SYSTEMATIC REVIEW

Resolving mystery behind autonomous retrogression of low-grade gliomas: A systematic review

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Abstract

Objective: To review evidence-based data on spontaneous retrogression of low-grade gliomas with respect to interval till regression, type of glioma and patient outcome.

Method: The systematic review comprised medical literature in English language published from January 1997 to January 2017 on Scopus, PubMed and Google Scholar databases to establish consensus about the possible mechanism of spontaneous regression, the role of therapeutic intervention and failure of management strategies in low-grade gliomas. Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed during the review.

Results: Of the 176 articles identified, 73(41.5%) were shortlisted for detailed assessment. Of them, 10(13.7%) were included; 5(50%) case reports and 5(50%) case series. There were 23 cases of spontaneous regression; 15(65.2%) males and 8(34.7%) females. The interval of regression varied from 3 months to 15.5 years, and the most commonly presenting low-grade glioma type was optic pathway glioma 11(47.4%).

Conclusion: The phenomenon of regression was most evident in optic pathway glioma. Literature suggested that low-grade gliomas should undergo serial imaging before implying any therapeutic intervention. However, the evidence-based proof, large-scale experimental studies and ethical considerations are still required to standardise this strategy.

Keywords: Pilocytic astrocytomas, Desmoplastic infantile ganglioglioma, DIG, Desmoplastic infantile astrocytomas, DIA, Diffuse astrocytoma, Spontaneous regression.

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Introduction

Glioma is the tumour of glial cells of the brain and spinal cord. Glial cells serve to maintain homeostasis, form myelin and provide support to neurons in the central nervous systems (CNS) and the peripheral nervous system (PNS). Glioma accounts for most of the malignant neoplasms of CNS.

Low-grade gliomas (LGG) represent a diverse group of primary brain tumours that often arise in young and otherwise healthy patients and generally have better prognosis than high-grade gliomas (HGGs). The World Health Organisation (WHO) updated the classification of CNS tumours in 2016. The discussed LGGs included were Astrocytic tumours (e.g. pilocytic [WHO Grade I], pleomorphic xanthoastrocytomas [WHO Grade II], diffuse astrocytoma [WHO Grade II]), oligodendrogliomas [WHO Grade II], oligo-astrocytomas [WHO Grade I], ependymal tumours (e.g. subependymoma [WHO Grade I], myxopapillary ependymoma [WHO Grade I], ependymoma [WHO Grade II]) and neural/glial tumours (e.g. dysembryoplastic neuroepithelial tumours [WHO Grade I], gangliocytoma [WHO Grade I], ganglioglioma [WHO Grade I], desmoplastic infantile ganglioglioma/ astrocytoma [WHO Grade I], and papillary glioneural tumours [WHO Grade I]).[1]

In addition to this histological classification, recent studies have shown keen interest in molecular analysis of LGGs. Predictability of prognosis is highly dependent upon an accurate diagnosis of gliomas. For which some recently identified molecular markers like 1p/19q codeletion, O6-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) methylation status and isocitrate dehydrogenase (IDH-1 & IDH-2) mutation has somewhat contributed to predicting the natural course of the disease.[2] Other recently studied molecular markers include B-Raf proto-oncogene serine/threonine kinase (BRAF) fusion events and MYBL-1 alterations.[3] According to the updated WHO classification, the nomenclature of diffuse astrocytoma is based upon both histological as well as molecular analysis of the tumour. Therefore, it is important to take molecular profile of a tumour into account.[1]

The incidence of desmoplastic infantile ganglioglioma (DIG) is greatest in children <18 months of age with male predominance. It comprises about 0.5-1.0% of all CNS-related tumours.[4] Pilocytic astrocytomas (PIA) (WHO Grade I) usually manifest in first and second decades of life (age 5-14 years). According to the report of Central Brain Tumor Registry of the United States (CBTRUS) in 2018, its incidence

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in United States was 2.9 per million people.[5] The diffuse LGGs, which include diffuse astrocytoma (WHO Grade II) and oligodendroglioma (WHO Grade II) usually present between second and fourth decades of life. About 40% of all the CNS tumours are gliomas in which astrocytomas (75%) constitute the majority. Other subgroups, such as oligodendroglioma, DIG, ependymomas and other subtypes, account for rest of the 25%. Most frequent presenting features are seizures, mental disturbance, headache with nausea and focal neurological deficit.[6]

Management of such tumours can be problematic because of indolent nature and unpredictable behaviour. The most appropriate approach depends upon the location of tumour, its likely nature and patient's individual characteristics.[6] There are a number of case reports showing spontaneous regression of LGGs which is the primary focus of this systematic review.

However, theories about the mechanism behind the phenomenon of regression still require an immense volume of research and evidence-based explanations. Augmented apoptosis, immune system, hormonal alterations, oncogenic DNA suppression or decreased vasculature to the tumour are some popular proposed mechanisms in medical literature.[7] The term 'spontaneous regression' can be explained as partial or total dematerialisation of tumour either in the absence of any medical intervention or in the presence of therapy which is relatively inadequate to influence the neoplastic nature of the tumour. Regression is not confined to the CNS tumours alone, as tumours of various sites in the body, like renal cell carcinoma, testicular germ cell tumours, melanoma or basal cell carcinoma, demonstrate similar phenomenon. Spontaneous regression is relatively more often in primary brain tumours.[8]

Spontaneous retrogression of LGGs is a peculiar and poorly understood phenomenon. Not much extensive research, like clinical trials and cohorts, has been conducted on this topic which hinders an in-depth understanding of the topic. The current systematic review of cases that reported autonomous retrogression of LGGs was planned to fill the gap in literature. To the best of our knowledge, no systematic review has ever been conducted on this topic.

Methods

The systematic review and meta-analysis comprised medical literature in English language published from January 1997 to January 2017 to establish consensus about the possible mechanism of spontaneous regression, the role of therapeutic intervention and failure of management strategies in low-grade gliomas. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[9] were followed during the review.

The study types included were case reports and case series published in the English language reporting outcome in human subjects only, those studies in which tumours resolved on their own or by an extent of interventions, like surgical, radiotherapy or chemotherapy, which does not influence the tumourogenicity of gliomas[10] and studies reporting spontaneous regression restricted to LGGs.

Those excluded were cohorts, both prospective and retrospective, letter to editor, commentaries, cross-sectional surveys and documentaries. However, these were used to bridge and link the outcomes of our study with past medical research in the 'Discussion' section. Also excluded were studies in non-English language literature; studies which assessed the outcome in pathologies other than LGGs; interventions other than partial resection or adjuvant short-term <6 months radiotherapy and chemotherapy; studies with multiple/aggressive surgical intervention; studies without definitive numbers or values; experimental animal trials; and studies with figurative or graphics-based result presentation without any detailed case reporting. Two authors independently retrieved the data in accordance with the mentioned eligibility criteria. Any disagreement was resolved by collaborative discussion.

Literature Search Strategy

A detailed literature search was conducted by two independent authors using the key medical subject heading (MeSH) and non-MeSH terms, like "low grade gliomas (LGG)", "spontaneous regression", "pilocytic astrocytomas (PIA)", "desmoplastic infantile ganglioglioma (DIG)", "desmoplastic infantile astrocytomas (DIA)", "optic glioma", "oligodendroglioma" and "ganglioglioma" to search Scopus, PubMed and Google Scholar databases. Relevant terms or synonyms other than key words were utilised to conduct comprehensive search in accordance with the pre-specified eligibility criteria. All the searched articles were exported and cited through Endnote. In case of unavailability of full text or incomplete data, the corresponding author was contacted.

Data Extraction Strategy

Data was collected and compiled on a pre-defined evidence table on Microsoft (MS) Word. Titles and abstracts in the initial search were screened for potential inclusion or exclusion of the study.

Data Collection

The collected data included author, year of publication, patient's age and gender, study design, type of tumours, interval till regression and patient outcome. Any disagreement was resolved with collaborative consensus

among the reviewers.

Quality Assessment and Risk of Bias

Since the meta-analysis in this systematic review was not conducted on the outcomes, the assessment of the quality of the extracted data and the risk of bias were done at the study level and the body of evidence was not presented. Pierson approach[11] was used to assess validity of all the case reports/series. It is a 5-component scheme which scores the quality and validity of case reports/series. Scores are assigned to 5-component domains which includes documentation, uniqueness, educational value, objectivity and interpretation. Each domain can be scored between 2 points (maximum score) to 0 points (minimum score) according to the defined criteria for case presentation and validity of data. Interpretation of ratings is based upon total score for an individual study. Study with scores 9-10 has high likelihood of valid data and appropriate reporting. Caution should be exercised about the clinical value of studies if the scores are 6-8. Scores of ≤5 validate the insufficiency of study to pertain substantial clinical evidence.[11] All the selected cases reports/series were evaluated accordingly.

Data Analysis and Primary Outcomes

The data was entered on a pre-specified table. Age at the time of presentation and interval of regression was assessed in terms of mean±standard deviation (SD). Frequencies and percentages of gender and the type of tumour were also assessed. Total number of adjuvant therapies, like surgical debulking, radiotherapy and chemotherapy, was also noted. The primary target was the assessment in terms of patient outcome.

Results

Of the 176 articles identified, 73(41.5%) were shortlisted for detailed assessment. Of them, 10(13.7%) were included; 5(50%) case reports and 5(50%) case series (Figure). There were 23 cases of spontaneous regression. Of them, 15(65.2%) were males and 8(34.7%) were females. Age at presentation ranged from 2 days to 19 years, while the interval of regression varied from 3 months to 15.5 years. In a few cases, regression was assessed after performing surgical intervention [12,13Case-5,14-16], adjuvant radiotherapy or chemotherapy [13Case 10] or both [17,15Case-1] (Table 1).

The most commonly presenting LGG type was optic pathway glioma 11(47.4%), followed by PIA and DIG 14(17.4%) each (Table 2).

As for patient outcome, 13(56.52%) patients were healthy and asymptomatic on follow-up, whereas 10(43.47%) showed visual problems which included deficit in visual acuity (VA), visual field defects, depression of vision, defects in visual memory, optic disc atrophy and, in severe cases, complete blindness on the affected side. Out of 10 adverse patient outcomes, 4(40%) cases [17,13Case5,13 Case 10,14] had adjuvant therapies surgery and chemo, while 6(60%) were left to regress spontaneously with appropriate imaging on follow-ups. Out of 23 cases, 1(%) reported the sole use of chemotherapy, 6(%) discussed the regression after performing exclusive surgical intervention whereas 2(%) cases reported the use of adjuvant therapy (Table 3).

Pierson's 5-component scheme was applied on data to evaluate the validity and educational value of case reports (Table 4).

Spontaneous Regression Assessment Methods

Assessment of regression of glial tumour is somewhat troublesome, time-consuming, controversial and lacks accuracy due to unavailability of clinical guidelines. Commonly utilised imaging tests and clinical methods seen in studies on spontaneous regression were neurological assessment on presentation and follow-up; imaging-based studies, like non-enhanced/enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI); immunohistochemical (IHC) studies to assess apoptosis-related molecules like Bcl 2, Fas, Bax and Fas ligand; and histopathology of the tumour sample. All cases followed the standard method of care, considering patient's health as the priority outcome.

Exclusion of Publication Bias

To assess publication bias in this systematic review, search of grey literature, like dissertations, conference proceedings, theses and technical reports, was conducted by two reviewers independently, and any disagreement was resolved with collaborative discussion.

Overview of Individual Cases

Spontaneous regression is a peculiar phenomenon. No study has confirmed the exact mechanism behind it. Few commonly believed mechanisms include apoptosis, immune system, oncogenic DNA senescence, hormonal alterations and decreased vasculature of the tumour. The focus of our review was to assess the possible mechanism, recurrence rate and role of any therapeutic intervention which influenced the outcome of regression.

Samadian et al. reported the regression of pilocytic astrocytoma which was complicated with Steven Johnson Syndrome (SJS) which results in the induction of multiple immune mechanisms. It was suggested that manipulation in the immune system can alter the neoplastic course of glioma either due to perforin-mediated necrosis or tumour cell apoptosis.[17] DIG is a subgroup of glioma with

Table-1: Review of cases reported on spontaneous regression in the past two decades.

Author/ Year of publication	Patient(age/sex)	Type of Tumour	Interval Till Regression	Patient's Outcome
Samadian et al in 2016[17]	7 years/ Male	Pilocytic Astrocytoma	15 Months	Left eye blindness after a month of partial resection
Takeshima et al in 2003[12]	9 month/ Female	Desmoplastic Infantile Ganglioglioma(DIG)	10 years (120 months)	Asymptomatic
Takeshima et al in 2003[12]	6 months/ Male	Desmoplastic Infantile Ganglioglioma(DIG)	7 months	Asymptomatic
Parsa et al in 2001[13] CASE 1	5 years/ Male	Optic pathway glioma	12 years (144 months)	Decreased visual acuity with optic disc atrophy in right eye
Parsa et al in 2001[13] CASE 2	4 Years/ Female	Pilocytic astrocytoma,type 1	12 years (144 months)	At the age of 17, no growth on MRI but depressed inferior field in right eye was found.
Parsa et al in 2001[13] CASE3	3 month/ Female	Optic chiasma glioma	3 years, 7 months (43 months)	MRI at age of 4 years showed small residual tumor. Girl was visually handicapped, but was otherwise healthy.
Parsa et al in 2001[13] CASE 4	13 years, 6 months/ male	Optic chiasma glioma	1 year (12 months)	At 16 years of age, complete resolution occurred. Patient was asymptomatic.
Parsa et al in 2001[13] CASE 5	13 years/ male	Optic chiasma glioma	1 year (12 months)	At age 20 years, tumour was regressed with complete inferonasal field defect.
Parsa et al in 2001[13] CASE 6	14 years/ female	Optic chiasma glioma	3 months	After a year and 8 months, tumour resolved but recession of left eye as compared to right eye was found.
Parsa et al in 2001[13] CASE 7	11 years/female	Optic chiasma glioma with family history of NF-1	5 years, 10 months (70 months)	At age of 18 years, tumour regressed but right visual field of patient was completely depressed.
Parsa et al in 2001[13] CASE 8	4½ months/male	Optic pathway glioma	6 months	At the age of 12 years, depressed left eye visual field was observed on perimetry.
Parsa et al in 2001[13] CASE 9	3 months/ male	Optic pathway glioma	3 years ,1 month (37 months)	At the age of 4 years, patient was completely healthy with no visual defects.
Parsa et al in 2001[13] CASE 10	6 months/ male	Optic pathway glioma	15 years, 6 months (186 months)	At age of 16 years, tumour showed marked regression but right eye was presented with temporal heminopia with left eye being defective in superior visual field.
Giorgio Perilongo et al in 1999[19] Case 1	41 month/ Male	Optic pathway glioma with NF-1	10 months	A year later, lesion was stable on MRI. Patient was asymptomatic.
Giorgio Perilongo et al in 1999[19] Case 2	31 month/ Female	Optic chiasma glioma with NF-1	6 month	A year later, no change on MRI. Visual acuity was decreased.
Schmandt S.M et al in 1999[20]	3 years 7 months/ Male	Pilocytic astrocytoma with NF-1	4 years, 6 months (54 months)	Asymptomatic
Massimo Gallucci et al in 2000[21]	19 years/ Male	Pilocytic astrocytoma	5 years, 7 months (67 months)	Asymptomatic
Paul Steinbok et al in 2006[14]	2 years old/ Male	Cerebellar astrocytoma	11 years (132 months)	Asymptomatic
Tamburrini et al in 2003[15] Case 1	2 months/ Female	Desmoplastic infantile ganglioglioma(DIG)	1 year, 10 months (22 months)	Asymptomatic

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Table-1: Review of cases reported on spontaneous regression in the past two decades. *(Continued from previous page)*

Author/ Year of publication	Patient(age/sex)	Type of Tumour	Interval Till Regression	Patient's Outcome
Tamburrini et al in 2003[15] Case 2	9 months/ Male	Desmoplastic infantile ganglioglioma(DIG)	9 months	At the age of 12 years, neuropsychological test showed mild deficit in complex visual memory.
Tsuji K et al in 2008[16]	3 months/ Male	Desmoplastic infantile astrocytoma(DIA)	12 months	Asymptomatic
Thompson Jr et al in 2005[22] Case 1	2 days old/ Male	Brainstem glioma	4 years (48 months)	Asymptomatic
Thompson Jr et al in 2005[22] Case 2	1 week old/ Female	Brainstem glioma	10 years (120 months)	Mild facial palsy. Otherwise, asymptomatic

Table-2: Frequencies and percentages of each tumour.

Type of Tumour	n (%)
Optic Pathway Glioma	11 (47.8)
Pilocytic Astrocytoma	4 (17.4)
Desmoplastic Infantile Ganglioglioma	4 (17.4)
Brainstem Glioma	2 (8.7)
Cerebellar Astrocytoma	1 (4.34)
Desmoplastic Infantile Astrocytoma	1 (4.34)

Table-3: Details of resection and adjuvant therapies given in each case.

Degree of Removal	Adjuvant	References
Partial resection of the tumour	Phenytoin	17
Partial resection of the tumour	None	12Case 1
Subtotal resection of the tumour	None	12Case 2
None	None	13Case 1
None	None	13Case 2
None	None	13Case3
None	None	13Case 4
De-bulking of right side of chiasma	None	13Case5
None	None	13Case6
None	None	13Case 7
None	None	13Case 8
None	None	13Case 9
None	Chemotherapy of vincristine and actinomycin D for 18 months.	13Case 10
None	None	19case 1
None	None	19case 2
None	None	20
None	None	21
Subtotal resection was done	None	14
Partial removal at 2 months and complete removal at 16 months.	6 chemotherapy cycles	15case 1
subtotal resection of the tumor	None	15case 2
Partial resection of the tumor	None	16
None	None	22case 1
None	None	22case 2

significant propensity to regress on its own. Two cases reported by Takeshima H. et al. suggest that such reversion of tumours can possibly be due to continued destruction of tumour cells by apoptosis. IHC analysis of both tumours showed increased expression of apoptosis-promoting molecules like Bax, Fas and Fas ligand, whereas declined production of Bcl 2 molecule, which is anti-apoptotic in nature, was noted. This too suggests that induction of apoptosis can be the possible cause of spontaneous regression in this case.[12] Parsa et al. reported the regression of fliomas in 13 cases out of which we reported the first 10. Among those cases, one patient underwent de-bulking of the tumour while another case received vincristine as a chemotherapeutic. Other than that, no surgical or therapeutic intervention was used.[13] Spontaneous regression of LGG associated with neurofibromatosis type-1 was relatively common. The first ever reported clinical case of glioma, too, was associated with NF-1.[18] Perilongo G. et al. in 1999 reported two cases of NF-1-associated optic pathway gliomas with the review of 6 similar cases. It was concluded that NF-1-associated glioma is a common phenomenon in the paediatric population.[19] Schmandt SM et al. reported a case of PIA associated with NF-1, which showed bimodal regression.[20] A case reported by Gallussi. M et al. discussed spontaneous involution of a PIA without any surgical or chemotherapeutic intervention which was not associated with NF-1. The outcomes of patients either with or without NF-1 association were quite similar after spontaneous reversion.[21] The role of NF-1 in tumour regression is still obscure. Surgical traumatisation can be one of the possible mechanisms of involution. Gliomas that underwent subtotal or complete surgical resection illustrated a tendency to regress within a few years. Steinbok P et al. reported regression of cerebellar astrocytoma after surgical resection.[14] The maximum interval of regression after partial surgical resection was 11 years in te current literature review. Some residual tumour was found after resection which showed complete regression on serial imaging with the passage of time.[14] Similar cases of DIG were reported which underwent subtotal resection and had no recurrence history of the tumour even after long-term follow-up.[15,16] Time interval of this spontaneous regression phenomenon is variable. Thompson Jr et al. reported two cases of brainstem gliomas. Neither patient underwent surgery, nor any

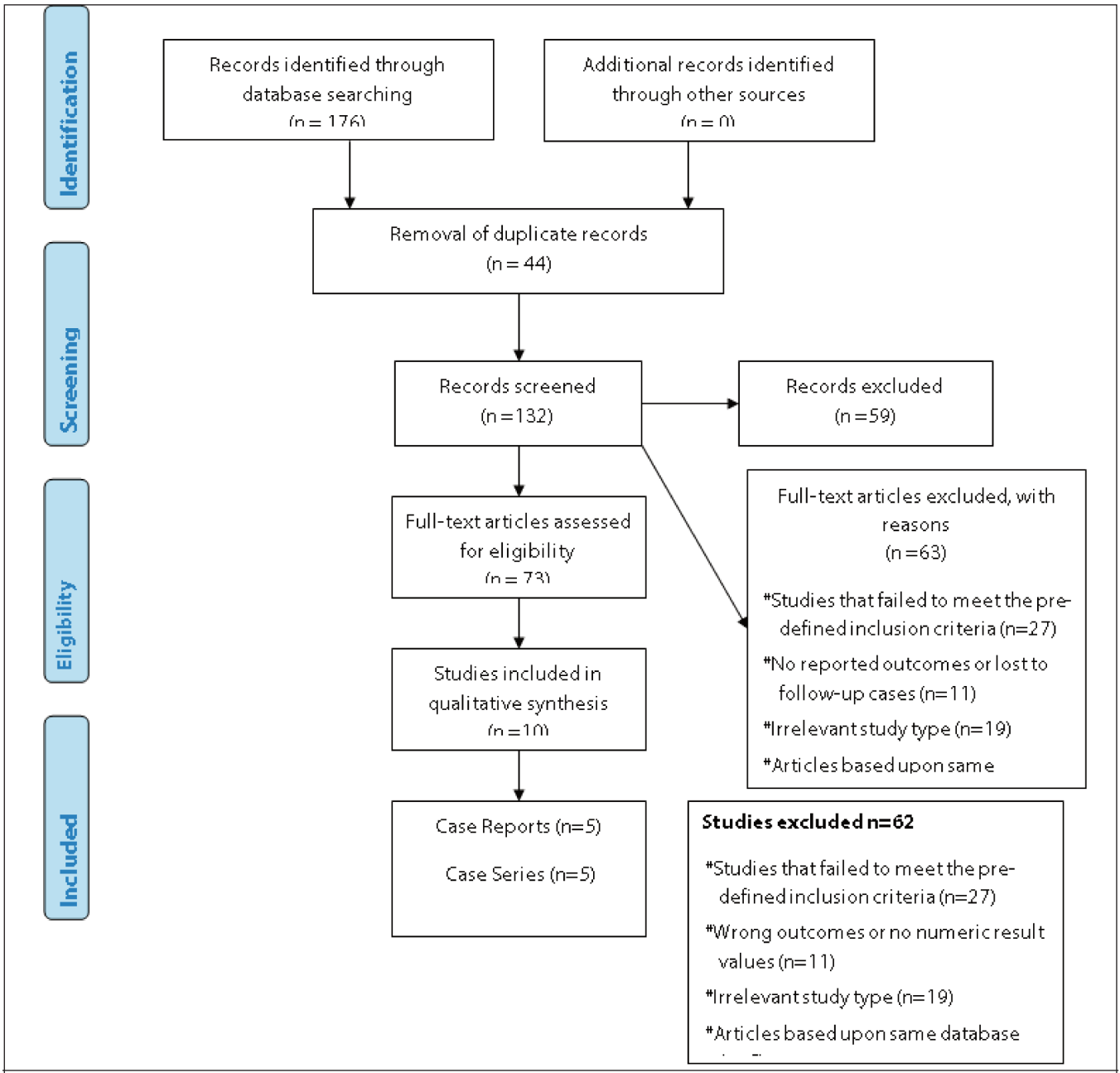

Figure: Data extraction strategy in accordance to PRISMA flow diagram for the study.

radiation treatment or chemotherapy; both underwent routine neurological and MRI examinations. Despite the similar circumstances, the interval of regression between the two varied significantly.[22]

Risk of bias within individual studies is a point to highlight here as the extent of surgical resection and the amount of chemotherapeutic dosage was not fixed in cases which required such interventions. Such variables might affect the outcome, tumourogenesis and therapeutic approach of LGGs.

Discussion

Spontaneous regression is a much prevalent phenomenon in different types of tumours. It is believed that medical or surgical interventions are difficult to bare and might impact the quality of life of the suffering individual. But the possibility and success of spontaneous regression is still questionable.

A retrospective study by H. Daffau on 178 patient's database was evaluated for LGG prognosis after resection with minimum follow-up of 8 years. Out of 178 patients, 16

Table-4: Pierson's 5-component scheme to evaluate the validity and educational value of case reports.

Authors	Documentation	Uniqueness	Educational Value	Objectivity	Interpretation	Total Score
Samadian M., et al 2016	2	0	1	1	2	6
Takeshima H., et al 2003	2	1	2	2	1	8
Parsa CF., et al 2001	1	2	1	1	1	6
Perilongo G., et al 1999	1	2	1	1	2	7
Schmandt SM., et al 2000	2	1	1	1	1	6
Gallucci M., et al 2000	1	1	1	2	2	7
Steinbok P., et al 2006	1	0	2	1	1	5
Tamburrini G., et al 2003	2	1	1	2	1	7
Tsuji K., et al 2008	1	0	2	2	1	6
Thompson Jr WD., et al 2005	2	1	1	1	2	7

Implications of total score: (9–10) = report is likely to be a worthwhile contribution to the literature (6–8) reader should be cautious about validity and clinical value of report. (5 or less) report is of insufficient quality for publication.

fulfilled the inclusion criteria. There was no relapse in 50% of the patients, five needed additional treatment whereas one case was subjected to re-resection of tumour. It was suggested to surgically excise diffuse LGGs to reduce the risk of recurrence or malignant growth.[23] Proper follow-up and screening should be done before deferring therapeutic interventions to nullify the possibility of worse outcome.

The importance to classify LGGs on molecular basis as well has been promoted recently. Specific mutation and gene deletions not only predict the prognosis of tumour but also result in increased efficacy of chemotherapy. Ryall S and associates reviewed the significance of IDH mutation and 1p/19q co-deletion with prolonged cell survival. Association of MGMT promoter methylation, IDH mutation and 1p/19q co-deletion with response rate of chemotherapy was also significantly discussed in their study.[24] Cheng W et al. found that IDH-1 mutation when combined with histopathological grading strongly predicted the overall survival in LGG patients. Prognostic significance of IDH-1 mutation was assessed using six-gene signature model.[25] A study by Zapotocky M .et al on molecular comparision between BRAF-V600E, BRAF-fusions, FGFR1-TACC1 and MYBL-1 suggested that BRAF-V600E is associated with significantly worse prognosis as compared to other molecular prognostic factors.[26] Therefore, it is as important to classify LGGs on the molecular basis as on the histopathological grounds.

Therapeutic intervention does not always assure complete resolution of the tumour even if it is benign in nature. Merchant TE et al. reported the failure of three-dimensional (3D) conformal radiotherapy (CRT) in paediatric patients having low-grade astrocytoma and ependymoma. This phase II trial took place at a tertiary care centre. Glioma treated with CRT reported 6 failures in patients with ependymoma and 4 failures with low-grade astrocytomas.[27]

Ethics is a major concern with any new therapeutic approach even when wait-and-watch approach is being followed. However, ethical considerations are much bigger concern associated with preferred cancer treatment modalities, like surgery, radiotherapy and chemotherapy. Surgery possess a great concern of tumour metastasis which not only decrease the life expectancy of the patient but is also contradictory to the 'Do no harm' rule of medical ethics.[28] Similarly, radiation of CNS tumours can results in acute brain reaction which includes oedema. Many chemotherapeutic agents are anti-metabolites which can cause deficiencies of essential components, like folate deficiency with methotrexate-induced chemotherapy.[29] Cost effectiveness is another concerning factor in long-term treatment of CNS tumours. It is troublesome for low-income population to afford expensive standard therapeutic care for slowly regressing tumours. Spontaneous regression is much cost-effective, and, hence, is a considerably impactful way to treat LGGs.[30] Therapy-associated outcome does not ensure complete regression of tumour. Therefore, suggestion of deferring aggressive intervention as long as the risks of intervention outweigh the risks of observation alone is considerable. This is usually the case in patients who are not in the extremes of age, who are asymptomatic or mildly symptomatic and in whom the tumour size is small and not growing rapidly. This group also includes cases in which imaging and tissue analysis are highly suggestive of LGG.

Limitations

The major limitation of the current literature review is the unavailability of expert statistician for the analysis of publication bias by applying standard tools, like Egger's Test. Another major hindrance was the availability of valuable data in languages other than English for which a language-translator could not be arranged.

Conclusion

Spontaneous regression of LGGs was found with certain tumour types, like PIA and DIG. LGGs have frequent tendency to regress on their own, and, as such,, deferring therapeutic interventions can be a considerable option in clinical approach. It might raise some ethical issues which need to be dealt with accordingly. To avoid any uneventful outcome, molecular analyses with histopathology of tumour cells is necessary to provide an additional edge for diagnostic accuracy and predictability of prognosis. Immense clinical-based evidence is required to fill the knowledge gap which is necessary to implement this

method as the standard approach of treatment.

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