Journal of NeuroVirology (2000) 6, Suppl 2, S147–S151

www.jneurovirol

Clinical infections and multiple sclerosis: contribution from analytical epidemiology

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Epidemiological studies have suggested that exogenous factors may play a role in the etiology of multiple sclerosis and that the environmental component may be viral, but, as yet, there is insufficient evidence to draw any definite conclusions concerning any of the viruses so far proposed. The case-control approach failed to give any definitive conclusion. While the frequency of each common childhood illness is not significantly different between cases and controls, there are more consistent data suggesting that cases do report a later age at infections: this applies particularly to measles, rubella, mumps and EBV infection. Several studies have proved that viral or bacterial infections or reactivations could trigger the clinical attacks in relapsing-remitting MS. *Journal of NeuroVirology* (2000) **6,** S147–S151.

Keywords: multiple sclerosis; epidemiology; infectious diseases

Data from epidemiological studies on multiple sclerosis (MS), showing a nonhomogeneous geographical distribution, a variation in trend in some areas of the world, the evidence of possible clusters, and a change in risk in migrants, have supported the role of environmental factors in the etiology of MS (Granieri *et al*., 1993; Kurtzke, 1993). The hypothesis that an infectious agent is responsible for triggering MS is perhaps one of the most enduring, most frequently studied and most biologically plausible. Although no virus has been found which can explain the development of MS, epidemiological studies have pointed towards a viral involvement in this disease. The epidemiological data support a viral cause for MS as evidenced from migration and cluster studies. Migration from an area where MS is common, to an area where it is rare affects the risk of MS, provided migration occurs early in life. A childhood infection could explain this effect. The case-control approach, used to test this hypothesis, had not led to definitive conclusions. (Granieri and Casetta, 1997).

Table 1 summarizes the results of most case-control studies on childhood diseases and MS (Alter and Speer, 1968; Cendrowski *et al*., 1969; Wilhelm, 1970; Panelius *et al*., 1973; Currier *et al*., 1974; Alter and Cendrowski, 1976; Poskanzer *et al*., 1980; Andersen *et al*., 1981; Haile *et al*., 1982; Sullivan *et al*., 1984; Compston *et al*., 1986; Berr *et al*., 1989; Operskalski *et al*., 1989; Italian MS Study Group, 1989; Koch-Henriksen, 1989; Souberbielle *et al*., 1990; Hopkins *et al*., 1991; Hays, 1992; Gronning *et al*., 1993; Casetta *et al*., 1994; Lauer and Firnhaber, 1994; Materljan, 1994; Milonas, 1994; Gusev *et al*., 1996; Zilber and Kahana, 1996; Kurtzke *et al*., 1997).

This research method still involves several limitations particularly regarding the difficulty in collecting reliable information about remote events. Furthermore, the results from these studies greatly depend on the methodology adopted, as far as the choice of case and controls, and the interview procedure are concerned. The validity of data, based on a questionnaire suggests substantial inaccuracy in the patients' reports but the direction and degree of inaccuracy does not appear to be different between cases and controls. Some studies have indicated a higher frequency of measles infections in cases, but the global evaluation of the various studies considered together indicate that the frequency of common childhood diseases is similar for cases and normal controls (Granieri and Casetta, 1997).

Table 2 shows the results of a metaanalysis carried out on case-control studies regarding childhood infectious diseases (personal data). On the whole there are no significant differences between the groups.

While the frequency of each common childhood illness is not significantly different between cases and controls, there are more consistent data suggesting that cases report a later age at infections.

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Table 1 Results of most case-control studies on MS and childhood infectious diseases

Year	*First author*	*Cases/controls*	*Results*	*Year*	*First author*	*Cases/controls*	*Results*
1968	Alter	36/72	No differences	1989	MS group	318/1975	No differences
1969	Cendrowski	300/300	No differences	1989	Koch-Henriksen	324/324	No differences
1970	Wilhelm	36/36	No differences	1990	Souberbielle	230/230	No differences
1973	Panelius	229/229	No differences	1991	Hopkins	16/117	No differences
1974	Currier	60/60	No differences	1992	Hays	63/63	<frequency of mumps
1976	Alter	40/40	No differences	1993	Gronning	155/200	<frequency of pertussis
1980	Poskanzer	82/153	No differences	1994	Lauer	150/150	No differences
1981	Andersen	92/276	No differences	1994	Casetta	104/150	No differences
1982	Haile	72/72	No differences	1994	Milonas	200/200	>frequency of measles
1984	Sullivan	88/88	No differences	1994	Materljan	46/92	No differences
1986	Compston	177/164	>frequency of mumps	1996	Gusev	155/155	No differences
1989	Operskalski	145/145	No differences	1996	Zilber	94/94	>frequency of measles
1989	Berr	63/63	No differences	1997	Kurtzke	56/147	>frequency of measles

Table 2 Clinical infections and MS: metanalysis

Disease	*No of cases*	*No of controls*	*Overall OR*	*95% CI*
Measles	2017	3882	1.06	0.92–1.22
Rubella	1035	1223	0.97	0.83–1.13
Mumps	1267	3098	0.91	0.79–1.06
Whooping cough	1241	1072	1.09	0.92–1.3
Chickenpox	1311	3154	0.98	0.85–1.12

A higher proportion of children show positive titers to many viral diseases early in life in areas where MS is rare compared with those where MS is common (Alter *et al.*, 1986). Also mortality rates from a variety of infectious diseases correlate negatively with MS mortality. This is consistent with the evidence that MS is less frequent among people belonging to low socioeconomic classes or living in countries where the general level of sanitation is low, the result of which generally leads to earlier infection (Lowis, 1990). The inverse relation between MS risk and birth order position is consistent with the above assumption.

An increased MS risk has proved to be associated with a higher age at childhood infection as summarised in Table 3 (Panelius *et al.*, 1973; Alter and Cendrowski, 1976; Poskanzer *et al.*, 1980; Andersen *et al.*, 1981; Haile *et al.*, 1982; Sullivan *et al.*, 1984; Compston *et al.*, 1986; Italian MS Study Group, 1989; Hays, 1992; Gronning *et al.*, 1993; Lauer and Firnhaber, 1994; Materljan, 1994; Bansil *et al.*, 1996; Bachmann and Kesserling, 1998).

Several studies have found that persons with MS tend to have measles at a later age than controls. Panelius *et al.* (1973) demonstrated a trend towards older age of infection by measles in cases compared to controls; Alter and Cendrowski (1976) found that more patients than controls reported an infectious disease in the age period 5–9 years. Although none of the childhood infections differed in frequency among the study subjects, the average age of measles infection peaked later among patients than controls (7 vs 4v years). Data from a study by Haile *et al.* (1982) suggested that the risk of MS is increased by a factor of 1.9 if measles infection occurs between 5 and 9 years of age. Poskanzer *et al.* (1980), in a comparative study with other areas of the UK, reported higher age of infection by measles and mumps in all individuals in their study but there were no differences between cases and controls, although age at chickenpox infection was lower in cases. Compston *et al.* (1986) demonstrated a higher age at infection for measles and rubella. Some authors also made this observation for mumps (Hays, 1992). A multicenter Italian study (1989), as well as a German investigation (Lauer and Firnhaber, 1994) reported a relationship between the occurrence of a group of childhood diseases after 6 or 9 years of age, although the relationship was not significant for any single childhood disease. More recently a case-reference study demonstrated a significantly higher mean age at measles infection in cases compared to the normal Swiss population 7.5 vs 6.4). MS patients had measles infection as well as mumps, rubella, varicella and mononucleosis at a later age (Bachmann and Kesserling, 1998), confirming previous data.

Possible interpretations of the pattern which emerges from the studies include the hypothesis that MS is a sequel to delayed exposure to a common infectious agent. Thus, infection early in life may protect against MS and conversely later infections when the immune system has matured may increase the risk. In general, the studies do not

Table 3 Common infectious diseases and MS: age at acquisition

First author, year	*Country*	*Results*	*First author, year*	*Country*	*Results*
Panelius, 1973	Finland[1]	Trend to contract measles later	Hays, 1992	Canada, UK	Mumps at later stage
Alter, 1976	USA	Mean age at measles peaked later	Gronning, 1993	Norway	Trend to contract measles later
Poskanzer, 1980	Orkney and Shetland	Infections at later age	Lauer, 1994	Germany	Later acquisition of at least one ID
Andersen, 1981	Denmark	No differences	Casetta, 1994	Italy	Measles at early age, rubella, pertussis
Haile, 1982	UK	Measles at later age	Materljan, 1994	Croatia	Trend to contract measles later
Sullivan, 1984	USA	Measles at later age	Bansil, 1996	India	No differences
Compston, 1986	UK	Rubella, Measles at later age	Bachmann, 1998	Switzerland	Later acquisition of measles, mumps, rubella, chickenpox
Italian MS group, 1989	Italy	Number of infectious diseases after 6 years			

allow us to implicate any specific agent as the cause of MS, but they do suggest the existence of an age-linked period of susceptibility to infectious exposures in genetically prone subjects.

One candidate for such an infection was found to be Epstein-Barr virus (Munch *et al*., 1997). Various researchers have demonstrated higher titres of EBV antibodies in MS cases compared to controls (Munch *et al*., 1997, 1998). Alter *et al*. (1986) compared the data on positive serologic titers to childhood infections in high and low MS frequency areas and generally found a much lower percentage of seropositives in the areas at high MS risk. EBV seropositives aged 4–6 years in northern Europe were 41 to 50% whereas at the same age they were 76 to 95% in some developing countries. In a case-control study (Martyn *et al*., 1993) recall of infectious mononucleosis (IM) was associated to a significant relative risk of 1.9 which increased to 2.9 in subjects seropositive for EBV. People reporting IM before age of 18 years had a relative risk of 7.9. The studies lend support to the notion that IM usually indicating a late EBV infection, is associated with an increased risk for the individual to develop MS. It confirms previous evidence on an epidemiological relationship between late exposure to childhood diseases and subsequent MS.

A strong positive association for a history of IM was found among MS patients in another case-control study (Operskalski *et al*., 1989). A combined analysis of case-control studies on this specific topic showed that EBV clinical infection almost doubles the risk of MS (Overall Odds Ratio=1.91). Most epidemiological studies are retrospective: the history of earlier diseases is recalled for cases and controls. Prospective studies, in which exposed people are followed to the possible occurrence of the disease, are very rare because of the low population risk of MS and the long follow-up period required. In addition, reliable population MS statistics and follow-up of a large number of unexposed matched controls are necessary. By cross-referencing a cohort of IM cases with an MS register in Sweden, three MS cases were recruited, corresponding to a relative risk of 3.7 for MS to occur after IM (Lindberg *et al*., 1991).

The Danish historical prospective study compared data from the national State Serum Institute with the national MS registry. Among the people with positive antibodies 16 cases of MS were found. The expected number was 5.7, the risk ratio being 2.81. Among the negative subjects the expected number of MS cases was found (Haahr *et al*., 1995).

In a study on clustering of MS patients in Norway, MS patients within the same birth cohort were found to have lived significantly closer to each other than would be expected during ages 13–20 years. The authors found the results compatible with a common infection occurring after puberty (Riise *et al*., 1991). It has also been proposed that MS is caused by a dual infection with retrovirus and EBV (Haahr *et al*., 1992).

On the whole, when acquiring at least one childhood disease later age is the most consistent positive result in spite of the considerable differences in the age groups considered: this applies particularly to measles, rubella, mumps and EBV infection. The possibility that unspecific infections may trigger the disease onset and modify disease activity is also gaining credence.

Viral exposure has been shown to trigger acute exacerbations and some studies have demonstrated that other infectious diseases also precede relapses, and, when recurrent, are associated with neurologic progression. Various studies have recently focused on the possibility that viral or bacterial infections or reactivations could trigger the clinical attacks in relapsing-remitting MS. Sibley *et al*. (1985) showed, in a prospective study, that 27% of relapses were related to an infection and that about 9% of viral infections were followed by relapses.

A significant excess of relapses corresponding to a relative risk of 1.3 has been recorded following upper respiratory and gastrointestinal infections and serological diagnosis of five common viral infections (Andersen *et al.*, 1993). A seasonal variation in the MS relapse rate has been found with a minimum in summer. There was a significant correlation between the number of relapses and the number of common infections which explains the periannual distribution and seasonal variations in relapses.

Other authors have reported that patients experiencing exacerbations have more frequently had significant bacterial infection compared with a group of patients with quiescent disease. Considering together viral and bacterial infections diagnosed before relapses, almost 50% of patients could have had an exacerbation of their disease in response to an infectious process (Rapp *et al.*, 1995).

More recently urinary (Metz *et al.*, 1998) and upper respiratory tract (Edwards *et al.*, 1998) infections have been associated with MS relapses with a relative risk of 2.1, which increases to 3.4 in serologically confirmed upper respiratory tract infections (Edwards *et al.*, 1998). Although the evidence of involvement of viruses in the etiology of MS is largely circumstantial, some patterns of association are constant, with little evidence for direct viral infection of CNS but a more consistent age-related immune response to several common viruses.

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