Measuring symptons and functioning in glioma patients

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CHAPTER 3

Prediagnostic symptoms and signs of adult glioma: the patients' view

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Abstract

Background

Little is known about the symptoms glioma patients experience in the year before diagnosis, either or not resulting in health care usage. This study aimed to determine the incidence of symptoms glioma patients experienced in the year prior to diagnosis, and subsequent visits to a general practitioner (GP).

Methods

Glioma patients were asked to complete a 30-item study-specific questionnaire focusing on symptoms they experienced in the 12 months before diagnosis. For each indicated symptom, patients were asked whether they consulted the GP for this issue.

Results

Fifty-nine patients completed the questionnaires, 54 (93%) with input of a proxy. The median time since diagnosis was 4 months (range 1-12). The median number of symptoms experienced in the year before diagnosis was similar between gliomas with favourable and poor prognosis, i.e. 6 (range 0-24), as were the five most frequently mentioned problems: fatigue (n=34, 58%), mental tiredness (n=30, 51%), sleeping disorder (n=24, 41%), headache (n=23, 39%) and stress (n=20, 34%). Twenty-six (44%) patients visited the GP with at least one issue. Patients who did consult their GP reported significantly more often muscle weakness (11 vs 3, p=0.003) than patients who did not, which remained significant after correction for multiple testing, which was not the case for paralysis in hand/leg (10 vs 4), focussing (11 vs 6) or a change in awareness (9 vs 4).

Conclusions

Glioma patients experience a range of non-specific problems in the year prior to diagnosis, but only patients who consult the GP report more often neurological problems.

Introduction

Gliomas are the most common malignant primary tumours of the brain, with reported incidences of 5.6 and 7.8 per 100,000 persons for women and men, respectively[1]. Patients may present with a variety of symptoms, often linked to the tumour location and grade[2, 3]. Several symptoms, such as seizures, motor impairments and loss of consciousness, have an acute presentation, while other symptoms have a more gradual course, including headache, personality change or cognitive problems[4].

Earlier recognition of symptoms may lead to an earlier diagnosis, possibly resulting in less morbidity. However, recognizing symptoms and complaints as a presentation of a brain tumour may be difficult for both patients, their relatives and health care professionals, as symptoms may be non-specific (i.e. not indicating a specific disease or involving a specific body system, such as fatigue)[5]. Other factors that may contribute to a delayed diagnosis are patient characteristics, for example a change in personality and avoidance or adaptation and lack of recognition by a health care professional and/or the relatives[5].

In the last decades, studies reporting on the presenting symptoms of glioma mainly concerned retrospective medical record studies[2, 3, 6-17], some of which did not describe glioma patients separately from other brain tumour patients[18-20]. Moreover, most studies described categories of symptoms only (e.g. isolated cranial nerve symptom[3], motor symptomatology or mental change[6]), and not the specific symptoms included in the various categories. The most commonly reported symptoms or symptom groups in these studies were seizures[2, 3, 6-16, 21], headache[2, 3, 6, 9, 11, 13, 17, 21-23], nausea[3, 6, 11, 21, 23], motor impairments[3, 6, 9, 11, 17, 21], sensory problems[3, 6, 21], visual problems[3, 6, 9, 11, 17, 21, 23], confusion[3, 9, 11, 17], memory problems[9, 11, 17, 21, 23], a change in consciousness[6, 17, 21, 23], problems with language or speaking[3, 6, 9, 11, 17, 21] and a change in personality[6, 9, 21].

Patients' symptoms at the time of diagnosis or during treatment were most frequently described. Yet, little is known on the full range of health problems patients experienced in the period before diagnosis, as well as any health care usage due to these problems. One method to identify symptoms in the period before diagnosis is to extract information from the medical records of health care professionals, e.g. a general practitioner (GP)[24, 25]. A systematic review on prediagnostic symptoms in primary care showed that only new-onset epilepsy was able to predict which patients would be diagnosed with a brain or central nervous system tumour (i.e. positive predictive value of 1.2%)[26]. However, it is likely that patients did not visit a health care professional for all their symptoms, if any.

The objective of this study was to determine the incidence of symptoms Dutch glioma patients experience in the year prior to diagnosis, as well as the number of visits to a GP related to these issues. Moreover, we aimed to determine for which

symptoms glioma patients visited the GP, and whether subgroups of patients reported different prediagnostic symptoms.

Methods

Study design and patients

This was a cross-sectional study including consecutive patients with a histologically confirmed grade II-IV glioma (according to the WHO 2016 classification criteria), up to one year after diagnosis, who visited the neuro-oncology outpatient clinic of the Haaglanden Medical Center in The Hague, The Netherlands, between July 2016 and April 2019. In addition, their proxies (e.g. relatives or friends) were invited to help the patient completing the questionnaire. The time frame of a maximum of 12 months after diagnosis was chosen to minimize recall bias concerning the prediagnostic, self-reported symptoms.

The study was approved by the medical ethical review board, and all patients and proxies provided written informed consent prior to participation.

Assessments

Sociodemographic and clinical characteristics of the patients were retracted from the medical records, or through a short questionnaire (e.g. level of education). Also, information was collected on whether the patient completed the 30-item questionnaire on prediagnostic symptoms and healthcare use together with their proxy, as well as the nature of the relationship with their proxy. This 30-item study-specific questionnaire included questions on prediagnostic symptoms, consulted health care professionals in the year prior to diagnosis, and the presence of comorbidity and other chronic complaints in the year prior to diagnosis (see Supplementary File 1). The symptoms mentioned in the study-specific questionnaire were based on the literature[3, 27, 28] and semi-structured interviews with five experts (three neuro-oncologists, one neuropsychologist and one nurse specialized in neuro-oncology) about the presenting symptoms in patients with glioma. During these interviews, each of the symptoms on the list derived from the literature were systematically discussed. The experts were asked to estimate the frequency of each symptom using a four-point Likert scale, ranging from (1) 'never', (2) 'unusual', (3) 'less common' to (4) 'common'. Only symptoms with a mean score >3 were included, resulting in the inclusion of 30 symptoms. For each symptom, patients were asked to indicate if they had experienced that symptom in the 12 months before the diagnosis (Yes/No). If the answer was yes, they were also asked to report if they consulted their GP for this problem (Yes/No), as in the Netherlands, the GP is the gatekeeper to hospital- and specialist care. The questions

on comorbidity were based on an existing questionnaire used by the Dutch Central Bureau of Statistics (CBS) on 19 different comorbidities[29]. We also asked patients which other healthcare professionals were consulted in the year prior to diagnosis. Patients were encouraged to complete the questionnaires together with their proxy, in order to minimise recall bias.

Statistical analysis

Descriptive statistics were used to the report the sociodemographic and clinical characteristics of the participants and their proxies, the number of visits to the GP and for which symptoms, the other consulted healthcare professionals in the year prior to diagnosis, and the level of comorbidity. Furthermore, the occurrence of neurological symptoms (question 1, 2, 3, 20, 21 and 22) and non-specific symptoms (question 4, 5, 24, 28, 29 and 30) was described separately for patient who did and did not visit the GP. Differences in the frequency of symptoms between patients who did and who did not visit their GP for any symptom, and between patients with poor (i.e. IDH wildtype and both IDH-mutant and wildtype glioblastoma) and favourable prognosis (grade II and III IDH mutant) glioma were compared by means of Chi-Square tests.

All data were analysed using the SPSS statistical package (version 23.0, SPSS, Chicago, Illinois). The level of statistical significance was set at 0.05 for all analyses, and the Benjamini-Hochberg procedure was used to correct for multiple testing in each comparison.

Results

Patient characteristics

Of the 126 patients who were considered eligible and were invited for participation, 59 (47%) returned the questionnaires. Forty-five (76%) questionnaires were returned without missing data, and when items were missing, this number was low (on average 97.5% of the incomplete questionnaires was filled in). Moreover, 54 (93%) patients completed the questionnaire with the help of a proxy, which was the spouse in most cases (89%). Non-responders (n=67) did not differ significantly from responders (n=59) regarding any of the measured variables, including age (57 vs 60 years, p=0.345), sex (64% versus 68% male, p=0.710), tumour type (22% versus 10% poor prognosis, p=0.093) and tumour grade (73% versus 81% grade IV, p=0.144).

Table 1 shows the characteristics of the 59 participating patients. The majority was male (40/59, 68%) with a median age of 60 years (range 43-85) and a median time since diagnosis of 4 months (range 1-12). The most frequent diagnosis was glioblastoma (48/59, 81%) - for only 24/48 patients the Isocytrate Dehydrogenase (IDH) status was

available and all were IDH wildtype - followed by IDH mutant astrocytoma (5/59, 8%), IDH mutant, 1p19q codeleted oligodendroglioma (4/59 7%) and astrocytoma IDH wild type (2/59, 3%). All 59 patients had undergone resection or biopsy, 55 (93%) received radiotherapy and the majority of patients (47/59, 80%) received chemotherapy. Most patients (40/59, 68%) reported any comorbidity, particularly problems with the musculoskeletal system (20/59, 34%), neurological problems (16/59, 27%) and heart and vascular disease (15/59, 25%).

Table 1. Characteristics of 59 patients with a glioma participating in a survey on prediagnostic symptoms and signs

Age, years; Median (range); n=59	60 (43-85)
Sex; No (%) male; n=59	40 (68%)
Time since diagnosis (months) (range); n=59	4 (range 1-12)
Tumour type; n=59	
Diffuse astrocytoma, IDH mutant	2 (3%)
Oligodendroglioma, IDH mutant, 1p19q codeletion	4 (7%)
Anaplastic astrocytoma, IDH wildtype	2 (3%)
Anaplastic astrocytoma, IDH mutant	3 (5%)
Glioblastoma	48 (81%)
Tumour grade; n=59	
II	6 (10%)
III	5 (9%)
IV	48 (81%)
Tumour location; n=59	
Left hemisphere	31 (53%)
Right hemisphere	29 (49%)
Frontal	23 (39%)
Occipital	5 (9%)
Temporal	23 (39%)
Parietal	15 (35%)
Cerebellum	2 (3%)
Midline	3 (5%)
MGMT-status	
Methylated	15 (25%)
Unknown/not determined	8 (14%)
1p19q-status	
Co-deletion	5 (9%)
Unknown/not determined	21 (36%)
IDH-status	
Mutated	9 (15%)
Unknown/not determined	23 (39%)
Treatment; n=59	
Biopsy; No (%)	8 (14%)
Partial resection; No (%)	43 (73%)
Macroscopic resection; No (%)	8 (14%)
Chemotherapy; No (%)	47 (80%)
Radiotherapy; No (%)	5 (93%)

Table 1. Continued

Level of education* n=56	
Primary school	6 (10%)
Lower secondary school	11 (20%)
Upper secondary school	16 (29%)
Short cycle tertiary	14 (25%)
Bachelor or equivalent	0 (0%)
Master or equivalent	7 (13%)
Doctoral or equivalent	2 (4%)
Comorbidity n=59	
Any	40 (68%)
Diabetes	2 (3%)
Pulmonary	6 (10%)
Dermatological	5 (9%)
Bowel disorder	5 (9%)
Incontinence for urine	2 (3%)
Heart and vascular disease	15 (25%)
Neurology	16 (27%)
Musculoskeletal system	20 (34%)
Proxy relationship with patient n=56	
Spouse	49 (89%)
Child	6 (11%)
Intensity relationship with patients n=54	
Living together	46 (78%)
Daily	7 (12%)
Weekly	1 (2%)

*Categories: Primary school (Entry age: 5-7 years old. Duration: ± 4-7 years. Programs typically designed to provide students with fundamental skills in reading, writing and mathematics and to establish a solid foundation for learning.) Lower secondary school (Entry age: 10-13 years old. Duration: ≥2 years. First stage of secondary education building on primary education, typically with a more subject oriented curriculum.) Upper secondary school (Entry age: ≥13 years old. Duration: ≥2 years. Second/final stage of secondary education preparing for tertiary education and/or providing skills relevant to employment.) Post-secondary, non-tertiary (Duration: 0.5-3 years. Programs providing learning experiences that build on secondary education and prepare for labour market entry and/or tertiary education.) Short cycle tertiary (Duration: 2-3 years.
Practical/technical/occupationally specific programs leading to professional qualifications) Bachelor or equivalent. Master or equivalent. Doctoral or equivalent

Frequency of symptoms

Table 2 shows the frequency of symptoms patients' experienced in the year prior to diagnosis. The five most frequently reported symptoms were fatigue (34/59, 58%), mental tiredness (30/59, 51%), sleeping disorder (24/59, 41%), headache (23/59, 39%) and stress (20/59, 34%). Patients reported a median of six symptoms in total (range 0-24, see figure 1). Double vision, stress and burnout were significantly more often reported in patients with a favourable prognosis compared to patients with a poor prognosis, but these differences were no longer significant after correction for multiple testing (table 2).

Table 2. Frequency of signs and symptoms and related visits to GP in 59 patients with glioma; All figures are numbers (%).

In the 12 months prior to diagnosis, did you experience problems with:	12 months before diagnosis	GP visit related to symptoms	Grade II and III IDH mutant glioma (low-grade glioma); n=9	IDH wildtype and glioblastoma (high grade glioma); n=50	p-value	Not visited the GP; n=33	Visited the GP; n=26	p-value
1. The extent to which you were aware of the things around you (awareness)	13 (22%)	6 (46%)	2 (22%)	11 (22%)	0.988	4 (12%)	9 (35%)	0.040
2. Seizure(s)	12 (20%)	2 (8%)	3 (33%)	9 (18%)	0.297	8 (24%)	4 (15%)	0.405
3. Changes of personality or character	15 (25%)	3 (20%)	4 (44%)	11 (22%)	0.158	5 (15%)	10 (39%)	0.043
4. Mental tiredness (motivation to do activities or to the ability to endure less)	30 (51%)	5 (17%)	6 (67%)	24 (48%)	0.307	14 (42%)	16 (62%)	0.148
5. Sleeping (falling asleep, waking up during the night or waking up early in the morning)	24 (41%)	2 (8%)	4 (44%)	20 (40%)	0.804	14 (42%)	10 (39%)	0.760
6. Attention (ability to hold attention)	18 (31%)	2 (11%)	4 (44%)	14 (28%)	0.328	8 (24%)	10 (39%)	0.243
7. Short-term memory	16 (27%)	5 (31%)	2 (22%)	14 (28%)	0.722	6 (18%)	10 (39%)	0.085
8. Long-term memory	5 (9%)	1 (20%)	0	5 (10%)	0.326	3 (9%)	2 (8%)	0.849
9. Mood (fear, depression)	14 (24%)	4 (29%)	3 (33%)	11 (22%)	0.466	5 (15%)	9 (35%)	0.084
10. Recognizing a stimulus (sound, picture,	8 (14%)	2 (25%)	3 (33%)	5 (10%)	0.062	5 (15%)	3 (12%)	0.690
11. Thinking (speed of thinking or logical thinking)	20 (34%)	3 (15%)	5 (56%)	15 (30%)	0.139	10 (30%)	10 (39%)	0.515
12. Complicated mental tasks (planning, calculating, time management)	17 (29%)	2 (12%)	5 (56%)	12 (24%)	0.056	7 (21%)	10 (39%)	0.150
13. Understanding language (written text or a conversation)	12 (20%)	3 (25%)	1 (11%)	11 (22%)	0.459	5 (15%)	7 (27%)	0.269
14. Expressing language (speaking or writing language)	19 (32%)	3 (16%)	3 (33%)	16 (32%)	0.938	10 (30%)	9 (35%)	0.727
15. Fine motor skills (closing buttons on a shirt)	8 (14%)	1 (13%)	1 (11%)	7 (14%)	0.817	4 (12%)	4 (15%)	0.719
16. Reduced field of view (the area you see when you keep your head still is reduced)	16 (27%)	4 (25%)	2 (22%)	14 (28%)	0.722	7 (21%)	9 (35%)	0.254
17. Double vision	3 (5%)	1 (33%)	2 (22%)	1 (2%)	0.012	1 (3%)	2 (8%)	0.422
18. Awareness of the position of the limbs	8 (14%)	2 (25%)	1 (11%)	7 (14%)	0.817	2 (6%)	6 (23%)	0.060

In the 12 months prior to diagnosis, did you experience problems with:	12 months before diagnosis	GP visit related to symptoms	Grade II and III IDH mutant glioma (low-grade glioma); n=9	IDH wildtype and glioblastoma (high grade glioma); n=50	p-value	Not visited the GP; n=33	Visited the GP; n=26	p-value
19. Sensibility disorder (tingling sensation or diminished or numb feeling somewhere on your body)	12 (20%)	5 (42%)	4 (44%)	8 (16%)	0.053	4 (12%)	8 (31%)	0.080
20. Focussing on one particular task	17 (29%)	2 (12%)	3 (33%)	14 (28%)	0.747	6 (18%)	11 (42%)	0.044
21. Paralysis of for example hand or leg	14 (24%)	5 (36%)	1 (11%)	13 (26%)	0.338	4 (12%)	10 (39%)	0.019
22. Weakness in muscles	14 (24%)	5 (36%)	2 (22%)	12 (24%)	0.909	3 (9%)	11 (42%)	0.003
23. Altered speech	17 (29%)	6 (35%)	3 (33%)	14 (28%)	0.747	8 (24%)	9 (35%)	0.386
24. Tingling sensation	11 (19%)	2 (18%)	3 (33%)	8 (16%)	0.223	5 (15%)	6 (23%)	0.442
25. Headache	23 (39%)	6 (26%)	2 (22%)	21 (42%)	0.267	13 (39%)	10 (39%)	0.942
26. Nausea	11 (19%)	3 (27%)	2 (22%)	9 (18%)	0.767	6 (18%)	5 (19%)	0.919
27. Vomiting	7 (12%)	2 (29%)	2 (22%)	5 (10%)	0.301	4 (12%)	3 (12%)	0.946
28. Stress	20 (34%)	5 (25%)	6 (67%)	14 (28%)	0.025	10 (30%)	10 (39%)	0.515
29. Fatigue	34 (58%)	5 (15%)	7 (78%)	27 (54%)	0.188	20 (61%)	14 (54%)	0.605
30. Burn-out	7 (12%)	2 (29%)	3 (33%)	4 (8%)	0.032	3 (9%)	4 (15%)	0.462
In total (median, range)	6 (0-24)		8 (0-21)	5 (0-24)	0.267	5 (0-24)	7.5 (1-21)	0.058

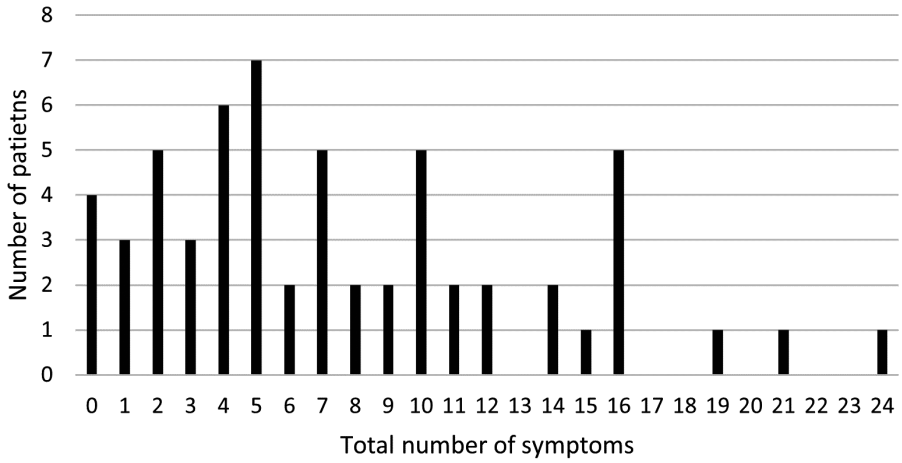

Figure 1. Distribution of the total number of symptoms reported per patient

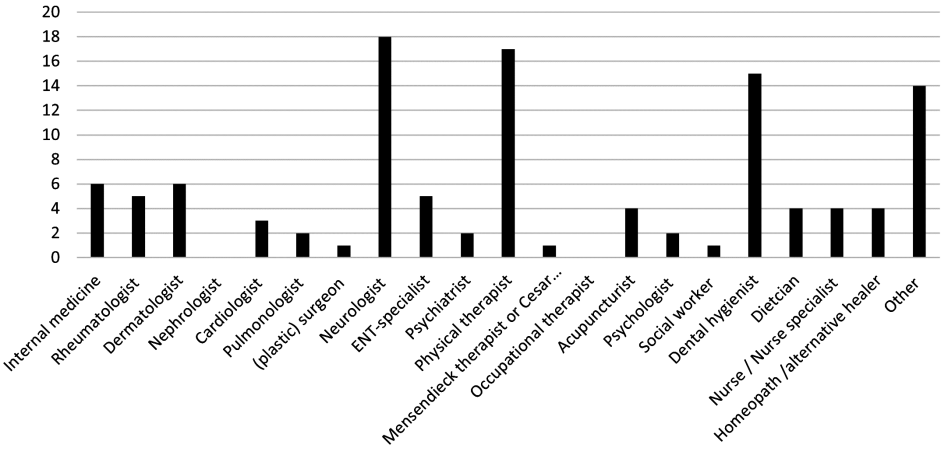

Figure 2. Number of patients visiting health-care professionals

Visits to the general practitioner

Twenty-six (44%) patients visited the GP with at least one symptom. Weakness in muscles was significantly more often reported by patients who visited the GP than patients who did not (11 versus 3, p=0.003). Paralysis of for example hand or leg (10 versus 4), awareness of things around (9 versus 4), changes of personality or character (10 versus 5) and focussing on one particular task (11 versus 6) were reported more often by patients visiting the GP, but did not remain significant after correcting for multiple testing (Table 2). Moreover, patients visiting the GP reported more symptoms

in total (median 7.5, range 1-21) than patients that did not visit the GP (median 5, range 0-24), although this was not significant (p=0.058). Of the patients who did and did not visit the GP for their symptoms, 22 versus 20 reported neurological symptoms only, 20 versus 24 non-specific symptoms only, and 18 versus 17 patients reported both neurological and non-specific symptoms, respectively.

Health care usage

Patients reported that they visited several other health care providers in the year prior to diagnosis, mostly the dentist (78%, 45/58), followed by the neurologist (31%, 18/59), physical therapist (29%, 17/59) and the dental hygienist (26%, 15/58) (figure 2).

Discussion

In this study, we found that more than half of the patients reported fatigue in the year before diagnosis, and that mental tiredness, sleeping disorder, headache and stress were also frequently reported symptoms. These symptoms did not depend on tumour type, i.e. grade II and III IDH-mutant glioma versus IDH wildtype glioma and glioblastoma. An important finding is that patients do not visit the GP for all their complaints, but if they did, this was mostly because of weakness in muscles.

Patients in this study most frequently reported more general or non-specific symptoms, such as fatigue, headache and stress, which are not usually characteristic symptoms for a glioma and could also be a self-contained symptom, whether or not related to another disease. Another study, using data from medical records of GPs, showed that it is difficult to distinguish glioma patients from 'other' patients visiting the GP with respect to their prediagnostic symptoms[30]. Typically, persons do not visit the GP for these common complaints if not sufficiently severe or not having a negative impact on functioning in daily life, which was also observed in our study. In the general population, patient-reported difficulty with initiating sleep or maintaining sleep was found in 16-21% of patients[31]. We found that 41% reported a sleeping disorder, indicating that this is a serious problem in this patient population, even before diagnosis. Similarly, headache and stress (reported in 39% and 34% of patients in our study, respectively) are also frequently reported in the general population, with 46% of the general population reporting headache in the past year[32] and 13% of patients in a Swedish population reporting stress[33]. Nineteen percent of patients visited the GP with stress in the employed population in Norway versus 25% in our population[34], and only 5.4% of patients with headache in the general Dutch population versus 26% in our population[35].

In contrast, patients with disease-specific symptoms, such as problems with awareness, a sensibility disorder, weakness or paralysis and altered speech, which can all be classified as neurological problems, who also reported non-specific symptoms in most cases, did visit the general practitioner more often. It is plausible that these neurological symptoms could not be attributed to more common or less severe disorders, and therefore required follow-up or work up at a hospital as it is important to rule out severe diseases.

This study has several strengths. Most studies assessing prediagnostic symptoms, or symptoms patients present with at diagnosis, use data from medical records at the GP. With that design it is likely that not all symptoms which patients experience are detected. After all, patients do not always visit a health care professionals, e.g. GP with their symptoms or mention all their symptoms when they visit the emergency department or outpatient clinic. Furthermore, with the participation of the proxies, is it likely that a more comprehensive overview of all complaints experienced was provided. Some limitations of our study, and of studies using questionnaires in general, should also be acknowledged. First, selection bias should be taken into account, since not all patients could be included due to their physical or mental condition. This might hamper generalisability of our study results to the whole glioma patient population. In this study, however, there were no significant differences between important clinical characteristics between patients who participated and those who did not. Moreover, due to the inclusion of patients that were diagnosed in 2015, the IDH status was only available for half of glioblastoma patients. Besides, growth rate is also an important factor in the onset and nature of prediagnostic symptoms, although we did not find differences between patients with different molecular profiles. We also lack knowledge on the exacttime of onset of the symptoms (only a wide period, i.e. 12-3 and 3-0 months prior to diagnosis), and whether specific symptoms were the trigger for the GPs to refer the patients to the neurologist that subsequently led to the diagnosis of the brain tumour. Furthermore, recall bias is also an important issue, as patients have to remember symptoms they experienced in the year before diagnosis and treatment, while having a disease in which cognition can be affected as well. Indeed, more than 60% of brain tumour patients have impaired neurocognitive functioning in any domain prior to anti-tumour treatment[36], which progresses over time[37].

To minimise the effect of recall bias, patients were included up to one year after diagnosis, and were asked to fill in the questionnaire with a proxy, who may remember similar or even other symptoms. Recall bias varies between diseases, with remembering the diagnosis of cancer having false positive rates of 5% and false negatives of around 17%[38]. Similarly, recall bias may occur with respect to location and severity of symptoms, e.g. the agreement between two measurements on the location of pain was found to be low to moderate, while the agreement on the severity of pain was low[39]. Although

recall bias may have impacted our results, this approach was considered more solid than exploring symptoms described in the medical records of certain health care professionals, such as GPs or the hospitals, as we expected that not all patients would visit health care professionals with their complaints, or that not all complaints would be reported in the medical records. Ideally, a large prospective cohort of healthy participants should be screened for their symptoms over time, and in time those diagnosed with a glioma could be evaluated for their prediagnostic symptoms. However, this would require a large number of participants, a long follow-up time and considerable resources. Lastly, we asked proxies to help the patient complete the questionnaire together and therefore we do not know whether there were differences between the reported symptoms by the patient or the proxy. Instead, our approach provided a 'consensus insight' into the patients symptom burden, reflecting both the patient and proxy views. For example, a change in personality will probably only be noticed by a proxy and not the patient. In a study by Walter et al, it has been reported 'something was not quite right' or 'changed' about the patient, and these changes were often noticed earlier by others than the patient[40].

In conclusion, recognizing a glioma based on prediagnostic symptoms is challenging as most patients report non-specific symptoms[5]. However, healthcare professionals seeing patients with new neurological symptoms should also ask if they experience non-specific symptoms, and consider the diagnosis of a glioma with the corresponding workup.

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Supplementary File 1. Study-specific questionnaire

Early symptoms in glioma patients

Patient code: | | | | | | | | | |

Date: | | | - | | | - | | | | |

Why this questionnaire?

With this questionnaire we want to gain more insight in the symptoms patients with a brain tumour experience before their diagnosis. Brain tumours can cause several symptoms, for example loss of strength, sensory disorders, language problems, seizures or headaches. Furthermore, many patients with a brain tumour experience disorders in memory or concentration.

Currently it is unclear which symptoms patients experience before the diagnosis of a brain tumour. With this research, we want to explore if there are specific symptoms that will help with the timely recognition of new patients with a brain tumour.

Instructions for completing the questionnaire

We ask you to complete the questionnaire <u>together with your partner or proxy.</u> In this way, we will obtain a more comprehensive overview of your symptoms.

When completing the questions, only your opinion and experience count. There are no wrong or right answers. It is important that you consider the mentioned time frame (i.e. last year) during completion of the questions.

The questionnaire consists of two parts. The first part is about the symptoms you experienced that are related to your brain tumour <u>in the 12 months prior to your diagnosis.</u> The second part is about the doctors and other health care professionals you visited <u>in the 12 months prior to your diagnosis</u> and other disorders and complaints you experienced during this period.

Before you fill out the questionnaire

- Take your time, you can complete the questionnaire in stages if needed.
- Please do not skip any of the questions and answer the questions as complete as possible.
- Tick only one answer, unless otherwise indicated.
- If you make a mistake, please colour this box completely black.
- Do not think too long about one answer.

The date of your diagnosis was: _____ / _____ / 20

Consider this date during the following questions.

First, note the date of today: _____ / _____ / 20

This part is about the symptoms you experienced and are related to your brain tumour. We are interested in the symptoms you experienced in the 12 months prior to your diagnosis.

	In the 12 months prior to your diagnosis, did you experience problems with:	No	Yes	Did you consult your GP for this problem?
1	The extent to which you were aware of the things happening around you (e.g. awareness)	☐	☐	☐
2	Epileptic seizures	☐	☐	☐
3	Change of personality or character	☐	☐	☐
4	Mental tiredness (e.g. motivation to do things or being able to endure less)	☐	☐	☐
5	Sleeping (e.g. falling asleep, waking up frequently, or waking up too early in the morning)	☐	☐	☐
6	Attention (e.g. maintaining attention)	☐	☐	☐
7	Short term memory	☐	☐	☐
8	Long term memory	☐	☐	☐
9	Mood (e.g. fear, depression)	☐	☐	☐
10	Recognizing a stimulus (i.e. sound, image, touch, smell or taste)	☐	☐	☐
11	Thinking (e.g. the speed of thinking or thinking clearly)	☐	☐	☐
12	Complicated mental tasks (e.g. planning, calculating, time management)	☐	☐	☐
13	Understanding language (e.g. written text or a conversation)	☐	☐	☐
14	Expressing language (e.g. speaking or writing language)	☐	☐	☐
15	Fine motor skills (e.g. closing the buttons of a shirt)	☐	☐	☐
16	Reduced visual field (e.g. the area you see when your head is not turning is reduced)	☐	☐	☐
17	Double vision	☐	☐	☐
18	Awareness of the position of your limbs	☐	☐	☐
19	Sensory disorders (e.g. tingling sensation or diminished or numb feeling somewhere on your body)	☐	☐	☐
20	Focussing on a particular task	☐	☐	☐
21	Paralysis in hand or leg	☐	☐	☐
22	Weakness in muscles	☐	☐	☐
23	Altered speech	☐	☐	☐
24	Tingling sensation	☐	☐	☐
25	Headache	☐	☐	☐
26	Nausea	☐	☐	☐
27	Vomiting	☐	☐	☐
28	Stress	☐	☐	☐
29	Physical tiredness	☐	☐	☐
30	Burn-out	☐	☐	☐

Comorbidity

The next part of the questionnaire is about a number of chronic diseases and disorders that are common. Please indicate for each condition if you experienced symptoms in the 12 months prior to your diagnosis of a brain tumour. If yes, please also answer the follow-up questions in the section below the disease or disorder.

		Yes	No
1	Do you have diabetes?	☐	☐
	a If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	b Are you currently using insulin?	☐	☐
	c Have you started using insulin within 6 months after the diagnosis of diabetes?	☐	☐
2	Have you ever suffered from a stroke, cerebral haemorrhage or cerebral infarction?	☐	☐
	a If yes, have you had this in the last 12 months?	☐	☐
	b If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	c Do you still experience health problems due to this condition?	☐	☐
3	Have you ever had a heart attack (myocardial infarction?)	☐	☐
	a If yes, have you had this in the last 12 months?	☐	☐
	b If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	Have you had any other severe heart condition in the 12 past months (e.g. heart failure or angina)?	☐	☐
	a If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
4	Have you ever had any form of cancer (malignant condition)?	☐	☐
	a If yes, have you had this in the last 12 months?	☐	☐
	b If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	c With which type(s) of cancer have you been diagnosed?	☐ Leukaemia ☐ Lung cancer ☐ Bowel cancer ☐ Breast cancer ☐ Prostate cancer ☐ Skin cancer ☐ Other	

Please indicate (yes/no) if you experienced the following conditions in the 12 months prior to your diagnosis.

				If yes, have you visited the general practitioner for this condition in the 12 months prior to your diagnosis?	
		Yes	**No**	**Yes**	**No**
1	Migraine or (regular) severe headache	☐	☐	☐	☐
2	High blood pressure	☐	☐	☐	☐
3	Narrowing of the blood vessels in the stomach or legs (also called intermittent claudication, but not varicose veins)	☐	☐	☐	☐
4	Asthma, COPD, chronic bronchitis or lung emphysema	☐	☐	☐	☐
5	Psoriasis or chronic eczema	☐	☐	☐	☐
6	Dizziness with falling	☐	☐	☐	☐
7	Severe or persistent bowel disorders, longer than 3 months	☐	☐	☐	☐
8	Involuntary urine loss (incontinence)	☐	☐	☐	☐
9	Osteoarthritis of the hips or knees	☐	☐	☐	☐
10	Chronic joint inflammation (rheumatoid arthritis)	☐	☐	☐	☐
11	Severe or persistent disorder of the back (including spinal disc herniation)	☐	☐	☐	☐
12	Severe or persistent disorder of the neck or shoulder	☐	☐	☐	☐
13	Severe or persistent disorder of the elbow, wrist or hand	☐	☐	☐	☐

Which of the following healthcare professionals have you visited or consulted in the 12 months prior to your diagnosis of a brain tumour?

	No	Yes
General practitioner	☐	☐
Internal medicine physician	☐	☐
Rheumatologist	☐	☐
Dermatologist (physician for the skin)	☐	☐
Nephrologist (physician for the kidney)	☐	☐
Cardiologist (physician for the heart)	☐	☐
Pulmonologist (physician for the lung)	☐	☐
(Plastic) surgeon	☐	☐
Neurologist	☐	☐
ENT specialist	☐	☐
Psychiatrist	☐	☐
Dentist	☐	☐
Physical therapist	☐	☐
Mensendieck therapist or Cesar therapy	☐	☐
Occupational therapist	☐	☐
Acupuncturist	☐	☐
Psychologist	☐	☐
Social worker	☐	☐
Dental hygienist	☐	☐
Beautician	☐	☐
Dietician	☐	☐
District nurse / Home health nurse	☐	☐
Homeopath /alternative healer _____	☐	☐
Other: _____	☐	☐
Other: _____	☐	☐

Educational level

☐	Primary school	☐	Lower secondary school
☐	Upper secondary school	☐	Post-secondary, non-tertiary
☐	Short cycle tertiary	☐	Bachelor or equivalent
☐	Master or equivalent	☐	Doctoral or equivalent

Current or last profession: _____

For proxies only:

Relation to the patient

- ☐ Partner
- ☐ Parent
- ☐ Other:
- ☐ Sibling
- ☐ Child

Intensity of contact with the patient

- ☐ Living together
- ☐ Weekly
- ☐ Daily
- ☐ Monthly

Duration relationship in years: ☐☐