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Clinical Study

The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children

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ABSTRACT

Medulloblastomas (MB) and primitive neurectodermal tumours (PNET) are known to affect children more than adults. To estimate the magnitude of the differences between the incidence of adults and children, the incidence rates, ratios and time trends of MB and PNET in children and adults are measured using data from the Surveillance, Epidemiology and End-Results (SEER) database. Between 1973 and 2007 in the SEER 9 registries, 1372 people were diagnosed with a MB and 530 with a PNET. The overall incidence rate of MB and PNET is approximately 1.5 and 0.62 per million population in the USA. Children (1–9 years of age) with MB had an incidence rate of 6.0, compared to 0.6 in adults, and therefore children are 10 times more likely to be affected by an MB than adults. Children are 4.6 times as likely to be afflicted by a PNET than adults. The difference in incidence rates based on sex existed only in children. Our study confirmed that the incidence rates of MB has not changed over time.

1. Introduction

A medulloblastoma (MB) brain tumour has a predilection for affecting children, and is estimated to affect 9.6 children per million, and 0.54 adults per million.[1,2] Furthermore, the literature is unclear as to the incidence rate changes over time, with some studies describing an increasing incidence of this tumour, while others suggest it is decreasing.[1,3]

Typically, MB and PNET have been considered a single entity, but due to recent work, and the World Health Organization separation of these two entities, MB and PNET should be considered separately.[3–6] In 2002, Pomeroy et al. differentiated MB from PNET using microarray techniques: these diseases should now be considered two separate entities even though several studies continue to group them together.[7]

In clinical practice, incidence rates and ratios provide the clinician with a baseline measurement, and become important in observing new trends. For example, if a tumour type is known to afflict children 5 times more than adults, and a particular hospital or department sees an equal ratio of children and adults, the knowledge of baseline incidence rates and ratios provides the clinician with a rationale to further investigate this anomalous distribution.

The purpose of this study is to review the incidence of MB and PNET since 1973 throughout the USA in adults, adolescents and children to provide an estimate of baseline rates and ratios.

2. Materials and methods

The Surveillance, Epidemiology and End Results (SEER) database was used to identify patients with MB in the following World Health Organization categories: medulloblastoma (9470/3); desmoblastic medulloblastoma (9471/3); medullomyoblastoma (9472/3); large cell medulloblastoma (9474/3); and primitive neurectodermal tumours (9473/3). In 1973 there were nine SEER registries collecting data prospectively, and most often entire States participated. Progressively more regions (most often States) joined the SEER registry, which now includes 17 regions/registries. Four age groups were used in this analysis, based on the SEER data 5-year age ranges and that the median age of children diagnosed with these tumours is 9 years of age: (i) "infants", 0–1 years of age; (ii) "children", 1–9 years; (iii) "adolescents", 10–19 years; and (iv) "adults", those greater than 19 years. The choice of this age classification was due to the visual observation in our study, as well as others,[8] of a steeper drop in the incidence rates between the 15-year to 19-year age group and the 20-year to 24-year group than between other age groups.

Incidence rates and confidence intervals (CI) were obtained from the SEER 9 registry as this is the only registry that provides

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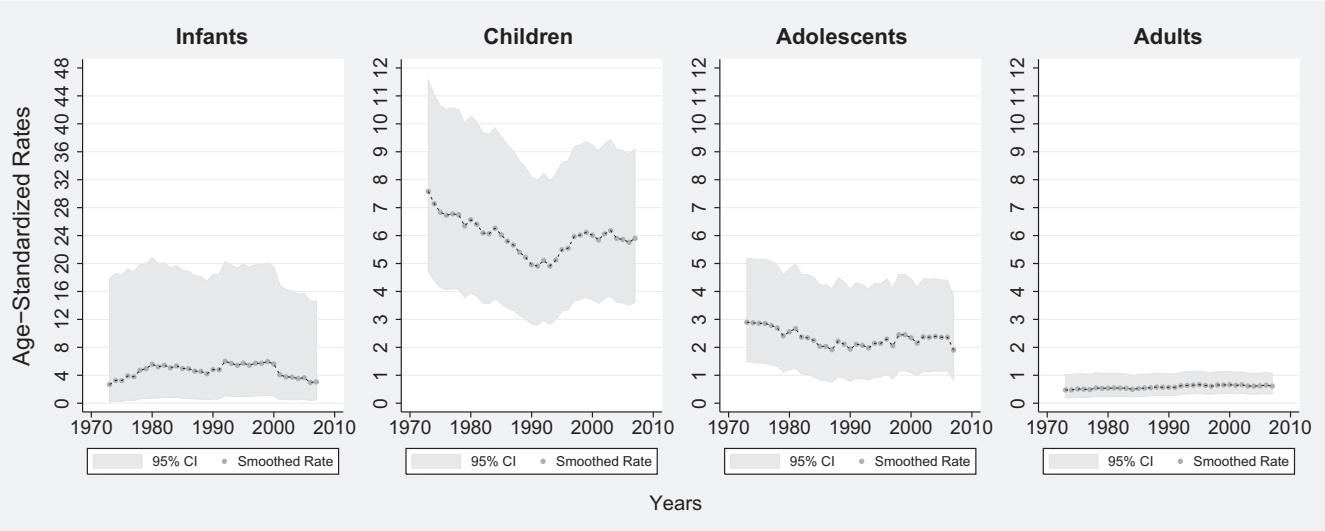

Fig. 1. Age-adjusted incidence rates and 95% confidence intervals (CI) according to year of diagnosis and by age group showing that the incidence of this tumour has neither increased nor decreased since 1973.

Table 1
Incidence rates and rate ratios of medulloblastomas

	Incidence rate per million (95% CI)	Incidence rate ratio
Overall	1.58 (1.50, 1.67)	–
Age group		
Infants*	4.56 (3.45, 5.91)	7.86
Children*	5.96 (5.52, 6.44)	10.28
Adolescents*	2.34 (2.08, 2.62)	4.03
Adults	0.58 (0.52, 0.64)	1.00
Sex		
Male (overall)*	1.93 (1.79, 2.06)	1.58
Infants	4.22 (2.78, 6.14)	0.86
Children*	7.59 (6.89, 8.35)	1.78
Adolescents	2.98 (2.57, 3.44)	1.78
Adults	0.65 (0.57, 0.75)	1.28
Female (overall)	1.22 (1.11, 1.33)	1.00
Infants	4.92 (3.32, 7.02)	1.00
Children	4.26 (3.73, 4.86)	1.00
Adolescents	1.67 (1.36, 2.02)	1.00
Adults	0.51 (0.43, 0.59)	1.00
Race		
Black (overall)*	1.03 (0.85, 1.24)	0.61
Infants	2.96 (0.96, 6.92)	0.59
Children*	3.97 (3.03, 5.10)	0.63
Adolescents	1.52 (0.98, 2.24)	0.61
Adults*	0.36 (0.23, 0.55)	0.57
Other (overall)	1.44 (1.19, 1.73)	0.85
Infants	3.11 (0.85, 7.96)	0.63
Children	6.11 (4.72, 7.77)	0.97
Adolescents	2.20 (1.44, 3.23)	0.88
Adults	0.42 (0.26, 0.63)	1.59
White (overall)	1.69 (1.59, 1.67)	1.00
Infants	4.94 (3.63, 6.56)	1.00
Children	6.30 (5.77, 6.86)	1.00
Adolescents	2.50 (2.19, 2.83)	1.00
Adults	0.63 (0.56, 0.70)	1.00

* Indicates non-overlapping confidence intervals (CI) when compared to the reference category, and therefore a significant difference at is present.

information from 1973 until 2007.[9] (The 17 SEER registries were used to extract incidence data for analysis of registry comparisons). Incidence rates and ratios were age-standardised to the US standard 2000 population. Unsmoothed age-standardised data are presented in tables and the smoothed estimates were plotted. Moving averages with a 4, 1 and 4 window was used, to reduce irregularities such as the random fluctuations observed to provide a clearer view of the underlying behaviour of the data. We did not include the category of children below the age of 1 year in the calculation of moving averages, as it would not fulfil the assumption of equidistant categories during its calculation.

Non-overlapping CI were used to indicate significant differences between categorical variables. All statistical analyses were performed on Stata version 11.1 (College Station, TX, USA).

3. Results

The SEER 9 registries listed 1372 patients diagnosed with MB and 530 with PNET between 1973 and 2007: a total of 57 infants, 653 children, 293 adolescents, and 369 adults were diagnosed with MB, and 34 infants, 183 children, 94 adolescents and 219 adults were diagnosed with PNET.

The overall incidence of MB was approximately 1.5 per million population, and 0.62 per million population for PNET. Age groups were clear predictors of incidence (Fig. 1). Children (1–9 years of age) had an incidence rate of 6.0 per million children, compared to 0.6 per million adults (>19 years of age), which is an 10-fold difference in the incidence of MB in children compared to adults (Table 1).

Table 2 demonstrates a similar yet different pattern. PNET occurred more commonly in the younger populations except that the magnitude of the difference between children and adults was less than in MB, as children were 4.6 times as likely to be affected than adults. There were no other demographic predictors of incidence noted in PNET.

During childhood, males were 1.58 times as likely as females to be diagnosed with an MB, but this difference was found in children only. Those categorized as "black" were 0.61 times as likely to be diagnosed with an MB as those considered to be "white", and this was significant only in children and adults.

3.1. Incidence time trends

It became clear through visual observation that there was no increase in incidence noted since the early 1970s as none of the point estimates and error margins were significantly different from each other (all error estimates overlapped). Therefore, it appears that the incidence of this tumour has neither increased nor decreased since 1973 (Fig. 1).

Table 2
Incidence rates and rate ratios of primitive neurectodermal tumors

	Incidence rate per million (95% CI)	Incidence rate ratio
Overall	0.62 (0.57, 0.67)	
Age group		
Infants*	2.72 (1.88, 3.80)	6.26
Children*	1.66 (1.43, 1.92)	4.61
Adolescents*	0.75 (0.61, 0.92)	2.08
Adults	0.36 (0.32, 0.42)	1.00
Sex		
Male	0.71 (0.64, 0.80)	1.37
Female	0.52 (0.45, 0.59)	1.00
Race		
Black	0.61 (0.47, 0.79)	0.97
Other	0.54 (0.39, 0.73)	0.86
White	0.63 (0.57, 0.69)	1.00

* Indicates non-overlapping confidence intervals (CI) when compared to the reference category, and therefore there is a significant difference.

3.2. Incidence across registries

Fig. 2 illustrates the incidence rates in 17 of the SEER registries, of which none are significantly different to any other (all CI overlap). The various SEER registries did not show evidence of any significant differences between the 17 registries analysed (all CI crossed).

4. Discussion

The data analysed in this study demonstrate three important features of MB incidence. First, MB are 10 times more likely to be diagnosed in children than adults. Second, the male sex is a risk factor for the development of MB in children only and not a risk factor in adults. Third, neither sex nor race was a predictor of the development of PNET, whereas these demographic features are factors in the development of MB in children (race only in adults).

The finding of a steady incidence rate over time is in contradiction to the findings of Thorne et al., who found that the incidence rates were 9.6 per million population between 1976 and1984, and 1.7 per million children between 1985 and 1991.[1] Overall, the data presented here do not support that the incidence of this tumour has changed over time.

Recent studies have shown that MB in adults and children are histologically and genetically different diseases, with more mutations being observed in childhood MB than in adult tumours.[10–12] The recent genome-wide study by Parsons et al. found fewer passenger mutations in children compared to adults, yet the same amount of driver mutations (probable cancer-causing mutations).[12] Giordana et al. showed that nuclear polymorphism and Homer-Wright rosettes were more frequently expressed in pediatric MB as compared to their adult counterparts. This trend was also seen when comparing proliferation indices between the two tumours, where the median PCNA and MIB-1 values were 25% and 20% respectively in children and 51% and 35% in adults, which were both significant.[10] Korshunov et al. also found genetic differences between pediatric and adult MB. In adult MB they found that CDK6 amplification, 10q loss, and 17q gain were powerful prognostic markers. In children MYC/MYCN oncogene amplifications had a high prognostic value, which were rarely observed in adult tumours.[11] Finally, adults and children have a similar prognosis until 4 years post-diagnosis when children become less likely to die of the disease than adults.[13] Overall, this suggests that most childhood MB, although histologically similar, have different genetic profiles and behave differently to adult MB.

The SEER database regularly performs quality control checks on its data collection systems. A previous quality control study found that the SEER registries were reporting approximately 98% of all incident cases, which indicates that the incidence reported here is accurate.[14] However, the histological confirmation of each sample can be inaccurate because of a lack of a central histological review, and the effect of time on the change in procedures used to classify tumours, as well as the changing of tumour classifications, which is particularly relevant to MB and PNET, in which the distinction has not always been clear.

The incidence differences in adults and children highlight that the tumourigenic mechanism involved in the development of MB is more likely to be associated with features found in children as distinct from adults. This could be, for example, exposure to

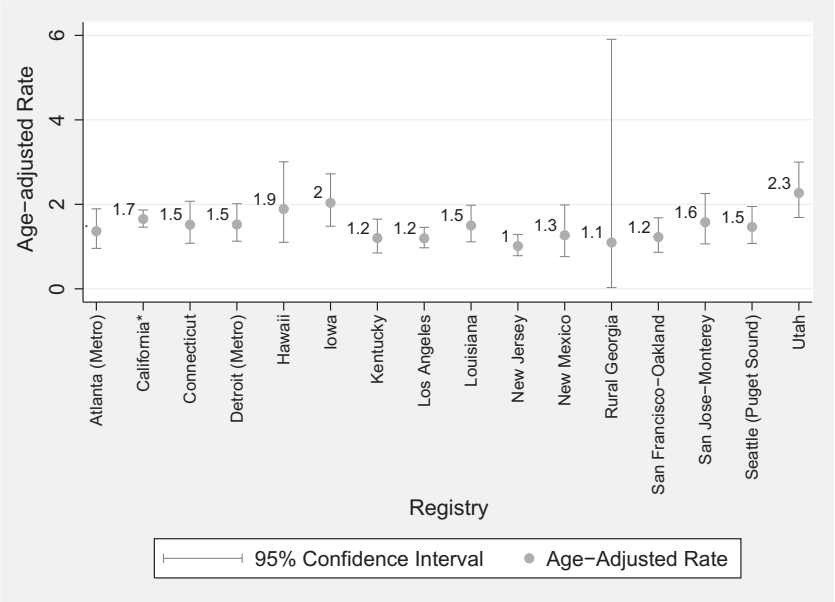

Fig. 2. Incidence of medulloblastoma in 17 Surveillance, Epidemiology and End-Results (SEER) registries (* California excluded Los Angeles, and the San Francisco–Oakland and San Jose–Monterey registries, which are shown separately) illustrating that none are significantly different to any other (all confidence intervals [CI] overlap). Included point estimate of rates are per million population. The Atlanta metro rate is 1.4 per million population. The Alaska registry is not shown as it had no cases of MB.

vaccines[8] or to cellular mechanisms associated with growth.[12] Although the tumour mechanism(s) or exposure(s) associated with the initiation of MB is unclear, it causes children to be 10-times more at risk of being afflicted with this tumour than adults.

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