Guillian-Barré Syndrome and Acute Disseminated Encephalomyelitis related to the Bivalent Oral Poliovirus Vaccine

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It is now well established that immunity to previous pathogen exposures can profoundly alter responses to unrelated pathogens. This phenomenon is known as heterologous immunity, and while it can beneficially influence protective immune responses it can also result in severe immunopathology [1,2]. For example, elaborate research in animal models has demonstrated that sequential heterologous viral infections can act in concert to precipitate a full-blown clinical manifestation of an autoimmune disease, and do so in cases where single exposures do not cause sufficient tissue destruction and concurrent overt manifestation of the autoimmune pathology even in genetically identical mice [3].

It is particularly noteworthy that heterologous immunity may also play a role in adverse events associated with vaccinations, particularly in infants and young children who sequentially receive multicomponent vaccines, many of which include live attenuated viruses [1,2,4]. Moreover, vaccines in and of themselves have been associated with both induction and exacerbation of many autoimmune diseases, presumably in uniquely susceptible individuals [5]. While some traditionally considered susceptibility factors include genetic background (i.e., certain HLA profiles), personal or family history of autoimmune diseases and prior adverse reactions to vaccines (re-challenge phenomena) [6], an additional factor that must be considered is pathogen exposure before or after vaccination, particularly if both events precede the manifestation of an autoimmune pathology in a temporally plausible association.

It is against this background that the present editorial addresses the article by Tasher et al. in the current issue of *IMAJ* [7] on the possible association of three cases of Guillain-Barré syndrome (GBS) and one case of acute disseminated encephalomyelitis (ADEM) that were reported following the recent bivalent oral poliovirus vaccine (bOPV) campaign in Israel. All four cases involved young children (age range 11 months to 6 years), and although they all occurred within a plausible timeframe following vaccination (< 6 weeks) the authors conclude that there was no evidence for a causal association between the administration of the bOPV vaccine and the reported autoimmune neurological manifestations. The basis for this conclusion was that more plausible causes for the triggering of the autoimmune disease had been identified. The authors thus exonerated the involvement of bOPV due to the following observations:

- Negative poliovirus polymerase chain reaction test in the stool (three cases) and cerebrospinal fluid specimens (one case)
- GBS manifested following a gastrointestinal and respiratory infection (one and two cases respectively) occurring within 3 weeks of the onset of the disease. The ADEM case was similarly preceded by 6 days of a febrile illness. These exposures according to Tasher et al. were more plausible triggers than bOPV
- In all these cases repeated doses (at least three) of the inactivated polio vaccine (IPV) were given in the past without any sequelae.
- There was no evidence in the literature supporting a causal relationship between bOPV and ADEM.

Regarding the first observation, it is well known that the active presence of a replicating virus is not necessary for the induction of an autoimmune pathology since the pathology might have developed post-infection via an immune mediated mechanism. In fact, studies in animal models examining heterologous immune responses have shown that the infectious agent essential for initiating the autoimmune process in susceptible targets can be cleared by the host immune response prior to infection with the secondary virus, the latter being responsible for disease acceleration and overt manifestation [3,8]. For example, in transgenic mice expressing the lymphocytic choriomeningitis virus (LCMV) antigens in oligodendrocytes, infection with LCMV led to infection of tissues in the periphery but not in the central nervous system (CNS) [8]. These mice cleared the virus within 7 to 14 days post-infection, and following clearance they developed a chronic inflammatory response in the CNS. When these LCMV-immune mice were later challenged with two unrelated viruses, pichinde virus (PV) and vaccinia virus (VV), both of which cross-activated LCMV-specific memory T cells, the CNS disease was dramatically

exacerbated, resulting in loss of myelin and clinical motor dysfunction.

From this and other examples [3,8] we can infer that primary infections/immune challenges can subclinically prime individuals for the later development of autoimmune disease. Therefore, long after the initial triggering immune stimulus/infection has been cleared a heterologous immune challenge can push the subclinical disease into an overt manifestation. The priming infectious agent typically shows molecular mimicry with self antigens and generates a memory pool of autoreactive T cells that are not in sufficient numbers to cause extensive tissue damage but can be further stimulated by the heterologous infection, causing them to rapidly expand and induce a full-blown manifestation of the disease.

Of further relevance, in a review of epidemiological data on vaccine-associated paralytic poliomyelitis (VAPP) associated with the exclusive use of OPV published in *JAMA* [9], the authors noted that isolation of poliovirus is helpful but not necessary to confirm a case of paralytic poliomyelitis. In other words, isolation of poliovirus itself neither confirms nor excludes diagnosis. Similarly, Shibazaki et al. [10] who described a case of ADEM with acute paresis and brain magnetic resonance imaging abnormalities in a 27 year old woman occurring 7 days post-OPV vaccination did not detect any viral cultures in cerebrospinal fluid and stool of their patient. Nonetheless, citing a study by Arlazoroff et al. [11], they noted that no virus was detected in 24% of patients with confirmed VAPP, hence the negative viral culture result in their patient did not rule out the possible triggering role of the virus. Notably, cases of ADEM following OPV administration have also been reported in pediatric patients [12,13].

The second and third argument presented by Tasher et al. against the causal role of bOPV in triggering GBS and ADEM are clearly refuted by the consideration of heterologous T cell cross-reactive responses. First, an individual's infectious history has a major influence on shaping the environment conducive for the induction of autoimmunity, or pushing a pre-existing subclinical autoimmune process toward a clinically manifest outcome, even if no disease and/or only subclinical autoimmunity would result in an otherwise healthy and immunologically naive individual [1-3,8]. While the primary triggering agent (i.e., microbial or viral infection, or vaccination) may in and of itself be insufficient to cause a full-blown autoimmune disease, it might act in concert with one or more subsequent secondary antigenic challenges that would change the initially established T cell hierarchy. Importantly, while this change can occur through a homologous immune challenge-mediated shift in immunodominance, manifested in a rapid expansion of a previously subdominant autoreactive T cell clone, the same can also occur through a heterologous challenge with an unrelated pathogen [3,8]. As a result, autoreactive T cells would accumulate over a disease-inducing threshold, thus leading to a clinical manifestation. Notably, not only is heterologous exposure increasingly implicated in immune mediated pathologies, but current research demonstrates that the order in which the pathogenic/immune triggers challenge the host appears to be crucially important in determining the severity of the response. For example, in transgenic mice expressing the LCMV nucleoprotein in the pancreatic islets, a PV infection following the LCMV infection leads to full-blown diabetes while infection with PV *alone* fails to induce diabetes despite the presence of a cross-reactive T cell population [3]. Similarly, the reverse scenario in which PV is either given twice or as a first infection followed by infection with LCMV does not lead to full-blown diabetes in these mice.

Thus in humans, an autoimmune disease could similarly result from a combined effect of two or more unrelated but immunologically cross-reactive pathogens, especially in uniquely predisposed individuals. In light of these data, the argument that all children previously received IPV without any sequelae is irrelevant and invalid and cannot be used to dismiss the possible involvement of bOPV in reported neurological manifestations, especially given the fact that soon after (2–5 weeks from the bOPV injection) all cases experienced a challenge with a heterologous infectious agent.

It should also be noted that IPV is regarded as a safer vaccine than OPV and it is for this reason that Western countries switched to its use in order to eliminate VAPP associated with the extensive use of OPV [9]. Of further relevance is the fact that in 1994, the U.S. Institute of Medicine published a report on the findings of an interdisciplinary committee which over an 18 month period examined putative serious adverse events associated with the administration of routine childhood vaccinations [14]. The committee reviewed all available scientific and medical data, from individual case reports (published and unpublished) to controlled clinical trials, and found that the available evidence favored the causal association between OPV and GBS. In light of this finding, the possibility of a similar causal association occurring during the Israeli bOPV vaccination campaign should have been examined with more scrutiny.

Tasher et al. further state that typically there is a latency of 3 to 14 days (within 1 day to 3 weeks of immunization) between a febrile illness or vaccination and the onset of neurological symptoms; therefore, due to the allegedly long latency (32 days after bOPV) the causal implication for the vaccine is much less likely. While it is true that a large proportion of GBS patients have an infectious exposure 1 to 4 weeks prior to onset of neuropathic symptoms, longer latency periods are recognized as plausible, typically up to 6 weeks [15] (although it should be noted that autoimmune phenomena can in some cases have substantially longer latency periods, many months after vaccination or infectious disease exposure). For example, following the swine flu vaccination program of 1976–1977, vaccinated GBS cases with "extensive" paresis or paralysis occurred in a characteristic epidemiologic pattern closely approximated by a log-normal curve, suggesting a causal relationship. The relative risk of acquiring "extensive" disease in a 6 week period following vaccination ranged from 3.96 to 7.75 depending on the particular baseline estimate of expected normal or endemic incidence [16]. Of more specific

relevance, Anlar and co-researchers [17] reported four pediatric cases (under 5 years of age) after a nationwide OPV campaign in Turkey in 2000. The latency period between OPV administration and symptomatic onset of the illness was 7 to 30 days. Moreover, as in the cases reported by Tasher et al., virological examination of stool samples for poliovirus was negative in all the children. Two of them died of respiratory insufficiency.

Another relevant study suggesting a causal role of OPV in triggering GBS following a mean latency period of 31 days post-vaccination was reported by Kinnunen and colleagues [18]. This study was conducted in Finland where continuing surveillance of GBS from 1981 to 1986 revealed an increase in the incidence of GBS following a nationwide vaccination campaign against polio. At that time, Finland like Israel generally used IPV, but an outbreak of 10 cases of poliomyelitis between August 1984 and January 1985 prompted the OPV vaccination campaign. During and shortly after the vaccination campaign in which 94% of the Finnish population received OPV during a 5 week period, an unexpectedly high number of GBS cases were reported. Ten cases occurred in the first quarter and 6 in the second quarter of 1985, the times corresponding to the vaccination campaign. Ten patients were diagnosed with GBS within 10 weeks after vaccination with OPV, with the mean time of onset at 31 days post-vaccination. According to the assessment by the U.S. Institute of Medicine [19], the observation of an increased incidence of GBS in Finland temporally associated with a nationwide OPV vaccination campaign provided a special opportunity to study the association between GBS and OPV in that it took advantage of two unique factors: a continuing surveillance of GBS that identified cases in the population over a 6 year period and a national program of vaccination over a 5 week period. The data showed an increase in the number of cases of GBS temporally associated with the vaccination program, and this increase was statistically significant. Moreover, the diagnosis of GBS was made by using consistent criteria throughout the observation period. Altogether, the consistency of diagnostic criteria and the statistically significant differences in the incidence of GBS suggested that the increase was not due to chance or bias in case reporting. On the basis of these observations, the U.S. Institute of Medicine favored acceptance of a causal relation between OPV and GBS [19].

With regard to the above cited evidence supporting a possible causal role for OPV in triggering GBS and possibly other autoimmune neurological manifestations, it should be asked what objective criteria, if any, did Tasher et al. use to conclude that *Campylobacter jejuni* and other detected infectious triggers were a "more probable cause" for the reported neurological manifestations than the bOPV vaccine? While it is not in dispute that *C. jejuni* can trigger GBS, not every individual infected *with C. jejuni* will develop the disease. In fact, based on their investigation of the incidence of GBS in a large cohort of persons with laboratory-confirmed *C. jejuni* infection, McCarthy and Giesecke [20] concluded that GBS is a rare outcome of *C. jejuni* infection. They studied a cohort of 29,563 cases of *C. jejuni* infection that was derived from the Swedish national laboratory reporting system for 1987 to 1995. Nine cases of GBS were detected, a rate of 30.4 per 100,000. Of special relevance were the striking differences in rates of GBS following *C. jejuni* infection found in different age groups. In particular, not a single case of GBS was detected in children and adolescents. Among the 20,856 adults aged 20–59 years, three cases were detected resulting in a rate of 14 per 100,000; the remaining six cases occurred in the 2417 people over the age of 59, which translates to a rate of 248 per 100,000. This suggests that GBS following *C. jejuni* infection may be particularly common among the elderly but virtually absent from the adolescent and pediatric population, an observation that completely invalidates the argument by Tasher et al. that *C. jejuni* was a more probable trigger of GBS than bOPV, especially in the light of the above cited investigations supporting a causal association in the latter case.

To conclude, given that the primary aim of pediatric vaccination programs is to reduce childhood mortality and morbidity, a thorough understanding of non-specific vaccine effects is needed. Indeed, these effects can be highly deleterious, resulting in severe immunopathology and induction and/or acceleration of autoimmune diseases in otherwise healthy individuals. Moreover, given that vaccines represent a special category of drugs that are given predominantly to healthy individuals, and for prophylaxis against diseases to which an individual may never be exposed, the emphasis on safety is paramount. Some of the questions that must be addressed urgently are: how does vaccine exposure affect the outcome of subsequent infections with unrelated pathogens, and in particular, what are the consequences of repetitive administrations of multiple vaccines in shaping the immune response to future immune challenges? What other examples of heterologous T cell immunity might negatively influence vaccine outcomes? In which order should vaccines be given to minimize adverse events? Should children be screened for subclinical infections prior to vaccinations? In view of the accumulated evidence from epidemiological studies as well as animal models on heterologous immunity and the unexpected ubiquity of T cell cross-reactivity, vaccination is likely to have many unforeseen effects on subsequent immune responses involving unrelated pathogens, other vaccines and the courses of any preexisting subclinical diseases or immune-genetic susceptibilities. It is therefore imperative to better understand these issues in order to correctly assess adverse events following vaccinations and endeavor to minimize the risk of their occurrence.

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