Measuring symptons and functioning in glioma patients

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PART ONE

CHAPTER 2

Prediagnostic presentations of glioma in primary care: a case–control study

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Abstract

Background

This study aimed to assess the prevalence of symptoms glioma patients may present with to the general practitioner, and whether these can be distinguished from patients with other central nervous system disorders or any other condition.

Methods

Glioma patients were matched to controls using anonymized general practitioner registries. Prevalences were evaluated in the five years prior to diagnosis.

Result

Central nervous system patients reported significantly more motor symptoms in the period 60-24 months, (p=0.039). Moreover, <6 months before diagnosis central nervous system patients differed significantly in mood disorders/fear compared to 'other controls' (p=0.012) but not glioma patients (p=0.816).

Conclusion

Glioma patients could not be distinguished from both control groups with respect to the number or type of prediagnostic symptoms.

Introduction

Gliomas are the most common malignant primary brain tumours in adults[1, 2]. Of these, glioblastoma is the most frequently occurring subtype. The annual age-adjusted incidence of primary malignant tumours ranged from 4.53 to 8.18 per 100,000 population[3]. Nearly all glioma patients have an incurable disease with a dismal prognosis. These patients not only have cancer, but also a progressive brain disease, and may therefore experience symptoms such as increased intracranial pressure (drowsiness and headache), progressive motor dysfunction, seizures, and changes in cognition, behaviour and personality[4-8].

Patients are often diagnosed with glioma after presenting with a focal neurological deficit, a first seizure or more diffuse symptoms such as drowsiness and headache[9, 10]. Currently, little is known about the onset of symptoms and signs of glioma in the year(s) before diagnosis. One study, in which semi-structured interviews with 28 glioma patients and their partners were conducted, showed that most patients first consult their general practitioner (GP) about their symptoms, and that the time between onset of symptoms and diagnosis of glioma varies widely between patients[9, 10]. The latter could be due to a gradual onset of symptoms, a lack of recognition of these symptoms by the patient, or because the GP made another differential diagnosis. A better insight into these early symptoms, especially symptoms and signs that could distinguish glioma patients from other patients with central nervous system diseases or any other condition, may help earlier identification of patients with glioma. This may subsequently lead to earlier initiation of anti-tumour treatment in these patients, which could be beneficial. For example, early introduction of chemoradiation at the time of diagnosis in patients with low-grade glioma improves progression-free and overall survival[11].

This study aimed to identify the prevalence of symptoms and signs in the five years prior to glioma diagnosis from extracted medical records of the GP, and to determine whether these can be distinguished from patients with other central nervous system (CNS) diseases and patients visiting the GP for any other condition. In addition, we aimed to assess if glioma patients visit the GP more frequently in the years before diagnosis compared to control patients.

Methods

Identification of potential signs and symptoms

Possible early clinical symptoms were identified by means of a literature study and semi-structured interviews with health care professionals involved in the care of glioma patients.

For the literature study, an article reporting on the presenting symptoms in glioma patients[12] was used to create a list of potential prediagnostic symptoms for glioma patients. Next, we developed a search strategy in Pubmed (conducted up to the 15th of October 2015) in which the terms related to 'glioma', 'prediagnostic' and one of the 'symptoms' as identified in the article by Posti et al [12]. were used. Articles were eligible if a population of adult glioma patients was described, including a description of the specific symptoms at diagnosis or before initial treatment, as well as the percentage of patients experiencing those symptoms. Reviews, case reports and case series (<20 patients) were excluded, as well as articles describing treatment of recurrent glioma, articles including children, or articles focusing on multiple brain tumour patients without a separate description of symptoms of glioma patients.

Semi-structured interviews with five experts (three neuro-oncologists, one neuropsychologist and one nurse specialized in neuro-oncology) in the field of glioma were conducted in person by one researcher (MCMP). Experts were asked to rate the frequency of occurrence of all symptoms glioma patients could present with (as identified in the literature review) on a 4-point Likert scale, ranging from 'never' to 'frequent', and to indicate if prediagnostic symptoms and signs were missing.

Next, we selected signs and symptoms that were reported in >25% of the glioma patients in the eligible articles identified with the literature search, and those symptoms with a mean score ≥3 (representing often to frequent) as identified in the semi-structured interviews for further analyses. Comparable symptoms were categorized into one category and all categories of symptoms were subsequently recoded into International Classification of Primary Care (ICPC) codes. These ICPC codes are widely used by GPs to code complaints, symptoms, and diseases since the mid 90s of the last century[13].

Study population

Three groups of patients were included: glioma patients, patients with other CNS diseases, and 'other' patients. These 'other' patients were defined as those patients that did not meet the criteria for the other two groups (e.g. patients with back pain or the flu). Patients in the 'CNS disease' and 'other' groups were the controls for glioma patients and were matched in a 1:1:1 ratio to glioma patients on age (range 5 years older or younger), sex and date of diagnosis (month and year).

Glioma patients were selected from two sources. First, patients with a histologically confirmed glioma who visited the neuro-oncology outpatient clinic in the Leiden University Medical Center in Leiden, or the Haaglanden Medical Center in The Hague, the Netherlands, between September 2005 and September 2015 were selected. Second, additional patients were selected from an anonymized GP database, the Registration Network of General Practices associated with Leiden University (RNUH—LEO). This

database comprises data of 44.350 patients from 19 GP's in four practices in Leiden (The Netherlands) and the surrounding area, and contains information on the medical history, prescriptions, diagnostic record, and morbidity of patients, and coded symptoms and signs via ICPC codes. Glioma patients were selected from this database if their medical record contained an ICPC code coding for central nerve system neoplasm, they were adults (≥18 years), diagnosed from 2002 onwards, and if the GP had described the diagnosis 'glioma' in the free text of the medical record. All relevant data in the database was extracted for patients identified via this database. For glioma patients identified via the outpatient clinics, their medical record was requested at their GP.

All control patients were selected from the RNUH-LEO database. ICPC codes representing central nervous system diseases were used to select CNS patients (see supplementary Table 1 for the used ICPC codes). All remaining codes were eligible for the 'other' control patients. The study was approved by the local medical ethical review board and glioma patients selected from the outpatient clinic provided written informed consent for participation in this study, including insight in their medical record at their GP. Patients selected from the RNUH-LEO database were prone to an "informed opt out" procedure, since their data was anonymized.

Data extraction

All visits to the GP of both glioma patients and controls were reviewed during 5 years prior to the index date (i.e. date of diagnosis of the glioma patient). The number of visits were evaluated, as well as the signs and symptoms during each visit. Actual visits to the GP were counted as a visit (including a visit for a procedure, such as an influenza vaccination), while telephone consultations were only counted if they addressed a new symptom or sign. In case the GP described the ICPC codes within the medical records, these codes were used. If the ICPC codes were not provided, we recoded the symptoms and signs using the ICPC code system.

Statistical analysis

Baseline demographic and clinical characteristics of glioma patients and their controls, as well as the number and type of symptoms, were described using descriptive statistics. Period prevalence (i.e. the number of current cases (new and pre-existing) over a specified period of time) was calculated for the number of visits and selected symptoms, and compared between groups with the Chi-square test. Since the number of visits and symptoms was expected to rise in the months prior to diagnosis in glioma and CNS control patients, not only the period prevalence for the complete five years was calculated, but also for the time intervals (a) 5 years to 2 years, (b) 2 years to 6 months and (c) 6 months up to diagnosis. Lastly, we have explored if patients experienced multiple symptoms during the five-year observation period.

All statistical analyses were performed using SPSS version 23 (SPSS, Chicago, IL, USA). All tests were two-sided and $p<0.05$ was considered to be significant.

Results

Literature review and semi-structured interviews

Eleven symptoms identified in 14 articles with the literature review were found to have an incidence of more than 25%; seizures, headache, motor impairment, confusion, language problem, memory problem, personality change, change in consciousness, nausea, visual problem and sensory problem[14-26]. The five participating health care providers agreed that 8/11 (i.e. seizures, motor impairment, confusion, language problem, memory problem, personality change, change in consciousness and visual problem) (pre)diagnostic symptoms occurred frequently (i.e. mean score ≥3). Missing symptoms included burnout, mood swings, fatigue and problems with concentration, processing of information, planning and initiation (see Supplementary Table 2). Ten symptoms were merged because they showed similarity, resulting in nine symptom categories that were recoded into ICPC codes (see Supplementary Table 3): seizures, headache, motor impairments, cognitive/mental impairments, visual disorders, mood disorders/fear, sensory complaints, metabolic/endocrine symptoms and general symptoms (e.g. tiredness, overall deterioration).

Patient population

Patient characteristics are presented in Table 1. Thirty-six glioma patients were matched with 36 CNS control patients and 36 'other' control patients. The median age of patients ranged between 60-61 years, and the majority in all groups was men (58%), suggesting that the matching procedure was successful. Patients in the CNS control group were mostly diagnosed with stroke (28%), other head trauma (11%), concussion (14%) or depression (22%). Patients in the 'other' control group had musculoskeletal (17%) or skin (14%) problems, an infection (14%), or other problems (56%).

Prevalence and type of symptoms

A total of 10/36 (28%) glioma, 9/36 (25%) CNS and 18/36 (50%) 'other' control patients visited the GP with one symptom from the nine categories, while 8/36 (22%) glioma patients, 15/36 (42%) CNS patients and 13/36 (36%) 'other' patients visited the GP with ≥2 symptoms (see Figure 1). Thirty-one per cent of glioma patients (11/36), 28% (10/36) of CNS patients and 39% (14/36) of 'other' control patients did not report any of the nine symptoms, but did present with other symptoms, for example painful miction, eczema or a fractured tibia.

Table 1. Characteristics of patients with glioma and CNS and 'other' control patients

	Glioma (n=36)	CNS controls (n=36)	'Other' controls (n= 36)
Age, years; median (range)	61 (26-79)	61 (26-79)	60 (26-79)
Men; no. (%)	21 (58%)	21 (58%)	21 (58%)
Diagnosis			
Glioma	36 (100%)		
Stroke		10 (28%)	
Other head trauma		4 (11%)	
Concussion		5 (14%)	
Depression		8 (22%)	
Epilepsy		3 (8%)	
Other		3 (8%)	
Musculoskeletal system			6 (17%)
Skin			5 (14%)
Infection			5 (14%)
Other			20 (56%)

Number of visits to the general practitioner

The number of visits with any symptom or sign to the GP did not differ significantly between groups over the five year period (median of 17 versus 24 and 23 visits in glioma, CNS controls and 'other controls, respectively; p=0.381). Similarly, no significant differences were found in the number of visits in the smaller time intervals (see Table 2).

Table 2. Total and median (range) number of visits to the general practitioner for any sign or symptom per time period, separately for the three groups

	All patients (n=108)	Glioma patients (n=36)	CNS controls (n=36)	Other controls (n=36)	p-value
Whole period (5 years), median (range)	2491 20 (0-102)	711 17 (0-60)	989 24 (0-102)	791 23 (0-65)	0.381
5-2 years (36 months), median (range)	1425 11 (0-62)	399 9 (0-32)	582 14 (0-62)	444 12 (0-38)	0.187
2 years to 6 months (18 months), median (range)	728 5 (0-30)	217 4 (0-23)	273 5 (0-30)	238 5 (0-23)	0.939
6 months to diagnosis (6 months), median (range)	338 2 (0-15)	95 2 (0-15)	134 2 (0-15)	109 3 (0-14)	0.522

In general, glioma patients did not differ from the other groups with respect to the prevalence of the nine symptoms (see Table 3). Mood disorders/fear was the most prevalent symptom in all three patient groups in all three time periods. In addition, general symptoms and sensory complaints were frequently reported. There was a significant difference between CNS patients and 'other' controls (8 versus 0, respectively, *p*=0.014) in the 6 months prior to diagnosis regarding the prevalence of mood disorders/fear but not compared to glioma patients (5 versus 8, p=0.816). Moreover, in the 60-24

months prior to diagnosis, four CNS patients presented with motor symptoms where the glioma patients and patients with other symptoms did not (both p=0.039).

We have also explored if patients experienced multiple symptoms during the five-year observation period, and which these were (Table 4). Mood and general symptoms were observed in seven glioma and six CNS patients, while this combination was found in three 'other' controls. Mood and sensory symptoms occurred in six glioma patients, in nine patients in the CNS disease group, and only one time in the 'other' control group. Moreover, visual and sensory problems were observed in three glioma, five CNS and one 'other' patient, whereas visual problems and mood symptoms were observed in four glioma patients, six CNS patients and not in the 'other' patients. There were only a few patients in each group in whom ≥3 symptoms were observed during the study period (data not shown).

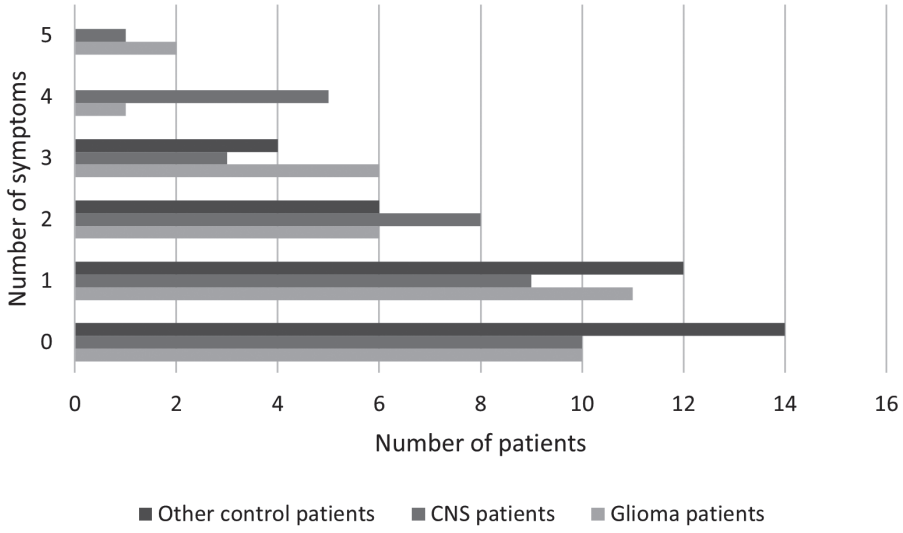

Figure 1. Number of prediagnostic symptoms patients present with to the general practitioner per patient group.

Discussion

This case-control study did not show a difference in the frequency of GP visits nor in the prevalence of presenting symptoms and signs in the five years before diagnosis between glioma patients, patients with other CNS disease or patients with any other condition. It may therefore be difficult for a GP to distinguish glioma patients from

Table 3. Period prevalence of symptoms in the nine categories, separately for glioma, CNS and 'other' control patients, and separately for the three time periods and the complete five-year period

	Total 5 year period				5-2 years (36 months)			
	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value
Seizure	1	1	0	0.361	0	0	0	1.000
Headache	4	4	2	0.646	3	3	1	0.536
Motor impairments	3	6	1	0.126	0	4	0	0.016
Cognitive/ mental impaiments	1	3	3	0.546	0	2	3	0.236
Progressive loss of vision	5	6	4	0.601	2	5	1	0.180
Mood disorders/fear	15	18	9	0.088	7	14	8	0.087
General symptoms	11	9	8	0.716	7	5	2	0.198
Sensory complaints	11	10	7	0.537	5	7	4	0.623
Metabolic/endocrine	1	0	2	0.361	0	0	0	1.000

	2 years to 6 months (18 months)				6 months to diagnosis (6 months)			
	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value
Seizure	1	1	0	0.604	0	1	0	0.368
Headache	0	0	1	0.368	2	1	0	0.358
Motor impairments	3	2	1	0.602	1	1	0	0.604
Cognitive/ mental impaiments	0	0	1	0.368	1	1	0	0.604
Progressive loss of vision	2	1	0	0.368	1	2	3	0.615
Mood disorders/fear	8	10	5	0.349	5	8	0	0.014
General symptoms	2	5	4	0.497	3	1	3	0.532
Sensory complaints	6	2	2	0.192	2	2	2	0.998
Metabolic/endocrine	1	0	1	0.604	0	0	1	0.368

both patients with other CNS diseases and those with other conditions based on their prediagnostic symptoms, hampering timely referral to a neuro-oncologist.

An explanation for the absence of differences between glioma patients and the other groups, besides the fact that they may simply not be there, may be that detecting glioma-specific symptoms and signs is difficult when only routine care data are the source. First, patients may not visit the GP with their complaints. This could be the case in control patients as well, however, one study described that specifically glioma patients with headache were found to often delay their help-seeking because they found another cause for this symptom in the everyday life context[10]. Similarly, experts in this study mentioned that glioma patients often report that they associated mental and cognitive symptoms with being tired or a high workload, suggesting that this would also be a reason not to visit the GP with their complaints. Indeed, underreporting of symptoms by glioma patients may be due to lack of insight in their illness as a

Table 4. Number of patients presenting with multiple symptoms in glioma, CNS and 'other' control patients in the whole five year period

	Seizure & headache	Seizure & motor	Seizure & cognitive problems	Seizure & visual problems	Seizure & mood disorder	Seizure & general symptoms	Seizure & sensory problems	Seizure & metabolic problems	Headache & motor problems	Headache & cognitive problems	Headache & visual problems	Headache & mood disorder	Headache & general symptoms	Headache & sensory problems	Headache & metabolic problems	Motor problems & cognitive problems
Glioma	0	0	0	0	0	0	0	0	0	0	0	2	2	2	1	0
CNS patients	0	0	0	1	1	0	1	0	1	0	1	2	2	1	0	0
Other control patients	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0

consequence of the condition itself. Second, GP's usually prioritize only one major complaint in their registration and may thus not always be consistently registering all complaints and diagnoses with which the patient presents in one visit, potentially resulting in missing data. Moreover, the format of using ICPC codes during registration may have resulted in imprecise data. One ICPC code can contain more than one symptom; for example, the code P20 contains memory, concentration, and orientation disorders. Furthermore, some GP's did not register the ICPC codes, for which cases we had to derive the code from text parts for these symptoms. Due to misinterpretation, this may have resulted in inaccurate data. The way of registering symptoms may have therefore refrained us from obtaining information on the occurrence of more unlikely symptoms, or certain combinations of symptoms. Third, our study design may have not been optimal. Unfortunately, tumour-related information such as tumour grade was not available in this anonymised dataset. It therefore remains unknown whether the prediagnostic symptoms differed between subgroups of glioma patients, even though differences might be expected due to differences in tumour biology and growth rate. Indeed, due to the slow growth rate, it may be possible that we included patients with delayed diagnosis of childhood low-grade glioma[26]. Another limitation of the study design is that we were not able to verify if CNS or other controls did not have a brain tumour. Furthermore, the number of glioma patients identified with this approach may have been too small to obtain an appropriate representation of the prediagnostic

	Motor problems & visual problems	Motor problems & mood disorder	Motor problems & general symptoms	Motor problems & sensory problems	Motor problems & metabolic problems	Cognitive problems & visual problems	Cognitive problems & mood disorder	Cognitive problems & general problems	Cognitive problems & sensory problems	Cognitive problems & metabolic problems	Visual problems & mood disorder	Visual problems & general symptoms	Visual problems & sensory problems	Visual problems& metabolic problems	Mood disorder & general symptoms	Mood disorder & sensory problems	Mood disorder & metabolic problems	General symptoms & sensory problems	General symptoms & metabolic problems	Sensory problems & metabolic problems
	1	3	3	2	0	0	0	0	0	0	4	2	3	0	7	6	1	6	1	1
	2	4	2	3	0	1	2	1	1	0	6	2	5	0	6	9	0	3	0	0
	0	1	0	1	0	0	2	0	0	0	0	0	1	0	3	1	1	3	1	0

symptoms and signs in glioma patients. With the low incidence of this disease, a large regional or national registry may yield better results, but is still under construction in the Netherlands. In the United Kingdom (UK), The Health Improvement Network (THIN) comprises records of over 11 million individuals in more than 500 primary care practices across the UK, covering around 6% of the population[27]. This database was used in a study on the prediagnostic presentations in Parkinson patients, which resulted in the inclusion of 8166 patients and 46755 matched controls, allowing a more extensive statistical analysis, for example a big data analysis, and generalisability of the results[28]. Moreover, sampling control patients that are diagnosed in the same year as the patients could cause inclusion bias, since patients that do not frequently visit their GP, or those who switched GP in the five years prior to diagnosis, could not be included in this study. Lastly, the literature search was conducted up to the 15th of October 2015 and therefore more recent studies were not included. However, it is doubtful whether the presenting symptoms of glioma have changed in the past years.

Mood disorders or fear of disease was the most reported problem in this study, during all time periods. The finding that the prevalence of mental health problems ranges from 4.3%-26.4% in the general population supports this[29]. Nevertheless, patients with CNS disease had the highest prevalence which could be due to our inclusion criteria, as patients in the CNS group were included if they had, for example, depression as a diagnosis. Thus, although glioma patients often visit the GP with mood

disorders, or fear of disease (in general), it may be difficult for a GP to consider glioma as diagnosis, as this symptom does not distinguish these patients from other patients. Therefore, when mood disorders occur, all CNS disorders should be considered by the GP, including glioma.

In conclusion, our exploration did not reveal solid indications that would enable us to distinguish glioma patients from CNS and 'other' control patients based on the number of visits to the GP, nor based on the specific prediagnostic symptoms in the five years prior to diagnosis. Possibly, a study design in which a questionnaire is used to inventory if glioma patients experienced certain symptoms and signs in the year prior to diagnosis could be considered an alternative to elucidate symptoms and signs experienced by the patients for which the GP is not consulted.

References

1. Behin A, Hoang-Xuan K, Carpentier AF, Delattre JY. Primary brain tumours in adults. Lancet. 2003;361(9354):323-31.

2. Central Brain Tumor Registry of the United States. 2018 CBTRUS fact sheet (2018).http://www.cbtrus.org/factsheet/f actsheet.html.

3. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro-oncology. 2018;20(suppl_4):iv1-iv86.

4. Oberndorfer S, Lindeck-Pozza E, Lahrmann H, Struhal W, Hitzenberger P, Grisold W. The end-of-life hospital setting in patients with glioblastoma. JPalliatMed. 2008;11(1):26-30.

5. Pace A, Di LC, Guariglia L, Jandolo B, Carapella CM, Pompili A. End of life issues in brain tumor patients. JNeurooncol. 2009;91(1):39-43.

6. Sizoo EM, Braam L, Postma TJ, Pasman HR, Heimans JJ, Klein M, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. NeuroOncol. 2010;12(11):1162-6.

7. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004;3(3):159-68.

8. Koekkoek JA, Dirven L, Reijneveld JC, Sizoo EM, Pasman HR, Postma TJ, et al. End of life care in high-grade glioma patients in three European countries: a comparative study. Journal of neuro-oncology. 2014;120(2):303-10.

9. Davies E, Clarke C. Early symptoms of brain tumours. Journal of neurology, neurosurgery, and psychiatry. 2004;75(8):1205-6.

10. Salander P, Bergenheim AT, Hamberg K, Henriksson R. Pathways from symptoms to medical care: a descriptive study of symptom development and obstacles to early diagnosis in brain tumour patients. Family practice. 1999;16(2):143-8.

11. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. The New England journal of medicine. 2016;374(14):1344-55.

12. Posti JP, Bori M, Kauko T, Sankinen M, Nordberg J, Rahi M, et al. Presenting symptoms of glioma in adults. Acta Neurol Scand. 2015;131(2):88-93.

13. Bentsen BG. International classification of primary care. Scandinavian journal of primary health care. 1986;4(1):43-50.

14. Scott GM, Gibberd FB. Epilepsy and other factors in the prognosis of gliomas. Acta Neurol Scand. 1980;61(4):227-39.

15. Moots PL, Maciunas RJ, Eisert DR, Parker RA, Laporte K, Abou-Khalil B. The course of seizure disorders in patients with malignant gliomas. Arch Neurol. 1995;52(7):717-24.

16. Riva M, Salmaggi A, Marchioni E, Silvani A, Tomei G, Lorusso L, et al. Tumour-associated epilepsy: clinical impact and the role of referring centres in a cohort of glioblastoma patients. A multicentre study from the Lombardia Neurooncology Group. Neurol Sci. 2006;27(5):345-51.

17. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg. 2008;108(2):227-35.

18. Bauman G, Fisher B, Watling C, Cairncross JG, Macdonald D. Adult supratentorial low-grade glioma: long-term experience at a single institution. International journal of radiation oncology, biology, physics. 2009;75(5):1401-7.

19. van Breemen MS, Rijsman RM, Taphoorn MJ, Walchenbach R, Zwinkels H, Vecht CJ. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol. 2009;256(9):1519-26.

20. Iuchi T, Hasegawa Y, Kawasaki K, Sakaida T. Epilepsy in patients with gliomas: incidence and control of seizures. J Clin Neurosci. 2015;22(1):87-91.

21. Yuile P, Dent O, Cook R, Biggs M, Little N. Survival of glioblastoma patients related to presenting symptoms, brain site and treatment variables. JClinNeurosci. 2006;13(7):747-51.

22. Liigant A, Haldre S, Oun A, Linnamagi U, Saar A, Asser T, et al. Seizure disorders in patients with brain tumors. Eur Neurol. 2001;45(1):46-51.

23. Bussiere M, Hopman W, Day A, Pombo AP, Neves T, Espinosa F. Indicators of functional status for primary malignant brain tumour patients. Can J Neurol Sci. 2005;32(1):50-6.

24. Lowry JK, Snyder JJ, Lowry PW. Brain tumors in the elderly: recent trends in a Minnesota cohort study. Arch Neurol. 1998;55(7):922-8.

25. Frankel SA, German WJ. Glioblastoma multiforme; review of 219 cases with regard to natural history, pathology, diagnostic methods, and treatment. J. Neurosurg. 15(5), 489–503 (1958).

26. Litofsky NS, Farace E, Anderson F, Jr., Meyers CA, Huang W, Laws ER, Jr. Depression in patients with high-grade glioma: results of the Glioma Outcomes Project. Neurosurgery. 2004;54(2):358-66.

27. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Informatics in primary care. 2011;19(4):251-5.

28. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 2015;14(1):57-64.

29. Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, et al. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. Jama. 2004;291(21):2581-90.

Supplementary Table 1.

ICPC codes used for the selection of CNS control patients	
K89	Passing cerebral ischemia/TIA
K90	Cerebrovascular accident (CVA)
N71	Meningitis/encephalitis
N72	Tetanus
N73	Other infectious disease(s) nervous system
N79	Concussion
N80	Other injury head
N81	Other injury nervous system
N85	Birth defect nervous system
N86	Multiple sclerosis
N87	Parkinsonism, Parkinson's disease
N88	Epilepsy (all forms)
N89	Migraine
N90	Cluster headache
N91	Facial nerve paresis/Bell's palsy
N92	Trigeminus neuralgia
N99	Other disease nervous system
P70	Senile dementia/Alzheimer
P71	Other organic psychosis
P72	Schizophrenia
P73	Affective psychosis
P76	Depression

Supplementary Table 2.

Symptoms and signs found in literature study and semi-structured interviews, sorted by category			
Literature search	**Prevalence in literature**	**Semi-structured interviews**	**Score HCP**
Seizure	3.1%-82.8%%	Epilepsy	4
Memory problem	15%-36.7%	Short term memory	4
Visual problem	2%-39%	Progressive loss of vision	4
Motor impairment	3%-44%	Neurological deficit extremities	3.8
		Neurological deficit of the trunk	3.25
		Neurological deficit in one half of the body	3.25
		Difficulties fine motor skills	3
		Weakness extremities	3
Change in consciousness	3%-39%	Periods of reduced consciousness	3.4
		Alertness	3.33
Confusion	13.4%-57%	Orientation	3.25
		Processing of information	3.8
		Initiating	3.5
		Planning	4
		Concentration	3.8
		Mood swings	3
Personality change	1%-34%	Personality change	3.2
Language problems	4%-36.4%	Aphasia	3
Headache	19.7%-86%		
Nausea	0%-45%		
Sensory problems	1%-23%		
		Burn out	4
		Tiredness	4
		Stress	4

Supplementary Table 3.

ICPC codes used in the nine categories of prediagnostic symptoms	
Seizure	
N07	Convulsions (including febrile seizure)
N88	Epilepsy (all forms)
A06	Fainting/syncope
Headache	
N01	Headache [ex. N02,N89,R09]
N02	Tension headache
N03	Facial pain
N89	Migraine
N90	Cluster headache
N92	Trigeminus neuralgia
Motor impairments	
A28	Disability/handicap
D17	Incontinence for stool
D21	Swallowing problems
L19	Symptoms multiple/non-specified muscles
L28	Disability/handicap musculoskeletal system
N04	Restless legs
N18	Paralysis/weakness [ex. A04]
N19	Speak-/phonation disorder
N28	Disability/handicap nervous system
N91	Paralysis facial nerve /Bell's palsy
P10	Stammering/stuttering/tics
U04	Incontinence for urine [ex. P12]
Cognitive/mental impairments	
P20	Memory-/concentration-/orientation disorder
P71	Other organic psychosis
P73	Affective psychosis
P80	Personality-/character
P85	Mental retardation/intellectual disability
P98	Other/non-specified psychosis
Progressive loss of vision	
F01	Pain eye
F04	Mouches volantes/flashing/flickering
F05	Other visual symptoms/complaints [ex. F94]
F13	Altered sensation in eye
F14	Altered eye movements
F16	Symptoms/complaints eye lids
F17	Symptoms/complaints glasses
F18	Symptoms/complaints contact lens(es)
F28	Disability/handicap eye/adnexa of the eye
F29	Other symptoms/complaints eye/adnexa of the eye
F94	Blindness (every degree/form)
F95	Strabismus/squint
F99	Other disease(s) eye/adnexa of the eye

Supplementary Table 3. Continued

ICPC codes used in the nine categories of prediagnostic symptoms	
Mood disorders /fear	
P01	Anxious/nervous/tensed feeling
P03	Down/depressed feeling
P04	Irritable/angry feeling/behaviour
P05	Feeling/behaving old
P06	Sleeplessness/other sleeping disorder
P07	Libido loss/reduction
P08	Sexual satisfaction loss/reduction
P27	Fear for psychic disease
P28	Disability/handicap psychic disease
P29	Other psychic symptoms/complaints
P74	Anxiety disorder/anxiety
P75	Hysteria/hypochondria
P76	Depression
P77	Suicide attempt
P78	Neurasthenia/surmenage
P79	Other neurosis
P99	Other psychic disorder
Z27	Fear of having a social problem
A13	Concern about side effect medicine
A25	Fear of death
A26	Fear of cancer
A27	Fear of other disease
F27	Fear of disease eye
N26	Fear of cancer nervous system
N27	Fear of other disease nervous system
General symptoms	
A04	Fatigue/weakness
A05	Overall deterioration
A29	Other general symptoms/complaints
A85	Drug side-effect
N29	Other symptoms/complaints nervous system
N99	Other disease(s) nervous system
Sensory complaints	
H02	Hearing complaints [ex. H84,H85,H86]
H03	Tinnitus
H82	Vertigo syndrome/labyrinthitis [ex. N17]
N05	Tingling fingers/feet/toes
N06	Other sensibility disorder/involuntary movements
N16	Other alterations smell/taste
N17	Vertigo/dizziness [ex. H82]
N93	Carpal tunnel syndrome
N94	Other peripheral neuritis/neuropathy
Metabolic/endocrine	
T01	Excessive thirst
T02	Excessive appetite
T03	Decreased appetite
T05	Nutritional problem adult [ex. T06]