FUNCTIONAL OUTCOME AFTER SURGICAL EXCISION OF CORTICAL MENINGIO-ANGIOMATOSIS

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ABSTRACT

Objective: To study the functional outcome after surgical excision of cortical meningio-angiomatosis (MA) in terms of seizure control and neurological disability.

Methods: Four patients with MA were diagnosed with refractory epilepsy. All were surgically treated.

Results: Four cases of MA were reported three males and one female. Median age at presentation was 19 years (range 9–23 years). All patients had refractory seizures for 1–18 years with a median of 8 years. Two patients had exclusively simple partial seizures, with secondary generalization; the other two patients had complex partial seizures, with secondary generalization. CT and MRI were done for all patients. The lesion was in the right frontal lobe in one patient, left frontal in one patient, left tempopolar in one patient and right temporal in one patient. After surgical resection, three patients remained seizure free without antiepileptic treatment and the fourth patient became controlled on monotherapy of antiepileptic treatment. No patients had added neurological deficit in the postoperative follow-up period of six months to eight years (mean 4.7 years).

Conclusion: MA commonly presents as refractory epilepsy. Although MA occurs infrequently, it is important to establish the correct diagnosis. Surgical excision is usually associated with good functional outcome with the patients either stop the antiepileptic treatment or become controlled on smaller doses.

Key words: Epilepsy, meningio-angiomatosis, surgery.

INTRODUCTION

Meningio - angiomatosis (MA) is considered a benign congenital focal hamartomatous malformation of the leptomeninges often involving the cerebral cortex underneath. Meningio-angiomatosis (MA) is rare; for the first time it was described in 1915 in association with neurofibromatosis.¹⁻³ Later some cases were described without the associated with neurofibromatosis (NF) and were found to be sporadic.⁴⁻¹²,²⁷

The most common clinical presentation of MA is by seizures that are intractable and difficult to control, other clinical presentations include headaches, however cases can present incidentally during imaging of the brain to another reason. The appearance of MA on imaging is non-specific and may resemble cystic gliosis, angiomia, meningioma, oligodendroglioma, arteriovenous malformation. Histopathologically, Meningioangiomatosis show meningoovascular proliferation and leptomeningeal calcification.¹¹ Immunochemical results are inconsistent among cases, does not add to the diagnosis, and do not support a meningeal origin.¹⁰ The electrophysiological characteristics of seizure-producing MA lesions have not been well described. Furthermore, although epilepsy surgery is briefly described as producing good results in MA,¹⁰,¹¹,¹²,¹³,¹⁴,¹⁵ outcome assessment is not described, and attention has not been given to the diagnostic and therapeutic problems faced by clinicians treating this condition. In the current study, the clinical, imaging and pathological features of MA are delineated. In addition, the surgical outcome in symptomatic cases was assessed.

METHODS

Patients

Four cases of MA were identified and confirmed by histopathological examination from 2001 to 2008 at Alexandria main University hospital, Alexandria, Egypt. Clinical features, the association with neurofibromatosis in patients and their family, and the results of imaging and electrophysiological investigations were obtained. Data on the surgical outcome (seizures, antiepileptic drugs and neurological deficits) were addressed.

All imaging studies were reviewed. The following immunohistochemical stains were performed on each case to determine the origin of proliferating or lesional cells: cytokeratin (low molecular weight, cam 5.2) to assess epithelial differentiation; vimentin, a nonspecific marker of mesenchymal cells; epithelial membrane antigen, a marker of arachnoid cap cells, positive in most meningiomas; S-100 protein, found in cells with neuroectodermal differentiation; glial fibrillary acidic protein (GFAP), an intermediate filament in cells of astroglial differentiation; smooth muscle actin, a marker of smooth muscle in blood vessel walls. Cases were included if histopathological descriptions contained at least one of the two classical features of MA, i.e. leptomeningeal proliferation and meningoovascular proliferation.
RESULTS

Patients

Four cases of MA were reported; three males and one female, all were surgically treated. Median age at presentation was 19 years (range 9–23 years). All patients had refractory seizures for 1–18 years with a median of 8 years. Two patients had exclusively simple partial seizures, with secondary generalization, the other two patients had complex partial seizures, with secondary generalization. The lesion was in the right frontal lobe in one patient left frontal in one patient, left tempopolar in one patient and right temporal in one patient. After surgical resection three patients remained seizure free without antiepileptic treatment and the fourth patient became controlled on monotherapy of antiepileptic treatment. No patients had added neurological deficit in the postoperative follow-up period of six month to eight years (mean 4.7 years).

Case presentation

The patient number three, a 13-year-old boy presented with progressively severe intractable epilepsy, which starts as partial seizures affecting his right side with secondary generalization to tonic-clonic seizures. His seizures started when he was 1 year old. Neurological examination revealed a mild right-sided hemiparesis. There were no clinical or radiological stigmata of neurofibromatosis (NF). An electro-encephalogram (EEG) revealed abnormal electrical activity over the left frontoparietal regions. An unenhanced head computed tomography (CT) showed hyperintense partially calcified, gyriform mass in the frontal lobe, resembling a partially calcified arteriovenous malformation. Moderate contrast enhancement was seen at this area of hyperintensity. (Fig.1) Brain MRI showed a slight thickening and a mild increase in signal intensity within the cortex over the convexity of the frontal lobe with calcified, gyriform mixed signal pattern. On post-gadolinium T1-weighted images, a bright signal was noted (Fig.1). After complete surgical resection, the histopathology revealed MA (Fig.2). The patient has a persistent, mild right-sided hemiparesis but remains seizure-free without antiepileptic drugs. The diagnosis of meningioangiomatosis was made on the basis of the clinical, radiological findings, and histopathological confirmation was obtained.

Histopathology

All patients’ MA lesions were confined to the leptomeninges, with variable involvement of the underlying cortex. All lesions showed cortical vascular proliferation and perivascular cellular proliferation. Cases were easily classified into those with predominantly cellular (patients 1 and 3) and those with predominantly vascular (patients 2 and 4) lesions. Predominantly cellular cases demonstrated moderate to high cellularity. Varying architecture was noted, consisting of focal areas of rhythmic palisading patterns. All cellular cases had lesional cells that in areas appeared to emerge from the perivascular location and infiltrate the cortex. This occurred centrally within the lesions, where cellularity was most dense. Peripherally, the perivascular relationship of the cells became evident. The blood vessels in these cases had a similar appearance, i.e. they were thin-walled, slit-like. Predominantly vascular cases contained thick-walled, hyalinized and calcified blood vessels with minimal perivascular cell proliferation. Despite cellularity, the proliferating cells in all cases were without significant atypia, mitoses or necrosis, and in no case the proliferating cells demonstrated cortical invasion. All cases contained a meningeal component. Of these, three showed calcification in areas of meningeal proliferation and within the cortex.

Extensive pericellular reticulin deposition occurred in one of the two cellular cases (patients 3). In all other cases, reticulin was confined to blood vessels. One case (patient 4) demonstrated cortical dysplastic neurons adjacent to the MA focus. All cases showed gliosis within and adjacent to the lesion. On immunostaining, the proliferating cell population expressed vimentin uniformly. Results for other markers were mostly negative. Our results illustrate the variability of immunostaining and suggest that proliferating MA cells do not correspond to a known, normally occurring cell type. Notably, epithelial membrane antigen, a known meningotheial cell marker, was focally positive in only one case (patients 2).
Fig. 1. Pre and post contrast CT scan of the representative case showing the left frontal lesion. Notice the calcification in the non contrast CT scan (upper left). Middle; sagittal and axial T1 contrast and coronal T2 of the same case. Lower; postoperative CT scan after total excision.

Fig 2 (A&B): Demonstrate the heterogeneous pattern of cellularity and vascularity giving an uneven appearance. Haematoxylin and eosin, X120. (C&D) Higher power demonstrates subpial and perivascular cell proliferation. Haematoxylin and eosin, X180.
DISCUSSION

MA is considered a hamartomatous lesion of the leptomeninges and adjacent cerebral cortex. It was first described by Bassoe and Nuzum \(^{(3)}\) in 1915. The term ‘meningo-angiomatosis’ was first used by Worcester-Drought et al., \(^{(40)}\) in 1937. Many cases have been reported in NF patients and others are reported sporadic. \(^{(1,12,27)}\) In sporadic cases the mean patient age was found to be somewhat younger, the commonest presentation is partial seizures, which is progressively difficult to control, also other clinical presentation may be headaches but some cases are also found incidentally during brain imaging for other reasons. \(^{(29)}\) The literature suggests higher occurrence in males and in the right hemisphere. MA usually affects the frontal or temporal regions; infrequently some cases may show involvement of the third ventricle, thalamus or brainstem. \(^{(11,19)}\)

The characteristic pathological findings include leptomeningeal meningovascular proliferation with a variable degree of calcification. \(^{(1,36)}\) The degree of calcification can vary from numerous psammoma bodies histologically to dense calcification and even ossification. \(^{(20)}\) The fibroblastic and angiomatous proliferation can extend in a linear fashion along the Virchow-Robin perivascular spaces, thereby appearing to ‘penetrate’ the cortical grey matter. \(^{(1)}\) Also the cortical changes include the presence of neurofibrillary tangles, which represent degenerative changes in entrapped neurons. Neurofibrillary tangles are not associated with amyloid plaques or granulovacuolar degeneration, may be a reactive phenomenon rather than an intrinsic MA component. \(^{(29)}\)

The histological spectrum can be broadly classified into predominantly cellular and predominantly vascular lesions. Although each lesion is unique, increased cortical vascularity and perivascular cellular proliferation are constant findings. The main histopathological features are leptomeningeal meningothelial proliferation and meningovascular proliferation. Except for bone formation, our four cases demonstrate the full range of recognized histological morphologies, i.e. calcification, gliosis, perivascular connective tissue proliferation, dysplastic neurons, and large-vessel hyalinization. In many cases, proliferating perivascular cells infiltrate the cortex in association with marked cellularity and reactive gliosis. Unless the pathologist is familiar with the histological features of MA, these features may lead to the erroneous diagnosis of malignancy, as illustrated by our case 3 and other cases in the literature. \(^{(14)}\)

Immunohistochemistry has limited diagnostic value, as staining patterns vary among MA cases. Some immunostaining was done in 24 published cases, although often not in a panel. Results of our immunostaining panel parallel those in the literature, i.e. only vimentin, an intermediate filament protein of fibroblasts and mesenchymal cells, is consistently positive. Epithelial membrane antigen, a marker for arachnoid cap cells, and cam 5.2, co-expressed in 10% of meningiomas, are often negative in MA. GFAP, S-100 and neuronal specific enolase show inconsistent staining and factor VIII was not expressed by the lesional cells. These findings do not support a meningothelial origin for the perivascular cells. Instead, it is possible that a pluripotent cell line undergoes differentiation towards various cell types. Results of electron microscopy are sparse and inconsistent in the literature. Some cases suggest a meningothelial derivation, i.e. interdigitating cell membranes, cell junctions and intermediate filaments, while others lack such features. \(^{(10,11,18,19,20)}\) Atypical neuronal inclusions resembling Pick bodies have been recently described in sporadic MA. \(^{(26)}\)

The pathogenesis of MA remains unclear. Proposed hypotheses \(^{(19,31)}\) suggest that: (i) MA is a hamartoma that undergoes degenerative changes, and association with NF in some cases supports this theory; (ii) MA results from invasion of brain tissue by a leptomeningeal meningioma, though not all cases have a meningial component and features of malignancy are typically absent; (iii) a cortical vascular malformation induces perivascular meningothelial proliferation of cells from vessel walls or from pluripotent arachnoid cap cells in Virchow– Robin spaces. Leptomeninges and arachnoid cap cells normally surround blood vessels as they penetrate the cortex. Conceivably, chronic leptomeningeal stimulation by the underlying cortical lesion could result in MA histopathological changes.

The pathological differential diagnosis of MA includes the Sturge-Weber syndrome, angiomas, meningiomas, sarcoïd or tubercular meningitis, and glioma.

MA does not have a typical CT or MRI appearance. On CT scans without contrast, the non calcified areas of the lesion may range from isodense to moderately hypodense. Calcifications may be seen as either linear or granular in nature. \(^{(1,33)}\) The degree of contrast enhancement is variable. On MR scans MA tend to be iso- to hypointense to grey matter on T1-weighted images, hyperintense on T2- weighted images with areas of dense calcification producing marked T2 shortening and thus appearing as hypo-intense areas often within the center of the lesion. \(^{(11,29,36)}\) Contrast enhancement is variable. Because of the nonspecific appearance, MRI may erroneously suggest low-grade tumour, vascular malformations, or cystic encephalomalacia. CT and MRI enhancement occurs with sufficient frequency to blur the distinction between MA and other lesions.
Total surgical resection is the treatment of choice for MA, with the prognosis being very good with complete cure from seizures in most cases.\textsuperscript{12,27}

**Seizure Outcome Following Surgery**

Seizure-free rates in the current series and in the literature were 75 and 68%, respectively.\textsuperscript{10,11,17,21,22,27,29,31,36} Seizures improved in one (25%) of our four patients, compared with 30% improvement in the literature. The case which showed only improvement had temporal (limbic and neocortical) seizures, in this case the sclerosed amygdala and hippocampus was not resected during surgery, also in this case MA was partly removed.

Age, MA location and size, duration of illness and interictal EEG findings did not correlate with seizure outcome. The only single factor emerged as determinant of seizure outcome following resection of MA lesions was complete resection. Therefore, our data suggest that seizure outcome after surgery is variable and that resection of the lesion and of epileptogenic cortex is required.

**Conclusions**

The wide spectrum of EEG and imaging expressions of MA often impedes the clinical diagnosis. Although histopathological diversity is common, MA can be classified into cases with predominantly cellular features and those with predominantly vascular features. Little diagnostic gain accrues from immunostaining because of its variability. Sporadic MA commonly presents as refractory focal epilepsy, but other clinical presentations are recognized. Although MA occurs infrequently, it is important to establish the correct diagnosis. Extraxional epileptogenesis and variable seizure outcome must be considered when planning surgical treatment. Finally, the association of symptomatic MA with NF is extremely unusual.

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