***Short Communication***

# Family History of Autoimmune Thyroid Disease and Childhood Acute Leukemia[1]

**Florence Perillat-Menegaux, Jacqueline Clavel,[2] Marie-Françoise Auclerc, André Baruchel, Guy Leverger, Brigitte Nelken, Noël Philippe, Danièle Sommelet, Etienne Vilmer, and Denis Hémon**

Institut National de la Santé et de la Recherche Médicale, INSERM U170, 94807 Villejuif, France [F. P., J. C., D. H.]; Institut National de la Santé et de la Recherche Médicale, Institute of Hematology, Saint-Louis Hospital, 75010 Paris, France [M-F. A.]; Department of Pediatric Hematology, Saint-Louis Hospital, Paris, France [A. B.]; Department of Pediatric Hematology, Armand Trousseau Hospital, Paris, France [G. L.]; Department of Pediatric Hematology-Oncology, Jeanne de Flandre Hospital, Lille, France [B. N.]; Department of Pediatric Hematology, Debrousse Hospital, Lyon, France [N. P.]; Department of Pediatric Hematology, Brabois Hospital, Nancy, France [D. S.]; and Department of Pediatric Hematology-Immunology, Robert Debré Hospital, Paris, France [E. V.]

## Abstract

**The association between a familial history of autoimmune disease and childhood acute leukemia was investigated in a French case-control study that, overall, was designed to assess the role of perinatal, infectious, environmental, and genetic factors in the etiology of childhood acute leukemia. Familial histories of autoimmune disease in first- and second-degree relatives were compared in 279 incident cases, 240 cases of acute lymphocytic leukemia (ALL) and 39 cases of acute non-lymphoblastic leukemia (ANLL), and 285 controls. Recruitment was frequency matched by age, gender, hospital, and ethnic origin. Odds ratios (OR) were estimated using an unconditional regression model taking into account the stratification variables, socioeconomic status, and familial structure. A statistically significant association between a history of autoimmune disease in first- or second-degree relatives and ALL (OR, 1.7; 95% confidence interval (CI), 1.0–2.8) was found. A relationship between thyroid diseases overall and ALL (OR, 2.0; 95% CI, 1.0–3.9) was observed. This association was more pronounced for potentially autoimmune thyroid diseases (Grave's disease and/or hyperthyroidism and Hashimoto's disease and/or hypothyroidism) (OR, 3.5; 95% CI, 1.1–10.7 and OR, 5.6; 95% CI, 1.0–31.1, respectively for ALL and ANLL), whereas it was not statistically significant for the other thyroid diseases (thyroid goiter, thyroid nodule, and unspecified thyroid disorders) (OR, 1.6; 95% CI, 0.7–3.5 and OR, 1.3; 95% CI, 0.2–7.0, respectively, for ALL and ANLL). The results suggest that a familial history of autoimmune thyroid disease may be associated with childhood acute leukemia.**

## Introduction

Leukemia is the most common cancer in childhood worldwide, and, with the exception of ionizing radiation, rare genetic syndromes, and certain chemotherapeutic drugs, its etiology remains unknown. Previous studies have suggested that autoimmune diseases overall (1, 2) and specifically autoimmune thyroid diseases (1), multiple sclerosis (3), and ulcerative necrosis (4) among family members might be associated with childhood leukemia. The present study was designed to assess the role of environmental and genetic factors in the etiology of childhood acute leukemia. In this study, autoimmune diseases were identified by specific questions, and the present paper analyzes the relationship between childhood leukemia and a reported familial history of diabetes mellitus, thyroid disease, rheumatoid arthritis, or other autoimmune disease among first- or second-degree relatives.

## Patients and Methods

The cases were children under the age of 15 years hospitalized for recent diagnosis of primary leukemia between January 1, 1995 and December 31, 1999 in the hospitals of Lille, Lyon, Nancy, and Paris (France). The controls were children hospitalized in the same hospital as the cases, mainly in orthopedic and emergency departments, and residing in the same area as the cases. Recruitment was frequency-matched by age using five categories ($<2$, 2–3, 4–6, 7–10, and $\geq 11$ years), gender, hospital, and ethnic origin using three categories (Caucasian, North African, and others). Of the mothers of the 282 cases and 291 controls who were eligible for interview during the interviewers' working hours, the mothers of 2 cases and 2 controls refused to participate. One control child who was adopted, three control children for whom the questionnaires were incomplete, and one case child who was conceived with sperm from a sperm donor were excluded. Finally, a total of 279 incident cases of acute leukemia confirmed by cytology and 285 controls were included in the study.

The mothers of the cases and controls were interviewed when the index child was in complete remission or in good condition (on average, 2 months after diagnosis), using a standard questionnaire administered by trained medical interviewers. Interviews were performed in the hospitals under strictly similar conditions and at the same time for the cases and controls. The questions addressed the sociodemographic characteristics, lifetime medical history of the index child, and smoking habits, beverage consumption, lifetime occupational history, and familial medical history of the parents. When mothers had lost contact with their relatives, the data were considered missing. Data were missing for three cases and three controls. The

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[2] To whom requests for reprints should be addressed, at INSERM U170, 16 avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France.

*Table 1* Sample description for the cases and controls

| | Cases ($n$ = 240) | Controls ($n$ = 285) | $P$ |
|---|---|---|---|
| Diagnosis categories for controls | | | |
| Traumatism (fractures, pounds, burns, . . .) | — | 151 | |
| Osteo-articular diseases (arthritis, osteomyelitis, . . .) | — | 100 | |
| Digestive, urinary and genital symptoms | — | 17 | |
| Minor congenital disorders | — | 6 | |
| Others | — | 11 | |
| Stratification variables | | | |
| Gender | | | ns[a] |
| Male | 166 | 168 | |
| Age (yrs) | | | 0.01 |
| <2 | 33 | 51 | |
| 2–3 | 84 | 51 | |
| 4–6 | 83 | 79 | |
| 7–10 | 41 | 63 | |
| ≥11 | 38 | 41 | |
| Hospital | | | ns |
| Lille | 38 | 26 | |
| Lyon | 36 | 35 | |
| Nancy | 23 | 21 | |
| Paris | 182 | 203 | |
| Ethnic origin | | | ns |
| Caucasian | 243 | 236 | |
| North African | 15 | 23 | |
| Caribbean | 4 | 5 | |
| African | 2 | 6 | |
| Asian, Middle Eastern | 2 | 6 | |
| Mixed, others | 13 | 9 | |
| Sociodemographic characteristics | | | |
| Maternal education | | | ns |
| ≤High school | 189 | 176 | |
| >High school | 90 | 108 | |
| Paternal education | | | ns |
| ≤High school | 181 | 171 | |
| >High school | 87 | 99 | |
| Socioprofessional categories | | | ns |
| Professional, technical workers, administrators, and managers | 147 | 160 | |
| Clerical, sales, and services workers | 55 | 49 | |
| Factory and agricultural workers | 77 | 76 | |
| Familial characteristics (means ± SD) | | | |
| Mean no. of family members | | | |
| First-degree | 3.3 (±1.1) | 3.2 (±1.0) | ns |
| Second-degree | 9.7 (±3.9) | 9.2 (±3.3) | ns |
| First- and second-degree | 12.9 (±4.3) | 12.4 (±3.6) | ns |
| Average age of the first-degree relatives (yrs) | | | |
| Parents | 30.0 (±5.4) | 30.2 (±5.5) | ns |
| Siblings | 8.7 (±6.0) | 8.9 (±5.8) | ns |
| Average age of the second-degree relatives (yrs) | | | |
| Grandparents | 58.3 (±9.0) | 58.4 (±9.4) | ns |
| Aunts and uncles | 29.9 (±9.5) | 29.5 (±9.7) | ns |

[a] ns, $P > 0.05$.

interviewers were not aware of the index child's family history before the interview. Familial medical history was collected for first-degree relatives (parents and siblings) and for second-degree relatives (grandparents, uncles, and aunts). Autoimmune diseases were systematically investigated for using a closed checklist including synonyms. Unfortunately, no medical validation of the diagnoses was available. The following diseases were considered autoimmune or potentially autoimmune: Graves' disease and/or hyperthyroidism; Hashimoto's thyroiditis and/or hypothyroidism; diabetes mellitus; rheumatoid arthritis; ankylosing spondylitis; multiple sclerosis; systemic lupus erythematosus; Behçet's syndrome; Crohn's disease; celiac disease; Landry-Guillain-Barré syndrome; and psoriasis.

Statistical analyses were performed using the SAS software package. The analyses were conducted by leukemia type (ALL[3] *versus* ANLL). ORs were estimated using an unconditional logistic regression model including stratification variables (*i.e.*, gender, age, ethnic origin, and hospital). Potential confounding by sociodemographic characteristics and familial structure was considered in the various analyses. A familial history of solid neoplasm or hematological neoplastic disease, for which the present authors had previously found an associ-

[3] The abbreviations used are: ALL, acute lymphoblastic leukemia; ANLL, acute nonlymphoblastic leukemia; OR, odds ratio; CI, confidence interval.

*Table 2* Association between autoimmune disease[a] and childhood acute leukemia

| | ALL ($n$ = 240) | | | | ANLL ($n$ = 39) | | | |
|---|---|---|---|---|---|---|---|---|
| | Ca[b] | Co | OR[c] | 95% CI | Ca | Co | OR | 95% CI |
| Any autoimmune diseases | | | | | | | | |
| First or second-degree relatives | 44 | 32 | **1.7** | (1.0–2.8) | 8 | 32 | **2.2** | (0.9–5.5) |
| First-degree relatives | 18 | 14 | **1.5** | (0.7–3.2) | 2 | 14 | **1.0** | (0.2–4.8) |
| Second-degree relatives | 30 | 23 | **1.6** | (0.9–2.9) | 7 | 23 | **3.1** | (1.1–8.6) |
| First or second-degree relatives | | | | | | | | |
| 0 | 196 | 250 | **1.0** | Reference | 32 | 250 | **1.0** | Reference |
| 1 | 33 | 27 | **1.5** | (0.8–2.6) | 7 | 27 | **2.2** | (0.8–5.8) |
| 2+ | 11 | 5 | **2.9** | (0.9–8.9) | 1 | 5 | **2.0** | (0.2–22.1) |
| | | | $P$ trend = 0.03 | | | | $P$ trend = 0.15 | |
| Thyroid diseases | | | | | | | | |
| All thyroid diseases | | | | | | | | |
| First or second-degree relatives | 27 | 18 | **2.0** | (1.0–3.9) | 4 | 18 | **1.8** | (0.5–6.4) |
| First-degree relatives | 12 | 5 | **3.2** | (1.0–9.8) | 1 | 5 | **1.6** | (0.2–16.6) |
| Second-degree relatives | 19 | 13 | **1.8** | (0.8–4.0) | 4 | 13 | **2.8** | (0.7–10.9) |
| Thyroid diseases potentially autoimmune | | | | | | | | |
| First or second-degree relatives | 12 | 5 | **3.5** | (1.1–10.7) | 3 | 5 | **5.6** | (1.0–31.1) |
| First-degree relatives | 7 | 2 | **5.0** | (1.0–26.0) | 0 | 2 | | |
| Second-degree relatives | 6 | 3 | **2.9** | (0.6–12.6) | 3 | 3 | **17.2** | (2.3–132) |
| Other thyroid diseases | | | | | | | | |
| First or second-degree relatives | 17 | 13 | **1.6** | (0.7–3.5) | 2 | 13 | **1.3** | (0.2–7.0) |
| First-degree relatives | 5 | 3 | **1.9** | (0.4–9.2) | 1 | 3 | **5.4** | (0.5–59.6) |
| Second-degree relatives | 14 | 10 | **1.6** | (0.7–3.9) | 2 | 10 | **1.5** | (0.3–8.5) |
| Diabetes mellitus | | | | | | | | |
| First or second-degree relatives | 10 | 13 | **0.9** | (0.4–2.3) | 1 | 13 | **0.8** | (0.1–6.9) |
| First-degree relatives | 2 | 5 | **0.4** | (0.1–2.5) | 1 | 5 | **1.5** | (0.2–14.5) |
| Second-degree relatives | 9 | 10 | **1.1** | (0.4–3.0) | 0 | 10 | | |
| Psoriasis | | | | | | | | |
| First or second-degree relatives | 16 | 9 | **1.7** | (0.7–4.1) | 2 | 9 | **1.5** | (0.3–8.4) |
| First-degree relatives | 5 | 4 | **1.2** | (0.3–5.1) | 1 | 4 | **3.5** | (0.3–38.1) |
| Second-degree relatives | 11 | 6 | **1.7** | (0.6–4.8) | 1 | 6 | **1.5** | (0.3–8.5) |
| Rheumatoid arthritis | | | | | | | | |
| First or second-degree relatives | 1 | 1 | **0.9** | (0.1–16.7) | 1 | 1 | **11.4** | (0.6–217) |
| First-degree relatives | 0 | 0 | | | 0 | 0 | | |
| Second-degree relatives | 1 | 1 | **0.9** | (0.1–16.8) | 1 | 1 | **11.3** | (0.6–215) |
| Multiple sclerosis | | | | | | | | |
| First or second-degree relatives | 2 | 3 | **1.0** | (0.2–5.9) | 1 | 3 | **2.1** | (0.2–23.9) |
| First-degree relatives | 0 | 1 | | | 0 | 1 | | |
| Second-degree relatives | 2 | 2 | **1.6** | (0.2–10.8) | 1 | 2 | **4.2** | (0.3–58.1) |
| Crohn's disease | | | | | | | | |
| First or second-degree relatives | 3 | 0 | | | 1 | 0 | | |
| First-degree relatives | 0 | 0 | | | 0 | 0 | | |
| Second-degree relatives | 3 | 0 | | | 1 | 0 | | |

[a] Autoimmune diseases included Graves disease and/or hyperthyroidism, Hashimoto thyroiditis and/or hypothyroidism, diabetes mellitus, rheumatoid arthritis, rheumatoid spondylitis, multiple sclerosis, systemic lupus erythematosus, Behcet disease, Crohn's disease, coeliac disease, Landry-Guillain-Barré syndrome, and psoriasis.
[b] Ca, cases; Co, controls.
[c] The ORs were derived from an unconditional logistic model, adjusted for age, gender, hospital, maternal educational level, age of relatives, and number of relatives.

ation with acute leukemia (5), was also considered as potential confounder.

## Results

Out of the 279 cases included in the study, ALL was diagnosed in 240 cases, and ANLL was diagnosed in 39 cases. There were no significant differences between the cases and controls with respect to gender, hospital, or ethnic origin (Table 1). Sixty percent of the cases were aged 2–6 years, *versus* 45% for the control. The cases and controls did not differ in terms of their maternal or paternal educational level or socioprofessional category. The cases and controls were very similar with respect to familial characteristics such as mean number of family members and average age of the first- or second degree-relatives.

Overall, a relationship between a history of autoimmune disease in first- or second-degree relatives and ALL (OR, 1.7; 95% CI, 1.0–2.8; Table 2) was observed, and an OR of 2.9 (95% CI, 0.9–8.9; $P$ trend = 0.03) was associated with a history of two or more autoimmune diseases in the family. An association between thyroid diseases, taken together, and ALL (OR, 2.0; 95% CI, 1.0–3.9) was observed. This association seemed restricted to potentially autoimmune thyroid diseases (Graves' disease and/or hyperthyroidism and Hashimoto's disease and/or hypothyroidism), for which an OR of 3.5 (95% CI, 1.1–10.7) for ALL and an OR of 5.6 (95% CI, 1.0–31.1) for ANLL were observed, whereas there was no association with the other thyroid diseases (thyroid goiter, thyroid nodule and unspecified thyroid disorders) [OR = 1.6 (95% CI, 0.7–3.5) and OR = 1.3 (95% CI, 0.2–7.0), respectively, for ALL and ANLL]. No association between childhood leukemia (ALL or ANLL) and diabetes mellitus, psoriasis, rheumatoid arthritis, or multiple sclerosis was demonstrated. Analyses conducted sep-

arately for mother's relatives and father's relatives did not show any difference in incident association between the presence of autoimmune disease on the mother's side or father's side of the family.

The results remained unchanged after adjustment for the familial histories of solid or hematological neoplasms that were associated with childhood leukemia in the present study. When we introduced in the same model family history of cancer and family history of autoimmune disease, both results remained unchanged. Having a familial history of both cancer and autoimmune disease, especially autoimmune thyroid disease, increased the ORs: an OR of 4.6 (95% CI, 1.8–11.7) for ALL and an OR of 6.4 (95% CI, 1.3–31.3) for ANLL were associated with a familial history of both cancer and autoimmune disease among first- or second-degree relatives (21 ALL cases, 4 ANLL cases, and 8 controls), and an OR of 9.7 (95% CI, 1.1–89.7) was associated with a familial history of both cancer and potentially autoimmune thyroid diseases in first- or second-degree relatives (5 ALL cases and 1 control).

## Discussion

An association between childhood acute leukemia and a familial history of autoimmune disease was observed in this case-control study including 240 ALL cases, 39 ANLL cases, and 285 controls. The association with thyroid disease was especially clear.

The hospital-based design of the study was chosen because case and control blood samples were required. Special care was therefore paid to selecting an appropriate control group. Controls were included from many diagnostic categories, none of which were related to the variables of interest. Sociodemographic characteristics and familial structure probably did not influence the results because they were very similar for the cases and controls, and adjustments for sociodemographic status and familial structure did not change the results.

Differential recall bias seems unlikely for first-degree relatives because a mother would be unlikely to omit or be unaware of a history of autoimmune disease in herself, her index child's father, or her children. The figures observed for the first-degree relatives' histories of thyroid diseases are very similar to those observed for second-degree relatives and do not suggest differential recall bias. Another argument against differential recall bias for familial thyroid disease resides in the specificity of the results for potentially autoimmune thyroid diseases, compared with other thyroid diseases. However, a differential recall bias cannot be ruled out for the other diseases, mostly described for second-degree relatives, which may have been over declared by the cases' mothers.

The associations between autoimmune disease and childhood leukemia reported in this paper were not explained by the history of cancer in first- or second-degree relatives, observed previously in the same study (5). There was no case of thyroid cancer in the thyroid disease group.

For the rarest autoimmune diseases (*i.e.*, rheumatoid arthritis, Crohn's disease, multiple sclerosis, and even diabetes mellitus), the study suffered from a lack of power, which was increased by the fact that the relatives were young.

Associations between childhood leukemia and familial autoimmune diseases have been reported in several previous epidemiological studies. Till *et al.* (1) first reported that diseases selected as having a probable or possible autoimmune etiology in first- or second-degree relatives were significantly more frequent for children with leukemia than for the control children [OR = 2.3 (recalculated from the published data); $P < 0.02$; Ref. 1]. In that study, thyroid disorders such as thyrotoxicosis and myxedema were more frequent in cases than in controls [OR = 4.3 (recalculated from the published data); $P = 0.01$]. In a large case-control study, Buckley *et al.* (3) found a relationship between maternal multiple sclerosis and childhood acute lymphoblastic leukemia (relative risk, 4.0; 95% CI, 1.3–9.3). We did not observe that association in our study, but the numbers were very small. Woods *et al.* (2) found that cases reported a history of autoimmune disease among their maternal relatives more often than did controls, but the association was not statistically significant (relative risk, 1.76; $P = 0.10$).

An elevated incidence of acute leukemia before the age of 19 years has been reported among the offspring of men with diabetes mellitus in Denmark (SIR, 2.2; 95% CI, 1.0–2.6; Ref. 6), but our data for less than 15 children did not show that association. Finally, a case-control study conducted in children aged <18 months did not evidence any association between a family history of autoimmune diseases and childhood leukemia (7), but the power of that study is also questionable because of the probable young age of the relatives.

To the best of the authors' knowledge, there is currently no hypothesis for the mechanisms by which a familial history of familial autoimmune thyroid diseases may influence the risk of childhood leukemia. The association is observed with both second- and first-degree relatives and not only for mothers, and thus it does not suggest an association with disease-related medication use or a hormonal effect during pregnancy.

In short, the results reported herein suggest that a familial history of autoimmune thyroid disease may be involved in the etiology of childhood acute leukemia.

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