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MINIREVIEW

Clinical Manifestations of Genetic Instability Overlap One Another

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Cancer syndromes are characteristic associations of specific malignancies with various congenital anomalies. In addition to such diseases, an increased prevalence in general of chromosomal instability, malformations, immunodeficiencies, altered growth and development, and reproductive loss has been observed in both childhood leukemias and solid tumors. The overlap among these congenital disorders suggests their common prenatal, possibly genetic origin and thus the existence of a nonspecific genetic instability leading to various clinical manifestations of disturbancies in cell division. Seeking for related features in family members of a patient with malignancy may be of clinical value in detecting predisposition to cancer. (Pathology Oncology Research Vol 10, No 1, 12–16)

Keywords: genetic instability, cancer-prone diseases, mild errors of morphogenesis, premature centromere division, predisposition to cancer

Introduction

The exponentially increasing number of molecular genetic findings nearly every day disclose new details of the etiology and pathomechanism of various types of congenital disorders and malignancies. A significant part of the new knowledge demonstrates specific correlations between genomic and/or proteomic alterations and given tumors or leukemias. At the same time, a great amount of similarly increasing data refer to nonspecific associations of malignancies with different pathological features being mainly congenital in the broadest sense of the word. Here we would like to call attention to the fact that these tumor-associated phenomena are associated also with each other, and in common they may represent a constellation, that may be regarded as a „nonspecific genetic instability". Irrespective of the underlying, possibly specific molecular background, this condition may manifest itself by clinically recognizable symptoms of one or two pathological events involved, but may also indicate a predisposition to other latent pathology.

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Malignancy and chromosome instability

Since the discovery of trisomy 21 in Down syndrome it has been a commonplace that children with chromosome aberrations are often subject to malignant diseases. On the other hand, certain tumors are characterized by specific cytogenetic changes.[69] It is also known that spontaneous or induced chromosome fragility may be a cancer-prone condition,[16] however, apart from certain cancer syndromes, chromosome analysis is rarely done in seemingly symptomless individuals. Cytogenetic damage in cancer patients before therapy has scarcely been studied. The findings so far suggest that one may reckon with a heritable susceptibility to DNA damage, and thus susceptibility to cancer, in the general population.[11,67]

We can not go into details of genetic instability at the molecular and chromosomal levels;[25,72] as an example, we only focus on the disturbances of centromere separation. These certainly play a role in carcinogenesis,[77] but may be responsible for errors in the development of the immune system and in morphogenesis as well. It was shown in earlier studies that „out-of-phase" centromere separation is a possible mechanism of aneuploidy[20,43] and premature centromere division (PCD) might be regarded as a manifestation of chromosomal instability.[8,48] As reviewed by Plaja et al[66] and Kajii et al,[31] several case reports have recently been published on PCD in children with various malformations, immunodeficiency and in part with mental retar-

dation and malignancy. Since Wilms tumor was the most common malignant disease in these patients, the occurrence of multiple PCDs in a girl with nonsyndromic Wilms tumor seemed to be of special interest.[50] The significance of too early or too late centromere separation is still under discussion; the possibility of exogenous origin[40] or of being a harmless hereditary phenomenon in some families,[39] can not yet be excluded. Nevertheless, it would be improper to ignore the occurrence of this easily recognizable, conspicuous cytogenetic event in subjects with mainly multiple congenital diseases.

Malignancy and malformation

The association of tumors with malformations has been studied for a long time. Specific combinations of given congenital anomalies with given malignancies have been described as „cancer syndromes", such as Down syndrome, the chromosome breakage syndromes, or the WAGR (Wilms tumor, Aniridia, Gonadoblastoma, mental Retardation) complex.[18] A large series of studies have dealt with the association of congenital anomalies and cancer in general. The main results prior to 1997 were reviewed by Friedman.[23] He also analyzed the problems of interpreting the findings from different approaches, however, the previous surveys, in common with some more recent reports[3,7,53,58] led to the conclusion that cancer patients, and especially children with neoplasia, tend to have more developmental abnormalities. At the same time, the authors of recent reports claim that malformations might have some factors that inhibit or delay as well as promote the development of malignancies[58] or that tumor suppressor genes participate also in differentiation and embryogenesis.[7] A molecular link role of homeobox genes between development and cancer has also been suggested.[10,21,59]

This is in accordance with the findings of studies seeking for malformations in selected groups of malignancies, such as central nervous system tumors,[30] (specifically medulloblastoma[17]) or familial testicular cancer.[60] In addition, new combinations have also been described: recent reports suggest association between, for instance, cancer and cartilage-hair hypoplasia,[42] inguinal hernia and Ewing sarcoma,[13] prune belly syndrome and congenital renal neoplasia,[74] Goldenhar syndrome and acute myeloid leukemia,[64] Dubowitz syndrome and rhabdomyosarcoma,[1] COACH syndrome and multifocal liver tumors,[35] Schinzel-Giedion syndrome and malignant sacrococcygeal teratoma,[70] and situs inversus and gastric lymphoma.[56] At the same time, no association was found between soft tissue sarcoma and birth defects[26] and between nonsyndromic cleft lip/palate and other malformations and cancer.[73]

Of special interest is the recent report by Jakab *et al.*[29] describing associations of malignancies with rare genetic disorders, others than malformation syndromes, such as Duchenne muscular dystrophy and ichthyosis vulgaris.

A special approach to association of malformation with malignancy is the search for mild errors of morphogenesis (minor malformations and anomalies, informative morphogenetic variants) in patients with malignant diseases. Several studies have shown that these small morphological aberrations of prenatal origin, arising during or after organogenesis[61,62] occur more frequently in patients with malignancies than in the general population.[19,36,45,49] We also demonstrated that both malformation-type and variant-type anomalies are more common in children with childhood acute lymphatic leukemia (ALL) and in their sibs than in control subjects of similar age, and the difference persists even if familial cases are excluded from the evaluation.[49] Methodological problems of such surveys have repeatedly been discussed,[9,22,44,52,62] however, the results are unequivocally in favour of a high prevalence of disturbed morphogenesis in patients with malignancy. Furthermore, analysis of mild errors of morhogenesis seems to be more sensitive: where neoplasia was not significantly related to major malformations, the association with minor malformations and anomalies proved to be convincing.[45] In other instances, examinations of major and minor defects confirmed each other: the association of Wilms tumor with spina bifida occulta[32] could be confirmed later by demonstrating an excess of cutaneous signs of spinal dysraphism in children with Wilms tumor.[51]

In summary, in spite of certain inconsistencies, the results so far suggest a genetic association between malignancy and malformation,[49,57,75,80] both being related in some way to chromosome instability.

Immunodeficiency, autoimmune diseases

According to Ming et al[55] there are 45 recognized primary immunodeficiency disorders, but immunodeficiency has been reported in at least 105 other syndromes. Immunodeficiency is present in only a portion of patients with these disorders, however, in 49 syndromes it is an obligatory feature of the disease. The associated anomalies include malformations (both major and minor), congenital metabolic disorders, and chromosome abnormalities. The classical examples of such combinations are the chromosome breakage syndromes, like Fanconi anemia or ataxia-teleangiectasia, but meticulous examination of the patient may disclose associated anomalies in many other instances. This has been the case in the so-called „bone marrow failure syndromes",[2] in many of which hidden morphological and functional anomalies and/or dyskeratotic signs may be discovered, and the hypersensitivity to clastogenic agents of the seemingly normal chromosomes may occasionally be demonstrated by means of mitomycin C or diepoxybutane treatment. We also found an increased

number of PCDs in such a patient,[33] a phenomenon observed sporadically in children with primary immunodeficiency.[47]

The problem of autoimmune diseases is still controversal. The combinations among juvenile rheumatoid arthritis, celiac disease, type 1 diabetes mellitus and others, and their association with chromosome instability, mild errors of morphogenesis, and growth disturbances have been studied in only small groups of patients by means of different approaches. The results so far do not permit definite conclusions, nevertheless, several data refer to interrelations/overlaps among manifestations of „genetic instability" also in this group of diseases.

Growth, development and accelerated aging

Intra- and extrauterine growth retardation is characteristic of practically every numerical and structural chromosome aberration. This is not a rule in children with malignancies. On the contrary, the pretreatment height of ALL-patients seems to be greater than that of healthy controls.[46] This can be explained in part with the increased production of tissue growth factors, however, even birth weight was found to be higher in some instances, as in patients with Wilms tumor manifesting itself at the toddler age.[78] Failure to thrive in immunodeficient children is probably secondary to recurrent infections. Similarly, delay in psychomotoric development is significantly influenced by environmental factors, but in contrast to chromosome aberrations, it is not an obligatory feature of malignancies associated with malformations and/or other congenital disorders.

Progeroid syndromes constitute a special group of congenital disorders.[28,41] These syndromes are characterized by accelerated aging of the vessels and connective tissue in general, by severe intra- and extrauterine growth retardation, in part by minor physical anomalies, infertility, and occasionally also by increased chromosome fragility and tumors.

Reproductive loss

The frequency of stillbirth and infant death is significantly higher in families with malformation syndromes and with certain types of malignancy. Some observations suggest that mothers of leukemic children reported more miscarriages than mothers of healthy controls.[12,54,65,76,79] Kaye et al[34] found that for ALL diagnosed before 2 years of age there was a 2.7 fold risk of the disease if the previous pregnancy had resulted in fetal loss. It has also been demonstrated that reproductive loss was significantly more frequent in families with childhood rhabdomyosarcoma[24] and with a possible genetic predisposition to cancer (Li-Fraumeni syndrome, neurofibromatosis) than in sporadic cases and controls.[27]

The association of cytogenetic abnormalities with reproductive loss is self-evident: parents of children with chromosome aberrations may have latent chromosome imbalance (often at the molecular level) in spite of their ostensibly normal karyotype. Recently, a high frequency of PCD was found in two series of couples with recurrent spontaneous abortions.[4,6]

Why to speak about nonspecific „genetic instability"?

The risk of malignancies as well as congenital disorders is influenced by specific genes, combination of predisposing mutations, immunological effects, environmental factors, and developmental processes. Several cancer syndromes are caused by a germline mutation in a single gene (e.g. RB1 gene in retinoblastoma), but in other cases, as e.g. in Wilms tumor, several loci are involved, i.e. several germline mutations occur in tumor suppressor genes. Polymorphisms (single nucleotide polymorphisms) play also a significant role in the susceptibility to a wide variation of diseases, including cancer.[63] The common consequence of various mutations is genetic (genomic) instability at the levels of microsatellites[5] to chromosomes, manifesting itself as aneuploidy.[15,38,71] This instability may be responsible for disturbancies in normal cell division, segregation, cellular growth, and apoptosis, consequently it may generate different congenital disorders, but all this does not explain the overlap among clinical manifestations of various nature. The matter is even more complicated by the fact that the combination and severity of clinical signs and symptoms is extremely variable: whereas in well determined syndromes the association of malignancy with malformations and/or other features is fairly consequent (this is why, we can speak about syndromes), in the majority of the cases there is only a statistical overlap among congenital phenomena with a wide range of variations. Since these may be the products of both genetic and epigenetic effects, the interpretation of their excess is very difficult.[14] However, the finding that their increased prevalence is seen only when they are evaluated together, suggests a nonspecific overall susceptibility to various clinical manifestations of this „genetic instability". The phenomenon may be somewhat mysterious, but similar nonspecific, general effects have already been observed as in the case of the „ring chromosome syndrome", in which severe growth retardation is a common symptom, irrespective of the chromosome affected.[37] We admit that in individual cases some of the associations mentioned here could be attributed by chance, and a bias towards reporting such rare associations can not be excluded, however, these case reports are in line with systematic studies and it seems plausible to consider them when discussing the relationship among clinical signs of a possibly common origin.

From a merely practical point of view, this means that the discovery of one of the factors, as e.g. malignancy in a

child, may stimulate the physician to look for the others in him or her and in the sibs, as for possible signs of predisposition. The question whether this is practicable and justified can not yet be answered, but we think that the idea deserves further consideration and studies.

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