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Childhood brain tumours, early infections and immune stimulation: A pooled analysis of the ESCALE and ESTELLE case-control studies (SFCE, France)

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ABSTRACT

Background: Few studies have investigated whether early infections and factors potentially related to early immune stimulation might be involved in the aetiology of childhood brain tumours (CBT). In this study, we investigated the associations between CBT with early day-care attendance, history of early common infections, atopic conditions (asthma/wheezing, eczema, allergic rhinitis), early farm residence/visits and contact with animals.

Methods: We pooled data from two nationwide French case-control studies, the ESCALE and ESTELLE studies. Children with a CBT diagnosed between 1 and 14 years of age were identified directly from the French National Registry of Childhood Cancers, while population controls were recruited from telephone subscribers. Odds-ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression adjusted for potential confounders.

Results: The analyses included 469 cases and 2719 controls. We found no association between attending a day-care centre (OR: 0.9, 95%CI: 0.7–1.2) or having had repeated common infections (OR: 0.9, 95%CI: 0.7–1.2) in the first year of life and the risk of CBT. There was also no association with a history of asthma/wheezing (OR: 0.8, 95%CI: 0.56–1.1). Farm visits (OR: 0.6, 95%CI: 0.5–0.8) as well as contact with pets (OR: 0.8, 95%CI: 0.6–1.0) in the first year of life were inversely associated with CBT.

Conclusions: Our findings suggest a protective effect of early farm visits and contact with pets, but not with other markers of early immune stimulation. This might be related to immune stimulation but needs further investigation.

Abbreviations: CBT, childhood brain tumours; ICCC-3, International Classification of Childhood Cancer 3rd edition; SFCE, Société Française de lutte contre les Cancers et leucémies de l'Enfant et de l'adolescent (French society against childhood and adolescent cancers and leukaemias); ICDO-3, International Classification of Diseases-Oncology; ENT, ear-nose-throat; URTI, upper respiratory tract infections; LRTI, lower respiratory tract infections; OR, odds ratio; CI, confidence interval; UKCCS, United Kingdom Childhood Cancer

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1. Introduction

After leukaemias, brain tumours are the second most common type of childhood cancer. With about 400 cases diagnosed in mainland France every year (3.6 per 100,000 child-years), they represent about 23% of incident cases of childhood cancer [1]. Childhood brain tumours (CBT) are classed into large heterogeneous groups according to the ICCC-3 classification [2], with about 10% of ependymomas and plexus choroid tumours, 38% of astrocytomas, 21% of embryonal tumours, and 16% of other gliomas in France mainland [1]. On the average, the five year survival rate in France is about 72%, but with wide variations by age and subtype [3].

The aetiology of CBT is generally unknown. The only established environmental risk factor is ionising radiation at medium or high doses [4,5]. Some genetic dispositions, such as neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome, are also linked with a higher risk of CBT. Suspected risk factors include exposure to pesticides, traffic pollution, parents' occupational exposure, radiofrequencies, parental age, maternal smoking, alcohol use and nutrition [4,5].

Early infections and factors related to early immune stimulation have been mostly studied for childhood leukaemias [6] but might also be involved in the development of CBT. To date, there are only a few studies of potential infections or immunological markers and their association with CBT. History of early common infections has been rarely researched and so far there is no evidence of an association with CBT [7]. Exposure to common infections in infants is difficult to ascertain retrospectively. Birth order [8,9] or attending day-care centres [10,11], which favour early infections through contact with other children, can be used as proxy indicators. Studies which have looked at the association between these markers of infection and CBT have produced mixed findings [7,12–17]. Indicators of abnormal immune system responses include the tendency for atopic conditions such as asthma/wheezing, eczema and allergies while indicators of early immune system stimulation may include living on a farm, frequent farm visits, early animal exposure or breast feeding. Whereas studies of brain tumours in adults have consistently reported an inverse relationship with atopic conditions [18–20] the findings from studies of CBT have been more inconsistent [21–23]. Studies to date do not suggest strong associations between living on a farm or early contact with animals [24,25] or breastfeeding [26].

In a previous paper, we reported no associations between breast feeding and CBT [27]. In this study, we aimed to investigate the associations between CBT and the main subtypes with a marker of early infectious exposure (early day-care attendance), history of early common infections, atopic conditions (asthma, eczema, allergic rhinitis) as well as early farm visits, farm residence and animal contact in France by pooling data from two nationwide case-control studies, the ESCALE and ESTELLE studies.

2. Methods

The ESCALE and ESTELLE studies were designed to investigate the role of environmental and genetic risk factors of childhood cancers including factors related to infections in early life which were conducted with the support of the French society against childhood and adolescent cancers and leukaemias (SFCE). Both studies have been described elsewhere [27–29]. The study protocols complied with the French regulations relating to databases and ethics and the pertinent ethical approvals were obtained. The ESCALE study included children diagnosed in 2003–2004 with a malignant brain tumour as well as children with leukaemia, lymphoma or neuroblastoma. The ESTELLE study included children diagnosed in 2010–2011 with a malignant or non-malignant brain tumour as well as children with a leukaemia, lymphoma, neuroblastoma, Wilms' tumour or hepatoblastoma.

2.1. Cases and controls

In brief, children newly diagnosed with a CBT (defined as group III of ICCC-3) were identified directly in the paediatric oncology departments by the network of the French National Registry of Childhood Cancers (RNCE). Malignant CBT were defined according to the International Classification of Diseases-Oncology (IDCO-3) [30] as tumours with a behaviour code of 3. They were eligible if they were under 15 years of age and resident in mainland France at the time of diagnosis. For both studies children were ineligible if they had been adopted or if the biological mother was not available, did not speak French or had severe psychological or social problems, or if the child was in palliative care or had died (Supplementary Fig. S1).

Population controls were selected from French mainland landline telephone subscribers using quota sampling methods. Procedures differed slightly between ESCALE and ESTELLE. For ESCALE, listed and unlisted telephone numbers were randomly generated by incrementing by one the last digit of the listed telephone numbers while for ESTELLE, allocable telephone numbers were randomly generated. Quotas were used to obtain overall at least one control per case for each year of age, each gender and each type of cancer. The quotas also ensured that the control groups had the same distribution as the overall population in regards to the number of children aged less than 15 years living in the household, adjusted by age. Children with a history of cancer were ineligible. Similar to cases, children who had been adopted or whose biological mother was not available or did not speak French were ineligible (Supplementary Fig. S2).

The participation rate in ESCALE was 80.1% for cases and 71.2% for controls. In ESTELLE cases participation was 94.1% and 85.5% among cases and controls, respectively (Supplementary Figs. S1 and S2).

2.2. Data collection

Data were collected using computer assisted structured telephone interviews with case and control mothers carried out by the same trained interviewers. Mothers were also asked to have the child's personal health record with them for the interview so they could confirm relevant details. Mothers of case children were interviewed on average six months after diagnosis. Questions were asked about demographic and socio-economic characteristics, parental occupational exposures, childhood environment and lifestyle.

In both the ESCALE and ESCALE studies, mothers were asked if their child ever attended a day-care centre or another type of external group day-care (shared nanny, private shared child care) and the child's age at the first time of attendance. Mothers were also asked if the child ever had common infections before the age of one year (tonsillitis, otitis, common cold, laryngitis, bronchiolitis, other pulmonary infections, gastroenteritis, urinary tract infections) and the frequency of these illnesses. In addition, they were asked if the child had any ear-nose-throat (ENT) operations before three years of age. The interviews also contained questions on prior atopic conditions confirmed by a doctor (asthma/wheezing, eczema, hay fever (only in ESTELLE)). If the child ever had asthma/wheezing, they were asked the type of treatment. In addition, mothers were also requested to give details of each residence during the child's life. They were also asked to recall if the child had ever visited a farm before the age of one year, the frequency of those potential visits (never, several days per year, several days per month, at least several days per week), and if the child had regular contact with a wide range of pets (including cats, dogs, birds or rodents) or farm animals at least once a week during the first year of life (including cows, sheep, pigs, horses and poultry).

2.3. Data management

We defined any external childcare as attending either a day-care centre, having a shared nanny, or attending private shared childcare.