Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study

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Abstract

Objective To determine whether exposure to low doses of ionising radiation in infancy affects cognitive function in adulthood.
Design Population based cohort study.
Setting Sweden.
Participants 3094 men who had received radiation for cutaneous haemangioma before age 18 months during 1930-59.
Main outcome measures Radiation dose to frontal and posterior parts of the brain, and association between dose and intellectual capacity at age 18 or 19 years based on cognitive tests (learning ability, logical reasoning, spatial recognition) and high school attendance.
Results The proportion of boys who attended high school decreased with increasing doses of radiation to both the frontal and the posterior parts of the brain from about 32% among those not exposed to around 17% in those who received >250 mGy. For the frontal dose, the multivariate odds ratio was 0.47 (95% confidence interval 0.26 to 0.85; P for trend 0.0003) and for the posterior dose it was 0.59 (0.23 to 1.47; 0.0005). A negative dose-response relation was also evident for the three cognitive tests for learning ability and logical reasoning but not for the test of spatial recognition.
Conclusions Low doses of ionising radiation to the brain in infancy influence cognitive abilities in adulthood.

Introduction

Ionising radiation may impair the developing human brain and adversely affect cognitive processes, as documented among children exposed in utero after the bombing of Hiroshima and Nagasaki or treated with radiation for ringworm of the scalp.[1-5] Evidence also comes from children treated for leukaemia or brain tumours[6-9]; but in these studies it is difficult to distinguish the effect of radiation from that of underlying diseases or treatment.[7] Existing data are based mostly on high doses of ionising radiation (≥1 Gy), therefore little is known about the effects of low doses of radiation or a possible threshold value and the effect of age at exposure. Computed tomography, which delivers high doses of ionising radiation, is increasingly being used in even young children after minor head trauma. The dose delivered to the brain of an infant during computed tomography of the skull is around 120 mGy.[10]

We analysed cognitive function in a large population based cohort of men at the time of military enlistment who had received low dose ionising radiation for cutaneous haemangioma before age 18 months. Based on previous experience, we hypothesised that damage to the frontal part of the brain would have a more severe effect on mental capacity than damage to the posterior part.

Participants and methods

Our cohort comprised all boys treated by radiotherapy for cutaneous haemangioma aged under 18 months at the Karolinska University Hospital in Stockholm. This cohort has been described previously.

Around 95% of Swedish men aged 18 or 19 years are tested before military service, and from the military register we obtained information on age at enlistment, education, number of siblings, birth order, father's occupation (a proxy for socioeconomic status), and cognitive test results.

Treatment for cutaneous haemangioma before age 18 months included β rays, γ rays, or x rays. During the study period, the most common treatment was with applicators containing radium-226.[11 12] X ray treatments mainly involved contact therapy (≤60 kVp, half value layer <1.0 mm aluminium). Some children were treated more than once. The dose from treatments was measured from the original applicators or the original depth-dose curves and tables. The location of the haemangioma was estimated from treatment records. Members of the cohort were categorised as either those who had enrolled at high school at the time of military tests or those who had not.

The Swedish psychological tests for military enlistment include tests of general instructions, concept discrimination, technical comprehension, and spatial recognition. The first three of these are believed to measure general verbal ability and to be sensitive to education. All test scores assigned during one particular year were standardised to a mean of 5 and a range from 1 to 9.

Statistical methods

We used logistic regression to model the probability of having entered the equivalent of high school using the categorical explanatory variables for estimated absorbed dose to brain, age (months) at treatment, number of siblings, father's occupation, and year of military test. Doses (mGy) were divided into five categories: 0, 1-20, >20-100, >100-250, and >250.

Differentiation between an individual's logical reasoning and other abilities was computed as the difference between the spatial recognition test and the average of the three remaining tests. The differences were also tested by analysis of variance with the

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explanatory variables used in the logistic regression of high school attendance.

Results

During 1930-59, 4577 boys aged under 18 months received radiotherapy for cutaneous haemangioma. After exclusions 2211 men were included in the analysis of cognitive function and 2551 in the analysis of high school attendance (see bmj.com).

The mean number of haemangiomas per child was 1.5 (range 1-16). Overall, 49% (n = 1380) of the men were irradiated when aged under 6 months, 39% (n = 1098) at 6-11 months, and 12% (n = 338) at 12-17 months. The mean age of the men at first treatment was 7 months (median 6 months). The average estimated absorbed dose to the brain was 52 mGy (median 20 mGy, range 0-2800 mGy) and the largest contribution came from irradiation of haemangiomas in the head region. The average and median dose to the frontal part of the brain was slightly higher than to the posterior part. An estimated dose of 100 mGy or more was delivered to the frontal part of the brain in 661/2816 (23.5%) men and to the posterior part in 384/2816 (13.6%).

High school attendance

A decrease in high school attendance was seen in all socioeconomic groups at radiation doses greater than 100 mGy when compared with the lowest dose of 1-20 mGy. No consistent difference was seen between the two lowest dose categories (1-20 mGy and >20-100 mGy); however, the increment of exposure was limited, with median values of only 0 and 30-40 mGy.

We found an overall statistically significant decreasing probability of attending high school in relation to radiation dose (table 1). Adjustment for potential confounders changed risk estimates only marginally. The relative decrease in high school attendance was greater for sons of low level white collar workers. The dose-response relations in the three socioeconomic classes, however, were not significantly different from each other when dose was used as a continuous variable.

The statistical power to separate the effect of dose to the frontal and posterior part of the brain was low due to a high degree of colinearity between dose estimates ($r = 0.84$, $P < 0.0001$). The dose to the frontal part of the brain provided a slightly better fit to the data than did the dose to the posterior part. Adding frontal and posterior doses did not significantly improve the fit of the model ($P = 0.29$). We found no evidence of a possible modifying effect by age at treatment.

Table 1 Odds ratios and 95% confidence intervals of high school attendance in relation to dose of radiation to the brain in 2551 Swedish men irradiated for cutaneous haemangioma when aged under 18 months

Dose to brain (mGy)	Crude odds ratio (95% CI)	Multivariate* odds ratio (95% CI)
Frontal dose		
0	1.00	1.00
0-20	1.03 (0.81 to 1.31)	1.14 (0.86 to 1.51)
>20-100	0.86 (0.70 to 1.06)	1.06 (0.88 to 1.36)
>100-250	0.58 (0.45 to 0.74)	0.70 (0.52 to 0.94)
>250	0.43 (0.26 to 0.72)	0.47 (0.26 to 0.85)
Odds ratio per 50 mGy	0.86 (0.81 to 0.91)	0.89 (0.83 to 0.95)
P for trend†	<0.0001	0.0003
Posterior dose		
0	1.00	1.00
1-20	0.99 (0.76 to 1.27)	1.06 (0.79 to 1.43)
>20-100	0.83 (0.69 to 1.01)	0.99 (0.79 to 1.24)
>100-250	0.44 (0.32 to 0.60)	0.55 (0.38 to 0.79)
>250	0.43 (0.19 to 0.98)	0.54 (0.23 to 1.47)
Odds ratio per 50 mGy	0.81 (0.75 to 0.88)	0.86 (0.79 to 0.93)
P for trend†	<0.0001	0.0005

*Adjusted for number of siblings, age at treatment, father's occupation, and year of test.
†Based on dose treated as continuous variable.

Table 2 Mean test results adjusted for number of siblings, age at treatment, and year of test in relation to radiation dose to frontal part of brain in 2211 Swedish men irradiated for cutaenous haemangioma when aged under 18 months. Values are means (standard errors) unless stated otherwise

		Category of military test		
Dose to brain (mGy)	No	Concept discrimination and general instruction	Technical instruction	Spatial recognition
0	638	5.50 (0.07)	5.45 (0.08)	5.36 (0.09)
1-20	400	5.67 (0.09)	5.40 (0.10)	5.37 (0.11)
>20-100	677	5.63 (0.07)	5.37 (0.08)	5.49 (0.08)
>100-250	410	5.42 (0.09)	5.31 (0.10)	5.48 (0.10)
>250	86	5.34 (0.18)	4.78 (0.21)	5.44 (0.21)
P for trend*		0.03	0.003	0.50

*Based on mean value in each strata and dose treated as continuous variable.

Cognitive tests

In univariate analyses, a significant dose-response relation was seen for all cognitive tests except spatial recognition. Frontal dose had a stronger association with the outcome variables than did posterior dose and was therefore considered in further analyses. In the multivariate setting, significant trends of decreasing test results with increasing dose were seen for concept discrimination and general instruction and technical comprehension. No trend was seen for spatial recognition (table 2).

To investigate whether the difference in dose-response between cognitive tests reflecting learning ability and logical reasoning was consistent within the men, we used as a response variable the individual difference between the results of the spatial recognition test and the average of the three tests. The unadjusted individual discrepancy between the different tests increased significantly with dose ($P = 0.0002$). Furthermore, both the significance and the estimated changes per unit dose remained essentially unchanged after adjustment not only for the potential confounders ($P = 0.0003$) but also for high school attendance ($P = 0.0008$).

Discussion

External radiotherapy to the head of infants with dose levels that overlap those from computed tomography may adversely affect intellectual development. In Sweden, during the period under investigation, academic performance was the principal determinant of high school attendance.

Military test results reflecting the difference between learning ability and logical reasoning were affected by the dose of radiotherapy but not influenced by age at treatment, father's occupation, or high school attendance. Furthermore, our a priori expectation that exposure to the frontal part of the brain would have a more severe effect on cognitive function was indirectly supported by the fact that cognitive tests that tap frontal processes seemed to be more affected by radiation.

We did not find an influence of age at exposure to ionising radiation, probably due to the narrow age range of 18 months.

On the basis of our findings, it is possible that diagnostic radiation with computed tomography of the head exceeds the individual threshold in several patients. A recent Swedish survey reported an average dose of 68 mGy to the brain of an adult after one computed tomography scan to the head and an estimated 30% higher dose to a child.[13] A recent US study estimated that the dose to an infant exceeded 100 mGy.[10]

The advantages of our study included having a large cohort, minimal losses to follow up, and the fact that the cohort members did not have other diseases such as leukaemia that could, by themselves or through therapy, confound the results. Lastly, selection bias was minimised as the results relied on internal comparisons rather than on external standards.

The results of other studies are generally compatible with our findings, although earlier investigations have focused on exposures in utero, higher doses, or children with malignancies that could confound the results. Studies of children irradiated for ringworm of the scalp share some similarities with this trial, and their results are generally compatible with our findings.[5]

Conclusion

Irradiation of the brain with dose levels overlapping those imparted by computed tomography can, in at least some instances, adversely affect intellectual development. Although formal diagnostic protocols do not advocate computed tomography in cases of minor head injuries, clinical practice dictated by legal and financial considerations does not always adhere to these protocols. The risk and benefits of computed tomography scans in minor head trauma need re-evaluating.

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What is already known on this topic

High doses of ionising radiation to the developing human brain cause mental retardation

It is unknown whether low level exposure in infancy has more subtle effects on cognitive function

What this study adds

Intellectual development is adversely affected when the infant brain is exposed to ionising radiation at doses equivalent to those from computed tomography of the skull

Diagnostic evaluation of children with minor head injures needs to be re-evaluated

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A memorable patient

The price of presumption

Assembling on the surgical ward for our first ward round, we were like snowmen on parade, with freshly starched white coats and stethoscopes shyly peeping from pockets. I was to clerk a young man, take a full history, and make an examination.

As I sat at the patient's bed his fear was almost tangible. Being psychiatrically inclined, I inquired of the source of his anxiety. He told me that he had dived into a swimming pool and injured his left knee, which had required treatment. I wasn't quite clear what treatment he had already received and had not the opportunity to read his case notes. He spoke of an operation to his leg, and, because he seemed anxious, I specifically asked him if he had any particular worries (although I had already concluded he had a cancer phobia). Reluctantly, he admitted that he was frightened that he had cancer and that the diagnosis was being kept from him.

As undergraduates, we were supposed to take a history, examine, and make an assessment. Therapy was certainly not part of our mandate. However, I boldly dismissed his dread and then asked to examine the offending part, certain I could reassure him. As he drew back the blanket I could see the right leg was perfectly normal. The left leg, I noted with dismay, was missing. Clearly an amputation had been performed. I was mortified, embarrassed, and quite inarticulate. It seemed that he had had an osteogenic sarcoma with secondaries. In 1963 chemotherapy had yet to arrive. Concluding the examination, I crept away without further comment.

I thought of him from time to time, hoping I would never see him again. Towards the end of the surgical attachment, however, we were doing "rounds" on the same ward. There was little apparent empathy with the mute suffering of people patiently enduring the detachment of the "professionals." I passed a side ward and caught sight of a gaunt and pitiable figure in bed. Our eyes locked in mutual recognition. It was my patient. His pleading burning eyes begged for reassurance—just once again.

Ashamed, I turned away in despair and hurried on. A week later he was dead.

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