The apparent excess of acute promyelocytic leukemia in infant acute leukemias in Brazil

Acute promyelocytic leukemia (APL) is an uncommon variant of acute myelogenous leukemia (AML) in childhood. This subtype of leukemia is distinguished by balanced reciprocal translocations between chromosomes 15 and 17 resulting in a PML/RARα fusion transcript, which plays a crucial role in their pathogenesis. Epidemiological studies have reported a 5% to 10% incidence of APL between AML in adulthood. APL patients are referred to as having bimodal age distributions; however, this occurs seldomly in children less than 2 years of age. A high frequency of APL in Latino AML patients have been reported recently, and led to the hypothesis that APL could be related to ethnic background and/or exposure to distinct environmental factors. With this letter we add more information about the increased prevalence of APL in Latino children raising questions about earlier environmental exposures. We also suggest the in utero origin of the PML/RARα fusion gene based on the short period of environmental exposure of the cases reported herein. Since June 1999 a non-population based registry, called The Brazilian Group for Infant Acute Leukemias Studies was created with the following aims: i) to conduct an immunophenotypic and molecular study in children under 2 years of age with acute leukemia, in order to determine the associations with selected risk factors in acute infant leukemias (AIL) from different regions of Brazil; ii) to characterize the more frequent chromosomal abnormalities detected by molecular markers in AIL in Brazil. All children included in this study were newly diagnosed and previously untreated. The genotype was characterized by cytogenetics and molecular analysis with well-established techniques such as RT-PCR and FISH. In a preliminary evaluation of the dataset, a high prevalence of MLL rearrangements (85%) was found as expected; however, an unusually high frequency of APL (5 out of 45, 11% of AML cases) was found amongst other chromosomal abnormalities. The mean age of the AIL cases was 16 months (ranged 14 to 21 months). The mean leukocyte count was 10,900/mm³ in four cases the t (15; 17) (q22; q21) was identified by conventional cytogenetics and/or by RT/PCR and in one case the karyotype was characterized by add(15) i that is a rare variation of the classical translocation. They were treated with All-trans Retinoic Acid and Idarubicin according to the AIDA protocol. One patient lacks follow-up, three are dead after 3 years since diagnosis and one is alive after 3 years since diagnosis. Enquiries on maternal behaviour demonstrated that living in rural towns and being exposed to agricultural products (pesticides and/or herbicides) was a common factor among the mothers. Furthermore, the frequencies of APL in a series of 392 children’s AML (0-16 years of age) in our laboratory 51 (13.0%) were APLs.

Since the first report using molecular markers in identical twins with concordant leukemia and retrospectively with Gutherie cards, several authors have demonstrated that gene fusions such as AF4/MLL, TEL/AML1, AML1/ETO, CBFB/MYH11 and PML/RARα in acute leukemia arose before birth. However, only the most common translocation in infants that involves MLL gene fusions has been associated with maternal transplacental exposure. The former study investigated the effects of selected exposures [medicines, tobacco, alcohols, pesticides, chemical solvents and herbicides] in utero in children who developed AIL, demonstrated a specific association of exposure to pesticides with AMLs (OR 5.08; 95% CI 1.84-14.04).

The present data support the previous results related to the high frequency of APL in Latino AML. The apparent excess of APL in a Brazilian series of IAL could be potentially related to distinct environmental factors rather than to ethnic background. The above mentioned PML/RARα fusion gene arising early in life should be evaluated in an extended cooperative study, since limited epidemiological study is available worldwide to support the apparent associations with environmental exposure.

References