Neurocysticercosis, familial cerebral cavernomas and intracranial calcifications: differential diagnosis for adequate management

Neurocisticose, cavernoma cerebral familiar e calcificações intracranianas: diagnóstico diferencial e acompanhamento adequado

Emerson Leandro Gasparetto¹, Soniza Alves-Leon², Flavio Sampaio Domingues³, João Thiago Frossard³, Selva Paraguassu Lopes⁴, Jorge Marcondes de Souza³

ABSTRACT

Neurocysticercosis (NCC) is an endemic disease and important public health problem in some areas of the World and epilepsy is the most common neurological manifestation. Multiple intracranial lesions, commonly calcified, are seen on cranial computed tomography (CT) in the chronic phase of the disease and considered one of the diagnostic criteria of the diagnosis. Magnetic resonance imaging (MRI) is the test that better depicts the different stages of the intracranial cysts but does not show clearly calcified lesions. Cerebral cavernous malformations (CCM), also known as cerebral cavernomas, are frequent vascular malformations of the brain, better demonstrated by MRI and have also epilepsy as the main form of clinical presentation. When occurring in the familial form, cerebral cavernomas typically present with multiple lesions throughout the brain and, very often, with foci of calcifications in the lesions when submitted to the CT imaging. In the countries, and geographic areas, where NCC is established as an endemic health problem and neuroimaging screening is done by CT scan, it will be important to consider the differential diagnosis between the two diseases due to the differences in adequate management.

Keywords: neurocysticercosis; epilepsy; cavernomas; familial cerebral cavernous malformation; computerized tomography; magnetic resonance.

RESUMO

A neurocisticercose (NCC) é um importante problema endêmico de saúde pública em algumas áreas do mundo, sendo epilepsia sua manifestação clínica mais comum. Múltiplas lesões intracranianas, geralmente com calcificações visualizadas em tomografia computorizada de crânio, são interpretadas como um dos critérios diagnósticos na fase crônica da doença. A ressonância magnética é o melhor teste de imagem para identificar a doença em diferentes estágios de sua forma cística mas apresenta limitações para demonstrar lesões calcificadas. Malformações cavernosas cerebrais, ou cavernomas, são malformações vasculares comuns ao sistema nervoso e epilepsia é também a sua forma mais frequente de apresentação. Na sua forma familiar cavernomas apresentam-se tipicamente com múltiplas lesões encefálicas e, frequentemente, com focos de calcificações na TC. Em alguns países, e determinadas regiões geográficas, onde neurocisticercose é endêmica, a neuroimagem mais usada para diagnóstico é a TC de crânio. Nesse contexto torna-se importante estabelecer bases para o diagnóstico diferencial entre as duas doenças, devido às diferentes formas de acompanhamento e tratamento adequado.

Palavras-chave: neurocisticercose; epilepsia; malformação cavernosa cerebral familiar; cavernoma cerebral; tomografia computorizada; ressonância magnética.

NEUROCYSTICERCOSIS

Cysticercosis is the result of the infestation of the larval form of "T. solium" and neurocysticercosis (NCC) is the established involvement of the central nervous system (CNS). The disease is endemic in developing countries, more prominently in Latin America and in some regions of Asia and Africa. NCC is also becoming an emerging infectious health problem in developed countries due to immigration. Contamination of humans by consumption of the T. solium eggs leads to person-to-person or auto-infestation but the real prevalence of NCC is not yet established. NCC is commonly described

¹Universidade Federal do Rio de Janeiro, Departamento de Radiologia, Rio de Janeiro RJ, Brazil;
²Universidade Federal do Estado do Rio de Janeiro, Departamento de Neurologia, Programa de Epilepsias, Rio de Janeiro RJ, Brazil;
³Universidade Federal do Rio de Janeiro, Departamento de Neurocirurgia, Rio de Janeiro RJ, Brazil;
⁴Aliança Cavernoma Brasil, Brasília DF, Brazil.

Correspondence: Jorge Marcondes de Souza; Departamento de Neurocirurgia, Universidade Federal do Rio de Janeiro; Rua Rodolpho Rocco, 256, Hospital Universitário; 25622-826 Rio de Janeiro RJ, Brasil; E-mail: jormarcondes@gmail.com

Conflict of Interest: There is no conflict of interest to declare.

Received 02 September 2015; Received in final form 16 November 2016; Accepted 22 December 2015.
as the leading cause of epilepsy in endemic regions, although
the distinction of seizures occurrence and epilepsy related to
NCC has not achieved complete elucidation. With cerebral
cyst degeneration there is a contrast enhancement of the le-
sion surrounded by edema on CT as well as high signal imag-
es on MRI T2 sequences and gadolinium enhancement on T1
images supposedly due to inflammatory reactions.

Epilepsy, in general grounds, is defined by unprovoked
seizures in more than one occasion and usually correlates
with the most probable condition directly involved on its de-
velopment. Although there are evidences supporting seizures
as the most common manifestation of NCC in the symptom-
atic patients NC can be asymptomatic in some cases and
seropositivity through enzyme-linked immune transfer
loit assay (EITB) does not always indicate active disease nor
CNS involvement. Carpio detected that the proportion of
the seropositivity in epileptic NCC patients was the same re-
ported in the general population in the same geographic ar-
ae. On the other hand there is a chance of dual disease, like
temporal lobe epilepsy with hippocampal sclerosis and NCC,
in endemic regions, being involved in the pathogenesis of epi-
lepsy in patients diagnosed with NC and the differential di-
agnosis will only be reached by means of special neurophysi-
ological testing. Evidence-based data from well designed
prospective studies to establish the surrogates for epilepsy
due to NCC is scarce, showing the importance of dif-
ferential diagnosis with other diseases on the determination
of NCC as seizures etiology and the risk of overestimation
of neurocysticercosis as a prime cause of seizures.

FAMILIAL CEREBRAL CAVERNOUS
MALFORMATIONS (FCCM)

Cavernous malformations are common cerebrovascu-
lar abnormalities, affecting 0.4–0.8% of the general popula-
tion. Pathologically, CCM are defined by clusters of di-
lated capillary cavities, in back-to-back disposition, lined by
a single layer of endothelium, lacking smooth muscle and no
intervening brain parenchyma (Figure 1).

Cavernomas may occur in the brain or spinal cord as an
isolated single lesion. The familial form of cerebral cavernomas
(FCCM) is characterized by multiple brain lesions (Figure 2),
usually as the result of loss-of-function mutations in one of the
known CCM genes, namely CCM1 (KRIT1), CCM2 (MGC4607)
and CCM3 (PDCD10). The pattern of inheritance of the fa-
milial form is of autosomal dominance and its proportion
in the CCM population has been estimated as high as 50% in
Hispanic-American patients and 10–40% in other popula-
tions. Mutations in the CCM1, CCM2 and CCM3 genes ac-
count generally for 50–65%, 15–19% and less than 10% of the
FCCM cases, respectively. In the United States, mainly in the
State of New Mexico and southwestern regions, there has been
described a high frequency of a Common Hispanic Mutation

of the gene CCM1/KRIT1 (Q455X, rs 267607203) in families of
Mexican heritage up to the point where most insurance com-
panies are paying for its screening.

The New Mexico CCM cohort recently reported a study
searching for association between inflammatory biomarkers
and aggressiveness of the disease, with most patients having
multiple lesions and epilepsy as the main symptoms.

In an ongoing study for a Register of Disease for Cerebral
Cavernomas in Brazil, the CCM cohort at the Federal
University of Rio Janeiro has also detected the predominance
of CCM1 mutational profile in the studied families.

In another multicenter study it was reported a very ag-
gressive profile of FCCM cases due to mutations of the gene
CCM3, with a mean age at presentation of 12 years and an
excessive lesion burden, meaning 33% of the patients having
more than 100 lesions and 78% with more than 20 lesions. Epilepsy was also the most common symptom of this aggressive form of the disease.

Epilepsy is the more common manifestation of the cerebral cavernomas, with most studies showing seizures as leading symptom in 40% to 70% of the cases.1-3 The mechanisms of seizures pathogenesis in CCMs are disputed but there is a literature trend toward rendering hemosiderin, from de blood products leaked from the endothelial cells junctional defect, the main cause due to its epileptogenic effect.4,5,6

Hemispheric cavernomas are associated with higher tendency of seizures than other mass lesions in the brain parenchyma, with the potential for evolution for refractory epilepsy in 40% of the cases.4 Al-Shahi detected, in a prospective study in Scotland that, for adults without lesional hemorrhage or focal neurological deficit, cavernomas were more frequently multiple in the patients with seizures (43%) than in the ones without seizures (6%).4

THE QUEST FOR THE NEUROIMAGING

In the geographic areas of the world where NCC is more prevalent, CT is the more utilized imaging test and, regarding the calcifications of the late phase of the disease, it would be the neuroimaging for confirmation of diagnosis. Carpio et al. listed, in the methodology of a case control-study of cysticercosis, in Ecuador, CT as the imaging test of choice and have described their proposed CT criteria for the lesional characterization. Alive cysts are depicted as one or more hypodense areas, variable in size and without constrast enhancement whereas the transitional ones as cysts with contrast enhancement. Inactive lesions are depicted as rounded, hypodense, without enhancement and with areas of calcification.

MRI is the best test for definition of the cyst stage in their evolution in the brain on T1, T2, FLAIR sequences, including the inflammatory aspects when using enhanced images with gadolinium infusion (Figures 3A, B and C) although not as accurate in detection of calcifications. Diffusion weighted images were demonstrated as better defining the scolex and increasing the confidence for the NCC diagnosis by MRI. A recent review on NCC showed that MRI findings are better predictive for the stage of the cysts and diffusion-weighted images and apparent diffusion coefficient maps allowing better demonstration of the cysticerci in their colloidal phase. Calcified cysts were described as not well depicted and there was a suggestion that more sophisticated sequences, as susceptibility-weighted protocols, would be necessary. Cavernous malformations, on the other hand, are not well seen on CT images, where the lesions will range from non-visualization to the mildly enhancing, variable format and, very often, with calcification. Batra et al.
described, in their series of CCMs at the Johns Hopkins University, 58% of the specimens with thrombosis and 41% with calcifications\(^\text{31}\). MRI is the neuroimaging test of choice in CCM, with the typical pattern of “popcorn” appearance in the sequences T1 and T2 sequences, result from the mixed old and new blood residua inside the lesions, usually with hyperintense core and a hypointense dark surrounding rim\(^\text{32}\). The sequences with higher sensitivity to the hemosiderin susceptibility effect are much more accurate in depicting the hemosiderin deposits in the lesions and the worldwide most used ones are the gradient-echo imaging (GRE) or susceptibility-weighted imaging (SWI) sequences. We have shown that SWI sequence has superior accuracy in detecting small lesions and its usefulness in detecting familial cases of CCM and a more accurate lesional burden\(^\text{33}\).

As an example of possible misdiagnosis that an initial screening with CT scan might create we present a case of a 25-yrs-old female, with recent episode of seizures and cranial MRI test showing typical multiple cerebral cavernous malformations (Figure 4A). She was an index case of a familial form of CCM living in a small town in Brazil, in a geographic area known as endemic for cysticercosis. Her father was diagnosed as harboring neurocysticercosis for the last 30 years, and treated accordingly, based on epileptic profile and his CT scan with multiple calcifications (Figure 4B).

The multiple typical CCM lesions diagnosis of his daughter raised the high probability of familial cavernomas and, accordingly, his cranial MRI showed several characteristic cavernous lesions matching the calcified areas on CT scan (Figures 4C and D).

Likewise, many patients of the CCM cohort of the Universidade Federal do Rio de Janeiro, which has a consolidated follow-up of 22 Brazilian families, harbor multiple intracranial calcifications on CT imaging and epilepsy as the main symptoms (Figures 5 A, B, C and D). The use of calcifications seen on cranial CT as a valid surrogate for neurocysticercosis, in those circumstances, would certainly constitute a misdiagnosis.

An interesting confounding aspect is that there are few studies showing familial aggregation of NC\(^\text{28,34}\) and, on this situation, it would be reasonable to use MRI scan to establish the differential diagnosis with FCCM. As the familial form of cavernomas is more prone to develop epilepsy\(^\text{24}\) and also characterized by multiple brain lesions, often calcified on the CT scan, ranging from a few to uncountable ones, the different nature of the two diseases certainly raises the importance the correct diagnosis.

Figure 4. (A) MRI on coronal T2 image depicts two cavernous lesions at the mesiobasal and subcortical left temporal lobe (A); CT scan with calcified lesions on the right and left hemisphere (B); MRI Axial T2 imaging shows left justa-ventricular and right cortical frontal typical cavernous malformation (C); G-Echo sequence showing the lesions with usual low signal of the lesions (D).
Cavernous malformations are prone to bleeding and have a 2.4% person/year rate of lesional hemorrhage\textsuperscript{13}. The prevalence on the general population is estimated on 0.4–0.8% and the familial form around 50% of them, rendering the formal diagnosis and counseling clearly an important step on management. The misdiagnosis between the NCC and FCCM has several important consequences deserving awareness of the medical and, specially, neurologic community. Patients with CCM, erroneously diagnosed as NCC, might receive prescription of medications for NCC treatment, namely praziquantel, and submitted to unnecessary side effects. Genetic counseling on cases of familial cavernomas will not be done rendering patients unaware of the probabilities, and consequences, of their offsprings having the disease. Likewise, the suggestion for annual/bi-annual MRI checking for new lesions or biological changes in the known CCMs will not be made.

Prevention of intracranial bleeding in CCM patients usually includes counseling to avoid medications such as AAS or any other anti-thrombotic drugs, as well as anticoagulants, like coumadin, heparin or heparinoids, and this will not be done having the misdiagnosis of neurocysticercosis been made\textsuperscript{35,36}.

In conclusion, with the widespread access to the MRI technology it might be worthwhile to consider reviewing the prevalent paradigm for NCC diagnosis, when calcified cysts are detected in cranial CT in patients suffering from seizures in endemic areas. Cavernous malformations are lesions that bleed spontaneously, leading to the risk of intracranial hemorrhage. In its familial form, with multiple lesions and frequent calcification, there are real chances for being confounded with calcified cysts due to NCC when cranial image done only by CT scan.

Although MRI notoriously does not clearly detect calcification, it is the best neuroimaging test of choice for correct diagnosis of cerebral cavernous malformation, including the SWI or GRE for detection of familial form, and NCC.

In the geographical areas where NCC still prevails as an important endemic health problem the differential diagnosis with familial cavernous malformations should be taken into consideration whenever facing patients with seizures and multiple intracranial calcifications on CT scan, for the adequate management of the diseases.

Figure 5. A CT scan image showing left basal ganglia calcification (A); Another left subcortical frontal calcification in the same patient (B); MRI FLAIR axial depicting typical cavernoma imaging at the left basal ganglia (C); More lesions detected by MR-SWI sequence than other sequences (D).