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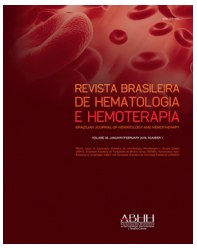

Original article

Do immunoglobulin G and immunoglobulin E anti-L-asparaginase antibodies have distinct implications in children with acute lymphoblastic leukemia? A cross-sectional study

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ABSTRACT

Background: L-Asparaginase is essential in the treatment of childhood acute lymphoblastic leukemia. If immunoglobulin G anti-L-asparaginase antibodies develop, they can lead to faster plasma clearance and reduced efficiency as well as to hypersensitivity reactions, in which immunoglobulin E can also participate. This study investigated the presence of immunoglobulin G and immunoglobulin E anti-L-asparaginase antibodies and their clinical associations.

Methods: Under 16-year-old patients at diagnosis of B-cell acute lymphoblastic leukemia confirmed by flow cytometry and treated with a uniform L-asparaginase and chemotherapy protocol were studied. Immunoglobulin G anti-L-asparaginase antibodies were measured using an enzyme-linked immunosorbent assay. Intradermal and prick skin testing was performed to establish the presence of specific immunoglobulin E anti-L-asparaginase antibodies *in vivo*. Statistical analysis was used to investigate associations of these antibodies with relevant clinical events and outcomes.

Results: Fifty-one children were studied with 42 (82.35%) having anti-L-asparaginase antibodies. In this group IgG antibodies alone were documented in 10 (23.8%) compared to immunoglobulin E alone in 18 (42.8%) patients. Immunoglobulin G together with immunoglobulin E were simultaneously present in 14 patients. Children who produced exclusively IgG or no antibodies had a lower event-free survival (p-value = 0.024). Eighteen children (35.3%) relapsed with five of nine of this group who had negative skin tests suffering additional relapses (range: 2–4), compared to none of the nine children who relapsed who had positive skin tests (p-value < 0.001).

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Conclusion: Children with acute lymphoblastic leukemia and isolated immunoglobulin G anti-L-asparaginase antibodies had a higher relapse rate, whereas no additional relapses developed in children with immunoglobulin E anti-L-asparaginase antibodies after the first relapse.

Escherichia coli L-asparaginase is key in the treatment of childhood acute lymphoblastic leukemia (ALL).[1] High-intensity L-asparaginase regimens result in better outcomes than lower-dose schemes.[2] The intravenous or intramuscular route can be used to administer L-asparaginase; the latter is well tolerated and does not appear to result in increased hypersensitivity reactions[3] whereas the former is more immunogenic.[4] More recently it was shown that the intravenous administration of pegylated L-asparaginase is also associated with a higher risk of allergic reactions.[5] The L-asparaginase molecule is highly reactive, has a complex quaternary structure and elevated molecular weight and it can elicit production of immunoglobulin (Ig)G anti-L-asparaginase antibodies. These antibodies can cause severe allergic and hypersensitivity reactions, albeit rarely fatal, in children suffering a severe reaction, mostly mediated by IgG and complement.[3,6] In these cases, substitution for L-asparaginase conjugated covalently with 5000 molecular weight polyethylene glycol is indicated, although one third of those switched to the pegylated enzyme still have allergic reactions due to the fact that the source of both preparations is the same bacterium.[7,8] Interestingly, treatment with the enzyme derived from *Erwinia chrysanthemi*, which can substitute the typical variety of *Escherichia coli*, may not be necessary for some children with severe allergies to *E. coli* L-asparaginase who have received at least half of intended doses.[9] Important aspects for better therapeutic results and less frequent side effects include new sources of L-asparaginase to increase its availability, improved pharmacodynamics and pharmacokinetics and safer toxicological profile.[10]

Decreased efficacy of L-asparaginase due to high titers of IgG antibodies may be due to neutralizing antibodies, increased enzyme clearance, delayed absorption after intramuscular administration, and direct interference with its enzymatic activity.[11]

Currently, there are no commercially available, clinically validated assays for IgG or IgE anti-L-asparaginase antibodies. Moreover, the specificity of anti-L-asparaginase antibodies to predict inactivation has been low in comparison to measuring L-asparaginase activity itself; many patients develop anti-L-asparaginase antibodies without clinical allergic reactions or inactivation of the enzyme, and antibody levels in children with and without hypersensitivity overlap.[12]

Importantly, no correlation has been found between IgG antibody titers and the severity of the allergic reaction.[13] This is probably because IgG anti-L-asparaginase antibody assays are used as a surrogate for the diagnosis of L-asparaginase allergy, and non-allergic ALL children can develop specific IgG anti-L-asparaginase antibodies, rendering its diagnostic utility controversial.[14] Specific IgE anti-L-asparaginase antibodies, on the other hand, contribute to clinical symptoms through mediator release from mast cells.[15] Thus, controversy on the meaning of anti-L-asparaginase antibodies remains although its prognostic significance and clinical utility has been studied for over 30 years.[16] Several important questions remain, including what is the association between IgE anti-L-asparaginase antibodies and ALL clinical events other than allergic reactions. Furthermore, the time during which IgG and IgE antibodies can be detected has not been established.

This study investigated the production of IgG and IgE anti-L-asparaginase antibodies in children diagnosed with B cell ALL treated with a standardized dose of *E. coli* L-asparaginase and determined the association of these two antibodies with the clinical course and risk of relapse.

Methods

A transversal descriptive cross-sectional study was conducted in the Hematology, Allergy, and Immunology Departments, of the "José Eleuterio González" University Hospital of the Universidad Autónoma de Nuevo León, Monterrey, Mexico. Under 16-year-old patients with diagnosis of B-cell ALL confirmed by flow cytometry at any stage of treatment after induction to remission therapy were included. Children taking anti-H1 or anti-H2 antihistamines were excluded. The study was approved by the Institutional Review Board and Ethics Committee of the institution and parents signed informed consent forms.

Induction to remission therapy consisted of prednisone 60 mg/m^2, vincristine 1.5 mg/m^2, and six doses of L-asparaginase of 6000 IU/M^2/intramuscular on Days 8, 12, 16, 20, 24, and 36. Children with high-risk ALL received two additional doses of L-asparaginase on Days 2 and 8 of re-induction and three doses of doxorubicin (40 mg/m^2); triple intrathecal chemotherapy for central nervous system (CNS) prophylaxis was administered four times. Consolidation included single doses of cytosine arabinoside (1.5 g/m^2) and methotrexate (1.5 g/m^2) administered in a one-day intravenous infusion. This was followed by one month of 6-mercaptopurine taken daily and weekly methotrexate. Re-induction included 15 days of prednisone, three doses of vincristine, two of doxorubicin for high-risk and one for standard-risk patients, two doses of L-asparaginase and two of triple intrathecal prophylaxis. Ten days after re-induction, maintenance was started for 90 weeks with oral 6-mercapthopurine at 50 mg/m^2/day and weekly methotrexate starting at 30 mg/m^2/day and adjusted to maintain the absolute leukocyte count between 3.0 and 5.0 $\times$ 10^3/μL. Every six weeks during the first year of maintenance, and

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