Relation between electromagnetic fields and acute leukemia in children with Down syndrome


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Summary

The aim of this study was to analyze the risk of exposition to electromagnetic fields (EMF) in the expression of acute leukemia (AL) in children with Down syndrome (DS). A case control study. Four Pediatric Hospitals from Mexico City. Cases: 42 children with AL and DS. Controls: 124 children healthy with DS. The proximity and type of powerlines nearby to the residence was assessed. Direct measurements of EMF at the front door of the residence was measured with a gaussometer. The exposition was divided by three methods: Goldstein and Goldstein (GG), Kaune and Savitz (KS), and by the gaussometer. The exposition to EMF by the GG’s classification, the odds ratio (OR) to developing of AL, was of 6.0, confidence intervals 90% (CI 90% 1.25,28.26) in women with cancer familial antecedents. With the KS’s classification the OR was of 4.13 (CI 90% 0.94,18.16) at the level high vs low, and the OR was of 2.89 (CI 90% 0.76, 11.01) at the level medium vs low. For the level 6 mG or more, the OR was 2.49 (CI 90% 1.07,5.79). The exposition to ELF-EMF could be a risk factor to developing AL only in children with high susceptibility to the disease.

Introduction

The etiology of acute leukemia (AL) remains unknown, but it may be the result of a complex interaction between host susceptibility genetic factors and different environmental carcinogenic agents, such as “in utero” radiation, child exposure to oil derivates, parents and child exposure to solvents or other occupational factors, such as paternal exposure to motor vehicle exhaust, hydrocarbons and paints. Finding genes contributing to the expression of leukemia in the healthy population is must difficult, but will allow to assess the interaction between genes and environment (Mejía-Aranguré et al. 2003).

Children with Down Syndrome (DS) have been found to be highly susceptible for the development of AL. The relative risk varies between 15 and 50; therefore the study of these children may lead to the identification of the causes of AL in the general population (Robison, 1992). Some authors speculate that the reason for the increased risk is the intrinsic susceptibility of the trisomic cell to carcinogenic agents. Several genes on chromosome 21 have been found to be disrupted in leukemia. This is the case of AML1, a gene present within the critical trisomic chromosome 21 region of DS patients that encodes a transcription factor, essential for normal hematopoiesis; variations of AML1 expression either by allele inactivation or by amplification may result in disruption of normal hematopoiesis and leukemia. This is certainly an attractive candidate gene for the predisposition to AL, but other genes may also be involved in the hematologic abnormalities of DS. Two of them, ETS2 and ERG, are proto-oncogenes on chromosome 21, that are either rearranged or amplified in human tumors (Barton and Nucifora, 2000).

The potential adverse health effects of the exposure to extremely low-frequency electric and magnetic fields (EMF) was initially brought to prominence by an epidemiologic report two decades ago from Denver on childhood cancer and the association is a controversy. Laboratory research has given no consistent evidence that EMF of the magnitude encountered in every day life for a substantial period can affect biological processes or that EMF affects the risk of cancer in animals. Recently, the International Agency for Research on Cancer designated EMF as a class 2B carcinogen “possibly carcinogenic”, based on “consistent statistical associations of high level residential magnetic fields with a doubling of the risk of childhood leukemia”. To our knowledge no study done analyzing the exposure to these agents has produced conclusive results regarding to the development of AL in childhood (Repacholi and Greenebaum, 1999). It is therefore likely that some environmental factors may unchain the disease only in highly susceptible subjects.

The aim of this study was to analyze the risk of the exposition to EMF in the expression of AL in children with DS. The investigation of the influence of these factors in children with DS will be of great value, due to the reported increased incidence of AL in DS children.
Materials and Methods

Design
A Case-control study was designed.

Setting
Four Pediatric Hospitals from Mexico City; they attending the 95% of the cases of AL of the children resident in the city. Three Specialized Schools for children with DS, of different points of the city.

Participants and interventions
Cases: 42 children with AL and DS. Controls: 124 children healthy with DS. The children parents were interviewed with a questionnaire in which they were asked to summarize the exposition of the children. A questionnaire adapted from the National Cancer Institute Questionnaire modules (http://dceg.cancer.gov/QMOD/) was used to obtain demographic information and environmental factors.

The proximity and type of powerlines nearby to the residence was assessed. Technicians blinded to the subjects’ case or control status drew diagrams and recorded systematically the distance from the home of any overhead power lines within 50 m of the residence, including transmission lines, thick and thin three-phase primary-distribution lines, any secondary distribution lines and first-span secondary distribution lines. The exposition was divided in “very high” and “not very high”. The degree “very high” was the stratum high of Kaune-Savitz and the degree “not very high” was the union of medium with low of Kaune-Savitz. The modified Kaune-Savitz wire-code categories were as follow: High wiring code; one or more transmission or three-phase primary lines pass within a distance of 20 m of the home under study. Medium wiring code; one or more transmission or three-phase primary lines pass within 46 m of the home under study, or one or more open secondaries pass within a distance of 26 m of the home under study. Low wiring code (the reference group); all homes not in the other two categories.

Direct measurements of magnetic fields at the front door of the residence was measured with a gaussometer. Technicians blinded to the subjects’ case or control status used an Emdex-C meter. Two minutes outdoor measurement made within 1 m (3 ft). An analysis just included two categories 2 or more mG and below 2 mG. Another analysis was with three level: lower 2 mG, 2.1 to 5.9 mG and 6 and more mG. Below 2 mG is considered the exposition of reference. Above 6 mG corresponded to the percentile 90 between the controls.

Control Variables
Maternal age over 35 at the pregnancy of the index child; weight of the child at birth greater than 2500 g (median value); cancer familial antecedents; socioeconomic level; exposition to pesticides and hydrocarbons; density of traffic greater than 25056 vehicles/day (median value).

Analysis
Odds Ratios (OR) and 90 per cent confidence intervals (90% CI) were calculated. Stratified analyses were used to assess the presence of confounding and effect modification. Multiple confounders were examined in logistic regression analyses.

Results
The controls were similar to the case patients, except for socioeconomic level, weight at birth and cancer familial antecedents. In the bivariate analysis the association between the exposition to 6 and more mG was of 2.41 (90% CI 1.0,5.9). With the classification “high” and “medium” of Kaune and Savitz, the ORs were 2.42 and 2.67, respectively, but the confidence intervals were very imprecise (Table 1).

Table 2 shows the logistic regression models, the OR when the exposition was higher 6 mG was of 2.49 (90% CI 1.07,5.79). With Kaune and Savitz classification the OR more important was in the level high, it was of 4.13 (90% CI 0.94,18.16). With Goldstein and Goldstein classification, there were two interaction very important, the interaction between exposition to EMF and sex (OR=0.21, CI 90% 0.05,0.84) and the interaction between exposition to EMF and cancer familial antecedents (OR=4.12, CI 90% 1.00,17.21). By this we decided to make a logistic regression model for women with cancer familial antecedents; the OR of exposition to EMF was in this group of 6.0 (90% CI 1.25,28.26).

Conclusion
In Mexican children with DS the exposition to EMF could constitute a risk factor for the expression of AL. The EMF could be a risk factor to developing AL only in children with high susceptibility to the disease.
Table 1. Exposition to Electromagnetic fields (EMF), measurements of 60-Hz residencial magnetic field level and wire coding in children with Down syndrome.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Down syndrome and AL (42)</th>
<th>Down syndrome without AL (124)</th>
<th>OR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>EMF 6 and higher mG</td>
<td>10</td>
<td>23.8</td>
<td>13</td>
<td>10.5</td>
</tr>
<tr>
<td>EMF 2.01-5.99 mG</td>
<td>9</td>
<td>21.4</td>
<td>39</td>
<td>31.5</td>
</tr>
<tr>
<td>EMF 0 – 2.00 mG</td>
<td>23</td>
<td>54.8</td>
<td>72</td>
<td>58.1</td>
</tr>
<tr>
<td>Kaune and High</td>
<td>19</td>
<td>45.2</td>
<td>55</td>
<td>44.4</td>
</tr>
<tr>
<td>Savitz coding Medium</td>
<td>21</td>
<td>50</td>
<td>55</td>
<td>44.4</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>4.8</td>
<td>14</td>
<td>11.3</td>
</tr>
<tr>
<td>Goldstein and Very high</td>
<td>19</td>
<td>45.2</td>
<td>55</td>
<td>44.3</td>
</tr>
<tr>
<td>Goldstein coding Not very high</td>
<td>23</td>
<td>54.8</td>
<td>69</td>
<td>55.6</td>
</tr>
</tbody>
</table>

AL= Acute leukemia; OR= odds ratio; 90% CI= 90 per cents confidence interval

Table 2. Risk of Childhood acute leukemia among children with Down syndrome according to levels of 60-Hz residential magnetic fields and the Kaune-Savitz and Goldstein and Goldstein code.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>OR **</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMF &gt;2 mG</td>
<td>1.24*</td>
<td>0.67 – 2.30</td>
</tr>
<tr>
<td>EMF 2.1 - 5.99 mG</td>
<td>0.80*</td>
<td>0.38 - 1.69</td>
</tr>
<tr>
<td>EMF ≥6 mG</td>
<td>2.49*</td>
<td>1.07 - 5.79</td>
</tr>
<tr>
<td>Exposition to EMF “High” vs “Low””</td>
<td>4.13**</td>
<td>0.94 - 18.16</td>
</tr>
<tr>
<td>Exposition to EMF “Medium” vs “Low”</td>
<td>2.89**</td>
<td>0.76 - 11.01</td>
</tr>
<tr>
<td>Exposition to EMF “High and Medium” vs “Low””</td>
<td>3.06**</td>
<td>0.81 - 11.46</td>
</tr>
<tr>
<td>Exposition to EMF (“very high” vs “not very high”)</td>
<td>6.0***</td>
<td>1.25 - 28.26</td>
</tr>
</tbody>
</table>

* For each category was realizad a model. OR denotes odds ratio, and CI confidence interval. These odds ratios have been adjusted for weight at birth, maternal age > 35 years, socioeconomic level, cancer familial antecedents and traffic density.
** For each category was realized a model. These odds ratios have been adjusted for sex, socioeconomic level and cancer familial antecedents.
*** This OR was adjusted for weight at birth, maternal age > 35 years and socioeconomic level. This model only included women with cancer familial antecedents.

Discussion
This is the first study that evaluates the interaction between the exposition to EMF and the susceptibility to AL in a group of children with increased susceptibility (presence of DS) as compared with the group of DS children with no AL. All previous studies analyzing the influence of environmental factor on the expression of AL, considered that genes may be important factors determining host susceptibility.

Our study considered the susceptibility as the main criterion for selection. For this reason, even if we had a small sample size, it was possible to identify significant associations between several external factors and the development of AL in children with DS, as shown in case-control studies that analyze gene-environmental interactions.

This study showed one of the highest risks reported with the accurate measurement of EMF. The way that this measurement was done was according to the protocols of the most important groups in the world that have evaluated this variable (Linet et al. 1999). In this study an
important association between the exposition to EMF higher or equal to 6 mG and the development of AL was found. It is important to emphasize that the population exposed to these levels was 23.8% in the cases and 10.5% among the controls. When considering the levels of exposition over 2 mG, in this study 45.2% was found among the cases and 42% among the controls. In the United States of America the average that has been reported exposed to these levels is of 11.4%, in Canada the 15.4%, in the United Kingdom 2.3%, and in Germany 2.0% (UKCC, 1999). This shows that in children with DS living in Mexico City, the frequency of exposition to higher levels than 2mG is higher to the one reported in other countries.

The configuration of the cable was measured following the international protocols, too. The confidence intervals of the OR that were obtained in this study were not precise, however the estimation of the OR were some of the highest that had been reported up to now and go from 0.62 to 3.77 (Greenland et al. 2000). Savitz and Poole have dare to point out that if risks between 3 and 4 were obtained it would certainly support more the possibility of a causal effect of the EMF to developing AL (Savitz and Poole, 2001), situation observed in this study. These elevated risks support the hypothesis that the weak effects could turn to be more obvious only in persons with high susceptibility to the exposition or to the sickness (Mejía-Aranguré et al. 2003).

In the present study, children were born highly susceptible because of DS but only some developed AL, suggesting that several factors may be the unchaining events. In fact, the Greaves’ hypothesis suggests that children born with genetic susceptibility to develop leukemia, will express the disease only when exposed (Greaves, 2002).

Childhood leukemia is clearly an heterogeneous disease with individual subtypes in which the response to chemotherapy is different and the causes may also be different. It is possible that acute leukemias share causes, as shown for lymphomas or thyroid cancer in children.

Most studies on risk factors in children’s cancer, claim that etiology is unknown. Since AL is increasing worldwide and of course Mexico and particularly Mexico City are not an exception; new medical and molecular approaches should be implemented.

Nowadays, the investigation of leukemia at the molecular level with this new approach, even if the causes of the disease are still unknown, will provide a better understanding of the disease to use new treatments and for the use of new molecular based therapies which are being considered. Preventive strategies may also be designed, because the mechanisms underlying the carcinogenesis process are being unraveled. Research on the risk factors that lead to leukemia is relevant to identify strategies to develop protective policies and interventions.

Acknowledgement

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References


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