The descriptive epidemiology of childhood leukaemia and childhood brain tumours - a comparison

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Summary

- The aetiology of childhood leukaemia has been associated with exposure to infections and there is some emerging evidence for similar links to CNS tumours.
- A comparison of the descriptive epidemiology of these two conditions may offer some insights into other similarities.
- International incidence rates of childhood leukaemia and CNS tumours show a significant, positive association.
- There is a small but statistically significant and consistent rise in the rates of CNS tumours across 3 decades. The rates of leukaemia and ALL may appear to be increasing but this is not statistically significant overall.

Introduction

The likelihood of infections being involved in the aetiology of childhood leukaemia is a concept which has been accepted for many decades although mechanisms to explain the biological process remain undetermined (1). For example, it is not clear whether a single agent (virus) is involved in the disease process as is the case in some animal species or whether it is the individual’s immune system which may aberrantly respond to a common infection. Epidemiological work in support of an infectious hypothesis has included studies of time-space and spatial clustering (2) and population mixing as a proxy for exposure to infections (3). The latter scenario has been proposed by Kinlen in the context that an influx of people into isolated communities may result in excesses of childhood leukaemia as a consequence of mini-epidemics of common infections to which leukaemia is a rare response.

A further hypothesis proposed by Greaves for acute lymphoblastic leukaemia (ALL), the most common subtype of leukaemia, suggests that immunological isolation in infancy from common or endemic infections increases the risk of developing the disease. ALL may frequently be initiated by a chromosome translocation event in utero, although a second postnatal promotional event is necessary for clinical leukaemia to develop (4,5). This promotional event may be exposure to a common infection in later life whereby immunological isolation in infancy has failed to prime the immune system for an appropriate response.
Childhood leukaemia is the most common malignancy in the paediatric age range (30%) but the second most frequently occurring group are central nervous system (CNS) tumours (25%) (1). A large body of research has examined a putative infectious aetiology for leukaemias whereas scant attention has been paid to CNS tumours. These neoplasms can be induced in experimental animal models by a number of viruses, including retroviruses, papoviruses and adenoviruses, although there is little epidemiological support for this occurring in humans. Live polio vaccines contaminated with SV40 have been linked to an increased risk of developing CNS tumours but initial observations have not been supported by more detailed powerful studies.

Direct examination of brain tumour tissue for evidence of viral DNA has been positive in a proportion of cases within separate pathological series but the mechanism of malignant transformation remains unknown. An infectious aetiology may be inferred by geographical distributions of children with CNS tumours. Analyses from the North of England have shown clustering in time and space, seasonality of birth (6) and an inverse association for population mixing (a proxy for infectious exposure) around the time of birth (7). The involvement of infections and immune responses in brain tumour aetiology warrants further attention.

Recent and emerging work on childhood CNS tumours is tentatively suggesting an involvement with infections in contrast to childhood leukaemia where this is widely accepted. We thought it would be informative to briefly compare the recent descriptive epidemiology of these 2 paediatric conditions searching for other similarities.

**Materials and Methods**

Details of children diagnosed under the age of 15 with leukaemia (n=789) or a CNS tumour (n=598) between 1974 and 2001 were extracted from the Yorkshire Register of Cancer in Children and Young People (8). Diagnostic groups and subtypes were categorised according the International Classification of Childhood Cancers (ICCC) (9). This population-based specialist cancer register covers a geographical area of 12,000 km$^2$ and a childhood (0-14 years) population of 700,000. The proportion of histologically verified tumours is in excess of 85% and has remained steady for both leukaemia and CNS tumours over the time period of study. Age- and sex-standardised incidence rates, with 95% CI, were calculated and changes over time assessed using log-linear regression.

The international incidence of childhood (ages 0-14 years) leukaemia and CNS tumours was compared using data from Parkin et al (10) and the Automated Childhood Cancer Information System (www-dep.iarc.fr/accis.htm). For each country, world standardised incidence rates were extracted for the period around the early/mid-1990s and correlation assessed using Pearson’s correlation coefficient.

**Results**

The underlying standardised incidence rates for leukaemia and CNS tumours from the Yorkshire register show the young age (0-4 years) peak for leukaemia (accounted for ALL) compared to more
stable rates for CNS tumours, apart from PNETs which are found predominantly in those under 10 years. There is an overall male excess for both leukaemia and CNS tumours with M:F ratios of 1.2 and 1.2 respectively. Although for the largest subgroup of CNS tumours, astrocytomas the M:F ratio was 1.0 compared to 1.5 for PNETs/medulloblastomas. The time trends for leukaemia and ALL (0.6%/year) show increases over time which were not statistically significant. There is a small but statistically significant rise in incidence of 1.5%/year for CNS tumours accounted for by males in the 'other CNS' group.

Examining total childhood cancers, European rates reflected the heterogeneity of cancer rates worldwide (10). A comparison of the incidence rates within European populations is given in a Figure 1 as a scatterplot. A significant (p<0.01) positive correlation of 0.55 (95% CI: 0.21-0.77) was found between incidence rates of leukaemia and CNS tumours from 27 European countries. Countries with low rates of both leukaemia and CNS tumours included Romania and Poland, whereas Finland and Denmark exhibited high rates of both diseases.

**Figure 1** Scatter-plot of incidence rates (world standardised) for leukaemia and CNS tumours from 27 European countries (Ages 0-14 years)

**Discussion**

A significant, positive correlation was found between international incidence rates of leukaemia and CNS tumours across Europe. The European incidence data, although contemporary, did not contain any assessment of data quality for each country. It is therefore possible that variation between countries may be explained by differential ascertainment. However, it might be expected that poor ascertainment would be present for both conditions although leukaemias may have higher levels of completeness due to better pathways of care and available treatments. This is an area needing further investigation to consider how the correlation differs across age groups and time periods. Variation in the size of the correlation within specific diagnostic subtypes also warrants further examination. Although our analysis included a fairly selective group of countries, we plan to examine data from non-European countries to test the hypothesis that the correlation between leukaemia and
CNS tumours is also present. We also aim to examine factors which may explain the relationship between both diseases, and also testing for cross-clustering.

The data on which the incidence analyses are based were derived from a high quality register. The distribution of incidence rates by age and sex and tumour type reflect those reported before in Yorkshire and in the UK. The Yorkshire data makes it appear that the rates of leukaemia and CNS tumours are rising in parallel. However, this masks important differences as the increase for brain tumours is statistically significant whereas for leukaemia this was not the case. It is vital to look at time trends of rare disease over long periods of time to avoid spurious effects and misinterpretation of the results. Our data fulfil this requirement. Similarities in the descriptive epidemiology of different diseases are worthwhile investigating when searching for potentially common aetiological pathways.

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References