Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 28 January 2011, doi:10.4414/smw.2011.13155
Cite this as: Swiss Med Wkly. 2011;141:w13155

Risk factors for a first epileptic seizure symptomatic of brain tumour or brain vascular malformation

A case control study

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Summary

PRINCIPLES: The risk of seizures increases in patients with brain tumours (BT) and brain vascular malformations (BVM), but not all risk factors are known. We aimed to identify factors that increase the risk of a first seizure in patients with BT or BVM.

METHODS: Multicentre case-control study; 102 cases with a first seizure as a presenting symptom of BT or BVM; 121 hospital controls with BT or BVM, but without seizures, matched by centre, gender and age.

RESULTS: In the univariate analysis, the risk of first seizure (Odds Ratio, 95% Confidence Limits) was 6.4 (2.3–17.6) for supratentorial lesions, 4.7 (2.4–9.3) for cortical involvement, 2.5 (1.0–7.7) for family history of seizures, and 2.1 (1.2–4.1) for frontal location. The types of lesion with higher risk were low grade glioma (4.7; 1.7–13.9) and cavernous malformations (13.2; 2.1–58.0). After multivariate analysis, including all the imaging characteristics and family history, the strongest independent predictors of first seizure were cortical involvement (OR 4.0; 2.0–8.1) and type of lesion (low grade glioma: 4.0; 1.3–12.8; cavernous malformations: 12.6 (1.5–103.5).

CONCLUSIONS: Cortical involvement and type of lesion are the independent risk factors for a first-ever seizure as a presenting symptom of BT or BVM.

Key words: *epilepsy; risk factors; case control; seizure; brain tumours; brain vascular malformations*

Introduction

Seizures are the presenting symptom in 20–40% of patients with brain tumours (BT) [1–4] and up to 30% of those with brain vascular malformations (BVM) [5]. Age, cortical site, histological type and location are independent predictors of acute symptomatic seizures [2–4, 6–8], although available information comes only from clinical series without an adequate group of matched controls. However, other factors that are known to increase the risk of idiopathic/cryptogenetic seizures [9, 10] might have a role for symptomatic seizures too. We performed a study to establish whether alcohol consumption is a risk factor for a first symptomatic seizure [11]. Since alcohol use might also have a confounding effect for some "aetiologies", we considered this confounding variable in our study design. Therefore we matched cases and controls for the underlying "cause", selecting the three most frequent: stroke, head trauma, and BT/BVM. The main finding of the study was that alcohol use did not increase the risk of a first acute or remote symptomatic seizure in both sexes and in any of the three "aetiologies". The study collected information on several other risk factors, including family history of seizures, and pre-, peri-, and postnatal risk factors. Here we examine patients

with BT and BVM aiming to identify factors associated with higher risk for seizures at clinical presentation.

Patients and methods

The design of this multicentre study has been extensively described [11, 12]. Eighteen referral neurological and neurosurgical departments in Northern Italy (listed in the Appendix) participated. In brief, we observed 725 patients with a first seizure or a first medically evaluated seizure consecutively admitted to one of the participating hospitals. Inclusion criteria were age of 15 years or older, having had a seizure in the 48 hours before hospital admission, evaluation by a neurologist, seizure described by eye witnesses or, for generalised tonic-clonic seizures, at least three of the following criteria: loss of consciousness, urinary or faecal incontinence, laceration of tongue or cheek, and post-ictal confusion or Todd's paralysis. Seizures were classified according to the 1981 proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures [13]. A first seizure was defined as the first seizure (or the first cluster of seizures within a 24-hour period) ever experienced by the patient, excluding febrile seizures; a first medically evaluated seizure was the first seizure ever evaluated by a physician in patients who had had previously unevaluated seizures of any type. We enrolled 340 patients with idiopathic/cryptogenic seizures, and 385 with symptomatic seizures, classified according to the ILAE Guidelines for Epidemiologic Studies on Epilepsy [14]; in 109 of these, seizure was found to be symptomatic of a BT or BVM. Seven cases had a diagnosis of BT/BVM 3–26 months before the first seizure; according to the ILAE Guidelines [14] they were classified as unprovoked seizures and were not included in this study. The other 102 cases, where seizure was the presenting symptom of BT/BVM, were classified as provoked or acute symptomatic seizure according to the ILAE Guidelines [14].

Controls

We searched two controls for each case from the list of patients admitted to the Emergency Room, with a negative history of epileptic seizures (excluding febrile seizures). Controls had a diagnosis of BT/BVM within seven days before hospital admittance and were matched to cases according to centre, age (±5 years) and gender.

Questionnaire, risk factors and clinical characteristics

The definition of risk factors has been reported in previous papers [9, 12]. The diagnosis of BT or BVM was based on CT-scans in our original study [11]. Here, we made any effort to retrieve CT-scan and MRI reports, clinical charts, and surgery and anatomy reports to classify the histological type. CT or MRI reports were not found for 4 cases and 4 controls. Available information was evaluated by two neurologists, blind against each other and to the status of case or control. A third neurologist decided when the first two disagreed. The other study variables were defined as follows: *site of the lesion:* supratentorial vs. sub-tentorial and cortical vs. subcortical (patients with both supra- and sub-tentorial lesions or both cortical and subcortical lesions were considered supratentorial or cortical); *number of lesions:* single or multiple; *location:* frontal, parietal, temporal, occipital lobes, and other locations (lesions involving more than one lobe were assigned to all the involved lobes; in the analysis, any involved lobe was considered no matter whether the lesion had mono or multilobar extension); *side* (only for frontal, parietal, temporal, or occipital lobe single lesions): left, right, bilateral; *cortical atrophy*, o*edema, and leukoaraiosis* were considered when described in the radiological report.

Conduct of the study

Interviews were done within 48 hours of the seizure (cases) or on admission (controls), after informed consent was given. When the interview was impossible (patient unable to cooperate), the next-of-kin was interviewed (proxy respondent). When neither the patient nor the proxy was available or able to respond, the case was considered lost. When neither the control nor a proxy was available, the control was replaced.

Statistical analysis

The distribution of the risk factors in cases and controls was estimated by calculating the odds ratios (OR), with 95% confidence limits (CL). The chi-square test and the Student's two-tailed t-test were used where appropriate. Missing data were handled in ways that always gave conservative estimates of the risk under study. The significance level was set at 0.05. Sample size was calculated for the main study [11]; for this *post-hoc* analysis, the present sample (102 patients, 1.2 controls per case, alpha error = 0.05) had a power (1-beta) of 0.22 and 0.52 for an OR of 2.0 and 3.0, assuming a 4% prevalence of exposure (e.g., family history of seizures), and of 0.68-0.98 assuming a 26% prevalence of exposure (e.g multiple metastases) [15]. The independent role of different risk factors was analysed by a model of linear logistic regression [16], deriving the maximum likelihood estimates of the OR and the corresponding 95% CL for each variable. In the forward stepwise selection model, the significance level for retention of risk factors was settled at 0.05.

Results

We included 102 cases: 93 with a first ever seizure, and 9 with a first medically evaluated seizure. Simple partial seizures with or without secondary generalisation were the predominant pattern (62 patients) followed by generalised tonic-clonic seizures [21] and by complex partial seizures with or without secondary generalisation [19]. We collected 121 of the 204 expected controls (59%), giving a ratio of 1.2 controls per case. Cases and controls were similar in regard to weight, height, schooling, marital status, place of birth, residency and use of proxy responders (data not shown). Cases were younger than controls (mean age 57 vs. 61 years, $p < 0.01$) and were more frequently employed (58% vs. 38%, $p < 0.005$). Family history of seizures showed a statistically significant correlation with the occurrence of a first symptomatic seizure on univariate analysis (table 1).

None of the other pre-, peri-, and post-natal factors was singularly associated with an increased risk, but there were more cases than controls with at least one of these risk factors (12 vs. 6), yielding a significant risk of seizure (2.6,1.1–7.2). Imaging reports were available for 98 cases and 117 controls. Factors increasing the risk of a first symptomatic seizure included in decreasing order (table 2): type of lesion – low grade glioma (LGG) and cavernous malformation (CM) –, a supratentorial lesion, a cortical lesion, and frontal lobe location. After adjustment for all the other imaging characteristics, the risk was still high for LGG (4.2; 1.2–15.2), cortical lesion (2.7; 1.1–6.6), and frontal location (2.6; 1.2–5.8), whereas supratentorial lesion (2.5; 0.6–9.6), and CM (7.8; 0.8–73.4) were no longer significant. In the stepwise multivariate analysis, including all the imaging characteristics and family history (the sole variable significant in the univariate analysis), the strongest independent predictors of first seizure were cortical involvement (OR 4.0; 2.0–8.1) and type of tumour (LGG: 4.0; 1.3–12.8; CM: 12.6 (1.5–103.5).

Discussion

In this case-control study of BT and BVM patients with provoked seizure, the factors found to independently predict seizure occurrence were cortical involvement and the type of lesion. It is well known that BT increase the risk of seizures by up to 40 times [8, 18] compared to controls; in this study we were not interested in the global risk of seizures carried by patients with BT or BVM, but we searched whether it is possible to recognise specific features that characterise the risk profile of persons with a BT or BVM presenting with a first seizure. The risk was highest for LGG, in agreement with clinical series [2–4, 6, 8]. We found a high seizure risk for CM too, that seems to be specific to this type of BVM, since it was not increased for other BVM. However, this must be considered with caution, since we cannot exclude a possible selection bias; only ¼ to ½ of CM present with seizures in clinical series [19], whereas the others were diagnosed after haemorhage, headache, or incidentally. Our control group ascertained through Emergency Room admissions may have prevented the inclusion of CM without seizures. Other characteristics, such as multiple tumours [7], age [4] or parietal, temporal and frontal locations [2–4, 7, 8] are often reported to increase the risk of seizures, but have never been tested with an adequate control group as here.

Although our study design didn't allow us to evaluate age, it allowed many risk factors to be tested in the group of patients with BT or BVM and seizures, compared to controls with the same pathology but without seizures, and matched for age and gender. We found no increase of risk for multiple lesions, and the frontal lobe was the only location that increased the risk of seizures. The risk was higher for persons with a family history of seizures, although this was still not evident after adjustment for the other covariates. Family history has never been evaluated in provoked seizures due to BT/BVM. Interestingly, we found a similar pattern for seizures as the initial presentation of ischemic stroke [12]. A role for genetic factors in alcohol withdrawal seizures [20] has been suggested. All of these observations point to a possible genetically-defined predisposition for symptomatic seizures.

Table 1: Risk factors for a first seizure symptomatic of brain tumour or brain vascular malformation (102 cases and 121 controls).

Risk factor[a]	***Cases*/Controls**	***OR* (95% CL)**[b]
Family history of seizures		
First degree relatives with seizures	9/1	11.6 (1.9–52.7)
Other relatives with seizures	2/4	0.6 (0.3–4.1)
Any relative with seizures	10/5	2.5 (1.0–7.7)
Pre- and peri-natal factors		
Complications of pregnancy	1/0	–
Low gestational age	6/4	1.8 (0.7–7.0)
Low birth weight	1/0	–
Complications during delivery	5/2	3.1 (0.8–14.6)
Post-natal factors		
Psychomotor retardation	4/2	2.4 (0.7–12.7)
Febrile seizures	2/0	–
History of hypertension	26/32	1.0 (0.6–1.8)
Metabolic alterations at admission	4/9	0.5 (0.2–2.1)
Epileptogenic drugs	7/4	2.2 (0.8–7.8)
Fever	3/1	3.6 (0.7–24.7)
History of cerebral palsy	0/0	–
Lifestyle factors		
History of drug addiction	1/2	0.6 (0.2–7.6)
ADAA >50 g/day[c]	10/8	1.4 (0.6–4.2)
ADAA ≤50 g/day[c]	51/61	0.9 (0.6–1.8)

a) See text, methods section, for definition of the risk factors.
b) OR = Odds Ratio; CL = Confidence Limits. Reference category includes those without the risk factor.
c) ADAA = average daily intake of absolute alcohol. Reference category includes non drinkers and occasional drinkers (36 cases and 40 controls). Ex-drinkers (5 cases and 12 controls) are not considered in the table.

Many other factors (listed in table 1) increase the risk for a first idiopathic/cryptogenetic seizure [9, 10]. In an attempt to evaluate their effect in the presence of a powerful seizure aetiology such as a BT, we ascertained them in our patients, taking advantage of our study design that controlled for confounding variables. Although it is likely that the small sample size prevented us to from recognising any significantly association, cases carrying at least one pre- or perinatal factor were more than controls. This finding and that of family history suggest that even in the presence of a BT or a BVM, the risk of seizures is not completely explained by the "aetiological" factor.

Our study has several limitations. Firstly, this investigation was a *post-hoc* analysis of a survey on alcohol intake and a first symptomatic seizure [11], therefore blind evaluation of histological type was not planned and we must be confident about the information from CT-scans, MRIs, and clinico-pathological charts. Secondly, for the same reasons, it was unfeasible to retrieve most images and the evaluation of CT scans and MRI was based on reports, thus, the role of imaging risk factors should be interpreted with caution. Thirdly, the possibility cannot be excluded that a number of controls could present epileptic seizures in the follow-up. However, this bias cannot be eliminated and is not likely to affect the risks found to be significant in the present investigation. Finally, the multicentre nature of our study could increase variability in data collection, however, this was prevented by matching cases and controls within the same participating hospital. On the other hand, since cases and controls were drawn from many hospitals, mostly first-referral, a selection bias is unlikely and our results may be generalised to different populations.

The study was funded by Regione Piemonte, Ricerca Scientifica applicata, 2004 and by a grant from Prof. Torgano, Novara in memory of Annalisa.

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Table 2: Risk factors for a first seizure symptomatic of brain tumour or brain vascular malformation (98 cases and 117 controls with available imaging reports).

Risk factor [a]	***Cases*/Controls**	***OR* (95% CL)** [b]
Metastasis (single)	10/13	0.9 (0.5–2.4)
Metastasis (multiple)	22/30	0.8 (0.5–1.7)
Glioblastoma	8/25	0.3 (0.2–0.9)
Meningioma	16/23	0.8 (0.5–1.7)
Low grade glioma	14/4	4.7 (1.7–13.9)
Cavernous malformations [c]	10/1	13.2 (2.1–58.0)
Other vascular malformations [d]	5/5	1.2 (0.5–4.8)
Other tumours	1/7	0.2 (0.1–1.9)
Tumour not specified	12/9	1.7 (0.8–4.4)
Cortical vs. noncortical [e]	85/68	4.7 (2.4–9.3)
Supratentorial vs. subtentorial	94/92	6.4 (2.3–17.6)
Oedema (yes/no)	60/83	0.6 (0.4–1.2)
Cortical atrophy (yes/no)	5/9	0.6 (0.3–2.4)
Leukoaraiosis (yes/no)	0/7	–
Multiple lesions (vs. single)	28/31	1.1 (0.7–2.1)
Frontal lobe (yes/no) [f]	31/21	2.1 (1.2–4.1)
Parietal lobe (yes/no) [f]	22/21	1.2 (0.7–2.4)
Temporal lobe (yes/no) [f]	20/23	1.1 (0.6–2.2)
Occipital lobe (yes/no) [f]	5/7	0.8 (0.4–3.2)
Side (right vs. left – 25 cases and 28 controls)	44/33	1.5 (0.8–3.2)

a) See text, methods section, for definition of the risk factors.
b) OR = Odds Ratio; CL = Confidence Limits; Reference category includes those without the risk factor.
c) None had signs of recent bleeding. Location was: cases: 2 multiple, 1 deep-seated, 5 frontal, 1 temporal, 1 parietal lobe; controls: 1 deep-seated.
d) Location was: cases: 5 temporal lobe; controls: 2 deep-seated, 1 frontal, 1 parietal, 1 occipital lobe. Type was classified according to Al-Shahi and Warlow [17] as: haemangioma (0 cases and 1 control), arteriovenous malformation (4 and 1), and aneurysm (1 and 2).
e) Considering only supratentorial involvement the OR is 3.3 (1.6–7.6)
f) Reference category is patients without involvement of that specific lobe (either unilobar or multilobar) .

Study funding/potential competing interests

The study was funded by Regione Piemonte, Ricerca Scientifica applicata, 2004 and by a grant from Prof. Torgano, Novara in memory of Annalisa. Dr. Ivashynka is supported by an EFNS fellowship.

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