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SMALL HEAD SIZE FOLLOWING IN UTERO EXPOSURE TO ATOMIC RADIATION, HIROSHIMA AND NAGASAKI

広島および長崎における原爆放射線胎内被曝後の小頭症

ROBERT W. MILLER, M.D. WILLIAM J. BLOT, Ph.D.



ATOMIC BOMB CASUALTY COMMISSION

国立予防衛生研究所-原爆傷害調査委員会

JAPANESE NATIONAL INSTITUTE OF HEALTH OF THE MINISTRY OF HEALTH AND WELFARE

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ATOMIC BOMB CASUALTY COMMISSION HIROSHIMA AND NAGASAKI, JAPAN

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SUMMARY

For the first time, dose estimates have been related to small head circumference induced by exposure in utero to the atomic bomb. There was a progressive increase with dose in the frequency of the abnormality among persons whose mothers were exposed before the 18th week of pregnancy. In Hiroshima the minimum dose-producing effect was 10-19 rad, but in Nagasaki no effect was observed under 150 rad. At maternal doses of 150 rad or more in both cities, small head circumference was often accompanied by mental retardation. The observations at low doses in Hiroshima are not directly applicable to medical radiology because of the possible influence of neutrons (nil in Nagasaki) and perhaps to interactions with other environmental disturbances, more widespread in Hiroshima than in Nagasaki.

INTRODUCTION

The only teratogenic effect of ionizing radiation demonstrated to date in man has been small head circumference, more severe and accompanied by mental retardation in proportion to the mother's proximity to the hypocenter of the Hiroshima atomic bomb. 1-4 The effect was virtually limited to persons exposed in utero 7-15 weeks since the mother's last menstrual period. The original (1954) atomic bomb survivor study sample has been enlarged and a fixed cohort of persons in utero at the time of the atomic bombs (ATB) of Hiroshima and Nagasaki has been established. Dose estimates have been determined for almost the entire sample exposed in utero.

METHODS

ABCC has constructed a fixed sample cohort of Hiroshima and Nagasaki children who were in utero ATB. The sample consists of a group of persons

要約

原爆放射線胎内被曝によって誘発された小頭症と線量推定値との関係を今回はじめて検討した. 妊娠第18週以前に被爆していた母親からの子供にこの異常の頻度が線量とともに増加することが認められた. 広島では, 最低線量効果は10-19 rad でみられたが, 長崎では, このような影響は150 rad 未満においては認められなかった. 広島・長崎両市ともに母親の線量が150 rad 以上である場合に,小頭症が知能遅滞を伴っていることが多かった. 広島で認められた低線量の影響は, 医療用放射線の場合にはすいが)の影響もありうるし, またおそらくはその他の環境的攪乱(長崎よりも広島のほうが広範囲)の相互作用があったであろうからである.

緒言

電離放射線の唯一の奇形発生影響として今日までヒトに認められているものは小頭症であるが、これは広島では母親の被爆距離に反比例して小頭症が重篤になり、知能遅滞をも伴うものである.1-4 その影響は、母親の最終月経期から7-15週間に胎内被曝した者にかぎってみられた、最初(1954年)に設定された原爆被爆者の調査対象者は拡大され、広島・長崎における原爆時胎内被爆者の固定群が設定されている。胎内被爆群のほとんど全員についての線量推定値も決定されている。

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ABCCでは、原爆時胎内で被爆した広島・長崎の子供の 固定調査群を設定している.この調査群は、近距離胎内

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proximally exposed (within 2000 m) to the atomic bomb matched by gestational age and sex with groups of persons who were either distally exposed (3000-4999 m) or who were not in the cities (NIC) ATB. Thereafter these last two groups will be referred to as nonexposed controls. The children in this sample were scheduled for yearly clinical examinations from 1956 through 1965 on days close to their 10th through 19th birthdays.

Gestational age for each member of the sample was calculated from the date of conception, as estimated by subtracting 38 weeks from the child's date of birth and adjusting for pre- or post-maturity. Head circumference was said to be small if on one or more examinations it was at least 2 standard deviations below the average for the age and sex of the subject in each city, and was on all previous and subsequent examinations at least 1 standard deviation below the average. The average used for comparison was obtained from the combined data for children in each city who were in the nonexposed group (previous reports showed no significant differences in head circumference, between those distally exposed or NIC). 6,7 Mental retardation was judged by clinical examination and history, 4 and was diagnosed only if so severe that the subject was unable to perform simple functions.

Individual radiation dose estimates in rad were calculated for almost all the pregnant women in this study. The estimates were based on shielding configurations as well as distance from the bomb. 8

RESULTS

Data were available on head circumference, intelligence, and dosimetry for 388 children in Hiroshima and 99 in Nagasaki in the proximal exposed group of the sample cohort (Table 1). These totals were derived after exclusion of 49 children in Hiroshima (36 never examined, 11 with inadequate data for dose estimates, and 2 with Down's syndrome due to chromosomal defect before exposure), and 1 in Nagasaki (never examined).

The relationship of gestational age to small head circumference with or without mental retardation is shown in the Figure 1. The more abundant data for Hiroshima revealed that the frequency of effects and their severity, as shown by marked mental retardation, were greatest when exposure occurred between 3-17 weeks of gestation. Some effect beyond the 17th week was noted in both cities.

The data were examined to determine the lowest radiation dose at which an effect on head circum-

被曝群,この群の妊娠期間と性が一致する遠距離胎内被爆群(3000-4999 m)および原爆時両市にいなかった群から成っている.5 本報告では,この後者2群を非被爆対照群とよぶ.この調査対象者については,1956年から1965年まで,第10回から第19回目の誕生日の前後に毎年1回検診を行なった.

原爆時妊娠期は対象者の生年月日から38週間を引き、早産と遅産について補正を行なったうえで推定した。頭囲については、1回以上の検診時において、頭囲がその対象者と同じ性・年齢の者の平均値よりも2標準偏差少ない場合、また、すべての検診時において平均値よりも1標準偏差少ない場合を、頭囲が小さいものとした。対照に供した平均値は各市非被爆対照者を用いて算定したものである(頭囲については、以前の調査成績によれば、遠距離胎内被爆者と市内にいなかった者との間に有意な差はなかった).6・7 知能遅滞は検診および病歴調査4に基づいて判定し、単純な行動が果たされないほど重篤であった場合にのみ知能遅滞とみなした。

本調査の母親のほとんど全員について、個人線量推定値 (rad 単位)を算定した.この推定値は、遮蔽状態および被爆距離をもとにして得たものである.8

結 果

対象群のうち,近距離胎内被曝群について知能および線量推定に関する資料の入手されているものは,広島で388例,長崎で99例であった(表1).この数は,広島の49例(36例は未検診,11例は適当な線量推定資料未入手,2例は被爆前の染色体異常によるDown症候群),および長崎1例(未検診)を除いたものである.

妊娠期間と、知能遅滞を伴う小頭症、または知能遅滞を伴わない小頭症との関係を図示した。例数の多い広島では、妊娠3-17週に被曝した場合は、影響の頻度や程度(明確な知能遅滞を伴う)が最も高いことが認められた。妊娠17週以降の場合でも両市において若干の影響が認められた。

感受性が最も高い妊娠18週未満に胎内にあった者におけ る頭囲に対する影響の探知できる最低の放射線量を決定

FIGURE 1 SMALL HEAD CIRCUMFERENCE AMONG PERSONS EXPOSED IN UTERO TO THE ATOMIC BOMB, ACCORDING TO GESTATIONAL AGE

図1 妊娠期間別にみた胎内被曝者における小頭症

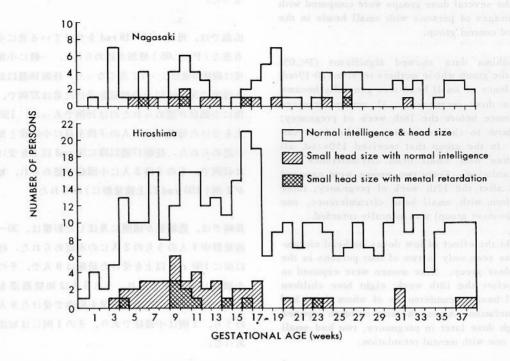


TABLE 1 FREQUENCY OF SMALL HEAD CIRCUMFERENCE ACCORDING TO CITY,

GESTATIONAL AGE AND RADIATION DOSE

表 1 小頭症の頻度:都市,妊娠期間および放射線量別

その平均低よりも	Gestational Age (weeks)					
Dose	Hiroshima *		Nagasaki*			
	0-17	18+	0-17	18+		
NIC, distal	- 31/764	s, the	10/2	246		
0-9 rad	4(1)/63†	4/65†	0/1	0/9		
10-19	6(1)/54	0/44	0/7	0/6		
20-29	6/24	1/14	1-01-20/5	2/7		
30-39	4/8	0/10	2/4	0/6		
40-49	3/11	0/6	0/6	0/3		
50-99	9(2)/20	2/24	0/9	0/11		
100-149	2/4	0/10	0/2	1/5		
150+	5(5)/13	1(1)/8†	8(3)/9	2(1)/9		
Unknown	1/7	0/3	0/0	0/0		
Total (in city)	40(9)/203	8(1)/185	10(3)/43	5(1)/56		

^{*} Among persons with small head circumference some also had mental retardation (numbers given in parentheses).

小頭症が認められた者に知能遅滞が伴う場合もあった(その数はかっこ内).
t Denominator includes one person with mental retardation and normal head circ

[†] Denominator includes one person with mental retardation and normal head circumference. 分母には小頭症を伴わない知能遅滞の 1 例が含まれている.

ference was detectable in the under-18-week gestational age period, the period of greatest susceptibility. The percentages of persons with small heads in the several dose groups were compared with the percentages of persons with small heads in the nonexposed control group.

The Hiroshima data showed significant (P<.05) excess in the group whose mothers received 10-19rad. The prevalence of small head size generally became greater as dose increased; 37 women received 50 rad or more before the 18th week of pregnancy; 16 gave birth to children with small head circumferences. In the group that received 150+rad, all five children with small head circumference had mental retardation. Forty two women were exposed to 50+rad after the 17th week of pregnancy; three bore children with small head circumference, one (in the 150+ dose group) was mentally retarded.

In Nagasaki the effect of low doses on head circumference was seen only in two of four persons in the 30-39 rad dose group. Nine women were exposed to 150+rad before the 18th week; eight bore children with small head circumferences of whom three had mental retardation. Among the nine children exposed to this high dose later in pregnancy, two had small head size, one with mental retardation.

Height during adolescence was less than usual among those exposed in utero within 1500 m from the hypocenters. 6,7 Hence, accompanying smaller head circumference at high doses was small stature. Stature in our study was said to be "small" if on one or more examinations it was at least 2 standard deviations below the average for the age and sex of the patient in each city.

To examine the relation between small head circumference and small height at low doses, the percentages of children with small height according to gestational age and dose are listed in Table 2. While a significantly greater frequency in small head size was noted at doses as low as 10-19 rad in Hiroshima and continued to hold for all higher dose groups, only for doses in excess of 150 rad was the frequency of small stature significantly increased. Of the 18 persons with small stature exposed before 18 weeks' gestation in the two cities, 14 had small head circumference of whom 10 were mentally retarded. At high dosage (150+rad) seven of eight children had small head circumference, with six also mentally retarded.

DISCUSSION

Intrauterine radiation exposure induced small head circumference at very low doses - the lowest yet

するために、資料を調べた. 各線量群にみられた小頭例の率と、非被曝対照群における小頭例の率との比較を行なった.

広島では、母親が10-19 rad を受けている者に小頭症の有意な (P < .05) 増加が認められた。一般に小頭症の頻度は線量の増加につれて高くなった。妊娠18週以前であった母親で50 rad 以上の線量を受けた者は37例で、その子供に小頭症が認められたのは16例であった。150 rad 以上を受けた母親では5人の子供全員に小頭症と知能遅滞が認められた。妊娠17週以降に50 rad 以上を受けた母親は42例で、その子供3人に小頭症が認められ、知能遅滞が1例(150 rad 以上線量群に)みられた。

長崎では、低線量が頭囲に及ぼした影響は、30-39 rad線量群中4人のうちの2人にのみ認められた。妊娠18週以前に150 rad以上を受けた母親は9人で、その子供に小頭症は8例認められ、うち3人は知能遅滞を伴っていた。妊娠後期にこの高線量を胎内で受けた9人の子供のうち、2例は小頭症であり、その1例には知能遅滞があった。

爆心地から1500m未満で胎内被曝した者では、青年期の身長が通常よりも低かった.6.7 したがって、高線量の場合には、小頭症に伴って低身長がみられた. 本調査における身長は、1回以上の検診において、対象者と一致する年齢および性の者の平均値よりも少なくとも2標準偏差低かった場合に「低い」とみなした.

低線量における小頭症と低身長との関係を調べるため、 妊娠期間および線量別にみた低身長例の頻度を表 2 に示 した. 広島では10-19 rad の低い線量でも、小頭症の頻 度が有意に高く、そしてより高い線量群にもこれが認め られたが、身長の低い頻度は 150 rad 以上の線量の場合 にのみ有意に高かった. 両市で妊娠18週以前に胎内被曝 した者で身長の低かった18例のうち、14例は小頭症であ り、そのうち10例には知能遅滞があった. 150 rad 以上 の高線量においては、8人の子供のうち 7 人は小頭症で あり、そのうち 6人には知能遅滞も認められた.

考 察

胎内放射線被曝はきわめて低い線量において小頭症を誘発した。この線量は人体に肉眼で探知できるような影響

TABLE 2 FREQUENCY OF SMALL HEIGHT ACCORDING TO CITY, GESTATIONAL AGE
AND RADIATION DOSE

表 2 身長の低いものの頻度: 都市, 妊娠期間および放射線量別

	Gestational Age (weeks)				
Dose	Hiroshima		Nagasaki		
THE PERMIT TOWN	<18	18+	< 18	18+	
NIC, distal	- 37/776	earry arr	- 16/246	rdg evil 11	
0-9 rad	5/66	1/65	0/1	0/9	
10-19	2/56	1/45	0/7	0/6	
20-29	1/26	1/14	0/5	1/7	
30-39	0/10	0/11	0/4	1/6	
40-49	0/12	0/6	0/6	0/3	
50-99	2/20	0/24	0/9	0/11	
100-149	0/4	1/10	0/2	0/5	
150+	5/13	0/8	3/9	1/9	
Unknown Total	0/7 15/214	0/3 4/186	0/0 3/43	0/0 3/56	

known to produce a grossly detectable effect in man. The abnormality was found in excess among children whose mothers received as little as 10-19 rad in Hiroshima. The dose to the fetus or embryo may be still less, because to some extent the mother's body shielded the child. The effect may have been escaped if by good fortune the mother's pelvis came between the fetus and the radiation.

The main stimulus to skull growth is brain growth. Radiation apparently causes general cell depletion of the developing brain, with secondary small head circumference. When depletion is great enough, mental retardation occurs. 9-11 With less depletion intelligence is within normal range, but may be reduced as compared with the child's full potential had he not been irradiated. It appears therefore that even small intrauterine exposures may deprive the individual of some intelligence.

Because the sample was defined as of age 10 years, statistical evaluation of head circumference could not be made for children who died or were examined only before this age. Six persons in the proximal exposed sample were examined prior to age 10 but not subsequently.2 The mothers of two received doses of over 150 rad before the 18th week of gestation. Both children had small head size and were mentally retarded. Nine other persons not in our fixed cohort but believed to have been within 2000 m ATB were examined prior to age 10 and had maternal radiation doses estimated. Only one received more than 150 rad (at gestational age 10 weeks). The child was mentally retarded with small head circumference. Inclusion of these cases, not feasible in the statistical procedure used, would have accentuated the high dose effect.

をもたらす最少量である. 広島では母親が10-19 rad の低い線量を受けた場合でも, その子供に普通より多くの異常が認められた. 胎児または胚胎が受けた線量は, 母・ 体がある程度胎児を放射線から遮蔽しているのでさらに少ないであろう. 幸運にも母親の骨盤が胎児と放射線の間にあった場合には, 影響をまぬがれているのかもしれない。

頭蓋骨の成長に対する刺激のうち、主要なものは脳の成長である。放射線は発育中の脳に対して一般に細胞の減少をもたらし、二次的に小頭症を起こすのである。細胞の減少が強い場合には知能遅滞が起こる。9-11 細胞の減少が少ない場合、知能は正常範囲内に留まるが、もし被曝していないで完全に成長した場合と比較すれば、知能には減退があるかもしれない。すなわち、微量の線量を胎内で受けると知能の減退が起こるのかもしれない。

対象群は10歳現在の者をもって設定されたので、この年齢以前に死亡した者またはこの年齢以前に検診を受けた者については、頭囲についての統計学的検討を行なうことはできなかった。近距離胎内被曝者で10歳以前に検診を受けておない。2 2人の母親は妊娠18週以前に150 rad 以上の線量を受けていた。いずれの子供も小頭症および知能遅滞が認められた。そのほか、原爆時2000m未満で胎内被曝した者9例(固定集団に属さない)については10歳未満で検診を行ない、母親の放射線量をも推定した。妊娠10週の時に150 rad 以上の線量を受けた者はわずか1例であったがその子供には知能遅滞と小頭症が認められた。これらの例を含めることは、用いた統計学的検査法では可能でなかったが、もし含めれば高線量の影響をいっそう強調したであろう。

Head circumference and height were very significantly correlated in the nonexposed group. Hence among the exposed group smaller height would also be expected with smaller head circumference. However, the occurrence of exceptionally small height (less than 2 standard deviations of the mean) failed to accompany small head circumference except at such high doses (150+rad) that nearly all of those with small height were mentally retarded.

In Nagasaki no effect on head circumference was consistently seen at doses of less than 150+rad. Similar unexplained differences between the cities in radiation effects have also been observed with respect to leukemia 12 and other cancer. 13 In each instance progressive increases beginning at low doses were observed in Hiroshima, but in Nagasaki an effect occurred only among the heavily exposed.

The quality of radiation differed in the two cities. At 10-49 rad, fission neutrons accounted for more than one fifth of the total (gamma+neutron) radiation in Hiroshima, but only a negligible percent in Nagasaki. Attenuation of neutrons by the mother's body would be even greater than for gamma radiation. If the difference in effect on head size in the two cities were due to neutrons, their relative biological effectiveness (RBE) would have to be substantially greater than that of gamma rays (RBE=1). In any event, because a neutron influence cannot be excluded, the low-dose effects in Hiroshima may not be directly applicable to medical x-irradiation.

Although circumstances other than radiation exposure may impair brain growth (e.g., malnutrition or severe illness during early infancy) 14,15 the general increase in small head circumference according to increasing dose in Hiroshima indicates that the effect was due to radiation. Radiation dose fell to nil at about 2000 m in Hiroshima (3000 m in Nagasaki) whereas the thermal and mechanical effects of the blast extended to about 4000 m. 16 Hiroshima is located on flat land, the area of destruction extended in all directions, whereas in Nagasaki it was localized to one of several valleys that the city comprises. Nutritional and economic deprivation in Hiroshima was consequently more extensive than in Nagasaki. Thus, though small head circumference in Hiroshima may be attributed to low-dose radiation exposure, it is not known whether the effect would have been as great in the absence of other severe environmental disturbance.

非被曝群では、頭囲と身長との間にきわめて有意な相関が認められた。したがって、被曝群における小頭症には低身長が伴うものと考えられる。しかし、小頭症に特に低身長(平均値の2標準偏差未満)の伴うことはなかった。ただし、高い線量(150+ rad)においては、低身長の者のほとんど全員に知能遅滞が認められた。

長崎では、150 rad 未満の線量では頭囲に対する影響は認められなかった。両市間において、このように説明できない差異が白血病¹² およびその他の癌¹³ についても観察されている。このような影響は、広島では各例において低線量でも観察され、線量の増大とともに漸増していたが、長崎では影響は強度被曝者のみに認められた。

放射線の線質には両市間に差があった. 10-49 rad の線域で核分裂の際放出される中性子は、広島では総線量(ガンマ+中性子)の光以上を占めたが、長崎では無視できる量にすぎなかった。 母体による中性子の減弱は、ガンマ線の場合よりも大きい。両市における頭囲に及ぼす影響の差が中性子によるものであったとすれば、中性子の生物学的効果比(RBE)はガンマ線のそれ(RBE=1)よりも相当大きいはずである。いずれにしても中性子の影響は除外できないので、広島で認められた低線量の影響を直ちに医療用X線被曝に適用することはできない.

放射線被曝以外の状態,たとえば、新生児期における栄養不良または重篤の疾患^{14,15}が脳の成長に障害をもたらすこともありうるが、広島で線量増加につれて小頭症が増加していたことは、その影響が放射線によるものであったことを示す。広島では約2000m(長崎では3000m)の距離で放射線量は0に下がったが、原爆の熱の影響と物理学的影響は約4000mにまで及んだ。16 広島は平坦であるので、破壊は全方向にわたったが、起伏に富んだ長崎では破壊は一つの谷間に限定された。その結果、広島における栄養上および経済上の障害は長崎の場合よりも広範囲に及んだ。広島の小頭症は低線量の放射線被曝によるものかもしれないが、その他の重大な環境上の攪乱がない場合に影響がこれほど大きかったであろうか否かは明らかでない。

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