Are sunlight deprivation and influenza epidemics associated with the onset of acute leukemia?

Timo Timonen, Simo Näyhä, Tapani Koskela, Eero Pukkala

From the Department of Internal Medicine, Oulu University Hospital, Oulu, Finland (TT); Department of Public Health Science & General Practice, University of Oulu, Oulu, Finland (SN); Finnish Institute of Occupational Health, Helsinki, Finland (SN); Finnish Meteorological Institute, Helsinki, Finland TK); Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland (PE).

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Correspondence:
Simo Näyhä, Department of Public Health Science & General Practice, P.O. Box 5000, FI-90014, University of Oulu, Finland.
E-mail: simo.nayha@oulu.fi

ABSTRACT

Month of diagnosis of 7,423 cases of acute leukemia (AL) in Finland during 1964-2003 were linked with data on influenza and solar radiation. Acute myeloblastic leukemia (AML) showed the highest risk in the dark season. During the light season, the incidence decreased by 58% (95% confidence interval, 16-79%) per 1,000 kJ/m^2/d increase of solar radiation. Independent of solar radiation, AML increased by 9% (95% confidence interval, 0-19%) during influenza epidemics. Reoccurring at the same time annually, darkness-related vitamin D deficiency and influenza could cause successive and co-operative mutations leading to AL with a short latency.

Key words: acute leukemia, seasonality, sunlight, vitamin D, influenza.

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The seasonal occurence of acute leukemia (AL) and its association with monthly variations of solar radiation and influenza epidemics have remained unclear.[1-3] However, the alleged viral origin of leukemia[3-5] and the possible role of vitamin D deficiency associated with winter darkness[6] have prompted further studies. Two well-known hypotheses suggest that childhood leukemia could arise as a rare abnormal response to common infections either due to low herd immunity (the population mixing hypothesis)[5] or with a delayed exposure to infections.[4] It has been hypothesized that vitamin D deficiency associated with winter darkness might stimulate leukemic proliferation and block differentiation through dysregulation of growth factors.[6] This would cause one mutation, followed by influenza causing another mutation and manifest leukemia.[6] In view of Gilliland's[7] two-hit hypothesis proposing a combined effect of two mutations, a short latency period of leukemia would therefore be a possibility. Situated in the far North, between the 60 and 70° N latitudes, Finland has wide annual variations in sunlight. This, together with its genetically homogeneous population, makes it ideal for studies of seasonal factors in leukemia. We used information from the nationwide Finnish Cancer Registry (FCR) for a period of 40 years to identify effects of influenza and solar radiation on the seasonal pattern in AL.

Design and Methods

The data on incident cases of AL during 1964-2003 were drawn from the FCR, the coverage of which is practically complete. The information included age, sex, place of residence, and cell type and time of diagnosis of the leukemia. The number of ALs recorded was 7,998, but in 575 cases the month of diagnosis was missing, which left 7,423 cases for study. The ALs were divided into myeloblastic (AML, 4,480 cases), lymphoblastic (ALL, 2,301 cases), and other or unknown type (called here NUD, 642 cases). There were 1,716 children (aged <15 years) and 5,678 adults (aged ≥15 years). The proportion of children was 5% in AML, 56% in ALL and 36% in NUD.

The month of diagnosis for a subset of 259 patients with AL was known directly from bone marrow examinations.[6] In 86% of these, the month of diagnosis was the same or within one month before or after that in the FCR record, and in 9% the difference was 2-4 months. The monthly means of daily global radiation from the sun (direct, indirect and reflected radiation combined) during the period 1964-2003 were obtained from three observation stations of the Finnish Meteorological Institute located at latitudes 60.5°N (Jokioinen in southern Finland), 62.4°N (Jyväskylä in central Finland) and 67.4°N (Sodankylä in northern Finland). The number of cases of

leukemia were linked with the radiation data on the basis of the subject's place of residence, grouping areas to southern, central and northern Finland. Based on the vernal (March 21) and the autumnal (September 23) equinox, the year was divided into the light and dark seasons (April-September and October-March). At the Summer Solstice, the length of the day in the southern, central and northern study area is approximately 19, 20 and 21-24 hours, respectively, and at Winter Solstice, 6, 4-5 and 0-3 hours respectively.

The data on influenza epidemics were based on virus isolations and serodiagnostics carried out by the Finnish National Public Health Institute since 1969. Included were influenza A and B, parainfluenza, and influenza of undefined type. Each month from January 1969 through December 2003 was coded as epidemic or nonepidemic. An epidemic period included months during which 95% of virological diagnoses of the epidemic season were made. Out of a total of 420 months, 113 (27%) were defined as epidemic. The length of the epidemics averaged 3 months (range 1-5 months).

Statistical methods

The monthly numbers of cases were stratified by sex, age and year and corrected to correspond with months of equal length (30.44 days). The association of the dark season with the counts of AL was examined by Poisson regression adjusted for sex, age group and secular trend, the result being expressed as risk ratio (RR) and its 95% confidence interval (CI).

Further analyses used solar radiation and influenza epidemics as explanatory factors. These analyses were restricted to years 1969-2003 because there were no data on influenza before 1969. All analyses were corrected for extra-Poisson variation (over-dispersion) and repeated at lags of 0-6 months. Autoregressive terms up to 6 months were considered. The adjustments for sex and age did not change the results and were omitted from the final analyses. The shape of the association between monthly solar radiation and leukemia was explored by a generalized additive model with a Poisson error and logarithmic link.

Results and Discussion

Seasonal patterns

Total AL showed a bimodal seasonal pattern with higher numbers of cases in the dark and cold months and lower numbers in the light and warm months and December ($\chi^2_{df=11}$ = 22.2; p~0.023); (Table 1, Figure 1). The pattern was similar for AML ($\chi^2_{df=11}$ = 22.4; p ~0.021) and ALL ($\chi^2_{df=11}$ = 9.35; p~0.590) but indefinite for NUD ($\chi^2_{df=11}$ = 7.76; p~0.734). Based on Poisson regression, AML was slightly more common during the dark than the light season (RR =1.05; 95% CI 0.98-1.12), ALL showed no difference (RR=0.97; 95% CI 0.89-1.06),

Table 1. New cases of acute leukemia in Finland, 1964-2003, by month of diagnosis. Numbers corrected to correspond months of length 30,44 days.

Month	*Myeloblastic*	*Lymphoblastic*	*Other or unknown*	*Total*
Jan	414	190	55	659
Feb	393	184	44	622
Mar	392	194	58	644
Apr	385	210	63	658
May	370	204	52	626
Jun	362	169	51	582
Jul	317	197	53	567
Aug	363	186	42	591
Sep	390	202	50	642
Oct	389	191	60	639
Nov	375	203	58	636
Dec	330	171	56	556
Total	4480	2301	642	7423

nor did NUD (RR= 1.07; 95% CI 0.90-1.27) or total AL (RR=1.02; 95% C.I. 0.97-1.07). The excess during the dark vs. light season was greater among people aged 65 years or more in AML (RR=1.08; CI 0.98-1.12) and in the total AL (RR=1.08; 95% CI 1.00-1.17).

A separate comparison of childhood ALL between the dark vs. light season showed no difference in the age group 0-1 years (RR=0.91; 95% CI 0.65-1.28), a significant deficit in the age group 2-4 years (RR=0.82; 95% CI 0.70-0.98), and no difference in the age group 5-14 years (RR 1.02; 95% CI 0.86-1.19).

Association of AL with solar radiation and influenza

The generalized additive model identified two ranges of radiation, i.e., < 19,000 kJ/m^2/d (corresponding to months August to April) and ≥19,000 kJ/m^2/d (May to July) with different but sufficiently linear slopes. The regressions were therefore conducted piecewise, with separate regressions within each range.

The analyses were tried using different lags. Within the range of <19,000 kJ/m^2/d, radiation showed no association with AML at any lag (Table 2). At values of ≥19,000 kJ/m^2/d, AML decreased by 58% (95% CI 16-79%) per 1,000 kJ/m^2/d increase in radiation once radiation was lagged by one month. At lags other than this, no significant effects of radiation were found. Independent of radiation, influenza was associated with an increase of AML of 9% (95% CI 0-19%) at zero lag, this effect attenuating to 0% at 3 months' lag. The interaction between radiation and influenza was not significant (p~0.88). Adding autoregressive terms of 0 to 5 months did not change the results. Similar analyses on ALL and NUD failed to show any association with radiation or influenza at any lags.

We showed a seasonal variation in AML in a national population in the north. A high incidence was independently associated with epidemic influenza and a low intensity of solar radiation.

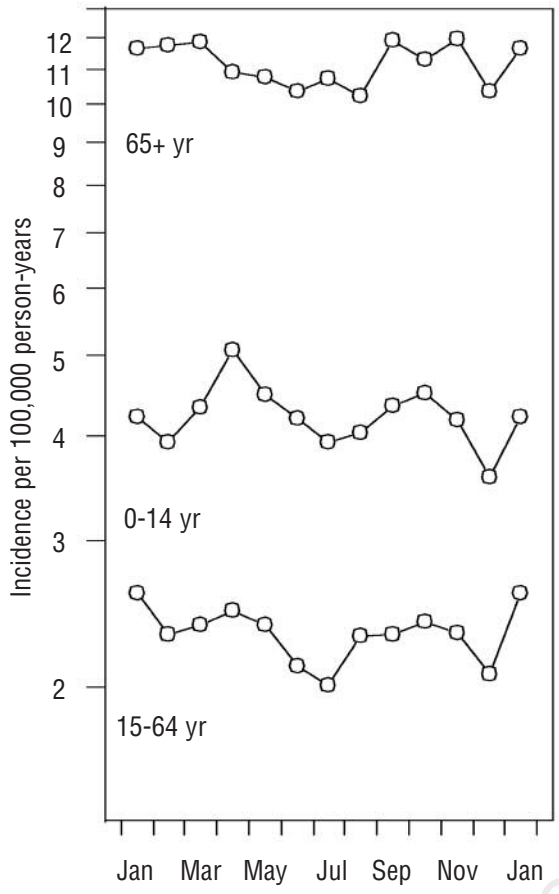

Figure 1. Monthly incidence of acute leukemia by month, 1964-2003.

The Finnish Cancer Registry covers practically all cases of cancer and the accuracy of variables used in this study is satisfactorily high. Therefore, data inaccuracies are not likely to cause bias in our main results. Less effectively functioning of health care during summer and Christmas holidays could artificially decrease the numbers of cases, as has been argued in the case of solid tumors.[8] This possibility seems unlikely here since the acute and fulminant symptoms of AL force the patient to seek immediate help.[1]

Seasonal effects in AL would presuppose a short latency period. This could be possible in the case of two coincident or successive mutations.[7] In Finland, 25(OH)D3 level varies by season, one quarter of adults having deficient levels (< 25 nmol/L) in winter.[10] As high levels of vitamin D induce myeloid differentiation and inhibit leukemic proliferation,[11] low levels could block this differentiation and stimulate leukemic proliferation by causing a silent pre-leukemic clone.[6] It was recently shown that AML-associated translocation products block vitamin D induced differentiation.[12] Influenza could cause a second mutation in progenitor cells already damaged by vitamin D deficiency in the current or previous winter, leading to manifest leukemia.[6] This could also happen in reverse order.[6] Since darkness and influenza recur approximately at the same time from year to year, repeated mutations that follow may add the proliferative advantage to hematopoietic progenitors of AML blasts.[7] In mouse models, oncogenic collaboration between two genes can lead to acute leukemia in 39 days.[13]

In Finland, there is also a seasonal variation in interferon gamma, with an increase in winter and a decrease in summer.[14] The adhesion of AML blasts to marrow fibroblasts is increased by upregulation of the stromal vascular adhesion molecule (VCAM-1) by interferon gamma and tumor necrosis factor α.[15] We therefore hypothesize that the increase of cytokines due to vitamin D deficiency and influenza could increase the adhesion of myeloblasts to the micro-environment in winter.

The B-cell precursors in ALL and myeloblasts express receptors, for example, for IL-1 and IL-3.[16,17] Since 1,25(OH)2-D3 inhibits the production of IL-1 and IL-3,[18] vitamin D deficiency would not adequately inhibit growth factors, resulting in proliferation without differentiation.[6] A growth factor mediated suppression of the apoptotic death of progenitors damaged by influenza virus is also a possibility.[6]

The low incidence of AL in December could be explained by higher levels of vitamin D in December than in March-June.[9] As there is no UV-b radiation in December in Finland, this high level of vitamin D must

Table 2. Relative risk (RR) of mean daily solar radiation and periods of epidemic influenza on monthly numbers of acute leukemia, 1969-2003. Adjusted for over-dispersion and secular trend. Solar radiation lagged by one month, influenza with no lag.

Explanatory factors	*Myeloblastic RR (95% CI)*	*Lymphoblastic RR (95% CI)*	*Other or unknown RR (95% CI)*	*Total RR (95% CI)*
All ages				
Solar radiation (change per 1,000 kJ/m²/d)				
Range 0-19,000 kJ/m²/d	1.01 (0.95-1.07)	1.02 (0.93-1.10)	0.86 (0.72-1.03)	1.00 (0.95-1.04)
Range ≥ 19,000 kJ/m²/d	0.42 (0.21-0.84)	1.03 (0.44-2.38)	2.35 (0.51-10.89)	0.67 (0.41-1.10)
Influenza epidemics				
Non-epidemic periods	1.00	1.00	1.00	1.00
Epidemic periods	1.09 (1.00-1.19)	1.04 (0.92-1.17)	0.77 (0.59-1.01)	1.05 (0.98-1.12)

be based on dietary factors, such as vitamin D containing food items frequently eaten during Scandinavian pre-Christmas and Christmas festivities which last all December. The typical diet at this time contains other differentiating agents such as vitamin A and butyrate, e.g. in bakery for example, in bread, cakes and pastries.

In contrast to AML, we found no increase of ALL associated with darkness or influenza. Unlike myeloid differentiation, there is no evidence that vitamin D would also regulate lymphatic differentiation. We actually found low numbers of ALL in the dark season among children aged 2-4 years, which is the peak age of common ALL. In Finland, the levels of 25(OH)2-D3 in children are satisfactory due to the vitamin D prophylaxis used since 1974 in community-based children's welfare clinics.[19] This may have been sufficient to prevent mutation in this age group.

Efforts to link maternal influenza during pregnancy to childhood ALL have given inconsistent results.[3] The prevailing pediatric hypotheses suggest that common infections and lack of immunity shortly before the diagnosis of leukemia could cause the disease.[4, 5] A recent study identified peaks in childhood ALL in the years immediately following epidemics of influenza or influenza-like disease.[20] The present study did not find any association of influenza and ALL, but we used a more accurate definition of influenza and examined only short-term temporal effects. The minor increase of AML during influenza epidemics could also be explained as the influenza simply triggering pre-existing cases.

Our observations are compatible with the previous assumption of sunlight deprivation and influenza as independent factors in AL which may initiate leukemogenesis with a short latency. Our strongest finding, the decrease of AML with increasing solar radiation, may also point to a protective effect of sunlight. Testable predictions from our study are that the risk of AML should increase in groups at risk of hypovitaminosis D and in people exposed to influenza, and decrease with adequate sunlight exposure, supplementation of vitamin D and vaccination against influenza.

Authors' contributions

TT designed the study, SN analyzed the data, TK provided the meteorological data, and EP provided the FCR data and participated in study design. All authors participated in writing the manuscript.

Conflicts of Interest

The authors reported no potential conflicts of interest.

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