Short Communication

Delayed infection, late tonsillectomy or adenoidectomy and adult leukaemia: a case–control study

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In a population-based case–control study among adults in Italy, of 261 lymphoid and 313 myeloid leukaemias and 1718 controls, a later age at adenoidectomy and tonsillectomy (after age 10 years) increased considerably the risk of lymphocytic (but not myeloid) leukaemia (odds ratio 4.2, 95% confidence interval 1.1–16.2). We propose that late infection is a proliferative stimulus for B-cells.

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Some adult diseases have been attributed to late exposure to common infectious agents – poliomyelitis (Nielsen et al, 2002), Hodgkin’s disease (Gutensohn and Cole, 1981) and multiple sclerosis (Lindberg et al, 1991) – but the evidence is not definitive. Perrillat et al (2002) found an inverse association between day-care attendance, repeated early common infections or surgical procedures for ear–nose–throat infections, and childhood leukaemia, with odds ratios (ORs) in the order of 0.5–0.6.

We conducted a population-based case–control study on leukaemias in adults in Italy. We examined the role played by two surgical operations, adenoidectomy and tonsillectomy, in modifying the risk of adult leukaemia. A late age at adenoidectomy and tonsillectomy has been proposed as a proxy for delayed infection with Epstein–Barr virus (EBV) (Perrillat et al, 2002). Our hypothesis is that late EBV infection or other exposures to infectious agents are a proliferative stimulus for B-cells, which causes symptomatic mononucleosis in normal conditions, but may be able to confer proliferative advantage to mutated cells.

METHODS

The areas included in the study are 11 Italian areas with different demographic and socioeconomic characteristics (town of Torino, provinces of Varese, Novara, Vercelli, Alessandria, Imperia, Ragusa, Siena, Forlí, Verona and Firenze; total population 7 million). In each centre, all the subjects suspected of having leukaemia, lymphoma or multiple myeloma were identified through periodical surveys in the hospital departments where leukaemias in adults in Italy. The sample was stratified according to 5-year age groups and sex, and its size was equal to the number of cases in the largest diagnostic group (NHL+CLL). Procedures for control sampling were based on computerised and regularly updated demographic files or through the files of the National Health Service, both of which are regularly updated.

Information about the known or suspect risk factors was collected through person-to-person interviews. Interviews were carried out preferentially at the subject’s home. The same procedures were followed for cases and controls. The only exception was represented by interviews to cases affected by acute leukaemia and the seriously ill, which were mostly carried out in the hospital. Subjects were encouraged to participate, by contacts with the general practitioners, and were successful in maintaining a high response rate. The interview was face-to-face and lasted approximately 1 h, as described elsewhere in more detail (Vineis et al, 2000a,b), and covered a medical history of the following diseases: measles, rubella, chickenpox, pertussis, herpes zoster, herpes labialis, herpes genitalis, mumps, infectious hepatitis, infectious mononucleosis, tuberculosis, malaria, other infectious diseases (specified by the subject), hay fever, allergic asthma, other (specified) allergies, peptic ulcer, ulcerative colitis, gluten intolerance, Crohn’s disease, other (specified) digestive diseases, diabetes...
TABLE 1 Lymphocytic and myeloid leukaemias: age at surgical interventions for adenoidectomy or tonsillectomy

| Lymphocytic OR (95% CI) | Myeloid OR (95% CI) |
|------------------------|---------------------|
| Adenoidectomy          |                     |
| No                     | 241/1524 1.0 (ref)  | 276/1524 1.0 (ref) |
| Yes                    | 20/94 0.8 (0.5 – 1.3)| 37/194 1.2 (0.8 – 1.7)|
| Age at intervention (y) |                     |
| <10                    | 4/103 1.0 (ref)     | 17/103 1.0         |
| 10 – 20                | 10/52 4.2 (1.1 – 16.2) | 9/52 1.0 (0.4 – 2.2) |
| 20+                    | 3/16 4.1 (0.2 – 4.1) | 2/16 0.9 (0.2 – 4.4) |
| Age unknown            | 3/23                | 9/23                |

Tonsillectomy

| Lymphocytic OR (95% CI) | Myeloid OR (95% CI) |
|------------------------|---------------------|
| No                     | 206/1270 1.0 (ref)  | 244/1270 1.0 (ref) |
| Yes                    | 55/449 0.9 (0.7 – 1.3)| 69/449 0.9 (0.6 – 1.1)|
| Age at intervention (y) |                     |
| <10                    | 15/203 1.0 (ref)    | 28/203 1.0 (ref)   |
| 10 – 20                | 18/118 1.8 (0.8 – 4.1)| 17/118 1.1 (0.6 – 2.0)|
| 20+                    | 15/114 1.5 (0.5 – 4.0)| 16/114 1.0 (0.6 – 2.3)|
| Age unknown            | 7/14                | 8/14                |

calc'd/cases/controls. Odds ratios (ORs) are age- and gender-adjusted. 95% CI=confidence interval.

and other (specified) metabolic diseases, rheumatoid arthritis, lupus erythematosus, periarteritis nodosa, scleroderma, other (specified) osteomuscular diseases, urticaria, eczema, psoriasis, other skin allergies, and other (specified) relevant diseases. Only diseases that had been formally diagnosed by a physician were considered. For each disease, the date of occurrence was determined, except for the ‘other, specified’ category. The overall refusal rate was 10% among cases and 19% among controls.

We computed age- and gender-adjusted ORs (Mantel-Haenszel) and their 95% CIs (Breslow and Day, 1980). We also fitted logistic regression models including age (continuous variable), gender and educational level.

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Overall, we interviewed 261 patients with lymphocytic leukaemia, 313 with myeloid leukaemia and 1718 controls. Table 1 shows the distribution of adult lymphocytic and myeloid leukaemias by adenoidectomy and tonsillectomy, and the age at which such operations were performed. The operations themselves were not associated with any risk modification. However, a later age at adenoidectomy and tonsillectomy (after age 10 years) increased considerably the risk of lymphocytic (but not myeloid) leukaemia. The fact that the increase in risk is limited to lymphocytic leukaemia enhances the biological plausibility of the association.

In a previous paper on non-Hodgkin’s lymphomas (NHl), we found that the age of occurrence of bacterial and viral diseases was significantly higher among NHL patients than in the controls. The association between later age at first bacterial or viral disease was limited to small families (OR = 1.95, 95% CI 1.26 – 3.00, for age 4 – 8 years at first infection; OR = 1.91, 1.19 – 3.06, for age 9+ years, compared with less than 4 years) (Vineis et al, 2000b). The association was more obvious for bacterial diseases (possibly because of a lower degree of misclassification). We repeated the same analyses for leukaemia, although limited by smaller numbers; ORs are presented in Table 2. In spite of statistical instability, there is the suggestion of a higher risk of lymphocytic leukaemia in smaller families and with older age at first infection. The same pattern was not apparent for myeloid leukaemias (data not shown). While data on age at first infection are likely to be affected by recall bias, surgical operations such as tonsillectomy or adenoidectomy should be recalled more faithfully.

In one previous study, tonsillectomy or appendectomy was found to increase the risk of childhood leukaemia, but the age at surgical intervention was not investigated (Schuz et al, 1999). A late age at adenoidectomy and tonsillectomy has been proposed as a proxy for delayed infection with EBV or other viruses (Perrillat et al, 2002). Our hypothesis is that late EBV infection is a proliferative stimulus for B-cells. Such an event causes symptomatic mononucleosis in normal conditions, but is able to confer proliferative advantage to mutated cells. An interesting model is represented by paroxysmal nocturnal haemoglobinuria (PNH), characterised by a somatic mutation of the PIG-A gene in haematopoietic cells (Rosse, 2001). The current hypothesis explaining the disorder suggests that there are two components: (a) haematopoietic stem cells with the characteristic defect are present in the marrow of many, if not all, normal individuals in very small numbers; (b) some aplastogenic influence suppresses the normal stem cells, but does not suppress the defective stem cells, thus allowing the proportion of these cells to increase. Clearly, the PNH model applies only indirectly to leukaemias because there is no reason to think that late infection is aplastogenic. Rather, mutations or chromosome damage would be necessary to induce leukaemia, but a proliferative stimulus (infection) causing a selection of the mutated clones would also intervene.
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