Bol Med Hosp Infant Mex. 2016;73(1):55–63

Boletín Médico del
Hospital Infantil de México (English Edition)

www.elsevier.es/bmhim

PUBLIC HEALTH

Molecular epidemiology of acute leukemia in children: causal model, interaction of three factors—susceptibility, environmental exposure and vulnerability period

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Received 2 December 2015; accepted 3 December 2015
Available online 21 February 2016

KEYWORDS
Leukemias;
Epidemiology;
Causality;
Children;
Molecular epidemiology

Abstract Acute leukemias have a huge morphological, cytogenetic and molecular heterogeneity and genetic polymorphisms associated with susceptibility. Every leukemia presents causal factors associated with the development of the disease. Particularly, when three factors are present, they result in the development of acute leukemia. These phenomena are susceptibility, environmental exposure and a period that, for this model, has been called the period of vulnerability. This framework shows how the concepts of molecular epidemiology have established a reference from which it is more feasible to identify the environmental factors associated with the development of leukemia in children. Subsequently, the arguments show that only susceptible children are likely to develop leukemia once exposed to an environmental factor. For additional exposure, if the child is not susceptible to leukemia, the disease does not develop. In addition, this exposure should occur during a time window when hematopoietic cells and their environment are more vulnerable to such interaction, causing the development of leukemia. This model seeks to predict the time when the leukemia develops and attempts to give a context in which the causality of childhood leukemia should be studied. This information can influence and reduce the risk of a child developing leukemia.
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PALABRAS CLAVE
Leucemias;
Epidemiología;
Causalidad;
Niños;
Epidemiología molecular

Epidemiología molecular de la leucemia aguda en niños. Modelo causal en el que intervienen tres factores: susceptibilidad, exposición ambiental y periodo de vulnerabilidad

Resumen La leucemia aguda representa una enfermedad con una enorme heterogeneidad morfológica, citogenética, molecular y polimorfismos genéticos asociados con la susceptibilidad. Presenta factores causales asociados con el desarrollo de la misma. Particularmente, cuando tres fenómenos se conjuntan, traen como resultado el desarrollo de la leucemia aguda. Estos fenómenos son la susceptibilidad, la exposición ambiental y un periodo que, para este modelo, ha sido denominado el periodo de vulnerabilidad. El presente marco teórico muestra cómo los conceptos de la epidemiología molecular han permitido establecer una referencia a partir de la cual es más factible identificar los factores ambientales relacionados con el desarrollo de la leucemia en niños. Posteriormente se muestran los argumentos para predecir que solo los niños susceptibles probablemente desarrollarán leucemia una vez que se exponen a un factor ambiental. Por lo que, por más exposición, si el niño no es susceptible a la leucemia, no la desarrollará. Además, esta exposición debe ocurrir durante una ventana de tiempo durante el cual las células hematopoyéticas y su entorno son más vulnerables, para que dicha interacción provoque el desarrollo de leucemia. Este modelo pretende predecir el momento en el cual se desarrollará la leucemia y trata de dar un contexto en el que la causalidad de la leucemia en niños deberá ser estudiada. A través de esto se podrá influir y disminuir el riesgo de que un niño desarrolle leucemia.
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1. Introduction

This model aims to lay the groundwork to identify factors associated with the development of acute leukemia (AL) in children. First, the concepts of molecular epidemiology are explained, which are those that give rise to this theoretical model. Subsequently, the components of the model are described and, finally, a description of the same is done.

2. Molecular epidemiology

For Shulte, molecular epidemiology emerges as an evolutionary state of the epidemiology in which it will not only be important to identify the risk factors of the diseases. The mechanisms that lead to their development can be identified through molecular epidemiology. From this point of view, it will result in the emergence of new theories and, with it, the maneuvers for disease prevention in the population can more accurately be directed.[1] The Shulte concept has proved some reactions: some in favor,[2–15] others against[16–18] and others, although they do not discard molecular epidemiology as a new discipline question it and expect its prompt strengthening.[19–23] Table 1 shows the most common definitions of molecular epidemiology.[14]

What allows us to speak of a new discipline are not only the techniques or tools applied in the epidemiology, but the concepts that this brings. These concepts are the internal dose, the effective biological dose, early biological effects and the altered function and structure, concepts that are made operational though the different biomarkers.[1] In this sense, the biomarkers can be divided into biomarkers of exposure, effect and susceptibility.[1] Exposure biomarkers are those of internal dose, biologically effective dose and target tissue dose. Susceptibility biomarkers include polymorphisms in genes involved in the metabolism of carcinogens, in DNA repair and in the control of the cellular cycle. Biomarkers of effect evaluate the early genetic alterations and the modulation of the nutritional and immunological state that lead to tumorigenesis.[4]

Molecular epidemiology has been proposed as an evolving state of the classic epidemiology, which for some only represents the incorporation of new techniques, the molecular techniques, in epidemiological designs,[16,20] whereas for others it represents the best way to explain the mechanisms related with the health-disease processes in human populations.[1,4] This provides the answer to the problem of epidemiology that, on establishing an association between an environmental factor and disease, leaves a ''black box''; i.e., that cannot clarify the mechanisms by which this factor causes the disease.[1] In such a case, the molecular epidemiology would contribute to the solution for this black box.[2,24]

However, molecular epidemiology does not only arise as an incorporation of new molecular techniques, as Shulte himself proposes. It arises from the identification of individuals who, despite being exposed to the same risk factors, do not present the same response, whether it is because they do not receive the same dosage (internal dose, effective biological dose) or because they respond metabolically in a different manner to the substance (susceptibility biomarkers). It also arises from the concern of identifying in a timely manner the damage caused by a toxic agent (effect biomarkers). This leads to the development of molecular epidemiology.[4,7,14]

It is then clear that in any epidemiological investigation it is possible to apply molecular epidemiology, although not

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