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Prediction of postoperative outcome with special respect to removal of hemosiderin fringe: A study in patients with cavernous haemangiomas associated with symptomatic epilepsy

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Summary

Purpose: In this study 30 patients with symptomatic epilepsy caused by cavernomas were investigated in a postoperative follow up study to assess predictors for postoperative outcome with respect to indications, time and approach of surgery.
Methods: Thirty patients with cavernomas refractory to medical treatment were scheduled for surgery based on the findings of high-resolution MR imaging and intensive EEG-video monitoring. Postoperative outcome of epilepsy was assessed by follow-up examinations based on the basis of classification by Engel and the International League against epilepsy (ILAE).
Results: The following variables were associated with good postoperative outcome: (1) complete resection of hemosiderin fringe surrounding the cavernoma was correlated to less postoperative seizure frequency versus incomplete resection of the hemosiderin fringe according to the outcome protocol of ILAE. (2) Lower duration of epilepsy at the time of operation was correlated to a better postoperative outcome with a benefit for recovery. (3) Absence of hemorrhage before surgery and unifocal seizure onset was a predictor for a favorable outcome, whereas bilateral or multifocal seizure onset zones showed poorer postoperative outcomes. (4) In patients with dual pathology (hippocampal sclerosis in addition to a cavernoma), lesionectomy plus hippocampectomy as opposed to lesionectomy only, had a better outcome than single lesionectomy.

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Conclusion: Postoperative outcome in patients with cavernomas should be the topic of further prospective multicenter studies involving a large number of patients. In addition to the ideal operation time and handling of dual pathology the role of extended resection including perilesional hemorrhages should be taken into account.

Introduction

Since the introduction of MRI, cavernous haemangiomas (cavernomas) are increasingly detected in patients with epilepsy. In the detection of cavernomas T2*weighted gradient echo sequences are superior to spin echo sequences.[1–5] At an incidence of 40–70%,[4,6,7] epilepsy is the most common clinical sign in patients harbouring intracerebral cavernomas, and is the leading cause of morbidity in these patients.[8] Surgical removal of the cavernoma (lesionectomy) would appear to be the most successful means of treating intractable epilepsy.[9] In this pilot study, 30 patients with symptomatic epilepsy caused by cavernomas were investigated by postoperative follow up to assess outcome predictors with particular emphasis on the indications for the timing of and the type of surgery.

Patients and methods

Thirty patients (m:f = 17:13) with cavernomas were scheduled for surgery based on the findings of intensive of high-resolution MR imaging and intensive EEG-video monitoring. In addition to routine MR sequences, FLAIR and gradient spin echo sequences (T2*wFLASH) were applied to better display perilesional hemosiderin. Follow-up examinations that averaged up to 4 years were based on standardized documentation and clinical examination. Preoperative high-resolution MRI including T1 and T2 weighted sequences comprising spin echo sequences and gradient echo sequences was available. The MR images were interpreted by two independent experienced neuroradiologists, who were in agreement concerning the location and diagnosis of the lesion. Intensive EEG monitoring including video monitoring and neuropsychological testing was applied to all patients. Lesionectomy (excision of the cavernoma only) was performed in 13 patients, and extended lesionectomy (including an additional 1–3 cm of perilesional tissue) in 11 patients. A modified temporal lobe resection comprising lesionectomy plus tailored resection of the temporal lobe, which also included hippocampectomy, was done in six patients. This approach was applied in patients with dual pathology, namely hippocampal sclerosis and cavernoma. With all procedures, including microsurgical lesionectomy, the firm glial layer, differing unequivocally in colour and consistency from normal brain, was removed. Extended lesionectomy implying was carried out if: (1) ECoG investigations demonstrated persistent spike activity in tissue adjacent to cavernomas scheduled for surgery, (2) in the presence of additional pathology, i.e. hippocampal sclerosis in the preoperative MR image, and (3) electrophysiology revealed distant epileptogenic foci incompatible with the described cerebrovascular lesion. When the cavernoma was in close proximity to critical areas with a risk of causing postoperative functional impairment only lesionectomy was performed. Postoperative outcome was assessed on the basis of the classifications by Engel[10] and the International League against epilepsy (ILAE)[11] (Table 1).

Results

The mean age at onset of the first seizure was 28.6 years (range: 5–60 years, S.D. = 15.5). The average age of the patients at the time of surgery was 39.4 years (range: 19–62 years, S.D. = 12.4). In 19 of the 30 patients investigated, more than three different antiepileptics, administered in combination, had already been applied (average: 3.4 drugs/patient), with no adequate control of the seizures being achieved. The temporal lobe was the most common location of the cavernomas in our study (70%), which were found equally in temporomesial and

Table 1 Outcome classification by the ILAE scheme

Outcome classification	Definition
1	Completely seizure free; no auras
2	Only auras; no other seizures
3	One to three seizure days per year; ± auras
4	Four seizure days per year to 50% reduction of baseline seizure days; ± auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
6	More than 100% increase of baseline seizure days; ± auras

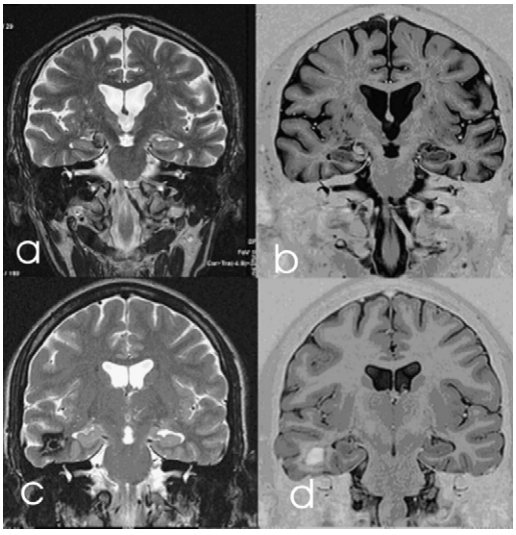

Figure 1 Temporomesial cavernoma and cavernoma of the white matter fraction of the right hemisphere (preoperative). (a) Temporomesial cavernoma, T2 weighted image; coronal slice positioning; (b) temporomesial cavernoma, inversion recovery; coronal slice positioning; (c) cavernoma of white matter fration, T2 weighted image; coronal slice positioning; (d) cavernoma of white matter fration, inversion recovery; coronal slice positioning.

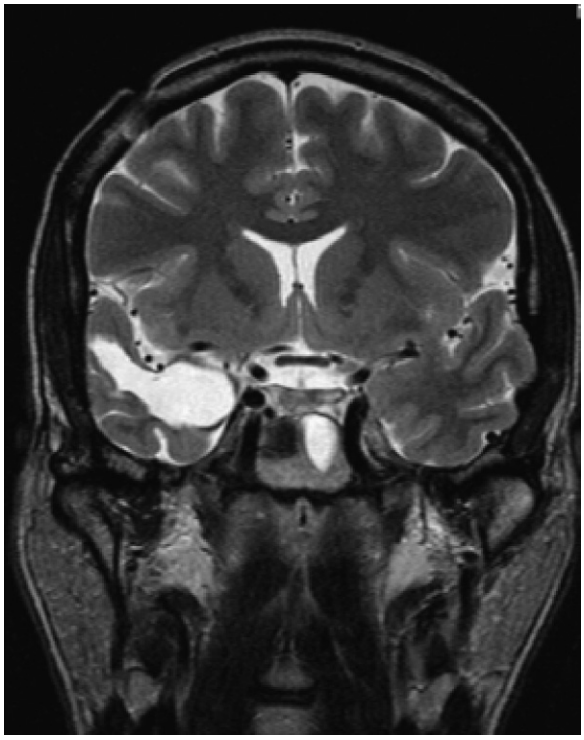

Figure 2 T2 weighted coronal imaging of a postoperative state of a cavernoma of the white matter fraction of the right temporal lobe with complete resection of the haemosiderin fringe.

temporolateral regions (Fig. 1). In seven patients the cavernoma was localized in the frontal lobe, in two patients in the occipital region. Two patients had multiple cavernomas located in one hemisphere. Postoperatively 16 patients (53.3%) were completely seizure free (Engel I A, ILAE 1); one patient experienced occasional isolated auras (Engel IB, ILAE 2); eight patients (26.7%) had a drastic reduction in the frequency and severity of seizures (Engel IIA-IIIB, ILAE 3—5); in four cases (13.3%) no improvement was seen (Engel IVA-IVB, ILAE 5). In one patient postoperative outcome was not classified because he did not attend the following up investigation. Our most important findings that require further investigation is the fact that extended resection including complete removal of surrounding hemorrhages was correlated with a reduced postoperative seizure frequency (ILAE 2.18) compared with incomplete resection of the hemosiderin fringe (ILAE 3.86) (Table 2; Fig. 2). Although non-parametric independent two group comparisons by Mann-Whitney Test revealed no statistical significance ($p = 0.079$), the trend is obvious in this point. In general, postoperative outcome revealed no correlation with the location of the cavernoma. There was no significant difference in the postoperative outcome in terms of the seizure frequency of patients with temporal cavernoma as compared with patients with extratemporal cavernoma. A comparison of postoperative outcome in patients with dual pathology (hippocampal sclerosis and cavernoma) shows that patients who underwent lesionectomy with additional (para)-hippocampectomy (43.3% of the cases) experienced a significant reduction in postoperative seizure frequency (ILAE2.9 S.D. = 1.77) in comparison with patients undergoing lesionectomy alone (56.6% of the cases) (ILAE2.1 S.D. = 1.75) ($p = 0.033$). Further important prognostic factors for postoperative outcome in our study were found to be: (1) early surgery of the cavernoma, which reduced the duration of preoperative epilepsy, was correlated with a better postoperative outcome (Table 3). The 91.7% of patients operated on within 2 years after clinical onset of epilepsy became seizure free. A comparison of postoperative seizure frequency by ILAE classification of the mentioned group (ILAE1.4) with that of the patients with an epilepsy duration of more than 2 years (ILAE3.0) revealed a significantly better ($p < 0.05$) outcome associated with a short (up to 2 years) illness duration. (2) Absence of preoperative hemorrhage and unifocal seizure was also a predictor of a favorable outcome, while bilateral or multifocal seizure onset zones were associated with a poorer postoperative outcome. The 28 out of 30 cavernoma patients showed signs of a previous hemorrhage. Twenty-

Table 2 Comparison of pre- and postoperative MRI findings to postoperative outcome

MRI hemorrhages preoperative	MRI haemorrhages postoperative	Postoperative outcome	Duration in years (y) of postoperative follow up
Intralesional	—	ILAE 1	Y 1/2
Intralesional	—	ILAE 4 extended resection not possible!	Y 4
Perilesional	Gliosis in neighboring region	ILAE 5	Y 1/2
Perilesional	—	ILAE 1	Y 4
Perilesional	—	ILAE 1	Y 2
Perilesional	Surrounding sclerosis	ILAE 5	Y 1
Intralesional	—	ILAE 3	Y 4
Perilesional	Older bleeding left temp. -parietal and intralesional	ILAE 4 multiple cavernomas	Y 4
Perilesional	—	ILAE 1	Y 4
Intralesional	—	ILAE 1	Y 3
Intralesional	Perilesional	ILAE 1 ILAE 6 bilateral activity	Y 1/2
Intralesional	Perilesional	ILAE 6 bilateral activity	Y 4
Perilesional	Perilesional	ILAE 4 2 lesions, bilateral activity	Y 4
Intralesional	—	ILAE 1	Y 1
Intralesional	—	ILAE 1	Y 3
Perilesional	—	ILAE 4 HS, 2 cavernomas	Y 1
Intralesional	—	ILAE 5 bilateral aktivity	Y 4
Perilesional	Perilesional	ILAE 1	Y 3
Perilesional	Perilesional	ILAE 2	Y 4
Perilesional	—	ILAE 1	Y 2
Intralesional	—	ILAE 1	Y 1/2
No bleeding	Perilesional	ILAE 1	Y 2
11 × Perilesional 10 × Intralesional 1 × No bleeding	6 × Perilesional 1 × Intralesional 15 × No bleeding	Last outcome average: ILAE 2.89	Average follow up in years: 2, 6

LE, lesionectomy TR, tailored resection.
ELE, extended lesionectomy (lesion and focal epileptic activity in EcoG).

Table 3 Postoperative outcome and possible predictors

Variables	All patients	Seizure free	Persisting seizures
Operated patients	30 (ILAE m. 2.4)	16 (53.3%)	14 (46.7%) (ILEA m. 3.9)
Mean age at first manifestation	28.6	33.4	23.1
Mean duration of epilepsy in years	10.9	4.6	18.1
Seizure frequency (days/month with attacks)	5.5	5.6	5.5
Unifocal/multifocal findings in EEG	13/17 (ILAE m. 1.5/3.1)	11/7	2/10
Haemorrhage	17 (ILAE m. 2.9)	8	9
Surgery	13 × Lesionectomy 11 × Extended resection 6 × Standard resection	9 × Lesionectomy 4 × Extended resection 3 × Standard resection	4 × Lesionectomy 7 × Extended resection 3 × Standard resection
Early first manifestation <16 years	6 (ILAE m. 3.3)	1	5
Localization	5 × Frontal 22 × Temporal 2 × Occipital 1 × Parietal	4 × Frontal 11 × Temporal 1 × Occipital	1 × Frontal 11 × Temporal 1 × Occipital 1 × Parietal
Multiple cavernomas	4 (ILAE m. 4.0)	0	4

ILAE m., ILAE mean.

one patients had MRI signs of a fresh or old hemorrhage. Patients with MRI evidence of intralesional or perilesional bleeds, and who were subsequently submitted to surgery, had a clearly poorer outcome than did those with no such preoperative signs of bleeding. Patients with preoperative MRI evidence of a fresh or old hemorrhage had an average postoperative result of 2.9/S.D. = 1.89 by the ILAE classification. This contrasts with 1.6 ($s = 1.19$) in patients with no pre-operative signs of hemorrhage. Almost 85% of the patients with monofocal activity became seizure free, compared with 41% of those with multifocal disease. The former group also showed a better outcome in the ILAE rating scale (1.5) compared with patients with preoperative multifocal activity (ILAE3.1) ($p = 0.017$). (3) None of the four patients with multiple cavernomas became seizure free after resection of the (single) lesion believed to be mostly responsible for epileptogenic activity.

Discussion

Cavernomas are congenital vascular malformations, which occur in 0.4—0.5% of the general population. Today they are classified as benign lesions, which in principle can be removed completely by surgical treatment. All studies are in agreement that early operation, which reduces the preoperative duration of epilepsy, is associated with a better outcome. These results are supported by our study as well as the overall positive effect of surgery in which up to 94% of the patients became seizure free, or at least experienced a marked reduction in seizure frequency.[12—14,8,6,15—17] With regard to the surgical approach to dual pathology, most authors support our findings that dual pathology (cavernoma + hippocampal sclerosis) must always be considered when evaluating different approaches of epilepsy surgery. (Para)-hippocampectomy together with lesionectomy results in a better postoperative outcome with a significant reduction of postoperative seizure frequency than lesionectomy of the cavernoma alone.[18—20] A more controversial point is the determination of the boundaries of cavernoma resection. Our results indicate that a satisfactory therapeutic outcome requires complete elimination of the epileptogenic foci in which extended lesionectomy should include perilesional tissue if the EcoG reveals focal epileptic activity in the latter. Comparable results were described by Casazza et al., Cosgrove. and Cohen et al.[6,19,21,22] In general the authors conclude that presurgical evaluation must be tailored to the individual's pathology. The results reported by Cosgrove et al. imply that the postoperative outcome of lesionectomy plus corticectomy is slightly superior to lesionectomy alone. Investigations of Cohen et al. indicate that patients with shorter seizure histories and fewer preoperative seizures can be effectively treated by lesionectomy alone, whereas those with longer histories and more seizures are not effectively treated by this procedure and may require more extensive resections. Studies which generally attribute epileptic activity to the hemosiderin fringe claim that epileptic activity is based on the iron content of hemosiderin[23—25] as well as gliotic tissue alteration[23] which is caused by recurring perilesional hemorrhage. But this point is still controversial. Studies of Casazza et al. and Zevgaridis et al. failed to find any substantial evidence that additional excision of the hemosiderin-stained tissue around the cavernoma provided better results than merely resection of the cavernoma.[21,26] Our data reveal that in patients who underwent epilepsy surgery the resection of the hemosiderin fringe of cavernomas is associated with a better postoperative outcome.

Conclusion

Because of the limitations in our study the role of surgery in the disease pattern mentioned above should be the topic of further prospective multicenter studies involving a large number of patients. In addition to the ideal operation time and handling of dual pathology the role of extended resection including perilesional hemorrhages should be taken into account. New diagnostic techniques (e.g. magneto-encephalography (MEG)) should be evaluated and integrated in the armamentarium of noninvasive diagnostic procedures of focal epileptic activity and its spatial correlation to cavernomas and surrounding hemorrhages.[27]

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