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3 **Resolving mystery behind autonomous retrogression of low-grade**
4 **gliomas; a systematic review**

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12
13 **Abstract**

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

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

24 **Results:** Of the 176 articles identified, 73(41.5%) were shortlisted for detailed
25 assessment. Of them, 10(13.7%) were included; 5(50%) case reports and
26 5(50%) case series. There were 23 cases of spontaneous regression; 15(65.2%)
27 males and 8(34.7%) females. The interval of regression varied from 3 months to

28 15.5 years, and the most commonly presenting low-grade glioma type was optic
29 pathway glioma 11(47.4%).

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

35 **Key Words:** Pilocytic astrocytomas, Desmoplastic infantile ganglioglioma,
36 DIG, Desmoplastic infantile astrocytomas, DIA, Diffuse astrocytoma,
37 Spontaneous regression.

38

39 **Introduction**

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

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

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

69 The incidence of desmoplastic infantile ganglioglioma (DIG) is greatest in
70 children <18 months of age with male predominance. It comprises about 0.5-
71 1.0% of all CNS-related tumours.⁴ Pilocytic astrocytomas (PIA) (WHO Grade
72 I) usually manifest in first and second decades of life (age 5-14 years).
73 According to the report of Central Brain Tumor Registry of the United States
74 (CBTRUS) in 2018, its incidence in United States was 2.9 per million people.⁵
75 The diffuse LGGs, which include diffuse astrocytoma (WHO Grade II) and
76 oligodendroglioma (WHO Grade II) usually present between second and fourth
77 decades of life. About 40% of all the CNS tumours are gliomas in which
78 astrocytomas (75%) constitute the majority. Other subgroups, such as
79 oligodendroglioma, DIG, ependymomas and other subtypes, account for rest of
80 the 25%. Most frequent presenting features are seizures, mental disturbance,
81 headache with nausea and focal neurological deficit.⁶

82 Management of such tumours can be problematic because of indolent nature
83 and unpredictable behaviour. The most appropriate approach depends upon the
84 location of tumour, its likely nature and patient's individual characteristics.⁶

85 There are a number of case reports showing spontaneous regression of LGGs
86 which is the primary focus of this systematic review.

87 However, theories about the mechanism behind the phenomenon of regression
88 still require an immense volume of research and evidence-based explanations.

89 Augmented apoptosis, immune system, hormonal alterations, oncogenic DNA
90 suppression or decreased vasculature to the tumour are some popular proposed
91 mechanisms in medical literature.⁷ The term ‘spontaneous regression’ can be
92 explained as partial or total dematerialisation of tumour either in the absence of
93 any medical intervention or in the presence of therapy which is relatively
94 inadequate to influence the neoplastic nature of the tumour. Regression is not
95 confined to the CNS tumours alone, as tumours of various sites in the body, like
96 renal cell carcinoma, testicular germ cell tumours, melanoma or basal cell
97 carcinoma, demonstrate similar phenomenon. Spontaneous regression is
98 relatively more often in primary brain tumours.⁸

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

105

106 **Material and Methods**

107 The systematic review and meta-analysis comprised medical literature in
108 English language published from January 1997 to January 2017 to establish
109 consensus about the possible mechanism of spontaneous regression, the role of
110 therapeutic intervention and failure of management strategies in low-grade
111 gliomas. Preferred Reporting Items for Systematic Reviews and Meta-Analysis
112 (PRISMA) guidelines⁹ were followed during the review.

113 The study types included were case reports and case series published in the
114 English language reporting outcome in human subjects only, those studies in
115 which tumours resolved on their own or by an extent of interventions, like
116 surgical, radiotherapy or chemotherapy, which does not influence the
117 tumourogenicity of gliomas¹⁰, and studies reporting spontaneous regression
118 restricted to LGGs.

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

131 **Literature Search Strategy**

132 A detailed literature search was conducted by two independent authors using
133 the key medical subject heading (MeSH) and non-MeSH terms, like “low grade
134 gliomas (LGG)”, “spontaneous regression”, “pilocytic astrocytomas (PIA)”,
135 “desmoplastic infantile ganglioglioma (DIG)”, “desmoplastic infantile
136 astrocytomas (DIA)”, “optic glioma”, “oligodendroglioma” and
137 “ganglioglioma” to search Scopus, PubMed and Google Scholar databases.
138 Relevant terms or synonyms other than key words were utilised to conduct
139 comprehensive search in accordance with the pre-specified eligibility criteria.
140 All the searched articles were exported and cited through Endnote. In case of

141 unavailability of full text or incomplete data, the corresponding author was
142 contacted.

143 **Data Extraction Strategy**

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

147 **Data Collection**

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

152 **Quality Assessment and Risk of Bias**

153 Since the meta-analysis in this systematic review was not conducted on the
154 outcomes, the assessment of the quality of the extracted data and the risk of bias
155 were done at the study level and the body of evidence was not presented.
156 Pierson approach¹¹ was used to assess validity of all the case reports/series. It is
157 a 5-component scheme which scores the quality and validity of case
158 reports/series. Scores are assigned to 5-component domains which includes
159 documentation, uniqueness, educational value, objectivity and interpretation.
160 Each domain can be scored between 2 points (maximum score) to 0 points
161 (minimum score) according to the defined criteria for case presentation and
162 validity of data. Interpretation of ratings is based upon total score for an
163 individual study. Study with scores 9-10 has high likelihood of valid data and
164 appropriate reporting. Caution should be exercised about the clinical value of
165 studies if the scores are 6-8. Scores of ≤ 5 validate the insufficiency of study to
166 pertain substantial clinical evidence.¹¹ All the selected cases reports/series were
167 evaluated accordingly.

168

169

170 **Data Analysis and Primary Outcomes**

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

177

178 **Results**

179 Of the 176 articles identified, 73(41.5%) were shortlisted for detailed
180 assessment. Of them, 10(13.7%) were included; 5(50%) case reports and
181 5(50%) case series (Figure). There were 23 cases of spontaneous regression. Of
182 them, 15(65.2%) were males and 8(34.7%) were females. Age at presentation
183 ranged from 2 days to 19 years, while the interval of regression varied from 3
184 months to 15.5 years. In a few cases, regression was assessed after performing
185 surgical intervention [¹², ¹³ Case-5, ¹⁴, ¹⁵, ¹⁶], adjuvant radiotherapy or
186 chemotherapy [¹³ Case 10] or both [¹⁷, ¹⁵ Case-1] (Table 1).

187 The most commonly presenting LGG type was optic pathway glioma
188 11(47.4%), followed by PIA and DIG 14(17.4%) each (Table 2).

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

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

201 **Spontaneous Regression Assessment Methods**

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

212 **Exclusion of Publication Bias**

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

217 **Overview of Individual Cases**

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

224 Samadian et al. reported the regression of pilocytic astrocytoma which was
225 complicated with Steven Johnson Syndrome (SJS) which results in the
226 induction of multiple immune mechanisms. It was suggested that manipulation
227 in the immune system can alter the neoplastic course of glioma either due to

228 perforin-mediated necrosis or tumour cell apoptosis.¹⁷ DIG is a subgroup of
229 glioma with significant propensity to regress on its own. Two cases reported by
230 Takeshima H. et al. suggest that such reversion of tumours can possibly be due
231 to continued destruction of tumour cells by apoptosis. IHC analysis of both
232 tumours showed increased expression of apoptosis-promoting molecules like
233 Bax, Fas and Fas ligand, whereas declined production of Bcl 2 molecule, which
234 is anti-apoptotic in nature, was noted. This too suggests that induction of
235 apoptosis can be the possible cause of spontaneous regression in this case.¹²
236 Parsa et al. reported the regression of gliomas in 13 cases out of which we
237 reported the first 10. Among those cases, one patient underwent de-bulking of
238 the tumour while another case received vincristine as a chemotherapeutic. Other
239 than that, no surgical or therapeutic intervention was used.¹³ Spontaneous
240 regression of LGG associated with neurofibromatosis type-1 was relatively
241 common. The first ever reported clinical case of glioma, too, was associated
242 with NF-1.¹⁸ Perilongo G. et al. in 1999 reported two cases of NF-1-associated
243 optic pathway gliomas with the review of 6 similar cases. It was concluded that
244 NF-1-associated glioma is a common phenomenon in the paediatric
245 population.¹⁹ Schmandt SM et al. reported a case of PIA associated with NF-1,
246 which showed bimodal regression.²⁰ A case reported by Gallussi. M et al.
247 discussed spontaneous involution of a PIA without any surgical or
248 chemotherapeutic intervention which was not associated with NF-1. The
249 outcomes of patients either with or without NF-1 association were quite similar
250 after spontaneous reversion.²¹ The role of NF-1 in tumour regression is still
251 obscure. Surgical traumatization can be one of the possible mechanisms of
252 involution. Gliomas that underwent subtotal or complete surgical resection
253 illustrated a tendency to regress within a few years. Steinbok P et al. reported
254 regression of cerebellar astrocytoma after surgical resection¹⁴. The maximum
255 interval of regression after partial surgical resection was 11 years in the current
256 literature review. Some residual tumour was found after resection which showed

257 complete regression on serial imaging with the passage of time.¹⁴ Similar cases
258 of DIG were reported which underwent subtotal resection and had no recurrence
259 history of the tumour even after long-term follow-up.^{15,16} Time interval of this
260 spontaneous regression phenomenon is variable. Thompson Jr et al. reported
261 two cases of brainstem gliomas. Neither patient underwent surgery, nor any
262 radiation treatment or chemotherapy; both underwent routine neurological and
263 MRI examinations. Despite the similar circumstances, the interval of regression
264 between the two varied significantly.²²

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

269

270 **Discussion**

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

275 A retrospective study by H. Daffau on 178 patient's database was evaluated for
276 LGG prognosis after resection with minimum follow-up of 8 years. Out of 178
277 patients, 16 fulfilled the inclusion criteria. There was no relapse in 50% of the
278 patients, five needed additional treatment whereas one case undergone re-
279 resection of tumour. It was suggested to surgically excise diffuse LGGs to
280 reduce the risk of recurrence or malignant growth.²³ Proper follow-up and
281 screening should be done before deferring therapeutic interventions to nullify
282 the possibility of worse outcome.

283 The importance to classify LGGs on molecular basis as well has been promoted
284 recently. Specific mutation and gene deletions not only predict the prognosis of
285 tumour but also result in increased efficacy of chemotherapy. Ryall S and

286 associates reviewed the significance of IDH mutation and 1p/19q co-deletion
287 with prolonged cell survival. Association of MGMT promoter methylation, IDH
288 mutation and 1p/19q co-deletion with response rate of chemotherapy was also
289 significantly discussed in their study.²⁴ Cheng W et al. found that IDH-1
290 mutation when combined with histopathological grading strongly predicted the
291 overall survival in LGG patients. Prognostic significance of IDH-1 mutation
292 was assessed using six-gene signature model.²⁵ A study by Zapotocky M et al
293 on molecular comparison between BRAF-V600E, BRAF-fusions, FGFR1-
294 TACC1 and MYBL-1 suggested that BRAF-V600E is associated with
295 significantly worse prognosis as compared to other molecular prognostic
296 factors.²⁶ Therefore, it is as important to classify LGGs on the molecular basis
297 as on the histopathological grounds.

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

304 Ethics is a major concern with any new therapeutic approach even when wait-
305 and-watch approach is being followed. However, ethical considerations are
306 much bigger concern associated with preferred cancer treatment modalities, like
307 surgery, radiotherapy and chemotherapy. Surgery possess a great concern of
308 tumour metastasis which not only decrease the life expectancy of the patient but
309 is also contradictory to the 'Do no harm' rule of medical ethics.²⁸ Similarly,
310 radiation of CNS tumours can results in acute brain reaction which includes
311 oedema. Many chemotherapeutic agents are anti-metabolites which can cause
312 deficiencies of essential components, like folate deficiency with methotrexate-
313 induced chemotherapy.²⁹ Cost effectiveness is another concerning factor in
314 long-term treatment of CNS tumours. It is troublesome for low-income

315 population to afford expensive standard therapeutic care for slowly regressing
316 tumours. Spontaneous regression is much cost-effective, and, hence, is a
317 considerably impactful way to treat LGGs.³⁰ Therapy-associated outcome does
318 not ensure complete regression of tumour. Therefore, suggestion of deferring
319 aggressive intervention as long as the risks of intervention outweigh the risks of
320 observation alone is considerable. This is usually the case in patients who are
321 not in the extremes of age, who are asymptomatic or mildly symptomatic and in
322 whom the tumour size is small and not growing rapidly. This group also
323 includes cases in which imaging and tissue analysis are highly suggestive of
324 LGG.

325

326 **Limitations**

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

332

333 **Conclusion**

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

343

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347

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444

445 **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	References
Samadian et al in 2016	7 years/ Male	Pilocytic Astrocytoma	15 Months	Left eye blindness after a month of partial resection	17
Takeshima et al in 2003	9 month/ Female	Desmoplastic Infantile Ganglioglioma(DIG)	10 years (120 months)	Asymptomatic	12
Takeshima et al in 2003	6 months/ Male	Desmoplastic Infantile Ganglioglioma(DIG)	7 months	Asymptomatic	12
Parsa et al in 2001	5 years/ Male	Optic pathway glioma	12 years (144 months)	Decreased visual acuity with optic disc atrophy in right eye	13
CASE 1					

Parsa et al in 2001	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.	¹³
CASE 2					
Parsa et al in 2001	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.	¹³
CASE3					
Parsa et al in 2001	13 years, 6 months/ male	Optic chiasma glioma	1 year (12 months)	At 16 years, 6months of age, complete resolution occur. Patient was asymptomatic .	¹³
CASE 4					

Parsa et al in 2001	13 years/ male	Optic chiasma glioma	1 year (12 months)	At age 20 years, tumor was regressed with complete inferonasal field defect.	13
CASE 5					
Parsa et al in 2001	14 years/ female	Optic chiasma glioma	3 months	After a year and 8 months, tumor resolved but recession of left eye as compared to right eye was found.	13
CASE 6					
Parsa et al in 2001	11 years/female	Optic chiasma glioma with family history of NF-1	5 years, 10 months (70 months)	At age of 18 years, tumor regressed but right visual field of patient was completely depressed.	13
CASE 7					

Parsa et al in 2001	4½ months/male	Optic pathway glioma	6 months	At the age of 12 years, depressed left eye visual field was observed on perimetry.	¹³
CASE 8					
Parsa et al in 2001	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.	¹³
CASE 9					
Parsa et al in 2001	6 months/ male	Optic pathway glioma	15 years, 6 months (186 months)	At age of 16 years, tumor showed marked regression but right eye was presented with temporal heminopia with left eye being defective in superior	¹³
CASE 10					

				visual field.	
Giorgio Perilongo et al in 1999 Case 1	41 month/ Male	Optic pathway glioma with NF-1	10 months	A year later, lesion was stable on MRI. Patient was asymptomatic.	¹⁹
Giorgio Perilongo et al in 1999 Case 2	31 month/ Female	Optic chiasma glioma with NF-1	6 month	A year later, no change on MRI. Visual acuity was decreased.	¹⁹
Schmandt S.M et al in 1999	3 years 7 months/ Male	Pilocytic astrocytoma with NF-1	4 years, 6 months (54 months)	Asymptomatic	²⁰
Massimo Gallucci et al in 2000	19 years/ Male	Pilocytic astrocytoma	5 years, 7 months (67 months)	Asymptomatic	²¹
Paul Steinbok et al in 2006	2 years old/ Male	Cerebellar astrocytoma	11 years (132 months)	Asymptomatic	¹⁴

Tamburrini et al in 2003 Case 1	2 months/ Female	Desmoplastic infantile ganglioglioma (DIG)	1 year, 10 months (22 months)	Asymptomatic	15
Tamburrini et al in 2003 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.	15
Tsuji K et al in 2008	3 months/ Male	Desmoplastic infantile astrocytoma (DIA)	12 months	Asymptomatic	16
Thompson Jr et al in 2005 Case 1	2 days old/ Male	Brainstem glioma	4 years (48 months)	Asymptomatic	22
Thompson Jr et al in 2005 Case 2	1 week old/ Female	Brainstem glioma	10 years (120 months)	Mild facial palsy. Otherwise, asymptomatic	22

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Table 2: Frequencies and percentages of each tumour.

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%

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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	¹² Case 1
Subtotal resection of the tumour	None	¹² Case 2
None	None	¹³ Case 1
None	None	¹³ Case 2
None	None	¹³ Case3
None	None	¹³ Case 4
De-bulking of right side of chiasma	None	¹³ Case5
None	None	¹³ Case6

None	None	¹³ Case 7
None	None	¹³ Case 8
None	None	¹³ Case 9
None	Chemotherapy of vincristine and actinomycin D for 18 months.	¹³ Case 10
None	None	¹⁹ case 1
None	None	¹⁹ case 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	¹⁵ case 1
subtotal resection of the tumor	None	¹⁵ case 2
Partial resection of the	None	¹⁶

tumor		
None	None	²² case 1
None	None	²² case 2

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Table 2: 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	1	1	1	2	2	7

M., et al 2000						
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

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

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

