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Childhood leukaemia and infectious exposure: A report from the United Kingdom Childhood Cancer Study (UKCCS)

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ABSTRACT

Data from a national case-control study are used to explore the relationships between childhood leukaemia, infant infection and three markers of infectious exposure – birth order, infant-activity group attendance and area-based deprivation. Amongst controls, clinically diagnosed infection in the first year varied little with birth order and infant-activity group attendance – with 4 in 5 children having at least one infection, and each child averaging around 2.9 (2.8–3.0). Amongst cases of acute lymphoblastic leukaemia (ALL), the levels of infection increased as the indices of infectious exposure increased – for example, odds ratios associated with at least one infection in the first year being 0.9 (95% confidence interval (CI): 0.6–1.4) for birth order one and 1.6 (95% CI: 1.1–2.2) for birth order two or more. By contrast, interview data were misleading, with mothers – particularly case mothers – consistently under-reporting. We conclude that the findings based on clinical data, combined with the markers of infectious exposure, confirm the observation that immune dysregulation among children who develop ALL is detectable from an early age.

1. Introduction

The potential aetiological role of infection in the development of childhood leukaemia has been the subject of many epidemiological studies and reports. To date, however, no specific agents have been identified and the mechanism by which infectious exposures might influence subsequent leukaemia risk remains a much debated topic.[1,2] A key reason for this uncertainty is the lack of consistency between study findings, and the present paper explores some of the reasons why this may occur.

Unravelling the relationship between disease risk and previous infectious exposure is not straightforward. With a view to quantifying children's likely exposure to infectious agents at various time-points, a wide range of proxies have been employed including family measures of socio-economic status and residential location[3,4]; parental indicators of social contact outside the home[1,5]; markers of the child's social activity such as birth order[6–8] and pre-school group attendance[9–11]; as well as infectious illness histories of both the child[8,12–17] and their mothers.[17–22]

In order to investigate the relationship between leukaemia and infection as comprehensively as possible, the United Kingdom Childhood Cancer Study (UKCCS) collected information on a number of markers of infectious exposure from multiple sources (www.ukccs.org). A unique facet of the UKCCS is that, in addition to asking mothers about their child's health, systematic abstractions of primary-health care

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data contemporaneously compiled before diagnosis/interview were also undertaken.[12,23] Using these data we have already demonstrated that children who develop leukaemia between the peak ages of 2 and 5 years have more infectious illness episodes in the first year of life than children who do not.[12] The present paper expands on this work by examining the relationship between childhood leukaemia, infectious illness episodes and three commonly used markers of childhood infectious exposure – birth order, maternal reports of infant social activity outside the home and a census-derived measure of deprivation. In addition, results based on clinical diagnoses of infection are compared with those based on maternal self-report.

2. Material and methods

The UKCCS is a national population-based case-control study, and full details of its conduct and ethical approvals have been previously described.[24] Briefly, children aged 0–14 years diagnosed with leukaemia between 1991 and 1996 in Great Britain were eligible. For each case, two controls matched by sex, month and year of birth and region of residence at diagnosis were randomly recruited from primary care population registers.

At interview, mothers were asked a series of structured questions about the infectious illnesses that their child had during their first year of life. This included general questions about colds, diarrhoea, vomiting, ear infections, eye infections and mouth infections; as well as more specific ones about illnesses such as measles and chicken pox. For each infectious illness episode, mothers were asked whether or not they had consulted a doctor and, if so, whether any medications had been prescribed. At the end of this section, mothers were also asked whether or not their child had any infections that they had not been asked about, and about other factors that may have influenced their child's exposure to infection during infancy. Mothers were also asked about their child's social activity with other infants and children outside the home in the first year of life. In particular they were asked whether they regularly (at least once a week) attended a nursery, play group, mother and toddler group, childminder, swimming, gym group or any other group. For each positive response, mother's were asked how old their child was when they first attended.[9]

At interview, consent to access the child's primary care (general practice – GP) records was also requested; and all information contained within these routinely compiled health records from birth until diagnosis (pseudo-diagnosis date for control children) was subsequently abstracted onto specially designed forms by centrally trained research staff. These data, which included all symptoms, diagnoses and drugs recorded at each consultation, were centrally coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)[25] and drugs to a schema based on the British National Formulary.[26]

The data analysed in this report are from the six UKCCS administrative areas that systematically abstracted GP records – one region routinely abstracted data on each case and both controls, whilst others opted for one control per case at varying times as the study progressed – three doing so almost from the outset, and two changing tack part-way through.[12] Importantly, in common with other components of the UKCCS that only collected additional data on one of the two individually matched controls, this control – the lowest numbered (first randomly selected) interviewed control in the series – was identified in advance of abstraction.[24,27]

Enumeration district 'deprivation' indices at birth were calculated using the same methods as described for the UK as a whole.[3] As in previous UKCCS publications,[12] in order to increase precision and statistical power all available controls were used as the comparison group. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression with adjustment for UKCCS administrative area of residence at diagnosis, sex and age at diagnosis (in single years).[28] The analyses presented here focus on the first 12 months of life, and cases diagnosed before 15 months of age and their corresponding controls are excluded. Also excluded are children who had Down's syndrome because of the known relationship between Down's syndrome and leukaemia and between Down's syndrome and infection.[29] All analyses were conducted using STATA.[30]

3. Results

Socio-demographic characteristics of the 811 leukaemia cases and 1288 controls are compared in Table 1. As expected, the sex and age distributions at diagnosis/pseudo-diagnosis were similar – the marginal non-significant differences reflecting the fact that in this dataset some cases were matched to one control and others were matched to two. The interval between the child's diagnosis/pseudo-diagnosis and parental interview was, on average, greater for controls than cases; and control children were around 6–10 months older than case children at the time of interview. With respect to indicators of infectious exposure, participating cases and controls were similar with respect to their birth order, but controls were significantly more likely ($P < 0.05$) to have regularly attended social groups outside the home and to live in more affluent areas at the time the child was born.

The relationship between infectious illness frequency in the first year of life and birth order, infant social activity outside the home and deprivation is summarised in Table 2. Control children received an infectious diagnosis from their GP an average of 2.9 (95% CI 2.8–3.0) times in their first year of life. This varied little with birth order or social activity outside the home. However, controls living in the most deprived areas (those in the highest deprivation quintile) had significantly more infectious illnesses diagnosed than those residing in more affluent areas. In comparison to controls, case children averaged significantly more infectious illness episodes overall (3.2; 95% CI 3.1–3.3; $P < 0.01$). Moreover, children with acute lymphoblastic leukaemia of birth order two or more tended to have more infectious illness episodes diagnosed in the first year of life (3.6; 95% CI 3.4–3.7) than controls (2.9; 95% CI 2.8–3.0) and cases of birth order one (2.7; 95% CI 2.5–2.9). The pattern was similar for children with all who regularly attended infant activity groups outside the home (3.3; 95% CI 3.1–3.5) and those in the lowest deprivation category (3.8; 95% CI 3.5–4.1).