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Review Article

The neurocognitive evaluation in the butterfly glioma patient. A systematic review

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ABSTRACT

Butterfly glioma (BG) is a rare glioma subtype defined by contiguous extension of the tumor into both hemispheres through the corpus callosum. The impairment of higher cognitive functions in BG patients is a well-known condition encountered in the clinical practice. Given the peculiar anatomical features and clinical repercussions of butterfly gliomas, we conducted a systematic review of the literature to assess the role of structured neurocognitive evaluation in this patient population.

A systematic search of the literature (Embase, Pubmed, Cochrane databases) was conducted following PRISMA guidelines to identify English language studies reporting on clinical evaluation, treatment strategies and outcomes in BG patients. Screening and extraction were conducted in duplicate. Results were analyzed qualitatively.

493 unique references yielded 49 full-text papers for review; 19 studies were included in the final analysis reporting on 181 patients. A descriptive approach was used in the majority of cases to report on patients' cognitive status, where memory loss, confusion and non-specific cognitive impairment were the most frequently reported issues (67–69% of cases). Three studies conducted specific neurocognitive evaluations: one series reported on the post-operative incidence of abulia/akinesis and its resolution, two case reports applied a complete battery of neuro-psychological tests assessing attention, executive functions and memory skills.

This review highlights a gap between the wide availability of validated neuropsychological tests and their utilization in the management of BG patients, according to the literature. Additional data from multi-institutional studies are needed to evaluate the actual implementation of these tests in the daily clinical practice.

1. Introduction

Butterfly glioma (BG) is a rare tumor subtype affecting 3–14% of patients with high-grade gliomas. BG is defined by its spread to both the cerebral hemispheres through the fibers of the corpus callosum [1–6] (Fig. 1). BG is treated through either biopsy or maximal safe resection, followed by adjuvant systemic chemotherapy and radiotherapy to the resection bed with potential addition of alternating tumor-treating fields [7,8]. Given the tumor localization and spread, extent of resection is often limited relative to other gliomas, contributing to reduced overall survival in patients affected by butterfly tumors [1–3,6].

The typical clinical presentation of BG is attributed to its effect on crossing callosal fibers, leading to an impaired integration of the information coming mainly from the frontal and parietal lobes. This integration dysfunction often results in a subtle clinical picture which can be difficult to characterize and includes a range of neuropsychiatric deficits including personality changes, inappropriate emotional response, abulia and attention deficits. Higher cognitive functions become involved in both motor and sensory circuits, which may result in dyslexia, dysgraphia or dyscalculia, as well as dysfunction of social interactions and behavior [9,10–14]. Similar symptoms can be observed in other pathological conditions involving the corpus callosum such as ischemic injury and congenital defects, including agenesis or dysgenesis of the corpus callosum [11,13,14].

The proper clinical evaluation of these patients goes beyond the standard neurological exam and requires the administration of specific

Abbreviations: BG, butterfly glioma; CC, corpus callosum; AVLT, Auditory Verbal Learning Test; MMSE, Mini Mental State Examination; WAIS, Wechsler Adult Intelligence Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CST, cingulate-sparing technique; SMA, supplementary motor area; KPS, Karnofsky Performance Status; LGG, low grade glioma; GBM, Glioblastoma; fMRI, functional magnetic resonance imaging; WAIS-R, Wechsler Adult Intelligence Scale-Revised; RCPM, Raven's Coloured Progressive Matrices; BVRT, Benton Visual Retention Test; RBMT, Rivermead Behavioural Memory Test; ICCTF, International Cognition and Cancer Task Force; RANO, Response Assessment in Neuro-Oncology group; NIHTB-CB, National Institute of Health Cognitive Toolkit battery

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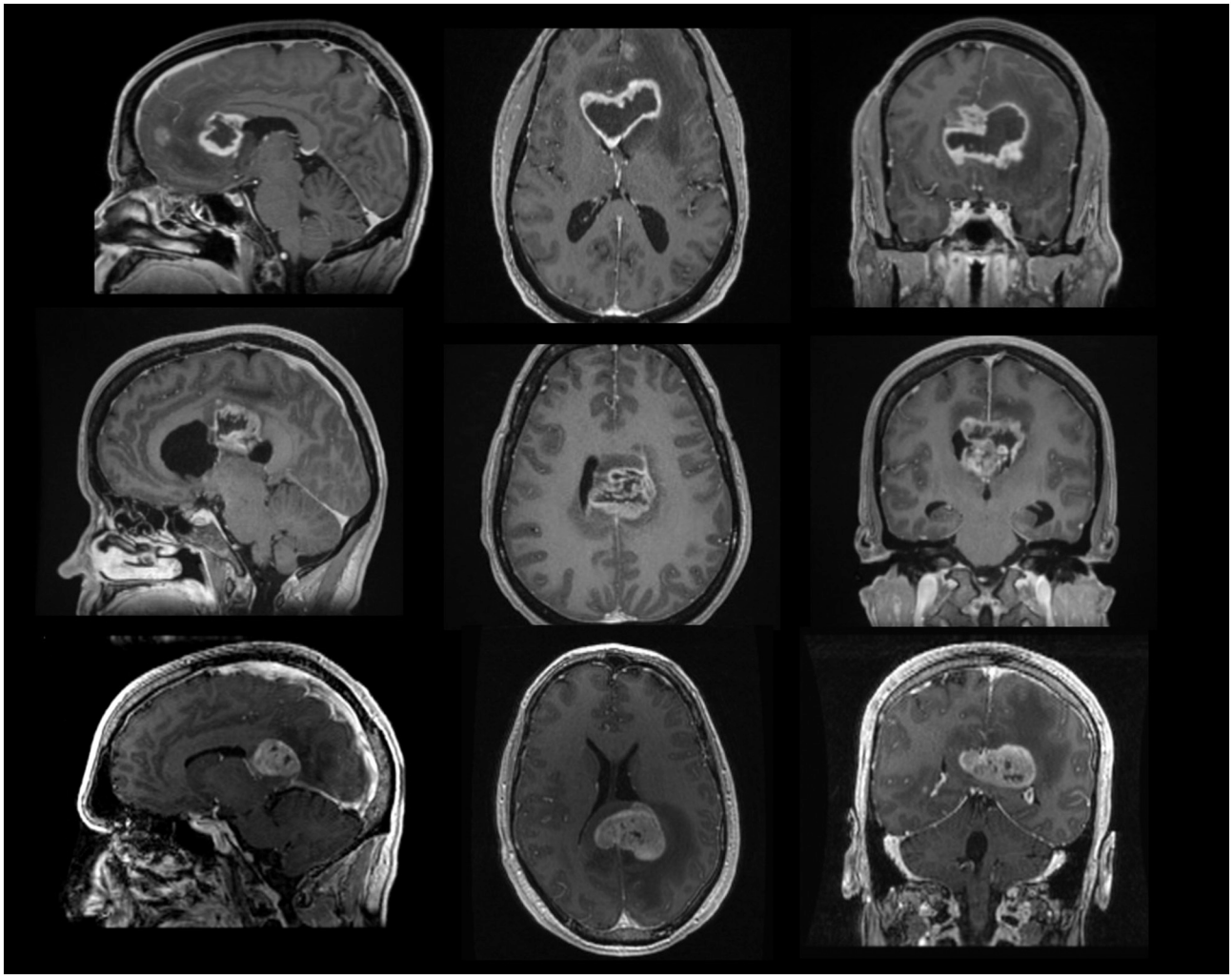

Fig. 1. Butterfly glioma on MRI. Magnetic resonance T1 contrasted images on sagittal, axial and coronal planes of three different butterfly gliomas. The top series shows a tumor located in the genu, the middle series a tumor located in the body and the bottom series a tumor located in the splenium of the corpus callosum.

neurocognitive tests. These tests were specifically developed to explore different cognitive domains: examples are the Auditory Verbal Learning Test (AVLT) which evaluates short-term memory, the Digit Span test which evaluates attention and executive functions, the Mini Mental State Examination (MMSE) and the Wechsler Adult Intelligence Scale (WAIS) are examples of tests exploring both fields [15–17].

Given the increasing evidence on the correlation between cognitive status and outcome in patients with glioma [5,18,19] and given the peculiar anatomical features and clinical repercussions of butterfly gliomas on patients, we conducted this review in order to understand how, in the current literature, the neurocognitive evaluation has been employed in this patient population.

2. Material and methods

2.1. Literature search

A systematic search of the literature was conducted according to PRISMA guidelines to identify English-language papers reporting on 1 ≥ patients affected by BG. PubMed, Embase and the Cochrane library were searched. Inclusion criteria were [1] histo-pathological diagnosis of high-grade glioma (III-IV WHO grade) [2], at least one lesion with contiguous involvement of both the corpus callosum and the cerebral hemispheres [3], studies providing information on patients' clinical condition and the related evaluation methods. Papers with mixed population of butterfly and non-butterfly glioma patients with no possibility of data breakdown between the two groups and papers presenting only low-grade glioma patients were excluded. The search terms used for the query in each database are listed below:

Pubmed

"glioblastoma"[TIAB] AND "butterfly"[TIAB] OR "glioblastoma"[TIAB] AND "bilateral"[TIAB] OR ("glioblastoma"[TIAB] AND "symmetric"[TIAB]) OR ("glioblastoma"[TIAB] AND "asymmetric"[TIAB]) OR ("glioblastoma"[TIAB] AND "corpus callosum"[TIAB]) OR ("glioblastoma"[TIAB] AND "bifrontal"[TIAB]) OR ("GBM"[TIAB] AND "butterfly"[TIAB]) OR ("GBM"[TIAB] AND "bilateral"[TIAB]) OR ("GBM"[TIAB] AND "symmetric"[TIAB]) OR ("GBM"[TIAB] AND "asymmetric"[TIAB]) OR ("GBM"[TIAB] AND "corpus callosum"[TIAB]) OR ("GBM"[TIAB] AND "bifrontal"[TIAB]) OR ("glioma"[TIAB] AND "butterfly"[TIAB]) OR ("glioma"[TIAB] AND "bilateral"[TIAB]) OR ("glioma"[TIAB] AND "symmetric"[TIAB]) OR ("glioma"[TIAB] AND "asymmetric"[TIAB]) OR ("glioma"[TIAB] AND "corpus callosum"[TIAB]) OR ("glioma"[TIAB] AND "bifrontal"[TIAB])

Articles: 750

Date: 09/20/2018

Embase

Glioblastoma AND butterfly OR glioblastoma AND bilateral OR glioblastoma AND symmetric OR glioblastoma AND asymmetric OR glioblastoma AND corpus callosum OR glioblastoma AND bifrontal OR GBM AND butterfly OR GBM AND bilateral OR GBM AND symmetric OR GBM AND asymmetric OR GBM AND corpus callosum OR GBM AND bifrontal OR glioma AND butterfly OR glioma AND bilateral OR glioma AND symmetric OR glioma AND asymmetric OR glioma AND corpus callosum OR glioma AND bifrontal

Articles: 1648

Date: 09/20/2018

Cochrane Library

Glioblastoma AND butterfly OR glioblastoma AND bilateral OR glioblastoma AND symmetric OR glioblastoma AND asymmetric OR glioblastoma AND corpus callosum OR glioblastoma AND bifrontal OR GBM AND butterfly OR GBM AND bilateral OR GBM AND symmetric OR GBM AND asymmetric OR GBM AND corpus callosum OR GBM AND bifrontal OR glioma AND butterfly OR glioma AND bilateral OR glioma AND symmetric OR glioma AND asymmetric OR glioma AND corpus callosum OR glioma AND bifrontal

Articles: 30

Date: 09/20/2018

Articles were first screened based on title and abstract, and if eligible, subsequently underwent full text review. The process of screening was conducted by two independent researchers (A.B, M.H.) following the structured PRISMA flowchart for systematic reviews and meta-analysis (Fig. 2). All discrepancies were resolved by discussion.

2.2. Data extraction and presentation

The following information were extracted from each of the eligible full text articles: study characteristics (authors, title, publication year, country of origin, journal impact factor), population and tumor characteristics (age, gender, histology, clinical presentation) type of cognitive test administered, characteristics of the intervention (biopsy, resection surgery) and outcomes (mortality, clinical and cognitive evaluation at multiple follow-ups). All data were stored into an excel sheet, data on age were expressed with mean or median and standard deviation or range according to the study; tumor volumetric data weren't available for all studies and weren't considered for the purpose of this work. The results of this review are presented in the form of a narrative summary.

3. Results

3.1. Studies characteristics

The literature search resulted in 493 unique papers. 49 papers underwent full-text screening, of which 19 papers were eligible for inclusion. Reasons for exclusion were: studies involving patients with high-grade gliomas however without butterfly features (12/30), mixed butterfly and non-butterfly patient series with no possibility of data breakdown between the two groups (9/30), patient series including only low-grade gliomas (3/30), patient series with unknown histology (3/30), data derived only from autopsy (2/30) and studies not including patients (1/30).

Characteristics of the 19 included studies are summarized in Table 1. The five major papers, reporting on more than two patients, were: three retrospective cohort studies comparing the outcomes between patients undergoing biopsy or resection [3,6,20], a retrospective case-control study analyzing the factors associated with outcomes between patients with BG undergoing biopsy or resection and patients with any other type of glioblastoma [2], and a cohort study evaluating the different incidence of abulia and akinetic mutism in patients undergoing two different resection techniques [10]. The remaining 14 papers were case reports on one or two patients [9,21,22–33].

The publication years ranged from 1990 to 2018 and the papers were geographically distributed as follows: 10 from Asia (Japan 3, India 3, Korea 2, Thailand 1, Singapore 1), 7 from North America (USA 5, Canada 2) and 2 from Europe (Turkey 1, Poland 1). Overall, these 19 articles reported on a total of 194 patients, with a M:F ratio of 1.2 (106:88) and an overall age range of 16 to 83 years. One study also included thirteen patients with grade II gliomas [10]; these patients were excluded producing a final population of 181 patients. The five major studies were respectively composed of 23 [3], 29 [20], 48 (out of 336 with generic GBM diagnosis) [2], 27 (out of 40) [10] and 39 high-grade glioma patients [6]. There were 16 pure GBM studies [2,3,20,22–24,26,27,29–33], one report of grade III gliomas [25], one study with mixed populations of low-grade and high-grade glioma patients [10], and one case reporting a 'mixed glioma with cysts'. [28] The anatomical distribution of the lesions according to the available information is reported in Table 2 (examples in Fig. 1).

3.2. Neurocognitive evaluation - symptoms and tests

There were a range of tools used for the evaluation of patients' neurocognitive status in the included studies. These tools could be categorized in the following two groups: plain symptomatologic description of the clinical picture and neuropsychological tests. A combination of one or more of these was generally applied.

3.3. Clinical picture

Symptoms including confusion, memory loss, language impairment, abulia and personality changes represented the most common symptoms reported with relation to patients' cognitive status.

Opoku-Darko et al. reported the presence of confusion/cognitive impairment in 20 patients (69%), altered consciousness in two (6.9%), and speech deficit in one patient (3.4%), at the time of diagnosis [20]. Chaichana et al. observed confusion/memory loss and language deficit in 67% and 20% of BG, respectively. The post-operative occurrence of language deficit was observed in 2 (0.5%) patients with no statistical difference between the biopsy and the resection group [2]. Dayano et al. reported confusion/memory loss in 13 (33.3%) patients and language deficit in 3 (7,7%) [6]. Dzuirzinsky et al. did not discuss patients' neurocognitive condition [3].

The most substantive evaluation of neurocognitive status was done by Burks et al., where particular attention was paid to the presence of abulia or akinetic mutism [10]. The authors excluded a priori patients with more than severe abulia, in order to assess its development in relation to the type of surgical treatment provided: the traditional surgical resection technique versus the proposed cingulate-sparing technique (CST). They also excluded patients with tumors involving the expected location of the supplementary motor area (SMA), given the potential for overlap with akinetic medial frontal lobe syndromes. Potential differences in each surgical approach were assessed to unveil factors associated with both temporary and persistent abulia/akinetic mutism. Pearson chi-squared test or Fisher exact test were used for categorical variables, whereas a paired-samples *t*-test was implemented for continuous variables. Patients were assessed for the presence of abulia or akinetic mutism immediately post-surgery and at 6 weeks. Eleven out of 25 patients (44%) treated with the standard technique developed abulia on the first post-operative day while only 1/15 (7%) patients undergone the CST experienced the same condition. The difference was statistically significant ($p = 0.01$, $\alpha = 0.05$). At the 6 weeks follow-up, patients experienced a resolution of symptoms of 36 and 100%, respectively, with no statistically significant difference between the two groups [10].

The case reports included in this review showed a wide spectrum of

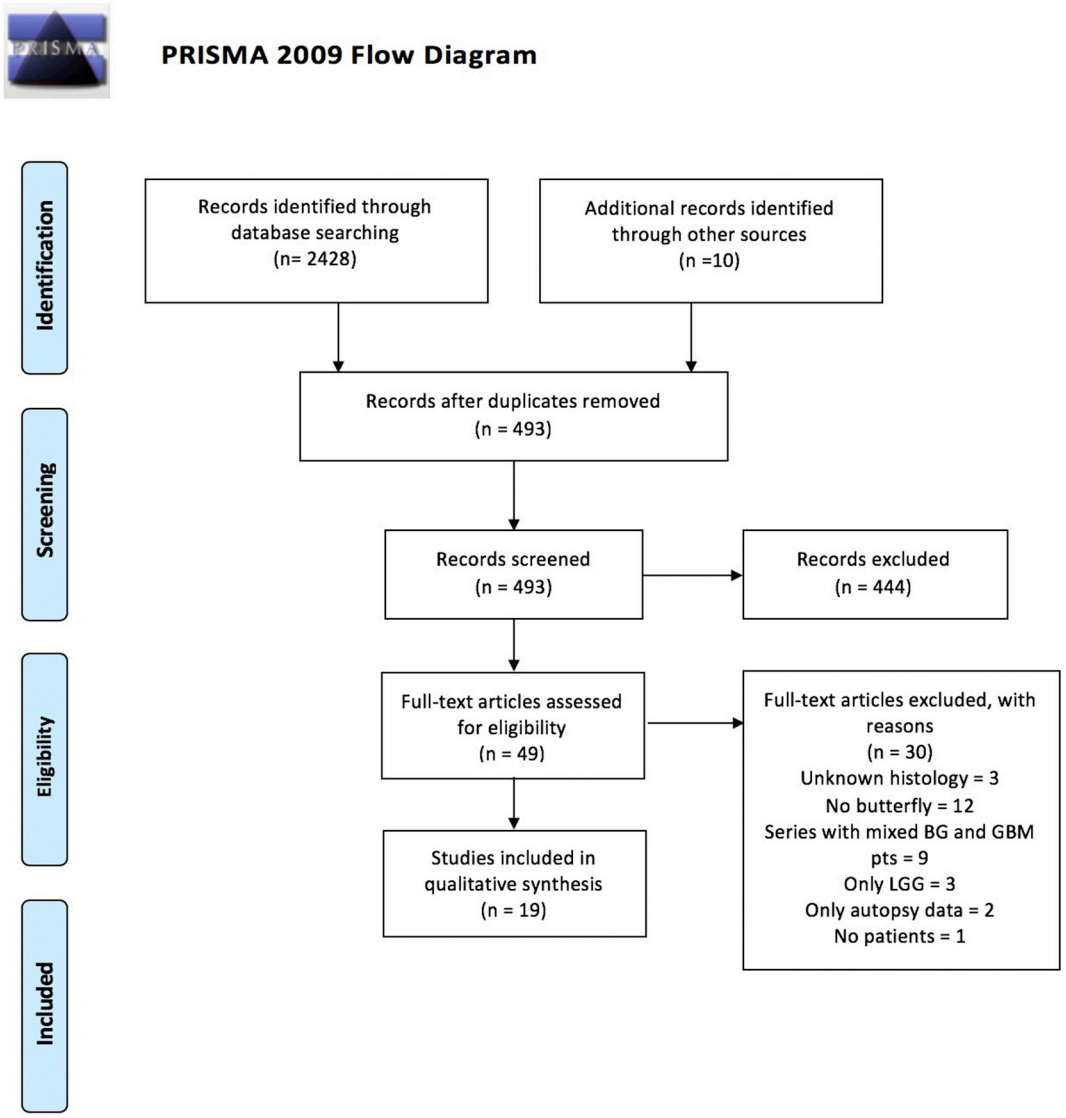

Fig. 2. PRISMA diagram. PRISMA flow diagram results. a. BG: butterfly glioblastoma, b. GBM: glioblastoma, c. LGG: low grade glioma.

clinical presentations: confusion/memory loss (43%), sleep disturbances (21%), language deficit (7%) and neuropsychiatric symptoms (29%), including hallucinations and personality changes. In the following three reports, the presence of specific neurocognitive symptoms was thoroughly described. One case involving the genu of the corpus callosum reported auditory, tactile and visual hallucinations, delusion of infestation, social withdrawal and speech paucity [28]. Two cases involving the splenium reported the presence of the following signs: avolition, anhedonia, psychomotor retardation in the first case [32], with acalculia, alexia, amnestic agraphia, constructional apraxia (left hand), ideomotor and ideational apraxia, right-left confusion, spatial disorientation, visuomotor ataxia, color anomia and tactile object anomia reported in the second case [29]. In this last case an additional left parietal lesion was also present which could be partially responsible for the clinical presentation [29].

A reference to the portion of the corpus callosum involved was reported for 112 patients. Of these, 63% were tumors involving the anterior part of the corpus callosum (rostrum, genu), followed by the splenium (28%) and the body itself (9%) (Table 2). It must be noted that in Burks et al., the involvement of the anterior part of the corpus callosum was an inclusion criterion of the study [10]. Given the low number of cases overall, it is difficult to describe separate syndromes specifically related to location of the lesion along the corpus callosum.

3.4. Neurocognitive tests

Some form of formal neuropsychological testing was conducted in 26% of patients. The most extensive use of specific tests for the evaluation of the neurocognitive functions was described in two of the 14 case reports. Osawa et al. reported the use of a battery of neurocognitive tests, administered both in the pre-operative and post-operative stages, which included: Mini Mental State Examination (MMSE), Kana-Hiroi test, Wechsler Adult Intelligence Scale-Revised (WAIS-R), Raven's Coloured Progressive Matrices (RCPM), Digit Span, Auditory Verbal Learning Test (AVLT), Benton Visual Retention Test (BVRT) and the Rivermead Behavioural Memory Test (RBMT) [29]. In Yapici-Eser et al., the patient was evaluated with Auditory Verbal Learning Test (AVLT), Digit Span, WAIS - visual memory and facial recognition test, with results suggestive of primary verbal and visual memory impairment [32].

In four of the five larger case series, no specific neurocognitive evaluation was reported [2,3,6,20]. In the Burks et al., all patients underwent preoperative and postoperative evaluation by physical and speech therapists, including neurocognitive testing, but the specific tests used were not further specified [10] (Table 3).

Table 1
Studies and patients' characteristics.

Author, year	Study design	Study objective	N of patients	Age	Sex
Kato T 1990 [23]	Case report	N/A	1	66	M
Murthy P 1997 [28]	Case report	N/A	1	50	F
Bauman GS 1998 [9]	Case report	N/A	2	42, 64	M
Osawa A 2006 [29]	Case report	N/A	1	64	F
Zakrzewska M 2007 [33]	Case report	N/A	1	16	M
Lee HO 2008 [26]	Case report	N/A	1	43	F
Agrawal A 2009 [21]	Case report	N/A	1	70	M
Witoonpanicha 2011 [30]	Case report	N/A	1	64	M
Chi 2012 [22]	Case report	N/A	1	62	F
Dziurzynski 2012 [3]	Cohort	Biopsy vs surgery outcomes	23	59 (median)	11 M|12 F
Lee HS 2012 [27]	Case report	N/A	1	53	F
Chaichana KL 2014 [2]	Case-control	Biopsy vs surgery outcomes/butterfly vs not butterfly outcomes	48 (total 336)	Biopsy: 54.2 ± 17.9 resection: 61.7 ± 12.8 (mean, SD)	25 M|23 F
Yamamoto 2016 [31]	Case report	N/A	1	77	M
Yapici-Eser H 2016 [32]	Case report	N/A	1	46	F
Krishnan 2017 [24]	Case report	N/A	1	54	M
Kumar 2017 [25]	Case report	N/A	1	35	F
Burks JD 2017 [10]	Cohort	Abulia following standard surgery or CST	27 (total 40)	Standard: 52, CST: 45 (median)	29 M|11 F
Opoku-Darko M 2018 [20]	Cohort	Biopsy vs surgery outcomes	29	Biopsy: 61.1 ± 2.9 resection: 56.9 ± 3.7 (mean, SD)	18 M|11 F
Dayani F 2018 [6]	Cohort	Biopsy vs surgery outcomes	39	Biopsy: 63.9 (24–80) resection: 51.2 (20–83) (mean, range)	23 M|16 F

CST: cingulate-sparing technique, SD: standard deviation, |: Separates patients based on gender when needed.

Table 2
Corpus callosum involvement.

Location	Number of patients
Genu	71
Body	10
Splenium	31
Total	**112**[a]

[a] The remaining 69 patients didn't have data on tumor location.

3.5. Post-operative follow-up

A description of the patient's neurocognitive evolution after treatment was reported in three case reports. Murthy et al. described a progressive deterioration of the memory skills and development of apathy at 4 and 8 months despite a resolution of the initial hallucinations [28]. Osawa et al. reported an overall progression of the symptoms at 2 months along with the eventual development of complete aphasia [29]. Chi et al. described a progressive worsening of the short-term memory skills at 6 and 12 months along with appearance of fatigue, disorientation and nausea [22].

Of the remaining case reports: 6/11 only referred to patients' survival which lasted less than three months from initial diagnosis, in 2/11 cases patients were lost to follow up after discharge. In 3/11 case reports, patients were still alive at 15, 18 and 70 months after surgery, respectively [9,21,23–27,30–33]. The development of post-operative abulia and its subsequent eventual resolution at 6 weeks was reported by Burks et al., as described above.

The analysis of the overall survival and the potentially related

Table 3
Data on neurocognitive evaluation for each study.

Neurocognitive evaluation (Yes = 1, No = 0)			
Study, year	Neurocog symptoms reported	Neurocog test administration	Type of neurocog test
Kato T 1990 [23]	1	0	N/A
Murthy P 1997 [28]	1	0	N/A
Bauman GS 1998 [9]	1	0	N/A
Osawa A 2006 [29]	1	1	MMSE, Kana-Hiroi test, WAIS-R, RCPM, Digit Span, AVLT, BVRT, RBMT
Zakrzewska M 2007 [33]	0	0	N/A
Lee HO 2008 [26]	0	0	N/A
Agrawal A 2009 [21]	0	0	N/A
Witoonpanicha 2011 [30]	1	0	N/A
Chi 2012 [22]	0	0	N/A
Dziurzynski 2012 [3]	0	0	N/A
Lee HS 2012 [27]	0	0	N/A
Chaichana KL 2014 [2]	0	0	N/A
Yamamoto 2016 [31]	1	0	N/A
Yapici-Eser H 2016 [32]	1	1	Digit Span, AVLT, WAIS visual memory
Krishnan 2017 [24]	1	0	N/A
Kumar 2017 [25]	1	0	N/A
Burks JD 2017 [10]	1	1	Not specified
Opoku-Darko M 2018 [20]	0	0	N/A
Dayani F 2018 [6]	1	0	N/A
Total	11	3	

KPS: Karnowsky Performance Status, MMSE: Mini-Mental State Examination, WAIS-R: Wechsler Adult Intelligence Scale-Revised, AVLT: Auditory Verbal Learning Test, BVRT: Benton Visual Retention Test, RBMT: Rivermead Behavioural Memory Test.

factors (extent of resection, adjuvant therapies, KPS, age, etc.) were the main elements evaluated by Opoku-Darko et al., Chaichana et al., Dziurzinsky et al. and Dayani et al. with no reference to the evolution of the clinical and neurocognitive situation of the patients [2,3,6,20]. In Opoku-Darko et al. one patient was reported to have abulia, along with expressive dysphasia and hemiparesis after surgery due to a thromboembolic complication [20], and Dayani et al. reported on the immediate post-operative deficits and their resolution in four patients [6].

4. Discussion

The standard of care in the treatment of butterfly glioma is either biopsy or maximal safe surgical resection followed by adjuvant radiochemotherapy with potential addition of alternating tumor-treating fields, in line with the standard management of high grade glioma [7,8,10,12]. The unique anatomical relationship of BG with critical neighboring circuits, limits the boundaries of a safe resection, resulting in a higher likelihood of significant residual tumor and subsequently impacting survival. In this setting, the association between the anatomical structures involved and the clinical picture, comprehensive of the patient's cognitive status, is critical to guide surgical decisions.

The proper evaluation of the cognitive status in glioma patients in general has gained more attention over the last 15 years leading to an increased appreciation of the role of the cognitive status in the clinical management and its correlation with outcomes. In 2008 Gorlia et al. were the first to observe in a large randomized trial the independent association of both pathological (O^6-methylguanine-DNA methyltransferase promoter methylation status) and clinical factors (MMSE score in their case) to survival [18]. Similarly, a single institution study on 91 patients published by Johnson et al. in 2012 provided preliminary evidence that executive and attention domains were particularly important for survival in newly diagnosed glioblastoma patients [34]. Nonetheless, in these as well as in other studies the evaluation of the cognitive status in patients with butterfly glioma, as a specific subpopulation, has never been addressed. The impairment of higher cognitive functions at various levels is typical in BG patients and a well-known situation encountered in the clinical practice.

The main neurocognitive domains affected by these tumors include the ones related to attention and language, being abulia and akinetic mutism the two main manifestations of tumor progression as well as post-operative morbidity [6,10].

In this review we explored the role of the structured neurocognitive evaluation in BG patients. We found that, in most studies, a general report of symptoms was the full extent of neurocognitive assessment in patients with BG. The presence or post-operative development of abulia was specifically reported in only one study [10]; other symptoms including hallucinations, loss of memory or confusion, language impairment, and change in personality were reported in 10 out of the 14 case reports and in two series [2,9,23–25,28,30–32].

KPS proved to be the most commonly used measure of the overall functional status, either as a part of inclusion criteria or in data analysis [2,3,10,20]. It must be noted nonetheless that the focus of KPS is the level of activity, regardless the responsible etiology: a low KPS can be equally due to a strength deficit as well as to an impairment in the cognitive status. The use of this score in the analysis of neurocognitive outcome is not adequate, therefore it wasn't considered here [35].

A formal neuropsychologic testing, either using a subset of tests or a full battery, was performed in only three of the included studies [10,29,32]. In the majority of cases, the cognitive status of the patients can only be deduced by the reported symptoms [2,9,20,23–25,28–32] (Table 3).

It's interesting to note that in the face of a clinical condition most frequently characterized by cognitive impairment, memory issues and confusion, we couldn't appreciate a consistent strong cognitive evaluation performed through validated instruments, as it is reported for other types of glioma instead [5,36,38].

The post-operative follow-up of patients' cognitive status was scarcely investigated as well, and specifically performed only by Burks et al. The authors demonstrated that the use of a cingulate sparing surgical technique (CST) was potentially protective from post-operative abulia compared to a traditional resection technique for BG lesions localizing to the genu or the corpus callosum. They highlighted the importance of identifying the Default Mode Network (DMN), as part of a more extensive circuit critical in the relationship between attention related tasks and rest phase, through the use of subcortical mapping [10,37].

Evaluation of cognitive recovery after surgery for glioma in eloquent areas was addressed in a recent review by Satoer et al. who found it difficult to draw definitive conclusions since not all the cognitive domains were assessed in all the studies, also advocating the need for studies with longer post-operative follow-up [38].

The initial subtle clinical presentation of BG patients is in great contrast with the aggressiveness of the pathology itself. The effort to minimize the incidence of post-operative neurocognitive deficits should rely on a precise and in depth pre-operative neurocognitive evaluation. In this context, a thorough neurocognitive examination may serve the same role as fMRI does in the pre-surgical planning for tumors located in eloquent areas and may provide valuable information to be considered in the surgical management of these patients [2,3]. Also, the evidence for a significant difference between some types of the presenting symptoms between BG and other glioma patients observed in Chaichana et al. points towards the recognition of the unique clinical characteristics of BG compared to the other GBM types (confusion/memory loss more common in the butterfly group p 0.0001, seizures and language deficit more common in the non-butterfly group with p 0.0005 and 0.05 respectively) [2]. This knowledge can and should inform discussion of expected peri-operative cognitive changes with the patients and their family, as well as the types of rehab services that may be required. Moreover, in light of the recent works pointing towards the advantages of a more aggressive surgical approach for BG patients [6,20], being able to accurately characterize the functionalities of the cerebral areas involved becomes of great importance.

In the last twenty years the interest in this pathology has increased, specifically in term of analysis of the possible treatments and outcomes, mainly overall survival [2,10,20,39,40]. Despite this, the results of this review suggest that the interest in the characterization of the cognitive status and the inclusion of this information in the clinical management of these patients has not followed the same path.

A thorough clinical evaluation of these patients should include specific tests for the evaluation of the different cognitive domains. The MMSE could be administered as first line but, given its low sensitivity, it's not able to differentiate between the different domains [41]. A thorough evaluation will likely require the involvement of a trained neuropsychologist. Examples of comprehensive and reasonable test batteries that could be implemented in the evaluation of patients with butterfly glioma are the one suggested by the International Cognition and Cancer Task Force (ICCTF) and the Response Assessment in Neuro-Oncology group (RANO) for the evaluation of cognition in patients with cancer, or the National Institute of Health Cognitive Toolkit battery (NIHTB-CB) [36,42]. The first one includes the Hopkins Verbal Learning Test-Revised (HVLT-R) for learning and memory assessment, the Trail Making Test for both processing speed and executive function assessment, and the COWA (as portion of the Multilingual Aphasia Examination) for executive function as well, while the NIHTB-CB investigates attention, visual and working memory and execution through seven different tasks.

It must also be considered that the involvement of different portions of the corpus callosum may lead to the impairment of different domains and so the choice of the most pertinent tests should be made accordingly.

This review is limited primarily by sample size and the retrospective nature of most included studies. The small numerosity and the nature of the studies (mostly case reports) didn't allow for additional, potentially useful quantitative analysis (e.g. subgroup analysis). Additionally, one

of the five retrospective series included in this review considered a mixed population of low-grade and high-grade gliomas, where the butterfly glioma generally refers to high-grade gliomas [3,20]. Despite these limitations, this review highlights the existing gap in the literature in the characterization of the unique clinical features of patients with butterfly glioma and the potential utility for neurocognitive testing in these patients. Classic BG is a relative low incidence presentation in high-grade glioma patients, and while we were unable to assess it in this study, neurocognitive assessment may very well be relevant also for patients with callosal involvement without complete contralateral spread.

Even if unusual for a review, case reports were included, in accordance with the particular nature of the question addressed. In our intention to understand how much the evaluation of the neurocognitive status of these patients weighted on the overall clinical picture drawn by clinicians, case reports have the advantage to focus on a single or a couple of cases allowing a better clinical characterization and description. As a matter of fact, the most in-depth neuropsychological description was found in two case reports [29,32].

The current literature on cognitive evaluation in butterfly glioma patients is scarce and inconsistent. This review supports the opportunity for physicians taking care of BG patients, neurosurgeons, neurologists and oncologists in particular, to use the available and validated neurocognitive evaluation tools although additional data from institutional and multi-institutional studies are required to understand the real level of implementation of these tests in the routine clinical practice. The application of a structured neurocognitive evaluation into patients' overall clinical management, along with the continuous advancement in surgical techniques, technologies and imaging, has the potential of not only increasing our understanding of the functioning of brain networks, but also to aid in extending our definition of what is considered maximal safe resection in BG, possibly leading to a positive significant impact on the quality of life and even survival of these patients.

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