Prenatal X-ray exposure and childhood brain tumours: a population-based case–control study on tumour subtypes

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We investigated childhood brain tumours by histological subtype in relation to prenatal X-ray among all children, less than 15 years of age, born in Sweden between 1975 and 1984. For each case, one control was randomly selected from the Medical Birth Register, and exposure data on prenatal X-ray were extracted blindly from antenatal medical records. Additional information on maternal reproductive history was obtained from the Medical Birth Register. We found no overall increased risk for childhood brain tumour after prenatal abdominal X-ray exposure (adjusted odds ratio (OR): 1.02, 95% confidence interval (CI): 0.64–1.62); primitive neuroectodermal tumours had the highest risk estimate (OR: 1.88, 95% CI: 0.92–3.83).

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From 1975 to 2002, the incidence rate of childhood brain tumours (CBTs) in the United States increased from 2.3 to 3.5 cases per 100 000 children (NCI, 2005). A step increase was noted in 1984–1985, for which suggested reasons were better diagnostic procedures with MRI and changes in the histological classification (Smith et al, 1998). However, in a Swedish study between 1973 and 1992, the increase was around 2.6% annually, with no time clustering (Hjalmars et al, 1999). It is still unclear, therefore, whether the observed trend is a true increase or an effect of better diagnostic procedures.

Few risk factors are considered as established: rare genetic disorders and high-dose ionising radiation for cancer therapy and tinea capitis (Ron et al, 1988; Bunin, 2000; Baldwin and Preston-Martin, 2004). Radiological examinations during pregnancy have in some studies been associated with a slightly increased risk of CBT in offspring (Bithell and Stewart, 1975; Rodvall et al, 1990; Shu et al, 1994). However, meta-analyses have found no clear associations (Gurney et al., 1999; Bunin, 2000; Linet et al, 2003).

During recent years, more focus has been on risk factors for the subtypes of CBT, since their cellular origins as well as geographic distribution differ. The few previously existing studies on prenatal X-ray and subtypes of CBT are based on retrospectively collected information and exposure frequency was low (Bunin et al, 1994; Schüz et al, 2001).

The aim with this study was to assess any association between prenatal exposure to diagnostic X-ray and primary CBT in a population-based case–control study, including subanalyses according to histological subtype. To avoid selection and recall bias, we performed a nation-wide study, where information on X-ray had been prospectively recorded in antenatal records.

MATERIALS AND METHODS

All children born between 1975 and 1984 in Sweden were eligible for this study. We used the nation-wide Swedish Cancer Register to identify children with brain tumours and for histological classification. The Cancer Register uses the 7th revision of the International Classification of Diseases (ICD-7) to facilitate comparison over time. Cases were children less than 15 years of age, diagnosed with brain tumour (ICD-7, code 193). The histological subtypes are defined through the three-digit pathohistological diagnosis code assigned by a pathologist. Controls were randomly selected children from the Medical Birth Register and frequency matched to cases by gender and year of birth. Controls had to be alive and residents in Sweden until the age of 15 years, which was ensured by using information from the Cause of Death Register and the Register of Population and Population Changes.

Medical information was abstracted from antenatal records, kept at local delivery archives and completed with data from the Medical Birth Register. Individual record linkage between registers and antenatal records was made possible by the Personal Identification Number (PIN), which is assigned to each Swedish resident and included in registers and medical records.

Sources of data

The Medical Birth Register contains prospectively collected information on more than 99% of all births in Sweden since 1973 (Cnattingius et al, 1990). The information is provided
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Statistical analyses

Logistic regression was performed to evaluate the association between prenatal exposure to diagnostic X-ray and incidence of CBT. Estimates of ORs and 95% confidence intervals (95% CIs) were calculated. In advance, we identified potential confounding factors that could interfere with both exposure and outcome, and for which it was possible to obtain information either from the registers or the antenatal records. The following confounders were included in the adjusted analyses: maternal age at birth, parity, multiple birth, mother’s country of birth (Nordic country (Sweden, Norway, Denmark, Finland and Iceland) or non-Nordic country), hypertension during pregnancy, mode of delivery, breech position, gestational age at birth, birth weight, head circumference at birth and level of hospital (primary, secondary or tertiary level). The statistical analyses were conducted with the SAS 9.1 software package.

The study was approved by the Ethics Committees at Karolinska Institutet and Uppsala University.

RESULTS

In children with CBT, 50.4% were boys and 49.6% girls. As we matched for gender, the distribution between sexes among controls was similar. There were no differences in maternal smoking habits during pregnancy between cases and controls (36% vs 37% smokers, respectively). However, the information on smoking habits was missing for 36.5% of the sample. Further maternal and foetal characteristics are presented in Table 1. Among children with CBT, it was more common to be the first-born child (P = 0.01) and to be born at a primary or secondary level hospital (P = 0.04) than for controls. There were no other significant differences in maternal and neonatal characteristics between cases and controls (Table 1).

Overall, 21.1% (n = 108) of the mothers to children diagnosed with CBT were exposed to X-ray during pregnancy compared to 21.2% (n = 111) of mothers to the children randomly selected as controls. For abdominal X-ray, the exposure frequency was 10.7% (n = 55) for cases and 9.4% (n = 48) for controls. Beside pelvimetry and X-ray for foetal position, abdominal X-ray included three scintigraphy of placenta, four scintigraphy of kidney, four plain abdominal X-rays and one colon examination. For both cases and controls, more than 96% of the abdominal examinations were performed in the last trimester. Non-abdominal examinations included 107 pulmonary and one each of skeletal, sinus and dental X-ray. Only three individuals in each group were exposed to X-ray more than once during the pregnancy.

Table 2 presents the distribution of CBT subtypes and age at diagnosis. Median age for diagnosis for all CBTs was 8 years. For subtypes, ependymomas had the lowest median age at diagnosis (4 years) and high-grade astrocytomas had the highest (9 years).

In Table 3, the ORs for prenatal X-ray are presented by tumour subtype. Since there were no differences between cases and controls in frequency or timing of exposure, analyses are restricted to children to mothers exposed to prenatal X-ray, regardless of number of examinations or time of exposure. Being prenatally exposed to abdominal X-ray was not associated with an increased overall risk of brain tumours compared with being unexposed (adjusted OR: 1.02, 95% CI: 0.64–1.62). When stratifying according to histological subgroups, we found that PNET had the highest risk estimates (adjusted OR: 1.88, CI: 0.92–3.83). Astrocytoma low and high grade had no increased ORs (adjusted OR: 1.02, 95% CI: 0.36–1.42 and adjusted OR: 1.06, CI: 0.39–2.86, respectively). As there were only 44 cases with ependymoma, it was not possible to perform multivariate analyses to adjust for possible confounders, and only crude risk estimates are presented. For similar reasons, germ cell tumours (n = 17) were included in all cancers and not analysed separately.
Table 1  Maternal and infant characteristics for 512 children diagnosed with brain tumour and 542 children serving as controls

|                          | Childhood brain tumour | Controls |
|--------------------------|-------------------------|----------|
|                          | N  | %     | N  | %     |
| Maternal age (years)     |    |       |    |       |
| 15–24                    | 178| 34.8  | 167| 31.9  |
| 25–34                    | 305| 59.6  | 320| 61.1  |
| 35–44                    | 29 | 5.7   | 37 | 7.1   |

| Birth order              |    |       |    |       |
| 1                        | 245| 47.9  | 210| 40.1  |
| >2                       | 267| 52.1  | 314| 59.9  |

| Multiple birth           |    |       |    |       |
| No                      | 502| 98.0  | 516| 98.5  |
| Yes                     | 10 | 2.0   | 8  | 1.5   |

| Mather born in a Nordic country |    |       |    |       |
| Yes                            | 491| 95.9  | 496| 94.7  |
| No                             | 21 | 4.1   | 28 | 5.3   |

| Gestational age at birth (weeks) |    |       |    |       |
| 22–32                           | 5  | 1.0   | 7  | 1.3   |
| 33–36                           | 24 | 4.7   | 23 | 4.4   |
| 37–41                           | 399| 77.9  | 412| 78.6  |
| 42–45                           | 81 | 15.8  | 78 | 14.9  |
| Missing                         | 3  | 0.6   | 4  | 0.8   |

| Mode of delivery               |    |       |    |       |
| Vaginal                        | 425| 83.0  | 422| 80.5  |
| Vacuum extraction              | 28 | 5.5   | 31 | 5.9   |
| Caesarean section              | 59 | 11.5  | 71 | 13.5  |

| Breech position                |    |       |    |       |
| No                             | 503| 98.2  | 513| 97.9  |
| Yes                            | 9  | 1.8   | 11 | 2.1   |

| Birth weight, SDSa             |    |       |    |       |
| SGA                            | 9  | 1.8   | 12 | 2.3   |
| AGA                            | 477| 93.2  | 493| 94.1  |
| LGA                            | 19 | 3.7   | 14 | 2.7   |
| Missing                        | 7  | 1.4   | 5  | 1.0   |

| Head circumference, SDSa       |    |       |    |       |
| SGA                            | 15 | 2.9   | 13 | 2.5   |
| AGA                            | 473| 92.4  | 487| 92.9  |
| LGA                            | 19 | 3.7   | 13 | 2.5   |
| Missing                        | 5  | 1.0   | 11 | 2.1   |

| Level of hospital              |    |       |    |       |
| Primary level hospital         | 161| 31.4  | 150| 28.6  |
| Secondary level hospital       | 248| 48.4  | 234| 44.7  |
| Tertiary level hospital        | 103| 20.1  | 140| 26.7  |
| Total                          | 512| 100.0 | 524| 100.0 |

AGA = appropriate for gestational age; LGA = large for gestational age; SDS = standard deviation score; SGA = small for gestational age. aCalculated by last menstrual period. bStandard deviation score, according to Niklasson et al (1991).

DISCUSSION

Prenatal X-ray exposure does not seem to increase the overall risk of CBT. However, for the subgroup of PNET, we found an increased OR of 1.88 (95% CI: 0.92–3.83). PNETs are found among the youngest children and is classified as an embryonic tumour. Medulloblastoma is the most common tumour in the PNET group, has a peak age of occurrence of 7 years of age and is located in the cerebellum. The other, and more rare tumours in the PNET group, may occur in the neonatal period (in rare cases congenitally), have a peak age at diagnosis of about 5 years of age and are mainly supratentorial (Sarkar et al, 2005).

It has been suggested that each cell type has a 'window of vulnerability' during which neoplastic transformation may occur (VandenBerg, 2001). Consequently, gestational age at exposure to X-rays might be of importance when evaluating risks for CBT. Since 96% of the abdominal X-ray examinations in this study were performed in the third trimester, it was not possible to evaluate the impact of time of exposure. However, the human brain grows and develops during the whole foetal period and there is currently no evidence that foetuses should be more sensitive to carcinogenic factors in the early gestational period.

In the present study, mean foetal absorbed radiation dose was hard to estimate since the X-ray examinations were not standardised and performed at several hospitals over a 10-year period. Foetal absorbed dose for an abdominal X-ray examination has been reported to vary between 0.1 mGy for a pelvimetry with one anterior–posterior and one lateral film (Axelsson and Ohlsen, 1979) to more than 4 mGy (Osei and Faulkner, 1999; ICRP, 2000). In dosimeter studies, radiation doses have been found to vary by a factor of 30 or more for the same type of examination depending on variations in radiological techniques, choice of film, etc. (Badr et al, 1997; ICRP, 2000). It is reported that prenatal exposure to a radiation dose of over 10 mGy may increase the risk of childhood cancer (Doll and Wakeford, 1997). Furthermore, it is suggested that there is no 'safe' threshold limit but instead a linear relationship between exposed dose and risk increase (Doll and Wakeford, 1997). Furthermore, it is suggested that there is no 'safe' threshold limit but instead a linear relationship between exposed dose and risk increase (Doll and Wakeford, 1997; National Research Council, 2006). Risk increases can be expressed as excess relative risk (ERR), and from previous studies of prenatal X-ray exposure, it is estimated that the ERR for childhood cancer for an absorbed dosage of 10 mGy is approximately 0.5 (Wakeford and Little, 2003). Although there are uncertainties concerning such risk estimates, the low radiation doses in the present study suggest that an ERR of more than 0.5 would not be expected.

The study had sufficient power to detect an OR of at least 1.7 for the overall risk of CBT. However, for the analyses stratified by histological subtypes, a larger population would probably have been needed to find statistically significant increased risks. For the subgroup PNET, which included 105 cases, we had a power of 52% to detect an OR of 1.9 at the 5% significance level. Since there are approximately 10–15 new cases of PNET among Swedish children annually, several more years had to be included to reach sufficient power. As the Medical Birth Register was founded in 1973, 2 years before the start of this study, this register could not have been used to reach the warranted number of cases with PNET, which would be needed to increase power. A study large enough to have sufficient statistical power for the subanalyses might be performed by pooling data from the Nordic countries all of which have
population-based national registries and similar health-care systems.

The strengths of this study include the population-based design, the large number of cases of CB Ts, the prospective and blinded data collection and the small number of missed cases. We were forced to exclude 5% of the cases and 3% of the controls, as we could not trace their antenatal records. Since the antenatal records are filled in and filled before any of the included cases were diagnosed with CB T, the exclusions should not have affected the risk estimates.

In two previous case–control studies on CB T subtypes, no increased risk after prenatal X-ray could be detected, neither for all CB Ts nor for PNET specifically (Bunin et al., 1994; Schuz et al., 2001). In these studies, retrospective interviews on exposure data were used and the risk of recall bias could not be excluded. In both studies, less than 5% of the study population were exposed to prenatal X-ray, whereas we had an exposure rate of 21%. The present study is, to our knowledge, the first study on X-ray and PNET. Although we have performed multivariate analyses and misclassification of exposure would be different between cases and controls. Furthermore, low birth weight is closely correlated to maternal smoking and adjustments for birth weight had only minor effects on the results.

Ultrasound has, during the last two decades, become the examination of choice for determining foetal status (position, multiple births, etc), and antenatal pelvimetry is rarely indicated. Nevertheless, abdominal radiation still occurs, for instance in CT scan on maternal indications. Risks with foetal diagnostic radiation could probably be extrapolated to the early childhood period, since the brain still develops and grows rapidly during the first years of life.

Our most important finding might not be the clinical implication, but in relation to the theory that prenatal or neonatal radiation might affect the various neural cell types differently. PNET are presumed to arise from undifferentiated neural stem cells and little is known regarding the molecular genetic events initiating carcinogenesis (Biegel, 1997). An interesting hypothesis would be that neural stem cells could be extra sensitive during their differentiation and that DNA damage caused by radiation could initiate malignant transformation, leading to the development of embryonic CNS tumours such as PNET. If an increased risk of PNET after radiation exposure is confirmed in future studies, this hypothesis could be tested further in laboratory or animal studies, as part of the complex work of mapping the pathogenesis of childhood brain cancer.

In conclusion, we found no increased risk for CB T after prenatal X-ray exposure when analysed as one group. When analysing according to subgroups, the embryonic tumours defined as PNET showed the highest risk estimates.

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