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Prediction of outcomes for brainstem cavernous malformation

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ABSTRACT

Objective: Brainstem cavernous malformation (CM) poses a challenge to neurosurgeons in terms of operability, postoperative complications and unpredictable outcomes. The present study was conducted to analyze the clinical parameters that might predict the outcomes and to summarize our center experience in treatment of brainstem CM.

Methods: A total 59 patients with radiological and histologically confirmed brainstem CM diagnosed between 2000 and 2012 were retrospectively reviewed. All but five patients were deemed amenable to surgical resection. Complete resection was attempted in all CM and was achieved in 58/59 patients. Modified Rankin scale (mRS) score dichotomized as mRS 0–2 (favorable outcome) or mRS 3–6 (unfavorable outcome) was employed for neurological status assessment. The association of various clinical parameters to the different brainstem location was evaluated. Predictors of the surgical outcomes were analyzed using the univariate and multivaraite regression statistics.

Results: Mean age of 32 female and 27 male patients was 34.3 years. The differences in size of cavernoma, conservative treatment and complications were significantly associated with various location of the CM in the brainstem. Clinical parameters including age at presentation ($p = 0.029$, OR = 0.061, CI = 0.009–0.414), favorable preoperative mRS ($p = 0.004$, OR = 0.058, CI = 0.009–0.343), pontine location of CM ($p = 0.018$, OR = 0.017, CI = 0.001–0.495), and early surgical treatment ($p = 0.05$, OR = 0.087, CI = 0.07–1.03) were independent predictors of favorable surgical outcomes. Mean long-term follow up of 42.9 months was available in 31/59 (52.5%). The mean size of CM was 22.5 mm; small size (<10 mm) at presentation was associated with favorable outcomes at long-term follow-up (univariate analysis, $p = 0.041$, adjusted $R^2 = 0.471$). Preoperative mRS ($p = 0.039$) and location of the CM ($p = 0.034$) in the brainstem were predictors of good surgical outcomes at long term follow-up.

Conclusion: Favorable surgical outcomes can be predicted in brainstem CM patients with early age at presentation, pontine location of the cavernoma, favorable preoperative mRS and those undergoing early surgery. The outcomes at long-term follow-up were associated with location of the CM in the brainstem, size of the CM and the preoperative mRS.

1. Introduction

Brainstem cavernous malformation (CM) account for 9–35% of intracranial CM [1]. Despite of recent surge in literature on brainstem CM, a general consensus for the optimal management of this formidable lesion is still lacking. The treatment options for brainstem CM are surgical extirpation of the lesion, conservative treatment and the radiosurgery [2–6]. Variable outcomes has been reported with each modality of treatment, however, for the lesions that abuts the pial surface of the brainstem and presents with mass effect and progressive neurological symptoms, favorable results with surgical resection has been reported in the literature [5–12]. The level of confidence with which a surgical treatment can be offered depends on the prediction of outcomes after the extirpation of this challenging lesion. The studies concerning analysis of the pre and perioperative factors that might influence surgical outcomes are lacking. We intend to summarize our experience of surgical management of brainstem CM and attempt to identify the factors that might predict the outcome.

2. Methods

A total of 59 patients with radiological and histologically confirmed brainstem CM diagnosed between 2000 and 2012 were retrospectively reviewed. The medical records, surgical records, and neuroimaging of all patients were analyzed. The inclusion criteria of the study were: (1) Symptomatic brainstem cavernomas; (2)

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Well-defined brain stem CM on T1/T2 or Gradient Echo Scanning (GES) MR imaging; (3) No prior radiotherapy was employed; (4) No other contributory lesions were detected on MR imaging exam. CM hemorrhage was defined as presence of intra or extra capsular CM bleeding, associated with sudden onset or progressive neurological symptoms. The acute hemorrhage was defined as the presence of acute blood either inside or outside of the CM capsule in patients with sudden onset of symptoms or aggravation of stable neurological symptoms. The presence of hemosiderin deposition around CM on neuroimaging was not considered as hemorrhagic episode. All patients presented with at least one hemorrhagic episode. However, due to the poor admission records for those patients admitted to other hospital for previous hemorrhagic events and the varying definition of the hemorrhagic events, the exact number of recurrent episodes was not sophistically classified. All patients initially presented with neurological symptoms.

MR imaging examinations imaging protocol included the following sequences: T1and T2-weighted images with and without gadolinium enhancement, fluid-attenuated inversion recovery images (FLAIR) and Gradient Echo Scanning (GRE). Slice thickness was 5 mm, and the field of view (FoV) varied between 18 and 30 cm. All the imaging studies were available for review. T2-weighted MR image depicted the low-density hemosiderin deposit around the high density of methemoglobin in CM presenting with multiple hemorrhages. Gradient echo scanning aided the diagnosis of small and multiple cavernomas. MR appearances of CM were divided into four types based on the radio-pathological classification of cerebral CM; given by Zabramski et al. [13]; (1) Type I (19/59, 32.2%) – T1, hypointense, T2 hypo or hyperintense core with pathological feature if subacute hemorrhage; (2) Type II (26/59, 44.1%) – reticulated mixed core on T1 and T2 with pathological feature of lesions with thrombosis of varying age, (3) Type III (8/59, 13.6%) – hypointense lesion with hypointense rim with pathological feature of chronic hemorrhage, (4) Type IV (6/59, 10.2%) – punctuate hypointense lesion in GES.

3. Surgical treatment

Surgical treatment was offered to all patients who had; (1) a symptomatic lesion presenting with acute presentation or suffering from progressive neurological deficits caused by CM mass effect, (2) lesions that were superficial and within 2–3 mm of the brainstem pial surface, (3) lesion that were deep and could be approached by a safe trajectory, (4) MR imaging showing acute, subacute or delayed hemorrhage. All but five patients underwent primary surgical resection at our institute. Surgeries were carried out within one month of the presentation to our facility; based on the severity of presenting symptoms, duration of CM history and presence of co-morbidities. The timing at which the surgery was offered was divided into early $\leq$2 weeks and delayed >2 weeks. Surgical approach was selected based on precise location of the tumor, minimization of damage to the surrounding structure, facilitation of complete resection of the lesion and identification of safe surgical zone. Intraoperative monitoring with neuronavigation, brainstem auditory evoked potential, mapping of the cranial nerve nuclei and neurophysiological monitoring was utilized as needed. Midbrain CM were resected mainly through the Poppen's suboccipital transtentorial approach (8/12), extended pterional (2/12), and suboccipital posterior midline (1/12); pontine CM were extirpated through suboccipital posterior median craniotomy (14/27), Poppen's approach (5/27), retrosigmoid approach (4/27) and extended pterional approach (1/27); the workhorse approach for the lesions at the pons, medulla and branchium pontis was suboccipital posterior median craniotomy with various extensions such as resection of the posterior arch of C1, the occipital condyle, and retrolabyrinthine petrous bone 59.3% (35/59) (Table 1). The safe entry zones included floor of fourth ventricle, lateral cistern, zone between the fifth cranial nerve and corticospinal tracts and the zone above or below the facial nucleus. After exposure of the brainstem, the hemosiderin layer around the CM was identified and utilized as the plane of dissection. In cases of well-organized hematoma within the CM, the hematoma was aspirated prior to resection of CM. The evacuation of the hematoma provided enough room for the safe excision of CM without any retraction of the brainstem tissue. No attempts were made to remove any hemosiderin stained tissue. Complete resection was attempted in all CM and was achieved in all but one case. During the surgical treatment meticulous coagulation and careful cutting of the anomalous vessels surrounding the CM was carried out. The resected CM were fixed in 10% formalin and embedded in paraffin, as a part of routine procedure. The histopathological examination of CM revealed sinusoidal dilated vessels of various sizes, hyperplasia of collagen, hyaline degeneration, fibrosis, calcification and hemosiderin deposits. The findings varied depending on the time of presentation of the cavernoma. All patients underwent MR imaging exam on postoperative day 3.

3.1. Follow-up and outcome

Follow up was conducted at 3, 6 and 12 month after surgery. The outcome was evaluated based on the medical records and the office chart review and by telephonic interview with the patients or family. The patients' outcome at 1-year follow-up was categorized according to the modified Rankin Scale (mRS) score as favorable outcome (mRS 0–2) or unfavorable outcome (mRS 3–6). The long-term outcome was evaluated by telephonic interview. Long-term follow-up data ranged from 12 months to 138 months (average 42.9 months). Preoperative mRS score was analyzed in all patients and compared to the postoperative mRS score. The pre and perioperative parameters for brainstem CM including age, gender, size of the CM, deep-seated or superficial, location within the brainstem, preoperative mRS, duration of the symptoms, number of hemorrhagic episodes, conservative treatment, timing of surgery, and the MRI appearance were analyzed as predictors of surgical outcomes.

3.2. Statistical analysis

Statistical analysis was performed with a statistical software package (SPSS 18.0). The data were presented as the mean $\pm$ SD, and the Pearson chi-square test and the Fisher exact test were used to assess the statistical significance between the clinical factors and outcomes on mRS scale. Univariate and multiple regression analysis were employed to analyze the predictors of the surgical outcome. The association of clinical parameters to the different locations in the brainstem was evaluated. A p-value of less than 0.05 was considered statistically significant.

4. Results

4.1. Demographics and preoperative parameters

The mean age of 32 female and 27 male patients (sex ratio 1.18:1) was 34.3 years (range 8–65 years). Fig. 1 demonstrates the age and sex distribution of all patients in the study. Forty two percent patients (25/59) had unfavorable preoperative mRS and 58% (34/59) presented with favorable preoperative mRS. Preoperative mRS was unfavorable in 75% (9/12) midbrain CM patients. Most common presenting symptom was headache 34% (20/59), cranial nerve deficits and hemiparesis 20/59 (34%) followed by ataxia and dizziness. The mean duration of the symptoms was 17.6 days; excluding 10 patients that presented with long duration (mean: