Risk modifier(s) of susceptibility to pediatric acute lymphoblastic leukemia

Acute Lymphoblastic Leukemia (ALL) is an acute form of cancer of the white blood cells, characterized by the overproduction and accumulation of immature precursors known as lymphoblasts.

ALL is the most common type of leukemia in children accounting for 25-30% of childhood malignancies.

What causes leukemia? Is unknown but, among other causes, an interaction between environmental factors and genetic predisposition has been proposed. We are all exposed to chemical toxins including negative smoking, pesticides, traffic fumes and household chemicals. The body has a machinery to deal with these substances in the form of enzymes which are protein substances that have the ability to breakdown the complex chemicals to simple ones, what is called metabolism. Two groups of enzymes are involved in this setting. Phase I enzymes are concerned with changing those chemicals into active substances capable of inducing carcinogenesis while phase II enzymes are concerned with inactivation of those products to protect the body from their harmful effects.

Why some children develop leukemia and others not?

The production and elimination of those harmful substances vary among individuals depending on the enzymes' activity that deals with such substances which varies from one individual to the other. An increase in the activity of phase I and/or decrease in the activity of phase II are associated with increased susceptibility while the reverse is associated with protection from cancer.

What is the cause of inter-individual variation in the activity of these enzymes?

As mentioned, enzymes are proteins; their structure and hence function is dictated by genes. A gene is made of a long stretch of DNA. DNA is made, among other molecules, of basic units called nucleotides arranged in a sequential pattern (DNA sequence). Minor differences in the nucleotide sequences do occur normally which is called polymorphism. Though it is normal that different people carry slightly different sequences, yet any change in the sequence, even in one nucleotide (what is called single nucleotide polymorphisms, SNPs) can cause a change in the structure and hence function of its protein product, in our case the enzymes. Also the polymorphism seems to be ethnic related.

An important group in phase II enzymes is called N-Acetyltransferases (NAT); NAT1 and NAT2 are the main players.

Three NAT2 enzyme types have been described with fast, intermediate and slow activity (acetylation). Slow activity enzymes are less efficient in metabolizing their target substances and hence may increase the risk of cancer.

We studied the impact of NAT2 polymorphisms on risk susceptibility to pediatric ALL in Egyptian children.

We first compared the relative frequency of different polymorphisms in normal controls, as a sample of Egyptian population, to those in other countries as reported in the literature. Then we compared the relative frequencies in normal controls to those in leukemic children.

The results showed, to start with, that the Egyptians have different distribution of polymorphisms compared to the western populations.

As regards susceptibility to leukemia, children with slow acetylator type characterized by low detoxifying activity are at a higher risk to develop leukemia varying from 2.7 up to 10 folds according to their enzymatic activity. On the other hand, children with rapid acetylator type, characterized by high detoxifying activity, are relatively protected.

That drew the attention that some changes in the DNA, no matter how trivial can predispose to or protect against some cancers.

Because of the variability in distribution of polymorphisms between different areas of the world, such studies have to be performed locally in each community. Results from one study cannot be extrapolated to other communities.

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