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Neural tube malformations and trace elements in water

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SUMMARY A retrospective case-control study was conducted to test the hypothesis that there is an association between the trace element content of domestic tap water and neural tube malformations in infants. Of 11 elements examined a notable difference was found only for zinc, this being lower in the cases than in the controls. This difference, however, was small and when allowance is made for the total number of statistical comparisons it is compatible with chance fluctuation. From the results of this study, together with the inconsistency of the literature as a whole, it is concluded that trace elements in tap water are unlikely to be of relevance to congenital malformations.

There has been interest in a possible association between trace elements in domestic tap water and neural tube malformations in infants since Fedrick found that the incidence of anencephaly in 10 areas in the United Kingdom was negatively correlated with total hardness.[1]

In 1976 this unit published the results of a study in South Wales in which the concentrations of 12 trace elements in samples of tap water were estimated, and the interrelationships between these and the incidence of neural tube malformations in 48 areas were examined.[2] Certain associations were found to be significant (at $P < 0.05$) and in particular Ba and Cu were negatively correlated. Al and Ca also showed significant but inconsistent associations.

In an attempt to examine this situation further, and in a rather different way, we have now conducted a case-control study.

Method

The Cardiff Births Survey was consulted to obtain a consecutive series of 108 live or stillborn infants with a neural tube malformation who had been born to mothers resident within the city of Cardiff. Each of these cases was matched with a control infant of the same sex, born within as short an interval as possible of the case, and having a mother of the same social class living in the same ward of the city. The home address of each case and control given at the time of birth was obtained.

In the next two years an attempt was made to obtain six samples of 'first flush' water from the kitchen tap of each dwelling. Sampling times were spaced so that specimens were obtained in times of heavy rain and of relative drought. Each sample was analysed for 11 trace elements by atomic absorption spectrophotometry and for each element the means of all available results were compared in the cases and the controls.

Results

Table 1 summarises the distributions of the trace elements in the case and control groups. It is evident that most of these distributions vary over a wide range and are highly skewed. Although this Table makes no allowance for the pair-matching it is apparent that there are no gross differences between the distributions in the case and control groups. The number of cases and controls for both of which a laboratory measurement of strontium was available is so small that this element was omitted from further statistical analysis.

The differences in trace element values for the case-control pairs were symmetrically distributed and reasonably Gaussian. Table 2 shows the mean differences and standard errors. Only for zinc was the mean difference significantly different from zero, the 95% confidence interval being -0.104 to -0.014 ppm. However, if allowance is made for multiple significance testing then this result is not particularly unlikely.

Discussion

The literature on the relationship between water trace elements (and hardness) and neural tube

Table 1 *Distribution of trace elements (mg/l) in case and control samples*

	Pb	*K*	*Mg*	*Na*	*Ca*	*Cu*	*Fe*	*Zn*	*Al*	*Mn*	*Sr*
CASES											
Minimum	< 0·001	0·40	1·0	3·2	12·0	<0·01	0·02	<0·01	<0·01	<0·001	0·02
Median	0·014	1·23	3·4	6·0	28·8	0·05	0·06	0·04	0·10	0·004	0·09
Maximum	0·102	2·07	4·4	7·0	40·4	0·56	0·51	0·45	0·38	0·050	0·13
No. sampled	100	101	102	102	102	102	90	101	83	82	36
CONTROLS											
Minimum	<0·001	0·44	1·2	3·3	12·6	<0·01	0·02	<0·01	0·02	<0·001	0·03
Median	0·014	1·28	3·4	6·2	29·1	0·05	0·06	0·05	0·10	0·004	0·08
Maximum	0·152	2·18	4·4	7·0	41·7	0·67	0·94	1·28	0·53	0·032	0·15
No. sampled	102	103	102	102	102	102	92	102	83	85	44

Table 2 *Mean differences (mg/l) in trace elements between cases and controls*

	Pb	*K*	*Mg*	*Na*	*Ca*	*Cu*	*Fe*	*Zn*	*Al*	*Mn*
Mean difference (case minus control)	−0·0004	−0·22	−0·05	−0·05	−0·46	−0·007	−0·011	−0·059	0·017	0·0008
Standard error of difference	0·0028	0·39	0·07	0·07	0·58	0·014	0·015	0·023	0·014	0·0011
t	−0·1	−0·6	−0·7	−0·8	−0·8	−0·5	−0·8	−2·6	1·3	0·7
No. of pairs	94	96	96	96	96	96	78	95	66	67

malformations provides conflicting and at best tenuous evidence that such a relationship does exist. The studies reported were mostly concerned with the statistical association between the incidence of neural tube defects and water trace elements across different geographical areas. Some, such as Fedrick,[1] Stocks,[3] Lowe, Roberts, and Lloyd,[4] and Morton, Elwood, and Abernethy,[2] have found statistically significant correlations, whereas others, for example, Fielding and Smithells[5] and Wilson, Watson, and Richards,[6] have found none. The meaning of these correlations, when found, is difficult to discern because not only may water trace elements be associated across areas with neural tube defects but they have also been shown to be markedly associated with deaths from ischaemic heart disease and total mortality. This very lack of specificity of the water effect makes it hard to credit it as a causal agent in neural tube defects.

We believe that our case-control study is a more direct approach to the hypothesis that the chemical composition of water influences the occurrence of neural tube defects than the studies mentioned above. Our study is admittedly small but nevertheless it should have enabled us to detect differences sufficiently large to be of practical interest. The only hint of a difference which we have found is for zinc, where on average there is a small deficit in the water supply of the cases. However, an average difference of about 0·06 ppm seems trivial and may be merely a chance fluctuation. It could be argued that it is the overall profile of trace elements which is important rather than individual elements, but while it is true that eight out of 10 trace elements were lower in the cases than in the controls, such a configuration is not unlikely by chance alone. In any case the differences were all small, and as hitherto the hypothesis being tested concerns individual but not necessarily pre-identified trace elements, the profile argument is too much like special pleading.

Our conclusion is that this case-control study provides no convincing evidence in favour of the trace element hypothesis. While a difference in Zn levels was detected, the inconsistencies between the present data and our earlier results,[1] and, indeed, the lack of consistency within all the published work, make it seem most unlikely that trace elements in water are of relevance to congenital malformations.

Reprints from Dr. P. C. Elwood, Director, MRC Epidemiology Unit (South Wales), 4 Richmond Road, Cardiff.

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