Vaccine-Attributable Autoimmune Diseases

It is only in a few rare cases that autoimmune pathology has been firmly considered as attributable to the use of modern vaccines. For example, a form of GBS, polyradiculoneuritis, was found associated with the 1976 to 1977 vaccination campaign against swine influenza using the A/New Jersey/8/76 swine-flu vaccine (39). The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations, and the period of increased risk was concentrated primarily within the five-week period after vaccination (relative risk: 7.60). Although this original Centers for Disease Control study demonstrated a statistical association and suggested a causal relation between the two events, controversy has persisted for several years. The causal relation was reassessed and confirmed in a later study focusing on cases observed in Michigan and Minnesota (40). The relative risk of developing GBS in the vaccinated population of these two states during the six weeks following vaccination was 7.10 whereas the excess cases of GBS during the first six weeks attributed to the vaccine was 8.6 per million vaccinees in Michigan and 9.7 per million vaccinees in Minnesota. The pathogenic mechanisms involved are still unknown. With subsequent influenza vaccines, no significant increase in the development of GBS was noted (41), and it is currently assumed that the risk of developing GBS following vaccination (one additional case per million persons vaccinated) is substantially less than the risk for severe influenza and influenza-related complications (42).

Another example of confirmed autoimmune adverse effect of vaccination is idiopathic thrombocytopenia (ITP) that may occur after measles-mumps-rubella (MMR) vaccination (43–47). The reported frequency of clinically apparent ITP after this vaccine is around 1 in 30,000 vaccinated children. In one study (43), the relative incidence in the six-week post-immunization risk period has been estimated to be 3.27 (95% CI, 1.49–7.16) when compared to the control period. In about two-thirds of the patients, platelet counts under 20,000 have been recorded. The clinical course of MMR-related ITP is usually transient but it is not infrequently associated with bleeding and, as shown in a study conducted in Finland, it can occasionally be severe (48). In this latter study, there was an increase in platelet-associated immunoglobulin in 10 of 15 patients, whereas circulating antiplatelet autoantibodies, specific for platelet glycoprotein IIb/IIIa, were detected in 5 of 15 patients. These findings are compatible with an autoimmune mechanism triggered by immune response to MMR vaccination. However, it should be noted that the risk for thrombocytopenia following natural rubella (1/3000) or measles (1/6000) infections is much greater than after vaccination (42). Patients with a history of previous immune thrombocytopenic purpura are prone to develop this complication, and in these individuals the risk of vaccination should be weighed against that of being exposed to the corresponding viral diseases (49).

Vaccine-Related Allegations of Autoimmune Adverse Effects

The advent of new vaccines and the increasing number of highly publicized reports that claim a link between certain immunizations and autoimmune disease have led to public concern over the risk of inducing autoimmune disease by immunization. For example, special concerns have been voiced recently in France regarding the potential association of MS with HB vaccination. Similarly, questions have been raised in the United States whether childhood vaccinations influence the rate of occurrence of type 1 diabetes. Such allegations, even if they are not confirmed, may have detrimental effects on vaccination programs at a global level and therefore require particular attention.

Hepatitis B and Multiple Sclerosis

The possible association of HB vaccination with the development of MS was primarily questioned in France, following the report of 35 cases of primary demyelinating events occurring at one Paris hospital between 1991 and 1997, within eight weeks of recombinant HB vaccine injection (50–52).

The neurological manifestations were similar to those observed in MS. There were inflammatory changes in the cerebrospinal fluid and high signal intensity lesions were observed in the cerebral white matter on T2-weighted MR images. After a mean follow-up of three years, half of them became clinically definite MS. These neurological manifestations occurred in individuals considered at higher risk for MS: a preponderance of women, mean age near 30 years, overrepresentation of the DR2 HLA antigen, and a positive family history of MS. These observations rapidly called the attention of the French pharmacovigilance system, and from 1993 through 1999, several hundred cases with similar demographic and clinical characteristics were identified. It is essential to note that this episode occurred in a very special context. In France, close to 25 million people received the HB vaccine during this period, of which 18 million were adults, and this represented about 40% of the total country population. No case was reported in children less than three years. Since these initial reports, at least 10 studies aiming at defining the significance of such observations have now been completed. They are summarized on Table 1. There was no significant association between HB vaccination and the occurrence of demyelinating events or MS in any of these studies. However, a common feature was an insufficient statistical power to definitely exclude such an association. Two studies are particularly illustrative of the difficulty of interpreting these data. First, a retrospective, hospital-based case-control study was carried out on patients experiencing the first episode of central nervous system (CNS) demyelination during the two–year period January 1994 to December 1995 (55) (121 cases and 121 matched controls). Adjusted odds ratio (OR) obtained from conditional logistic regression between a CNS demyelination and HB vaccine exposure during the previous 60 days, were 1.7 (95% CI, 0.5–6.3) and, during the previous 61 to 180 days, 1.5 (95% CI, 0.5–5.3). Second, a population-based case-control study using the general practice database in the United Kingdom analyzed 360 cases with incident MS and 140 cases of central demyelination. Each case was matched with up to six controls (63). The OR for exposure to HB vaccine in the 0 to 12 months period was 1.6 (95% CI, 0.6–4.0).

However, two recent studies bear a particular weight in confirming the lack of a significant association between HB vaccination and the occurrence of MS (54). Confavreux et al. conducted a case-crossover study in patients included in the European Database for MS who had a relapse between 1993 and 1997. The index relapse was the first relapse confirmed by a visit to a neurologist and preceded by a relapse-free period of at least 12 months. Exposure to vaccination in the two-month risk period immediately preceding the relapse was compared with that in the four previous two-month control periods for the