Neurol Sci (2000) 21:S853-S856

E. Merelli • F. Casoni

Prognostic factors in multiple sclerosis: role of intercurrent infections and vaccinations against influenza and hepatitis B

Abstract Since the first historical description of multiple sclerosis (MS) it has been known that febrile illnesses frequently trigger relapses of the disease. In spite of this knowledge, vaccination against influenza has been hampered for a long period by neurologists on the basis of anecdotal cases of post-vaccination encephalomyelitis. Randomized, double-blind, placebo-controlled studies during the past decade have shown that influenza vaccination of MS patients neither increases the relapse rate nor worsens the course of the disease. In contrast, the reduction of viral infection episodes leads to a lower number of exacerbations of MS. Influenza vaccination is safe and should be recommended to MS patients in order to avoid attacks of the disease.

After publication of case reports of hepatitis B (HB) vaccination followed by onset of MS, a media-driven scare campaign mainly in France was conducted. The French health authorities decided to suspend routine vaccination of adolescents in schools, invoking the "principle of precaution". This fact has caused widespread confusion and concern about the HB vaccination. Epidemiological studies in large populations have recently been performed to investigate a possible link between HB vaccination and MS: all results argue against a causal relation between HB vaccine and MS or other demyelinating diseases. Since the vaccination provides complete protection against hepatitis B and its severe long-term complications, the World Health Organization recommends continuing the implementation of the HB vaccination programs.

Key words Multiple sclerosis • Viral infections • Influenza vaccination • Hepatitis B vaccination

E. Merelli (✉) • F. Casoni
Neurological Department
University of Modena
Via del Pozzo 71, I-41100 Modena, Italy

Introduction

From the first description of multiple sclerosis (MS) by Charcot in the 1868, it has been known that febrile infections may trigger relapses of the disease. Nevertheless until 1985 the relation between infections and relapses has been reported only in anecdotal cases. The first controlled study [1] reported 170 MS relapsing-remitting (RR) patients followed for a period of 8 years with respect to viral infections and episodes of relapse. The follow-up period was divided into at-risk weeks (AR) with 779 viral episodes, and not-at-risk weeks (NAR) in which viral infections were not registered. In the AR weeks, the annual relapse rate was significantly higher than in the NAR weeks (0.64 vs. 0.23, $p < 0.0001$) and it was correlated with lower disability measured using the expanded disability status scale (EDSS). The viral diseases considered in the study were cold, influenza, and enteric and herpes infections. The frequency of the viral and episodes was approximately 20%-50% less in MS patients than controls, mainly in patients with greater disability. The authors suggest that MS patients have superior immune defences against common viruses due to an overactive immune system, but the hypothesis has not been fully clarified. In the following years it has been found that mainly upper respiratory tract infections (URTI) trigger MS attacks and increase the relapse rate. The adenoviruses, the respiratory syncytial virus, *Mycoplasma pneumoniae* and A and B influenza viruses were the infectious agents examined [2].

This relation between URTI and MS relapses was confirmed in further studies [3,4]. Different mechanisms of action by means infections trigger the MS relapses are postulated. Immunologists have invoked the possibility that viral antigens may result in molecular mimicry with the encephalitogenic tract of myelin, thus provoking the immune cascade at the basis of the disease [5]. Moreover, the infections may release superantigens inducing the production of proinflammatory cytokines, mainly interleukin (IL)-12, which in turn increases the secretion of interferon (IFN)-γ. IFN-γ increases the relapse rate of MS [6]. Finally, a theory of a "bystander activation" of resting encephalitogenic T cells by proinflammatory cytokines released from cells in response to viral infection has recently been formulated [7].

Influenza vaccination and MS relapses

Although the prevention of febrile illness is clearly advantageous for MS patients, a considerable controversy exists on the question whether to administer influenza vaccine to MS patients. The fear of clinicians to precipitate MS exacerbations in their patients caused by the vaccination against influenza is due to a small number of post-vaccination demyelinating cases anecdotally reported.

In the past decade, many favorable data have been reported regarding influenza immunization for avoiding MS relapses in the course of infectious episodes. In a study on a cohort of RRMS patients, cerebral lesions on T2-weighted MRI images were measured before and after influenza vaccination. The number of gadolinium-positive lesions did not differ in the two MRI investigations, suggesting that the vaccine does not influence the reactivation of the disease [8].

Recently, a multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in more than 100 MS patients showed that influenza immunization is neither associated with an increased exacerbation rate in the post-vaccination period nor with a worsening in the course of MS during the subsequent 6 months [9]. Another study confirmed that vaccination to avoid febrile illness significantly reduced the relapse rate of MS. However, the same study showed that vaccinated MS patients had less protection against influenza episodes despite a higher serum antibody level than that of normal subjects [10]. The failure of the vaccine to provide a complete protective effect in MS patients compared to healthy subjects may be caused by a defect in the immunoregulatory system of MS patients responsible for the high levels of antibodies. If this datum will be confirmed in additional studies, clinicians cannot rule out the possibility that in these patients the immunization may partially fail its aim. Moreover, in a large cohort of RRMS patients the relapse rate decreased from 33% in the pre-vaccination period to 5% after the immunization, while in primary progressive MS patients no clinical effects were registered in relation to the vaccination [11].

More recent results confirm the previously reported association between influenza infection and MS exacerbations, and indicate that the relative risk may be even higher when viral infection is serologically confirmed. This finding suggests that influenza viruses may have a triggering role in the events that lead to blood-brain barrier breakdown and to its inflammatory consequences. In spite of the fact that the Advisory Committee on Immunization Practices currently recommends annual influenza immunization for persons at risk for exacerbations of MS, this decision remains highly controversial, since many clinicians advise against influenza vaccination. Taking into account the literature and clinical experience, we may encourage MS patients to receive the influenza vaccination with full confidence in order to prevent the real risk that they will develop a relapse if infected by the virus.

Hepatitis B vaccination and MS

Another hot debate relates to the question if vaccination against HB may cause the development of MS in the vaccinated subjects.

Hepatitis B (HB) is caused by hepatitis B virus (HBV) transmitted by blood exchange and sexual contact. Hepatitis B may be passed from mothers to children during birth as is human immunodeficiency virus (HIV), and it is 50-100 times more infectious than HIV. The disease is diffused worldwide mainly in Africa, Asia and undeveloped countries; 4 million acute infections are registered each year; 2000 million persons have evidence of past HBV infection and 350 million are chronic carriers; and around one-quarter of these chronic carriers will develop cirrhosis or liver cancer within 30 years [12]. The vaccine against HBV has been available since 1981. Vaccination is mandatory in Italy and in more than 100 countries since 1991. HB vaccine is made using recombinant DNA technology; it contains only a portion of the outer protein of HBV and does not contain any live component. The vaccine is administered in 3 intramuscular doses to 1-year-old children, to adults at risk (mainly health workers) and to 12-year-old adolescents until 2003. Persons who respond to HB vaccine are almost totally protected against the acute disease as well as against the chronic consequences of infection, such as cirrhosis and liver cancer.

In Italy after the introduction of mandatory HB vaccination, the incidence of HB decreased from 12 to 3 new cases per year per 100 000 inhabitants [13]. In spite of the dramatic decrease of HB in vaccinated subjects, since 1994 the hypothesis of a potential causal relationship between vaccination and MS (and other demyelinating diseases) was brought to public debate by the French Health Authority after the publication of sporadic cases of MS or MS relapses after HB vaccination. Some years ago, researchers demon-

strated that part of rabbit myelin is closely related to the polymerase protein of HBV. Thus, when the polymerase protein of HBV is injected into a rabbit, an inflammation can be observed in its brain. However, it is unlikely that this has clinical relevance, because rabbit and human myelin differ in this region. Moreover, HB vaccine does not contain any DNA polymerase [14]. In October 1998, following a media-driven scare campaign, the French Ministry of Health suspended the HBV immunization of adolescents but not of infants and high-risk adults. The World Health Organization (WHO) criticized the decision for lack of scientific evidence and the high efficacy of the vaccine, and further emphasized that no evidence supports a causal association between MS and any vaccine [15]. Up to June 1998, the number of new MS cases reported after HB vaccination in more than 550 million subjects was 110 for the whole world, with 76 of these cases being reported in France. This disproportion between France and the rest of the world could be explained by the heightened awareness of the causal link hypothesis in France [14]. Moreover, a study of the National Commission of Pharmacovigilance on the neurological tolerance of all HB vaccines available in France was performed from December 1994 to December 1996. The rate of demyelinating diseases in temporal association with HB vaccination was 0.6 cases per 100 000 vaccines. This rate is significantly lower than the expected incidence of demyelinating diseases in the French population which is 1-3 cases of MS per 100 000 persons. Moreover, epidemiological data show that the geographical incidence and prevalence of HB are the opposite of those for MS. Scandinavia and Northern Europe have the highest rate of MS and lowest rate for HBV infection, while sub-Saharan Africa and Asia have the lowest rate of MS and the highest rate of HBV. Nevertheless some sporadic cases of MS following HB vaccination have been reported (Table 1). Since more than half of the described patients presented a personal or familial history or symptoms suggestive of a demyelinating disease before the HB vaccination, the authors suggest as precautionary measure to avoid HB vaccination in these subjects. Further data are needed to adopt a common strategy for these few cases in which the disease may yet be present at the moment of the vaccination or for the subjects with relatives affected by MS.

Epidemiological evidence for a causal association requires showing that MS or exacerbations of the disease occur more frequently in HB-vaccinated subjects than in a comparable (matched for age, sex and ethnicity) population of non-vaccinated individuals.

A retrospective cohort study was done on 27 229 subjects vaccinated against HB and on 107 469 non-vaccinated subjects enrolled in a US health-care database from 1988 to 1995 [19]. The rate of central nervous system demyelinating episodes (ON, ADEM, myelitis and MS) in the vaccinated group was compared with that in age- and sex-matched non-vaccinated individuals in the 3 years after vaccination. This study did not reveal significant differences between vaccinated and non-vaccinated subjets for demyelinating episodes at any time point analyzed. Another study was conducted in British Columbia on 288 657 adolescent students observed in the pre-vaccination period, from 1986 to 1992, and on 267 412 vaccinated adolescents between 1992 and 1998 [20]. This study reported the onset of 9 MS cases in the first period and 5 MS in the second, without any significant difference between the two groups. A recent paper reviewed all the published data on the possible link between HBV and MS and concluded: “the most plausible explanation for the observed temporal association between vaccination and MS is that it is a coincidental association” [14]. Several ongoing epidemiological studies in Europe as well as in the USA will help to clarify every possible doubt on this issue.

Presently, we may affirm that there is no scientific evidence suggesting a causal link between HB vaccination and MS and that the control of HB is of major importance, justifying the continued implementation of HB vaccination programs.

Table 1 HB vaccination and MS

	Period after HB vaccination	Cases
Herroelen et al. 1991 [16]	6 weeks	1 case of known MS 1 case without MS history with B7, DR2 HLA
Kaplanski et al. 1995 [17]	2 weeks	1 case of ADEM with B7, DR2 HLA
Tourbah et al. 1999 [18]	< 10 weeks	8 cases with ADEM or MS 2 with familiar MS 1 with ON 1 with Lhermitte’s sign

MS, multiple sclerosis; *ADEM,* acute disseminated encephalomyelitis; *ON*, optic neuritis

References

1. Sibley WA, Bamford CR, Clark K (1985) Clinical viral infections and multiple sclerosis. Lancet 8:1313-1315
2. Andersen O, Lygner PE, Bergstrom T, Andersson M, Vahlne A (1993) Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. J Neurol 240:417-422
3. Panitch HS (1994) Influence of infection on exacerbations of multiple sclerosis. Ann Neurol 36:S25-S28
4. Edwards S, Zvartau M, Clarke H, Irving W, Blumhardt LD (1998) Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. J Neurol Neurosurg Psychiatry 64:736-741
5. Levin MC, Krichavsky M, Berk J, Foley S, Rosenfeld M, Dalmau J, Chang G, Posner JD, Jacobson S (1998) Neuronal molecular mimicry in immune-mediated neurologic disease. Ann Neurol 44:87-98
6. Panitch HS, Hirsch RL, Schindler J, Johnson KP (1987) Treatment of multiple sclerosis with gamma interferon: exacerbations associated with activation of the immune system. Neurology 37:1097-1102
7. Wekerle H (1998) The viral triggering of autoimmune disease. Nat Med 4:770-771
8. Michielsens B, Wilms G, Marchal G, Carton H (1990) Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. Eur Neurol 30:258-259
9. Miller AE, Morgante LA, Buchwald LY, Nutile SM, Coyle PK, Krupp LB, Doscher CA, Lublin FD, Knobler RL, Trantas F, Kelley L, Smith CR, La Rocca N, Lopez S (1995) A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology 48:312-314
10. Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E (1997) Influenza virus vaccination of patients with multiple sclerosis. Multiple Sclerosis 3:243-247
11. De-Keyser J, Zwanikken C, Boon M (1998) Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. J Neurol Sci 159:51-53
12. Hadler SC, Margolis HS (1992) Hepatitis B immunization: vaccine types, efficacy, and indication for immunization. In: Remington JS, Swartz MN (eds) Current clinical topics in infectious diseases. Blackwell, pp 282-308
13. Tosti ME, Traversa G, Bianco E, Mele A (1999) Multiple sclerosis and vaccination against hepatitis B: analysis of risk benefit profile. Ital J Gastroenterol Hepatol 31:388-391
14. Monteyne P, André FE (2000) Is there a casual link between hepatitis B vaccination and multiple sclerosis? Vaccine 18:1994-2001
15. World Health Organization (1998) No scientific justification to suspend hepatitis B immunization. WHO 73:329-336
16. Herroelen L, de Keyser J, Ebinger G (1991) Central nervous system demyelination after immunization with recombinant hepatitis B vaccine. Lancet 338:1174-1175
17. Kaplanski G, Retornaz F, Durand J, Soubeyrand J (1995) Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. J Neurol Neurosurg Psychiatry 58:758-759
18. Tourbah A, Gout O, Liblau R, Lyon-Caen O, Bougniot C, Iba-Zizen MT, Cabanis EA (1999) Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS? Neurology 53:396-401
19. Zipp F, Weil JG, Einhaupl KM (1999) No increase in demyelinating diseases after hepatitis B vaccination. Nat Med 9:964-965
20. Sadovnick AD, Scheifele DW (2000) School-based hepatitis B vaccination programme and adolescent multiple sclerosis. Lancet 355:549-550