Chapter 1

Model for Identifying the Etiology of Acute Lymphoblastic Leukemia in Children

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1. Introduction

The incidence of ALL varies throughout the world; however, there is a greater frequency of the disease in those countries with a higher socio-economic level [1], with the exception that a higher frequency of ALL has been reported for some Hispanic cities [2]—cities that generally are considered to have a lower standard of living. The highest incidence of ALL has been reported for Costa Rica and for Mexico City [3].

It is accepted that ALL is the result of the interaction, which occurs at a specific moment of life, between environmental factors and susceptibility to the disease [4]. The theories concerning the origin of this illness have been focussed fundamentally on the B-cell precursors of ALL [1]. The most important of these theories was proposed by Greaves and Kinlen; several more recent variations, such as the adrenal theory and infective lymphoid recovery hypothesis have attempted to include these theories [5-8].

The theory of Greaves and that of Kinlen have been discussed in one of the chapters in this book. One of the limitations of the theory of Greaves is that it has not been possible to demonstrate it empirically. In his theory, Greaves argues that some cases of the pre-B ALL observed in the peak age of 2 to 5 years could be associated with an aberrant immune response displayed by an immature immune system. The early exposition to common infectious agents are required for the proper maturation of the immune system, lack of these expositions results in aberrant responses when children are finally in contact with the agent When follow-up studies were carried out in order to evaluate whether children who suffered infections during the first months of life had a greater risk of leukemia, it was not possible to demonstrate any such correlation. When kindergarten registries were used as information source, it was also not possible to demonstrate that there was an association with B-cell precursors of ALL, or in a specific manner in which ALL appears between two and five years of

age [9,10]. In addition, data are emerging from epidemiological databases that the idea of early infection being a protective factor for ALL originated due to a bias (non-differential misclassification) [11] and that, in reality, no such association exists. At any rate, determination of whether a child suffered from different infections during the first year of life is extremely difficult; for this reason, the empirical reference will need to be improved in order to lend greater support to this hypothesis.

Nevertheless, the principal importance of the hypothesis of Greaves cannot be questioned, because it does not exclude what epidemiological methods have been able to demonstrate concerning late infection [12]. These data are conclusive in showing that, in the majority of cases, ALL originates during intrauterine life [13] and that proliferation of the B cells, in fact, the time in which the highest peak of proliferation occurs, is during the first year of life [12]. All these findings permit the deduction that ALL requires a first "hit" in the intrauterine stage and another hit during a later stage of life and that some infections may play a very important role in the causality of B-cell precursors of ALL.

2. Exposure

ALL has been associated with different environmental risk factors [14,15]; however, the only environmental factor that is universally accepted as being associated with ALL is exposure to X-rays *in utero*[14]. The identification of environmental factors has had various problems, one of which is the effect of the sample size on statistical power [15-18]. ALL is an infirmity with a very low frequency, which makes it difficult for studies to attain a sample size appropriate for identifying an association with an environmental risk factor [16,17]. Another problem is that most of the environmental factors that are associated with leukemia, such as exposure to X-rays or exposure to very low frequency magnetic fields, have a very low frequency of occurrence [16,19,20]. The study design that has been used the most to search for associations with ALL is the case-control study; this type of study has the limitation that it has low efficiency for identifying associations when the frequency of exposure is very low [16,17]. Another limitation in determining environmental exposure is that the greater part of the instruments used to evaluate such exposures either have not been validated for this purpose or are not sufficiently sensitive to detect the presence of such exposure, as is the case for exposure to infections during the first year of life [11] or for exposure to extremely low frequency magnetic fields [19].

Most experimental designs have the limitation that they cannot evaluate various independent variables at the same time [21]. Multivariate analysis that is used to evaluate the effect of an independent variable, adjusted for the effect of various control variables or potential confounders, implies a modeling with only one or two predictor variables for the disease [21]. ALL is potentially the result of the presence not of one or two independent variables, but of many risk factors that act at the same time to provoke the development of the illness [1]. According to the multicausal theory, illnesses must have at least two risk factors that lead to the development of the illness; the majority of multivariate models, such as logistic regression, do not permit this type of simultaneous evaluations.

One of the limitations in trying to identify the association between environmental factors and the development of ALL is that not taken into account is the idea that, in order for a child to develop leukemia, it is not enough that the child be exposed to leukemiogenic factor, but that it is necessary that the child be susceptible to the infirmity [22-24]. If we start with the premise, postulated by Greaves, that ALL is the result of two hits, one that occurred in the intrauterine stage or in a stage very early in life and another hit that was necessary afterward [25,26], then this would predict that each child that develops ALL must have had a prior susceptibility for developing the infirmity; otherwise, the children that are exposed to the "second hit", given that they do not have the first, will not be able to develop the disease [13,27,28].

Consequently, an error that has been committed in many epidemiological studies is that these studies have been carried out without taking into account the susceptibility of the child for the infirmity [29]. Our group was the first to demonstrate that environmental factors have an important weight in the development of ALL in children with a high susceptibility for the illness, such as those with Down syndrome (DS) [7,29]. By including children with DS, not only as cases but also as controls, it has been possible to improve the precision of the sampling size, because even with relatively small sample sizes, it was possible to identify a number of important environmental factors associated with ALL [7,30].

3. Susceptibility

Susceptibility to ALL has been studied from two perspectives: one that deals with genes or syndromes that increase the risk of developing ALL; the other, with the genes or alterations that increase the effect of the environmental exposure for a child to develop ALL.

There are genetic rearrangements, such as MLL/AF4, the involvement of which in the development of ALL in children is indisputable [13]. In fact, Greaves postulated that the MLL/AF4 is a necessary and sufficient cause for the development of ALL in children, especially in infants [13,26]. However, some researchers have demonstrated that this rearrangement may appear with an important frequency in older children and that even the twin of the children that develop ALL could lose the MLL/AF4 rearrangement in later years of life [31,32]. In a chapter of this book, it is shown how exposure during pregnancy to inhibitors of topoisomerase II is a risk factor for the offspring of the pregnancy to develop ALL with the presence of genetic rearrangements MLL. There are no studies that demonstrate that children that are born with genetic rearrangements in MLL, upon exposure to determined environmental factors, have a greater risk of developing ALL. Such studies are difficult to perform, because the frequency of genetic rearrangements in MLL in children without ALL is estimated to be less that 1 in 10000 live births [13].

Among the syndromes that predispose to ALL are SD, ataxia, telangiectasia, and Fanconi anemia [24]. Although these children present an elevated risk for developing ALL, not all develop the disease [33]. It is possible that these children would have to be exposed to

some environmental factor in order to develop ALL, as has been demonstrated for children with SD [4,15,29,33,34].

There also exists susceptibility determined by polymorphisms that increase the effect of luekemiogenic factors, through which children develop ALL. Examples are those related to the polymorphisms of methyl-n-transferase and cytochrome p-450. Some polymorphisms of these genes have been associated to a greater toxic effect for benzene and other factors that are potentially leukemiogenic [35-39].

Some nutritional alterations also have been seen to increase the effect of some potentially leukemiogenic factors, a possible examples is reduction in the consumption of vitamin A, as it is known that vitamin A reduces the effect of exposure to carcinogens in tobacco smoke [40]. Tobacco smoke contains substances, such as benzene, which are known to have a leukemiogenic effect [41,42].

4. Vulnerable period

The frequency of ALL has a characteristic peak at 2–5 years of age [23,24]. In the Mexican population, there appears another age peak at 6–9 years of age [43]. This peak primarily results from B-cell precursor ALL and that has the genetic rearrangement ETV6/RUNX1 [13,23].

In an attempt to explain the cause of this peak, a series of hypotheses have been generated [23], among which that proposed by Greaves stands out. Greaves commented that this age peak reflects the start of a greater immunological response and, in particular, it is in direct relation to the capacity to produce immunoglobulins [12]. Greaves assumes that, after the first year of life, the possibility is increased that a previously mutated cell may undergo a second mutation and this brings with it the development of ALL [12].

In the case of ALL, it has been established that, for children who are born with a greater susceptibility to ALL, such as those children born with the genetic rearrangement that involves MLL, the age at onset of ALL is earlier, generally during the first year of life. It is estimated that those children have a 100% probability of developing ALL [13]. In contrast, children who are born with the genetic rearrangement ETV6/RUNX1 have a 25% probability of developing ALL and their peak age at onset (2–5 years of age) is later than that for the children born with the genetic rearrangement that involves MLL [13]. This leads one to think that the peak age of onset of ALL reflects the degree of susceptibility with which a child is born and, on the other hand, the degree of proliferation of the cells involved in the development of the disease [1,43]. A similar situation exists for retinoblastoma, in which the age at onset of ALL reflects the degree of proliferation of the cells in the retina and for osteosarcoma which appears earlier in females than in males, starting at the growth spurt in adolescence [1,28,44].

Another aspect that, despite its great importance in epidemiological research, is on occasions overlooked is the stage of life at which the exposure to a carcinogenic agent occurs. Greaves has pointed out the importance of the infection occurring at a particular period, 2–3

years of age [25], for development of ALL. Exposure of a child to radiation (x ray for example) in the earlier stages of life has been associated with a greater risk of ALL [45] and, in addition, the leukemia has a shorter latency period. Hertz-Picciotto et al. underscored the importance of evaluating the time of life or stage of development of the tissues at which the exposure occurs [46], because for two individuals who may have been exposed to the same factor, the effect of said exposure will vary according to the stage of development of the individual or of the particular organ [47-52]. Some of the factors that can influence the toxicity of a substance in an organism may vary according to the individual's age. Such is the case for the absorption, metabolism, detoxification, and excretion of xenobiotic compounds. Similarly, for children, there can exist an immaturity in the biochemical and physiological functions of the majority of the systems of the body, as well as variation in the bodily composition (content of water, fat, protein, and minerals) [48,52-54]. These factors may make the neonate, for example, very sensitive to chemical substances [52,53,55].

Considering the importance of the time at which the exposure occurs separately from the stage of development of the organism that may be affected, it is important to evaluate whether the exposure occurred in the prenatal stage, during the pregnancy, or in the postnatal period [28,50]. For example, exposures that affect a maternal ovum may have occurred peri-conceptionally or even a long time before conception, given that the ova are present, already formed, in the woman [47]. Among the exposures that affect the sperm or the substances that can concentrate in the semen, said exposures can only cause damage peri-conceptionally, because sperm and seminal fluid involved in the fertilization were formed hours, or a few days, prior to the conception [47]. It has also been observed that some substances that are stored in the fat or in the bones of the mother may be removed during the pregnancy and cause injury to the fetus [47]. Some significant exposure during pregnancy may be more related to the presence of the rearrangement MLL/AF4 [13,56], because the cases of leukemia that occur in infants generally belong to this type of leukemia, whereas exposures that occur at 2–4 years of age may be more related to the B-cell precursor ALL with ETV6/RUNX1, because this is the peak age of onset for this disease [13,43,57].

Infections may have another action: an increase in the proliferation of B cells may increase the risk that the cells being exposed to leukemiogenic agent would lead to ALL [7,12].

On the other hand, it is not only necessary that the cells have proliferated, but also it is necessary that, in that moment, there be a niche in the bone marrow which would permit the growth and the expansion of that leukemia clone [28]. In a book in the series In Tech, Pelayo has described the function of the microenvironment of the bone marrow in the development of ALL [58,59]. Today, it is known that the alterations not only must occur in the cancerous cells, what confers upon them the capacity for mutations and genomic instability, that changes the cycles of cell regulation and energy consumption, evades or destroys the immune system and generates mechanisms of inflammation that lead to tumor propagation [60]. In addition to all this, cancerous cells are capable of causing changes in their microenvironment to generate an environment in which a cancerous cell can form a "nest", a microenvironment that generates tumor invasion, and a microenvironment that favors the

development of metastasis [58-61]. Such changes in the cells make them even more vulnerable to exposure to carcinogenic substances [62-64].

5. Down syndrome model: Advantage of a design with cases and controls selected for susceptibility

Robinson was one of the first to propose that if a child with DS is studied, identification of the effect of the major portion of environmental factors in the development of ALL in children could be achieved [33]. Children with DS have a higher risk for developing leukemias, not only myeloid leukemias, but also lymphoblastic leukemias. In the lymphoblastic leukemias, the participation of the genes, *JAK 1* and *JAK2*, have a definite affect in these children developing the disease [65].

The study of children with a high susceptibility to ALL has permitted, even with a smaller sample size, the identification of the role that some environmental factors play in the development of ALL. The risks (odds ratios) encountered when comparing the population of children with ALL with DS and a population of healthy children with DS have been relatively higher than those reported when comparing healthy children without high susceptibility to the disease as controls. We have called this approach "studies of cases and controls selected by susceptibility". The advantages that we have reported about this design is that it improves the sampling power and the precision of the estimators [66].

6. Theory as a model of prediction

Theories are considered as a tool or instrument that can be used to predict [67].

The epidemiological theory that attempts to predict the origin of diseases in human populations is the Sufficient-Component Cause model [68]. This theory underscores the idea that diseases are multicausal and that it is necessary that at least two component causes must be present or have occurred for an individual to develop said disease. Upon completing the component causes of the disease, then a sufficient cause has been completed and, in such case, the person will develop the disease [68].

The criteria of demarcation to determine if a hypothesis is scientific or not are that the refutationism proposes that the hypothesis be deducible, that there exists a way to test the hypothesis empirically, and that the hypothesis be be falsifiable [67,68].

With respect to the multicausal theory and the Sufficient-Component Causes model, the empirical referent that the sufficient cause has been completed is only the disease itself; its origin is deducible because this theory assumes that all illnesses arises from the action of at least two component causes. However, there is no manner in which this hypothesis can be falsified, because whatever model proposed to show that the sufficient cause has been completed at the time of the attempt at falsification and consequently to demostrate that with

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the “sufficent cause completed“ the diseases was not developed. An argument that could emerge is that, as the sufficient cause was not reality completed, it is for this reason that the individual did not develop the disease. At this point, we are left without possibilities of demonstrating that said hypothesis may be falsifiable. In one sense, the illness itself is the sufficient cause and therefore stops being two separate variables and no longer fulfills its function of prediction, given that one cannot say that an individual completed the sufficient cause and consequently goes on to develop the disease; we know that the sufficient cause has been completed only when the individual becomes ill.

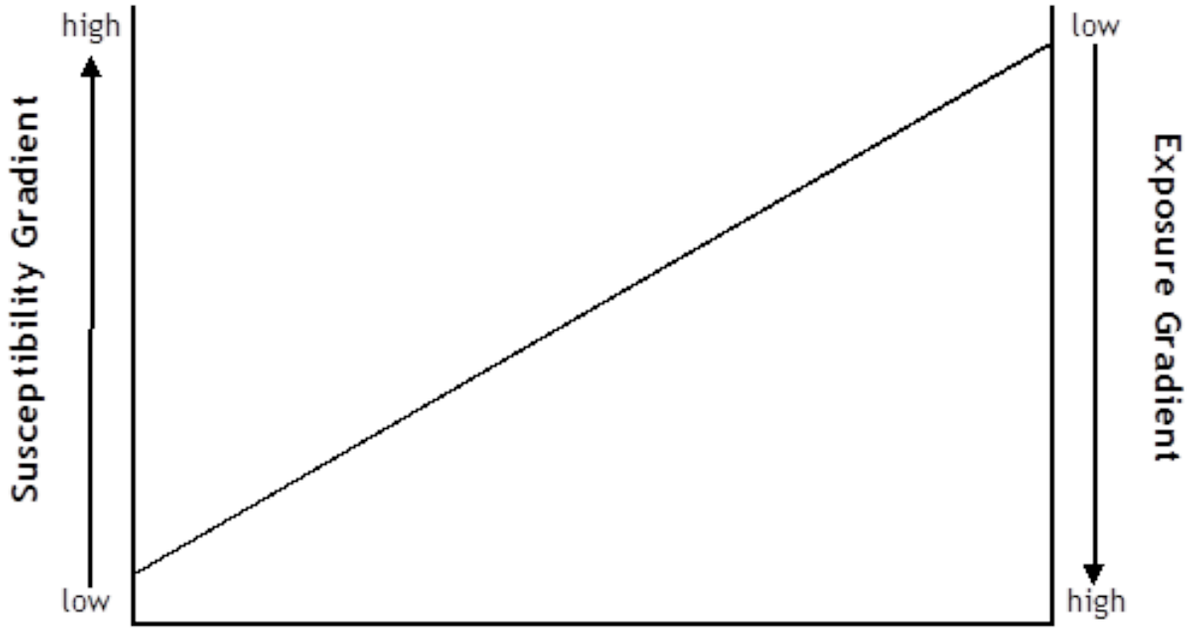

Figure 1. Interaction between a gradient of susceptibility to a disease and a gradient of exposure to environmental risk factors. To develop ALL, an individual with a higher susceptibility, as determined by the interplay of genetic factors, would need only a lower exposure, as determined by the unknown, possibly synergistic, interplay of the characteristics of the exposure. Conversely, the higher the exposure, the lower the susceptibility that would be needed to result in development of the disease.

The hypothesis that is set forth here is bounded by three phenomena, the "exposure", the "susceptibility", and the "vulnerable period" (Fig. 2). This model includes only these three component causes that are necessary for a child to develop the illness. As was described in the initial part of this chapter, these three phenomena are interrelated and there exists a gradient which indicates that, when there is an excess of one of these components, less is needed of the other two components in order to develop the illness (Fig. 1).

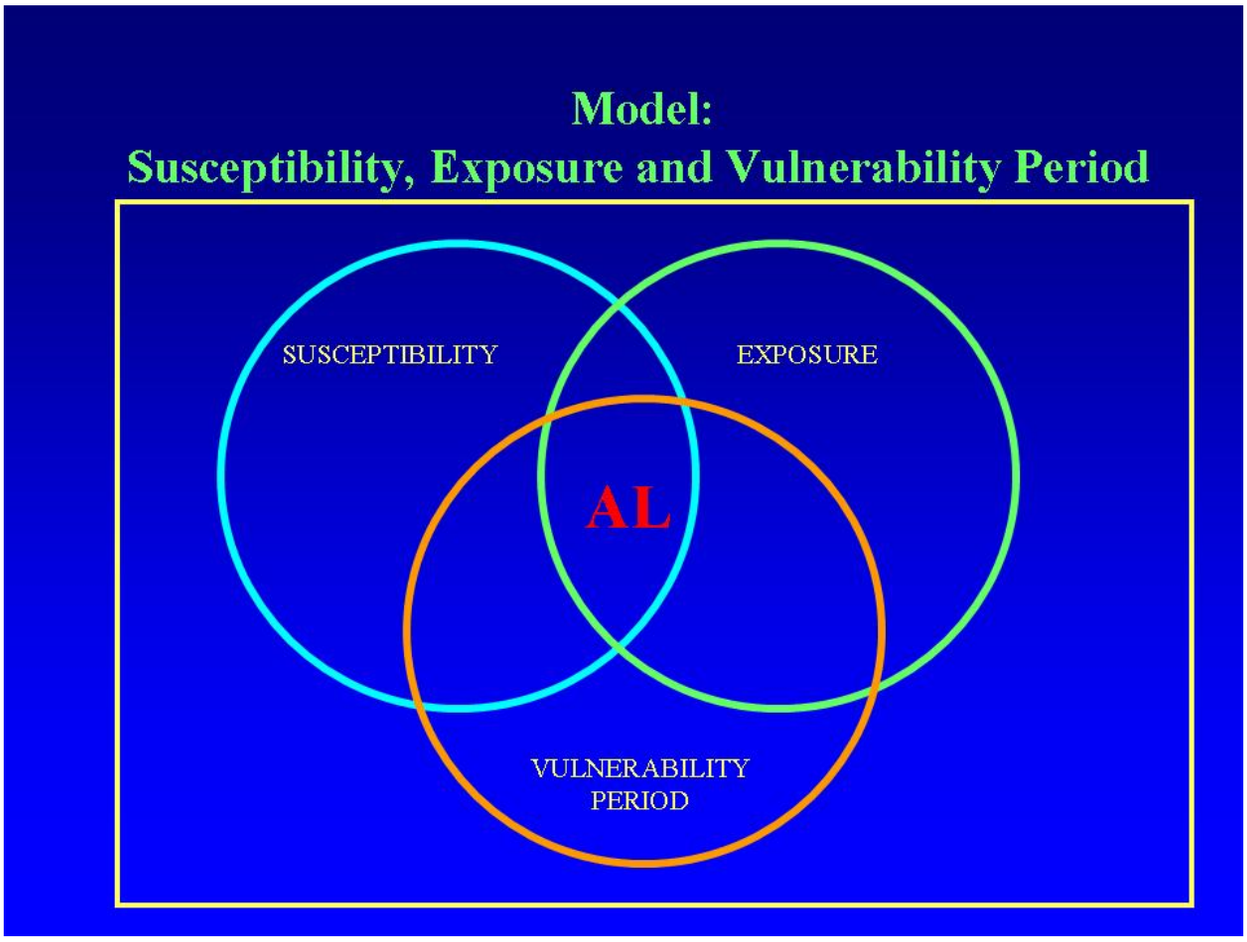

Figure 2. Interaction among the three phenomena. Acute lymphoblastic leukemia (AL) in childhood is the result of the interactions among three phenomena: the gradient of susceptibility, the gradient of exposure to carcinogenic environmental factors, and the tissue vulnerability period.

7. Conclusions

Current models to identify the environmental causes of ALL have limitations that could lead to years of studies and the investment enormous sums of money, yet still continue without successfully determining the factors associated with ALL.

This proposed model of susceptibility, exposure, and vulnerable period permits boundaries to be drawn around the factors that could potentially influence the development of the disease and, in addition, permits the development of new methods for the study of the environmental causes of ALL in children, such as the study of cases and controls selected by susceptibility.

Children that are born with a high susceptibility to ALL, such as children with SD, should be the first among those that should be protected from exposure to environmental factors that potentially provoke ALL, such as tobacco smoke [29], exposure to magnetic fields of ex-

tremely low frequency [69], etc. The approach of the precautionary principle should be followed, in that although the causal evidence is not absolute, the risk or the effect of the illness is so serious that putting oneself in contact the risk factor should be avoided [66,70]. Similarly, for children of parents who underwent elevated exposure to leukemiogenic factors during the pregnancy, it may happen that, although these children may have been born "normal", it is possible that they had been born with a high susceptibility to the ALL, which is not possible to identify simply by observation.

Susceptibility to ALL is a constitutive condition or one that is acquired in an early stage of life. Exposure to a leukemiogenic agent will have an affect to the extent of the intensity of the exposure and the degree of susceptibility to the disease or the intrinsic factors that modify the form in which the child's bodily tissues respond to this exposure. However, this must occur at a specific moment when a cell is proliferating and where the conditions around the cell are appropriate for the cell to be converted into a leukemic clone and finally develops the disease.

As the absolute truth described in the Bible says, "There is a time for everything…" [71]

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