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HIGH INCIDENCE OF ACUTE LEUKEMIA IN THE PROXIMITY OF SOME INDUSTRIAL FACILITIES IN EL BIERZO, NORTHWESTERN SPAIN

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Abstract
Objectives: To estimate the incidence of acute leukemia (AL) in El Bierzo (BZ) and to carry out a cross-association analysis in order to suggest some etiological clues. **Materials and Methods:** We registered all new AL cases diagnosed 2000–2005. Annual standardized incidence rate (SIR) was calculated by the direct method. A cross-association analysis was performed by non-parametric methods and we checked the potential interaction between putative etiological factors by calculating Chi-square-for-trend. **Results:** SIR was 5.1 cases per 100 000, surpassing the Spanish, European and world average figures and heterogeneous throughout the region. We detected a negative correlation between acute myeloblastic leukemia (AML) SIR in every municipality and both the air distance to the nearest thermoelectric power plant (TPP) (Rho = –0.409; p = 0.01) and to the point of maximum density of the high-power lines (HPL) network (Rho = –0.329; p = 0.04). Accordingly, SIR was higher in the municipalities situated < 7.5 km away from TPP (9.58 vs. 1.72; p = 0.004) or < 10 km away from HPL (3.90 vs. 3.19; p = 0.045). A positive relation between both factors was observed (Chi-square-for-trend = 9.209; p = 0.006). **Conclusions:** SIR of AL in BZ is higher than the Spanish average and that of most countries in the world. Residing near TPP or HPL confers a higher risk of AML, with synergistic effect between both factors.

Key words:
Acute leukemia, Benzo(a)pyrene, Industrial facilities, Electromagnetic radiation, Power lines, Thermoelectric power plant

INTRODUCTION

Leukemogenesis is a sequential process in which both genetics and environment are well-known contributing factors, the relative influence of each other still being unknown [1,2]. Many specific toxins have been implicated, relating the type of leukemia to the environmental exposure [3]. The only agents conclusively linked to hematopoietic system neoplasms [4–9] are benzene, ionizing radiations and chemotherapeutic drugs, but many others have also been implicated:

a) factors related to parenthood, mainly parental exposure to electromagnetic fields [10], solvents, heavy metals or hydrocarbons, as well as mothers' alcohol consumption during pregnancy [11],
b) professional exposure to diverse substances [12,13] (paints, glazes, pesticides, solvents),

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c) smoking habit, specially for some types of acute leukemia (AL) [14] in which a dose-dependent effect [15] has been described,
d) exposure to electromagnetic fields [16,17], more specifically, living less than 300 meters away from a high-power line (HPL), which seems to be an especially relevant factor during childhood [18],
e) exposure to environmental toxins that have been implicated in those people living in close vicinity to some industrial facilities that seem to bear a higher risk of developing AL [19, 20].

El Bierzo (BZ) is a region located in northwestern Spain, in the province of León, that displays specific orography characterized by a central depression with an average altitude of 500–600 m over the sea level, completely surrounded by a mountain ring of 1800–2100 m of altitude. It has 146 872 inhabitants grouped in 39 municipalities, with a population density of 44.8 inhabitants per square km, where people older than 65 represent 22% of the total population. It is one of the most industrialized zones in the northwest of Spain [21]. Coal mining industry peaked there in the second half of the 20th century, now being in decline. There are two thermoelectric power plants (TPP) in the area (one of them with the power over 1300 MW that is the second in the Spanish ranking according to power) that use coal and petroleum derivatives for combustion. In addition, a medium size metallurgical facility and an important cement factory are also located in BZ. As a consequence, 10% and 20%, respectively, of the total SO_2 and NO_X emissions in Spain are generated in the region [22]. BZ has also got an important network of HPL (400 Kv) [23], one of three major ones in the country, which are interlaced forming a cluster. Finally, BZ showed one of the highest indexes of natural gamma radiation in the Spanish territory, according to the data gathered during the recent years (average 0.20 μSv/h, with peaks of 0.24 μSv/h during the summer) [24].

It is the impression of most hematologists professionally linked to the region, both employed at the hospitals in the area as well as those working at reference hospitals, that the incidence of acute leukemia (AL) in BZ might be higher than expected. That is why we designed an observational study with the following aims:

a) to estimate the annual incidence rate of AL in BZ, both in the global dimension and for its different municipalities,
b) to compare it with that of other regions of Spain and the world,
c) to carry out a cross-association analysis to suggest some putative etiological factors.

MATERIALS AND METHODS

This study covered a 6-year period, from January 1, 2000 to December 31, 2005. All AL cases diagnosed in the only two hospitals of the region harboring hematology medical specialists, Hospital El Bierzo (public practice) and Clinica Ponferrada (private practice), were collected through detailed analysis of the information coming from both the Department of Hematology and central files of the two hospitals. Since AL patients require an immediate and complex study and specific therapy at the Department of Hematology, we are pretty confident that only an exceptional case could have been overlooked and passed unregistered in our files. In each case, data on the family history of hematopoietic neoplasms, place of residence, smoking habit, alcohol consumption, occupational history and key descriptive clinical information were gathered by the attending hematologist and transferred as anonymized (dissociated) data to a specific database.

Annual incidence rates were standardized to both the European and World Standard Populations by using the direct method [25,26]. Air distance in km from the head village of each of the 39 municipalities of BZ to the main points of interest (POI), such as pollutant facilities (PF) or the point of maximal density of high-power lines (HPL) network, was estimated online with the aid of Google Maps®. Analysis of the potential correlation between that distance and the annual age-adjusted incidence rate of AL in each municipality, was carried out by calculating the Spearman's ordinal correlation coefficient. After identifying those associations with a p-value of less than 0.10, we dichotomized the air distance by using cut-offs at 5.0, 7.5 and 10.0 km, as a means to check the reproducibility of the previous research findings in the field and to delimitate more precisely the area of epidemiological interest. Mann-Whitney's test, calculated with the use of exact methods, was applied to compare the annual age-adjusted incidence rate in each municipality, depending on the dichotomized distance to each POI.

Finally, in order to check the eventual interaction between, on the one hand, the vicinity to a TPP and, on the other, the proximity to the point of maximal density of the HPL network and their impact, on the incidence of AL in every municipality, we resorted to the Chi-square test-for-trend, calculated by the exact method, after arranging municipalities according to their proximity to none, only one or both POI.

P-values of less than 0.05 were considered to indicate statistical significance. All p-values presented are two-sided. Statistical analyses were performed using SPSS release 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Fifty-four AL cases were diagnosed throughout the covered period. Annual incidence rate of AL was 5.11 and 4.99 cases per 100.000 inhabitants, standardized to the European and World Standard Populations, respectively. 74.1% of the cases were myeloblastic (AML), 20.4% linfoblastic (ALL) and 5.5% were unclassifiable, with the AML to ALL ratio equaling 3.63. Crude incidence rates were higher in males (M/F ratio: 1.45). AL-type- and gender-specific incidence rates are shown in Table 1. The age-specific annual incidence rate of AL was 6.49, 3.11 and 14.90 per 100 000 inhabitants, respectively, for the 0–14, 15–64 and ≥ 65 year-old population strata.

Seventeen percent of the patients reported hematological neoplasms among their nearby relatives, 11.1% had previously been diagnosed with a neoplasm and 9.3% had professional exposure to toxins that have been implicated etiologically in AL in the medical literature. 31.5% of the patients declared being smokers, 27.8% reported that they customarily consume alcoholic drinks and 18.5% subjected themselves to both toxic habits.

A detailed description of AL cases grouped according to BZ municipalities is shown in Table 2. Spatial analysis of the geographical distribution of AL cases showed that the highest annual incidence rate concentrated in the

Table 1. Standardized incidence rates of acute leukemia in El Bierzo (Spain)

Type of leukemia	Overall		Male		Female	
	adjusted to		adjusted to		adjusted to	
	European population	world population	European population	world population	European population	world population
All acute leukemias	5.11	4.99	6.20	5.97	4.04	3.81
AML	3.40	3.06	3.90	3.44	2.69	2.69
ALL	1.70	1.59	2.07	2.53	0.90	0.90

AML – acute myeloid leukemia. ALL – acute lymphoblastic leukemia.
Figures show average annual incidence rates per 100 000 inhabitants in the period 2000–2005. Overall and specific figures for gender and leukemia type are shown. Unclassifiable cases account for the differences in the sums.

Table 2. Number of cases in each municipality, air distance to the nearest thermoelectric power plant and to the point of maximal density of high-power lines network, and age-adjusted incidence of AML, ALL and all types of acute leukemia

Municipality	Inhabitants	Cases (n)		Distance (km)		Age-adjusted incidence		
		AML*	Job exp.**	to TPP	to HPL	AML	ALL	overall
1	430	0	0	31.1	34.4	0	0	0
2	375	0	0	33.7	36.0	0	0	0
3	420	0	0	15.9	29.5	0	0	0
4	1 174	1	0	20.4	22.8	0	0	0
5	500	0	0	33.8	35.5	0	0	0
6	1 413	0	0	9.4	33.0	0	0	0
7	331	0	0	9.3	32.8	0	0	0
8	511	0	0	25.5	27.0	0	0	0
9	530	0	0	26.2	28.7	0	0	0
10	826	0	0	31.6	34.2	0	0	0
11	10 325	5	1	12.4	9.8	4.84	1.61	6.46
12	415	0	0	13.1	16.5	0	0	0
13	1 870	1	0	8.8	5.2	0	0	0
14	1 737	0	0	4.0	3.2	0	0	0
15	5 569	2	0	10.6	21.2	2.99	2.99	2.99
16	1 310	0	0	20.7	18.7	0	0	0
17	1 809	3	1	24.1	26.6	18.43	0	18.43
18	881	1	0	17.9	17.2	0	0	0
19	1 678	1	0	4.1	26.0	19.86	0	19.86
20	4 021	2	0	11.2	12.4	4.14	0	4.14
21	2 952	0	0	19.9	17.7	0	0	0
22	2 811	0	0	14.9	17.8	0	0	0
23	902	0	0	10.4	13.7	0	0	0
24	484	1	0	18.4	18.7	0	0	0
25	1 276	1	0	6.1	9.4	13.06	0	13.06
26	4 970	5	1	13.0	15.7	10.06	3.35	13.41
27	3 339	0	0	9.0	11.2	0	0	0
28	3 544	0	0	15.0	16.3	0	0	0
29	657	0	0	20.7	21.3	0	0	0
30	1 482	3	0	1.7	4.7	11.25	11.25	22.49
31	920	1	0	13.7	13.6	18.12	0	18.12
32	570	0	0	8.5	11.5	0	0	0
33	2 237	1	0	17.0	19.0	0	0	0

Table 2. Number of cases in each municipality, air distance to the nearest thermoelectric power plant and to the point of maximal density of high-power lines network, and age-adjusted incidence of AML, ALL and all types of acute leukemia – cont.

Municipality	Inhabitants	Cases (n)		Distance (km)		Age-adjusted incidence		
		AML*	Job exp.**	to TPP	to HPL	AML	ALL	overall
34	3 732	0	0	19.7	22.5	0	0	0
35	13 065	4	1	20.9	42.7	0	3.83	5.10
36	62 274	22	1	7.2	7.0	3.75	1.61	5.62
37	2 823	0	0	8.8	5.9	0	0	0
38	495	0	0	26.2	25.4	0	0	0
39	1 914	0	0	30.2	30.3	0	0	0

* Number of AML cases observed in each municipality.
** Number of cases with known job exposure to leukemogenic agents.
Distance to TPP – distance from each municipality to the nearest thermoelectric power plant.
Distance to HPL – distance from each municipality to the point of maximal density of high-power lines network.
AML – acute myeloid leukemia. ALL – acute lymphoblastic leukemia.
Age-adjusted incidence figures standardized to the European Standard Population are shown.

municipalities located in the centre of the BZ region (data not shown).

As far as distance from each municipality to the different POI is concerned, we observed a statistically significant negative correlation between standardized AML incidence rate and either air distance to the nearest TPP (Rho = –0.409; p = 0.01; Spearman), or air distance to the centre of HPL (Rho = –0.329; p = 0.04; Spearman; see Table 3). On the other hand, we did not observe such a phenomenon with other PF. The AML incidence rate was higher in the municipalities situated less than 7.5 km away from TPP (9.58 vs. 1.72; p = 0.004, Mann-Whitney) or less than 10 km away from the point of maximal density of the HPL network (3.90 vs. 3.19; p = 0.045; Mann-Whitney; see Table 4), which related to 13% and 18% of the BZ municipalities, respectively. Finally, we also found a positive interaction between both air distance to the nearest TPP and air distance to the centre of HPL as concerns standardized incidence rate of AML (see Table 5), as we noted that the incidence rate was maximal in the municipalities located in the proximity of both POI, medium in those situated in the proximity of only one of them

Table 3. Ordinal correlation between the age-adjusted incidence of acute leukemia and the air distance from each municipality to the main pollutant facilities of El Bierzo

Type of leukemia	Thermoelectric power plants	Metallurgical facility	Cement factory	High power lines network
AML	–0.409 (p = 0.010)	–0.251 (p = 0.123)	+0.108 (p = 0.512)	–0.329 (p = 0.041)
ALL	–0.255 (p = 0.117)	–0.145 (p = 0.379)	+0.103 (p = 0.534)	–0.190 (p = 0.247)

Abbreviations as in Table 1.
Two-tailed p-values for Spearman's Rho ordinal correlation coefficient are shown.

Table 4. Comparison of the annual age-adjusted incidence of AML as a function of the air distance from every municipality to the main points of interest, using different distance cut-offs

Incidence rate	TPP (5 km)	TPP (7.5 km)	TPP (10 km)	HPL (5 km)	HPL (7.5 km)	HPL (10 km)
AML	10.37 vs. 2.09 (p = 0.032)	9.58 vs. 1.73 (p = 0.004)	4.36 vs. 2.09 (p = 0.288)	5.63 vs. 2.57 (p = 0.804)	3.00 vs. 2.69 (p = 0.530)	4.70 vs. 2.30 (p = 0.045)

Abbreviations as in Table 2.
The distance to each facility was transformed into a binary variable. Distance cut-offs are shown in brackets.
In each column, the upper value shows the age-adjusted incidence of AML in those municipalities located near the facility, whereas the lower value shows the age-adjusted incidence of AML in those municipalities located beyond the cut-offs.
Two-tailed p-values for Mann-Whitney's U test, calculated with the use of the exact method are shown as well.

Table 5. Interaction between the proximity to a TPP and proximity to HPL, as relates to the annual age-adjusted incidence of AML in each municipality

AML annual incidence rate	None n (%)	One of them n (%)	Both n (%)
< 3.00 per 100 000	27 (87.1)	2 (50.0)	1 (25.0)
≥ 3.00 per 100 000	4 (12.9)	2 (50.0)	3 (75.0)

Abbreviations as in Table 1 and 2.
Distance cut-offs were 7.5 km. and 10.0 km, respectively, for TPP and HPL. Three different municipality subsets are shown according to their proximity to both, only one or none of the points of interest. Age-adjusted annual incidence cut-off was arbitrarily set to the third quartile of the AML distribution (Q2 = 0; Q3 = 3.00 cases per 100 000 inhabitants). The number on municipalities in each situation and the proportion of the total number of patients in each subset (Chi-square-for-trend = 9.209; two-tailed exact p-value = 0.006) are shown as well.

and minimal in the municipalities located away from both (7.01, 6.17 and 1.73 AML cases per 100 000 inhabitants, respectively; Chi-square-for-trend 9.209; p = 0.006).

The analysis of the correlation between the annual standardized incidence rate and air distance to any of the POI did not show any statistically significant values in the case of ALL.

DISCUSSION

The incidence of acute leukemia (mostly myeloid) in BZ is high, surpassing the Spanish, European and world average figures. According to the data from the Registro de Enfermedades Hematológicas de Castilla y León (REHCL, Castilla y León Hematological Disorders Registry) [27], BZ has a higher incidence of AL than the rest of the León province and other neighboring provinces in the Autonomous Community of Castilla y León. Its incidence is also one of the highest in Spain compared to the data published by the Registro Español de Leucemia (REL, Spanish Leukemia Registry) [28] and the Spanish National Centre of Epidemiology [29]. It can also be considered high when compared to that of our European and African neighboring countries [30].

Although AL biogenesis is likely to be a multifactorial process, the increased incidence that we have observed in BZ cannot be easily attributed to genetic factors, alcohol consumption, smoking habit, or exposure to occupational toxins, since their prevalence in this study is similar to that of the general population of Castilla y León [31] and to other published studies [6,28,32]. Accordingly, exposure to environmental toxins seems the most probable underlying factor and the most reasonable etiological hypothesis to which any additional research efforts should be addressed in the near future.

The orography of El Bierzo hinders the clearance of air emissions from the nearby PF and might explain in part the high incidence of AL in this area. The combustion of coal and petroleum derivatives at high temperatures generates an aromatic hydrocarbon, benzo(a)pyrene, with a high mutagenic potential [33,34], that has been involved in the development of AML, especially in the presence of some genetic polymorphisms [35]. Other pollutants such as SO_2, NO_X and several heavy metals reach high levels in the proximity of El Bierzo TPP [21]. The heterogeneous incidence of AL observed in BZ, higher in the area placed upstream from the point of maximum fluvial water pollution [36], makes the possibility of the transmission of pollutants by this route unlikely.

Electromagnetic radiation (ER) exposure has been frequently referred to in the medical literature as a potential etiological contributor in the development of AL [16–18]. It is a highly controversial issue, where both positive and negative results have been published, the critical/minimal field intensity for the effect, if any, being unknown. The International Agency for Research on Cancer reckons that so far the evidence is insufficient to consider ER exposure as a proven risk factor for AL [37], but the National Institute of Environmental Health Sciences recommends caution until the issue is definitively solved [38]. Our data, despite being more difficult to interpret than that from other PF, suggests that such caution is an intelligent attitude in this hot issue.

This study has several weaknesses and strengths. Among the former, we would like to drive the readers' attention to:

a) the fact that only aggregated data at a municipality level has been used for the cross-association analysis, instead of individual patient data,
b) the difficulty to locate precisely the ER sources because of its very network nature,
c) the lack of precise measurement of ER and potential pollutants exposition at individual levels,
d) the lack of an adequate control of potential occupational confounders at the individual level taking into account the lack of a detailed job history (only job description was identified),
e) lack of detailed information on the natural radiation exposure in each municipality, and finally,
f) the descriptive nature of this study that lacks a control group.

As regards putative risk factors exposure measurement, one must realize that it is always very difficult to define the period of interest, due to the long latency period operating in most neoplasms. Despite this shortcomings, we would like to stress that in our data:

a) the association between the AL incidence and air distance to PF and HPL was not observed for ALL while it was observed for AML (specificity),
b) this association was also observed when the issue of cut-off choice was minimized by using ordinal correlation techniques,
c) an interaction between the two putative main risk factors is very likely.

In our opinion, the results of this study (that are in agreement with the previous impression from the attending hematologists) deserve further research and, more specifically, allocating additional resources in order to put in place an analytical longitudinal study under the leadership of the health authorities of Castilla y León [39], thanks to which a more detailed measurement of the exposures and appropriate control over the occurring confounding and modification covariates would throw light on this potential health problem of El Bierzo.

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