Multiple sclerosis and ionizing radiation

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Abstract

The etiology of multiple sclerosis (MS) may involve exposure to infectious, chemical or physical agents damaging the blood-brain barrier and an autoimmune reaction against myelin breakdown products. Here we report a pooled analysis of 174 MS cases and 815 population controls from two case-control studies with regard to such a potentially damaging exposure, namely X-ray examinations, radiological work and treatment with ionizing radiation. Exposure was assessed by mailed questionnaires to the subjects. We obtained odds ratios of 4.4 (95% confidence interval, CI, 1.6-11.6) and 1.8 (95% CI 1.2-2.6) for radiological work and X-ray examinations, respectively; five cases but no control in one of the studies had been treated with ionizing radiation. Our data and some other observations reported in the literature suggest a contributory role for ionizing radiation to the development of MS in some cases.

The etiology of multiple sclerosis (MS) is unclear, but is thought to involve environmental as well as genetic factors [1, 2]. A tendency for cases to cluster [3] may indicate an infectious mechanism, and particularly measles, Epstein Barr, and canine distemper viruses have been discussed as possibly responsible agents [4 - 7]. Animal contacts, particularly to dogs, have appeared as risk factors in epidemiological studies [8]. The pathogenic mechanism of MS seems to involve a damage to the blood-brain barrier and an autoimmune reaction against myelin breakdown products. Such damage may result also from various physical or chemical exposures, such as mild trauma, electrical injury, organic solvents and other agents; genetic factors are probably involved as well [9,10].

We considered various occupational and environmental exposures in two case-control studies [11,12] and focused primarily on solvent exposure as also indicated to play a role in several other studies [13]. Here we wish to display also some other data from these studies and to hypothesize a possible etiologic role of ionizing radiation. This novel epidemiologic approach to an exposure that might be relevant for the development of MS requires a combination of the two studies to obtain a reasonably large number of exposed subjects for an evaluation.

Subjects and Methods

The first of our two studies [11] included cases of MS in ages 20 - 65 years diagnosed in the two largest hospitals in south-central Sweden in 1981 -1985, that is, the cases occurring in the two counties covered by these hospitals. Sweden has a continuously updated population register, and controls were randomly drawn from this register of the population in these two counties from where the cases were obtained. Exposure was assessed for cases and controls by means of a mailed ninepage questionnaire providing information about occupation with further details regarding specific exposures to certain agents at work places as well as contacts with animals. Medical care was also considered, especially X-ray treatment or examinations, along with the use of drugs. No clear information was given as to the specific purpose of the study, only that we were interested in various exposures and diseases. We obtained a response from 83 cases (response rate 89 per cent) and 467 controls (response rate 80 per cent) in these two counties.

Our second study [12] was very similar in design and included 91 responding cases (response rate 94 per cent) diagnosed in ages 20 - 61 years during 1983 - 1988 at the main hospitals in two counties in southeast Sweden. Correspondingly in age, 348 population controls responded (response rate 87 per cent) as randomly drawn from the register of the population in the counties from which the cases were derived. A very similar questionnaire to that used in the first study was mailed to the cases and controls for obtaining information about exposure. In both studies the cases and controls themselves answered the questionnaires and no proxy responders were involved. Further details regarding design issues may be found in the earlier reports of these studies [11,12]. The data presented here are supplied from the original files and, in part, also retrievable from the published studies.

Results

Table 1 shows the distribution of the cases and controls with regard to radiological work exposure either in hospitals or in the context of technical X-raying in industry. It may be noted from the table that the frequency of radiological work exposure among the controls appears as rather high (12 subjects out of 815 or 1.5%) based on general impressions of how common such work might be. It is unlikely, therefore, that an underestimation of the exposure frequency among the controls would explain the elevated Mantel-Haenszel odds ratio of 4.4 (95% confidence interval 1.6-11.6) obtained for radiological work exposure.

Table 2 shows the distribution of cases and controls with regard to X-ray examinations in the two studies. Dental X-ray or occasional other low dose examinations were included in the unexposed category, as estimated to have delivered a dose of less than 1 mGy to the red bone marrow [14]; the red bone marrow dose is referred to in lack of estimates for nervous tissue. A consequence of including the low dose exposures in the unexposed category would be that the Mantel-Haenszel odds ratio of 1.8 (95% confidence interval 1.2-2.6) is likely to be somewhat conservative.

Discussion

The results obtained in these further analyses of our two studies on MS are quite consistent, as both occupational and diagnostic exposure to ionizing radiation appears to be associated with this disease. The analyses of the data in the two tables may seem somewhat crude, however, not adjusting for potential confounding factors other than gender and study. The latter is a proxy for geographical area. Some uncontrolled confounding effects may persist, but a number of possible confounding factors were sought in the original studies with no indication of a significant such effect except for gender with regard to some occupational exposures. As MS develops over time, a five-year delay criterion was applied when assessing exposures, so as to avoid a confounding from factors appearing subsequent to onset of the disease. Nevertheless, some of the X-ray examinations could have been performed because of early symptoms of MS. To the extent that the association between MS and exposure to ionizing radiation is causal, the referral of dental X-ray or occasional other low dose examinations to the unexposed category, would have the effect, if any, of somewhat reducing the risk estimates obtained. If no causality is involved in the association found, any influence on the risk estimates from this kind of low dose exposure would be indifferent.

Although few studies of ionizing radiation as a determinant of MS have been reported there are some corroborating observations. First there is some ”internal support” in one of our own studies [12] as five cases but no control had been exposed to ionizing radiation for therapeutic purposes. We have also noted a report of four MS patients incorrectly diagnosed with CNS neoplasm, who were treated with radiation in tumoricidal doses. In these patients, the clinical course was rapid, suggesting that radiation might accelerate the demyelinating process [15]. Based on such cases, one could speculate that X-ray examinations might trigger demyelination in susceptible subjects.

The positive correlation of MS rates with latitude has been known for a long time [16] and has been taken to suggest a role of cosmic radiation [17, 18]. Interestingly enough, Resch [18] found a better correlation with geomagnetic latitude, a proxy for cosmic radiation, than with the geographical latitude. It may be noted however that the emigration pattern in the world is such that north Europeans carrying a high incidence of MS have settled in those areas which are relatively adjacent to the magnetic poles, that is, in parts of North America and Australia. The same possible confounding effect from the emigration pattern might affect also another hypothesis considering MS and latitude, namely a suggested suppressive effect of ultraviolet radiation on autoimmunity [19], a possibility clearly strengthened by a recent study [20].

However, to the extent that any of these hypotheses has any bearing on the causation of MS, the cosmic radiation hypothesis might be the better one but hardly excludes some preventive effect of ultraviolet radiation. The reason is that there is also some tendency towards higher rates of MS in elevated regions than in lowland areas [21], which to some extent opposes the idea of beneficial immunosuppression from ultraviolet radiation, that like cosmic radiation increases with altitude.

Some support for a role for ionizing radiation in the etiology of MS can be obtained also from experimental data on mice showing that low-dose gamma radiation can increase susceptibility to murine encephalomyelitis virus causing a chronic demyelinating disease similar to human MS [22]. Decreased activities of superoxide dismutase and glutathione peroxidase and an increased level of malonyl dialdehyde in erythrocytes of patients with MS have been reported, indicating a decreased antioxidative capacity [23] and therefore a likely increased susceptibility to ionizing radiation.

As found in several studies, including cancer research, chemical agents such as peroxides, metylmethacrylate, petroleum destillate solvents as well as trichloroetylene and even ethanol, may cause oxidative damage and induce autoimmune reactions in various tissues as modified by host genetic susceptibility and life-style factors regarding the individual response [24 - 30]. Likewise, ionizing radiation may cause free radical formation and oxidative damage and thereby be of importance in the pathogenesis of MS in susceptible individuals [25]. The epidemiological findings presented suggest a need for further epidemiologic research along this line.

References

1. Ebers GC, Kukay K, Bulman DE, Sadovnick AD, Rice G, Anderson C, Armstrong H, Cousin K, Bell RB, Hader W, Paty DW, Hashimoto S, Oger J, Duquette P, Warren S, Gray T, O'Connor P, Nath A, Auty A, Metz L, Francis G, Paulseth JE, Murray TJ, Pryse-Phillips W, Risch N, et al. : A full genome search in multiple sclerosis. Nat Genet 1996; 13:472-476.

2. Weinshenker BG: Epidemiology of multiple sclerosis. Neurol Clin 1996;14:291-308.

3. Riise T, Klauber MR: Relationship between the degree of individual space-time clustering and age at onset of disease among MS patients. Int J Epidemiol 1992; 21:528-532.

4. Cook SD, Dowling PC: A possible association between house pets and multiple sclerosis. Lancet 1977; 1: 980-982.

5. Cook SD, Dowling PC: MS and viruses: an overview. Neurology 1980; 30: 80-91.

6. Dhib-Jalbut S, Lewis K, Bradburn E, McFarlin DE, McFarland HF: Measles virus polypeptide-specific antibody profile in MS. Neurology 1990; 40:430-435.

7. Lowis GW: The social epidemiology of MS. Sci Total Environ 1990; 90:163-190.

8. Cook SD, Rohowsky-Kochan C, Bansil S, Dowling PC: Evidence for MS as an infectious disease. Acta Neurol Scand Suppl 1995; 161:34-42.

9. Poser CM: MS. Observations and reflections—a personal memoir. J Neurol Sci 1992; 107:127-140.

10. Poser CM: The role of the blood-brain barrier in the pathogenesis of MS. In: Salvati S, Ed. A multidisciplinary approach to myelin diseases. New York: Plenum Press, 1994: 221-229.

11. Flodin U, Söderfeldt B, Noorlind-Brage H, Fredriksson M, Axelson O: MS, solvents, and pets. A case-referent study. Arch Neurol 1988;45:620-623.

12. Landtblom A-M, Flodin U, Karlsson M, Pålhagen S, Axelson O, Söderfeldt B: MS and exposure to solvents, ionizing radiation and animals. Scand J Work Environ Health 1993;19:399-404.

13. Landtblom A-M, Flodin U, Söderfeldt B, Wolfson C, Axelson O: Organic solvents and MS: A synthesis of the current evidence. Epidemiology 1996; 7:429-433.

14. Bengtsson G, Blomgren P-G, Bergman V, Åberg L: Patient exposures and radiation risks in Swedish diagnostic radiology. Acta Radiologica 1978; 17:81-105.

15. Peterson K, Rosenblum MK, Powers JM, Alvord E, Walker RW, Posner JB: Effect of brain irradiation on demyelinating lesions. Neurology 1993; 43:2105-2112.

16. Limburg CC: The geographic distribution of MS and its estimated prevalence in the United States. Proc Association for Research into Nervous and Mental Disease 1950; 28:15-24.

17. Barlow J: Correlation of the geographic distribution of MS with cosmic ray intensities. Acta Neurol Scand 1960; 35 (Suppl 147): 108-130.

18. Resch J: Geographic distribution of MS and comparison with geophysical values. Soz Präventivmed 1995; 40:161-171 [Article in German].

19. McMichael AJ, Hall AJ: Does immunosuppressive ultraviolet radiation explain the latitude gradient for MS? Epidemiology 1997; 8:642-645.

20. Freedman DM, Dosemeci M, Alavanja MC: Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case-control study based on death certificates. Occup Environ Med 2000; 57: 418-421.

21. Lauer K: Environmental associations with the risk of MS: the contribution of ecological studies. Acta Neurol Scand Suppl 1995; 161:77-88.

22. Nicholson SM, Dal Canto MC, Miller SD, Melvold RW: Adoptively transferred CD8+ T lymphocytes provide protection against TMEV-induced demyelinating disease in BALB/c mice. J Immunol 1996; 156:1276-1283.

23. Dudek I, Zagorski T, Liskiewicz J, Kedziora J, Chmielewski H: Effect of gamma radiation on selected indicators of oxygen metabolism in erythrocytes of patients with MS. Neurol Neurotic Pol 1992; 26:34-39 [Article in Polish].

24. Toshniwal PK, Zarling EJ: Evidence for increased lipid peroxidation in multiple sclerosis. Neurochem Res 1992; 17:205-207.

25. Cooper RL: Multiple sclerosis: an immune legacy? Med Hypotheses 1997; 49: 307-311.

26. Chen MS, Wu JN, Yang SN, Hsieh WY, Liu JC, Fu E, Liu DD: Free radicals are involved in methylmethacrylate-induced neurotoxicity in human primary neocortical cell cultures. Chin J Physiol 1998; 41:203-209.

27. Gavino VC, Dillard CJ, Tappel AL. Release of ethane and pentane from rat tissue slices: effect of vitamin E, halogenated hydrocarbons, and iron overload. Arch Biochem Biophys 1984; 233:741-747.

28. Kensler T, Guyton K, Egner P, McCarthy T, Lesko S, Akman S: Role of reactive intermediates in tumor promotion and progression. Prog Clin Biol Res 1995; 391:103-116.

29. Nordmann R, Ribiere C, Rouach H: Ethanol-induced lipid peroxidation and oxidative stress in extrahepatic tissues. Alcohol Alcohol 1990; 25:231-237.

30. Yoshida S, Gershwin ME: Autoimmunity and selected environmental factors of disease induction. Semin Arthritis Rheum 1993; 22:399-419.

Table 1. Distribution of cases and controls in two studies with data on MS and radiological work exposure (Flodin et al 1988; Landtblom et al 1993) along with a pooled analysis.

			Exposed	Unexposed
Flodin et al 1983				
	Men			
		Cases	4	32
		Controls	4	236
	Women			
		Cases	0	47
		Controls	5	222
Landtblom et al 1993				
	Men			
		Cases	2	22
		Controls	2	170
	Women			
		Cases	4	63
		Controls	1	175
Total		Cases	10	164
		Controls	12	803
Crude odds ratio			4.1	(1.0)
Mantel-Haenszel odds ratio			4.4	(1.0)
- 95% confidence interval			1.6 - 11.6	

Table 2. Pooled cases of MS and controls from two studies with supplemented original data on X-ray examinations; subjects having had dental X-ray and other occasional, low dose examinations (see text) have been included among the unexposed.

			X-ray examinations	Unexposed
Flodin et al 1988				
	Men			
		Cases	24	12
		Controls	87	153
	Women			
		Cases	30	17
		Controls	108	119
Landtblom et al 1993				
	Men			
		Cases	9	15
		Controls	78	94
	Women			
		Cases	47	20
		Controls	102	74
Total		Cases	110	64
		Controls	375	440
Crude odds ratio			2.0	(1.0)
Mantel-Haenszel odds ratio			1.8	(1.0)
- 95% confidence interval			1.2 - 2.6	