Is primary CNS lymphoma really becoming more common?  
A population-based study of incidence, clinicopathological features and outcomes in Alberta from 1975 to 1996

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Summary

Background: The incidence of primary CNS lymphoma (PCNSL) is believed to be increasing in immunocompetent patients but this may not be universally true. The objective of this study was to determine in a population if the incidence of PCNSL is increasing, if the histologic subtypes are changing, and to describe the clinicopathologic and outcome characteristics of PCNSL.

Patients and methods: We identified all Alberta residents with a histologic diagnosis of PCNSL from 1 January 1975 to 31 December 1996 using the Alberta Cancer Registry. Annual age-standardized incidence rates (ASIR), clinicopathologic and outcome characteristics were determined.

Results: There were 50 immunocompetent PCNSL patients; the median age was 64 and 30 were male. Their median survival was 10.15 months. Histology was available for review in 37 (74%) patients: 19 (51%) were diffuse large cell, 16 (43%) were immunoblastic and 2 (5%) were unclassifiable malignant lymphomas. The ASIR ranged from 0.178-1.631/106 and no change in ASIR was found (test for trend, \( P = 0.26 \)) for gender or age. The ASIR of malignant gliomas did not change either but increased for all other non-Hodgkin's lymphoma (94.95-138.76/106; test for trend, \( P = 0.0001 \)) The number of brain biopsies increased from 1979-1985 (test for trend, \( P < 0.0001 \)) but remained stable from 1986-1996 (test for trend, \( P = 0.99 \)).

Conclusions: Unlike several other populations, PCNSL is not becoming significantly more common in Alberta. If this difference is real (i.e., not due to differences in cancer registry coding practices etc.) comparisons between Albertans and other populations in whom the incidence is rising may provide clues regarding the etiology of PCNSL.

Key words: brain tumors, epidemiology, incidence, primary central nervous system lymphoma

Introduction

Primary central nervous system lymphoma (PCNSL) is defined as extranodal lymphoma limited to the craniospinal axis without evidence of systemic disease. It is rare in immunocompetent patients with an incidence of only 1.5–2.8 per million [1, 2]. It comprises only 0.85–6.6% of all intracranial neoplasms [3–9] and 0.9%–4.2% of all extranodal non-Hodgkin’s lymphoma (NHL) [1, 7, 10–12]. In recent years several studies have reported an increase in the incidence of PCNSL which may be independent of improvements in imaging techniques and changes in nosology [2, 8, 13–17]. In one study [13] a dramatic, almost three-fold increase was seen over an 11-year period. However there are exceptions to this trend. In Southeast Scotland, Yau et al. [18] found that the previously published rise in PCNSL rates subsided without an obvious explanation. Similarly, using the Danish lymphoma registry, Krogh-Jensen et al. [1] found no change in PCNSL incidence in immunocompetent patients over a 23-year period.

To study potential regional incidence differences we studied PCNSL in Alberta, Canada which has a comprehensive cancer registry encompassing the whole province. Because the etiology of PCNSL is unknown this information may provide epidemiologic clues regarding its pathogenesis. We studied the characteristics of PCNSL patients in Alberta over a 22-year period (1975–1996) which corresponded to the introduction of routine CT scanning in Alberta and the implementation of significant refinements in the Alberta Cancer Registry. The objectives of this study were to determine, using population-based data, 1) if the incidence of PCNSL changed over this period, 2) if histologic subtypes were changing, and 3) to describe the clinical, histological and outcome characteristics of PCNSL patients on a population-wide basis.
Patients and methods

Case ascertainment

The Alberta Cancer Registry is a population-based cancer registry for the province of Alberta (population in 1996 of 2.8 million) which was established by an Act of the Provincial Legislature and has been operational since 1941. Endorsing legislation is in place requiring all hospitals, pathologic laboratories, radiographic facilities and cancer treatment centers to participate and all patients with a clinical, radiographic or histologic diagnosis of cancer (including those diagnosed at autopsy) are registered. We identified all Alberta residents with historically diagnosed PCNSL between 1 January 1975 and 31 December 1996 in the Cancer Registry and reviewed the patients’ charts. All identified cases were recorded as NHL with morphologic codes for extranodal NHL and with the primary site in the brain or CNS (International Classification of Diseases for Oncology Version II [19] topography codes C70.0–C72.9 and morphology codes 959–964 and 967–972). We excluded patients with any evidence of lymphoma outside the nervous system. We also excluded potentially immunocompromised patients who we defined as: any individual known to have a congenital immunodeficiency, an organ transplant, HIV seropositive, an AIDS defining illness other than PCNSL, use of intravenous drugs or, finally, never-married, men >18 years old as of 1 January 1982. We identified 113 patients in the Registry using the ICD-O codes described above. Of these 113 patients, 63 were excluded (after chart review) for the following reasons: 39 had systemic lymphoma, seven had other diagnoses, four had inadequate medical records for review, four had no histological diagnosis, six were HIV positive and three were single, adult males as of 1 January 1982. Of the 39 patients who had systemic lymphoma, the majority (90%) had systemic disease at initial staging. One patient could not be adequately staged at diagnosis and had systemic disease one year later. In the remaining 3 (8%) patients systemic disease was identified two years later.

The ASIR for all other NHL (ICD-O morphology codes 959–964, 967–972) all invasive brain cancers and all malignant gliomas were calculated to compare trends in the incidence of PCNSL.

Histopathology

Histological slides were available for review for 37 of the 50 patients. The slides were reviewed by a pathologist unaware of the original diagnosis to confirm the diagnosis and classify the tumor. All biopsy material was fixed in neutral buffered formalin, embedded in paraffin, and 3-5 micron sections were stained with haematoxylin and eosin (H&E). The tumors were classified using the National Cancer Institute Working Formulation [20]. In 27 patients, tissue blocks were available for immunohistochemical staining to identify the tumor phenotype. Immunohistochemical staining was done on paraffin sections using the avidin-biotin-peroxidase method, with the application of monoclonal antibodies CD45 (leukocyte common antigen), CD20 (B-cell), and CD45RO (T-cell) (Dako, Carpenteria, CA), and polyclonal CD3 (T-cell; Dako, Carpenteria, CA).

Incidence rates and statistical analysis

The statistical analysis was conducted using SPSS [21] software package for all descriptive analyses and S-PLUS [22] for all other analyses. Age-standardized incidence rates (ASIR) were calculated by the direct method and standardized to both the 1991 revised total Canadian population and the 1970 US standard population. The number of cases was averaged over three year blocks (1975 omitted to maintain the uniform three-year interval) to provide more stable incidence rates. Incidence rates of PCNSL in men versus women and those <65 versus ≥65 years of age were calculated separately and compared. Incidence rates were also determined for all other non-Hodgkin’s lymphoma and all invasive brain neoplasms over the same time period. Statistical significance of trend for unadjusted rates was assessed with a chi-square trend test [23]. Trends in age adjusted rates were assessed using Poisson regression [24]. The survival curves were generated by the Kaplan–Meier method [25].

Table 1. Age-standardized incidence rates (ASIR) of PCNSL in Alberta from 1975–1996 (cases per million).

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of cases</th>
<th>ASIR (Canada)*</th>
<th>ASIR (US)*</th>
<th>Crude rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976–1978</td>
<td>1</td>
<td>0.178</td>
<td>0.204</td>
<td>0.171</td>
</tr>
<tr>
<td>1979–1981</td>
<td>6</td>
<td>1.246</td>
<td>1.174</td>
<td>0.909</td>
</tr>
<tr>
<td>1982–1984</td>
<td>7</td>
<td>1.349</td>
<td>1.192</td>
<td>0.973</td>
</tr>
<tr>
<td>1985–1987</td>
<td>7</td>
<td>1.178</td>
<td>1.145</td>
<td>0.957</td>
</tr>
<tr>
<td>1988–1990</td>
<td>6</td>
<td>0.937</td>
<td>0.974</td>
<td>0.799</td>
</tr>
<tr>
<td>1991–1993</td>
<td>8</td>
<td>1.212</td>
<td>1.161</td>
<td>1.007</td>
</tr>
</tbody>
</table>

* ASIR standardized to 1991 Canada revised post censal population estimate.

** ASIR standardized to 1970 USA standard population.

The three cases in 1975 were omitted in the trend analysis.

Clinical, treatment, and outcome assessment

Patient charts, treatment summaries, survival information and autopsy data were reviewed. Performance status was assessed using the Karnofsky performance scale [26].

Results

Trends in PCNSL incidence

Fifty immunocompetent patients were diagnosed with PCNSL in the study period, making up 0.96% of all cases of NHL and 1.65% of all invasive CNS neoplasms. During the 22-year study period, no statistically significant change could be demonstrated in the trend for ASIR of PCNSL in Alberta (range 0.178–1.631/10^6; test for trend, P = 0.26; Table 1 and Figure 1). Similarly, no changes were found for male versus female or older versus younger patients. As with PCNSL, the incidence of all other primary brain neoplasms in Alberta did not change over the 22-year study period (range 50.95–62.249/10^6; test for trend, P = 0.36; Figure 1). However, the incidence of all other NHL (excluding PCNSL) increased significantly (range 94.95–138.76/10^6; test for trend, P = 0.0001; Figure 1).
Factors potentially influencing the number of PCNSL patients diagnosed include the number of brain biopsies and CT/MR scans done in this population. Unfortunately there were no data recorded on the frequency of neurodiagnostic imaging. Concerning surgical procedures, the rate of brain biopsies done in the province increased from 1979 to 1985 (e.g., 31 in 1979 versus 87 in 1985; test for trend, \( P < 0.0001 \)) but remained stable from 1986 to 1996 (e.g., 62 in 1986 versus 69 in 1996; test for trend, \( P = 0.9995 \)).

Clinical characteristics

Patients ranged in age from 11–82 years, with a median age of 64.0 (Table 2). The male to female ratio was 3:2. The median duration of symptoms prior to diagnosis was 62 days (range 7 days to 20 months). The median Karnofsky performance status at diagnosis was 70 (range 30–100). The most common presenting signs were headache, altered level of consciousness and pyramidal symptoms. Eight percent of patients experienced constitutional 'B' symptoms.

Staging investigations to evaluate concomitant leptomeningeal and intracocular lymphoma were done infrequently. Only 10 patients (20%) had lumbar puncture performed; 2 had positive cytology. Silt lamp examination was conducted in 8 patients (16%) and were negative in all. Evaluations to exclude systemic lymphoma were done at the discretion of the treating physician. All patients had a physical exam. Chest X-rays were done in 80% of patients. The majority had some form of abdominal imaging (CT scan or abdominal ultrasound – 64%), and a significant proportion underwent bone marrow biopsy (44%). Additional investigations included pelvic imaging (22%), bone scan (18%), gastrointestinal investigations (10%), lymphangiogram (8%) and mammography (6%). No patient had evidence of systemic lymphoma. An autopsy was done in 16% of patients, confirming that lymphoma was restricted to the central nervous system.

Radiographic features

Sixty-six percent of patients had a cranial CT scan alone, 12% had MRI and 20% had both. The majority (88%) of the lesions enhanced with contrast; no contrast was given to 12% of patients. Other radiographic features included hemorrhage (2.0%) and calcification (2.0%). In 26% of patients lesions were bilateral.

Histology

Histological material from 37 patients (74%) was available for review. In two, the tumors were categorized only as 'malignant lymphoma, unclassified'. Of the remaining 35, 19 (51.4%) were diffuse large cell lymphomas (one cleaved, 18 non-cleaved), and 16 (43.2%) were diffuse large cell, immunoblastic lymphomas. Of the latter, five (31.3%) demonstrated plasmacytoid features. Of the 27 cases could be phenotyped, all were B-cell.

Histological sections showed replacement of normal brain tissue by infiltrating sheets of malignant lymphocytes which were often angiocentric. Necrosis was identified in over half of the cases (51.4%). The mitotic rate

Table 2. Clinical features of 50 patients with PCNSL.

<table>
<thead>
<tr>
<th>Age</th>
<th>Median 64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>11–82</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 30</td>
</tr>
<tr>
<td>Female 20</td>
<td></td>
</tr>
<tr>
<td>Symptoms on admission</td>
<td>Neurologicala</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>Pyramidal</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Memory</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Sensory</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Visual field cut</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Symptom duration prior diagnosis</td>
<td>Median 62 days</td>
</tr>
<tr>
<td>Range</td>
<td>7 days–20 months</td>
</tr>
<tr>
<td>KPS pre-op</td>
<td>Median 70</td>
</tr>
<tr>
<td>Range</td>
<td>30–100</td>
</tr>
<tr>
<td>Survival</td>
<td>Median 10.15 months</td>
</tr>
<tr>
<td>Range</td>
<td>9 days–11.3 years</td>
</tr>
</tbody>
</table>

Abbreviation: KPS – Karnofsky performance status.
a Most patients had multiple symptoms so the total number exceeds 100%.
b B symptoms – fever, weight loss, drenching night sweats.
was high > 5 of 10 high power (400× magnification) fields in the majority of cases.

**Treatment and outcome**

Twenty-six patients (52%) had a biopsy, 12 (24%) a subtotal resection, three (6%) a radical subtotal resection, six (12%) a gross total resection and in three (6%) patients, the extent of surgery was unknown. Ten patients had no additional treatment. Thirty-four patients received radiotherapy (RT) and six had RT and chemotherapy. Of the patients who received only RT, 4 were excluded from analysis as they were treated as astrocytomas or the data unknown. For the remaining 30 patients, the total dose of radiation received averaged 4250 cGy (range 182 to 6000) delivered in 20 fractions (range 1–34). Of the six patients treated with combination chemo- and radiotherapy, four were treated with a combination of systemic and intrathecal chemotherapy, one received methotrexate plus CCNU and the drugs used in the others were unknown.

At the time of study termination, only 9 (18%) patients were alive (Figure 2). The median survival was 10.15 months (range 9 days to 11.3 years) men and women had equivalent survival. Older (>65) patients had a shorter survival than younger (≤65) patients (P < 0.01). By treatment group, the median survival was 18 days for the group who had only surgery and 10.3 months and 10.8 months for the RT only and the RT and chemotherapy groups respectively.

**Discussion**

In contrast to some epidemiological studies of PCNSL we did not find any significant change in the incidence of PCNSL among immunocompetent patients in our population. We found the yearly relative increase (estimated from the poisson regression model) was 1.038 (95% CI: 0.93–1.132), which remained stable despite improvements in neurodiagnostic imaging and significant increases in the frequency of brain biopsy.

Table 3 summarizes various studies evaluating the population-based incidence of PCNSL. It is difficult to compare these studies because the selection criteria for cases differed and the population (i.e., the denominator) used or crude rates were not always reported. Six studies reported a significant increase [8, 13, 16, 17, 27]. One [8] was not population-based and the observed increase may be attributable to changing referral patterns. Two others [16, 17] did not attempt to exclude AIDS patients or potentially immunocompromised individuals and are not directly comparable.

Both the Eby et al. [13] study and the Corn et al. [27] update reported dramatic increases in incidence with very low incidence rates in the early years and much higher rates in the later years in comparison with the results of others. We corroborated the low incidence rates from the early years using the population data available from SEER where the crude rate for brain lymphoma and microglioma for 1973–1982 is 0.722 per million. This is less than what we observed in Alberta and less than half of that reported by Spaun et al. [6] (1.83 per million) for a similar period (1972–1981). This finding may reflect differences in case identification during the early years of the SEER database. Since the statistically significant increase reported by Eby et al. [13] disappears if the two earliest time periods are excluded part of the apparent increase in incidence may be artifactual. In the later periods of the SEER data [27] incidence rates were higher (3.0 per million for 1991–1992) than those we and others [1, 18] have observed. This may reflect differences in the true incidence of PCNSL but since chart reviews were not done in those studies it is conceivable that their results were biased by the inclusion of patients who were immunocompromised or had CNS metastases from systemic lymphomas.

The strongest case for the increasing incidence rates of PCNSL among immunocompetent patients is made by Cote et al. [2]. Their study is both population-based and excludes AIDS patients by cross-linking AIDS and cancer registries. However, patient charts were not reviewed. Review of individual patient charts is necessary because most cancer registries do not have a separate code for PCNSL but code all NHL that involves the CNS similarly. We initially identified 113 patients with NHL affecting the CNS of whom 39 (35%) had systemic lymphoma and were excluded. In the study by Krogh-Jensen et al. [1] (whose results were comparable to our own) patients’ charts were also reviewed. As a result, more than half of the original cases identified in their registry were also excluded since those patients had systemic lymphomas (Dr. Krogh-Jensen, personal communication).
may suggest etiological factors for PCNSL whose cause differences in PCNSL incidence may exist. If so, this occurs, is rare.

Although the Epstein–Barr virus (EBV) is a major factor in PCNSL pathogenesis in immunocompromised patients it may not be etiologically important in immunocompetent patients. There are several differences between our population and others which could be relevant. Our population is very young – the average age in Alberta in 1991 was 31.1 [36], but our incidence rates were age-adjusted. Alberta is also racially homogeneous – in 1991 approximately 80% were Caucasian [37]; however, an independent association between race and PCNSL has not been reported. We were unable to determine other potentially important population differences such as occupation, the incidence of tonsillectomy or oral contraceptive use [38].

Others [1, 13, 17] have noted that the increased incidence of PCNSL may be part of a trend of increasing incidence of various tumour types. In comparison to the incidence of PCNSL, the incidence of all other NHL (excluding PCNSL) in our population appears to have increased significantly while the incidence of all other primary brain neoplasms has not. However, we were not able to examine the patients’ charts or conduct a historical review for patients with non-CNS NHL as we did for the cases of PCNSL and thus the potential for misclassification limits our ability to truly compare incidence rates among these groups.

It is unlikely that we missed any cases of PCNSL because reporting of all histologic, autopsy, and radiographic diagnoses of cancer are required by law in Alberta. It is possible that small changes in incidence were not detected by us because of our small number of patients and low statistical power. We realise that each study which did not find a change in incidence also had low statistical power. However, since the yearly relative increase we observed had a 95% confidence interval of 0.95–1.13, we can conclude that it is unlikely we would not detect the 3–10-fold increases reported by others [2, 13, 17, 27]. Alternatively, could there have been lower case ascertainment because neuroimaging and brain biopsies were not performed as often in Alberta? Access to diagnostic imaging and surgical biopsy should not be limiting factors because of the universal health care system in Canada; however, the utilization of these technologies may be limited. We cannot compare utilization rates but our incidence rates were stable despite the introduction of CT scans in 1985, MRs in 1990 and increases in brain biopsy rates. Furthermore, our incidence rates were comparable to those in other studies suggesting that we did not miss a significant number of PCNSL patients. Finally, it is possible that we excluded patients with PCNSL who subsequently developed systemic lymphoma [39, 40], but this phenomenon, if it occurs, is rare.

The most interesting possibility is that true regional differences in PCNSL incidence may exist. If so, this may suggest etiological factors for PCNSL whose cause remains unknown. Although the Epstein–Barr virus remains a major factor in PCNSL pathogenesis in immunocompromised patients it may not be etiologically important in immunocompetent patients. There are several differences between our population and others which could be relevant. Our population is very young – the average age in Alberta in 1991 was 31.1 [36], but our incidence rates were age-adjusted. Alberta is also racially homogeneous – in 1991 approximately 80% were Caucasian [37]; however, an independent association between race and PCNSL has not been reported. We were unable to determine other potentially important population differences such as occupation, the incidence of tonsillectomy or oral contraceptive use [38].

Two other results of our study deserve comment. First, some centers have reported a systematic change over time in the proportion of various histological subtypes [1, 2, 8, 31–35]; we did not observe this trend. We did find a larger percentage (42.2%) of diffuse immunoblastic lymphoma than others [1, 32–35], but the significance of this is unclear. Second, this study underscores the poor prognosis of this disease in an unselected population. The median survival of our patients was only 10.15 months. Our experience demonstrates the aggressive nature of untreated PCNSL. The disappointing survival rates may also reflect the conservative therapy most patients received as it was not until 1994 that multimodal therapy was used in Alberta following reports of its efficacy [35]. Only six of our patients received this therapy and follow-up is too brief to comment on its benefit. The dismal prognosis highlights the significant clinical challenge of this disease.

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