaciones vasculares, epilepsia de difícil control y múltiples hemorragias cerebrales. La evaluación inicial mostró disartria, hemiparesia izquierda 4/5, hiperreflexia, dismetría y disdiadococinesia izquierdas y una escala modificada de Rankin de 1 punto. La resonancia magnética cerebral mostró múltiples lesiones supra e infratentoriales con componentes heterogéneos en T1 y T2, con anillo con hipointensidad, dando una apariencia en palomita de maíz en la secuencia SWAN. Las pruebas genéticas reportaron un patrón heterogeneo KRIT1 c.1099dup (p. His367Profs*3) Se realizó análisis en familiares de primer orden, y se inició tratamiento antiepiléptico. Al día de hoy, el paciente está en escala modificada de Rankin de 3 puntos y con crisis epilépticas refractarias. **Conclusión.** Las MCC sintomáticas deben recibir tratamiento médico multidisciplinario. Si un paciente presenta más de una lesión, se deben realizar estudios de imagen y genéticos en familiares de primer orden. Es importante el seguimiento de estos pacientes con resonancia magnética anual para monitoreal el número y tamaño de las lesiones, y analizar el tratamiento médico y quirúrgico en caso necesario. **Ictus 2022;3(1):e14012203002**

Palabras clave—Cavernoma, Cavernomatosis Familiar, Resonancia Magnética, Epilepsia estructural.

INTRODUCTION

Cerebral vascular malformations are a heterogeneous group of disorders with varied clinical implications, which range from no symptoms to a severe neurological deficit. Cerebral Cavernous malformations (CCM) have an estimated prevalence of 0.1 to 0.5% in the general population, and 40% of these individuals may be symptomatic.[1] These lesions are characterized by dilated vascular spaces (also known as "caverns"), with a single layer of endothelium, no mature vessel wall features, and no intervening brain parenchyma, which may lead to intracerebral hemorrhage (ICH).[2] Due to their low flow, they are known to be angiographically occult, therefore visualization of the lesions is preferred with Magnetic Resonance Imaging (MRI), where the hemosiderin staining from blood products of various ages gives them the pathognomonic popcorn appearance.[3]

These lesions may have a sporadic presentation, or with an autosomal dominant hereditary pattern, incomplete clinical and radiological penetrance and a variable degree of expression.[4]

CASE REPORT

A 31-year-old male with a 17 year-history of difficult-to-treat epilepsy presented with progressive left lower extremity weakness for six months until impairing walking. Medical history included multiple vascular malformations in the brain since childhood, two previous hemorrhagic strokes, focal seizures characterized by masticatory movements and left arm clonic movements occurring about five times per month.

Initial evaluation revealed mild dysarthria, left hemiparesis (Medical Research Council Scale 4/5), hyperreflexia, left dysdiadochokinesia and dysmetria with a modified Rankin scale (mRs) score of 1. A head computed tomography (CT) revealed multiple hyperdense lesions on the frontal lobes, right temporal lobe, and left cerebellar hemisphere, suggestive of previous ICH. An MRI showed multiple supra and infratentorial parenchymal lesions with mass effect and heterogeneous components on T1-weighted and T2-weighted sequences (Figure 1), surrounded by a rim of signal loss on the Susceptibility-Weighted Angiography (SWAN) sequence, resembling a "popcorn" appearance (Figure 2) typical of brain cavernomas. Treatment with Valproate (1,600 mg/day) was initiated.

As part of the approach, genetic analyses were performed, as well as consultation with vascular and epileptic surgery teams. Genetic family history was unremarkable; a head CT was performed to all first-degree relatives without any lesions. Molecular testing reported a heterozygous mutation in KRIT1: c.1099dup (p.His367Profs*3), which is identified as a pathogenic genetic variant for familial cerebral cavernomatosis.

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At two years follow-up, the patient symptoms have worsened, with cranial nerve IV paresis, dysarthria, left hemiparesis (BMRC 3/5), bilateral dysdiadochokinesia, dysmetria, and gait imbalance with a mRs score of 3, due to recurrent ICH and recurrent epileptic seizures. Medical treatment was adjusted, adding levetiracetam (1,500mg/day), because of the large number of bleeding lesions, as well as the various difficult to approach locations, surgical treatment was not advised on this case.

DISCUSSION

We present a case of a patient with multiple large brain cavernomas with persistent epilepsy and focal neurologic deficits. CCM are vascular malformations that can occur anywhere in the nervous system. Most common symptoms include seizures 40-70%, focal neurologic deficits 35-50%, headaches 10-30%, and cerebral hemorrhage 32%.[7] According to location, supratentorial CCM frequently present with hemorrhage, seizures, and focal neurological deficits; whereas infratentorial CCM present with recurrent hemorrhages, and progressive neurologic deficits.[6,7] Our patient has multiple lesions in both supratentorial and infratentorial locations, with various neurological symptoms which have progressed from a nearly asymptomatic mRS of 1 to a mRs of 3.

Diagnosis of familial cerebral cavernous malformation is established with either one or both of the following: multiple CCM, or one CCM and at least one family member with one or more CCM, a heterozygous pathogenic variant in KRIT1, CCM2, or PDCD10 by molecular testing.[7,8] Our patient did not have any relevant family history, and a head CT scan was performed on his siblings, which showed no abnormalities. However, his genetic analysis found a pathogenic heterozygous variant in KRIT1; up to 62% of carriers of this mutation are symptomatic, initially presenting with seizures 55% and cerebral hemorrhages 32%.[8]

As multiple lesions are mostly seen in familial cases, it is mandatory to do genetic testing on such patients, even if there is no relevant family history. As an autosomal dominant disorder, the offspring of our patient has a 50% chance of inheriting the pathogenic variant, so genetic counseling is imperative in these cases.[5,7,8]

Management of these patients varies from case to case, as the symptoms are very heterogeneous, and the locations and number of lesions vary from patient to patient. A conservative approach is preferred for asymptomatic CCM with serial follow-ups to monitor any changes in the lesion, in this cases, prophylactic antiepileptic medication is not advised.[6,7,9] When the lesions become symptomatic, targeted treatment is indicated with antiepileptic drugs for CCM-related seizures, symptomatic treatment for headaches, and rehabilitation for neurologic sequelae.

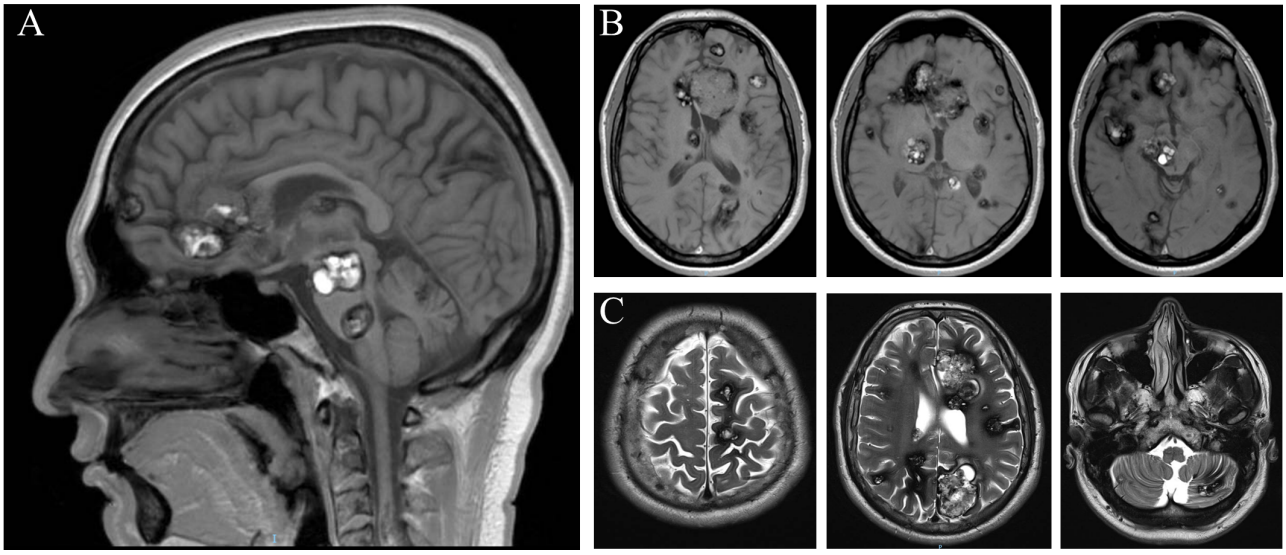

Figure 1: MRI. Sagital T1 (A) and axial T1 (B) and T2 (C) images that show multiple cavernomas in both supratentorial and infratentorial territories, including the brainstem, with mass effect.

Surgical approach may be considered for ICH, mass effect, intractable epilepsy, or progressive neurologic deficits.[6,7,9] Radiosurgery is an option for surgically inaccessible lesions that could be considered when there is a high bleeding risk.[10] In patients with multiple CCM, if one lesion can be determined as the epileptogenic zone, removal of just that one lesion may be an appropriate treatment.[9] However, surgical treatment remains controversial in severely affected cases like ours, with multiple large infra and supratentorial cavernomas.

Conclusion

Familial cerebral cavernomatosis continues to be a rare genetic disease; when a patient presents with more than one lesion, regardless of family history, a familial case should be suspected, molecular testing should be done as well as head CT screening for first degree relatives. As a progressive disorder, it is important to follow up any patient with CCM with an annual MRI to monitor the size and number of lesions, symptomatic medical treatment is indicated on a case-to-case basis, and surgical treatment should also be considered. Patients should have a multidisciplinary team to ensure a better outcome.

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References

[1] Toll A, Parera E, Giménez-Arnau AM, Pou A, Lloreta J, Limaye N, et al. Cutaneous venous malformations in familial cerebral cavernomatosis caused by KRIT1 gene mutations. Dermatology. 2009;218(4):307–13.

[2] Awad IA, Polster SP. Cavernous angiomas: Deconstructing a neurosurgical disease: JNSPG 75th Anniversary Invited Review Article. J Neurosurg. 2019;131(1):1–13.

[3] Stapleton CJ, Barker FG. Cranial cavernous malformations natural history and treatment. Stroke. 2018;49(4):1029–35.

[4] Mondejar R, Lucas M. Molecular diagnosis in cerebral cavernous malformations. Neurol (English Ed. 2017;32(8):540–5.

[5] Labauge P, Denier C, Bergametti F, Tournier-Lasserve E. Genetics of cavernous angiomas. Lancet Neurol. 2007;6(3):237–44.

[6] Bokhari MR, Al-Dhahir MA. Brain Cavernous Angiomas [Internet]. StatPearls [Internet]. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430871/

[7] Morrison L, Akers A. Cerebral Cavernous Malformation , Familial Summary Genetic counseling Diagnosis Suggestive Findings. GeneReviews. 2003;1993–2021.

[8] Choquet H, Pawlikowska L, Lawton MT, Kim H. Genetics of Cerebral Cavernous Malformations: Current Status and Future Prospects. J Neurosurg Sci [Internet]. 2016;59(3):211–20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4461471/

[9] Rosenow F, Alonso-Vanegas MA, Baumgartner C, Blümcke I, Carreño M, Gizewski ER, et al. Cavernoma-related epilepsy: Review and recommendations for management - Report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2013;54(12):2025–35.

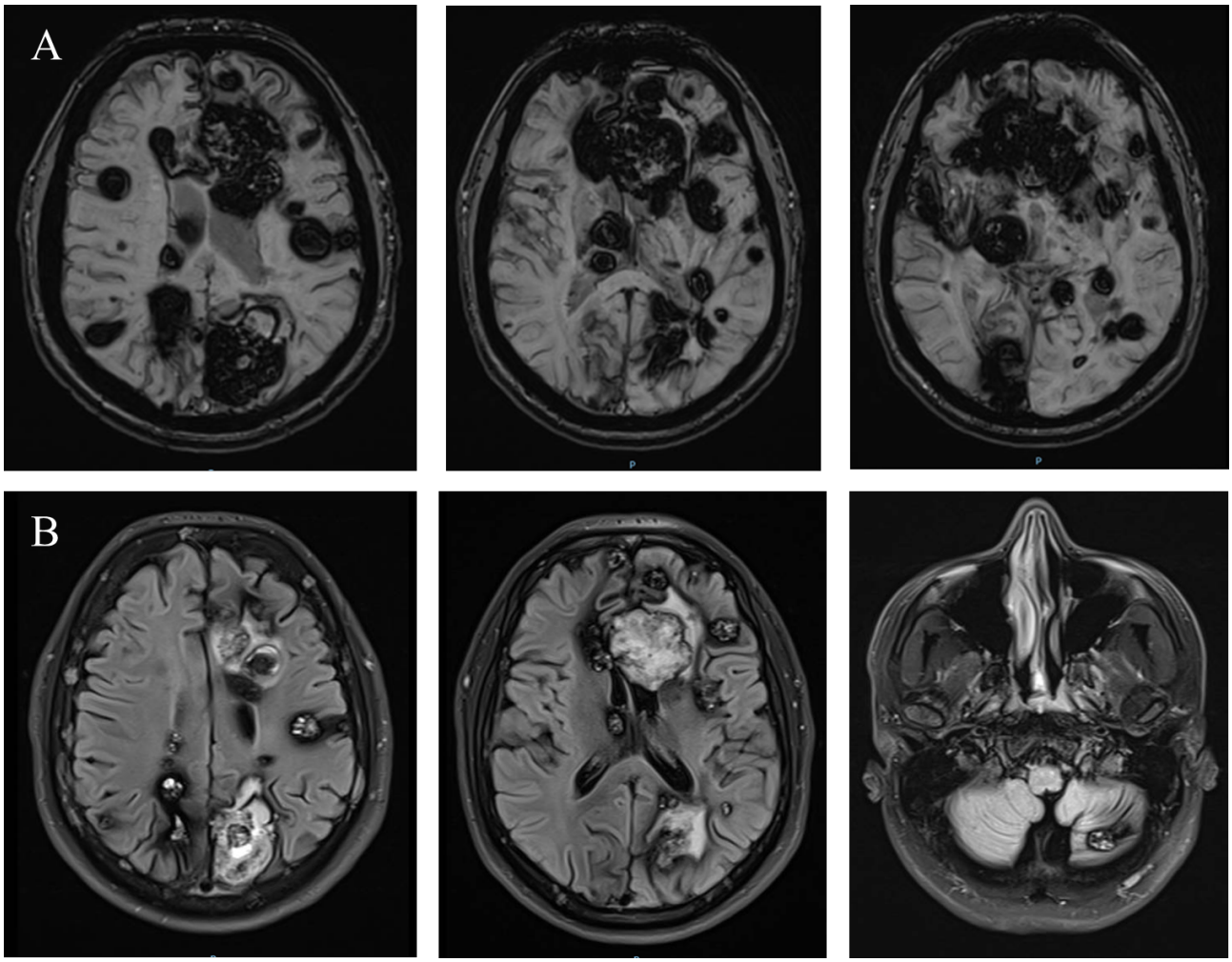

Figure 2: MRI. SWAN sequence (A) demonstrates the signal loss typical of cavernomas. FLAIR (B) shows the characteristic popcorn appearance of cavernomas.

[10] Chalouhi N, Jabbour P, Andrews DW. Stereotactic radiosurgery for cavernous malformations: Is it effective? World Neurosurg. 2013;80(6):987–91.