Seizures as presenting symptom in patients with intracranial meningioma

Andreas Mathisen Hasseleid – kull H-07

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Forord

Studentoppgaven ”Seizures as presenting symptom in patients with intracranial meningioma” er basert på et stort datamateriale innhentet fra Oslo Universitetssykehus (Rikshospitalet og Ullevål Universitetssykehus). Arbeidet har foregått i tidsrommet våren 2010 - høsten 2012. Vi har vært fire studenter involvert i prosjektet, der hver av oss har skrevet egne oppgaver. Motivasjonen for å velge nettopp dette temaet for oppgave var undertegnedes interesse for nevrologi.

Jeg vil takke veileder professor i nevrokirurgi Eirik Helseth og nevrokirurg Torstein Meling for inspirerende og kyndig veiledning. Jeg vil også takke Pål Rønning for god hjelp med statistiske utregninger. Til slutt vil jeg rette en takk til mine medstudenter Bernt Filip Kristiansen Hasseleid, Andreas Hessen Schei og Kristina Ødegård for hyggelig og godt samarbeid i forbindelse med innhenting og bearbeidelse av data.

Andreas Mathisen Hasseleid, 30. september 2012.

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Andreas Mathisen Hasseleid[1], Torstein R. Meling[2], Bernt Filip Hasseleid[1], Pål Rønning[2], Eirik Helseth[1,3]

[1]Faculty of Medicine, University of Oslo

[2]Department of Neurosurgery, Oslo University Hospital, Rikshospitalet

[3]Department of Neurosurgery, Oslo University Hospital, Ullevål

Summary

Objective:

To determine the fraction of patients presenting with seizures and explore possible associations between seizure as presenting symptom and sex, age, tumor location, laterality, histology, Karnofsky performance score and prognosis.

Materials and methods:

All patients who underwent primary craniotomy for a meningioma at the Oslo University Hospital, in the time period 1990 – 2010 were included in this study. The patients operated during the years 1990 – 2002 were identified by reviewing operative protocols from this time period, while patients operated after 2002 were identified from our prospectively collected tumor database. All charts were studied retrospectively. The total number of patients identified with a histological verified intracranial meningioma was 1469.

Results:

The frequency of seizures, raised ICP and focal neurological deficits as presenting symptoms were 29.6%, 31.7 % and 60.2%, respectively. Site of dural attachment, laterality of tumor, gender and Karnofsky score showed a significant association with seizures as presenting symptom, while age, WHO grade and right/left tumor location did not. Convexity- and parasagittal tumors most frequently presented with seizures. Falx-, lateral sphenoid wing- and supratentorial skull base had an intermediate frequency of seizures as presenting symptom, while tumors located in posterior fossa or brain ventricles rarely presented with seizures. Male gender and Karnofsky performance status $\geq$ 70 were positively associated with seizure as presenting symptom. Overall survival (OS) at 1-, 12- and 60- months were 98%, 96% and 88%, respectively. Seizures as presenting symptom was not significantly associated with survival.

Conclusions:

29.6% of the meningioma patients presented with seizures. Seizures as presenting symptom showed a significant positive association with convexity-/parasagittal tumor locations, male gender and high Karnofsky performance score. Seizures as a presenting symptom was not associated with survival.

Introduction

The crude incidence of all primary intracranial tumors in Norway is 24.2/100 000 person years and meningiomas account for 31% of them, with an incidence of 7.5/100 000 person years (www.kreftregisteret.no). Females have a well-known increased risk of developing meningiomas. Whereas the overall ratio of females to males in Norway is 1.2:1.0 for all primary intracranial tumors, meningiomas have a ratio of 2.8:1.0 (www.kreftregisteret.no). Meningiomas are divided into three grades according to WHO histological classification[1], and are further subdivided based on site of dural attachment/origin; e.g. convexity-, parasagittal-, falx-, supratentorial skull base-, posterior fossa- and intraventricular meningiomas.

The most common presenting symptoms for intracranial meningiomas are headache, seizures and focal neurological deficits[2,3,4]. The incidence of seizures in meningioma patients is especially associated with tumor location[5,2,6]. In general, supratentorial tumors are more likely to present with seizures than infratentorial tumors[3]. The significance of seizures as presenting symptom with respect to survival for meningioma patients is not established. In contrast, seizures as presenting symptom in glioma patients is associated with a favorable prognosis[7].

In this large consecutive surgical series of intracranial meningiomas (n = 1469) we have determined the fraction of patients presenting with seizures and explored possible associations between seizures as presenting symptom and sex, age, tumor location, laterality, histology, Karnofsky performance score, raised intracranial pressure (ICP), focal neurologic deficit and prognosis.

Materials and methods

Patients

All patients who underwent primary craniotomy for a meningioma at the Oslo University Hospital (Rikshospitalet and Ullevål) in the time period 1990 – 2010 were included in this study. The patients operated during the years 1990 – 2002 were identified by reviewing operative protocols from this time period, while patients operated after 2002 were identified from our prospectively collected tumor database. All charts were studied retrospectively. The total number of patients identified with a histological verified intracranial meningioma was 1469. Tumor location was determined based on surgical notes and available images.

Data

Data was obtained from medical records including clinic records of pre- and postoperative visits, operative notes, discharge summaries, pathology reports and radiological data. The following data were recorded: sex, age, seizures as presenting symptom (yes/no), symptoms and signs of raised intracranial pressure (ICP) as presenting symptom (yes/no), neurological deficit as presenting symptom (yes/no), preoperative Karnofsky performance score (KPS 0-100)[8], date of surgery, laterality of tumor (right, left, midline, bilateral), anatomical site of dural attachment/origin (convexity, parasagittal, falx, lateral sphenoid wing, supratentorial skull base, posterior fossa and intraventricular) and histological classification according to the World Health Organization-classification (grades I, II, and III)[1].

Seizure was regarded a presenting symptom if seizure or an equivalent term were used in the description of preoperative symptoms and signs. The chart review did not allow any more specific description or categorization of seizure type.

Vital status (dead or alive) and time of death was obtained from the Norwegian Population Register[10] January 27th, 2011. Surgical mortality was defined as death of any cause within 30 days of surgery.

Statistics

Summary statistics were calculated using the mean and percentages. Uni and multivariate analyses with respect to seizures as a presenting symptom were calculated using logistic regression. Results are given as odds ratios.

Survival curves were generated using the Kaplan Meier estimator. The logrank test was used to compare different survival curves. A p-value of < 0.05 was considered significant.

Ethics

The hospitals´ Data Protection Officials approved the study.

Results

Patient characteristics

This study includes 1469 patients undergoing craniotomy for a primary histological verified intracranial meningioma in the time period 1990 – 2010. Median age was 58 years (range 10 – 92 years) and 70.2% were females. Age distribution, presenting symptoms, tumor-location and histological grade according to WHO are given in Table 1.

Table 1: Patient characteristics of 1469 consecutive patients undergoing primary surgery for an intracranial meningioma at OUS in the time period 1990 – 2010.

		N (%)	Fraction (%) presenting with seizure
All		1469	435/1469 (29.6%)
Hospital	OUS-Rikshospitalet	954 (64.9)	-
	OUS-Ullevål	515 (35.1)	-
Gender	Females	1033 (70.3)	271/1033 (26.2%)
	Males	436 (29.7)	164/436 (37.6%)
Age	< 29	17 (1.2)	6/17 (35.3%)
	30 – 39	126 (8.6)	40/126 (31.7%)
	40 – 49	256 (17.4)	87/256 (34.0%)
	50 –59	396 (27.0)	118/396 (29.8%)
	60 – 69	352 (24.0)	99/352 (28.1%)
	70 –79	273 (18.6)	77/273 (28.2%)
	> 80	49 (3.3)	8/49 (16.3%)
Seizures	Yes	435 (29.6)	-
Neurological deficit	Yes	885 (60.2)	-
Raised ICP	Yes	466 (31.7)	-
Karnofsky score	≥70	1357 (92.4)	412/1357 (30.4%)
	<70	112 (7.6)	23/112 (20.5%)
Tumor location – side	Right	621 (42.3)	191/621 (30.8%)
	Left	631 (43.0)	203/631 (31.7%)
	Midline	194 (13.2)	35/194 (18.0%)
	Bilateral	23 (1.6)	6/23 (26.1%)
Tumor location	Convexity	391 (26.6)	166/391 (42.5%)
	Parasagittal	201 (13.7)	87/201 (43.3%)
	Falx	164 (11.1)	53/164 (32.3%)
	Lat sphenoid wing	94 (6.4)	26/94 (27.7%)
	Skullbase ST*	398 (27.1)	86/398 (21.6%)
	Posterior fossa	198 (13.5)	14/198 (7.1%)
	Intraventricular	23 (1.6)	3/23 (13.0%)
WHO grade**	I	1352 (92.0)	401/1352 (29.7%)
	II	77 (5.2)	21/77 (27.3%)
	III	32 (2.2)	10/32 (31.3%)

*ST=supratentorial
**WHO grade missing in 8 patients

Seizures as presenting symptom

The frequency of seizures, raised ICP and focal neurological deficits as presenting symptoms were 29.6%, 31.7 % and 60.2%, respectively. Site of dural attachment, laterality of tumor, gender and Karnofsky score showed a significant association with seizures as presenting symptom, while age, WHO grade and right/left tumor location did not (Table 1 and 2).

Convexity- and parasagittal tumors most frequently presented with seizures. Falx-, lateral sphenoid wing- and supratentorial skull base had an intermediate frequency of seizures as presenting symptom. While tumors located in posterior fossa or brain ventricles rarely presented with seizures. Laterally located tumors presented more often with seizures than midline tumors. Male gender and Karnofsky performance status $\geq$ 70 were positively associated with seizure as presenting symptom.

Table 2: Univariate and multivariate regression analyses of variables with possible association with seizures as presenting symptom in meningioma patients (n = 1469).

	Univariate		**Multivariate**	
	Odds ratio	**95% conf.int**	**Odds ratio**	**95% conf.int**
Age	0.992	(0.984, 1.001)	0.989	(0.980, 0.999)*
Sex				
Male			Ref	
Female	0.590	(0.465, 0.749)***	0.631	(0.490, 0.813)***
Preop Karnofsky	1.018	(1.008, 1.029)***	1.012	(1.001, 1.023)*
Side				
Right			Ref	
Left	1.068	(0.841, 1.356)	1.089	(0.846, 1.402)
Midline	0.496	(0.331, 0.742)***	0.751	(0.477, 1.184)
Bilateral	0.795	(0.308, 2.047)	1.108	(0.411, 2.991)
Location				
Convexity			Ref	
Parasagittal	1.034	(0.734, 1.459)	1.014	(0.712, 1.443)
Falx	0.647	(0.441, 0.950)*	0.665	(0.444, 0.996)*
Lateral spheoid wing	0.518	(0.316, 0.850)**	0.534	(0.324, 0.881)*
Supraorbital skull base	0.374	(0.274, 0.510)***	0.394	(0.279, 0.557)***
Posterior fossa	0.103	(0.058, 0.184)***	0.112	(0.063, 0.202)***
Intraventricular	0.203	(0.059, 0.696)*	0.192	(0.056, 0.665)**
Histology				
WHO I			Ref	
WHO III (anaplastic)	1.078	(0.506, 2.297)	0.702	(0.321, 1.534)
WHO II (atypic)	0.889	(0.531, 1.488)	0.728	(0.423, 1.251)

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Overall survival

Overall survival (OS) at 1-, 12- and 60- months were 98%, 96% and 88% , respectively (Figure 1). Seizures as presenting symptoms were not associated with survival (Log Rank test, p = 0.795).

Figure 1a: Kaplan Meyer curve of overall survival (OS) for surgically treated intracranial meningiomas (n = 1469).

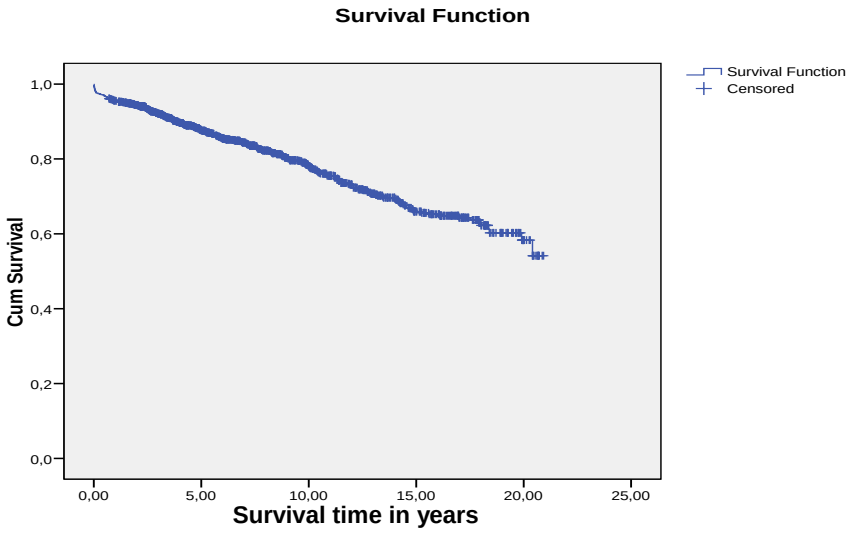
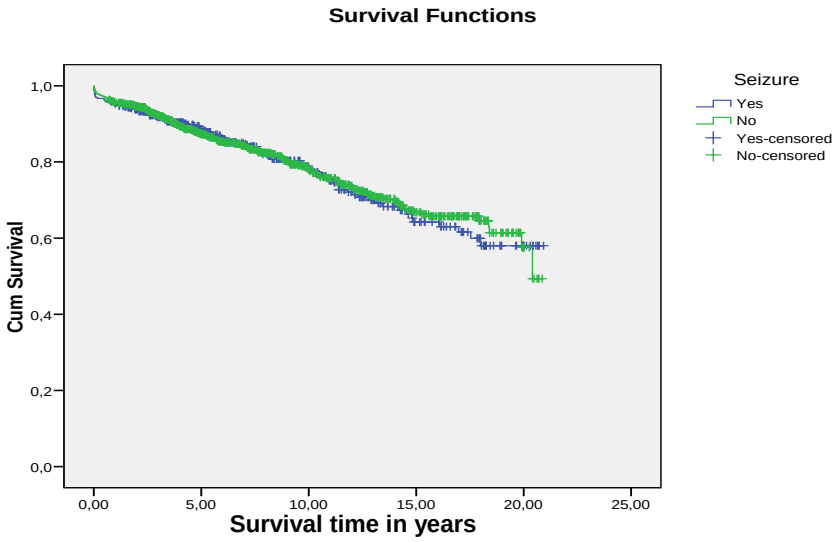


Figure 1b: Kaplan Meyer curve of overall survival (OS) for surgically treated intracranial meningiomas (n = 1469), correlated to seizure as presenting symptom (yes/no).



Discussion

In this retrospective study of 1469 patients who underwent primary craniotomy for a meningioma, 435 (29.6%) of the patients presented with seizures. Seizures were significantly correlated to anatomical site of dural attachment/origin, Karnofsky performance score and gender. Seizures as presenting symptoms were not associated with age, right- or left sided tumors nor WHO-grade. Seizures as presenting symptom in meningioma patients is not a prognostic factor with respect to survival.

Our 29.6% incidence rate of seizures as presenting symptom in patients with intracranial meningioma is well in line with previous reported incidence rates ranging from 20 – 50% [9,10,11,12,13,14,15,6,16,2].

Supratentorial meningiomas presented significantly more often with seizures than infratentorial meningiomas. These findings are in line with Cascino, who stated that seizures occur in 25-30% of patients with supratentorial tumors, but are rarely seen among patients with infratentoral tumors[17]. According to Chozick et al. 90% of meningiomas are supratentorial, and seizures as a symptom is reported with frequencies from 29% - 67%[18]. Of the supratentorially located tumors convexity- and parasagittal meningiomas presented most often with seizures. Similar associations between the anatomic location of the lesions and preoperative seizures have been reported by others[9,10,18,6].

A high Karnofsky score ($\geq$ 70) showed in our study a significant positive association with seizures as presenting symptom compared to a lower score (< 70). This is in contrast to recent findings made by Chaichana et al., who find an almost threefold higher risk of having preoperative seizures among patients with a KPS < 80[19].

Given that the prevalence of epilepsy in the general population is approximately the same between the genders[20], the higher prevalence of seizures as presenting symptom in the male patient population was somewhat suprising. Chaichana et al. have reported a similar observation[19]. This is in contrast to Lieu et al. where no sex differences regarding seizures as presenting symptom were found[6].

We found no statistically significant association between age and seizures as presenting symptom. However, there seemed to be a tendency of seizures appearing more frequently among the patient population under the age of 50 years. Similarily Chaichana et al. found preoperative seizures to be associated with younger age[19]. In contrary Lieu et al. reported a more frequent occurrence of seizures in the fifth and sixth decades[6].

As underlined by Lieu et al., the association between left and right-sided meningiomas and preoperative epileptic seizures has rarely been described. In their study they discovered no difference between neither pre- nor postoperative seizure rates and right or left hemisphere tumors[6]. Scott found a statistically significant difference in *post*operative seizure rates according to the hemispheric laterality of the meningioma[21]. In our study, there were equal number of lesions in the right and left hemispheres, and we discovered no statistical association between laterality and seizures as presenting symptom. Our series do not include data on the occurrence of postoperative seizures. Tumors with a predominant midline location less often showed seizures as presenting symptom.

Regarding histopathology, it has been stated both by Lieu et al. and Chow et al. that the histologic type of meningioma is not significantly correlated with epileptic seizures[6,15]. Our study showed no significant correlation between WHO-grade and preoperative seizures.

Whereas seizures in patients with gliomas are associated with long median survival time and is thus considered a positive prognostic factor for gliomas[7], we did not find any association between seizures and overall survival in our meningioma patients.

Seizures in the perioperative course

Seizures in patients with brain tumors are simple or complex seizures with or without secondary generalisation[22]. In patients with preoperative seizures, surgical removal of a meningioma is reported to eliminate seizures in 19 – 64% of the patients[9,10,18,6]. Chow et al. found that 32.7% of the patients with preoperative seizures had persistant seizures postoperatively, thus a history of preoperative seizures was shown to be a significant predictor for the occurrence of postoperative seizures[15]. New-onset postoperative epilepsy is reported to occur in 1 – 43 % of the patients, [23, 24,10,11,12,15,18,6,25,16]. New-onset epilepsy after surgery was a relatively common phenomenon in prior decades, but is now a less frequent event[25,16].

Use of antiepileptic drugs in the perioperative course

Prompt initiation of antiepileptic drugs (AED) is justified in meningioma patients presenting with seizures, and we usually continue AED after surgery. Discontinuation of AED is considered if no new seizures occur and EEG does not display signs of epileptogenic activity 6-12 months after surgery.

Prophylactic use of AED to prevent new-onset seizures after brain tumor surgery is, however, controversal[26,27]. AED will probably reduce the risk of new-onset seizures. On the other side, the rate of new-onset seizures after state of the art microsurgical removal of meningioma is fairly low[28,16], and AEDs have significant side effects and negatively affect health-related quality of life[29,30,31]. Taken together, the cost-benefit ratio for use of AED to prevent new-onset seizures is probably rather low. At the time being, we are not routinely using prophylactic AED to prevent new-onset seizures.

Conclusions

29.6% of the meningioma patients presented with seizures. Seizures as presenting symptom showed a significant positive association with convexity-/parasagittal tumor locations, male gender and high Karnofsky performance score. Seizures as presenting symptoms was not associated with survival.

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