

## Epidemiological survey of central nervous system germ cell tumors in Canadian children

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### Abstract

**Objectives** To determine the incidence and characteristics of pediatric patients with central nervous system (CNS) germ cell tumors (GCT) in Canada.

**Method** A national retrospective review of hospital charts was done on all patients with CNS GCT diag-

nosed between 1990 and 2004. Patients had to be under age 18 years at the time of diagnosis of a CNS germ cell tumor and be a resident of Canada. Information extracted included age and year of diagnosis, pathological diagnosis, location of tumor, evidence of disseminated disease at time of diagnosis and biological markers.

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**Results** One hundred and twenty-one cases were identified (83 germinoma; 38 non-germinoma germ cell tumor). The mean annual incidence of CNS GCT was 1.06 per million children (0.7 per million for germinoma; 0.3 per million for NGGCT). Though yearly incidences varied, there was no clear trend to increased incidence. Male predominance was noted (2.4:1 for germinoma; 11:1 for NGGCT). The primary locations were the pineal and suprasellar regions. At the time of diagnosis, disseminated disease was not uncommon (22% germinoma; 32% NGGCT).  $\beta$  human gonadotrophin was elevated in the serum, cerebrospinal fluid (CSF) or both in 7% of patients with germinoma and 36% of patients with NGGCT. Elevation of  $\alpha$ -fetoprotein in serum, CSF or both was seen in 34% of patients with NGGCT.

**Conclusion** The incidence of CNS germ cell tumors in Canadian children is similar to that observed in other Western countries.

**Keywords** Incidence · Germ cell tumors · Childhood

## Introduction

Germ cell tumors (GCT) of the central nervous system (CNS) are rare in children. These tumors have been divided by The World Health Organization into benign (mature teratomas) and malignant (germinoma and non-germinoma) tumors based on histology and the presence of tumor markers ( $\alpha$ -fetoprotein (AFP) and  $\beta$ -human chorionic gonadotrophin ( $\beta$ -HCG)). The NGGCT group consists of embryonal carcinoma, endodermal sinus tumor, choriocarcinoma and mixed germ cell tumors. This group of tumors is often associated with increased secretion of tumor markers, whereas CNS germinomas are typically non-secreting tumors. However, noticeable differences can be observed between reports, depending on the cut-off used for  $\beta$ -HCG for germinoma versus NGGCT and the interpretation of histological findings when they are discordant with the results of tumor markers.

Variations in incidence rates have been reported for different racial groups. In North America and Europe, germ cell tumors of the CNS have been reported to account for 0.1–2.4% of all childhood brain tumors; whereas, in Japan and the Far East, CNS germ cell tumors account for 2.1–9.4% [1–17]. The reason for this difference remains unclear, but it has been postulated that oriental populations have a higher genetic predisposition for these tumors. An additional explanation may be in patient definition

and tumor classification. Many of the previous reports were based on the experience of a single institution rather than population based. Histologic diagnoses of the tumors were not always available, reflecting differences in treatment philosophy. In some series, especially from Japan, patients with a homogeneous enhancing mass in the pineal region and lack of elevation of tumor markers were presumed to have a germinoma. Rather than pathological confirmation of the diagnosis, an empiric trial of radiotherapy was given. If the tumor responded to the therapy it was presumed to have been a germinoma. A survey of individual surgical experience for treating pineal region tumors conducted in the early 1990s showed that 80% of neurosurgeons from Asian countries would consider a trial of radiation for pineal tumors, whereas 77% of neurosurgeons in Europe and America would recommend definitive histological diagnosis as the initial procedure in the management of these tumors [18].

Canada has a government-funded, regionalized health care system, especially for specialized services. Children with brain tumors are treated at university-affiliated teaching hospitals. Thus, a systemic survey of all pediatric Canadian brain tumor programs would be expected to capture all childhood and adolescent cases of germ cell tumor. Assuming there is a genetic predisposition for malignant germ cell tumors, it is postulated that the incidence of malignant germ cell tumors of the CNS in Canada should be similar to that reported for United States and Europe but less than that reported for Japan.

## Method

### Case definition

The Canadian Pediatric Brain Tumor Consortium has representation from all of the Canadian university-affiliated teaching hospitals. A member of this Consortium from each center was identified to collect the relevant data from his or her center. Cases at each center were identified through a retrospective review of hospital medical records and/or clinic databases. To avoid the effect of increased identification secondary to advent of magnetic resonance imaging the identification period was from 1990 to 2004 inclusive.

### Inclusion criteria

Patients had to have a diagnosis of primary germ cell tumor of the CNS, had to be a resident of Canada, and under 18 years of age at the time of diagnosis.

## Data collection

Using a standardized questionnaire, information regarding sex, age at diagnosis, year of diagnosis, ethnic origin, pathological diagnosis based on World Health Organization classification, location of tumor, evidence of dissemination at time of diagnosis, spinal fluid cytology, and concentration of AFP and  $\beta$ -HCG in spinal fluid and blood was collected for each identified case. This information was forwarded to a central data collection site for analysis. For the purpose of the data collection, the cut-off for tumor markers was defined as follows: a value of  $\beta$ -HCG  $< 50$  IU/l associated with a histological diagnosis of germinoma was considered normal. In the absence of histological diagnosis tumors were considered, NGGCT if  $\beta$ -HCG  $> 50$  IU/l or any abnormal value of AFP.

## Data analysis

Data were entered into a central database using SPSS13 software. Descriptive statistics for sex, age at time of diagnosis, tumor location, and evidence of dissemination at time of diagnosis, spinal fluid cytology and secretory marker concentrations were calculated for the group as a whole, as well as for the pathological groups of germinoma and NGGCT. Incidence figures for the groups were calculated based on 2000 census data from Statistics Canada [19].  $\chi^2$  analysis was used for proportional differences. Differences in population means were calculated using student *t*-test. Significance level for this study was defined as  $p < 0.05$ .

## Ethical considerations

Each of the participating centers received approval from their local Research Ethics Review Boards prior to participating in this survey. No patient identifiers were included in the questionnaire or included in the central data collection.

## Results

### For group as a whole

Responses were received from all of the 17 institutions surveyed. Between the years 1990 and 2004 inclusive, 121 cases of malignant primary CNS germ cell were reported with a mean yearly incidence rate of  $1.06 \pm 0.44$  per 1,000,000 children under 19 years of age (95% CI 0.79–1.28). The mean age at time of diagnosis was 11.6 years (range 3–18 years). The male

to female ratio was 3.5:1. Sixty-five (53.7%) tumors were reported to involve the pineal region, 37 (30.6%) the suprasellar region, 10 (8.3%) bifocal, six (5%) the basal ganglia and three (2.5%) other regions. At the time of diagnosis, imaging evidence of disseminated/multifocal disease was present in 27 (22.3%) of the cases and 17 (22%) had positive CSF cytology. Serum AFP levels were available in 104 (77.6%) cases. Thirteen cases (12.5% of the cases in for which values were available) demonstrated levels above the institution's normal range. Cerebrospinal fluid levels of AFP were available in 75 (65.7%) cases. Twenty cases (26.5% of the cases for which values were available) demonstrated levels above the institution's normal range. Serum  $\beta$ -HCG levels were available for 101 (83.5%) cases. Twenty cases (20% of the cases for which values were available) demonstrated levels above the institution's normal range. Cerebrospinal fluid  $\beta$ -HCG levels were available for 79 (65.3%) cases. Twenty cases (16.5% of the cases for which values were available) demonstrated levels above the institution's normal range. When the AFP concentrations were available in both the serum and the cerebrospinal fluid, abnormal results (if present) were often obtained in both (Table 1). A similar pattern was noted for  $\beta$ -HCG secretion (Table 1).

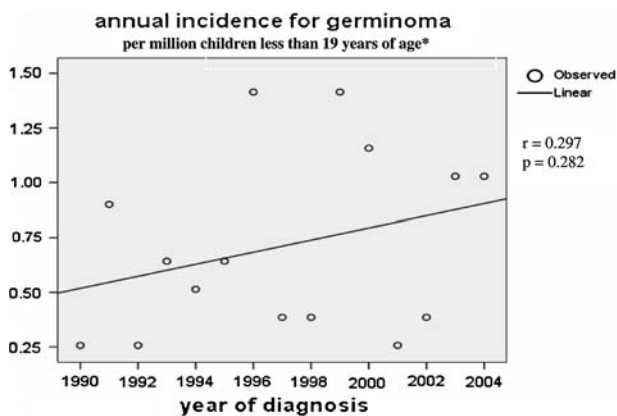
### Germinoma group

Eighty-three (69%) patients were diagnosed as having a germinoma giving a mean annual incidence rate of  $0.71 \pm 0.44$  per 1,000,000 children under 18 years of age (95% CI 0.48–0.91). There was a non-significant trend towards an increase in the annual incidence over the period of this study (Fig. 1). Pathological confirmation of this diagnosis was present in all cases. The mean age at time of diagnosis was 12.3 years (range 4–18 years). The male to female ratio was 2.8:1. Thirty-seven (44.6%) tumors involved the pineal region, 29 (34.9%) the suprasellar region, nine (10.8%) bifocal, five (6%) the basal ganglia and three (3.6%) other regions. At the time of diagnosis, imaging evidence of disseminated disease was present in 19 (14.5%) cases and 12 (15%) had positive cerebrospinal fluid cytology. Serum and CSF AFP levels were within normal ranges in all cases tested. Serum  $\beta$ -HCG levels were available for 69 (83.1%) cases. Six cases (8.7% of the cases for which values were available) reported levels above the institution's normal ranges. Cerebrospinal fluid  $\beta$ -HCG levels were available for 52 (62.6%) cases. Six cases (7.2% of the cases for which values were available) reported levels above the institution's normal range.

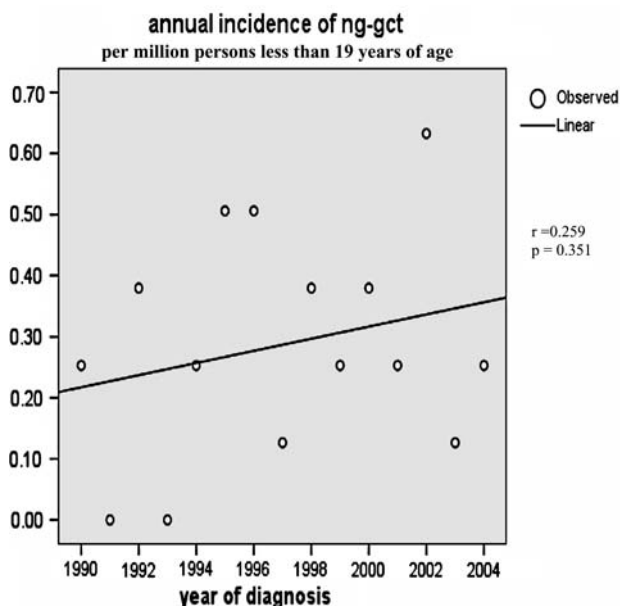
**Table 1** Comparison of the concentration of  $\alpha$ -feto protein (AFP) and  $\beta$ -human chorionic gonadotropin ( $\beta$ -HCG) between CSF and Serum

| Marker       | Tumor group | Number of patients with [Serum] & [CSF] normal | Number of patients with ↑[Serum] & [CSF] normal | Number of patients with [Serum] normal & ↑[CSF] | Number of patients with both ↑[Serum] & ↑[CSF] |
|--------------|-------------|--|---|---|--|
| AFP          | Total group | 52   | 4   | 3   | 5  |
|              | Germinoma   | 43   | 0   | 0   | 0  |
|              | NGGCT       | 9  | 4   | 3   | 5  |
| $\beta$ -HCG | Total group | 47   | 3   | 5   | 15   |
|              | Germinoma   | 39   | 2   | 2   | 4  |
|              | NGGCT       | 8  | 1   | 3   | 11   |

When the concentration of  $\beta$ -HCG in both the serum and cerebrospinal fluid was available, results were often abnormal in both (Table 1).



**Fig. 1** Change in annual incidence of germinoma per 1,000,000 persons less the 19 years of age



**Fig. 2** Change in annual incidence of NGGCT per 1,000,000 persons less than 19 years of age

### NGGCT group

Thirty-eight cases were diagnosed with NGGCT. The mean yearly incidence for NGGCT was  $0.29 \pm 0.18$  per 1,000,000 children under 18 years of age (95% CI 0.19–0.39). There was a non-significant trend towards an increase in the annual incidence over the period of this study (Fig. 2). Pathological confirmation of diagnosis was available in 13 of these patients. In the rest, the diagnosis was based on elevated biological markers in either CSF, serum or in both. The mean age at time of diagnosis was 10.5 years (range 3–16 years). The male to female ratio was 11:1. Twenty-eight (73.7%) tumors involved the pineal region, eight (21.1%) the suprasellar region, one (2.6%) bifocal, and one (2.6%) the basal ganglia. At the time of diagnosis, imaging evidence of disseminated disease was present in eight (31.4%) cases and five (13%) had positive cerebrospinal fluid cytology. AFP levels were available in 28 (73%) cases. Thirteen cases (46% of the cases for which values were available) reported levels above the institution's normal range. Cerebrospinal fluid levels of AFP were available in 32 (84%) cases. Twenty cases (62% of the cases for which values were available) reported levels above the institution's normal range. Serum  $\beta$ -HCG levels were available in 32 (84%) cases. Fourteen cases (44% of the cases for which values were available) reported levels above the institution's normal ranges. Cerebrospinal fluid  $\beta$ -HCG levels were available in 27 (71%) cases. Fourteen cases (51% of the cases for which values were available) reported levels above the institution's normal range. When the concentration of AFP in the serum and cerebrospinal fluid was available, it was often elevated in both (Table 1). A similar pattern was noted for  $\beta$ -HCG secretion (Table 1).

### Ethnicity

The ethnic origin of the cases is documented in Table 2. Though there is a trend for CNS germ cell tumors to occur more frequently in persons of or-

**Table 2** Distribution of germ cell tumors across ethnic groups in Canada

|           | % Canadian population <sup>a</sup> | % Total group | % Germinoma | % NGGCT |
|-----------|------------------------------------|---------------|-------------|---------|
| Caucasian | 50                                 | 59            | 61.4        | 55.3    |
| Oriental  | 5                                  | 11            | 10.2        | 13.2    |
| Other     | 6                                  | 1.8           | 2.4         | 0       |
| Unknown   | 39                                 | 27.3          | 25.3        | 31.6    |

<sup>a</sup> Based on census data

iental origin, this did not reach significance. Determination of ethnic origin of patients proved problematic in this study. This information was frequently missing from the hospital medical record. As well, the data for ethnic origin of Canadian children under 18 years was not reported in 39% of children during census collection.

## Discussion

The mean annual age-adjusted incidence rate for CNS germ cell tumors in Canada was found to be 1.06 per million children less than 18 years of age. Our incidence figures were similar to those reported from the Central Brain Tumor Registry of the United States (CBTRUS) [20], but significantly less than those for Japan [12, 21]. Unlike other studies, we were unable to demonstrate a significant trend of increased incidence rate of this tumor in our population. Kaneto et al. [10] reported a step-up increase in the 1980s followed thereafter by a plateau. CBTRUS data, which were collected over several decades, reported a significant trend to increased incidence rate [20]. In both these studies, cases were gathered over a time period in which imaging technology and diagnostic methods for CNS-GCT changed. In order to avoid the effect of these changes on tumor detection, the time period chosen for our study was 1990–2004 [22]. During this time period, the use of magnetic resonance imaging was already common practice in Canada.

The overall incidence of brain tumors in children under 18 years of age is similar between countries [9, 16]. A significant difference in the relative frequency of CNS germ cell tumors has been reported between countries. The frequency is reported to be significantly less in North American and European countries compared to Asian countries [1–17]. It has been postulated that there is an increased genetic predisposition for CNS germ cell tumors in persons of oriental background [11]. If this were correct, we would expect an increased rate of occurrence among children of

oriental background compared to children of other ethnic background living in Canada. Due to our small sample size and lack of information about ethnic backgrounds for a significant number of our cases as well as for the Canadian population, we are unable to confirm or refute this hypothesis.

Considering the rare occurrence of this tumor, minor differences in the method of case detection between studies could result in differences in incidence rates. Many of the previous studies are retrospective reviews reporting the relative frequency of this tumor relative to all brain tumors [1–8, 10, 11, 13–15, 17]. The cases were gathered using a single referral based institution tumor registry. The information describing the population from which the cases were drawn was often limited if present at all. This does not allow for accurate calculation of national incidence figures. The possibility that the case mix may have resulted from referral bias cannot be excluded. Using the data from a single institution could thus result in a biased calculation of the relative frequency of this tumor. In an attempt to control for this bias, in this study cases were gathered by means of a national survey of all Canadian institutions involved in care of children with brain tumors.

The accurate calculation of the frequency of this tumor depends on the sensitivity and specificity of the diagnostic methods being used. Diagnostic approaches have varied within and between countries [23]. The need for tissue diagnosis in all cases is a controversial topic in the medical literature. For example, a patient of oriental background with magnetic resonance imaging evidence of a homogeneous enhancing mass in the pineal region without evidence of elevated secretory markers is felt by some neurosurgeons to have a diagnosis of germinoma. As this tumor is highly radiosensitive a trial of radiotherapy may be undertaken without tissue diagnosis. If there is a response, this is considered confirmation of the diagnosis of germinoma. Radiation therapy is continued without surgical intervention. If there is no response, further investigations occur. As other tumors in this region can also be radiosensitive, in order to get an accurate diagnosis, others have recommended biopsy. However, biopsy in itself does pose the risk of mis-diagnosis secondary to inadequate or incomplete tissue sampling.

The use of secretory markers (AFP and  $\beta$ -HCG) for detection of NGGCT is not uniform across studies and often includes only serum and not CSF determination. Our study, and that of Allen et al. [24], shows that in some cases the cerebrospinal fluid values can be elevated without elevation in the serum value.

Thus, there is the potential for mis-classification of tumor type based on serum determination particularly if pathological specimens are not available.

Another difficulty with use of biological secretory markers is related to mild elevations in serum and/or CSF  $\beta$ -HCG levels in pathologically confirmed germinoma. Though the concentrations are reported to be less than occur in NGGCCT, a tumor diagnosis based on markers only may result in mis-classification in cases where pathological confirmation of diagnosis of germinoma is not present. The presence of elevated markers in some germinoma cases raises the question as to whether this group of germinomas should be classified as germinoma or mixed germ cell tumors. Results of treatment trials suggest that the secreting germinoma behaves similarly to non-secreting germinoma [25]. For this reason, we did not perform separate analyses for secreting and non-secreting germinomas in the present study. However, the cut-off value for  $\beta$ -HCG levels remains a matter of debate and several Japanese and Korean series include in their germinoma groups patients with  $\beta$ -HCG levels over 50 or 100 IU/l [25].

Our study is limited by its design. In order to meet the requirement of the Canadian Privacy Laws, access to certain types of information was limited. Information that might identify the patient could not be used nor were we able to perform a central review of pathological specimens or radiological studies. Information was obtained by a retrospective search of medical records in multiple centers by a local representative. Cases may have been missed through variation in diagnostic coding and chart retrieval methods used at the different institutions.

In conclusion, the mean annual incidence rate for germ cell tumors in Canada was approximately 1.06 per million children less than 19 years of age. The tumors were more frequent among males than females with a mean age of occurrence of 12 years. Germinoma were significantly more frequent than non-germinoma germ cell tumors. There was a non-significant trend to increased incidence of germ cell tumors in children of oriental origin. This study reviews all pediatric patients treated in Canada for CNS germ cell tumors, and the results provide important information for clinicians caring for these patients.

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