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Spatial clustering of childhood leukaemia with the integration of the Paediatric Environmental History

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ABSTRACT

Background: Leukaemia remains the most common type of paediatric cancer and its aetiology remains unknown, but considered to be multifactorial. It is suggested that the initiation *in utero* by relevant exposures and/or inherited genetic variants and, other promotional postnatal exposures are probably required to develop leukaemia. This study aimed to map the incidence and analyse possible clusters in the geographical distribution of childhood acute leukaemia during the critical periods and to evaluate the factors that may be involved in the aetiology by conducting community and individual risk assessments.

Materials and methods: We analysed all incident cases of acute childhood leukaemia (< 15 years) diagnosed in a Spanish region during the period 1998–2013. At diagnosis, the addresses during pregnancy, early childhood and diagnosis were collected and codified to analyse the spatial distribution of acute leukaemia. Scan statistical test methodology was used for the identification of high-incidence spatial clusters. Once identified, individual and community risk assessments were conducted using the Paediatric Environmental History.

Results: A total of 158 cases of acute leukaemia were analysed. The crude rate for the period was 42.7 cases per million children. Among subtypes, acute lymphoblastic leukaemia had the highest incidence (31.9 per million children). A spatial cluster of acute lymphoblastic leukaemia was detected using the pregnancy address ($p < 0.05$). The most common environmental risk factors related with the aetiology of acute lymphoblastic leukaemia, identified by the Paediatric Environmental History were: prenatal exposure to tobacco (75%) and alcohol (50%); residential and community exposure to pesticides (62.5%); prenatal or neonatal ionizing radiation (42.8%); and parental workplace exposure (37.5%)

Conclusions: Our study suggests that environmental exposures in utero may be important in the development of childhood leukaemia. Due to the presence of high-incidence clusters using pregnancy address, it is necessary to introduce this address into the childhood cancer registers. The Paediatric Environmental History which includes pregnancy address and a careful and comprehensive evaluation of the environmental exposures will allow us to build the knowledge of the causes of childhood leukaemia.

1. Introduction

Leukaemia remains the most common type of paediatric cancer (< 15 years old), and represents 30% of all childhood cancers (Hunger and Mullighan, 2015). Acute leukaemia (AL) accounts for more than 95% of all childhood leukaemia cases, including acute lymphoblastic leukaemias (ALL) (78%) and acute myeloblastic leukaemias (AML) (16%) (Puumala et al., 2013; Ries et al., 1999). The peak age of emergence varies, with ages 2–5 for ALL, while AML is more frequent in children younger than age one. In Spain, AL has a crude incidence mean of 46.1 cases per million children, corresponding to 36.0 million cases of ALL and 8.3 million cases of AML (Peris Bonet et al., 2014).

The aetiology of childhood leukaemia remains unknown, but it is believed that both constitutional and environmental factors are involved (Inaba et al., 2013; Knox and Gilman, 1996; Pui et al., 2008). Currently, a well-accepted hypothesis (Inaba et al., 2013) is that leukaemia emerges from precursor mutations initially developed in utero, as well as, from the mutations developed after various exposures to leukaemogenic agents during infancy. Several studies have utilized georeferencing systems to identify and analyse the clustering of child-

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hood leukaemia cases and investigate their possible associations with environmental factors through patient addresses at time of diagnosis (Alexander et al., 1997, 1998; McNally et al., 2009a). However, in the past decade, only a few studies that analyse the addresses during pregnancy, birth and diagnosis have emerged, showing more conclusive results with pregnancy and birth addresses. These studies support that development of childhood cancers initiates in utero or beginning of infancy, catalysed by a common exposure within a shared geographic area (Kreis et al., 2016; McNally et al., 2009b). Additionally, much progress has been made in the study of the geographical differences in areas with smaller populations, allowing the observation of major differences in low overall prevalence diseases like childhood AL (Ortega-Garcia et al., 2016).

According to the US National Cancer Institute, risk factors (RFs) with conclusive evidence for ALL include: exposure to ionizing radiation in utero, postnatal therapeutic radiation, and genetic conditions, such as Down syndrome (Ries et al., 1999). Additional RFs with inconclusive evidence include: prenatal exposure to tobacco and alcohol, parental occupational exposures, parental and child exposure to pesticides, postnatal infections, advanced maternal age, high birth weight, maternal history of foetal loss, birth order and assisted reproduction technology (Heck et al., 2013; Maule et al., 2009; Reigstad et al., 2016; Ries et al., 1999; Turner et al., 2010; Wigle et al., 2009). On the other hand, breast milk is considered to be a protective factor of childhood leukaemia, with protection increasing as duration of exclusive breastfeeding increases (Amitay and Keinan-Boker, 2015; Ortega-Garcia et al., 2008).

The Paediatric Environmental History (PEH) questionnaire is an integrative tool that allows for the registration of environmental risk factors related to childhood cancer and propose aetiological hypotheses in the study of clusters (Ortega-García et al., 2012). Utilizing a carefully collected PEH could help explore possible environmental exposures involved in the aetiology.

The aim of this paper is to analyse the geographic distribution of childhood AL in a European Region (Murcia, Spain) using the addresses at pregnancy, infancy and time of diagnosis and developing the PEH to conduct individual and community risk assessments.

2. Materials and methods

2.1. Study population

The Region of Murcia (RM) is a European Region located in southeast Spain, with a total population of 1,470,069 inhabitants in 2011. For the spatial cluster analysis, we consider the administrative division of census districts. In 2011, Region of Murcia was divided into 1220 census districts, with an average of 212 children under the age of 15, and a maximum of 698 and a minimum of 42.

The reference population (risk population) came from the 2001 and 2011 Spanish Census (INE, 2011). The total population (< 15 years) was 207,822 in 2001 and 259,083 in 2011. We performed linear interpolation to estimate the population between the censuses. For each census district we used the population at the census times immediately preceding and immediately following. For times before the first census time, the population size is set equal to the population size at that first census time, and for times after the last census time, the population is set equal to the population size at that last census time.

2.2. Patient registry

The MACAPEMUR (Environment and Paediatric Cancer in the Region of Murcia) database includes all patients under the age of 15 diagnosed with cancer within the RM since 1998. MACAPEMUR is a project that compiles the PEH of newly diagnosed cancer patients (Cárceles-Álvarez et al., 2015; Ferris Tortajada et al., 2004; Ortega-García et al., 2011). The single-province character of the RM and the centralized care reference units of Paediatric Oncohematolgy and the Paediatric Environmental Health Speciality Unit (PEHSU) at the Clinical University Hospital Virgin of Arrixaca facilitated the access to medical records. The hospital registry of the Clinical University Hospital Virgin of Arrixaca registers 100% of the children diagnosed with cancer in the RM. The classification of the cases is done by checking the clinical-pathological diagnosis with the International Classification of Diseases for Oncology (ICD-O-3) (IARC, 2011; Percy et al., 2000) and the International Classification of Childhood Cancer (ICCC-3) (Steliarova-Foucher et al., 2005) within 0–2 months after diagnosis. Over 99% of the cases are morphologically verified. Annually, a medical doctor performs an additional check of all cases to avoid misclassification and/or double registrations.

In all cases, the families are contacted in person or by phone. Once the diagnosis is made, a face-to-face interview is carried out by a doctor trained in paediatric cancer, environmental health and risk communication, who collects information on addresses at pregnancy, early childhood, and diagnosis; as well as another series of environmental data (Cárceles-Álvarez et al., 2015; Ferris Tortajada et al., 2004; Ortega-García et al., 2012). This study was approved by the Ethics Committee and the Institutional Review Board at the Clinical University Hospital Virgin of Arrixaca.

We identified 158 cases diagnosed with leukaemia between 1998–2013, and were grouped according to the criteria of the MACAPEMUR database. All families of patients were contacted to obtain consent and schedule interviews. Information was gathered by a pediatrician through: (1) face-to-face interviews with one or both parents present, (2) complementary phone calls to complete or verify data, (3) compiled data from primary care centres and/or local hospitals with records from the regional databases OMI-AP (Stacks, Consulting e Ingeniería en Software, S.L.U., Barcelona), Selene (UTE Siemens-Indra, Madrid), and Civitas (Steria Ibérica, S.A., Madrid).

The PEH questionnaire comprises a series of concise and basic questions through which the medical doctor identifies environmental exposures of concern and documents human carcinogens characterized by the International Agency for Research on Cancer (IARC) and by the US National Toxicology Program (IARC, 2016; US Department of Health and Human Services, 2014). Moreover, it includes residential address during pregnancy (PA), early childhood (PN) and time of diagnosis (DX) (Table 1) (Ferris Tortajada et al., 2004; Ortega-García

Table 1
Main sections of the paediatric environmental history.

Family history and associated constitutional symptoms.
Pedigree of at least 3 generations for:
a. History of cancer in the family tree.
b. Genetic and constitutional factors associated with childhood cancer.
c. Chronic, rare and family diseases.
d. Cause of deaths.
Detailed description of sources of exposure during pregnancy.
Maternal grandmother's (maternal egg formation) work during pregnancy and drugs in pregnancy.
Maternal grandfather's work during pregnancy.
Environmental exposures (preconceptional, conceptional, pregnancy, postnatal).
The data collection is distributed in the following sections:
1. General (affiliation and identification, and socioeconomic data), housing (before, during pregnancy, and postnatal), tobacco (before, during pregnancy, and postnatal), external environment (neighbourhood, daycare, school), lifestyle during pregnancy and postnatal care, perceptions (before, during pregnancy, and postnatal).
2. Nutrition during pregnancy and exercise.
3. Obstetric history (drugs, diseases, etc.).
4. Radiologic history of the parents.
5. Work history (both parents).
6. Background of the child (birth, neonatal, radiation history, diseases, vaccines, treatments, etc.).
7. Breastfeeding.
8. Nutrition of the child, exercise and lifestyle.
Type of tumour (tumour data, diagnosis, treatment, and evolution).