AAM Psychological Syndrome: Cingulate and Rectus Gyri Cavernous Angiomas Associated with Aggressiveness, Anxiety and Memory Disturbance. What do Those Lesions Have in Common in the Pathophysiological Mechanism?

Síndrome Psicológica AAM: Angiomas Cavernosos dos Giros do Cíngulo e Reto Associados a Agressividade, Ansiedade e Distúrbios de Memória. O que Essas Lesões Têm em Comum com o Mecanismo Fisiopatológico?

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ABSTRACT

We report three cases of patients with cavernous angioma in a series of 32 cases presenting as initial symptoms of aggressive behavior, anxiety and loss of memory. During the investigation they were diagnosed with cavernomas in limbic system. One man and two women with 58, 56 and 60 year-old, who presented the cavernomas respectively in callosum / cingulum area, gyrus rectus area, and cingulate gyrus. They were treated clinically with Carbamazepine 200mg 8/8 hours, Clonazepam 2mg daily, and Sodium Valproate 500 mg 6/6 hours orally. They showed no results for the ictal behavior disorder. However, after surgery with total removal of the cavernomas through a microsurgery the symptoms immediately finished. The authors discuss the possibility of such symptoms to be part of epileptic manifestation or simple compression of limbic pathways. Also is discussed if there is any possibility to those syndromes with cavernomas in different portions of frontal lobe to be caused by disturbance in the input fibers to nucleus accumbens and to nucleus of the solitary tract based on literature review. The proximity and inner connections in frontal lobe structures may be analyzed in the light of neurophysiology and neuroanatomy.

Key words: Limbic system; Cavernoma; Memory; Aggressive behavior; Anxiety; Nucleus accumbens.

RESUMO

Relatamos três casos de uma série de 32 pacientes com angioma cavernoso que apresentaram sintomas iniciais de comportamento agressivo, ansiedade e perda de memória. Durante a investigação foram diagnosticados como portadores de cavernomas no sistema límbico. Um homem e duas mulheres com idades de 58, 56 e 60 anos de idade, tiveram cavernomas nas áreas do corpo caloso e do giro do cíngulo, no giro reto e no giro do cíngulo, respectivamente. Clinicamente foram tratados com Carbamazepina 200 mg 8/8 horas, Clonazepam 2mg por dia, e Valproato de Sódio 500 mg 6/6 horas por via oral, sem resposta para o distúrbio de comportamento ictal. No entanto, após a cirurgia com remoção total das lesões através de microcirurgia, os sintomas imediatamente desapareceram. Os autores discutem a possibilidade de tais sintomas fazerem parte de manifestação epiléptica ou simples compressão das vias límbicas. Também discutem se há qualquer possibilidade de tais sintomas com cavernomas em diferentes porções do lobo frontal serem causadas por perturbação nas fibras de entrada para o núcleo accumbens e núcleo do trato solitário, com base em revisão de literatura. Sua proximidade e conexões internas com estruturas do lobo frontal podem ser analisadas à luz da neurofisiologia e da neuroanatomia.

Palavras-chave: Sistema límbico; Cavernoma; Memória; Comportamento agressivo; Ansiedade; Núcleo accumbens.

INTRODUCTION

Cavernous angiomas can be found in any topography of the brain, in different sizes, and present with varying clinical disorders. The latter include seizures (typically focal), progressive or transient neurological deficits, bleeding, headache, among others. Rarely, however, cognitive and behavioral symptoms are seen as presenting features of cavernomas2. On the contrary, cognitive and behavioral symptomatology
is frequently associated with dementia syndromes, substance abuse, and normal pressure hydrocephalus. Among cavernous angiomas, those specifically located in the limbic system have been reported as generating neuropsychiatric symptoms (such as aggressiveness and anxiety)\textsuperscript{3,8,12,16}. Interestingly, those sited at the uncus, hypothalamus, and septal area have been associated with memory disturbances\textsuperscript{10,13}. In regards to the pathophysiology of these associations, there have been studies with experimental models that tried to unveil the mechanisms underlying these clinical observations\textsuperscript{7}. Herein, we report three cases of cavernous angiomas presenting with neuropsychiatric symptomatology. Further, we discuss possible basic neuroscience explanations to this relatively unusual presentation of cavernomas.

**CASE 1**

A 58-year-old, multilingual female attorney presented to our service with a history of recurrent attacks of aggressive behavior for the past 6 months. These paroxysms lasted approximately one hour each, as frequent as 10 per day, and were accompanied with physical and swearing aggression. Interestingly, the swearing was usually done in Italian – which was not her primary language. These attacks were functionally affecting both her personal and professional life. Notably, she had never been diagnosed with any psychiatric disorder. Additionally, she also had frequent dyscognitive seizures, some of which with secondary generalization. Further, she underwent Psychiatry evaluation and started on haloperidol. As a result, her attacks became more frequent and associated with ictal loss of memory and anxiety. Thus, haloperidol was discontinued. She was referred to Neurology, and further investigated with electroencephalography and neuroimaging. The former showed spike and wave activity in both of her frontal lobes, while a brain MRI (Magnetic Resonance Imaging) revealed a T1- and T2-weighted hyperintense lesion in the cingulate gyrus (Figure 1a-b). The patient was then submitted to a brain MRA (Magnetic Resonance Angiography), which showed signs of hemorrhage but no arteriovenous malformations in the anterior or middle cerebral artery. She was diagnosed with a bleeding cavernoma (Figure 1c). At that point, she was transferred to our service, where she underwent a bifrontal craniotomy (Figure 1d) followed by dissection of the interhemispheric fissure (Figure 1e-f). A red tumor in the cingulate gyrus was observed and subsequently microsurgically resected. The hemossiderine deposition surrounding the lesion was also carefully resected (Figure 1g). The diagnosis of a cavernous angioma was confirmed by pathological examination. After the surgery, the patient’s behavioral attacks, as well as the seizures and EEG abnormalities, fully resolved. Her memory problem, however, persisted after surgery. Postoperative MRI (Figure 1h,j,k) showed total removal of the lesion. Six months after the operation her evoking memory was significantly better. At follow-up, five years after the surgery, she was completely functional and free of any antiepileptic medication.
Figure 1a. Case 1. Surgical view showing the microsurgical access to interhemispheric fissure and in the deep view signs of hemorrhage.

Figure 1b. Case 1. MRI axial images showed the mass with hypersignal in the deep frontal lobe seated on the right side.

Figure 1c. Case 1. Angio MRI showed a hemorrhage in frontal lobe without neither aneurysm nor arteriovenous malformation.

Figure 1d. Case 1. Neutral position of head to access the interhemispheric fissure to proceed the bilateral frontoparietal craniotomy.

Figure 1e. Case 1. Surgical view showing the microsurgical access to interhemispheric fissure and in the deep view signs of hemorrhage.

Figure 1f. Case 1. Surgical view showing the brown-red lesion being removed through a Takahashi forceps with the right hand and dissected with a left hand with microsurgical tip suction.
Case 2

A 56-year-old male engineer presented to us with a history of progressive anxiety and memory issues (resulting in learning difficulties) for the past 3 years, which functionally affected both his personal and professional life. Additionally, he also experienced sporadic dyscognitive seizures, some of which with secondary generalization. Based on a psychiatric assessment, he was diagnosed with depression disorder associated with anxiety and treated with Sertraline 100 mg qhs. Two months prior to presentation, he started having attacks of aggressiveness. These lasted approximately a week, and included physical aggression towards his wife. At that point, the patient was seen by a neurologist, who initiated Carbamazepine 200 mg q.i.d in combination with Clonazepam 2 mg qhs. As a result, his anxiety improved, but the memory problems and secondary learning difficulty persisted. He underwent an EEG study and a brain MRI. The former was normal, while the latter showed a lesion (seen both in T1 and T2) suggestive of a cavernoma in the genus of the corpus callosum with extension to the cingulate gyrus, and, inferiorly, to the fornix. The patient was then submitted to a bifrontoparietal craniotomy followed by complete microsurgical resection of the lesion (Figure 2a,b,c). Postoperatively, his aggressiveness and anxiety problems, as
well as the seizures, immediately resolved. The memory issue and learning difficulty, in contrast, persisted – up to 5 years of follow-up.

*Figure 2a.* Case 2. Surgical view of interhemispheric approach through a frontoparietal craniotomy.

*Figure 2b.* Case 2. Surgical view: Large vascular lesion, brown-red color inside the corpus callosum. Anterior and superiorly extended to cingulate gyrus, and inferiorly to fornix.

*Figure 2c.* Case 2. Surgical view: After total removal, with ox-cell to hemostasis the white structure is the corpus callosum and laterally the cingulate gyrus.

*Figure 3a.* Surgical view showing the exposition of frontal lobe.

*Figure 3b.* Resection of large cavernoma in frontal lobe, left gyrus rectum.
Case 3

A 60-year-old female who experienced a burst of irritability and aggressiveness in the context of depression, anxiety, and memory issues (with secondary learning difficulties) for 3 years. The paroxysms of aggressiveness included self-harm and physical aggression towards others. Additionally, she also had sporadic dyscognitive seizures, some of which with secondary generalization. The patient was assessed by a neurologist, who started her on Carbamazepine 200 mg t.i.d., Valproate 500 mg t.i.d. and Clonazepam 2 mg qhs. These medications, however, failed to control both her seizures and behavioral issues. Investigation with EEG and brain MRI was performed. The former revealed epileptiform discharges originating from her left frontal lobe spreading to ipsilateral temporal region, while the latter showed a lesion in the left gyrus rectus suggestive of a cavernoma. Subsequently, the patient underwent a left frontal craniotomy with intraoperative electrocorticography (ECoG) followed by microsurgical resection of the abovementioned lesion (Figure 3a,b). Remarkably, the intraoperative ECoG showed an epileptogenic area not in the topography of the left gyrus rectus lesion but surrounding the ipsilateral temporal lobe. Postoperatively, the patient’s seizures and behavioral changes immediately resolved. Thus, all medications mentioned above were discontinued. At follow-up 3 months after the operation, her memory problems were also resolved.

**Results**

We report three patients presenting with neuropsychiatric symptoms (attacks of aggressiveness, memory and anxiety issues, as well as dyscognitive seizures with/without secondary generalization) secondary to diagnosis of cavernoma. In the first two cases the lesions involved the cingulate gyrus, while in the third case the cavernoma was sited at the left gyrus rectus. Notably, after surgical therapy, all three patients immediately recovered from the aggressiveness, anxiety, and seizures. The memory issues, however, persisted.

Lesions in the gyrus rectus have been previously associated with aggressiveness, anxiety and memory. The proposed underlying mechanism consists in the connection between this gyrus and the orbitofrontal gyrus, septal and accumbens areas, uncus, hippocampus, and parahippocampus - through pathways of the limbic system. An alternative hypothesis would be that both the gyrus and cingulate gyri connect to the accumbens nucleus, which has an important role in modulating behavior and in managing memory. It has been experimentally shown that impulsive behavior can be selectively inhibited by producing lesions in the center and periphery of the nucleus accumbens in rats. Further, recent experimental studies have proposed a possible link between the periphery of the nucleus accumbens and the solitary tract nucleus. Such connection could be important in modulating memory based on experience.

Neurons located in the periphery of the nucleus accumbens also receive input from the limbic areas at the amygdala and hippocampus, structures responsible for acquisition of new information (Figure 4). Thus, given that the limbic system connects the rinencephalon to the mesial temporal lobe, the memory loss observed in our patients could be attributed to their epilepsy - represented by dyscognitive seizures and secondary generalization. In fact, the ictal aggressive behavior seen on Case 1 could also be secondary to her epilepsy.

The complete resolution of the aggressiveness and anxiety after surgery, shared by the three reported cases, may suggest that lesions in the cingulate and rectus gyri influence behavior and memory. Elucidation of the basic mechanisms connecting lesions at the cingulate and rectus gyri to neuropsychiatric symptoms is needed.
CONCLUSIONS

Clinicians and surgeons should be aware of the possible relationship between new-onset of neuropsychiatric symptomatology and potentially treatable intracranial lesions. As a result, a thorough neuroradiological investigation in patients with psychiatric conditions is of paramount importance.

REFERENCES


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