Invited editorial comment:
Study of minor anomalies in childhood malignancy

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Introduction

In the preceding paper, a distinguished group of investigators tackled, with only partial success, an exceedingly difficult subject, namely, the identification of "constitutional" factors that might predispose children to the development of cancer. Méhes et al. (this issue) [8] evaluated a group of children with leukemias and solid cancers, their sibs, and a group of control children for minor anomalies. These they found in 69.2%, 63% and 34.6% of the children, respectively, and concluded "...that childhood malignancy is associated with an increased incidence of minor anomalies: both might have a common prenatal origin." Here we shall not deal with the methodological aspects of associational studies, which are best addressed in an epidemiological setting. However, before endorsing, undeservedly, the recommendations of Méhes et al. [8] for a "...much larger prospective multicentre study ... to establish the diagnostic value of individual minor anomalies and/or their patterns ... in childhood malignancy", we do want to express some concerns about the terminological and biological aspects of such studies.

Terminology

Méhes et al. [8] found 34.6% of normal control children to have “minor anomalies”. If these kids are otherwise normal, why are they called “minor anomalies”? All children were evaluated for the 57 “dysmorphic features” listed in Table 4 of the paper by Méhes et al. and including deformities, dysplasias, mild malformations, and minor anomalies evaluated subjectively and objectively. Are then normal variants, minor anomalies, mild malformations, dysplasias, and deformities all identical concepts synonymous with “dysmorphic features”? Before clarifying the difference between these concepts, we want to make the strong recommendation to discontinue once and for all the use of the ugly and vapid construction “dysmorphic features”; it is a hiding place for uncritical minds that do not know the difference and/or do not want to do to the trouble to establish the difference between these several concepts.

Early in the 19th century, the verbal distinctions between ontogeny, phylogeny, and growth were not carefully drawn (all could be called *evolutio*. It was not until 1866 and 1886, respectively, that Haeckel coined the terms phylogeny and ontogeny [10] which Herbert Spencer then insisted on using in English scientific writing to make the distinction crystal clear between the development of species on one hand, and the development of individuals organism on the other [2]. It took almost 70 years after Goethe’s introduction of the term “morphology” before the term “morphogenesis” (or “morphogeny” as Haeckel called it) became established in English biologic writing. No one seems to have difficulties with the term “organogenesis” (morphogenetic events during embryogenesis); however, the term “phenogenesis” (coined by Eugen Fischer in 1939 [4] in derivation of Haecker’s “phenogenetics” [6] is unfamiliar to most clinical geneticists. We propose it be restricted to all morphogenetic events *after* organogenesis. This results in the following terminological outline [9].

\[
\begin{array}{c}
\text{Development} \\
\text{Of species:} \\
\text{Phylogeny, evolution} \\
\text{Of organisms:} \\
\text{Ontogeny} \\
\text{Prenatal:} \\
\text{Morphogenesis} \\
\text{Postnatal:} \\
\text{Growth and maturation} \\
\text{Embryonic:} \\
\text{Organogenesis} \\
\text{Fetal and postnatal:} \\
\text{Phenogenesis}
\end{array}
\]

Heuristically, organogenesis can be contrasted with phenogenesis as follows:
Organogenesis

A. Leads to *qualitatively* different developmental endproducts *within* an individual
B. Controlled by oligo- and polygenes, the latter mostly to “buffer” development
C. Involves thresholds, i.e. all-or-none traits
D. Defects of organogenesis are *malformations*, primary or secondary (disruptions)
E. Since *mild malformations* always involve defects of organogenesis, they are always *abnormal*, even though common in the “normal population”
F. Severe and mild malformations are studied clinically, pathologically, and anatomically

Phenogenesis

A. Leads to *quantitatively* documentable differences *between* individuals
B. By definition, controlled by polygenes; *phenogenesis* represents the process of developmental “fine-tuning”
C. Does not involve threshold decisions, i.e. only “shades” of differences
D. Defects of phenogenesis mostly results in *minor anomalies*
E. Minor anomalies (i.e. defects of phenogenesis) are phenotypically indistinguishable, from hence, developmentally identical to “normal variants”
F. Minor anomalies are studied anthropometrically, also with radiometry and cephalometry, photography, and subjective description

MCA syndromes:

G. “Multiple malformations syndrome”, a form of discontinuous, abnormal variability

Examples

H. Cleft palate – cleft uvula;
   Astenom-cleft xiphisternum;
   Radius agenesis – notched distal thumb phalanx;
   Micr(an)ophtalmia – coloboma of iris;
   Omphalocele – umbilical hernia;
   Alobar holoprosencephaly – single central upper incisor;
   Hemifacial microsomia – preauricular tag

H. Reduced TRC (10 LA in trisomy 18 syndrome), increased TRC (10 whorls in Ulrich-Turner syndrome); OFC ≥ 3 S.D. above or below mean; height ≥ 3 S.D. above or below the mean; head length ≥ 3 S.D. below mean in Down syndrome (hyperbrachycephaly); increased *a* and *c* ridge count in Ulrich-Turner syndrome, etc.

1 FLK: “Funny-looking kid”, a term not to be used in clinical practice, but still well-established in American pediatric didactic practice to refer to a child who *apparently* has multiple minor anomalies and is referred to determine the presence or absence of a (genetic) syndrome

In a word, mild malformations are defects of organogenesis, minor anomalies are defects of phenogenesis (and dysplasias defects of histogenesis—a process which overlaps both, but, on the whole, commences after the beginning of organogenesis). Other definitions are provided in the report of the International Working Group [11]. Thus, mild malformations, minor anomalies, dysplasias, and deformities are *not* synonymous. Developmentally and anatomically, minor anomalies and normal variants are identical but causally have totally different implications, the former being the most common effects of aneuploidy, each of which individually may also occur in the normal population. Ten low arches on the finger tips of one of our mothers is (we think) normal variability. The difference between these being established by examination of 1st degree relatives for normal family resemblance.

[7] Unless maternal exposure continues, recurrence risk ought to be negligible, and sibs ought not to show an increased incidence of minor anomalies. This could be a syndromal combination—i.e., pleiotropy seen in such genetic cancer syndromes as the Wiedemann-Beckwith syndrome, the Perlman syndrome, Bloom syndrome, and ataxia telangiectasia; or in primary aneuploidy syndromes with increased predisposition to malignancy, such as the aniridia-Wilms tumor syndrome and Downs syndrome (or for that matter, probably all aneuploidy syndromes given sufficiently long life-span for the development of tumor). Again, the normal sibs should not show an increased incidence of minor anomalies.

Biological implications

What if the incidence of minor anomalies were found truly to be increased in children with cancers? This could represent an association which is a biological entity now understood as “…derivatives of causally non-specific disruptive events acting in developmental fields” [7]. Examples of such associations are the fetal alcohol and diphenhydantoin disruption sequences with risk to the development of the several types of cancer described in both (neuroblastoma, ganglioneuroblastoma, Wilms’ tumor, leukemia/lymphoma, and others) [1, 3, 12]. Unless maternal exposure continues, recurrence risk ought to be negligible, and sibs ought not to show an increased incidence of minor anomalies. Or this could be a syndromal combination—i.e., pleiotropy seen in such genetic cancer syndromes as the Wiedemann-Beckwith syndrome, the Perlman syndrome, Bloom syndrome, and ataxia telangiectasia; or in primary aneuploidy syndromes with increased predisposition to malignancy, such as the aniridia-Wilms tumor syndrome and Downs syndrome (or for that matter, probably all aneuploidy syndromes given sufficiently long life-span for the development of tumor). Again, the normal sibs should not show an increased incidence of minor anomalies.

An increased incidence of minor anomalies in sibs without cancer might reflect the carrier state of an autosomal or X-linked recessive mutation producing or predisposing to cancer in the respective homozygotes or hemizygotes. Or, even less likely, transmission of an iceberg dominant with rare cancer in the propositi (tip of iceberg), and mostly mild disturbances of organogenesis and/or phenogenesis in the much larger number of heterozygotes. The WT syndrome [5] is a possible example that comes to mind; however, on the whole, the less obvious somatic pleiotropic effects of dominant cancer genes remain an essentially unexplored field.

At the moment, we would have difficulties interpreting the finding of a non-specific increase of multiple minor anomalies in non-cancerous sibs of propositi with cancer or leukemia who also have several minor, but different anomalies. Not having an explanation, of course, does not preclude doing the study; however, we would plead that it be a study paying