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Cognitive Function and Prenatal Exposure to Ionizing Radiation

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ABSTRACT It is clear from the many studies of the prenatally exposed survivors of the atomic bombing of Hiroshima and Nagasaki that exposure to ionizing radiation during gestation has harmful effects on the developing human brain, particularly if that exposure occurs at critical stages in the development of the neocortex. Data on a variety of measures of cognitive function, including the occurrence of severe mental retardation as well as variation in the intelligence quotient (IQ) and school performance, show significant effects on those survivors exposed 8–15 weeks and 16–25 weeks after ovulation. Studies of seizures, primarily those without known precipitating cause, also exhibit a radiation effect on those individuals exposed in the first 16 weeks after ovulation. The cellular and molecular events that subtend these abnormalities are still largely unknown although some progress toward an understanding has occurred. For example, magnetic resonance imaging of the brain of some of the mentally retarded survivors has revealed a large region of abnormally situated gray matter, suggesting an abnormality in neuronal migration, but cell killing could also contribute importantly to the effects on cognitive function that have been seen. The retardation of growth in stature observed in individuals exposed in the first and second trimesters of pregnancy suggests that the development of an atypically small head size, without conspicuously impaired cognitive function, may reflect a generalized retardation of growth. *Teratology 59:222–226, 1999.* © 1999 Wiley-Liss, Inc.

Actively dividing cells are known to be more sensitive to ionizing radiation than cells having completed division or differentiated cells that seldom undergo division (United Nations, ’86; ICRP, ’86). Prompted partially by this fact and partially by the findings of Goldstein and Murphy (’29) on children born to women who received radiotherapy in the course of pregnancy, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have conducted numerous studies on those survivors who were exposed prenatally to atomic radiation in Hiroshima and Nagasaki to identify and describe the effects of ionizing radiation on the growth and development of the embryo and fetus (see, for example, Miller et al., ’56; Wood et al., ’67; Blot, ’75; Schull et al., ’86, ’88; Otake et al., ’84, ’87, ’88, ’93; Dunn et al., ’90). Documentation of the deleterious effects of ionizing radiation on the developing human brain rests largely on these studies which we review briefly (see also Schull, ’95).

DEVELOPMENT OF THE BRAIN AND GESTATIONAL AGE

Gestational age at the time of exposure to ionizing radiation is the most important factor in determining the nature of the insult to the developing brain. Different functions of the primate central nervous system (CNS) are localized in different structures, with differentiation of these taking place at different stages of development and over different time periods. Generally, the embryonic stage in humans is taken to be the period up to the 8th week after ovulation, and the fetal stage the period from the beginning of the 9th week until parturition. Although the formation of most human organs is largely complete by the 8th week after ovulation, development of the cerebral cortex occurs rapidly in the interval from 8 to 15 weeks after ovulation. In fact, Dobbing and Sands (’73) have reported that the normal number of neurons in the cerebral neocortex of the human adult has been achieved at about 16 weeks after ovulation. To reflect these varied, known phases in the normal development of the brain, the ages of the survivors at the time of exposure have been grouped for analytic purposes. Development has been classified into four periods from the presumed day of ovulation, i.e., 0–7 weeks, 8–15 weeks, 16–25 weeks, and >26 weeks. By the end of the first period, the precursors of the neuronal and glial cells, the principal cells that make up the CNS, are mitotically active. In the second period, a rapid increase in the number of neurons occurs, these immature neurons lose their capacity to divide becoming perennial cells, and migrate from the proliferative zones to the cerebral cortex, their site of function. In the third period, in situ cellular differentiation accelerates, synaptogenesis that commences about the

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8th week after ovulation increases, and the definitive cytoarchitecture of the brain unfolds. The final period consists mainly of continued cytoarchitectural development, cellular differentiation, and synaptogenesis.

THE POPULATION OF PRENATALLY EXPOSED ATOMIC BOMB SURVIVORS

The first study population of prenatally exposed atomic bomb survivors was established from data collected in the course of the genetic studies conducted at ABCC ('48 to '53). Subsequently, a more systematic ascertainment began in Hiroshima ('53), and in Nagasaki ('55), based on the records of births occurring before May 31, 1946, but after the atomic bombing (August 6, 1945, in Hiroshima; August 9, 1945 in Nagasaki) (Schull and Otake, '86). Finally, in 1959, new, so–called clinical samples were established. These samples were selected on the basis of the 1950 national census and the ABCC master file, and were drawn from all survivors exposed prenatally within 2,000 m of the hypocenter who were residing within the contact area in Hiroshima or Nagasaki on October 1, 1950. The comparison groups, matched by sex and age (trimester), were randomly selected from among distally exposed survivors (3,000–4,999 m) and nonexposed survivors (>10,000 m) residing within the same contact area. Collectively, these individuals number 1,566 persons (1,242 in Hiroshima and 324 in Nagasaki) on whom DS86 doses are available. Of these individuals, 1,473 had their head size measured at least once between the ages of 9 and 19. The first clinical examinations were conducted in 1948, with most of the study subjects reexamined at 2-year intervals up until 1964. The population of schoolchildren on whom school performance is based consists of prenatally exposed school children enrolled in Hiroshima elementary schools in 1956.

In 1987, it became possible to assign individual dose estimates to these survivors based on the DS86 dosimetry system (Roesch, '87). These doses are individually calculated without using average correction factors; thus they allow better for the scattering of radiant energy that occurs within tissues. Since DS86 fetal absorbed doses are not as yet available, the absorbed dose to the mother's uterus is used as a surrogate. Parenthetically, it should be noted that the fetal absorbed doses under the T65 dosimetry system, used until 1987, were estimates of maternal shielded kerma multiplied by mean correction factors (Milton and Shohoji, '68; Kerr, '79).

RESULTS OF EPIDEMIOLOGICAL STUDIES

Severe Mental Retardation

The mentally retarded cases were identified on the basis of clinical observations and not IQ scores. A child was deemed mentally retarded if "unable to make simple conversation, to perform simple calculations, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized" (Wood et al., '67a, '67b). Because the date of ovulation is uncertain, time "after ovulation" (taken to be 2 weeks after the onset of the last menstrual period) is used in the estimation of the developmental age at exposure and in the grouping of the study cases.

Thirty cases of severe mental retardation were detected before 17 years of age. Of these, 18 (60%) had small heads, that is, the circumference of the head was two or more standard deviations below the age- and sex-specific means of the overall sample. Fifteen of these 18 cases (83%) were exposed at 8–15 weeks after ovulation. Empirically this is the period of maximum radiosensitivity. For a radiation dose of >0.01, a small head was observed in 15 of the 17 severely mentally retarded cases (88%) in the 8- to 15-week group, and in 2 of the 4 retarded cases (50%) in the 16- to 25-week group.

No threshold can be unequivocally demonstrated statistically in the occurrence of clinically identified mental retardation among those survivors exposed at 8–15 weeks after ovulation. Based on a linear dose-response relationship, the risk per Gy (DS86) is about 43%.

Intelligence Quotient

Intelligence quotient (IQ) data were collected during 1955–1956 at the Hiroshima and Nagasaki ABCC clinical facilities on the prenatally exposed and "nonexposed" survivors (those >10,000 m from the hypocenter). The examinees were 10–11 years old at that time. Of the study subjects, 11 were severely retarded and 8 (73%) had an IQ of<70, the IQs ranging from 56 to 64; the remaining three were untestable (Schull et al., '86, '88). The average IQ and its standard deviation were 63.8 + 8.5 for those survivors with a small head size accompanied by mental retardation, and 68.9 ± 11.9 for those with mental retardation but without small head size. On the other hand, the score for those survivors with small head size but without mental retardation was 96.4 ± 19.8. The average IQ score for the entire study population was 107.8 ± 16.4. Although no significant difference in average IQ was noted between the first two groups, the average IQ in these two groups was significantly less than the average of those with a small head only. No statistically significant difference was observed between the average IQ score of those with a small head without mental retardation and the average IQ of the entire study population.

No evidence of a radiation effect was seen among children exposed prior to the 8th week or 26 or more weeks after ovulation. While no heterogeneity exists among the different dose groups in the variances of IQ scores in children exposed at 8–15 and 16–25 weeks after ovulation, a significant heterogeneity was seen among the mean values. The diminution in mean scores of children exposed 16–25 weeks after ovulation was not as marked as the diminution at 8–15 weeks. When the IQ scores were regressed on the DS86 dose estimates, IQ diminished linearly with increasing dose in the children exposed 8–15 weeks after ovulation. The estimated decrease in IQ score under the linear dose-response model was 25–29 points per Gy of DS86 uterine absorbed dose.

School Performance

The school performances are based on the school records of lst to 4th grade students enrolled at 44 elementary schools in Hiroshima City in August and September 1956, including a school for the blind and an orphanage. The prenatally exposed children were 10–11 years old at the time, with the majority having completed the 4th grade, and included 14 severely mentally retarded individuals. A significant decline in average school performance was observed in the groups exposed at 8–15 weeks and 16–25 weeks, with this tendency most pronounced in the lower grades. As in the case of mental retardation and the IQ data, no evidence of a radiation effect was observed in children exposed at gestational ages of less than 8 weeks or ≥26 weeks (Otake et al., ’88). The correspondence in achievements in seven mandatory subjects (language, civics, arithmetic, science, music, drawing, and gymnastics), taking the first grade for example, was very high, ranging from a correlation coefficient of 0.62 (music and gymnastics) to 0.82 (language and arithmetic). Given the high correlation in the performance in the seven subjects, in the analysis the means of the seven performance scores were evaluated against the DS86 uterine absorbed dose. A significant decline in mean school performance with increasing dose was observed among those exposed 8–15 weeks and 16–25 weeks after ovulation. Simple regression reveals that the damage to the fetal brain at 8–15 weeks after ovulation is linearly related to the absorbed uterine dose, and this obtains even with the exclusion of individuals with severe mental retardation. Damage to the fetal brain of the group exposed 16–25 weeks after ovulation appears to be the same as that observed in the group exposed 8–15 weeks after ovulation.

Seizures

Seizures are often associated with defective development of the brain. It was suspected, therefore, that children with radiation-related brain damage might exhibit seizures more frequently than those children without such damage. Information on seizures was obtained from the child’s mother at the time of the routine biennial examinations. Among survivors exposed 0–7 weeks after ovulation, no record of seizures was noted even in the ≥0.10 Gy dose group. Seizures were most frequent among those exposed 8–15 weeks after ovulation. This was observed not only for seizures of unknown cause, but for all seizures as well, that is, for seizures with or without a recognizable cause for their occurrence such as fever, trauma, or reaction to vaccination. When the 22 children with severe mental retardation were excluded, the test of significance of the increase of seizures was suggestive but only for seizures of unknown etiology—those without a known precipitating cause (Dunn et al., ’90). The risk ratios for unprovoked seizures, following exposure in the 8th through the 15th week after ovulation, are 4.4 (90% confidence limits: 0.5–40.9) after 0.10–0.49 Gy and 24.9 (4.1–191.6) after 0.50 Gy or more when the severely mentally retarded cases are included, and 4.4 (0.5–40.9) and 14.5 (0.4–199.6), respectively, when they are excluded.

Small Head Size

Small head size is defined as a head circumference that is more than two standard deviations below the sex- and age-specific mean for the entire clinical study population. Small head size, as used here, encompasses two abnormalities, namely, microcephaly and craniostenosis. Microcephaly is a condition in which the cranium and cerebral hemispheres are abnormally small and is frequently accompanied by mental retardation and seizures. Craniostenosis is a condition in which the head remains small because of the early closure of the sutures of the calvarium and, although it resembles microcephaly grossly, there is no abnormality in the brain other than diminished size. Since it is difficult to determine brain size and it is known that the bones forming the cranial vault develop in close association with the growth of the brain and dura mater, retardation of brain development is commonly investigated by measuring head size.

Out of the 1,473 cases on whom at least one measurement of head size was obtained, 62 had a head circumference two standard deviations or more below the age- and sex-specific mean in the total sample at the time of measurement. Of the 30 mentally retarded cases alluded to above, 26 are members of this study group. Of these 26, 15 (58%) had a small head size. Most (86%) of the individuals with small head size were exposed in the first (55%) or second trimester (31%) of pregnancy (Otake and Schull, ’93). Unlike the situation with respect to mental retardation where no increase is seen in the group exposed 0–7 weeks after ovulation, the frequency of small head size is definitely elevated in this gestational age group. However, it is still unclear to what extent small head size is a symptom independent of mental retardation and by what mechanism radiation-related damage is caused.

Review of the relationship between small head size and such measurements of growth in size as height, weight, sitting height, and chest circumference, revealed significantly lower values among those with small head size in comparison with those individuals with a normal head size. Data on head size, height, and weight at 18 years of age in the clinical sample showed a linear relationship, with a marginally significant decrease with increasing dose (Otake et al., ’93). Using a growth curve model, the relationship between the estimated DS86 uterine absorbed dose and gestational age (weeks), or between the estimated uterine absorbed dose, the square of this dose, and gestational age of 455 prenatally exposed atomic bomb survivors was reviewed to examine retardation of growth and development. Comparisons were made by city, sex, dose, and fetal age. The most significant difference was observed between the two sexes. However, an analysis based on a linear-quadratic dose-response model showed no significant difference between males in Hiroshima and Nagasaki or between females in the two cities, excepting males in "all trimesters combined" and "first trimester." A statistically significant growth retardation was observed in all trimesters combined and the first and second trimesters of pregnancy.

The adolescent spurt in growth and development in Japanese males occurs at about the age of 14 on average. In view of this, an analysis of growth was made based on a linear dose-response relationship for each of the four measurements of stature on 704 individuals made from ages 10–13 years and on 838 individuals from ages 15–18 years. Division of the subjects into a pre- and a post-growth spurt group increases the number of subjects available for analysis and hence the statistical power of detecting a radiation-related difference. An effect of exposure on growth is apparent from ages 10–13 years, and it clearly continues from ages 15–18 years. In the former age group, growth retardation showed a highly significant difference for all trimesters combined, but a suggestive difference for the first trimester; whereas in the latter group, a significant retardation of growth was observed in both the first and second trimesters.

Neuromuscular Function

The relationship of two neuromuscular function tests, namely, grip strength and speed on a repetitive action test, to dose, anthropometric measurements (height, weight, sitting height, and chest circumference), and IQ scores was examined with city and sex factors considered as covariates. The tests were conducted between 1961 and 1962 (ages 15–16) (Yoshimaru et al., '95). When the mentally retarded cases were included, the grip and repetitive action tests showed the effects of radiation exposure to be statistically significant in the group exposed at 8–15 weeks, and suggestively significant in the 16- to 25-week group. When the mentally retarded cases were excluded, no effect of exposure was observed in the two types of tests in either of these two gestational age groups. With the mentally retarded cases included, the dose-related diminution of IQ scores was significant in both the group exposed at 8–15 weeks and the group exposed at 16–25 weeks after ovulation. With the mentally retarded cases excluded, only the 8- to 15-week group showed a significant diminution with dose. The results of an analysis of covariance of the two types of tests (grip and repetitive action) showed a significant relationship with IQ scores only in the >l6-week group, but not with dose. With the mentally retarded cases excluded, the relationship between the projected grip scores and projected repetitive action scores in the >16-week and <15-week groups, based on the standard results obtained using estimates of covariance analysis of the results of the grip tests and repetitive exercise tests suggests a diminution in IQ scores and possible small head size and mental retardation in the <15-week group.

MAGNETIC RESONANCE IMAGING OF THE BRAIN

Magnetic resonance images (MRI) of the brain of five mentally retarded cases exposed 8–15 weeks after ovulation have been obtained. The findings are as followings. A large region of ectopic gray matter was observed in the two individuals exposed in the 8th or 9th week after ovulation. This is strong evidence that neurons have failed to migrate to their natural functional sites. No distinct ectopic gray matter was observed in the two individuals exposed in the 12th or 13th week after ovulation; however, a mild macrogyria, indicative of a developmental disorder of the cortical region, was observed. Both individuals also exhibited a mega cisterna magna, and one had a distinctly atypical corpus callosum. Lastly, none of the changes observed in these four individuals was seen in the one individual exposed in the 15th week after ovulation. Although the brain was small, its cytoarchitecture appeared to be normal (Schull et al., '91).

IS THERE A THRESHOLD?

Clearly, there are uncertainties associated with these estimates of risk. The samples are small, errors may exist in estimated dose or gestational age, and the role of potentially risk modifying factors, such as maternal disease or malnutrition, is unknown and difficult to evaluate. Nonetheless, arguably the most pressing issue is whether a threshold exists for the radiation effects we have described. Such knowledge is not only of heuristic interest, but regulatory import as well. A priori, one might expect a threshold since presumably the effects described entail damage to more than one cell, and possibly a substantial number in some instances.

Accordingly, the efforts to reveal a threshold, if one exists, will now be briefly described. When the two cases of Down syndrome presumably unrelated to radiation are excluded from the 19 cases of severe mental retardation exposed 815 weeks after ovulation, and a linear threshold model is fitted to the data, the 95% lower bound of the estimated threshold ranges from 0.06 to 0.31 Gy, which suggests the presence of a threshold. As for the 16- to 25-week group, the 95% lower bound of the estimated threshold is 0.28 Gy, irrespective of whether the two cases of mental retardation presumably unrelated to radiation are or are not included (Otake et al., '96). When a similar model is fitted to the data on seizures, the 95% lower bound of the estimated threshold includes zero, so that the presence of a threshold cannot be established statistically (Dunn et al., '90). When a threshold model is fitted to the mean IQ scores (Schull et al., '88) and school performance scores no clear evidence of a threshold emerges(Otake et al., ’88); however we note that in both instances the mean scores are similar, to the scores of the control group in the low dose range (<O.10 Gy), and no excess risk is observed in pairwise comparisons of the lower dose groups. Finally, the estimated threshold obtained from the dose-response relationship for small head size is zero, or thereabouts (Otake and Schull, ’93).

Where does this leave us? First, it seems most unlikely that the epidemiologic data will ever provide a compelling answer to the question of whether a threshold does or does not exist. The data are simply too limited to expect more than has been described. Second, if an answer is to come, it must come either through the use of experimental animals, or a far better understanding, preferably at the molecular level, of how the brain functions than now exists, or both. For example, Fushiki and colleagues (’93) have shown that, at doses as low as 10 cGy, there is a significant reduction in N-CAM immunoreactivity in the matrix cell zone in an explant culture system using rat neocortex. Precisely why this occurs is not clear, but it is not unlikely that the most active site in N-CAM synthesis is significantly affected by radiation. Given the importance of N-CAM in neuronal migration, this could result in mismanaged migration and cognitive dysfunction.

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