Incidence of Childhood Central Nervous System Tumors in the Nordic Countries

Lisbeth Samso Schmidt, MD,1,∗ Kjeld Schmiegelow, MD, DMSC,2,3 Paivi Lahteenmaki, MD, PhD,4 Catarina Träger, MD, PhD,5 Tore Stokland, MD,6 Katrine Grell, MS,1 Göran Gustafson, MD, PhD5 and Joachim Schüz, PhD1

Background. The incidence rates of childhood central nervous system (CNS) tumors in the Nordic countries remain among the highest in the world. Large geographical and temporal variations in the incidence rates of CNS tumors have been reported. Increasing incidence rates would be a public health concern, as they might indicate increased exposure to environmental risk factors. Methods. All 3,193 children 0–14 years of age registered with a primary CNS tumor in 1985–2006 in the national cancer registries of the Denmark, Finland, Norway, and Sweden were identified. Tumors were classified according to the International Classification of Childhood Cancer version 3 (ICCC-3). Join-point analysis was used to detect changes in trends and to estimate annual changes in incidence rates. Results. The mean annual incidence rate of CNS tumors was 42 per million. No statistically significant change in time trends of incidence rates was observed during 1985–2006. Furthermore, the incidence by birth cohort was relatively stable during the study period. Conclusion. The incidence rates of childhood CNS tumors in the Nordic countries remain among the highest in the world. The stable incidence rates during the last 22 years indicate that major changes in environmental risk factors are unlikely. Pediatr Blood Cancer 2011;56:65–69. © 2010 Wiley-Liss, Inc.

Key words: astrocytoma; child; CNS tumor; incidence; Nordic countries

INTRODUCTION

Monitoring changes in incidence rates of childhood cancers has drawn considerable attention, since such changes could reflect changes in exposures to environmental risk factors, and hypothesis-driven research could lead to preventive measures. The incidence rates of childhood CNS tumors varies considerably internationally, with annual incidence rates ranging from 20 to 40 per million [1]; the highest incidence rates in the world are reported in the Nordic countries [2–5]. Increasing incidence rates have been reported in various parts of the world including Europe, Australia and USA [4,6–9], including the Nordic countries [2,5,10]; however, recent publications suggested that the incidence rates are leveling off [3,11–14] or even decreasing [15,16]. It remains to be determined whether the variations overtime reflect a true biological phenomenon or a change in the registration of benign tumors [17], better case ascertainment [18], changes in classification criteria [19], improved diagnostic tools [8,20], or social inequality in access to health care. Childhood tumor registration in the Nordic countries provides a unique tool for addressing these questions, as the Nordic cancer registries have a history of more than half a century; they are mandatory and regulated by law; and they are validated or supplemented with other independent data sources, such as pathology registries, hospital discharge registries, death certificate registries and independent childhood cancer registries, which ensure almost 100% coverage. In the present study, we describe the temporal trends of childhood CNS tumors in the Nordic countries in 1985–2006, overall and by histological subgroup according to the International Classification of Childhood Cancer, 3rd edition (ICCC-3) [21].

METHODS

The cases were all primary CNS tumors in children 0–14 years of age with a diagnosis made between 1 January 1985 and 31 December 2006, who resided in Denmark, Norway, Sweden, or Finland at the time of diagnosis. CNS tumors were defined according to main group III of ICCC-3 [21], which includes both benign and malignant primary tumors of the CNS but excludes germ cell tumors and lymphomas located in the CNS. Cases were identified from the national cancer registries [22]. In addition, we searched for incident cases in the childhood cancer registries of Sweden and Denmark and in the Nordic Society of Paediatric Haematology and Oncology database of solid tumors in Norway. Furthermore, diagnostic information on the Swedish and most of the Danish cases was re-abstracted and recorded on the basis of information from the medical records in connection with previous studies [3,5]. For tumors classified as gliomas, data from the Finnish Cancer Registry were supplemented with data from pathology reports in order to characterize them to a more specific level than that available in the Registry. Calculation of the incidence is based on yearly population data from the national population registries, which are continuously updated on an individual level regarding vital status and migration. Age-standardized rates (ASR) were calculated by the direct method from the age-specific incidence rates for 5-year age groups with the weights for the World Standard Population 2000–2025 provided by the World Health Organization. A piecewise log-linear model called “join-point analysis” [23] was used to detect changes in trends and to estimate both annual percentage change (APC)
<table>
<thead>
<tr>
<th>Histology</th>
<th>0–4 years</th>
<th>5–9 years</th>
<th>10–14 years</th>
<th>0–14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>788</td>
<td>690</td>
<td>740</td>
<td>616</td>
</tr>
<tr>
<td>Males</td>
<td>457</td>
<td>387</td>
<td>426</td>
<td>383</td>
</tr>
<tr>
<td>Females</td>
<td>331</td>
<td>303</td>
<td>314</td>
<td>233</td>
</tr>
<tr>
<td>Average annual incidence (IR)</td>
<td>182</td>
<td>182</td>
<td>182</td>
<td>182</td>
</tr>
<tr>
<td>Average annual change (%)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.25 to 1.25</td>
<td>1.25 to 1.25</td>
<td>1.25 to 1.25</td>
<td>1.25 to 1.25</td>
</tr>
</tbody>
</table>

Fig. 1. Age-specific incidence rates of childhood CNS tumors by histological subgroup.

and average annual percentage change (AAPC) in incidence rates.

The model was specified to include a maximum of four join-points, which could be placed in the middle of a year (e.g., 2003) or between two consecutive years (e.g., between 2003 and 2004). We denoted the latter join-points by adding 0.5 (e.g., 2003.5). We chose to let the model constrain the join-points to at least 2.5 years from each other and at least 3 years from the boundaries of the total study period. The best fitting model was searched on 4,499 randomly permuted datasets, according to the grid method [23] with overall significance level of 0.05, under the assumption of heteroscedastic variance and uncorrelated errors. Incidence rates by birth cohort were calculated by summarizing the incidence rates by increasing age group in consecutive years divided by the number of years of observation (i.e., 5 years for age groups and 15 years for the overall estimates). The study was approved by the national data protection boards in all four countries.

RESULTS

During 1985–2006, 4,263 children 0–14 years of age were registered with a primary CNS tumor. Of these, 280 were excluded (lipomas, hemangiomas, germ cell tumors, adenomas, neurofibromas), as they were not classified as CNS tumors in ICCC-3 main group III. Hence, the final number for analysis was 3,983 incident cases of CNS tumor (Table I). The overall age-adjusted incidence rate (ASR) was 42 cases per million; the rates were 43 in Denmark, 42 in Sweden, 40 in Norway, and 40 in Finland. The incidence of CNS tumors was slightly higher in males than in females, with a ratio of 1.2:1. Most of the difference was accounted for by a male predominance of embryonal CNS tumors (Table I). The most frequent tumor was astrocytoma, with an average annual incidence of 18 per million. The age-specific incidence rates varied by histological subgroup (Fig. 1). Most ependymomas occurred in the first 2 years of life. The age-specific incidence rate for embryonal CNS tumors was 10–12 per million in the first 2 years of life and lower after the age of 10 (incidence rate IR) 3–4 per million). Two peaks of age-specific incidence rates were observed for astrocytoma, at age 4 and 12 years, with incidence rates of 27 and 18 per million, respectively.

No time trend was observed in the join-point regression analysis, that is, the curve was compatible with a slope of 0 (Fig. 2). One
Fig. 2. Age standardized incidence of childhood CNS tumors in the Nordic countries 1985–2006. Including all histological subgroups classified as CNS by ICCC-3 (per million person years).

Fig. 3. Age standardized incidence rates by histological subgroup in the Nordic countries (per million person years).

Fig. 4. Age specific incidence rate of CNS tumors by birth cohort in the Nordic countries (per million person years).

DISCUSSION

The incidence of childhood CNS tumors has been stable in the Nordic countries during the past 22 years. With an average annual age-standardized incidence of 42 per million, the incidence remains among the highest in the world [1]. Interestingly, recent publications from registries in United Kingdom, USA, and Eastern Germany, which include both malignant and benign tumors, have reported that the incidence is leveling off at a level close to that in the Nordic countries [9,17,24].

CNS tumors in children are a heterogeneous group, with more than 100 histological rare and distinct entities and variation in classification and registration practices complicates the characterization of temporal trends. The high incidence in the Nordic countries probably reflects the completeness of the registries, due to national coverage, compulsory registration of both benign and malignant tumors, registration from various sources and a public health-care system that is free and offers the same diagnostic and medical care for all citizens. Smith et al. [8] argued that the observed temporal variations in USA are due to differences in registration and diagnostic tools and do not represent real differences in incidence. They linked the rapid, although relatively small rise in CNS tumor incidence among children in the mid-1980s to the increased availability of magnetic resonance imaging, by demonstrating that the incidence did not increase steadily but rather jumped from a relatively constant level before 1984–1985 to a steady but higher level after 1985.

Join-point was found with the Danish data only; while the incidence rate increased initially (1985–1995.5: APC, 5.7; 95% CI, 3.4–8.0), it then decreased (1995.5–2006: −3.8 (−5.9 to −1.7)). No join-points were observed for the other three countries. A statistically significantly decreased annual percentage change in the incidence of astrocytoma of 1.26% was observed, whereas a nonsignificant increase was observed for embryonal CNS tumor and other specified CNS tumors (Table II and Fig. 3). After stratification by age group, the highest incidence was observed in the youngest cases, with rates of 46.9 per million at 0–4 years, 42.8 at 5–9 years and 35.7 at 10–14 years. A small, statistically significant increase in incidence rate was observed for children 10–14 years of age, with an annual increase of about 1% there was a small, statistically nonsignificant decrease for 5–9-year-olds and an average annual change of close to 0

Table II. Annual and Average Annual Percentage Changes in Incidence Rates by Sex and Age Groups

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>No. of cases</th>
<th>Period</th>
<th>Annual change (%)</th>
<th>95% CI</th>
<th>Average annual change (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>2,134</td>
<td>1985–2006</td>
<td>0.11</td>
<td>−0.76 to 0.98</td>
<td>0.11</td>
<td>−0.71 to 0.93</td>
</tr>
<tr>
<td>Females</td>
<td>1,849</td>
<td>1985–2006</td>
<td>−0.11</td>
<td>−0.87 to 0.66</td>
<td>−0.11</td>
<td>−0.82 to 0.61</td>
</tr>
<tr>
<td>0–4 years</td>
<td>1,448</td>
<td>1985–2006</td>
<td>−0.02</td>
<td>−0.96 to 0.93</td>
<td>−0.02</td>
<td>−0.90 to 0.87</td>
</tr>
<tr>
<td>5–9 years</td>
<td>1,356</td>
<td>1985–2006</td>
<td>−0.67</td>
<td>−1.47 to 0.13</td>
<td>−0.67</td>
<td>−1.42 to 0.08</td>
</tr>
<tr>
<td>10–14 years</td>
<td>1,149</td>
<td>1985–2006</td>
<td>1.02</td>
<td>0.13 to 1.91</td>
<td>1.02</td>
<td>0.19 to 1.86</td>
</tr>
</tbody>
</table>

Pediatr Blood Cancer DOI 10.1002/pbc
tumors can reveal changes in the prevalence of environmental risk variation due to the small numbers of cases. Differences in temporal trend by age group may also reflect random specified CNS tumors observed in children 10–14 years of age. The diagnosis of more low-grade tumors such as dysembryoplastic neuroepithelial tumors or other benign tumors, the incidence will vary according to pathology reports, so that tumors originally classified as gliomas were reclassified, mainly as astrocytoma and other gliomas. The increasing incidence of childhood CNS tumors reported previously in Denmark [5] was reproduced in our study, as the join-point analysis suggested a peak in 1995. This was, however, followed by a decrease, leading to a stable trend over the entire period. However, it should be kept in mind that it is difficult to reliably detect changes in incidence rates of a rare disease such as CNS tumors in children in small countries and time trends become more stable when pooling data of the Nordic countries.

The international variation is also likely to reflect the use of many different, often not comparable classifications [21, 24, 26]. In order to meet the need for international standardization of childhood cancers, an international classification was proposed by Birch and Marder [27] on the basis of ICD-O morphology and topography codes, with updates [21]. One disadvantage of the classification, however, is that the degree of malignancy is not taken into account. Unfortunately, many authors who report results according to the ICCC classification fail to state whether they excluded certain codes in the original version of the classification. Furthermore, if a cancer registry has different inclusion criteria, for example, excluding dysmyeloplastic neuroepithelial tumors or other benign tumors, the incidence will not be comparable to international standards.

Overreporting is a potential problem in cancer registries such as those of the Nordic countries, which include hemangiomata, lipoma and hamartoma as intracranial tumors, whereas they might be classified as unspecified CNS tumors if no conclusive biopsy is available and there is clinical uncertainty after radiological imaging. We attempted to avoid overreporting in the present study by re-abstraction, re-coding and cross-checking data from various sources. Changing diagnostic practice and the introduction of new histopathological entities can also affect the incidence rates of histological subgroups over time. A substantial interobserver variability of the pathological evaluation is well recognized and may add further to the variation of the reported incidences [28]. Furthermore, the increasing use of neuroimaging and surgery in searching for the structural causes of epilepsy [29] might have resulted in the diagnosis of more low-grade tumors such as dysmyeloplastic neuroepithelial tumors, which might explain the increases in other specified CNS tumors observed in children 10–14 years of age. The differences in temporal trend by age group may also reflect random variation due to the small numbers of cases.

Detection of changing patterns in the incidence rates of CNS tumors can reveal changes in the prevalence of environmental risk factors and provide new hypotheses for their etiology. If exposures to environmental risk factors during pregnancy or in the early neonatal period are changing, we would have expected a birth cohort effect, but the incidence of CNS tumors by birth cohort was relatively stable during the study period. Nevertheless, the number of birth years studied was limited.

In summary, the age-standardized incidence rates of childhood CNS tumors in the Nordic countries have been stable over the past 22 years. It is therefore unlikely that major changes in environmental risk factors have occurred during this period.

REFERENCES