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Brain Abnormalities among the Mentally Retarded Prenatally Exposed Atomic Bomb Survivors

William J. Schull, Ph.D.; Hiromu Nishitani, M.D.; Kanehiro Hasuo, M.D.; Takuro Kobayashi, M.D.; Ikuo Goto, M.D.; Masanori Otake, Ph.D.

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業績報告書シリーズ

原爆胎内被爆精神遅滞者の脳異常[§]

Brain Abnormalities among the Mentally Retarded Prenatally Exposed Atomic Bomb Survivors

William J. Schull[1]　西谷　弘[2]　蓮尾金博[2]　小林卓郎[3]　後藤幾生[3]
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要　約

特定妊娠週齢における重度精神遅滞の増加は，小頭囲を伴う場合もそうでない場合も，広島・長崎の原爆胎内被爆が脳の発達に与えた最も顕著な影響であった。細胞死やニューロン移動異常など種々の生物学的機序がこの障害をもたらしたものと考えられる。ここでは，放射線に関連した脳障害を最も起こしやすい受胎期間である受胎後8～15週に被爆した精神遅滞者のうち，5名の脳の磁気共鳴画像診断による所見結果を示す。受胎後8週または9週に被爆した2名については，異所性灰白質の大きな領域を認めた。これは本来の機能部位へのニューロンの移動ミスを示す強力な証拠である。受胎後12週または13週に被爆した2名については明らかな異所性灰白質領域は認められなかったが，皮質領域の発達障害を意味する軽度の大回脳症を認めた。更に，両名の小脳延髄は巨大であった。最後に，脳発達のもっと後期の第15週に被爆した1名については，他の4名に見られた変化は何ら認められなかった。またその脳は小さいが，構築は正常のように考えられた。

これらの所見を電離放射線に胎内で被曝した際に起こる発生学的事象の観点から考察した。

[§]本業績報告書は研究計画書RP 5-87に基づく。本報告にはこの要約以外に訳文はない。承認 1991年9月13日。印刷1992年7月。

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Technical Report Series

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William J. Schull, Ph.D.[1]; Hiromu Nishitani, M.D.[2]; Kanehiro Hasuo, M.D.[2]; Takuro Kobayashi, M.D.[3]; Ikuo Goto, M.D.[3]; Masanori Otake, Ph.D.[4]

Summary

An increased occurrence of severe mental retardation, with or without accompanying small head size, at specific gestational ages has been the most conspicuous effect on brain development of prenatal exposure to the bombings of Hiroshima and Nagasaki. A variety of biological mechanisms could be responsible for this finding, including cell killing and mismanaged neuronal migration. We describe here the findings on magnetic resonance imaging of the brains of five of these mentally retarded individuals, all of whom were exposed in the 8th through the 15th weeks following fertilization, the gestational period shown to be the most vulnerable to radiation-related damage. In the two cases exposed at the 8th or 9th week following fertilization, large areas of ectopic gray matter are seen, strong evidence of a failure of the neurons to migrate to their proper functional sites. The two individuals exposed in the 12th or 13th week show no readily recognized ectopic gray areas but do show mild macrogyria, which implies some impairment in the development of the cortical zone. Moreover, both have mega cisterna magna. Finally, the one individual seen who was exposed still later in development, in the 15th week, shows none of the changes seen in the other four individuals. This person's brain, though small, appears to have normal architecture.

These findings are discussed in terms of the embryological events transpiring at the time of the prenatal exposure of these individuals to ionizing radiation.

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Introduction

An increased occurrence of severe mental retardation, with or without accompanying small head size, at specific gestational ages has been the most conspicuous effect on brain development of prenatal exposure to the atomic bombings of Hiroshima and Nagasaki.[1–4] A variety of biological events could be responsible for this finding, including cell killing and mismanaged neuronal migration. Several lines of evidence suggest that the latter may be a particularly important contributor. Data are, however, sparse and difficult to obtain; heretofore essentially the only source has been autopsies, and only four of these have occurred.

Heterotopic gray matter has been known to be associated with other abnormalities of brain development and function for over a century,[5,6] but until the advent of better methods of imaging the living brain, the prevalence and importance of heterotopic gray matter have been difficult to document. Recognition of heterotopic areas rested on pneumographic techniques that were not only invasive but also unsatisfactory in many respects.[7,8] Computed tomography improved matters somewhat,[9] but the introduction of magnetic resonance imaging (MRI) with its greater definition of gray and white matter has precipitated a flurry of interest and case studies and has provided previously unavailable opportunities to document the occurrence of brain abnormalities in the living.[10–15] The cost and time involved in MRI presently preclude its use in most epidemiological settings, but its judicious application could, for example, materially improve our understanding of specific brain developmental processes, such as neuronal migration, through the better delineation of the factors that intrude on the normal process. Accordingly, to gain some insight into its usefulness, an exploratory study of a limited number of mentally retarded individuals with small head size exposed prenatally to atomic bomb (A-bomb) radiation was initiated in 1987.

The purpose of the present report is to describe the findings to date on five individuals exposed in the 8th through the 15th weeks following fertilization, the gestational period at which recent studies have shown brain development to be most vulnerable to radiation-related damage.

Materials and Methods

Over the years, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have established at least three overlapping samples of individuals prenatally exposed to the bombings of Hiroshima and Nagasaki.[3] Differences among these samples reflect the different purposes for which they were initially chosen, such as the bases for clinical examinations or mortality surveillance.[3] The present study focuses on the so-called clinical sample, in which the follow-up is most complete and has extended over the longest period of time. Among the 1,598 nonexposed and exposed children in the In Utero Clinical Study Sample in Hiroshima and Nagasaki described by Otake et al.,[4] 30 cases with severe mental retardation have been seen, 22 in Hiroshima and 8 in Nagasaki. All of these cases of severe mental retardation were diagnosed before the age of 17, and these diagnoses have not been changed in any subsequent study of these individuals, including this report. Judgments of severe mental retardation were based upon clinical impressions and not on an IQ score, if such existed. An individual was deemed to be

severely mentally retarded if he or she was "unable to perform simple calculations, to make simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized."

Gestational age at exposure is based upon the inferred first day of the last menstrual period and has been calculated with the following function:

$$\text{Days of pregnancy ATB} = 280 - (\text{date of birth} - 6 \text{ or } 9 \text{ August } 1945) \ ,$$

where the mean duration of pregnancy is taken to be 280 days and the date of birth was obtained by interview with the individual or his or her mother. To obtain the age after fertilization, 14 days have been subtracted from the "days of pregnancy ATB" (at the time of the bombings). Age in days was changed to age in weeks by dividing by 7.

At the time the present study was begun, 22 of the 30 severely retarded individuals in the clinical sample were known to be alive, although not necessarily living within Hiroshima or Nagasaki, and potentially available for study. Participation was sought of all of those individuals with known small head sizes and with measured or apparent IQs in the 50–70 range. These criteria for selection were pragmatic, based largely on two considerations. First, an atypically small head suggests subvening brain damage since the size of the calvarium is primarily a response to the growth in volume of the brain itself. Second, the nature of the imaging process, which requires the subject to be immobile in a small tunnel for an appreciable period of time, could produce apprehension and hence movement if he or she does not have at least a minimal understanding of what is required. Retarded individuals with still lower intelligence quotients tend to have purposeless movements and are thus unable to be immobile. Use of sedation did not seem ethically defensible under the circumstances attending our study.

Among the 22 living mentally retarded individuals, 12 had been exposed between the 8th and 15th weeks following fertilization and met the criteria described above. Two individuals refused to participate and 3 resided outside of the contact area. Of the 7 remaining, 4 have been examined and the other 3 are presently in a hospital or otherwise not available. One other individual, NT, not in the clinical sample, was examined; she was born outside of the limits of the city and therefore was ineligible for inclusion in the original sample, but she is known to have been exposed in the developmental period of immediate interest.

In the visualization of the brain, a General Electric 1.5-tesla machine was used. Films of 38 proton-density slices are available on all cases, and normally either or both of seven coronal and five sagittal inversion recovery images. All of the images were acquired in a 256 × 256 matrix with a 20-cm field of view and were averaged over two excitations. At least two neuroradiologists, who were unaware of either the gestational age of the individual at the time of exposure or the actual A-bomb dose he or she received, read each image.

Case reports

Case 1. A sturdily built, but small (150-cm, 50-kg) 41-year-old male, KY (Master File [MF] No. [redacted]), born on 1 March 1946, with an atypically small head (51 cm) and low brow. Although sociologically he appears reasonably well

adapted and alert, he reads and writes poorly and cannot do sums. He is presently employed in a family-owned catering service doing simple tasks. He is married, but childless; his wife, who was not exposed, is also retarded.

A-bomb exposure. He was exposed at a distance of 1,060 m to an estimated uterine absorbed dose (DS86) of approximately 0.86 Gy at 8–9 weeks following fertilization. His mother, who exhibited severe epilation but did not report other symptoms, died of uterine cancer, and one sibling exposed at 12 years of age at the same location has died of cancer of the stomach.

Clinical impressions. A small, microcephalic male whose response to questions is slow, but who appears alert otherwise. His deep tendon reflexes were accentuated, and his finger motion was somewhat below normal, but no other unusual neurological findings were seen.

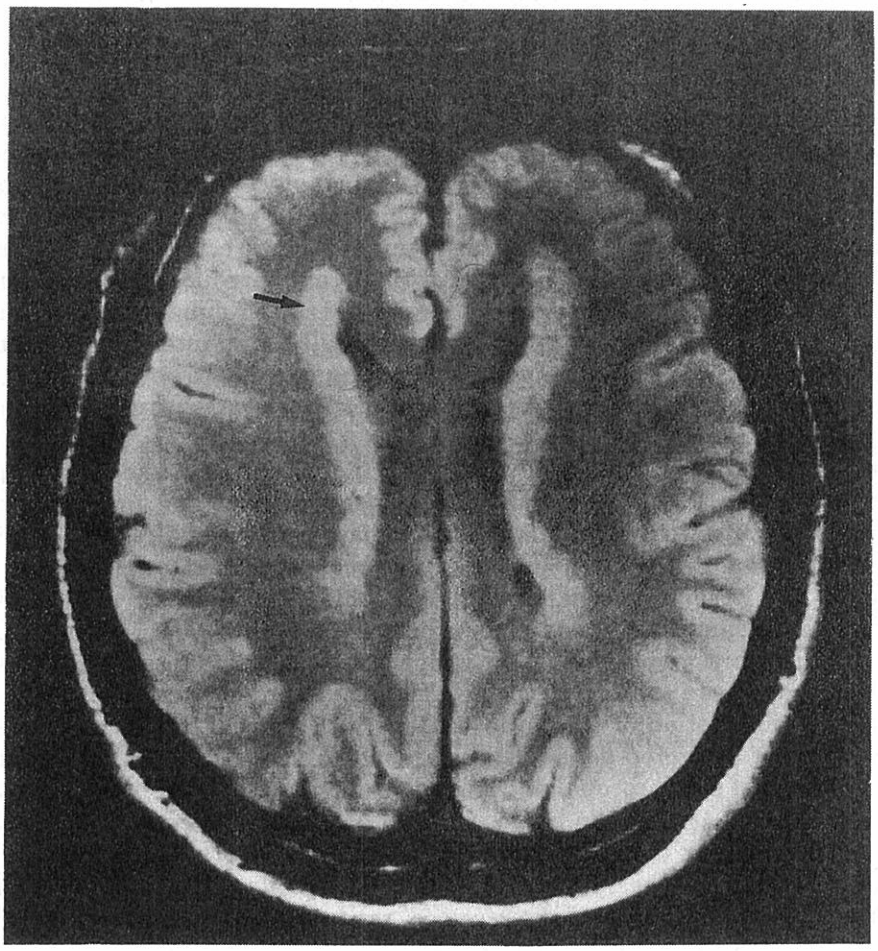

Figure 1. A 5-mm-thick transverse image at level 1122. The image was acquired with a spin-echo sequence with scan parameters TR = 2,000 ms and TE = 20 ms. Note the large, generally symmetrical areas of gray matter extending from the anterior to the posterior horn of both ventricles. (Case 1)

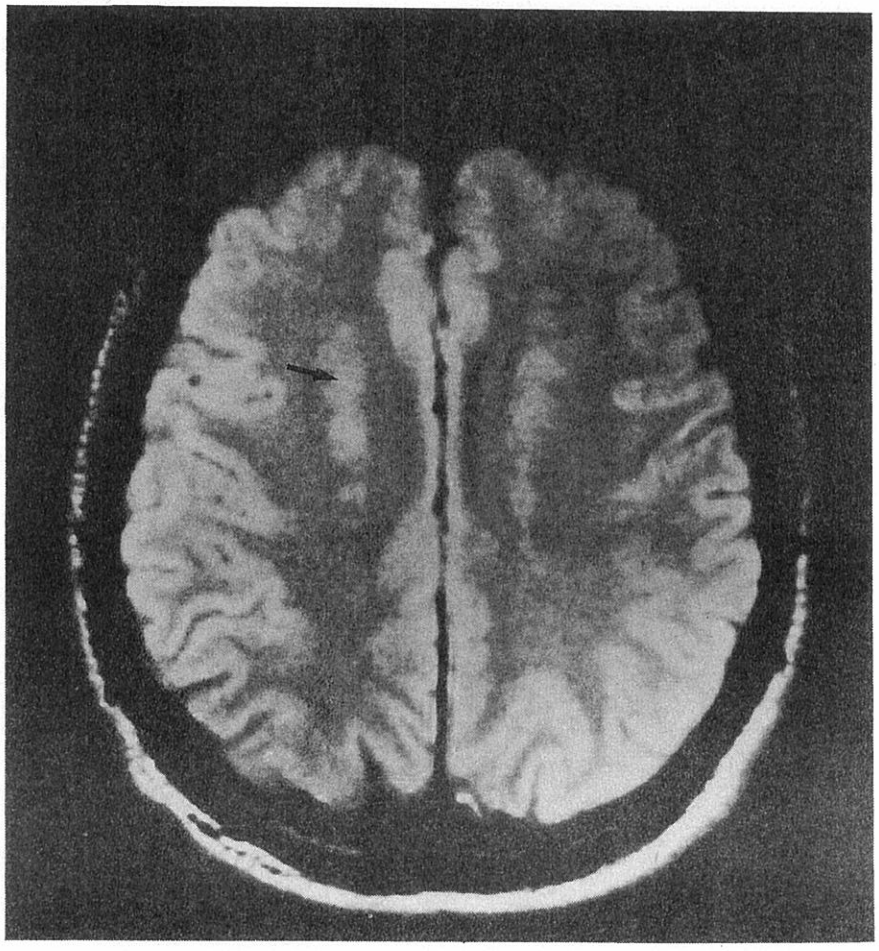

Figure 2. A 5-mm-thick transverse scan at level 1069. This image is primarily spin-density weighted. The scan parameters were TR = 2,000 ms and TE = 20 ms. Note the lumpy, irregular nature of the gray matter. (Case 1)

MRI findings. Extensive areas of ectopic gray matter were visualized lateral to both ventricles extending from the anterior to the inferior horn (see Figures 1–3). The ventricles themselves appear somewhat larger than normal. The development of the bilateral frontal sinus appears normal. The anterior commissure is abnormally widened, and the nucleus accumbens septi appears slightly thickened.

Case 2. A well-nourished, below average but not conspicuously small 41-year-old male, HK (MF No. [redacted], born on 24 February 1946, with an atypically small head (48.5 cm). No intelligence test score is available; however, he is moderately gregarious, affable, and curious about events that surround him. He reads and writes very poorly and cannot do sums. He is presently living at an

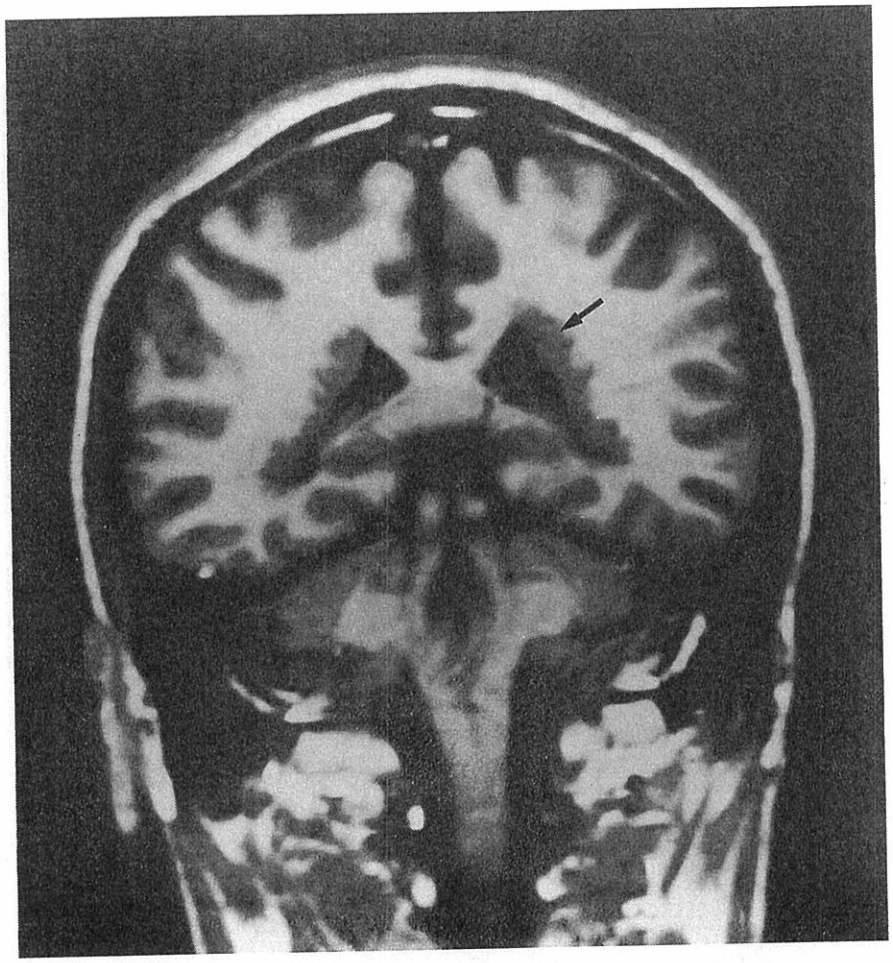

Figure 3. A 5-mm-thick coronal scan acquired at level 1130 with an inversion-recovery sequence. The scan parameters were TR = 1,500 ms, TE = 20 ms, and TI = 600 ms. Note the excessively large areas of gray matter lateral to both ventricles. The ventricles appear larger than normal relative to brain size and somewhat distorted. (Case 1)

institution for the mentally and sociologically handicapped, where he engages in simple farming activities.

A-bomb exposure. He was exposed at a distance of about 1,270 m to an estimated uterine absorbed dose (DS86) of approximately 0.69 Gy at 9 weeks following fertilization. His mother, who exhibited severe epilation, survives, but his father, exposed at the same location, died of cancer of the stomach at 72 years of age.

Clinical impressions. Neurological examination confirmed both his mental retardation and small head but established no other unusual findings.

MRI findings. The magnetic resonance images were distinctly abnormal. Extensive areas of lumpy gray matter are seen lateral to both ventricles extending from the anterior to the inferior horn (see Figures 4–6); the ventricles,

however, appear normal or nearly so in size and configuration. The anterior commissure is somewhat wider than normal, and the nucleus accumbens septi is thickened. Formation of the caudate lenticular bridge appears to be poor.

Case 3. A well-nourished, but small-statured (139-cm, 36-kg), 41-year-old microcephalic female, TT (MF No. [redacted], born on 27 January 1946. Her head circumference is 49 cm. Her intelligence test score (Koga Test) at the age of 11 was 56. She can neither read nor calculate adequately. Although she appears alert, her sense of time and place and her memory are poor. She presently works in an institution for the mentally handicapped packaging nails.

A-bomb exposure. She was exposed at a distance of about 1,110 m to an estimated uterine absorbed dose (DS86) of approximately 1.64 Gy at 13 weeks following fertilization. Her mother, who died at the age of 47 reportedly of a

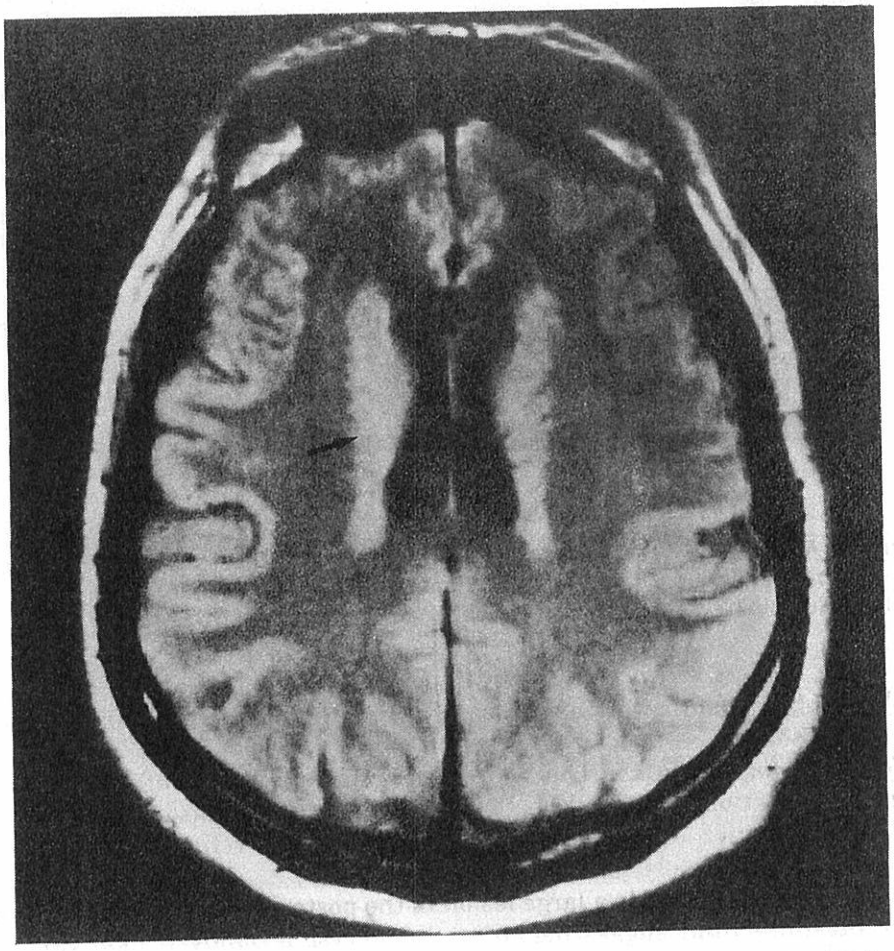

Figure 4. A 5-mm-thick transverse image at level 1137. The image was acquired with a spin-echo sequence with scan parameters TR = 2,000 ms and TE = 20 ms. Note the atypically large areas of gray matter lateral to both ventricles and the general similarity of this image to that in Figure 1. (Case 2)

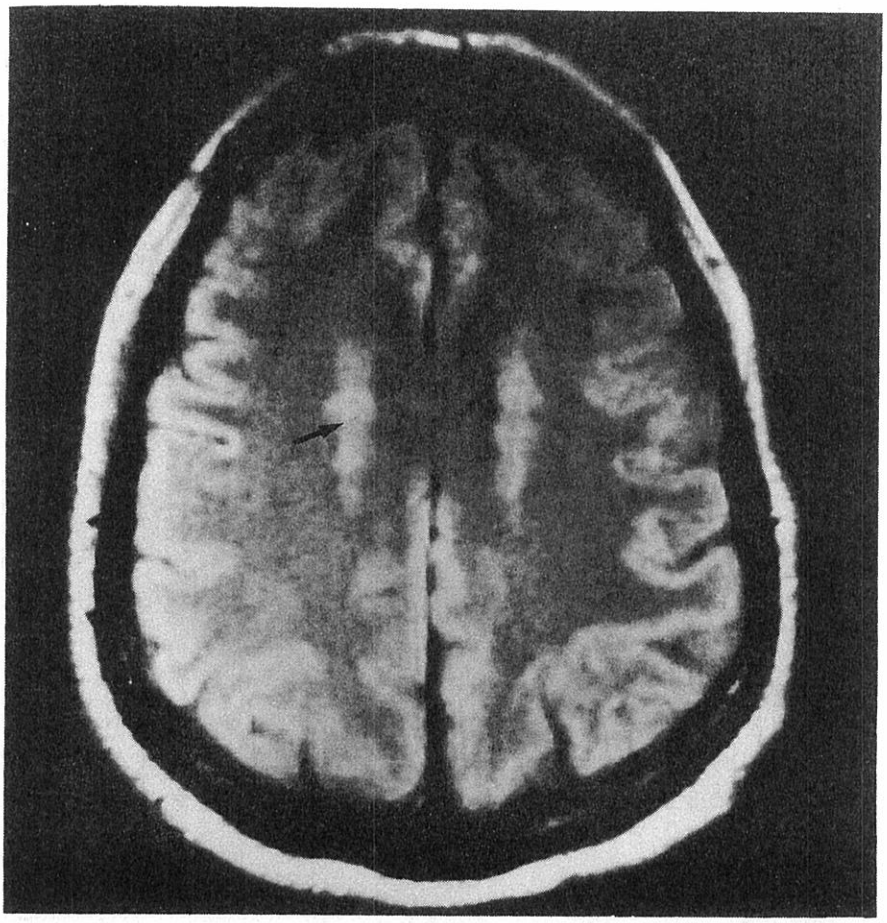

Figure 5. A 5-mm-thick transverse image through level 1138. The image was acquired with a spin-echo sequence with scan parameters TR = 2,000 ms and TE = 20 ms. Note again the lumpy irregular nature of the ribbons of gray matter. (Case 2)

cerebral infarct, had severe epilation following the bombing but did not report other symptoms.

Clinical impressions. The neurological examination confirmed both her mental retardation and small head. There was some increase in her jaw reflex and neck retraction reflex, but most other deep tendon reflexes were normal or at most only slightly elevated.

MRI findings. There is a large lesion in the posterior fossa with the intensity of cerebrospinal fluid, suggesting an arachnoid cyst, a Dandy-Walker variant, or mega cisterna magna. Since the lesion is symmetrical (see Figure 7), mega cisterna magna appears most likely. Although generally the architecture of the cerebrum seems normal, the gyri appear thicker than normal, particularly in the

frontal lobe, and the sulci are shallow and fewer, suggesting a mild macrogyria (Figure 8). In the left frontal lobe a small lesion is seen, possibly a lacunar infarct.

Case 4. A smaller-than-normal 41-year-old female, NT, born on 2 February 1946, who walks with a decided limp due to an unrepaired congenital dislocation of the hip, bilateral. Her sense of orientation in place and time are good, but her memory is poor. She reads simple material with difficulty and cannot do simple sums. She presently works in a special institution for the mentally handicapped packaging nails.

A-bomb exposure. She was exposed at a distance of 997 m from the hypocenter to an estimated DS86 uterine dose of 1.76 Gy in the 12th–13th weeks following fertilization. Her mother, who is still alive, exhibited all of the cardinal symptoms of acute radiation sickness—epilation, bleeding gums, and petechiae. Her mother had a cancer of the stomach removed surgically in 1983 and in the following year had 40 cm of her small bowel removed.

Clinical impressions. The neurological examination confirmed the dislocation of the hip, her mental retardation, and the presence of accentuated deep tendon reflexes but no other abnormal findings.

MRI findings. There is a large lesion in the posterior fossa extending leftward from the midline with the intensity of cerebrospinal fluid (Figure 9). Although this lesion has pressed the cerebellum forward, its development appears normal.

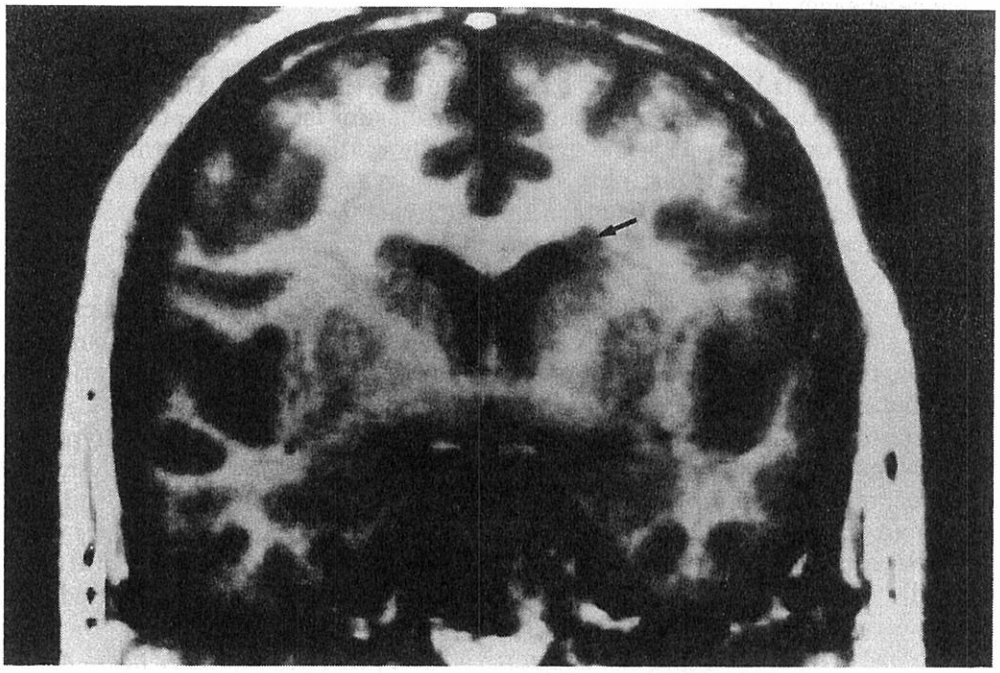

Figure 6. A 5-mm-thick coronal image at level 1094. The image was acquired with an inversion-recovery sequence with scan parameters TR = 1,500 ms, TE = 20 ms, and TI = 600 ms. Observe the areas of gray matter in addition to those associated with the caudate nucleus. Note too that the ventricles appear larger than normal relative to brain size and somewhat distorted. (Case 2)

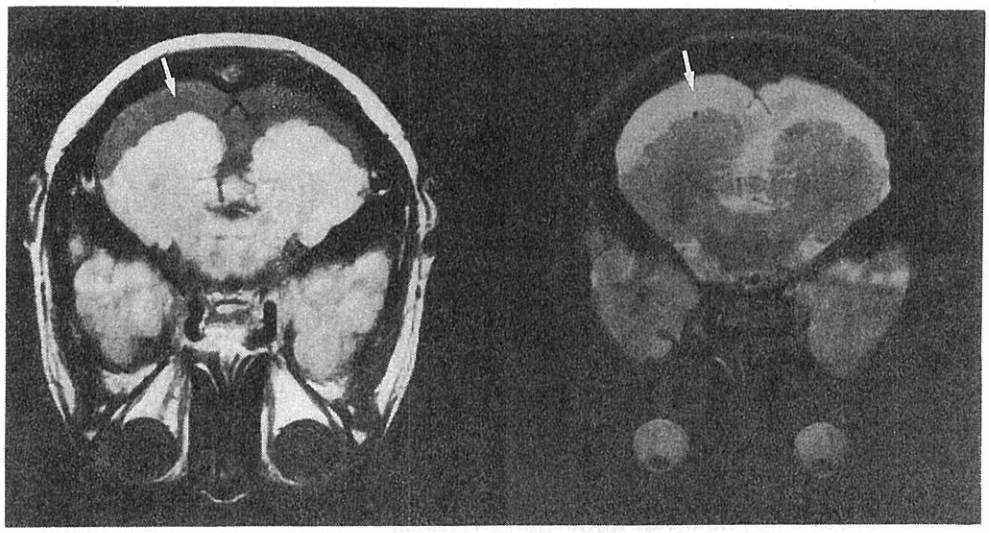

Figure 7. Two 5-mm-thick transverse images through level 1071. The images were acquired with a multislice spin-echo sequence. The scan parameters for the image on the left were TR = 2,000 ms and TE = 80 ms, and for the image on the right they were TR = 2,000 ms and TE = 20 ms. Observe the excessively large cavernous area posterior to the cerebellum. (Case 3)

The lesion itself is most likely a retrocerebellar arachnoid cyst. The third ventricle is smaller than normal, and the corpus callosum is located inferiorly to its normal position (Figure 10). The gyri, especially in the frontal palatal lobes, are larger than normal, suggesting a mild macrogyria, and the cingulate gyrus is underdeveloped (Figure 11). There is a small, hypointense area to the right of the corpus callosum on the T1-weighted image, possibly a lacunar infarct.

Case 5. A well-nourished, small-statured (156-cm, 50-kg), microcephalic 41-year-old male, MO (MF No. [redacted], born on 15 January 1946. His head circumference is 52 cm. His time orientation is good, place orientation is poor, and response to questions is slow. He appears alert, albeit somewhat apathetic. His immediate memory is fair, but long-term memory is poor.

A-bomb exposure. He was exposed at a distance of 1,091 m from the hypocenter in Nagasaki to an estimated DS86 uterine dose of 1.46 Gy. His mother, who survives, reported severe oropharyngeal lesions, severe epilation (90%), and mild petechiae.

Clinical impressions. Neurological examination revealed a short-statured, mentally retarded male with a small head. The jaw reflex was accentuated, but all other reflexes were present and within normal limits.

MRI findings. Aside from a diminutive brain, no abnormalities of an architectural nature were seen.

Discussion

Proper brain function is contingent upon a sequence of processes that must be spatially and temporally coordinated; these include neuronal proliferation, ag-

gregation and cytodifferentiation, neuronal migration, the growth of specific cell connections, neuronal death, and neurite consolidation. Failure of any one or a combination of these events could conceivably result in mental retardation. Experimental evidence on nonhuman primates indicates that ionizing radiation can and does impinge on a number of these processes, but there are little comparable human data. Only two mentally retarded A-bomb survivors have been autopsied. One of these, a female exposed to 0.01 Gy in the 31st week after fertilization, aside from exhibiting a small brain (1,000 g), appeared normal in other respects, both grossly and histologically; whereas the other, a male (brain weight = 800 g), exposed 12 weeks after fertilization to a DS86 uterine absorbed dose of 1.18 Gy, had massive misplaced gray areas similar to those seen in Cases 1 and 2.[16]

Although the number of cases examined is small, and speculations must be guarded, the magnetic resonance images are quite different among these five mentally retarded individuals. In the two cases exposed at the 8th or 9th week following fertilization, large ectopic gray areas can be seen, indicative of a failure of the neurons to migrate to their proper functional sites. This period corresponds to the first of the two migrational waves of neurons and, in particular, the one not associated with radial glial cells.[17,18] Normally, these neurons would be more deeply situated than subsequent migrants and would be involved in the conduction of stimuli interhemispherically or to other portions of the central nervous

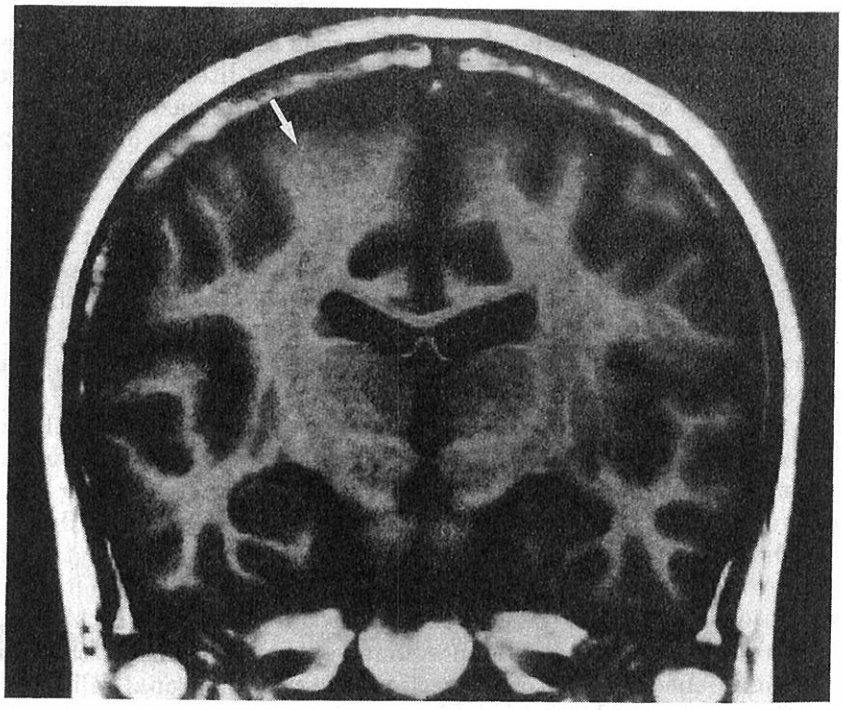

Figure 8. A 5-mm-thick coronal image at level 1099. The image was acquired with scan parameters TR = 1,500 ms, TE = 20 ms, and TI = 600 ms. Note the poorly defined gyri in the left hemisphere. (Case 3)

Figure 9. Two contiguous 5-mm-thick images located at level 1109. The images were acquired with a multislice spin-echo sequence. Scan parameters for the image on the left were TR = 2,000 ms and TE = 80 ms, and for the one on the right they were TR = 2,000 ms and TE = 20 ms. Note the large cavernous area posterior to the cerebellum, which is less symmetrical than that seen in Figure 7. (Case 4)

system. It warrants noting that the ectopic areas seen in these two cases differ substantially from those commonly reported in the literature.[12–14] The latter cases are typically unilateral and often subcortical, whereas the cases we report are bilateral, and the abnormal gray zones are ventricular or subventricular, suggesting a generalized failure to migrate rather than a localized interruption of migration.

The two individuals exposed in the 12th to 13th weeks, after much of the neuronal migration in the cerebrum has already occurred, show no readily recognized areas of ectopic gray matter but do show a faulty brain architecture, that is, a mild macrogyria, which implies some impairment of the development of the cortical zone. Moreover, both exhibit a mega cisterna magna, which also suggests an impairment of normal development.

Finally, the one individual seen who was exposed still later in development, in the 15th week, shows none of the changes seen in the other four individuals. Whether this implies radiation-related neuronal death is moot; for neurons to survive they must form connections, and the opportunities to do this are time limited. Those neurons that do not form connections die. Migrational errors cannot, therefore, be categorically excluded in this case; an alternative explanation could be impairment of the proper connectedness of the brain. As previously stated, there is experimental evidence showing that exposure at this time does lead to a diminished number of connections between neuronal cells.[19–22] If it is presumed that all or at least most of these connections have functional significance, then their diminution could compromise intellectual performance in some manner.

Although patently the numbers are small, it warrants noting that among the 17 mentally retarded cases in the clinical sample exposed to 0.01 Gy or more 8–15 weeks after fertilization, no less than 3 (18%) exhibit or have exhibited (in the case of the autopsied child) unmistakable evidence of profound migrational errors in the development of the cerebrum, and the frequency could be as high as 50% when based upon the 6 persons exposed in the "critical window" for whom brain studies actually exist. The former value is undoubtedly an underestimate of the true importance of migration, and the latter frequency could be an overestimate because of the nature of the sampling on which the evidence rests. However, it would appear clear that recognizable failures in migration are common occurrences following exposure to ionizing radiation in this critical period of brain development. This accords with experimental evidence.[23]

There are few human data to which those we have described can be compared. We are aware of no systematic studies of the frequency of heterotopia among the mentally retarded. Heterotopia has, of course, been seen, but is certainly not invariantly associated with retardation. Heterotopia is known to occur in fetal

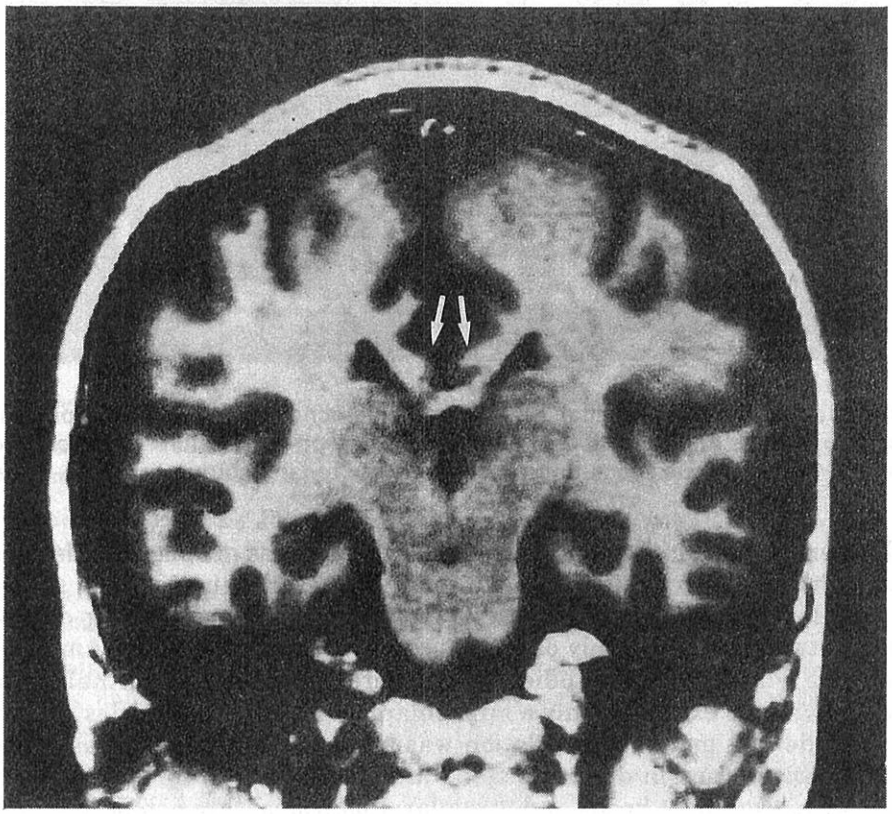

Figure 10. A 5-mm-thick coronal image at level 1125. The image was acquired with an inversion-recovery sequence with scan parameters TR = 1,500 ms, TE = 20 ms, and TI = 600 ms. Note both the poorly developed gyri in the right hemisphere and the atypical development of the cingulate gyrus. (Case 4)

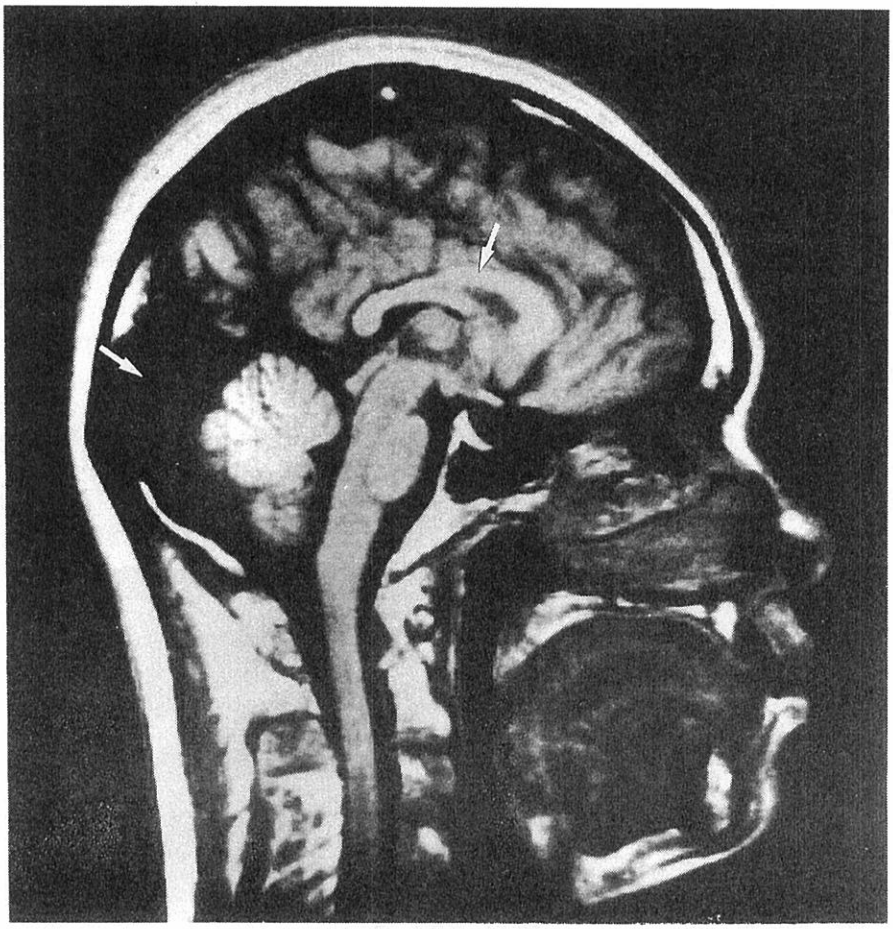

Figure 11. A 5-mm-thick sagittal T1-weighted spin-echo image. The scan parameters were TR = 400 ms and TE = 25 ms. Observe the compressed nature of the cerebellum and the large cavernous space to its posterior. Note too the corpus callosum. (Case 4)

alcohol syndrome, but the anatomical distribution of the misplaced cells does not accord with the distribution we have seen. Moreover, neuroimaging studies of individuals with the inherited Fragile X syndrome, where varying degrees of mental retardation commonly occur, have not revealed this defect. Among some 27 persons who have been studied, just 8 were found to be abnormal. Seven of these individuals exhibited only a mild enlargement of the ventricles, but in one case a moderate, generalized dilation was seen. Yet autopsy studies have disclosed abnormalities in dendritic spine morphology—very thin, long, tortuous spines with prominent heads and irregular dilatations were noted.[24]

This suggests a developmental error occurring after migration was completed.

Acknowledgments

This study would not have been possible without the cooperation of numerous individuals, in particular Mr. Minoru Omuta, advisor and confidant of many of the mentally retarded A-bomb survivors, who has done and continues to do much to publicize their plight. He and they gave selflessly and unstintingly of their time, since the examinations here described required the investment of a full day, for the appropriate facilities were not at hand in these cities. We respectfully dedicate this report to him and to the participants.

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