Commentary: Birth order and risk of childhood acute lymphoblastic leukaemia (ALL)

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In this issue of the International Journal of Epidemiology, Dockerty and colleagues report a case-control study in which a number of parental, familial and social factors were evaluated in relation to risk of different childhood cancers. The rationale of the study is a rather curious mix of four different hypotheses, only loosely interconnected by the parameters studied. But it does have two outstanding features—its very large size and a design that minimizes selection bias. These provide the potential for robust statistical inquisition of associations, or the lack thereof. Cases (age 0–14 years) total almost 11 000 including 3878 leukaemias, all accrued from the British National Registry of Childhood Tumours for the period 1968–1986. Controls were selected from the Office of Population Censuses and Surveys (OPCS, now Office for National Statistics) birth data and matched for gender, date of birth (6-month periods) and birth registration sub-district.

Somewhat ironically, given the study’s potential, none of the four hypotheses, as strictly defined, enjoys clear cut support in the resultant analyses, yet the results are very interesting and some striking associations did emerge. The most remarkable of these concerns parity and risk of leukaemia. The authors define one of their prior hypotheses as follows: ‘that firstborn children have a higher risk of childhood acute lymphoblastic leukaemia (ALL) and acute non-lymphocytic leukaemia (ANLL)’ (my italics; for ANLL read acute myeloid leukaemia [AML]). This idea rests on both historical data and the ‘delayed infection’ hypothesis that specifically address causality for the common B cell precursor variant of acute lymphoblastic leukaemia (cALL). Prior work on birth order has produced mixed results, with some studies reporting an increased risk of ALL for firstborns or for those with the next oldest sibling more than 5 years older than the index case as predicted by the delayed infection hypothesis. Other studies have found no impact of birth order (references provided in Dockerty et al.).

In the present study, the authors found a very striking association between decreasing risk for ALL and parity. Moreover, if this association was absent for AML and considerably more marked for children with ALL age 1–5 (i.e. mainly cALL) versus those with ALL at all ages. The odds ratios were even more impressive after adjusting for maternal age and deprivation scores. Risk of ALL (at ages 1–5) was roughly halved for those with four or more older siblings. The numbers involved, selectivity for cALL, the overall trend seen with birth order, the confidence intervals and P-values all are impressive enough to fully justify the authors’ conclusions that the result is ‘extremely interesting’.

All the more surprising and disappointing then that the authors’ discussion of the possible biological and aetiological meaning of these data is rather banal and very conservative. We are told that these data ‘could give some indirect support’ to the delayed infection hypothesis but that other explanations are also possible. The alternative on offer, as an example, is that first time pregnant women may be more likely to take certain medications during pregnancy. To date, there is no reported association, selective for ALL, that implicates medicinal exposure during pregnancy, but neither are such links as yet ruled out. Even to a non-epidemiologist, and one with a clearly vested interest in the infection hypothesis, it seems odd that remarkable data ably fulfilling one prediction of a prior and plausible hypothesis are interpreted in such a neutral or cautious fashion.

Part of the reason for this might lie in the hint the authors provide suggesting that they are less than convinced that infection hypotheses for childhood leukaemia enjoy robust epidemiological support. They refer to hypotheses on patterns of infection in early childhood or population mixing ‘not having been confirmed’ or some studies having provided little or no support. This is a rather cursory and inaccurate reading of the currently available data. It is true that the large-scale case-control studies specifically designed to test the ‘delayed infection’ hypothesis for ALL (i.e. the UK Children’s Cancer Study and a California case-control study) have yet to deliver their verdicts. Nevertheless, the evidence supporting infection via population mixing as a risk factor, at least in particular socio-demographic circumstances, is regarded as very convincing. Evidence for the delayed infection version of the infection idea is also now increasing, albeit that it is still short of the finishing post. For example, the protective effect of certain common infections in infancy and of Haemophilus influenzae B vaccination, would struggle to find any other cogent explanation. Dockerty et al. mention three studies that fail to support the delayed infection idea. One of these is an earlier Dockerty et al. paper that was based in New Zealand and was only able to accrue 97 cases of ALL (of all ages). Nevertheless in that paper they report an odds ratio of 0.67 (95% CI : 0.40–1.12) for children who had regular contact with other children in the first year of life. This may not have reached statistical significance but to regard it as contrary evidence or lack of confirmation is suspect logic. Dockerty et al. also recorded that infections in infancy recorded as simply ‘present’ or ‘absent’ had no apparent associations with risk of ALL. In one of the papers that has produced a striking association of cALL with this parameter, it was clear that diminished risk was linked to number of infectious episodes (ear infections). Other ‘negative’ studies quoted include that of Neglia et al. Although this study provided the link with deficit of infections in infancy referred to above these authors did fail to find an association (protection) with day care attendance in infancy (i.e. proxy for early infectious exposure). However, they rightly acknowledged that failure to take account of the size of the day care group (i.e. potential
numbers of infectious contacts) considerably weakens the power of the study. In a more recent report, Infante-Rivard et al. found a protective effect against ALL for both day care attendance in infancy and having older siblings when in infancy.

Clearly, studies designed to assess the infection hypothesis need to take the critical time windows into account—the first year of life and the period 3 to 12 months prior to diagnosis. They need also to quantify, whenever possible, the exposures or proxy measures used. Large case-control studies in progress should soon provide further support (or refute) the idea that an abnormal or delayed pattern of common infections is a critical component of the aetiology of the variety of childhood leukaemia that dominates the major incidence peak (2–6 years) in developed countries. Its importance lies in the potential for prophylactic intervention in infancy. In the meantime, this latest study by Dockerty and colleagues is an important contribution to the ongoing debate.

References


