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Intratumoural haemorrhage in intracranial germ cell tumours: A review of literature with an illustrative case

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1. Introduction

Intratumoural haemorrhage may be the first sign of an intracranial tumour and occurs in 5–10% of cases.[1] When haemorrhage occurs within the tumour, it is associated with a poor outcome.[2] Intratumoural haemorrhage occurs commonly in high grade gliomas and oligodendrogliomas but they have been also reported to occur in pituitary adenomas, meningiomas, pilocytic astrocytomas, hemangiomas and in cerebral metastasis.[3–7] Bleeding within the tumour occurs most likely due to tumour vascularization, neovascularization with microvascular proliferation and hyperplasia of endothelial cells along with poorly formed dilated vessels predisposing to haemorrhage within the tumour.[8] Haemorrhage within intracranial germ cell tumours (iGCTs) are exceedingly rare, reported mostly in cases of mixed germ cell tumours and choriocarcinomas.[2] Intracranial germ cell tumours are extragonadal germ cell tumours usually occurring in the suprasellar and pineal regions. They commonly occur in children and adolescents and are broadly divided into germinoma and non-germinomatous germ cell tumours. In the literature, the incidence of iGCTs are more in East Asian countries, specially Korea and Japan.[9]

The prognosis of iGCTs depends on the histological type of tumours with purely germinomas having an excellent outcome whereas yolk sac tumours, embryonal carcinomas and choriocarcinomas are associated with a poor outcome.[10] Intratumoural haemorrhage may cause acute onset cerebral oedema and raised intracranial pressure. Choriocarcinomas and mixed germ cell tumours are at an increased risk of haemorrhage and poor outcomes.[11] We report a case of a suprasellar germinoma in a child presenting with haemorrhage and the results of a systematic review of intracranial germ cell tumours with haemorrhage, their clinical features, management and reported outcomes.

2. Methods

The present study was performed according to the guidelines recommended by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Publicly available studies with deidentified patient data were included in the study. We included both case reports and case series in the study along with any cohort studies if available owing to the rarity of the presentation under review.

3. Data sources and searches

A comprehensive search of the literature was carried out in PUBMED interface. Keyword searches using the search terms “intracranial germ cell tumours”, “central nervous system germ cell tumours”, “haemorrhage” and “apoplexy”, used in combination, was performed in PUBMED and further relevant studies were identified by citation search. Details of the search strategy is available in Supplement 1.

4. Study selection

Studies which reported the presence of haemorrhage in intracranial germ cell tumours or central nervous system germ cell tumours, were included in the present study. Inclusion criteria were - 1. Studies

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reporting spontaneous haemorrhage in intracranial germ cell tumours, Exclusion criteria - 1. Haemorrhage after surgery/biopsy in intracranial germ cell tumours, 2. Diagnosis has not been confirmed, 3. Full text of the article not available, 4. Article not in English language. Owing to the rarity of the condition under investigation, case reports and case series were included. Conference proceedings or abstracts only were not included.

5. Data extraction

Initial search results were assessed by a single investigator. Review of title and abstract were done, and studies were shortlisted for further assessment. The shortlisted articles were further reviewed by two investigators independently for inclusion as per inclusion criteria. Differences were resolved by discussion. After a study met the inclusion criteria, data extraction was done using pre-designed template. The following data were extracted - Study name and citation, year of publication, age of the patient, sex, clinical symptoms and signs, location of the tumour, histological type, type of management, mortality.

6. Definitions

Haemorrhage was considered to be present when it was described radiologically or confirmed intraoperatively or at autopsy. The type of tumour was taken as described histopathologically or diagnosed with serum/cerebrospinal fluid (CSF) markers. Mortality was considered to be present when it was reported as such.

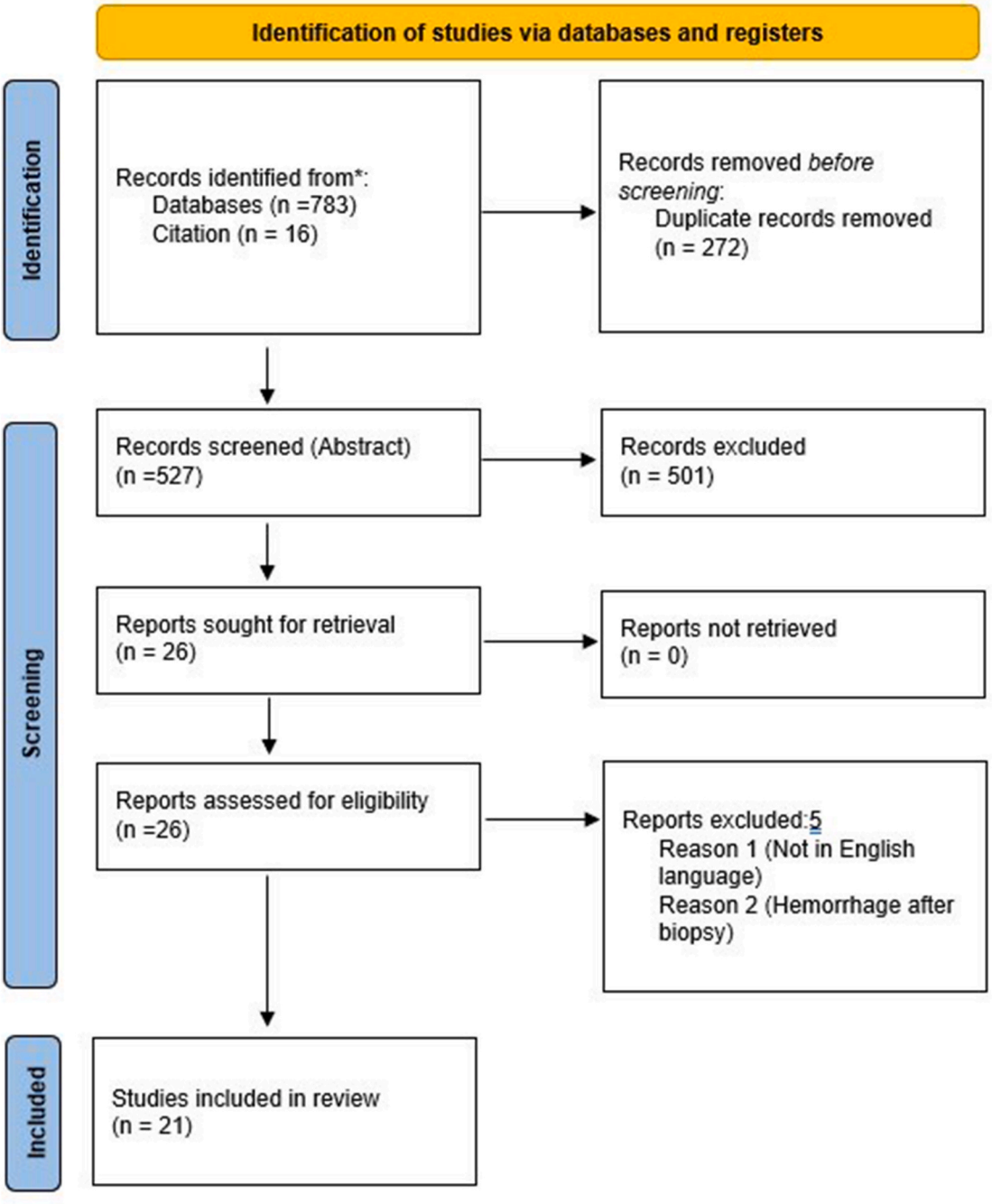

Fig. 1. – Prisma flowchart.

7. Data analysis

Statistical analysis was done using SPSS software version 25. For continuous variables, mean and standard deviations were reported. For categorical variables, frequencies and proportions were reported. Owing to the small number of cases, tests for significance were not carried out.

8. Results

783 studies were identified from PUBMED search and an additional 16 studies were identified from citation search. After removal of duplicates, abstract screening of 527 studies were done to see if they meet the inclusion criteria. 26 studies met the inclusion criteria and were sought for retrieval. Out of these 26 studies, 5 studies were excluded as they were either not in English language or the haemorrhage had occurred after surgery/biopsy. 21 studies were included for final analysis. Out of these 21 studies, 18 were case reports and 3 were case series. The PRISMA flow diagram for the identification, screening and inclusion process is given in Fig. 1. The details of the included and excluded studies are available in supplement 2 and 3 respectively. Critical appraisal of the included studies were done by two authors using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series (Supplement 4) .

52 patients were identified from the literature review, 19 from case reports and 33 from case series (Table 1). The mean age of the patients in the case report group was 15.24 years (SD 6.73). Mean age of patients with haemorrhage was reported in 1 case series (11.1 years, SD 4.3), two other case series did not report the mean age or sex ratio. Of the patients identified from case reports, 78.9 % were males and 21.1% were females. In the series reported by Chen et al, 70.6% were males and 29.4% were females.[2] The symptoms reported can be grouped into two major types – symptoms due to raised intracranial pressure and symptoms due to endocrine dysfunction. Headache, vomiting and blurred vision were the most common reported symptoms suggestive of raised intracranial pressure. Among the endocrine symptoms, polydipsia and polyuria suggestive of diabetes insipidus was the most common followed by precocious puberty. Two of the reported cases had neurodeficit in the form of hemiparesis and cranial nerve palsies and two patients had history of coma or loss of consciousness.

Mixed germ cell tumours were the most common histological type that presented with haemorrhage (29/52). The next most common histological type was choriocarcinoma (10/52) followed by germinoma (9/52). The other types were two cases of Yolk sac tumour and one each of endodermal sinus tumour and embryonal cell carcinoma. Pineal region was the most common location that presented with haemorrhage followed by suprasellar region. Four cases had synchronous pineal and suprasellar tumours. Type of management was reported in 36 cases, 28 out of 36 reported cases had received radiotherapy and 25 out of 36 received chemotherapy. 27 out of 36 had undergone some form of surgical treatment. Data about mortality was available in 36 patients. 18 patients out of 36 had died. From the case reports in which patient level data was available, patients were sub-grouped according to mortality (Table 2). Raised intracranial pressure was the most common symptom among patients who died. Choriocarcinoma was the most common histological type in patients who died. Pineal and suprasellar regions were the most common locations although ¾ patients with suprasellar germ cell tumours with haemorrhage died compared to 3/7 of pineal region tumours.

9. Illustrative case

An 11 year old girl presented with history of painless, progressive loss of vision in her right eye for 3 days along with intermittent episodes of headache for 1 week. There was no history of vomiting, convulsion,

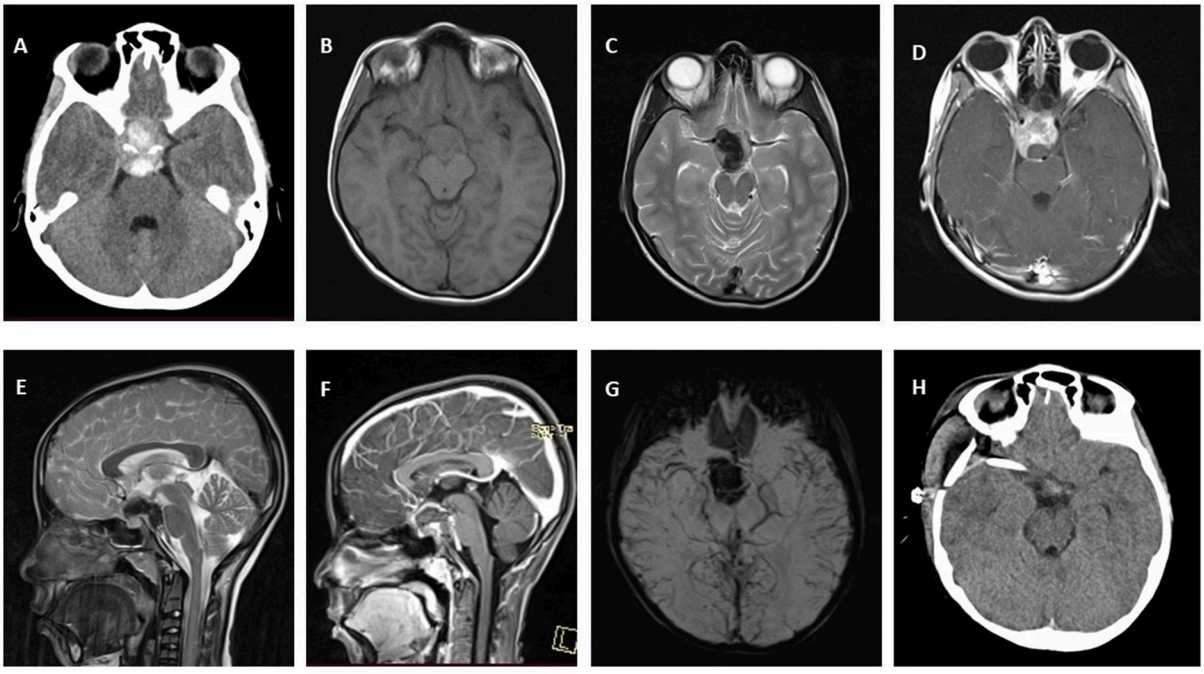

Fig. 2. A- Axial section of non-contrast CT head showing a hyperdense SOL in suprasellar region.
B – Axial section of T1 weighted MRI showing an isodense SOL in suprasellar region.
c – Axial section of T2 weighted MRI showing areas of hypointesities within the SOL in suprasellar region
D – Axial section of post-contrast T1 weighted images showing intense contrast enhancement in the SOL.
E – Sagittal section of T2 weighted image showing an SOL with areas of hypointensity in the suprasellar region. Pituitary gland can be seen separately.
F – Sagittal section of post-contrast T1 weighted image showing heterogenous contrast uptake within the SOL.
G – SWI sequence showing blooming within the SOL suggestive of haemorrhage.
H – Post-operative non-contrast CT of head. Ommaya reservoir in situ.

Table 1
Literature review of intratumoural haemorrhage in intracranial germ cell tumours.

Srl No	Author	Year	No. of patients	Age (Yrs)	Sex	Clinical features	Pathology	Location	Chemotherapy	Radiotherapy	Surgery	Mortality
Case Reports												
1	Hirano T[12]	1976	1	8	Female	Headache, vomiting, polyuria, polydipsia, diplopia	Teratoma with choriocarcinoma	Third ventricle	No	No	No	Yes
2	Rao CV[13]	1979	1	8	Male	Precoccious puberty, loss of vision, polyuria, polydipsia	Choriocarcinoma	Suprasellar region	Yes	No	No	Yes
3	Kawakami Y[14]	1980	1	11	Male	Precoccious puberty, headache, double vision, vomiting	Choriocarcinoma	Pineal region	Yes	Yes	Yes	No
4	Fujii T[15]	1981	1	11	Male	Headache, vomiting	Choriocarcinoma	Pineal region	No	No	No	Yes
5	Naganuma H[16]	1984	1	14	Male	Headache, vomiting, hemiparesis, horner's syndrome	Endodermal sinus tumour	Pineal region	Yes	Yes	No	Yes
6	Chan HS[17]	1984	1	9.5	Male	Headache, retroorbital pain, vomiting, blurring of vision	Choriocarcinoma	Pineal region	No	No	Yes	Yes
7	Bjornsson J[18]	1986	1	10	Female	Not described	Choriocarcinoma	Third ventricle	No	No	Yes	Yes
8	Page R[19]	1986	2	12	Female	Loss of vision, headache, altered sensorium	Choriocarcinoma	Sellar region with extension into bilateral cavernous sinus	No	No	Yes	Yes
				17	Male	Headache, blurring of vision, episodic drowsiness	Choriocarcinoma	Pineal region	Yes	No	Yes	No
9	Graziano SL[20]	1987	1	15	Male	Headache, vomiting, blurred vision	Mixed germ cell tumour	Pineal region	Yes	Yes	Yes	No
10	Tsunoda S[21]	1993	1	29	Male	Altered sensorium, raised ICP	Embryonal carcinoma	Suprasellar region with extension into third and lateral ventricle	Yes	Yes	Yes	Yes
11	Shinoda J[22]	2004	1	10	Male	Polydipsia, polyuria, precoccious puberty	Choriocarcinoma	Suprasellar region with extension into midbrain	No	Yes	No	Yes
12	Kamitani H[23]	2006	1	21	Male	Loss of consciousness	Mixed germ cell tumour	Medial temporal lobe with brainstem extension	Yes	Yes	Yes	Yes
13	Huang MN[24]	2006	1	22	Male	Proximal muscle weakness, hypernatremia	Mixed germ cell tumor	Hypothalamic	No	No	Yes	Yes
14	Koh EJ[25]	2009	1	14	Male	Hemiparesis, cranial nerve palsies	Mixed germ cell tumour	Cerebral peduncle	Yes	Yes	Yes	No
15	Ichikawa T[26]	2011	1	22	Male	Headache, vomiting	Mixed germ cell tumour with areas of hemangioblastoma	Cerebellum	Yes	Yes	Yes	No
16	Kim M[27]	2012	1	19	Male	Diplopia, headache, nausea, vomiting	Choriocarcinoma	Pineal region	Yes	Yes	Yes	No
17	Keenan C[28]	2021	1	8	Female	Headache, vomiting, hemiparesis, cranial nerve palsy	Mixed germ cell tumour	Suprasellar region	Yes	Yes	No	No
18	Yang X[29]	2022	1	29	Male	Headache, coma	Yolk sac tumor	Suprasellar, pineal and left temporal	No	Yes	Yes	Yes
Case series												
1	Chen JT[2]	2018	17	11.1 ± 4.3 (4–19)	70.6:29.4	Headache, vomiting, blurred vision, limb weakness, DI	Germinoma - 7, Yolk sac tumour - 1, Choriocarcinoma-1, Mixed GCT - 8	Pineal - 6, Suprasellar - 3, Pineal and suprasellar - 3, Basal ganglia - 4, Other −1	14	17	14	6
2	Li W[30]	2021	13	NR	NR	NR	Germinoma - 2, Mixed GCT - 11	NR	NR	NR	NR	NR
3	Liang L[31]	2002	3	NR	NR	NR	Mixed germ cell tumour - 3	NR	NR	NR	NR	NR

NR – not reported.

Table 2
Demography, clinical symptoms and management of patients from case reports.

		Mortality	
		No	Yes
Age (Years) (Mean ± SD)		15.14 (4.74)	15.29 (7.86)
Sex	**Female**	1	3
	Male	6	9
Symptoms	**Raised ICP**	4	8
	Endocrine	0	3
	Endocrine + Raised ICP	1	0
	Neurodeficit	2	0
	Not reported (1)		1
Pathology	**Choriocarcinoma**	3	6
	Mixed GCT	4	3
	Embryonal cell carcinoma	0	1
	Endodermal sinus tumour	0	1
	Yolk sac tumour	0	1
Location	**Pineal**	4	3
	Suprasellar	1	3
	Sella	0	1
	3rd Ventricle	0	2
	Synchronous Suprasellar and pineal	0	1
	Other	2	2
Management	**Radiotherapy**	6	5
	Chemotherapy	7	4
	Surgery	6	7

increased thirst or urination, unexplained weight gain or loss, any loss of smell or any behavioural changes. She had normal developmental history and was attending school regularly. On examination, she had only perception of light in her right eye with relative afferent pupillary defect, left sided vision was intact. There were no other cranial nerve palsies. Her motor, sensory and higher mental functions were intact. Laboratory investigations showed presence of secondary hypothyroidism. Her serum sodium, cortisol and prolactin levels were normal. Non-contrast computed tomography (NCCT) scan of head showed presence of a hyperdense space occupying lesion (SOL) in the suprasellar region without any hydrocephalus. Magnetic resonance Imaging (MRI) with contrast showed an avidly contrast enhancing SOL in the suprasellar region with blooming in SWI images compressing the right optic nerve (Fig. 2). She was taken up for urgent surgery. Right pterional craniotomy was done and trans-sylvian approach taken. A reddish tumour was present in the suprasellar region, soft in consistency with blood clots present in the tumour cavity. The tumour was decompressed through the interoptic, optico-carotid and carotid-occulomotor triangles followed by gross total excision. The pituitary stalk was identified and preserved along with the basal perforators arising from the internal carotid artery. She developed transient diabetes insipidus in the post-operative period which was managed medically. Histopathological examination of the excised tumour showed the presence of germinoma. She had improvement in her vision and on Visual Evoked potential (VEP) in the post-operative period. Post-operative serum alpha fetoprotein (AFP) and lactate dehydrogenase (LDH) were within normal limits, however, serum beta human chorionic gonadotropin (HCG) was mildly elevated. She was discharged to home with advice to follow up for chemo-radiation.

10. Discussion

Intracranial germ cell tumours (iGCTs) encompass 0.3–0.5% of all primary intracranial neoplasms and approximately 3% of primary malignant paediatric brain tumours according to Western literature.[32,33] However, series from Japan and Taiwan indicate that these tumours are far more common in Asia, where iGCTs make up 2–5% of all primary intracranial neoplasms and account for up to 15% of primary paediatric intracranial neoplasms.[32,33] Ninety percent of patients with iGCTs present with symptoms before the age of 20 years. Sixty-five percent of tumours occur in the second decade of life (11–20 years). The peak incidence is around 10–12 years of age. Intracranial germinomas appear mainly in the pineal and suprasellar regions. Less common locations are the basal ganglia, ventricles, thalamus, medulla oblongata or the cerebral hemispheres.[32]

Intratumoural haemorrhage is a rare presentation of iGCTs. A case series of 17 paediatric patients of iGCTs over a 14 year period was reported by Chen et al[2]They had attempted to identify the prognostic factors of iGCTs with haemorrhage by examining the clinical and radiological findings of these patients. They found that 6 of 17 patients had died (35.3%) and 52.9% had a poor outcome according to the modified Rankin scale. Among the prognostic factors, they identified haematoma volume and haematoma/tumour volume ratio to be significant predictors of poor outcome. However, only haematoma/tumour volume ratio was a significant predictor of mortality. The mean haematoma/tumour volume ratio was 15.7 ± 16.1% in the survivors and 46.0 ± 31.5% in the mortality group. The underlying pathologic type of the tumour (germinoma vs non-germinomatous germ cell tumours) and the location of the tumour didn't have a significant effect either on the outcome or on the mortality. The hematoma/tumour volume ratio is an interesting metric and warrants further exploration as a prognostic indicator in intratumoural haemorrhage. Unfortunately, we were not able to analyse its utility as a prognostic indicator as it was not reported in most of the studies that met the inclusion criteria for the review.

Similar effect of tumoural haemorrhage on survival was reported by Shinoda et al.[22] Patients with tumoural haemorrhage had a significantly worse survival compared to patients who did not had haemorrhage. Apart from tumoural haemorrhage, they also found less than subtotal resection, pineal region location and female sex to negatively affect the survival whereas patients who received chemotherapy and radiotherapy had a significantly better outcome. This negative effect of intratumoural haemorrhage on survival was however contradicted by Jiang et al, who had conducted a literature review to identify the prognostic factors associated with survival in intracranial choriocarcinomas.[34] They had identified 51 cases of primary intracranial choriocarcinoma meeting their inclusion criteria. On multivariate analysis, they found only the combination of chemotherapy along with surgery to be a significant predictor of survival. Presence of intratumoural haemorrhage didn't affect the survival.

In a retrospective review of intracranial germinomas and mixed germ cell tumours, Li et al had found that the incidence of intratumoural haemorrhage was significantly more in mixed germ cell tumours than in germinomas (68.75% vs 11.76%).[30] Liang et al also reported presence of intratumoural haemorrhage only in mixed germ cell tumours.[31] However, Chen et al noted presence of intracranial haemorrhage in 7 cases of germinomas and in 10 cases of non-germinomatous germ cell tumours.[2]

Clinical features suggestive of raised intracranial pressure was the most common clinical feature in our review followed by endocrine symptoms and focal neurodeficit. This is similar to the findings reported by Chen et al who reported headache, vomiting and blurred vision to be the most common symptoms in their cohort of patients.[2] In the present review, we found that pineal region tumours followed by suprasellar tumours most commonly **bled** however there were some unusual locations reported like hypothalamus, cerebellum and cerebral peduncles. This is similar to the cohort reported by Chen et al where pineal region was also the most common location followed by suprasellar region.[2]

The mechanism of intratumoural haemorrhage is speculative and not known exactly. Tumours contain two main types of vessels, neo-angiogenic vessels formed by angiogenic factors and co-opted vessels which are pre-existing vessels co-opted by the growing tumour.[35] Both these types of tumour vasculature are immature and fenestrated, lacking in tight junctions and blood–brain barrier.[36] These factors predispose to spontaneous vessel rupture and tumour bleed secondary to tumour necrosis. Vascular endothelial growth factor (VEGF) and matrix-metalloproteinases (MMPs) have been shown to be involved in

tumoural haemorrhage associated with metastatic brain tumours.[37]

There are several drawbacks of the present study. Publication bias is a significant drawback, all of the cases of iGCTs with haemorrhage may not have been reported in the literature. Two of the case series did not report mortality, demographic or management data. Only English language studies were included in the review. Due to the relatively small number of reported cases, statistical analysis was not performed. It would be interesting to note if there is any association between location, histology, demographic factors, type of management and the risk of mortality.

11. Conclusion

Intratumoural haemorrhage in iGCTs is a rare but intriguing presentation of iGCTs. Depending on the haematoma volume and the acuity of presentation, patients may require urgent management to achieve a favourable outcome. Literature suggests that intratumoural haemorrhage, particularly large volume haematomas, increases the risk of mortality. Early detection and prompt management should be instituted for this presentation. However, the optimum mode of treatment of this presentation of iGCTs have not been elucidated in the literature.

CRediT authorship contribution statement

Debajyoti Datta: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Partha Ghosh:** Supervision, Conceptualization. **Sutirtha Hazra:** Validation, Methodology. **Soutrik Das:** Validation. **Debajyoti Pathak:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wnsx.2024.100336.

References

1. Hamed M, Schäfer N, Bode C, et al. Preoperative metastatic brain tumor-associated intracerebral hemorrhage is associated with dismal prognosis. *Front Oncol*. 2021;11. https://doi.org/10.3389/fonc.2021.699860.
2. Chen J-T, Lee H-J, Chen Y-W, et al. Prognostic factors related to intratumoral hemorrhage in pediatric intracranial germ cell tumors. *J Chin Med Assoc*. 2019;82 (2):133–137. https://doi.org/10.1097/jcma.0000000000000015.
3. Mantia C, Uhlmann EJ, Puligandla M, Weber GM, Neuberg D, Zwicker JI. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. *Blood*. 2017;129(25):3379–3385. https://doi.org/10.1182/blood-2017-02-767285.
4. Gläsker S, Van Velthoven V. Risk of hemorrhage in hemangioblastomas of the central nervous system. *Neurosurgery*. 2005;57(1):71–76. https://doi.org/10.1227/01.neu.0000163250.71951.18.
5. Zhan R, Zhao Y, Wiebe TM, Li X. Acute hemorrhagic apoplectic pituitary adenoma. *J Craniofac Surg*. 2015;26(6). https://doi.org/10.1097/scs.0000000000002026.
6. Kim M-S, Kim SW, Chang C-H, Kim O-L. Cerebellar pilocytic astrocytomas with spontaneous intratumoral hemorrhage in adult. *Journal of Korean Neurosurgical Society*. 2011;49(6):363. https://doi.org/10.3340/jkns.2011.49.6.363.
7. Siedlecki Z, Nowak K, Grzyb S, Śniegocki M. Intracranial hemorrhages associated with meningiomas: own experience and literature review. *J Cancer Res Therapeut*. 2022;18(3):820. https://doi.org/10.4103/jcrt.jcrt_958_20.
8. Ostrowski RP, He Z, Pucko EB, Matyja E. Hemorrhage in brain tumor – an unresolved issue. *Brain Hemorrhages*. 2022;3(2):98–102. https://doi.org/10.1016/j.hest.2022.01.005.
9. Phi JH, Wang K-C, Kim S-K. Intracranial germ cell tumor in the molecular era. *Journal of Korean Neurosurgical Society*. 2018;61(3):333–342. https://doi.org/10.3340/jkns.2018.0056.
10. Takami H, Perry A, Graffeo CS, et al. Comparison on epidemiology, tumor location, histology, and prognosis of intracranial germ cell tumors between Mayo Clinic and Japanese consortium cohorts. *J Neurosurg*. 2021;134(2):446–456. https://doi.org/10.3171/2019.11.jns191576.
11. Lv X-F, Qiu Y-W, Zhang X-L, et al. Primary intracranial choriocarcinoma: mr imaging findings. *Am J Neuroradiol*. 2010;31(10):1994–1998. https://doi.org/10.3174/ajnr.a2194.
12. Hirano T, Kawai K, Tsuchiyama H. An autopsy case of H.C.G. secreting intracranial teratoma. *Pathol Int*. 1976;26(1):97–103. https://doi.org/10.1111/j.1440-1827.1976.tb03295.x.
13. Krishna Rao CVG, Govindan S. Intracranial choriocarcinoma. *J Comput Assist Tomogr*. 1979;3(3):400–404. https://doi.org/10.1097/00004728-197906000-00018.
14. Kawakami Y, Yamada O, Tabuchi K, Ohmoto T, Nishimoto A. Primary intracranial choriocarcinoma. *J Neurosurg*. 1980;53(3):369–374. https://doi.org/10.3171/jns.1980.53.3.0369.
15. Fujii T, Itakura T, Hayashi S, Komai N, Nakamine H, Saito K. Primary pineal choriocarcinoma with hemorrhage monitored by Computerized Tomography. *J Neurosurg*. 1981;55(3):484–487. https://doi.org/10.3171/jns.1981.55.3.0484.
16. Naganuma H, Inoue H, Misumi S, Nakamura M, Tamura M. Intracranial germ-cell tumors. *J Neurosurg*. 1984;61(5):931–937. https://doi.org/10.3171/jns.1984.61.5.0931.
17. Chan HS, Humphreys RP, Hendrick EB, Chuang SH, Fitz CR, Becker LE. Primary intracranial choriocarcinoma. *Neurosurgery*. 1984;15(4). https://doi.org/10.1097/00006123-198410000-00012.
18. Bjornsson J, Scheithauer BW, Leech RW. Primary intracranial choriocarcinoma: a case report. *Clin Neuropathol*. 1986;5(6):242–245.
19. Page R, Doshi B, Sharr MM. Primary intracranial choriocarcinoma. *J Neurol Neurosurg Psychiatry*. 1986;49(1):93–95. https://doi.org/10.1136/jnnp.49.1.93.
20. Graziano SL, Paolozzi FP, Rudolph AR, Stewart WA, Elbadawi A, Comis RL. Mixed germ-cell tumor of the pineal region. *Case report. J Neurosurg*. 1987;66(2):300–304. https://doi.org/10.3171/jns.1987.66.2.0300.
21. Tsunoda S, Sasaoka Y, Sakaki T, et al. Suprasellar embryonal carcinoma which developed ten years after local radiation therapy for pineal germinoma. *Surg Neurol*. 1993;40(2):146–150. https://doi.org/10.1016/0090-3019(93)90126-l.
22. Shinoda J, Sakai N, Yano H, Hattori T, Ohkuma A, Sakaguchi H. Prognostic factors and therapeutic problems of primary intracranial choriocarcinoma/germ-cell tumors with high levels of HCG. *J Neuro Oncol*. 2004;66(1–2):225–240. https://doi.org/10.1023/b:neon.0000013499.74404.81.
23. Kamitani H, Miyata H, Ishibashi M, et al. Mixed germ cell tumors with abundant sarcomatous component in the temporal lobe after radiochemotherapy of neurohypophyseal germinoma: a case report. *Brain Tumor Pathol*. 2006;23(2):83–89. https://doi.org/10.1007/s10014-006-0205-x.
24. Huang MN, Chen JJ, Lee KL, Tseng FY, Yu CL, Hsieh SC. Hypernatremic myopathy caused by a hypothalamic mixed germ cell tumor mimicking polymyositis. *Clin Rheumatol*. 2007;26(9):1591–1594. https://doi.org/10.1007/s10067-006-0481-1.
25. Koh EJ, Phi JH, Park SH, et al. Mixed germ cell tumor of the midbrain. *Case Report. J Neurosurg Pediatr*. 2009;4(2):137–142. https://doi.org/10.3171/2009.3.PEDS08290.
26. Ichikawa T, Hamazaki S, Sakai N, et al. Mixed germ cell tumor and hemangioblastoma in the cerebellum: report of a rare coexistence. *Brain Tumor Pathol*. 2011;28(3):279–284. https://doi.org/10.1007/s10014-011-0031-7.
27. Kim M, Yun J, Hur SM, et al. Successful synchronous chemotherapy and radiotherapy followed by consecutive chemotherapy without surgery for primary intracranial choriocarcinoma: a case report. *Oncol Lett*. 2012;4(6):1389–1391. https://doi.org/10.3892/ol.2012.901.
28. Keenan C, Ramirez N, Elijovich L, et al. A rare manifestation of choriocarcinoma syndrome in a child with primary intracranial germ cell tumor and extracranial metastases: a case report and review of the literature. *Pediatr Blood Cancer*. 2021;68 (6), e29000. https://doi.org/10.1002/pbc.29000.
29. Yang X, Wang Y, Chen G, Hong X. Multifocal primary intracranial yolk sac tumor in an adult patient: a case report and literature review. *Transl Cancer Res*. 2022;11(5):1429–1433. https://doi.org/10.21037/tcr-21-2561.
30. Li W, Kong X, Ma J. Imaging diagnosis of basal ganglia germ cell tumors: subtype features subtype imaging features of GCTs. *Br J Radiol*. 2021;94(1122), 20201453. https://doi.org/10.1259/bjr.20201453.
31. Liang L, Korogi Y, Sugahara T, et al. MRI of intracranial germ-cell tumours. *Neuroradiology*. 2002;44(5):382–388. https://doi.org/10.1007/s00234-001-0752-0.
32. Jorsal T, Rørth M. Intracranial germ cell tumours. A review with special reference to endocrine manifestations. *Acta Oncol*. 2012;51(1):3–9. https://doi.org/10.3109/0284186X.2011.586000.
33. Borde TD, Arimappamagan A, Srinivas D, et al. Intracranial germ cell tumors: spectrum of disease in an Indian cohort and management strategies. *J Neurosci Rural Pract*. 2018;9(3):291–297. https://doi.org/10.4103/jnrp.jnrp_86_18.
34. Jiang T, Raynald, Yang H, Zhang W, Li C. Predictive factors of overall survival in primary intracranial pure choriocarcinoma. *J Clin Neurosci*. 2019;61:93–101. https://doi.org/10.1016/j.jocn.2018.10.136.
35. Guyon J, Chapouly C, Andrique L, Bikfalvi A, Daubon T. The normal and brain tumor vasculature: morphological and functional characteristics and therapeutic targeting. *Front Physiol*. 2021;12, 622615. https://doi.org/10.3389/fphys.2021.622615. Published 2021 Mar 5.
36. Grasso G, Landi A, Alafaci C. Pathogenetic mechanisms of intratumoral hemorrhage in meningioma: the role of microvascular differentiation. *World Neurosurg*. 2016;95:599–600. https://doi.org/10.1016/j.wneu.2016.07.118.
37. Jung S, Moon KS, Jung TY, et al. Possible pathophysiological role of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) in

metastatic brain tumor-associated intracerebral hemorrhage. *J Neuro Oncol*. 2006;76 (3):257–263. https://doi.org/10.1007/s11060-005-6876-z.

Abbreviations

AFP –: Alpha feto protein
CSF–: Cerebrospinal fluid
HCG –: Human chorionic gonadotropin
iGCT –: Intracranial germ cell tumour
JBI–: Joanna Briggs Institute
LDH –: Lactate dehydrogenase
MMP –: Matrix metalloproteinases
MRI –: Magnetic resonance imaging
NCCT: Non-contrast computed tomography
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
SD –: Standard deviation
SOL–: space occupying lesion
SWI –: Susceptibility weighted imaging
VEGF –: Vascular endothelial growth factor