Acta Radiologica Oncology 20 (1981) Fasc. 3

FROM THE DEPARTMENTS OF PEDIATRICS AND CLINICAL GENETICS, UNIVERSITY OF UMEÅ, S-901 85 UMEÅ, SWEDEN.

MICROCEPHALY, MENTAL RETARDATION AND CHROMOSOMAL ABERRATIONS IN A GIRL FOLLOWING RADIATION THERAPY DURING LATE FETAL LIFE

K.-H. GUSTAVSON, S. JAGELL, H. K:SON BLOMQUIST and I. NORDENSON

Several reports have been published describing microcephaly, mental retardation and cataracts as frequent consequences of pelvic irradiation during fetal life (SWEET & KINZIE 1976). DEKABAN (1968) noted that the most frequent abnormalities were small birth size, stunted growth, microcephaly, mental retardation, retinal degeneration, skeletal and genital anomalies, and cataract formation. Anemia, lymphopenia, atrophy of the gonads, kidneys and bone marrow were described in a few patients.

Almost all these children were exposed to ionizing radiation early in pregnancy and it has been believed that irradiation of the fetus with a similar dose range after 20 weeks of gestation is unlikely to produce abnormalities leading to handicap (DEKABAN, SWEET & KINZIE, MILLER & BLOT 1972). For that reason it was considered of interest to report on a child, who was severely damaged by irradiation in utero in late pregnancy.

Case report

A girl born in 1966, as the fifth child of a 41-year-old para 5 woman. Carcinoma of the uterine cervix, stage IB, was diagnosed on the mother during the third trimester of the pregnancy. The tumour was irradiated through two opposite fields (32.5 MV) during the thirtieth to the thirty-third week of the pregnancy. A total of 40 Gy were given over the pelvic area including the head of the fetus with excellent effect on the tumour. Induction of the delivery failed and the girl was finally delivered by caesarean section in the thirty-sixth week of the pregnancy.

Somatic and psychomotor development. The newborn girl showed no signs of pre- or postnatal asphyxia and she had no visible congenital defects. A slight oedema was seen on the head and she had sparse, loosening hair on the head. Neonatal reflexes were normal. The first weeks of life were essentially normal. In the following 4 months the child was irritable and very sensitive to sounds, with muscular hypotonia and a tendency to opisthotonos and easily elicited Moro reflex when stimulated. Later on, the Moro reflex was clearly pathologic and she had muscular hypertonia when crying. She had jerky movements of arms and legs and minimal myoclonic movements in feet, hands and eyelids. The girl was irritable when nursed and cried with short high-pitched cries. She had daily frequent short myoclonic seizures in the extremities and of the head since 8 months of age. The epileptic fits were resistant to therapy. She developed flexion contractures of the elbows, thumbs, hips and knees and bilateral luxation of the hip joints.

The eyes of the child were initially normal but at 13 months of age several opacities were found in the vitreous body. The anterior chamber was shallow, the pupils were adherent to the lens due to synechiae, the optic disc was pale and dispersed signs of atrophy were found in the fundus. Progressing signs of bilateral cataract and microphthalmus were found from 2 years of age. She could follow flashlight movements for short periods.

Birth weight was 2 900 g, height 48 cm and head circumference 32 cm, which is normal for the length of pregnancy. The height followed a growth curve at −2 SD during the first 8 months of life and then successively dropped to −3

Accepted for publication 31 March 1981.

SD (Fig. 1). The girl was difficult to feed during the first years of life and her weight was only 9.5 kg at 2 1/2 years of age. At this time the parents were instructed to feed her through a gastric tube and she gained 6 kg during the following year and consequently became very fat.

She became microcephalous and the head circumference reached 42 cm at 12 months of age and did not increase significantly during the following 12 years (Fig. 2).

The dentition was somewhat late. The deciduous and permanent teeth were malformed, small and brownish with enamel hypoplasia.

The hair was sparse on her head. She never acquired any hair in the axillae but some slight pubic hair after 12 years of age.

She was almost lacking psychomotor development with no eye fixation, smile or babbling. Furthermore she had no head control or spontaneous movements. She never learnt to sit, stand, walk or speak.

Physical examination at 12 years of age showed a totally helpless, most severely mentally retarded, short, fat girl with microcephaly, abnormal teeth, bilateral microphthalmus and dense cataract unable to sit or perform any adequate movements or sounds.

Her reaction to pain was a slight cry but otherwise she could not give any contact or reaction to stimuli. She could not swallow and was fed through a gastric tube. Sometimes she made minimal but useless movements with her arms and legs. She did not move her fingers or hands. Her teeth were few, small, irregular and brownish. Her weight was 43 kg, her height 125 cm, the head circumference 44 cm and the abdominal circumference 102 cm. The left shoulder and the hips were luxated. Reflexes and tonus appeared normal in arms and legs.

She was nursed in her home throughout her lifetime and died there from pneumonia at the age of 13 years. Autopsy was not performed.

Laboratory data. Skull radiography, echoencephalography and EEG at one month of age were normal. Repeated radiographic and echoencephalographic examinations since 4 months of age revealed a microcephalic skull with internal hydrocephalus.

Repeated EEG showed general marked suppression of the cerebral activity with episodes of sharp-wave patterns of epileptic nature. The normal EEG development did not occur and the recordings were characterized as immature.

The bone marrow at 3 weeks of age showed hypocellular erythropoiesis but increased left-shifted myelopoiesis with increased cell size and swollen nuclei. Bone marrows at 1 1/2 and 3 1/2 years of age were strikingly hypocellular with depression of both erythro- and myelopoiesis.

During the first year of life she had moderate anaemia and neutropenia but normal reticulocyte, lymphocyte and thrombocyte counts in peripheral blood. Later on the peripheral blood values were completely normal.

Cytogenetic analyses were performed when the girl was 11 years old. Controls were 9 children, 13 to 18 years old, with no exposure to diagnostic or therapeutic irradiation. The techniques for cell-culturing and chromosome preparation were as previously described (NORDENSON et coll. 1976). G-banded metaphases were obtained by staining the slides essentially according to WANG & FEDOROFF (1972). The abberations were scored as recommended by WHO (BUCKTON & EVANS 1973). All cells with aberrations were photographed and karyotyped.

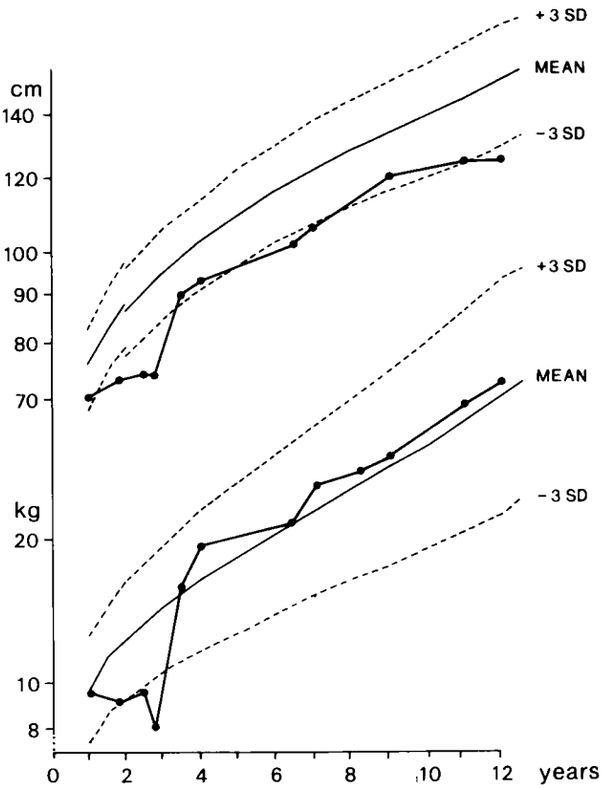

Fig. 1. Height (cm) and weight (kg) curves from the child (●—●) compared with normal development.

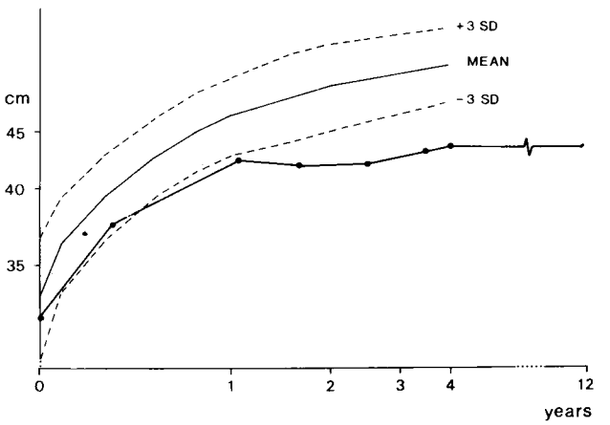

Fig. 2. Head circumference (cm) curve from the child (●—●) compared with normal development.

The frequencies of the different types of aberrations observed in the girl and in controls appear in the Table. The frequencies of both chromatid and chromosome breaks were significantly increased. As exposure to ioniz-

Table

Chromosomal abnormalities in peripheral blood from the girl (at age 11) and 9 controls (mean age 16.3, range 13–18 years). Frequencies per cell in parentheses

	Present case	Controls	p
No. of cells	195	1 045	
Gaps	4 (0.021)	24 (0.023)	NS
Chromatid breaks	6 (0.031)	6 (0.006)	0.001
Chromosome breaks*	13 (0.015)	0 (0.000)	<0.0005
Total	13 (0.067)	30 (0.029)	<0.01

* Only one of the cells with identical translocations is included.

ing radiation induces mostly chromosome type aberrations, it is of interest to notice that no such aberrations were found in the controls but 3 (one inversion, one translocation and one acentric fragment) in the patient. Furthermore, 4 cells had an identical translocation t (2q; 9q) possibly indicating clonal cell propagation.

Discussion

In a recent review MOLE (1979) concluded that the risk per dose unit to the foetus in diagnostic radiology is probably considerably less than previously believed. In therapeutic radiology it has been thought that even heavy irradiation of the human foetus after 20 weeks of pregnancy is not likely to produce severe abnormalities (DEKABAN). However, the present case had most of the abnormalities seen in children heavily irradiated during their first half of intrauterine life: microcephaly, mental retardation, stunted growth, microphthalmus, retinal degeneration, cataract, defective dentition. This indicates that heavy irradiation in utero as late as the seventh month may cause severe injury also during the intrauterine brain growth spurt which is characterized by glial multiplication and establishment of synaptic connections (DOBBING 1974).

The chromosome aberrations induced in vivo and in vitro by ionizing radiation may be stable or unstable; the unstable lesion being dicentrics, ring chromosomes and acentric fragments. Balanced translocations and inversions are stable aberrations. In this case, one acentric fragment was seen. The other abnormalities were stable structural rearrangements. Although the figures are very small there is evidence in other reports (BLOOM et coll. 1967, BUCKTON et coll. 1967, LITTLEFIELD & JOINER 1976) that the predominant type of lesions many years after radiation exposure is stable aberrations. BLOOM et coll. suggest that these aberrations persist because there is no loss of genetic material and thus they can survive many cell divisions.

Four cells carried an apparently identical translocation. As stimulated lymphocytes during 72 hours of culture may divide one, two and even three times, one cell with a stable rearrangement, may have up to four identical copies when the cells are harvested after 72 hours of culture. It is thus possible that the aberrant cell clone observed in the cultured lymphocytes from the present case has emerged during culturing time. On the other hand, cell clones with identical translocations or inversions are very seldom observed in routine screening of chromosomal aberrations. Furthermore, clones of cells with apparently identical lesions have been described in cytogenetic reports on irradiated subjects (BLOOM et coll., LITTLEFIELD & JOINER) suggesting a true clone formation.

In utero exposure to ionizing radiation increases the likelihood of neoplastic disorders in childhood, but such a disorder was not indicated in the present case.

The radiation exposure in utero was in this case very heavy (40 Gy) and it must be regarded as remarkable that the child survived and reached an age of 13 years.

SUMMARY

A human foetus was heavily irradiated in the thirthieth to the thirthy-third week due to carcinoma of the uterine cervix of the mother. Irradiation after 20 weeks of pregnancy is thought not to produce severe abnormalities. However, the child showed microcephaly, mental retardation, stunted growth, microphthalmus, retinal degeneration, cataract and defective dentition. Cytogenetically the frequencies of both chromatid and chromosome breaks were increased.

ACKNOWLEDGEMENTS

This report was supported by grants from the Swedish Medical Research Council (Grant No. 05445), the First of May Flower Annual Campaign for Children's Health and the Lion's Research Foundation, Department of Oncology, University of Umeå, Sweden.

Request for reprints: Dr Sten Jagell, Department of Pediatrics, University of Umeå, S-901 85 Umeå, Sweden.

REFERENCES

BLOOM A. D., NERIISHI S., AWA A. A., HONDA T. and ARCHER P. G.: Chromosome aberrations in leucocytes of older survivors of the atomic bombings of Hiroshima and Nagasaki. Lancet II (1967), 802.

BUCKTON K. E. and EVANS H. J. (Editors): Methods for the analysis of chromosome aberrations. WHO Report, Geneva 1973.

— COURT BROWN W. M. and SMITH P. G.: Lymphocyte survival in men treated with X-rays for ankylosing spondylitis. Nature 214 (1967), 470.

DEKABAN A. S.: Abnormalities in children exposed to x-radiation during various stages of gestation. Tentative timetable of radiation injury to the human fetus. Part I. J. nucl. Med. 9 (1968), 471.

DOBBING J: The later development of the brain and its vulnerability. *In:* Scientific foundations of paediatrics, p. 565. Edited by J. A. Davis and J. Dobbing. Heinemann Medical Books, London 1974.

LITTLEFIELD L. G. and JOINER E. E.: Cytogenetic follow-up studies in 6 radiation accident victims (16 years post-exposure). Excerpta Med. Int. Congr. Ser. 397 (1976), 137.

MILLER R. W. and BLOT W. J.: Small head size after in-utero exposure to atomic radiation. Lancet II (1972), 784.

MOLE R. H.: Radiation effects on prenatal development and their radiological significance. Brit. J. Radiol. 52 (1979), 89.

NORDENSON I., BECKMAN G. and BECKMAN L.: The effect of superoxide dismutase and catalase on radiation induced chromosome breaks. Hereditas 82 (1976), 125.

SWEET D. L. and KINZIE J.: Consequences of radiotherapy and antineoplastic therapy for the fetus. J. reprod. Med. 17 (1976), 241.

WANG H. G. and FEDOROFF S.: Banding in human chromosomes treated with trypsin. Nature 235 (1972), 52.