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Down's Syndrome clusters in Germany in close temporal relationship to the Chernobyl accident

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Abstract
In two independent studies using different approaches and covering West Berlin and Bavaria, respectively, highly significant temporal clusters of Down's syndrome were found. Both sharp increases occurred in areas receiving relatively low Chernobyl fallout and concomitant radiation exposures. Only for the Berlin cluster was fallout present at the time of the affected meioses, whereas the Nuremberg cluster preceded the radioactive contamination for one month. Hypotheses on possible causal relationships are compared. Radiation from the Chernobyl accident is an unlikely factor, also, because the associated cumulative dose was so low in comparison with natural background. Given the lack of understanding of what causes Down's syndrome, other than factors associated with increased maternal age, additional research into environmental and infectious risk factors is warranted.

1. Introduction

Down's syndrome (trisomy 21) is a major congenital chromosomal disorder resulting in most cases from nondisjunction during meiosis in oocytes. Although nondisjunction is not thought to show any particular sensitivity to ionizing radiation, two ecological studies of Down's syndrome prevalence in the aftermath of Chernobyl showed statistically significant increases in birth cohorts and in prenatal diagnoses for which conception occurred in the early phase of environmental contamination caused by the reactor accident, i.e. in early May 1986 in Berlin [1] and in fall 1986 to winter 1986/87 in Scotland [2]. Both studies covered areas where maximum exposures due to Chernobyl reached only about 10 % of annual natural exposures to ionizing radiation.

Our institute conducted a large geographical correlation study to generate hypotheses of possible adverse health effects from the Chernobyl accident. An increase of Down's syndrome was found in Northern Bavaria (O=10, E=4.4, O/E=2.27, 95%CI=1.2-4.1) in December 1986 in close temporal relationship to the occurrence of the Berlin cluster [3]. Further analyses revealed that the increase in Northern Bavaria was due mainly to four diagnoses made in the urban area of Nuremberg, Fuerth, and Erlangen (NFE). These three adjacent cities form a metropolitan area of app. 700,000 people and 6,117 life births in 1986. The four cases in this area is 8.9 times what would be expected from the North Bavarian long term average of 0.94 cases in 1,000 live births (O=4, E=0.45, O/E=8.9, 99% CI 1.8-22.6). A causal relationship to Chernobyl radioactivity was excluded because the area received very low contamination and because the peak occurred in December 1986. Since none of the affected infants was premature, the meiotic nondisjunction in the germ cells must have taken place before the onset of fallout from the Chernobyl accident.

2. Characteristics of the Studies, Results

Characteristics of both studies are given in Table I.

2.1 Description of the Berlin cluster

The West Berlin series is based on routine data from prenatal and neonatal diagnostic examinations from all relevant hospitals of the city. Sperling et al. [4] reported a significant increase of cases with trisomy 21 among the children born in January 1987 in West Berlin, where about 2 cases were expected against 12 observed. The mother of one child with Down's syndrome had not been in Berlin at the time of conception. The cluster contained both preterm and fullterm births.

No obvious common cause for the cluster was apparent to the authors except the temporal correlation with Chernobyl fallout. They concluded that internal exposure to ionizing radiation, especially ^{131}I was likely responsible for the cluster [1], either directly or indirectly via changed sexual behavior of the mothers due to thyroid dysfunction caused by the low-level ^{131}I exposure [4].

Table I: Main study characteristics, prevalences, peak values of Down's syndrome, and activity concentration in the Bavarian and West Berlin studies

	Bavaria [16]	West Berlin [4]
method	spatio-temporal comparison	time series analysis
case ascertainment	live births, data collection via records from children's hospitals	antenatal diagnosis, stillbirths, live births
study period	1984-1989	1980-1989
mean live births per year	119,000 Bavaria 52,000 North Bavaria 6,400 NFE	19,000
mean prevalence of Down's syndrome	$1.08/10^3$ Bavaria $0.94/10^3$ North Bavaria	$1.56/10^3$
highest value	$2.45/10^3$ North Bavaria in December 1986 ($8.1/10^3$ NFE)	$6.8/10^3$ in January 1987
exposure (time integrated activity concentration in the air for April 28 - May 8, 1986 [23])	^{131}I [Bq*h/m³] N. Bavaria 200-500 S. Bavaria 500-1000 ^{137}Cs [Bq*h/m³] N.&S. Bavaria 200-500	^{131}I [Bq*h/m³] 100-200 ^{137}Cs [Bq*h/m³] 50-100

The highest rate of Down's syndrome during the study period was found in Northern Bavaria one month before the peak occurrence in Berlin, i.e. December 1986. A more detailed analysis of the cases born in December 1986 was conducted to make sure that no preterm births were included, because this would lead to misclassification of conception in terms of pre- or post-Chernobyl exposure. Though the peak in December 1986 was the highest observed in the study, it is only slightly higher than several other peaks, and does not differ significantly from these.

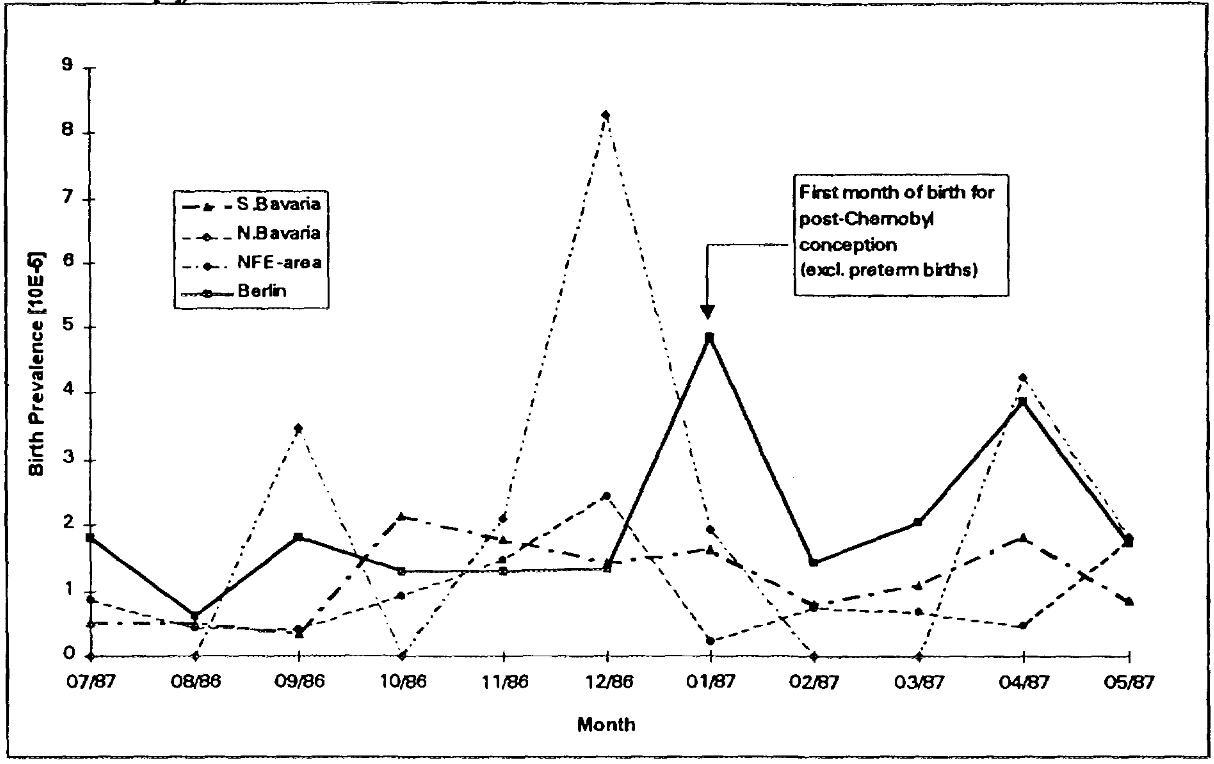
Fig. 1 depicts the prevalence rates of Down's syndrome in West Berlin, Southern Bavaria, Northern Bavaria, and the NFE-region for the time period described in [1]. This figure indicates that the variation within the Bavarian data set is much larger than in the Berlin series, even though the underlying population in Bavaria is larger. Berlin, it should be noted, is more urbanized and more homogeneous than Northern Bavaria in terms of socio-economic status.

3. Dosimetry

In view of the relatively short time period when nondisjunction is assumed to occur, a comparison of maximal exposure rates is also relevant. Therefore, maximal daily exposures are to be considered in exposure situations determined in part by short-lived radionuclides. Although for Southern Bavaria, the increase dose rate in the first day(s) of the Chernobyl fallout is up to ten times higher than natural background, the value for Berlin is in the range of local background, i.e. the dose rate was nearly double the background rate for a few days. Estimated average cumulative organ doses to the thyroid gland were 0.48 mSv and 2 mSv for Berlin and Southern Bavaria, respectively. The dose from iodine to the ovaries is even less by 3-4 orders of magnitude [5].

At the low contamination levels found for Berlin and the national average, microdosimetry concepts are relevant considerations. The energy deposition pattern of gamma and beta radiation from fission products is such that the minimal dose in a cell nucleus hit by one single electron track is in the range of 1 to 3 mSv. Lower macroscopic doses translate into only a fraction of the cell nuclei in the tissue being hit. This means that with the maximal additional daily exposure of 65 μSv for the thyroid and 6 μSv for the ovaries found for Berlin in April/May 1986, fewer than 1 in 200 oocyte nuclei could be directly affected by Chernobyl fallout.

Fig. 1: Birth prevalence of Down's syndrome in Berlin, Southern, Northern Bavaria, and NFE-Region, July 1986 - May 1987 (rates for Berlin were estimated from the figures given in [1] and [4])



As a remote possibility, an indirect mechanism acting via an altered thyroid function is not ruled out by Sperling et al. [4]. Despite some disputed reports that mothers of children with Down's syndrome have a higher prevalence of thyroid antibodies (e.g. [6]), thyroid doses in Berlin after Chernobyl were much too low to cause deterministic effects such as autoimmune reactions. In addition, the time course of such reactions would be difficult to reconcile with the malformation pattern under study.

4. Discussion

The cluster reported by Sperling et al. is statistically highly significant. But additional elements are lacking to suggest a causal relationship between the considered agent "radiation" and the observed health outcome "Down's syndrome". No cluster of Down's syndrome was found in other areas with higher fallout such as Finland [7] and Southern Bavaria. The increase found in Sweden was the only one in higher contaminated areas. It cannot be told from the publication [8], if the overall increase in 1987 was due to an outstanding increase in one single month.

To explain a short-term increase of Down's syndrome cases, radiation would have to act in a very small time window to interfere with chromosome segregation leading to nondisjunction events during meiosis of female germ cells. Such a deterministic effect is extremely unlikely at the low doses and dose rates considered here. Theoretically, bacterial or viral infections with their potential to change body parameters such as temperature and concentrations of cytotoxins such as radicals might increase the risk of nondisjunction but any important contribution from such pathways should show in statistics after major pandemics caused by infectious agents.

In view of the combined findings of Sperling et al. [1] and Irl et al. [3] nonradiogenic hypotheses should be explored to explain the Bavarian cluster and also the Berlin cluster. Even when we concede that geographical correlation studies are of limited value for testing causal relationships, the combined findings and their close temporal - and geographical - relationship (Northern Bavaria was one of only three surface travel gates to Western Berlin in times of the former GDR) should be carefully considered in view of other environmental and infectious agents.

Even when statistical fluctuations and other confounders, which will tend to cluster in time periods showing the largest deviations from long-term means, are taken into account, both the Berlin and the Northern Bavaria peaks in the Down's syndrome incidence remain remarkable. They represent the highest singular values in both series. Considering the hypothesis that an unknown infectious agent influencing the rate of nondisjunction has passed through the study areas from the South of Germany to the Northeast, an elevated risk in Southern Bavaria has been observed in October 1986, i.e. few weeks before the increased risk in Northern Bavaria. This elevation is significant, too (O=12, O/E=2, 95%CI=1.1-3.4). Still, there is little evidence that maternal infections increase the rate of Down's syndrome. In fact, the only conclusive risk factor is advanced maternal age at conception.

It is obvious that the hypothesis of a non-radioactive external factor is based on unproved theoretical assumptions and has been developed during the analysis of the two series. The reevaluation of the Bavarian data set revealed several significantly increased regional rates, which in two cases even were traced to spatial clusters. Increased rates in Southern Bavaria observed in February and October 1986, respectively, were geographically widespread in one case (October 1986), whereas the increase in February 1986 was due to a cluster occurring in the area of the city of Augsburg (O=4, E=0.43, O/E=9.3, 95%CI=3.0-22.4). The conclusion can be drawn that clusters of Down's syndrome are probably not as uncommon as might be suspected from looking at the Berlin data alone.

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