Individual Radiation Hypersensitivity and Radiological Protection

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Individuals with radiation hypersensitivity represent a challenge in terms of radiation protection. Recently the ICRP has published report No 79 on genetic susceptibility to cancer, which reflects the importance of this issue. This paper reviews the rapidly growing knowledge on high risk individuals and subgroups on the base of molecular genetics of cancer in a comprehensive manner.

In this context, this paper gives a brief introduction on radiation hypersensitivity of individuals.

CLINICAL OBSERVATIONS OF HIGH RISK INDIVIDUALS

Radiotherapists noticed years ago that some patients, receiving a tumour dose that was tolerated by the majority of patients with the same disorder, were seriously harmed and died due to radiation injury.

Morgan reported in 1967 the case of a nine year old boy who suffered from Morbus Hodgkin. This is a malignant disorder of the lymphatic system, which can be treated by irradiating the injured lymphnodes with gamma-rays. In this case, the region of lymphnodes above the clavicles should get a dose of 30 Gy and the mediastinum 40 Gy. Two weeks after the start of radiotherapy the boy had problems and pain while swallowing and developed an inflammation of the oesophagus. The therapy was stopped, but the boy died as a result of radiation injuries.

This patient suffered from ataxia teleangiectasia, a rare hereditary disorder, which becomes clinically present during the first or second year of life. The parents become aware, that the child can't walk normally and tends to stagger. Later on the speech becomes slurred, eye movements are abnormal. These patients have a high risk to develop leukemia or lymphomas in the first decade of life.

Several publications report an increased sensitivity to ionising radiation in these patients.

In 1967 the mechanism of radiation sensitivity was poorly understood. New insights in the molecular pathology of cancer and the mechanisms of inheritance have greatly increased and continue to increase our knowledge on individual radiation sensitivity.

MECHANISMS OF DISEASE

Cancer is now believed to be a genetic disorder mainly caused by dysfunction of three types of genes:

- Proto-oncogenes
- Tumour suppressor- genes
- DNA- repair genes

DNA-repair genes ensure that the genetic information of DNA is accurately copied, even in the presence of DNA-damage.

Proto-oncogenes and tumour suppressor genes control the cell cycle and cell survival. If there is a loss of function of these genes due to mutation for example uncontrolled cell growth occurs - one of the main features of cancer.

To understand the development of cancer (based on the disruption of tumour suppressor genes) one has to keep in mind that there are two copies of the genetic information. If there is a mutation affecting a gene on one chromosome then the other allele still has the gene with the correct information and may compensate for the injured gene. In this situation, the individual does not get cancer. But if the second copy of this special gene gets also mutated or deleted then cancer may develop.

This is the case for the so called "two hit model of cancer", which assumes that there must be two defective copies of the same gene to express the related disorder, e.g. cancer. In most cases, however, several genes have to be inactivated or overexpressed before cancer develops.

In the case of teleangiectasia the patient has inherited two damaged chromosomes from his parents, each of them carrying a mutation of the special, so-called, AT gene. The child will then have a mutated AT gene on both chromosomes. This status is called homozygosity and leads to the expression of the phaeotype of the related disorder, e.g. ataxia teleangiectasia.

If only one parent is carrying the mutated gene, then the child may inherit this mutated gene, but still has a healthy gene on his second chromosome. This status is called heterozygosity. The consequence of such
inherited germ line mutations is the distribution of this special mutation to each cell of the body.

With only some exceptions the phenotype of this individual will be normal, without expressing the related disorder. But it might happen that a "second hit" to one of the somatic cells damages the second healthy copy of that specific gene. The result of this event is "loss of heterozygosity" of the gene and as a consequence the related disorder may develop.

An example of this type of disease is the rare disorder retinoblastoma. Again the illness starts during early childhood. The parents perhaps note that one eye of their little child is turning out, when the child is tired.

An ophthalmologic examination reveals a tumour of the retina.

This is the most common tumour of the eye in early childhood and there are two forms of the disorder: a sporadic one and an inherited one. The inherited disorder is transmitted autosomal dominant. Only one parent is carrier of the mutated RB gene -very often the father- and the child carries one copy of the mutated gene in each cell of his body. This status is called heterozygosity-as mentioned above. The second hit- mutation of the copy of healthy gene- happens during fetal development of the retina when retinoblasts are rapidly dividing. Just one cell has to become mutated. The genome of the cell has then lost heterozygosity. Because the RB1 gene is a tumour suppressor gene the control of the cell cycle is lost and a tumour can develop.

Fig 1 Possible mutations of retinoblastoma gene

One somatic mutation

Two somatic mutations
This example, however, is a very simple one due to the monogenetic cause and autosomal dominant transmission of the disorder. For the most cases of radiosensitivity of individuals with heritable disorders predisposing to cancer the mechanism is much more complicated.

Fortunately, this second mutation of the same gene is a very rare event. But geneticists believe that the most important causes for such new mutations come from lifestyle and environment. Smoking and diet are
lifestyle factors while radiation (UVR and ionising radiation) and chemical genotoxic agents come from the environment. This latter context could explain observed radiosensitivity for secondary tumours of retinoblastoma patients.

In a study of 1603 retinoblastoma patients in the USA ENG could demonstrate that patients with inherited retinoblastoma experience a rapidly rising risk of tumour mortality compared with those with non-heritable retinoblastomas. This excess risk is further increased by prior radiotherapy. Thus, the mechanism of disease as explained above has clinical relevance.

**IMPLICATIONS FOR RADIOLOGICAL PROTECTION AND OPEN QUESTIONS**

Predisposition to cancer and higher risk after exposure to ionising radiation has so far been shown for heritable disorders which have high penetrance. "Penetrance means the probability that a given gene carrier will express the mutant gene genotype as neoplastic disease. This includes that there are carriers of mutant gene which do not develop cancer." ICRP 79

While homozygotes of such disorders are very rare in the population, only little is known about the frequency of heterozygotes. There is some discussion on the probability that AT heterozygotes may be predisposed to breast cancer. In this context the frequency of heterozygotes is estimated to be 1:200 in the population.

A very important question is, whether there are weakly expressed mutations (low penetrance genes) which show no family history of cancer development and radiosensitivity.

A further problem is the question to what extent cancer predisposing hereditary disorders are playing a role in individual radiosensitivity. To get more information on this topic ICRP proposes to re-examine irradiated groups like breast cancer cases from Hiroshima and Nagasaki. This examination must use molecular analyses because "conventional epidemiologic approaches to cancer risk in genetically predisposed subpopulations are unlikely to succeed fully" (ICRP 79 p 137). There are no data of family history of cancer cases in Hiroshima and Nagasaki.

While there is evidence for elevated individual risk with application of high doses there is no evidence for such a risk with low doses right now.

**THE ROLE OF GENE TESTS**

Gene testing will become more and more available as automation of tests will rapidly develop and DNA chip technology becomes available. Some of the questions mentioned above will get an answer by evaluating gene tests. At the moment genetic testing may be important for patients with a family history of cancer- especially with early onset-disease and planned radiotherapy.

Gene testing involves the examination of DNA of a person with different techniques. The DNA changes can be large, such as the loss of an entire chromosome and thus be visible under a microscope.

There also might be just one extra, missing or altered chemical base, which needs molecular analyses to be traced.

Gene tests involve some major problems on ethical, social and economic questions, because in addition to testing patients it is necessary to test other family members as well. These problems should be discussed in the society early before they are introduced generally and there is some urgent need in changing legislation to ensure strict confidentiality.

**CONSEQUENCES**

There is clinical evidence that the application of high doses can be dangerous in case of high risk patients suffering from special hereditary disorders. It should be a strict rule therefore, that every physician taking care of a patient, who should be treated by radiotherapy has to determine the family history of that patient, especially with respect to cancer cases, even if the radiotherapy in question does not apply to a tumour. Special care has to be taken, if there is a case of childhood or adolescent cancer in the family. In such cases genetic testing - if possible - might be worth a consideration. Consultation of a competent geneticist should be urgently advised.

Radiotherapy should not be started without a thorough written evaluation of the family history, perhaps together with a geneticist's statement.

Although there is currently no evidence for low doses, as applied in occupational exposition, to induce any harm in high risk patients, there is neither enough evidence to rule it out.

Thus as a first step to get more information in occupational medicine a full family history of cancer should be determined. In a general medical examination the family history ids usually taken. But in occupational
medicine not every physician asks questions on family disorders. When I asked a worker in a nuclear power plant questions about disorders of his family, he asked me: What concern have these questions to my job? Thus, some education of the public is necessary.

The American Medical Association together with the American Nurses Association and the National Human Genome Research Institute in 1996 started a National Coalition for Health Professional Education in Genetics. Everybody can link to the Internet Home page of this NCHPEG (http://www.nchpeg.org)

CONCLUSION

This paper is just an introduction to a more complex problem. But there is no doubt, that the issue will get growing importance for radiological protection in the future.

For more details you may read ICRP 79.

For additional information and discussion of this issue you should join the congress of the German Radiation Protection Society together with the association of National Societies Active in Radiation Research in October next year. It deals with Individual sensitivity to ionising radiation and its implication for radiation protection.

References