Birth Order in Malignant Hematological Disorders: A Challenge

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Commentary

A birth order effect (BOE) is a non-random occurrence of affected siblings in a sibship. Thus, in case of BOE the affected child has a specific and significant birth rank order by age, for example first child, early in the sibship, in the middle or late [1].

Occurrence

Birth order was originally discovered in families with congenic malformations. Sewall Wright was one of the pioneers within this field around the time nineteen twenties. He was well aware of the fact that BOE is not in accordance with a traditional Mendelian segregation. He also described a relationship between parents age and BOE, in polydactyl for example with a maternal age effect, and outlined the empiric risk for genetic counselling based on the general assumption that the presence of the mutation, sporadic versus inherited, which causes the malformation, could be related to parents age [1]. It is obvious that the study of BOE in a genetic disorder with unknown mode of transgenerational passage may contribute to the pathophysiological understanding, simply addressing the question “What is the genetic segregation in this inherited disease?” The malignant hematological disorders (MHD), both the lymphoproliferative disorders (LPD) and myeloproliferative disorders (MPD) are evidently genetic disorders in the sense that the susceptibility to disease is inherited. Thus, genome-wide-screenings have provided substantial evidence for the presence of susceptibility risk genes in a number of the diagnoses within MHD, especially in chronic lymphocytic leukemia, CLL [2-8], acute lymphoblastic leukemia (ALL) [9,10], monoclonal gammapathy of uncertain significance, MGUS [11,12] and in multiple myeloma [13,14]. Such diseases cannot develop unless inherited susceptibility is present in the genome. Whether persons with inborn susceptibility to MHD will develop disease or, alternatively, remain silent carriers is far from fully understood and a delicate matter for further investigation. Epigenetic and exogenous stimuli such as lymphotrophic infections seem to be factors of possible relevance [15-17]. The susceptibility genes represent the etiology to each of the diagnoses in MHD which pave the way for first step in the pathogenesis, namely a specific mutation to each of the diagnoses in either the lymphoproliferative- or the myeloproliferative differential pathway, where all diagnoses have a common characteristic: A mutated monoclone, expanding with autonomic proliferation outside the growth regulation otherwise seen in the production of normal blood cell.

Segregation and Birth Order Effect

Susceptibility to several diagnoses within MHD can be present in the same family. This so called pleiotropic pattern is clearly seen in genealogical investigations of pedigrees to affected families without convincing signs of a Mendelian pattern in the transgenerational segregation of the susceptibility genes [18,19]. Pseudo-dominant segregation, when the inheritance of recessive genes mimics a dominant Mendelian pattern, has been discussed [20], but not definitely confirmed so far. Genealogical investigations of family trees from affected Scandinavian families, especially CLL [18,19] confirm that the predominant element in the segregation of CLL is a parent – offspring pair, in which both the parent and the offspring is affected, and that the pattern of segregation is supposed to be due to mono-allelic genes influenced by epigenetic stimuli in such a way that no Mendelian mode is detectable [21]. A possible BOE in the transgenerational transfer of MHD-susceptibility has been hotly debated with a remarkable inconsistency in published findings. In CLL, genealogical studies showed BOE while other studies based on large-scaled screenings of cohort-data from cancer registries did not (for review see 18,19). In ALL, two recent large-scaled screenings, each with a very high sample size, detected BOE [22,23] while no BOE could be seen from screening of a Danish material [24]. BOE was not seen in AML [25] and not in Hodgkin’s lymphoma [26]. Furthermore, a relationship between BOE and effect of treatment has been described, having siblings and increasing
birth order were associated with reduced survival in ALL and AML [27]. BOE is undoubtedly weak and varyingly expressed in the different diagnoses within the entity of MHD. If BOE is a result of epigenetic mechanism it must be assumed that the BOE is different from population to population, and thus different in the cohorts studied because the epigenetic stimuli, including stimuli from lymphotrophic infections, vary over time and place. It makes no sense to search for BOE unless the genealogy is completely safe and each family tree included is adjusted for miscarriages, stillbirths and extramarital children. This indeed, is a great technical and practical challenge that actually requires the family and ethical committee’s permission to inquire about other family members, to verify the diagnoses in the national cancer registry, and to talk about healthy family members, alive or dead. The necessary confidential genealogical information obtained by face-to-face interview with a patient presupposes that the doctor and the patient know each other well and that all information will remain anonymous and unrecognizable. In addition, the number of cases of MHD detected will always be lower than the real number, particularly with regard to low-gra d malignant disorders with few or no symptoms, for example overlooked stage A CLL and MGUS. Furthermore, family members with susceptibility but without disease will escape undetected throughout the investigation of pedigrees. Finally, it is a weakness about birth order estimation that the cohorts for study will always contain living persons who theoretically later in life may develop disease and therefore should have been included. There is a great risk of overlooking BOE and thereby detecting false negative BOE as typical Type 2 error. This risk increases when examined for BOE in today’s families with a small number of children compared to families of yesteryear.

**Pathogenesis**

In CLL, but not in the other malignant lymphoproliferative disorder, a patrilineal but no matrilineal birth order effect has been observed among male siblings in Scandinavian families [18, 19]. Is this position of male CLL patients late in the sibship in patrilineal inheritance (Table 1) explained by acquired tolerance in the mother. In this scenario, the physiological pregnancy related microchimerism between mother and fetus is caused by a two-way traffic of lympho- and monocytes between mother and fetus across the utero-placental barrier [28-32]. Thus, the mother may accumulate increased tolerance to the non-self from the paternal half of the fetus with increased number of pregnancies, births, abortions and stillborn children, and with an increased number of male partners so that eventually, the mother will be able to tolerate and to accept the paternal CLL susceptibility and the paternal susceptibility to pleiotropic diagnoses within MHD in spite of an underlying mechanism based on maternal imprinting. We now have proof that the CLL susceptibility can be accumulated. In some few of our pedigrees where both parents have CLL we see a very high occurrence of CLL among their children and we interpret this as an additive effect [19]. It is a different situation than the accumulated maternal susceptibility because of tolerance but it shows that susceptibility potentially can accumulate. Male predominance is well known in CLL and may be explained by this combination of accumulated maternal tolerance and maternal imprinting together with the presence of an allele-specific, epigenetic modifier, such as a silencer in which DNA methylation and imprinting together with the presence of an allele-specific, epigenetic combination of accumulated maternal tolerance and maternal predominance is well known in CLL and may be explained by this than the accumulated maternal susceptibility because of tolerance we interpret this as an additive effect [19]. It is a different situation in CLL, but not in the other malignant lymphoproliferative disorders, with the exception of ALL. Hodgkin’s lymphoma and a few other cases, are mainly seen in people after their fertile life and without any influence on their reproduction. If this is so, then it is...
an advantage to have the dangerous genetic susceptibility uneven in the sibship in term of a BOE so that the predominant proportion of susceptibility, the patrilineal male susceptibility, is directed towards sibs who have healthy older siblings. From a genetic point of view, this means that the mother during the pregnancy directs the father-son susceptibility to sons who have unaffected older siblings. Referring to the mother-fetus two-way interaction, there can be a net epigenetic and microchimeristic traffic from first child to mother to second child to mother, etc. Unaffected in this context means sons who do not have the maternally imprinted gene or sons who have this gene as silent bystander without disease. Unfortunately, we do not know much about such unaffected family members [46]. In the other lines: father-daughter, mother-son and mother- daughter, we do not see such a BOE. The main part of the father-son susceptibility comes naturally from father-son transmissions and, theoretically, also from the mother’s genome as a genetic baggage she has from affected male ancestors. If so, an accumulation of patrilineal male susceptibility takes place. It is tempting to see this as an explanation for the male predominance in CLL.

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References


