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Some Observations Concerning Leukemia in Twins

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INTRODUCTION

The first report of leukemia occurring in both members of a twin pair was by Seigel in 1928. Since this time many more case reports and epidemiologic studies have appeared in the literature. In recent years, however, published reports on leukemia in twins have been less common. This waning interest is certainly not due to overstudy, since even the most basic questions concerning the occurrence of leukemia in twins have yet to be definitively answered. Apparently, research on this subject is at an impasse due to the difficulty of obtaining study populations and the lack of substantial experimental data in the records of the few twin registries in existence. This report represents an update on the observations and comments on this subject begun in 1970 by Keith and Brown [4].

CONCORDANCE IN TWINS

Concordance for leukemia among both members of a twin pair has been recorded by many authors [1–5]. Both members of a monozygous (MZ) twin pair are more likely to suffer from hematologic malignancy than a dizygotic (DZ) twin pair. Dizygous twins likewise have a higher rate of concordance for leukemia than do siblings or a pair of individuals otherwise related [4, 6–9]. Over the years the reported estimates of concordance for acute lymphocytic leukemia (ALL) in MZ twins have been remarkably consistent and range from 17% to 25% [2, 9–12].

The most striking relationship between ALL and concordance in MZ twins is seen when twin pairs are analyzed according to age group. Concordance for leukemia shows an inverse correlation with the age of onset of disease. Infant twin pairs less than two years of age have a concordancy of nearly 100% [4, 5, 13, 14]. The observed degree of

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concordancy then decays with time, although adult MZ twins still seem to retain an increased tendency to concordance over that which would occur by chance.

Leukemia appears to be the only malignancy with such a pronounced tendency toward concordance among twins. The majority of reported concordant leukemia cases have been due to ALL. This is not surprising since ALL is the most common leukemia of childhood—the period of greatest concordancy. It remains to be determined more precisely what is the extent of concordancy of the other forms of leukemia.

While the literature depicts a clearly significant relationship between leukemia and concordancy in MZ twins, and to a lesser extent in DZ twins, there are several caveats to the interpretation of these data. The incidence of leukemia in twins apparently is no greater than that of the general population; therefore, truly prodigious numbers of twin pairs must be studied before definite conclusions can be drawn as to exact rates of concordance for various hematologic malignancies in MZ vs DZ twins. Ideally, large-scale prospective studies would be required to answer these questions. Such studies in theory might be accomplished with a national twin registry; as yet, however, no such investigations exist. The existing retrospective studies tend to be flawed due to biased problems with the determination of zygosity in twin pairs, and inadequate population sizes for appropriate statistical analysis.

THEORETICAL CONSIDERATIONS

Hypotheses attempting to account for observed concordance focus on the identical genetic makeup of twins and their similar intrauterine and perinatal environment. If genetics alone were to dictate the appearance of leukemia, one would expect overall concordance to be 100% in MZ twins. The fact that this is not so indicates that whatever genetic influences are involved cannot be supremely operative; a modulating environmental effect must also act [5, 9, 12, 15].

It is sometimes noted that MZ twins who are concordant for leukemia have chromosomal abnormalities which could have been inherited [16–19]. For the most part, however, childhood leukemia in twins does not seem to be due to shared chromosomal defects, even though a predisposition to ALL is noted in some trisomic or other genetic syndromes [8, 11].

It has been suggested that the very strong relationship between concordant leukemia in MZ twins in infancy and childhood may reflect a single intrauterine neoplastic event shared between the twins [20]. By virtue of cojoined placental circulation, leukemic cells could be transfused freely between members of a twin pair. Since DZ twins occasionally have cojoined placental circulations, this mechanism could operate independent of zygosity. At present, this hypothesis is the one most favored in the literature. Unfortunately, as yet, no study has provided concrete evidence supporting the existence of this phenomenon.

Another possible explanation for concordance rests upon the increased in utero radiation exposure accruing to twin pairs as a result of diagnostic radiologic procedures [15]. No minimal threshold level of in utero radiation exposure for leukemogenesis has ever been proven. It is possible, nonetheless, that one or more roentgenograms of the maternal abdomen can provide sufficient radiant energy for a detectable increased risk of leukemia to the progeny, especially if the exposure is during the first trimester [21]. To date, no studies have seriously addressed this issue in relation to twin concordance. Although the potential teratogenic and carcinogenic effects of in utero radiation exposure have received considerable attention since the early work of Alice Stewart in 1956 [39], existing data

are inconclusive and contradictory. It remains to be seen whether in utero radiation exposure has anything to do with leukemia concordancy in twins.

Since the observation that maternal leukocytes can breach the placental barrier and gain access to the fetal circulation [22], it has been apparent that the direct metastasis of malignant cells from mother to fetus is possible. Although occurrences of this phenomenon have been reported [15], nonetheless the incidence must be extremely rare in view of the paucity of observations over the years. It is unlikely that this mechanism accounts for many cases of twin concordance.

The delicate interplay between genetics and environment in the genesis of leukemia has been highlighted by recent evidence that all nonlymphocytic and chronic leukemias may involve chromosomal abnormalities [23]. It is suspected that these chromosomal defects represent acquired genetic events, a concept which is supported by a lack of strong concordance in MZ twins for these malignancies. MZ twins discordant for leukemia most certainly represent a differential environmental effect on identical genomes. MZ twins, discordant for leukemia with identifiable antigenic and genetic differences, presumably reflect acquired genetic changes associated with leukemia. Leukocyte DNA sequences similar to the RNA tumor viruses have been found in the leukemic twin in several MZ twin pairs discordant for leukemia [24–26]. This finding supports the hypothesis of a viral etiology of ALL with postnatal infection, and tends to discount the theory of congenital transmission of tumorogenic viral genome sequences in the germ line. Several investigators have attempted to demonstrate antigenic heterogeneity between the leukocytes of healthy and leukemic twins through lymphocyte cytotoxicity reactions [27–31]. In general, results have indicated that the leukocyte of patients with leukemia have non-HLA antigenics which can stimulate the lymphocytes of their healthy identical twins and HLA-compatible family members. These observations also support the concept that discordance in MZ twins for leukemia indicates the postnatal aquisition of leukemogenic influences.

THERAPEUTIC CONSIDERATIONS

Therapeutic management of individual members of a twin pair with leukemia has changed considerably in the past three decades not only because of general progress in medicine but also as a specific result of the twin state. Since the 1950s, attempts have been made to transfer bone marrow grafts from healthy twins to identical twins afflicted with hematologic malignancy who already had undergone intensive chemotherapy and/or irradiation [32–35]. The early reports of this operation were disappointing and usually were followed by tumor recurrence and death of the patient. Some of these poor outcomes may have been due to the fact that only end-stage patients were selected for this then experimental therapy. In spite of these initially poor results, some twins obtained lasting remissions. Long-term effects were mild, the procedure was well tolerated, and therapeutic attempts continued. With our present state-of-the art technology, results are so positive that bone marrow grafting between MZ twins discordant for leukemia is now recommended early in the course of therapy [36–38].

SUMMARY

In summary, the phenomenon of concordant leukemia in twins remains a fascinating area of interest to the clinician. In spite of the active research on this subject in the past, unanswered questions of major medical significance remain: (1) the reason for high

childhood concordance rates for ALL is unknown; (2) the degree of concordance for nonlymphocytic leukemias is obscure; and (3) the exact incidences of concordance and risks to co-twins need to be clarified.

Studies of twins with leukemia will continue to be important in the elucidation of the specific roles played by genetics and the environment in the inception of leukemia. Undoubtedbly, continued study of this phenomenon will make more contributions to our knowledge and our ability to treat this disease.

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