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Mortality from motor neuron disease in Japan, 1950–1990: association with radioactive fallout from atmospheric weapons testing

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Abstract

Motor neuron disease (MND) is a progressive and invariably fatal disease affecting the nuclei of the pyramidal tract and anterior horn cells. Despite intensive research into environmental agents associated with the onset or course of the disease, there is no single factor that can be confidently linked over time with regional, national or international variations in mortality rates. However, unusual variations in MND mortality rate in Japan from 1950–1990 were found to correlate highly significantly with variations in radioactive fallout released by atmospheric weapons testing in the Pacific. This association could be explained by the ingestion of alpha-emitting radionuclides acting upon a pre-existing susceptible subpopulation, a hypothesis which is consistent with recent research on the epidemiology and pathology of MND. However, it is likely that radiation is only one of many factors that act singly or in combination to accelerate the condition in subpopulations susceptible to MND.

Keywords: Amyotrophic lateral sclerosis; Mortality; Motor neuron disease; Japan; Radiation; Aetiology; DNA repair

1. Introduction

Reported mortality from motor neuron disease (MND), in contrast to many other diseases, is a reliable indicator of the underlying patterns of the disease over the last three decades. The majority of studies of MND mortality in industrialised countries have reported significant rises, particularly amongst older age groups (Buckley et al., 1983; Flaten, 1989; Gunnarson et al., 1992; Yoshida et al., 1986; Lilienfeld et al., 1989). Some studies have suggested that a changed environment may be involved (Chancellor and Warlow, 1992), but it has proved difficult to identify any single factor, or group of factors in combination, to explain more than a small proportion of the observed variation (Williams and Windebank, 1991). Recent research by the authors has indicated that the majority of the regional and international variation in MND mortality can be explained by differences in population life expectancy and that no new aetiological factors are needed to explain the general rise in mortality from MND (Neilson et al., 1993a). As life expectancy has increased, it appears that discrete subpopulations susceptible to MND are now surviving to ages at which the disease is expressed, rather than dying earlier from unrelated conditions. But not all national or international variation in mortality can be explained by increased life expectancy as there are unusual, and possibly unique, patterns of mortality in some industrialised countries which do not appear to conform to expected international patterns. Analysis of these exceptional cases is of considerable importance in the search for further aetiological clues to MND.

Japanese mortality from MND during the period 1950–1990 is one such case which deviates from the curve typical of other industrialised countries (Neilson et al., 1993b). Instead of a gradual and consistent rise in mortality over the postwar period, a sharp rise occurred in Japan during the period 1950–1963 followed by an equally sharp fall from 1963–1975, after which a gradual rise in mortality has been evident. Earlier analysis has demonstrated, despite variations in mortality over time, that there is a consistent underlying subpopulation susceptible to MND in Japan (Neilson et al., 1993b). The early exceptional rise and later fall in mortality can be explained by an environmental factor (or factors) prematurely depleting this sus-

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ceptible subpopulation. The gradual recovery of the size of the susceptible subpopulation is now leading to an increase in mortality to previously expected levels.

Several factors have been investigated to account for this unique national pattern of mortality, including urbanisation and industrialisation (Kondo, 1978) and specific factors applicable to local foci of excess mortality (Yase, 1970; Kondo, 1978,1984). Despite some evidence that mortality rates differ statistically between rural and urban areas, environmental causes have not been readily identified at a national level. Nutritional variables have been implicated, although extrapolating from aggregate studies to the effects of specific dietary components has proved unrewarding. Rising postwar rates of mortality from MND are no different amongst individuals substantially exposed to (primarily) gamma radiation from atomic bombs in Hiroshima and Nagasaki than amongst the remainder of the Japanese population (Kondo, 1978). However, recent laboratory research does implicate alpha radiation in a wide range of pathological damage (Kadhim et al., 1992). An investigation of the exposure of the Japanese population to other forms of radiation is important, including data on fallout from atmospheric weapons tests conducted in the Pacific area during the 1950s and early 1960s on Johnson Island, Bikini Atoll, Mururoa and various parts of Western Australia. These tests produced a substantial component of alpha-emitting radionuclides of strontium, iodine and caesium prior to the comprehensive test ban treaty enforced in 1963. We have therefore investigated the association between data on fallout from atmospheric weapons testing and mortality from MND in Japan in the context of recent research on the aetiology of the disease.

2. Material and methods

Mortality data for motor neuron disease was obtained from Japanese government sources for the years 1951 to

Table 1
Age-adjusted MND mortality rates in Japan among men, women and the total population; dose equivalent radiation exposure from atmospheric weapons testing, 1951–1985

Year	MND mortality rate amongst					Dose equivalent for			
	Men	Women	25–54	55+	All	Fetus	Infant	Child	Adult
1951	0.66	0.39	0.58	2.12	0.52	5.1	10.0	9.0	8.2
1952	0.69	0.39	0.60	2.22	0.54	4.7	13.0	9.6	7.8
1953	0.71	0.38	0.61	2.18	0.54	10.0	24.0	21.0	18.0
1954	0.74	0.39	0.62	2.34	0.56	8.6	28.0	21.0	15.0
1955	0.74	0.40	0.63	2.42	0.57	9.5	29.0	30.0	24.0
1956	0.76	0.40	0.60	2.59	0.58	12.0	39.0	35.0	29.0
1957	0.76	0.42	0.60	2.65	0.59	18.0	54.0	50.0	41.0
1958	0.79	0.43	0.62	2.70	0.61	26.0	90.0	76.0	58.0
1959	0.84	0.45	0.67	2.90	0.64	31.0	97.0	98.0	82.0
1960	0.87	0.48	0.69	3.08	0.67	12.0	37.0	34.0	25.0
1961	0.87	0.48	0.66	3.23	0.67	17.0	68.0	46.0	34.0
1962	0.85	0.47	0.63	3.16	0.66	43.0	140.0	110.0	87.0
1963	0.87	0.45	0.60	3.22	0.65	64.0	210.0	190.0	150.0
1964	0.86	0.44	0.59	3.10	0.65	52.0	170.0	160.0	110.0
1965	0.84	0.44	0.54	3.10	0.63	35.0	110.0	100.0	71.0
1966	0.83	0.43	0.54	2.91	0.62	19.0	69.0	59.0	42.0
1967	0.80	0.40	0.52	2.73	0.60	11.0	46.0	36.0	27.0
1968	0.79	0.38	0.53	2.50	0.58	9.2	42.0	33.0	24.0
1969	0.75	0.36	0.49	2.45	0.55	8.3	37.0	29.0	22.0
1970	0.75	0.35	0.48	2.47	0.54	8.8	37.0	30.0	22.0
1971	0.69	0.32	0.43	2.45	0.50	8.6	37.0	31.0	22.0
1972	0.66	0.30	0.41	2.32	0.48	6.8	28.0	24.0	18.0
1973	0.65	0.30	0.40	2.35	0.47	5.5	24.0	19.0	14.0
1974	0.67	0.32	0.43	2.39	0.48	5.4	23.0	20.0	15.0
1975	0.65	0.31	0.41	2.46	0.47	4.6	19.0	17.0	13.0
1976	0.60	0.31	0.39	2.40	0.45	4.2	18.0	14.0	11.0
1977	0.56	0.30	0.34	2.43	0.42	4.7	18.0	15.0	12.0
1978	0.57	0.31	0.33	2.48	0.43	4.6	17.0	16.0	12.0
1979	0.58	0.30	0.31	2.53	0.43	3.9	16.0	13.0	9.8
1980	0.58	0.33	0.32	2.57	0.45	3.0	13.0	10.0	8.0
1981	0.57	0.34	0.32	2.55	0.45	3.8	15.0	12.0	9.5
1982	0.56	0.35	0.31	2.65	0.45	3.0	13.0	10.0	7.9
1983	0.56	0.34	0.30	2.67	0.45	2.5	11.0	8.7	6.9
1984	0.56	0.34	0.28	2.80	0.45	2.1	9.6	7.9	6.2
1985	0.56	0.35	0.27	2.80	0.45	2.1	9.6	7.9	6.2

1985 inclusive. The data was coded using the International Classification of Diseases, codes ICD-7 356, ICD-8 348 and ICD-9 335.2 (WHO, 1985). Autopsy examination of patients with a death recorded as MND during the 1960s have revealed that the accuracy of death certification accuracy is around 95% for MND in Japan (Kondo, 1978), comparable to the levels found elsewhere (O'Malley et al., 1987; Hoffman and Brody, 1971). There is no evidence that the accuracy of certification was lower during the 1950's at a time when the mortality rate was rising substantially, or in subsequent decades when the mortality rate was lower. Examination of non-MND deaths has revealed that false negative reporting is very rare (Kondo, 1978).

Radiological data identifying radiation exposure from weapons testing is routinely recorded by the National Radiological Protection Board (NRPB) (Dionian et al., 1987). Data for the years 1951–1985 were obtained from published sources and provide the mean effective dose equivalent (μSv) from all exposure pathways received by a foetus, an infant aged under one year, a child under 7 years and an adult. The predominant pathway in all cases is via ingestion and the absolute value of the dose reflects diet, metabolic rate and levels of activity. Although there is a difference in magnitude between the groups, the time course of all three dose curves is almost identical.

Mortality from MND was age-standardised to the 1950 population of Japan and standardised rates were calculated for those aged 25–54 years, greater than 55 years, men, women and the total population. Pearson's correlation and F-tests were employed to establish the degree of association between the mortality rate in these age groups and the radiation dose received. Correlations were performed against the dose equivalent received by a foetus, infant, child and adult. As there is little reason to expect a simple linear relationship, the correlation with the logarithm of each dose was also calculated for further correlation tests. The age-standardised mortality rate and the dose equivalent radiation exposure are reported in Table 1.

3. Results

The age-adjusted rates of MND mortality were seen to rise from 1951 to a peak in 1963, then fall substantially over the subsequent three decades in both men and women and across all age bands (Fig. 1). Dose equivalent expo-

Table 2
Correlation (Pearson's R) between age-specific and age-adjusted MND mortality rates, and the logarithm of dose equivalent radiation exposure for each age group and both sexes, 1951–1985

Group	Logarithm of dose-equivalent radiation exposure for:			
	Fetus	Infant	Child	Adult
0–4	−0.7047 **	−0.6797 **	−0.6899 **	−0.6893 **
5–9	0.6225 **	0.5272 **	0.5430 **	0.5604 **
10–14	0.8494 **	0.8114 **	0.8122 **	0.8149 **
15–19	0.7675 **	0.7818 **	0.7708 **	0.7571 **
20–24	0.5450 **	0.5420 **	0.5384 **	0.5274 **
25–29	0.6551 **	0.5808 **	0.5896 **	0.5977 **
30–34	0.7408 **	0.6420 **	0.6585 **	0.6773 **
35–39	0.7739 **	0.6948 **	0.7137 **	0.7216 **
40–44	0.8959 **	0.8383 **	0.8447 **	0.8553 **
45–49	0.7341 **	0.6678 **	0.6734 **	0.6852 **
50–54	0.8444 **	0.8046 **	0.8066 **	0.8141 **
55–59	0.8190 **	0.8212 **	0.8099 **	0.8040 **
60–64	0.6955 **	0.6886 **	0.6888 **	0.6945 **
65–69	0.3124	0.3570	0.3398	0.3380
70–74	0.3196	0.3673	0.3476	0.3464
75–79	0.1574	0.2468	0.2253	0.2061
80–84	0.5544 **	0.5927 **	0.5700 **	0.5591 **
85 +	0.1457	0.0030	0.0248	0.0480
M25–54	0.8183 **	0.7591 **	0.7650 **	0.7721 **
M55 +	0.7543 **	0.7874 **	0.7756 **	0.7707 **
Men	0.9113 **	0.9009 **	0.8955 **	0.8919 **
W25–54	0.8363 **	0.7613 **	0.7726 **	0.7868 **
W55 +	0.2449	0.2782	0.2585	0.2569
Women	0.7942 **	0.7422 **	0.7402 **	0.7520 **
A25–54	0.8232 **	0.7539 **	0.7630 **	0.7743 **
A55 +	0.6211 **	0.6527 **	0.6372 **	0.6338 **
All	0.8983 **	0.8711 **	0.8673 **	0.8695 **

** $p < 0.001$.

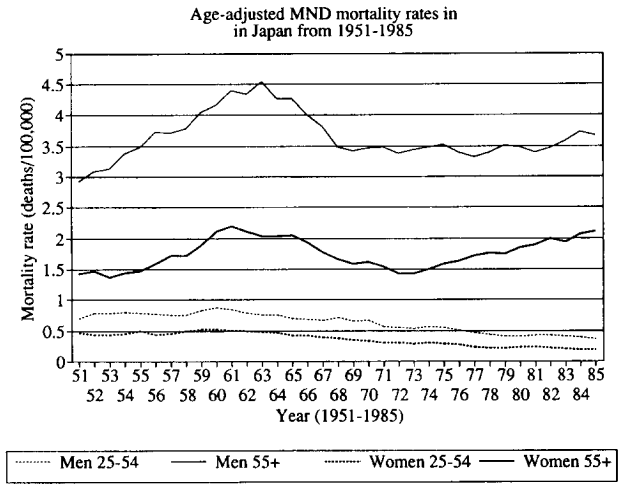

Fig. 1. Age-adjusted MND mortality rates for men and women aged 25–54 years and over 55 years in Japan, 1951–1985.

sure increased across the decade up to 1963, the year in which the comprehensive test ban treaty came into force, then declined steadily in all subsequent years. The pattern, shown in Fig. 2, closely mirrors the pattern of MND mortality in Japan.

The age-adjusted MND mortality rate amongst men, women and the total population correlated significantly with dose over the 31 years of the study ($R > 0.66$; $p < 0.001$ in all cases). Examination of the data revealed that the association was not a linear one, and a better fit could be made between the MND mortality rate and the logarithm of radiation dose ($R > 0.71$; $p < 0.0001$). Statistical tests (Table 2) show that the logarithm of the foetal dose (representing an integrated dose over a few months) provides the best fit of the four available dose curves.

Further tests of the logarithm of foetal dose were carried out to assess the degree of association between radiation dose and MND mortality rates in all age-bands available for analysis and for both sexes (Table 2) and in only one age-group (0–4 years) was there a negative association. In all other age groups the association was positive, and was particularly high for all ages 5–64 years and 80–84 years, reaching the greatest statistical significance in the fourth decade of life. Tests on the two sexes separately indicated that the effect was strongest in men, applying to men both younger and older than 55 years. The correlation for women age greater than 55 was non-significant, but still positive.

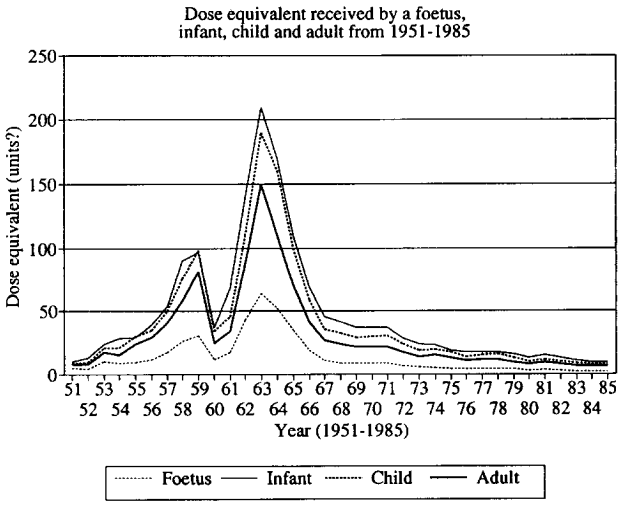

Fig. 2. Dose equivalent radiation exposure from atmospheric weapons testing received by a fetus, infant, child and adult, 1951–1985.

4. Discussion

There is no reason to doubt that the observed pattern of MND mortality in Japan is a reflection of the underlying incidence of the disease. An artefact explanation based on continuous improvement in case ascertainment rates since the 1950s is unlikely to account for the unique rise and then fall of recorded mortality from MND in Japan. Since the range of radiation products released by atmospheric weapons testing is substantial, the results concerning exposure to radiation are difficult to interpret. Even if the distribution of fallout products is relatively uniform globally, the uptake, ingestion and effects of different products can be very variable amongst different individuals or in different countries with different life styles. These latter factors could account for the unique pattern of Japanese mortality and its association with fallout from atmospheric weapons testing. These findings warrant further investigation, especially in the light of hypotheses supporting a biological role of radiation amongst other mutagens in the genesis and course of the disease, particularly those linking pre-existing susceptibility to possible effects of mutagenic insults.

The close temporal relationship between increased fallout and the relatively rapid rise in MND mortality suggests that the potency of the mutagenic agents was high, or that they were acting upon pre-existing cellular damage in susceptible individuals. Whether the accelerated mortality was due to enhanced cellular damage resulting in a shortened period to the appearance of symptoms, or whether the course of the disease following the appearance of symptoms was itself accelerated is unclear from this data. Both processes may have occurred uniformly across all age groups. Because of the skewed age-distribution of mortality, the effect reaches higher statistical significance in the age bands containing large numbers of deaths and amongst men.

Another plausible hypothesis which might account for the observed relationship between radioactive fallout and increased mortality from MND in Japan is based on defects in DNA repair mechanisms (Mann and Yates, 1974; Davidson et al., 1981a,b; Tandan et al., 1987,1988; Mazzarello et al., 1992). According to the DNA hypothesis for

the aetiology of MND (Bradley and Krasin, 1982), MND-susceptible individuals have congenitally deficient DNA repair mechanisms arising either from a genetic abnormality or from an error in intrauterine development. Exposure to a series of mutagenic insults may result in the gradual accumulation of defects through errors in repair processes, with eventual failure to synthesize proteins essential to cell survival. Post-mitotic motor neurones are particularly vulnerable to such chronic damage.

The recent discovery of genetic loci strongly linked to certain forms of familial ALS (FALS) (Siddique et al., 1990) is particularly important. The subsequent identification of the role of the mutated locus in a number of FALS families (Rosen et al., 1993) as coding for the enzyme superoxide dismutase (SOD1), essential for the elimination of superoxide and oxygen free radicals from the body and the protection of cells from oxidation damage, is consistent with the proposed pathological mechanism for sporadic MND, especially as such damage may be associated with the effects of alpha radiation, as with the effects of other mutagenic agents.

The relationship of FALS cases to sporadic MND is of importance because the low proportion of recognised FALS cases may not be a true indication of the extent and the findings of Rosen et al. (1993) could have relevance to a larger number of cases (Bowling et al., 1994). For epidemiological reasons, there is a substantially lower possibility of accurately tracing family pedigrees for the majority of late onset sporadic cases. For example, 95% of all cases of MND occur after the age of 50 years, when half of all susceptible individuals may already have died from an unrelated cause. Therefore the ascertainment of good pedigrees in first as well as second generation relatives is problematic, especially in relation to those in whom susceptibility may actually be present but has not been recognised or recorded (Jones et al., 1994). This argument suggests that the proportion of sporadic cases which may be eventually identified as a form of FALS could increase substantially.

Even if substantial numbers of further FALS cases are identified in the future, this does not imply that the expression of the disease is statistically uniform, as it has not proved to be in many existing FALS cases. Environmental factors are probably linked with the individual expression of the disease, as well as with overall aggregate patterns of mortality.

5. Conclusions

The findings of this study, if substantiated by further research, are significant in relation to the unique pattern of mortality observed in Japan particularly in the three immediate post war decades. The epidemiological evidence indicates that the changes in mortality were real, resulting in a lower mean age at death, affected men more than women, and by inference resulted in a significant reduction in the size of the sub-population susceptible to MND. The data on atmospheric fallout indicates that if indeed the statistical relationship with MND mortality was a biological effect, then that effect was substantial and evident over a relatively short time period. The findings of the study are not inconsistent with the relatively widespread existence of a mutation conferring susceptibility to MND, similar to that recently reported in relation to FALS.

This study has evaluated a statistically significant association between the unusual, and possibly unique patterns of mortality from MND in postwar Japan, and fallout from atmospheric nuclear weapons testing in the Pacific. The statistical association is striking and can be argued to have biological as well as statistical plausibility, but further work is needed to investigate factors associated with mortality from MND in other countries over the same period, not least to identify other variables in Japan which might confound, or reinforce the association noted here.

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