Risk of leukemia in twins

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Nickels, Zhou and Wiemels provide a brief but provocative report on acute leukaemia in twin children and young adults in this issue of *Haematologica*.[1] Provocative because of three unexpected observations: (i) first-born twins were more at risk of leukemia than second-born ones; (ii) the methylation profiles of neonatal blood spot mononuclear cell DNA of first- and second-born twins were different; and (iii) there was a very low rate of leukemia concordance in twins. Space does not permit a discussion of all of these points so this Editorial focuses on the reported low concordance rate. This conflicts with a body of prior data and has practical consequences.

Concordance of clinical acute leukemia in twin children, i.e. both twin siblings having leukemia, has been recorded since 1882.[2] A review in 2003 reported 74 cases in children aged between 1 and 14 years old, most, but not all, with acute lymphoblastic leukemia (ALL).[2] Most pairs were diagnosed within 12 months of each other but occasionally the second twin was diagnosed years (3 to 9) later.[2] Twin concordance of leukemia after the age of 10 is extremely rare. Concordant cases are all in identical or monozygotic twins and almost invariably (when recorded) in identical twins who shared a single or monochorionic placenta *in utero*. Depending when the single fertilized egg splits, twins can be monochorionic (~60%) or dichorionic (~40%) with two independent placentas.[2]

The explanation for twin concordance of leukemia in identical twin children is not, as might be first assumed, attributable to a shared or inherited susceptibility. The biological mechanism involved was first suggested by Wolman in 1962 and then by Clarkson and Boyse in 1971 (reviewed by Greaves *et al.*[2]) and is based on the recognized blood cell chimerism in identical, monochorionic twins. This was the idea that leukemia might originate prenatally in one twin with subsequent transfer of cells (a quasi-metastasis) to the other twin via intra-placental vascular anastomoses before birth.

Validation of this interpretation required demonstration that leukemic cells in twins with concordant leukemia are monoclonal or have a single cell origin i.e., in one twin. This was provided by systematic studies on sets of twins with concordant ALL who were shown to share identical (but not inherited), clonotypic DNA sequences for genomic fusion genes – *KMT2A:AF4* (in infants), *ETV6:RUNX1* and *BCR:ABL1* (reviewed by Greaves[3]) or IgH (mostly the DJ region).[4] This result would only be possible if ALL was frequently initiated *in utero* and if the clonal markers used were common, early or leukemia-initiating, acquired, genetic lesions. All cases were monochorionic, a requisite for intra-placental cell transfer except for rare cases of double but fused placentas.

The underlying biology of leukemia in identical twin children is therefore unambiguous and accords with other, direct evidence of an *in utero* origin in most, but probably not all, cases of ALL in non-twin young patients.[3] What is arguably less clear is the actual rate of concordance. Or, to put it another way: if a child is diagnosed with leukemia what is the risk of a similar leukemia in any identical twin sibling? This question is asked of consultant physicians by parents of twin children of whom one has a diagnosis of leukemia. And, anecdotally at least, we know they have in the past been given widely divergent answers of a risk between one in a million and 100%.

A historical concordance rate, or risk, of between 5-25% was reported in a 2003 review.[2] These rates did not take into account placental status so will have under-estimated rates in the ~60% of monozygotic twins who are monochorionic. These calculated risks were not based on data from cohorts of twins,[1] but rather on several different regional or national databases (listed in table 1 of the article by Greaves *et al.*[2]), providing some confidence that, although not very accurate, the range of numbers was likely to be in the right ball park. By comparison, the risk to a dizygotic twin or non-twin sibling of a case of ALL is round 3 times elevated over the background risk of any child of ~1 in 2,000.[5]

In both the original observations of Clarkson and Boyse and later studies it was evident that the concordance rate was significantly higher in infants with ALL (maybe close to 100%) than in older children. So much so that Clarkson and Boyse suggested that infant ALL was initiated *in*

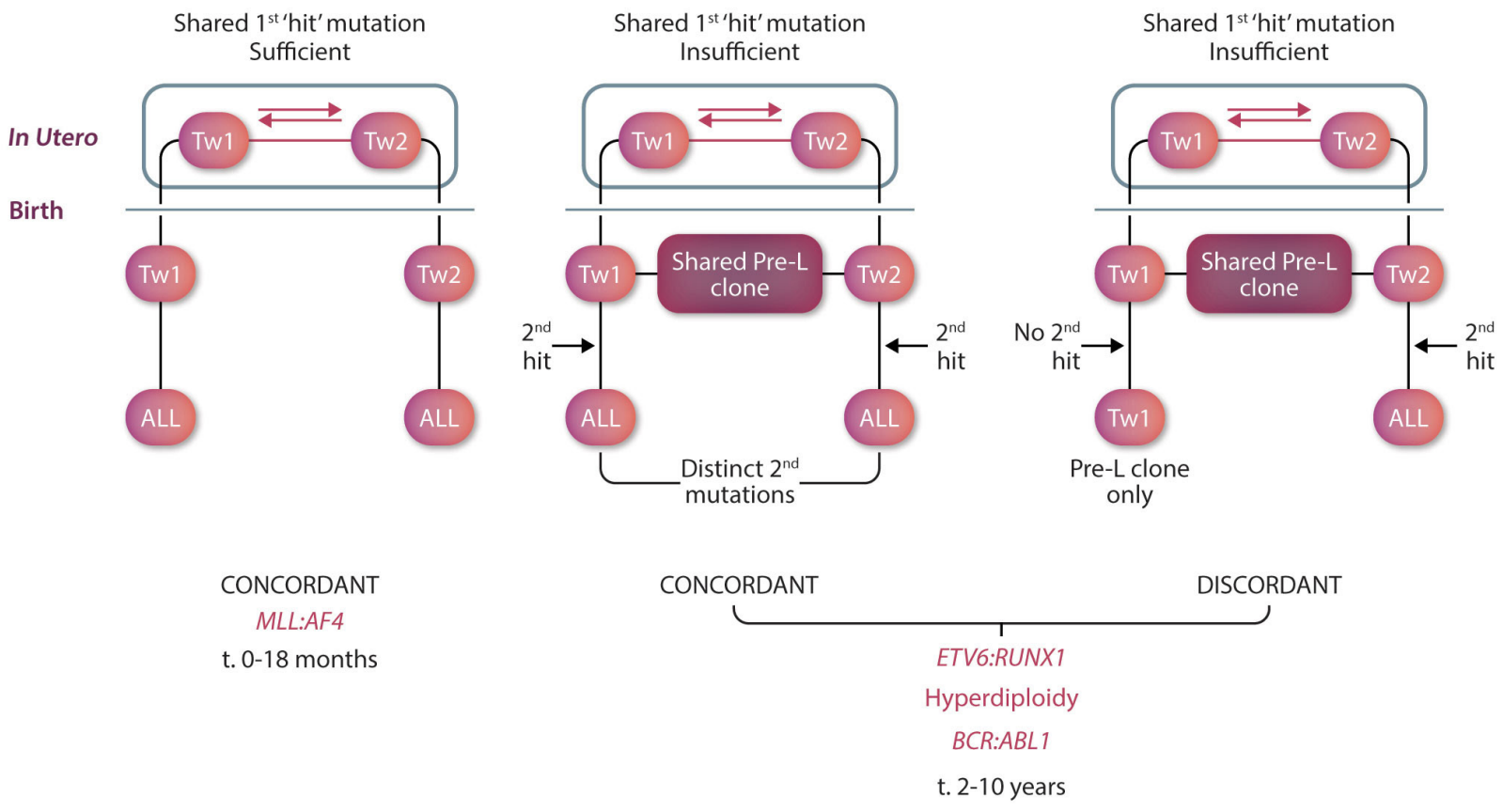

Figure 1. Concordance and discordance of acute lymphoblastic leukemia in monozygotic, monochorionic twins. The graphic illustrates three different outcomes when acute lymphoblastic leukemia is initiated *in utero* in a twin pair dependent upon the particular initiating or founder mutation and the presence or absence of secondary mutations, postnatally, based on previously published data.[2,3] Red lines *in utero* between one twin (Tw1) and the other (Tw2) represent interconnecting vasculature and exchange of blood. ALL: acute lymphoblastic leukemia; t: time; Pre-L: pre-leukemic clone.

utero but that ALL in older children was post-natal in origin.[6] This interpretation failed to recognize the multistep (pre-post-natal) nature of ALL.[3] Figure 1 illustrates the likely sequence and number of essential genetic events in identical, monochorionic twins leading to concordant or discordant leukemia. This model has the premise that *KMT2A* fusions are likely sufficient, as a single hit, to cause leukemia[7] in contrast to the common genetic abnormalities in childhood ALL – hyperdiploidy and *ETV6:RUNX1* – which require co-operating genetic post-natal events.[3] This view is endorsed by the genomics of ALL subtypes[8] and the finding that healthy co-twins of patients with ALL have low levels of clinically silent but putative pre-leukemic cells in their blood.[9] Most (75-95%) identical twin children of whom one has a diagnosis of ALL will therefore be discordant for the secondary events but not the first. This is unsurprising given that around 99% of newborn children carrying pre-leukemic clones with *ETV6:RUNX1* do not develop ALL, indicating a relatively severe bottleneck in transition to overt ALL.[3]

There is currently no accepted or standardized recommendation for clinicians treating pairs of twins of whom one has been diagnosed with leukemia. However, our advice to clinicians treating such rare cases (less than 1% of childhood leukemias overall) and advising parents has been to consider the risk to the second twin as very high and meriting investigation, for at least 1 year, using appropriate molecular markers for pre-leukemic cells in blood. This would not be necessary if the obstetric records (or parental recall) indicated the twins were dichorionic and, therefore, not at an elevated risk over that of other siblings.

In contrast to these data, Nickels *et al*. recorded a much lower concordance rate.[1] Their cohort included a total of 255 cases of leukemia in twins between 0 and 39 years of age based on merging data from a California birth registry with the Californian Cancer Registry between 1988 and 2022. There was no identification of monozygosity or placental status. One half of twins born on the same day were assumed to be identical and of these, some 60% would be monochorionic. Nickels and colleagues took these considerations into account when calculating their risk estimates. No genetic data of cases in the registry were available or reported.

There were only nine pairs of twin infants (<1 year) of whom at least one had either ALL (6 pairs) or acute myeloid leukemia (AML) (3 pairs). This translates to approximately four pairs that were likely identical and monochorionic. One concordant pair was found and these twins had a diagnosis of AML suggesting a concordance rate of around 25% overall for monozygotic, monochorionic twins. This does indicate a high concordance rate but significantly less than 100%. This lower than anticipated value could be in part a reflection of the very small sample size and/or the fact that not all infant acute leukemias involve single-hit *KMT2A* fusions.

The other relevant calculation was the risk or rate of leuke-

mia in twins aged 1 to 10 years old. Nickels *et al*. reported 148 cases of ALL in a twin in this age range, which might translate into around 60 cases that were both monozygotic and monochorionic. Based on the prior estimates we would then expect between three and 15 concordant case pairs. However, only one pair was identified and this pair had different blood cell cancers (one labeled 'B' ALL, the other Burkitt cell leukemia). Therefore, according to the data accessed by Nickels *et al*., there was not a single concordant case pair with pro-B infant ALL or common variant (B cell precursor) childhood ALL in California between 1988 and 2022.

Nickels *et al*. calculated an overall (ALL plus AML) concordance rate of childhood acute leukemia (1 to 10 years of age) of 2.1% for monozygotic twins. This might then equate to ~4% for monochorionic cases but still significantly less than the 5-25% previously calculated based on monozygosity alone.

England and Wales have a similar population size and annual incidence rate of childhood leukemia as those of California. Over a 30-year period (1993-2023), data and biological samples from a total of 12 concordant twin pairs, two pairs of infants and ten pairs of children aged 1-10 years, in England and Wales were referred to our research Institute in London. This is approximately 10 times the concordance rate found by Nickels *et al*.[1]

The possible basis for this marked discrepancy is not apparent but could, in principle, relate to case ascertainment or biological differences between UK and Californian (largely Hispanic) ALL or twinning. This is an important issue to resolve, perhaps via other large cancer registries in Scandinavia and elsewhere. In the meantime it would be prudent to err on the side of caution and continue to advise parents on a likely, relatively high risk to any healthy (monozygotic, monochorionic) co-twin and the value of monitoring for levels of pre-leukemic cells which could provide reassurance (in most cases) or an opportunity for early intervention that could be beneficial.[10]

Disclosures

No conflicts of interest to disclose.

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