IMPLICATIONS OF DEFERRED DIAGNOSIS OF PAEDIATRIC INTRACRANIAL GERM CELL TUMOURS

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Abstract

AIMS This study analysed the clinical features of children with intracranial germ cell tumours (IC-GCTs) treated at two European centres. We retrospectively reviewed timelag between symptoms onset, clinic-radiological findings, diagnosis and outcomes. METHODS Symptoms at diagnosis were divided into four groups: 1)raised intracranial pressure (RICP); 2)visual impairment; 3)endocrinopathy; 4)other. Total diagnostic interval (TDI), defined as the interval between symptom onset (including retrospective recall of symptoms) and definitive diagnosis of IC-GCT, was calculated and compared to survival rates. RESULTS Our cohort included 55 children with a median follow-up of 78.9 months (0.5-249.9). The majority (63.6%) had germinomas and 10.9% were metastatic at diagnosis. IC-GCTs were suprasellar (41.8%), pineal (36.4%), bifocal (12.7%) or in atypical sites (9.1%). The most common presenting symptoms were related to RICP (43.6%); however, by the time of tumour diagnosis, 50.9% of the patients had developed endocrine dysfunctions. All pineal GCTs manifested with RICP or visual impairment. All suprasellar GCTs presented with endocrinopathies. TDI ranged between 0.25-58.5 months (median 4 months). Pineal GCTs had the shortest TDI (median TDI 1 month versus 24 months in suprasellar GCTs, $p<0.001$). TDI >6 months was observed in 47.3% of patients and was significantly associated with endocrine presenting symptoms. No statistically significant difference was found in progression-free survival and overall survival between patients with TDI >6 months and with TDI ?6 months. CONCLUSION Approximately half of our patients had TDI >6 months, mostly with endocrine deficiencies as presenting symptoms. TDI >6 months was not associated with increased relapse rate or mortality.

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Abbreviations table

AFP	alpha-fetoprotein
Beta-HCG	beta-human chorionic gonadotropin
CI	confidence interval
CSF	cerebral spinal fluid
HI	healthcare-related interval
IC-GCTs	intracranial germ cell tumours
IQR	interquartile ranges
MRI	magnetic resonance image
NGGCTs	non-germinomatous germ cell tumours
OR	odds ratio
OS	overall survival
PFS	progression-free survival
PI	patient-related interval
PLAP	placental alkaline phosphatase
RICP	raised intracranial pressure
TDI	total diagnostic interval
TI	tumour-related interval
TYA	teenage and young adult
WVI	whole ventricular field irradiation

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ABSTRACT

AIMS

This study analysed the clinical features of children with intracranial germ cell tumours (IC-GCTs) treated at two European centres. We retrospectively reviewed timelag between symptoms onset, clinic-radiological findings, diagnosis and outcomes.

METHODS

Symptoms at diagnosis were divided into four groups: 1)raised intracranial pressure (RICP); 2)visual impairment; 3)endocrinopathy; 4)other. Total diagnostic interval (TDI), defined as the interval between symptom onset (including retrospective recall of symptoms) and definitive diagnosis of IC-GCT, was calculated and compared to survival rates.

RESULTS

Our cohort included 55 children with a median follow-up of 78.9 months (0.5-249.9). The majority (63.6%) had germinomas and 10.9% were metastatic at diagnosis. IC-GCTs were suprasellar (41.8%), pineal (36.4%), bifocal (12.7%) or in atypical sites (9.1%). The most common presenting symptoms were related to RICP (43.6%); however, by the time of tumour diagnosis, 50.9% of the patients had developed endocrine dysfunctions. All pineal GCTs manifested with RICP or visual impairment. All suprasellar GCTs presented with endocrinopathies. TDI ranged between 0.25-58.5 months (median 4 months). Pineal GCTs had the shortest TDI (median TDI 1 month versus 24 months in suprasellar GCTs, p<0.001). TDI >6 months was observed in 47.3% of patients and was significantly associated with endocrine presenting symptoms. No statistically significant difference was found in progression-free survival and overall survival between patients with TDI >6 months and with TDI [?]6 months.

CONCLUSION

Approximately half of our patients had TDI >6 months, mostly with endocrine deficiencies as presenting symptoms. TDI >6 months was not associated with increased relapse rate or mortality.

INTRODUCTION

Background

Diagnosis of intracranial germ cell tumours (IC-GCTs) occurs predominantly in children with peak incidence during the second decade of life [1-3].

The two most frequent brain locations are the pineal gland and the suprasellar region or both sites simultaneously ("bifocal disease"). IC-GCTs can also arise in the basal ganglia, thalamus, cerebral hemisphere, and cerebellum [4,5].

According to the WHO classification system, IC-GCTs are divided into germinomas (GTs) and non-germinomatous (NGGCTs) [6]. Germinomas comprise 60-65% of all paediatric IC-GCTs. IC-GCTs can also be divided into "secreting" and "non-secreting" tumours based on the presence of tumour markers measured in the cerebral spinal fluid (CSF) and/or serum: alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-HCG) [7].

Different CT and RT treatment regimens have been developed in Western Countries [8-11] and in Japan[12]according to histology and prognosis. Intracranial germinomas have an excellent overall survival (OS) >90%, whereas the prognosis for patients with recurrent IC-NGGCTs is poor[13,14].

Clinical presentation and deferred diagnosis

Initial symptoms depend upon location and size of the tumour. Pineal tumours typically cause obstructive hydrocephalus with headache, vomiting, papilledema, and lethargy. Pineal tumours may also present with 'Parinaud's syndrome', caused by tectal plate compression. Patients with IC-GCTs may show behavioural changes, poor school performance and altered neurology, especially in tumours arising within the basal ganglia. Suprasellar GCTs most commonly cause hypothalamic/pituitary dysfunctions and may compress the optic chiasm causing visual field defects [15, 16].

A prolonged symptom interval (i.e. the time from symptom onset to diagnosis) has been reported in several paediatric brain tumours[17–19]. Reports from two institutional series have identified a wide variation in symptom interval, with diagnosis occurring up to 3 years from symptom onset [17,18]. In recent single-centre studies, 54% [17] and 30%[15] of patients with IC-GCT had a symptom interval >6 months. In another study 17/181 patients with IC-GCT (9%) had a deferred diagnosis of >3 months and survival in a small subset of germinoma patients (13/119 cases; 11%) was negatively affected [20]. Other previous studies have identified that children with shorter symptom intervals have more aggressive tumours, suggesting a relationship between diagnostic delay and survival[21,22].

Our study evaluates retrospectively the clinical features and outcomes of paediatric patients with IC-GCTs treated at two centres over 25 years. We reviewed the timing interval between symptoms onset, radiological

manifestations, and definitive diagnosis of IC-GCT.

METHODS

Study design and population

We retrospectively analysed data of patients (<18 years old) who were diagnosed with IC-GCT between January 1996 and December 2019 at the Royal Marsden Hospital, Sutton, UK and at San Raffaele Hospital, Milan, Italy. Only patients affected by primary IC-GCT with available complete information were included.

Data collection included patient demographics, height and weight measurements, timing, and features of symptoms at diagnosis, laboratory data (tumour markers, hormonal levels), tumour location, histology and staging. Since laboratory tests were performed in different institutions, we stratified tumour markers into 4 categories: normal, mild, moderate, and severe elevation. We chose 5 IU/L and 10 ng/mL as cut-off values for normal HCG and AFP levels, respectively; 50 IU/L and 25 ng/mL as cut-off levels distinguishing mild and moderate HCG and AFP levels; >500 IU/L and > 1000 ng/mL for severe HCG and AFP levels. Placental alkaline phosphatase (PLAP) staining on pathologic specimens was reported when available. Brain and spine MRI were mandatory for diagnosis and staging. Metastatic IC-GCT was defined as the presence of >1 intracranial focus (except for bifocal disease), spinal metastases, metastases outside the CNS, or the presence of tumour cells in CSF cytology. Definition of bifocal disease required radiological synchronous detection of tumour in both the pineal gland and the suprasellar region. The diagnosis of IC-GCT was histologically confirmed in 52/55 cases (94.5%). For two pathological undetermined specimens clinic-radiologic suspicion of IC-GCT was confirmed by raised CSF tumour markers; one patient did not undergo any biopsy as presumptive diagnosis of IC-GCT was based on tumour localization (bifocal disease with leptomeningeal dissemination).

Symptoms at diagnosis were classified into four groups: 1)raised intracranial pressure, RICP (headache, vomiting); 2)visual impairment; 3)endocrinopathy (polyuria/polydipsia, poor growth); 4)other (neurological signs, ataxia, fatigue, behavioural changes, worsen school performance).

Outcome measures and definitions

The key outcome measures regarding diagnostic intervals were calculated for each patient **(Fig. 1)** . Total diagnostic interval (TDI) was defined as the interval between date of the first reported symptom onset (including retrospective recall of symptoms) and diagnosis. Patient-related interval (PI) was defined as the interval between symptom onset and initial referral to a healthcare specialist; healthcare-related interval (HI) was defined as the interval between specialist evaluation and first brain MRI; tumour-related interval (TI) was defined as the interval between first brain MRI and definitive diagnosis of IC-GCT. Time lag to diagnosis from the first symptom longer than 6 months (TDI >6 months) was identified in all patients, to allow direct comparison of our results with previous studies[15,17,21,23], whereas PI, HI and TI were investigated only when an endocrine disorder was the presenting symptom. Subgroup analyses by age at diagnosis, tumour grade and tumour location were also performed.

We recorded oncologic treatments (chemotherapy, surgery, radiotherapy), tumour recurrence and death.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges (IQR) and were compared with the Mann-Whitney U test and Kruskal-Wallis H test (independent groups) or Wilcoxon signed rank test (paired groups). Categorical variables are presented as numbers/percentages and were compared with the χ^2 test or Fisher's exact test. Results of logistic regression are reported as odds ratio (OR) and 95% confidence interval (CI). The survival rate was estimated using the Kaplan–Meier method. Five-year progression-free survival (PFS) and OS were calculated from diagnosis to the date of last follow-up, progression, or death. P-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics (v.24; IBM Corp.-USA) and RStudio (v.1.3.1093; RStudio, PBC).

RESULTS

Baseline characteristics/demographics

Fifty-five children (52 from Royal Marsden Hospital and 3 from San Raffaele Hospital) were included. The characteristics of the study population are detailed in **Table 1** . The median age at tumour diagnosis was 12 (IQR 9–16) years, with a peak age between 9 and 10 years. Adolescents aged >11years accounted for 60% of cases. Most patients were boys (67.3%) and prepubertal at the time of diagnosis (54.5%).

Germinomas comprised most diagnoses (63.6% of the cohort). Children <5 years old (n=2) were diagnosed with teratoma, whilst germinoma occurred more frequently in older patients (p=0.052), especially in the 11-18 age group (n=24, 75%). Seven biopsies reported mixed GCT, all with a germinoma component.

Regarding the distribution of histology according to tumour locations, germinomas were significantly dominant in the suprasellar region (82.5%, p=0.047); together, NGGCTs accounted for 57.9% of the pineal tumours. Teratomas were also found in suprasellar region (n=3) and in atypical sites (n=2, right cerebropontine angle and thalamus). Seven cases occurred bifocally (7/55, 12.7%); among them, five were germinomas and two did not receive a histopathological diagnosis.

Six tumours were metastatic at diagnosis (10.9%), of which 4/6 were germinomas.

Serum AFP and beta-HCG were available for 53/55 (96.4%) and 52/55 (94.5%) subjects, respectively **(Table 1)** . For cytological detection of microdissemination, sampling of CSF was obtained; however, data on CSF tumour markers were missing for 6/55 subjects. Of the 4 tumours with severely elevated serum HCG, one case was teratoma and the remaining 3 cases had a mixed histology. Similarly, serum AFP was severely raised only in NGGCTs (2 yolk sac tumour, 1 teratoma and 1 mixed histology). On the contrary, normal levels of serum AFP and HCG were reported in 41 cases and 39 cases, respectively; they were all germinomas, aside from one teratoma that showed normal serum HCG levels and moderate elevation of both CSF HCG and AFP. PLAP results on biopsy samples prior to treatments were available in 30/55 cases (54.4%) and all of those that showed a positive PLAP staining were then diagnosed with germinoma, except for one (mixed histology with a predominant yolk sac component).

Treatment

Biopsy was performed in 46 patients and gross tumour resection in 8. Forty-two children received chemotherapy, which differed across time and centres, according to the International CNS Germ Cell Tumour Study Group and the Children's Oncology Group guidelines [8,24,25]. For 7 relapsed GCTs rescue treatment consisted in an aggressive approach of myeloablative high-dose chemotherapy (Etoposide/Thiotepa) followed by autologous stem cell transplant.

Radiation therapy was delivered to 50/55 patients (90%), with a median age of 11.6 years (range 5.4-18.3) at first radiation treatment. Among them, 13/50 patients (26%) received craniospinal irradiation (CSI) of 24-30.6 Gy (with boosted metastasis irradiation of 16 Gy in 8 cases), 9/50 patients (18%) whole brain irradiation of 54 Gy, 2/50 patients (4%) whole ventricular field irradiation (WVI) of 24 Gy without primary site simultaneous integrated boost, 21/50 patients (42%) WVI of 24 Gy with boost (16 Gy) and 5/50 patients (10%) received focal irradiation only (40-54 Gy).

Clinical presentation

The presenting symptoms included those attributable to RICP (24/55; 43.6%), endocrine disturbances (17/55; 30.9%), visual impairment (5/55; 9.1%) and other symptoms such as neurological signs, behavioural changes, and fatigue (9/55; 16.4%). Retrospectively, two patients exhibiting headache and visual disturbance reported previous history of uninvestigated endocrine manifestations (precocious puberty and polyuria/polydipsia). Among those patients who displayed endocrinopathy as first symptom, the majority (12/17; 70.6%) had diabetes insipidus, 4 patients (23.5%) with poor growth, and 1 boy (5.9%) with precocious puberty. By the time of tumour diagnosis, however, over half of the patients had developed hydrocephalus (29/55; 52.7%) or endocrine dysfunctions (28/55; 50.9%).

The symptom profile differed by tumour location: pineal GCTs manifested with symptoms of hydrocephalus (19/20) or visual defects (1/20), whereas all suprasellar GCTs initially caused symptoms related to endocrinopathies. Among the 7 bifocal tumours, 3 patients presented with RICP symptoms, 2 with an endocrinopathy (polyuria/polydipsia in both cases), 1 with diplopia and 1 with fatigue for 3 months.

Diagnostic intervals analysis

Overall, the TDI ranged from 0.25 to 58.5 months (median 4 months, mean 12 months); most patients were diagnosed within 10 months after the onset of symptoms. A statistically significant difference was found in subgroup analysis of TDI by tumour location and histology ($p<0.001$ and $p=0.006$, respectively). Pineal GCTs had the shortest interval compared with other locations, with a median TDI of 1 month (range 0-17) versus a median TDI of 24 months (range 0.25-58.5) in suprasellar GCTs (**Fig. 2**). Ranking of tumour histology identified germinoma as the one with the longest interval, but also with the most skewed distribution, with a median TDI of 7 months (range 0.25–58.5) and a mean TDI of 16.5 months. Patients aged <5 years and aged 5–11 years had similar TDI (median 6.3 months and 7.4 months, respectively), whilst older patients displayed a shorter TDI but with a wider range (median 3 months, 1–19), although without statistical significance ($p=0.88$).

TDI >6 months was observed in 26/55 patients (47.3%), whose demographic and clinical characteristics are summarized in**Table 2.** There was no significant correlation for TDI >6 months with age, histology, and metastatic disease at diagnosis, but we found a negative correlation with height at diagnosis ($p=0.043$). Regarding location of disease, pineal site was observed less frequently in those with TDI >6 months (3/26 patients; 11.5%) than in those with a TDI [?]6 months (17/29 patients; 58.6%) ($p<0.001$), whereas suprasellar tumours were predominant in the TDI >6 months group (17/26; 65.4%) ($p=0.002$). TDI >6 months was less associated with boys (86.2% vs 46%; $p=0.003$), although the role of sex was confounded by the 100% male predominance among pineal GCTs and the 67.3% among the whole cohort. The pattern of presenting symptoms differed significantly in those with TDI >6 months. Endocrine symptoms were more frequent (n=17/26; 65.4%) in those with TDI >6 months compared with those who were diagnosed in less than 6 months (n=0) ($p<0.001$). In contrast, RICP was an infrequent initial symptom (n=4/26; 15.4%) in those with TDI >6 months but was typically observed in those with TDI [?]6 months (n=20/29; 69%) ($p<0.001$).

Eight patients (14.5%) were followed with serial MRI for a median of 27 months (range 0.25–58.5) before the eventual diagnosis of IC-GCT. Nearly all (7/8; 87.5%) presented with central DI; the remaining patient exhibited poor growth. In the first MRI study, all cases demonstrated pituitary stalk thickening. Serum and CSF markers were initially mildly raised only in one patient. Progressive changes in the size of the infundibulum and/or development of new symptoms (especially hydrocephalus) led to biopsy, that was diagnostic for germinoma in all patients but one who did not undergo biopsy for the neuroradiological evidence of bifocal tumour.

In a subgroup of patients with endocrinopathies as presenting symptoms (17/55; 30.9%), we performed subgroup analysis of different lag intervals, referred as PI, HI and TI, stratified by age groups. PI and HI account for 78% of the TDI, collectively. PI did not differ significantly among the three age groups ($p=0.83$), although the >11 age group had the longest PI with a range from 8 to 26.5 months (median 18 months), compared with <5 age group (median 12) and the 5-11 age group (median 7.5). SI was also similar across age groups (median 1.0 vs 1.0 vs 1.8 months, $p=0.19$). Finally, the longest TI was found in subjects aged >11 years ($p=0.14$).

Outcomes

With median follow-up time from diagnosis of 78.9 months (range 0.5 to 249.9), 14 patients (25.4%) experienced relapses (5-year PFS 78.2%, 95%CI 0.67-0.91) (**Fig. 3A**). Eleven patients (20%) died of disease within 20.6 months (range 0.7–75.5) from diagnosis, resulting in 5-year OS of 80.2% (95%CI 0.70-0.92) in the whole cohort (**Fig. 3B**). GCTs in deceased subjects had various histology (germinoma n=2, NGGCTs n=7, undetermined n=2) and tumour location (suprasellar n=1, pineal n=5, bifocal n=2, other n=3).

OS and PFS were not statistical different between patients with TDI >6 months and with TDI [?]6 months (HR 0.39; 95% CI 0.10-1.48; p=0.168 and HR 0.39; 95% CI 0.14-1.05; p=0.05, respectively)**(Fig. 3C and 3D)** .

DISCUSSION

In this observational, retrospective cohort study we reviewed the different clinical presentations of patients diagnosed with IC-GCT and analysed the impact of several factors on diagnostic delay.

The prevalent histology was germinoma, whilst infants and young children <5 years old were affected exclusively by NGGCTs, congruently with previous reports [2,26]. This finding suggests that IC-GCTs in this age group may belong to a biologically different subset as proposed by others [27]. Elevated tumour markers were suggestive of NGGCT, although normal levels did not exclude the diagnosis of IC-GCT (teratoma or germinoma in our cohort)[28].

The clinical presentation depends on the size and position of the tumour. Our study confirmed that endocrine deficiencies manifested in sellar/suprasellar IC-GCTs, whereas pineal GCTs presented with symptoms of hydrocephalus. Moreover, a progression of symptoms was identified from the first initial presentation and most patients developed symptoms of RICP, which led to eventual diagnosis. In suprasellar tumours, hydrocephalus is usually a late and more insidious event but can be life-threatening and may contribute to visual and neurocognitive sequelae [29].

The median time to diagnosis of IC-GCT in our cohort was 4 months, shorter than the Japanese report [21]. Nevertheless, we have shown that the interval from the first symptom to diagnosis may vary significantly and, in some cases, may extend to nearly 5 years, confirming the wide variation already reported[17,18,23]. DI was often an early clinical manifestation in our cohort (70.6% of subjects who displayed endocrinopathy as first symptom), as described in other studies [18,19,30]. In a subset of patients with nondiagnostic first MRI, infundibular thickening was present with DI. The ideal management of these patients is unclear. Maghnie et al [31] reviewed the outcomes of 29 children with central DI and infundibular thickening on the first MRI. In these children, the eventual diagnosis was idiopathic DI in 18 cases, Langerhans cell histiocytosis in 5, GCT in 5, and autoimmune polyendocrinopathy in 1. Because GCTs were rarer than idiopathic DI, the authors recommended pursuing the diagnosis of GCT only in those patients with progressive infundibular enlargement.

A limitation of our study is that the estimated duration of symptoms is subject to recall bias. We acknowledge that the first symptom was derived from referral information and clinical notes and, consequently, the symptoms that patient/family described may not necessarily have been reported to healthcare professionals at the time. Only two patients were able to recognize in retrospect and define the onset of unnoticed endocrine manifestations several months prior to referral for headache or visual impairment.

In our study, nearly half of patients (47.3%) had TDI >6 months. Jennings et al.[26] in a meta-analysis of 215 patients, found that 35% of the patients were symptomatic for >6 months before being diagnosed with GCT. In 2007, Crawford et al. [15] analysed time from symptom onset to diagnosis in 30 patients with IC-GCTs: a small proportion of patients (9/30) had a time to diagnosis >6 months. Like our findings, however, the authors identified endocrinopathies as the major feature in deferred diagnosis. In our analysis, deferred diagnosis was also associated with tumour location. Pineal site of disease, which usually presents acutely with RICP, was less frequently associated with TDI >6 months. Conversely, patients with TDI >6 months were shorter, suggesting that endocrinopathies including poor growth, presented before the diagnosis of GCT and maybe neglected by both families and clinicians. Our results therefore highlight the difficulties faced in diagnosing this rare tumour.

No correlation between diagnostic delay and metastatic disease were found, differently from previous studies [17,23]. While Phi et al.[20] reported a significant association of deferred diagnosis with a poorer outcome in a subset of germinoma cases (n=13) among a cohort of 181 patients with localised IC-GCT, this result was not seen in other single-centre studies [15,17] nor in our multicentre study. In our cohort, OS and PFS was

similar in patients with and without deferred diagnosis.

Analysis of diagnostic sub-intervals in patients with endocrinopathies as presenting symptoms showed a lengthy TI in those subjects presented with DI and thicken pituitary stalk on MRI: the "occult" sellar tumours were only recognized on biopsy with a latency of up to 58.5 months. In a recent retrospective study of 55 cases from a large pituitary centre in China, average duration of MRI follow-up was 21.5±21.2 months in this subset of patients [32]. While TI depends sometimes on unchangeable and unpredictable factors (e.g. size and location of tumour for biopsy), time from onset of symptoms until first MRI, i.e. PI+HI, is clinically more relevant, because it gathers the importance of patient/family awareness (PI) with the clinical suspicion of the clinician to make an early diagnosis (HI). HI in our cohort was modest and did not appear to contribute considerably to TDI. A prolonged HI could also be due to lack of resources within the healthcare system. For example, waiting times for tertiary care clinics or for an MRI under general anaesthetic can cause substantial delays of weeks or months. The National Institute for Health and Care Excellence guideline suggests that paediatric patients with a suspected brain tumour should wait no longer than 4 weeks for an MRI[33]. While it is difficult (and less relevant as we demonstrated) to make changes to national healthcare service resources, education to improve awareness among healthcare professionals to aid early diagnosis is imperative. In 2011 the HeadSmart campaign was launched in the United Kingdom to enhance knowledge of brain tumour symptomatology and led to a reduction of the interval to diagnosis from a median of 14 weeks in 2006 to just 6.7 weeks in 2013[34].

As in other published studies [35,36], we found that TDI also increased with age, with the PI contributing the most towards TDI in the 12–18 age group. Since this deferred presentation trend has been noted across all specialties, there has been an increasing focus on teenage and young adult (TYA) groups in healthcare over the last decade[37]. The reasons for delays in the TYA group are multifactorial; adolescence is a period of unique psychological and physical change. It is well known that young people have difficulties forming therapeutic relationships with healthcare professionals and accessing health services[38]. Identifying ways to engage young people and empowering them with knowledge and resources (i.e. school visits, social media, celebrity ambassadors), may create an opportunity for earlier diagnosis.

CONCLUSION

Patients with IC-GCT are often evaluated by a broad spectrum of paediatric providers. Lack of specific clinical symptoms and an interval between initial symptoms and radiological detection contribute to the diagnostic difficulties. If an endocrine abnormality appears clinically or from laboratory results, especially together with the presence of neurological symptoms, an IC-GCT should be considered, and a brain MRI should be performed. Early diagnosis is important to minimise late effects from tumour growth and treatment, although we demonstrated no significant difference in PFS and OS in patients with and without deferred diagnosis. Therefore, in most cases the cerebral alterations could be monitored until a formal diagnosis is reached.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest. FC is partly funded by the Giant Pledge via the Royal Marsden Cancer Charity. The Paediatric Neuro-Oncology and Drug Development Units receive charitable funding from the Hall-Hunter Foundation via the Royal Marsden Cancer Charity.

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FIGURE LEGEND

Figure 1 – Diagnostic intervals between symptom onset and definitive diagnosis of Intracranial Germ Cell Tumour (IC-GCT). Patient-related Interval, Healthcare-related Interval, and Tumour-related Interval only apply to tumours presenting with endocrine symptoms.

Figure 2 – Total diagnostic interval by tumour location.

Figure 3 – Kaplan-Meier curve of 5-year progression-free survival (panel A) and overall survival (panel B) at last follow-up in the entire cohort. Five-year progression-free survival (panel C) and overall survival (panel D) for all patients with TDI >6 months (orange dashed curve) and TDI [?]6 months (blue solid curve) diagnosis.

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