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REVIEW ARTICLE

Infectious Agents in Childhood Leukemia

José Arellano-Galindo,[a] Alberto Parra Barrera,[b] Elva Jiménez-Hernández,[c] Sergio Zavala-Vega,[a] Guillermina Campos-Valdéz,[a] Juan Xicohtencatl-Cortes,[d] Sara A. Ochoa,[d] Ariadnna Cruz-Córdova,[d] María del Pilar Crisóstomo-Vázquez,[e] Juan Carlos Fernández-Macías,[a] and Juan Manuel Mejía-Aranguré[f,g]

[a]*Área de Virología, Laboratorio de Infectología, Hospital Infantil de México Federico Gómez, Ciudad de México, México*
[b]*Laboratorio de Cáncer y Hematopoyesis, Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, Ciudad de México, México*
[c]*Departamento de Hematología Pediátrica, Unidad Médica de Alta Especialidad, Centro Médico Nacional la Raza, Instituto Mexicano del Seguro Social, Ciudad de México, México*
[d]*Laboratorio de Investigación en Bacteriología Intestinal, Hospital Infantil de México Federico Gómez, Ciudad de México, México*
[e]*Laboratorio de Parasitología de Investigación, Hospital Infantil de México Federico Gómez*
[f]*Unidad de Investigación en Epidemiología Clínica, Unidad Médica de Alta Especialidad, Hospital de Pediatría, Ciudad de México, México*
[g]*Coordinación de Investigación en Salud, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Ciudad de México, México*

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Acute leukemia is the most common pediatric cancer, representing one-third of all cancers that occurs in under 15 year olds, with a varied incidence worldwide. Although a number of advances have increased the knowledge of leukemia pathophysiology, its etiology remains less well understood. The role of infectious agents, such as viruses, bacteria, or parasites, in the pathogenesis of leukemia has been discussed. To date, several cellular mechanisms involving infectious agents have been proposed to cause leukemia following infections. However, although leukemia can be triggered by contact with such agents, they can also be beneficial in developing immune stimulation and protection despite the risk of leukemic clones. In this review, we analyze the proposed hypotheses concerning how infectious agents may play a role in the origin and development of leukemia, as well as in a possible mechanism of protection following infections. We review reported clinical observations associated with vaccination or breastfeeding, that support hypotheses such as early life exposure and the resulting early immune stimulation that lead to protection.

Key Words: Leukemogenesis, Infectious agents, Early exposure, Delayed exposure, Pediatric cancer, Acute leukemia.

Introduction

Acute leukemia (AL) is the most common cancer in children, representing one-third of all cancers that occur in under 15 year olds, with varied incidence worldwide (1). Although there is a high incidence of childhood leukemia throughout the world, it is particularly prevalent in Hispanic residents in the USA and in Mexican children (2–6). In 2011, the average reported incidence worldwide was 57.6 million children, of which acute lymphoblastic leukemia (ALL) was the most frequent with 49.5 million cases (7). Several advances have increased our knowledge on the pathophysiology related to leukemia, for example, the existence of leukemic stem cells and the plasticity and regulation of leukemic niches (8,9). However, the etiology of leukemia remains less well understood. The existence of different subtypes of leukemia that show heterogeneity in pathophysiology, clinical manifestations, and response to treatment, as well as prognosis suggests different etiologies

Address reprint requests to: Juan Manuel Mejía-Aranguré, PhD, Unidad de Investigación en Epidemiología Clínica, UMAE Hospital de Pediatría, Silvestre Frenk, and Coordinación de Investigación en Salud, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Avenida Cuauhtémoc 330, 4° Piso Edificio de la Academia Nacional de Medicina, 06720, Ciudad de México, México; Phone: (+52) (55) 5761-0841; FAX: (+52) (55) 5761-0841; E-mail: juan.mejiaa@imss.gob.mx

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(10,11). A genetic susceptibility has been established because patients with Bloom syndrome, neurofibromatosis, Fanconi anemia, ataxia telangiectasia, and trisomy 21 normally have a high risk of AL, as well as others (12). Although the etiology in most cases is unknown, perinatal factors could provide answers to describe the physiopathogenic mechanism related to AL (13). Some of these perinatal factors could include obesity at birth (14), use of household pesticides (15), parental smoking (16), maternal diet (17), or paternal occupational exposure to solvents and hydrocarbons (18). Additionally, the role of infectious agents has been proposed as a contributor to the pathogenesis of leukemia (19,20). However, contact with such agents can also be beneficial in the development of immune stimulation and protection *versus* the risk of leukemic clones. In this review, we analyze the existing hypotheses on how infectious agents are suggested to play a role in the origin and development of leukemia, as well as in possible mechanisms of protection following infection. We review reported clinical observations associated with vaccination or breastfeeding that support the hypotheses such as early life exposure and the consequent early immune stimulation that lead to protection. In this review, active infection was considered based on CMV concepts for transplant patients as: the detection of such microorganism *in situ* by a laboratory method sensitive enough to prove its presence (21), whereas infectious agents were considered in this context based on the concepts of hot pathogenic agent interaction, to all agents either bacterial, viral, fungus or parasite, which is able to infect its host and cause several forms of infection (it is latent when the genetic expression is suppressed or low but the infectious agent is present, it is an active infection when the infectious agent can be detected, but it is not associated with symptoms or symptomatic infection when the infectious agent is detected and its association with clinical symptom is possible) (22).

The Hypothesis of Early or Delayed Life Exposure to Infection

One hypothesis has proposed that the delay of exposure to infection observed during pre- or perinatal life could initiate events of leukemogenesis (23,24). Thus, early exposure to infectious agents could be beneficial in reducing the risk of leukemia, because it may mean that infection in early life favors the activation of mechanisms in the immune system that appear to stimulate a form of protection (23,24). It has been suggested that exposure to infection is responsible for early immunomodulation (23). An inverse association was observed between common maternal infection and ALL, whereas a positive association was observed in cases in which common infections led to hospitalization, implying that the link depended on the intensity of the symptoms. This correlates with the hypothesis that the estimulation of the immune response is developed during infancy (25,26). Such results are supported by more recent observations that, maladaptive immune activation observed in newborns delivered by cesarean section showed an increased risk of ALL (26). The vertical transference from the mother to infants either during gestation or lactation is another important factor to consider. It is believed that, several infectious agents can be transferred to infants when the mothers have an active infection either by viruses or bacteria, such as: hepatitis B, herpes, cytomegalovirus, as well as *Chlamydia trachomatis* or *Neisseria gonorrhea,* which has been found in some cases to be responsible for active infection or symptomatic infection (27–29). Regarding lactation, a preliminary study analyzed the vertical transference of CMV by lactation, where the CMV viral load was measured at the same time in breast milk, saliva and blood of the newborn (30). Our preliminary results show that some host mechanisms have control over the vertical transference of CMV that prevent the risk of symptomatic infection despite an active infection being present in the newborns. Although, participation of the immune system, microRNAs, lactoferrin, oligosaccharides, and so on (31) control and keep the equilibrium host-pathogen agent, it also promotes contact and exposes the newborn to such infectious agent (32). A mechanism of interaction such as early contact is required under the disequilibrium of these mechanisms in the binomial mother-newborn, however, the infectious agent can show its pathogenicity and lead to symptomatic infection in the newborn.

The Influence of Viral Infection in Leukemogenesis

By using metagenomic sequencing, it has been possible to find known and unknown viruses—namely those belonging to the families *Papillomaviridae* and *Anelloviridae*—that infect the serum of mothers during pregnancy of children with leukemia (33). Despite anelloviruses previously being considered candidates for a possible association with leukemia (34), a recent analysis of viremia during pregnancy did not show an association (33). Additionally, studies that have investigated the association of enterovirus—a member of the *Picornaviridae* family and a common cause of gastrointestinal infection in children—with the risk of leukemia found that, the risk was significantly lower in children infected with enterovirus than in the cohort of non-infected children (35).

Two models have been proposed to explain how viruses could play a role in the development of childhood leukemia. The first relies on the direct transforming ability of viruses; however, studies suggest it is unlikely that a single transforming agent is involved in the pathogenesis of common ALL (36). In the second model, the effect might be due to the problems caused by abnormal immunological responses to congenital, neonatal, or post neonatal infections, which in turn promote secondary genetic or immunological alterations. In this case, the action of microorganisms may