

## Fatigue in low-grade glioma

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**Abstract** The aim of this study was to determine the prevalence and severity of fatigue in long-term survivors with a low-grade glioma (LGG), and to analyze the relationship between fatigue and demographic variables, disease duration, tumor characteristics, former tumor treatment modalities, antiepileptic drug (AED) use, self-reported concentration, motivation, and activity. Fifty-four patients with stable disease (age range, 25–73 years) who were diagnosed and treated more than 8 years ago were included in this study. Fatigue was analyzed with the Checklist Individual Strength (CIS). Thirty-nine percent of the LGG patients were severely fatigued, with older patients being most affected. Severe fatigue was associated with AED use, and with reduced self-reported concentration, motivation, and activity. No relation was found between fatigue and gender, histology, tumor laterality, disease duration, type of neurosurgical intervention and radiation treatment. Fatigue is a severe problem in a large proportion of long-term surviving LGG patients.

**Keywords** Fatigue · Low-grade glioma · Prevalence studies · Quality of life

### Introduction

Low-grade gliomas are primary malignant brain tumors of glial origin [1]. The median survival time for patients with LGG ranges from 5 to 15 years [2, 3], and some patients may survive in a stable state for many years after the diagnosis and initial treatment. Frequent symptoms experienced by patients with LGG are epileptic seizures and cognitive disturbances [4, 5].

Fatigue is frequently reported by patients with cancer [6]. During treatment, in advanced stages of the disease, and after curative treatment, fatigue has been described as a major problem. In the last 10 years, the amount of research on the relationship between cancer and fatigue has increased remarkably [7]. However, little is known about the variables associated with the initiation and persistence of cancer-related fatigue [8]. The assumption is that fatigue develops during the treatment phase, but later on there seems to be no clear relationship between persistent fatigue and initial disease and treatment variables [7–11]. Estimations of fatigue during treatment of cancer range from 25% to 75% [7]. In addition, based on several cross-sectional and longitudinal studies, fatigue seems to be a problem for a considerable number of cancer survivors [7, 8, 11–14].

Clinical practice suggests that fatigue is also important in glioma patients. However, the level of fatigue and its associated factors have not been studied extensively in LGG patients. Studies assessing fatigue in this patient group mostly use only a limited number of items from a quality of life instrument [15–17]. However, the most

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comprehensive approach to assess fatigue would be using a multidimensional instrument [18], because fatigue is a multidimensional concept with several modes of expression (physical, cognitive, and affective) [7]. In one cross-sectional study, fatigue was assessed in 39 LGG patients with help of the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire, containing three items for fatigue. The majority of these patients reported tiredness and about half of them had sleep disturbances [15]. In another quality of life study, LGG patients scored higher on the subscale fatigue compared to control subjects, using the Profile of Mood States to measure affective disturbances [16].

In this study the following research questions are addressed: (1) What is the prevalence and severity of fatigue in LGG patients? (2) Is fatigue associated with demographic variables (age and gender), disease duration, tumor characteristics (histology and tumor laterality), former tumor treatment modalities (type of neurosurgical intervention, post-surgery radiotherapy), the use of AEDs, or with self-reported concentration, reduced motivation and activity?

## Methods

### Patients

Fifty-eight patients aged 25–73 (mean 48) years with a LGG diagnosed and treated 8–29 years ago were approached for this study. These patients were part of a group of LGG patients recruited between 1997 and 2000 for a large nationwide study into the neuropsychological status and quality of life [5]. We exclusively approached long-term survivors of a histologically proven LGG without signs of tumor recurrence, and who already participated in a follow-up study on cognition and quality of life between 2004 and 2005.

### Recruitment procedure

We sent a fatigue questionnaire to the 58 patients, together with a letter from the research coordinator in the summer of 2006, explaining the intention of the study. Furthermore, an informed consent form was enclosed. Those patients who were willing to participate in the study were asked to complete the questionnaire, and sign the informed consent form at home.

### Measures

Fatigue and fatigue related symptoms were measured with the Checklist Individual Strength (CIS). The CIS is a

multidimensional fatigue scale; it measures four aspects of fatigue during the previous 2 weeks, namely: fatigue severity (eight items), concentration problems (five items), reduced motivation (four items), and reduced activity (three items) [19, 20]. Each item is scored on a seven-point Likert scale. Total scores of every subscale are obtained by adding the individual items, with high scores indicating a high level of fatigue, a high level of concentration problems, low motivation, and a low level of activity. Patients with a score of 35 or higher on the fatigue severity subscale are considered to be severely fatigued. This cut-off value is based on data obtained in patients with chronic fatigue syndrome [20].

### Statistical analysis

Data analysis was accomplished using SPSS software, version 12.0. As a result of small sample size we had to use a non-parametric approach when selecting statistical methods. Mann–Whitney tests were conducted to test the differences between groups. To test the relation between fatigue and age, disease duration, self-reported concentration, motivation and activity, comparisons were made between severely fatigued (CIS  $\geq$  35) and non-severely fatigued (CIS < 35) LGG patients. The level of statistical significance for all tests was set at *P* value less than 0.05.

## Results

### Patient characteristics

Fifty-four of the 58 patients we approached (93%) completed and returned the CIS questionnaire. One patient was unable to participate due to foreign residence. One patient declined participation in the study, and the reasons of two other non-participants are unknown. Non-participants did not differ from the participants with respect to gender, histology, disease duration, type of neurosurgical intervention, and AED use. On the other hand, the non-participants were slightly younger (mean 43.5 years), and none of them had received radiotherapy. Information about the characteristics of the LGG patients is listed in Table 1.

### Fatigue prevalence and severity

The mean CIS-fatigue severity score of the sample LGG patients was 28.2 (SD 15.5). The CIS-fatigue cut-off score of  $\geq$ 35 for severe fatigue was crossed by 21 patients. Hence, 39% of the LGG patients experienced severe fatigue. The remaining 33 patients were classified as non-severely fatigued.

**Table 1** Low-grade glioma patient group ( $n = 54$ ): characteristics

| Characteristics                      | Data                      |
|--------------------------------------|---------------------------|
| Mean age <sup>a</sup>                | 48 (SD 11.8, range 25–73) |
| Gender: M                            | 28 (52%)                  |
| Mean level of education <sup>b</sup> | 4.1 (SD 2.0, range 1–8)   |
| Mean disease duration <sup>a</sup>   | 15.0 (SD 4.0, range 8–29) |
| Histological diagnosis               |                           |
| Astrocytoma                          | 39 (72%)                  |
| Oligodendroglioma                    | 10 (19%)                  |
| Oligoastrocytoma                     | 5 (9%)                    |
| Tumor location                       |                           |
| Left-sided                           | 32 (59%)                  |
| Right-sided                          | 20 (37%)                  |
| Midline                              | 2 (4%)                    |
| Neurosurgical intervention           |                           |
| Biopsy                               | 17 (31%)                  |
| Resection                            | 37 (69%)                  |
| Radiotherapy                         |                           |
| Yes                                  | 29 (54%)                  |
| No                                   | 25 (46%)                  |
| Antiepileptic drug use               |                           |
| Yes                                  | 26 (48%)                  |
| No                                   | 26 (48%)                  |
| Missing                              | 2 (4%)                    |
| Type of antiepileptic drug use       |                           |
| Monotherapy                          | 14 (54%)                  |
| Polytherapy                          | 12 (46%)                  |

Data are number (%) of patients, unless otherwise indicated

<sup>a</sup> Years

<sup>b</sup> Education was assessed by a Dutch scoring system ranging from unfinished primary education (level 1) to university education (level 8)

**Fatigue related to patient, tumor and treatment characteristics**

To test the relationship between age, disease duration, and fatigue, comparisons were made between severely fatigued (CIS  $\geq 35$ ,  $n = 21$ ) and non-severely fatigued (CIS  $< 35$ ,  $n = 33$ ) LGG patients. Severely fatigued patients were older than the non-severely fatigued patients (Mann–Whitney,  $P = 0.012$ ). We did not find any differences in disease duration for severely and non-severely fatigued patients (Mann–Whitney,  $P = 0.404$ ). Fatigue severity was not related to gender (Mann–Whitney,  $P = 0.640$ ), and no association could be established between histological diagnosis (astrocytoma and oligodendroglioma) and fatigue severity (Mann–Whitney,  $P = 0.766$ ). Due to the small number of patients with mixed glioma (oligoastrocytoma), data of these patients were excluded from the analyses. Furthermore, the association between tumor laterality and fatigue severity was investigated, while excluding midline

tumor locations because of the small sample size ( $n = 2$ ). Results of a Mann–Whitney test indicated that there was no association between tumor laterality and fatigue severity ( $P = 0.435$ ).

No association was found between type of neurosurgical intervention and fatigue severity (Mann–Whitney,  $P = 0.081$ ). Approximately half of the LGG patients ( $n = 29$ ) received radiotherapy. Again, no effect was found between former radiation treatment and fatigue severity (Mann–Whitney,  $P = 0.993$ ). However, patients treated with AEDs were more fatigued (Mann–Whitney,  $P = 0.004$ ), irrespective of the use of mono- or polytherapy (Mann–Whitney,  $P = 0.738$ ) (Table 2).

**Fatigue related problems: concentration, motivation and activity**

To test the association between fatigue and self-reported concentration, motivation and activity, comparisons were made between severely fatigued (CIS  $\geq 35$ ) and non-severely fatigued (CIS  $< 35$ ) LGG patients. Severely fatigued LGG patients reported reduced motivation, a lower

**Table 2** Tumor and treatment characteristics in relation to fatigue

| Variables                     | N  | Mean CIS-fatigue (SD) | $P$ -value <sup>a</sup> |
|-------------------------------|----|-----------------------|-------------------------|
| Histological diagnosis        |    |                       |                         |
| Astrocytoma                   | 39 | 27.2 (15.2)           | 0.766                   |
| Oligodendroglioma             | 10 | 29.1 (18.5)           |                         |
| Oligoastrocytoma <sup>b</sup> | 5  | 34.6 (12.3)           |                         |
| Tumor location                |    |                       |                         |
| Left-sided                    | 32 | 27.4 (15.5)           | 0.435                   |
| Right-sided                   | 20 | 30.7 (15.8)           |                         |
| Midline <sup>b</sup>          | 2  | 17.5 (13.4)           |                         |
| Neurosurgical intervention    |    |                       |                         |
| Biopsy                        | 17 | 33.8 (15.7)           | 0.081                   |
| Resection                     | 37 | 25.7 (15.0)           |                         |
| Radiotherapy                  |    |                       |                         |
| Yes                           | 29 | 28.3 (15.0)           | 0.993                   |
| No                            | 25 | 28.2 (16.4)           |                         |
| Antiepileptic drug use        |    |                       |                         |
| Yes                           | 26 | 34.5 (14.6)           | 0.004                   |
| No                            | 26 | 22.2 (13.9)           |                         |
| Missing                       | 2  |                       |                         |
| Type of antiepileptic drug    |    |                       |                         |
| Monotherapy                   | 14 | 33.6 (14.6)           | 0.738                   |
| Polytherapy                   | 12 | 35.7 (15.2)           |                         |

Abbreviation: CIS, Checklist Individual Strength

<sup>a</sup> Mann–Whitney tests were conducted to analyze the association between fatigue and tumor and treatment characteristics

<sup>b</sup> Variables which were excluded in testing

**Table 3** Fatigue-related problems: concentration, motivation and activity

| CIS-subcales                | Non-severely fatigued patients<br>( <i>n</i> = 33) | Severely fatigued patients<br>( <i>n</i> = 21) | <i>P</i> -value <sup>a</sup> |
|-----------------------------|--|--|------------------------------|
| Mean CIS-concentration (SD) | 14.5 (7.8)   | 26.1 (7.5)                                     | <0.001                       |
| Mean CIS-motivation (SD)    | 9.5 (4.8)  | 17.0 (6.8)                                     | <0.001                       |
| Mean CIS-activity (SD)      | 6.4 (3.9)  | 14.5 (5.8)                                     | <0.001                       |

Abbreviation: CIS, Checklist Individual Strength

<sup>a</sup> The Mann–Whitney test was conducted to test the differences between non-severely and severely fatigued LGG patients

level of activity, and more problems with concentration (Mann–Whitney,  $P < 0.001$ ) (Table 3).

## Discussion

In this study, we found that 39% of long-term survivors with a LGG experience severe fatigue. Few studies assessed fatigue in LGG patients [15–17]. In one quality of life study, fatigue is mentioned as a problem for the majority of glioma patients [15]. The current study confirms these results. However, the 39% prevalence rate of severe fatigue is the highest found among all cancer patients measured with the CIS. Only the percentage of severe fatigue in a sample of breast cancer survivors (38%) 2.5 years after curative treatment equals our findings [12]. This percentage declines to 24% after a follow-up period of 2 years. Other cross-sectional and longitudinal studies investigating the prevalence and course of fatigue show similar results, revealing that fatigue continues to decrease during the first years after curative treatment. For about a quarter of cancer survivors fatigue remains a problem [21]. Since the LGG patients in our study finished their treatment more than 8 years ago, the percentage of severe fatigue of nearly 40% is remarkably high. It is important to note that the LGG population differs from non-glioma cancer populations. In these non-glioma cancer studies, patients are considered to be disease-free. In contrast, LGG patients are considered to be never completely free of disease [5]. As a consequence, being confronted with a life-threatening illness can lead to feelings of depression and anxiety for the future, which both may be correlated with fatigue [6, 22–27]. Furthermore, LGG patients have specific cognitive problems [5], which presumably may also be related to fatigue.

Moreover, our results show that fatigue is related to other problems. Severely fatigued LGG patients have more problems with regard to self-reported concentration, and they experience reduced motivation and activity. These results are comparable to the extent of problems

experienced by patients with chronic fatigue syndrome. However, compared to severely fatigue disease-free cancer patients, the LGG patients in our study report more problems with concentration [6].

In this study no association was found between gender and fatigue severity, but fatigue complaints were more severe in older LGG patients. Also in testicular cancer patients [28] and in patients with hematological malignancies [29, 30] the older patients reported more fatigue, whereas in breast cancer patients the younger participants were more fatigued [31].

Furthermore, we found no relation between fatigue severity, tumor characteristics, and former tumor treatment. In one prospective quality of life study it was demonstrated that patients with a high-grade glioma in the right hemisphere were more fatigued than those with a left-sided tumor [32]. However, in most studies, no associations were found between tumor-related variables and fatigue intensity with regard to disease duration [23, 25, 26, 29, 33–35], type of cancer [27, 36], disease stage at diagnosis [23, 25–27, 33, 37], size of the original tumor [25, 26, 37], number of nodes involved [25] and tumor recurrence [33].

Literature data suggest that fatigue arises during the active treatment phase in nearly all cancer patients, but little is known about the etiology of persistent fatigue [7–11]. Some studies suggest that patients with more aggressive former treatments are more at risk for persistent fatigue [21, 31, 38, 39], but others do not find a strong association between initial cancer treatment and off-treatment fatigue [7–11]. In our study, no differences in fatigue severity were observed for patients who had a biopsy and for patients who underwent a resection. Furthermore, no differences were observed in patients with or without prior radiotherapy. However, fatigue was significantly more pronounced in patients that used AEDs.

This study has its limitations. Small sample size was the reason we had to exclude some variables from the analyses (i.e., oligoastrocytomas, tumors in midline locations). Furthermore, we have no data of current epileptic activity in this study. Therefore, we are not able to distinguish whether seizures or the use of AEDs contributed to the experience of fatigue. It would be very interesting to study a larger group of glioma patients with emphasis on fatigue, AED use, and epilepsy burden. Nonetheless, we conclude that fatigue is a major problem in LGG patients. The current study demonstrates that almost 40% of long-term survivors with a LGG experience severe fatigue. These findings are important because fatigue has a serious impact on quality of life [40]. Furthermore, a decreased level of quality of life in LGG patients is significantly related to shorter survival [41]. Assessment and treatment of fatigue in LGG patients need to be further investigated, potentially resulting in improvement of quality of life.

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