

# Vaccination-Induced Bilateral Optic Neuritis: Rare but Existing

Giora Pillar MD<sup>1</sup> and Elias Toubi MD<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Carmel Medical Center, Haifa, Israel

<sup>2</sup>Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, Haifa, Israel

Both affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

**KEY WORDS:** bilateral optic neuritis, vaccination, H1N1 influenza vaccine, immune mediated disease

IMAJ 2012; 14: 690-691

**O**ptic nerve neuritis is a relatively infrequent inflammatory disease of the optic nerve, with a prevalence of approximately 0.1%. The most important clinical characteristic is the rapid development of vision loss over 1–2 days, which can worsen due to heat or exercise and is frequently associated with eye pain and/or headache. The signs consist of reduced visual acuity, reduced peripheral vision, decreased perception of brightness, and a change in color vision.

Optic nerve involvement has rarely been reported in patients with autoimmune diseases such as systemic lupus erythematosus and is extremely rare as the presenting feature in such diseases [1]. Optic neuritis was noted in some reports to follow infectious diseases. In one report it developed 2 weeks after the onset of acute hepatitis C [2]. To further evaluate the role of infections in the development of neuromyelitis optica, 19 patients positive for anti-aquaporin-4 antibody were screened for 24 viral and bacterial infections. Serological evidence of recent viral infection was found in 7 of 15 patients screened during the acute phase of the neurologic illness, which was significantly higher than that seen in the control group [3].

The impact of viral infections on many immune mediated diseases was

widely investigated. In almost one-third of SLE patients, acute parvovirus B19, cytomegalovirus and hepatitis B infections were well documented at the onset of SLE [4]. Genetic abnormalities in toll-like receptors such as TLR3 and TLR4 have been associated with susceptibility to viral infections and a predisposition to autoimmunity [5]. This well-established association between viral infections and autoimmune diseases raises thoughts on the issue of immune mediated diseases being a result of vaccination. Being mostly adjuvanted (aluminum salts, mineral oils, toll-like receptor agonists), vaccines are more effective in inducing higher T cell activity and longer B cell memory with high titers of neutralizing antibodies. For this reason adjuvants were reported to potentially inflict illness of an autoimmune nature. The suggestion to establish the syndrome ASIA (Autoimmune Syndromes Induced by Adjuvants) was based on the idea that “adjuvant-induced diseases” may occur infrequently and are therefore worth considering [6,7].

Of the reported vaccination-induced immune mediated adverse disorders (mostly adjuvanted), the most frequent are myalgia, chronic fatigue, arthralgia, and the appearance of autoantibodies such as antinuclear antibodies, specifically anti-cytoplasmic and anti-ssDNA antibodies. Less frequent are neurological manifestations frequently associated with demyelization, irritable bowel syndrome, and cognitive impairment, all listed in the suggested criteria for the diagnosis of ASIA syndrome [8-10]. Due to the rarity

of vaccination-induced autoimmunity, many studies pointed to the fact that this occurs probably in subjects with a specific genetic background such as HLA-DRB1, and HLA-DQB1 [11]. When ASIA is considered, one should try to define the causal relationship between vaccination and autoimmune manifestations. Causality is always considered when clinical symptoms appear in relation to a given vaccine. In this case, a well-confirmed relationship over time is required. A less defined issue in this respect is the latency period between the vaccination and the appearance of post-vaccination symptoms. Classically, most autoimmune disorders appear within days to 3–4 weeks after vaccination. However, some reported the appearance of adverse effects in previously healthy individuals up to 6 months following influenza vaccination [12].

The development of post-vaccination optic neuritis is rare but has been reported. In one case, in a 16 year old girl, a nearly complete visual loss in association with chiasmal neuritis developed following a recent immunization against human papillomavirus [13]. A diagnosis of vaccine-induced optic neuritis was also reported in a 9 year old girl who was referred to the hospital with decreased vision and pain in the left eye a week after hepatitis B vaccination [14]. Later, in 2011, two cases of central nervous system involvement were reported following H1N1 vaccine. In the first one, optic neuritis was reported in a previously healthy child a few weeks after vaccination, and the second in a health care worker in whom seizures and retrograde amnesia with cerebrospinal fluid changes developed following H1N1 influenza vaccine [15,16].

SLE = systemic lupus erythematosus  
ASIA = autoimmune syndromes induced by adjuvants

As stated above, most vaccine-induced adverse effects were related to various adjuvants. In this issue of *IMAJ*, Rubinov and co-authors [17] report on the development of bilateral optic neuritis 2 weeks following influenza vaccination in an otherwise healthy 18 year old male. The temporal relationship between the vaccination and the optic neuropathy was supported by the short period between the appearance of symptoms and the vaccination.

However, this case was different in that H1N1 vaccine was adjuvant free and only traces of thimerosal were present. Although not well established, and mostly in infants/children, side effects related to thimerosal-containing vaccines have been reported. For example, an increase in the incidence of Kawasaki's disease was attributed to the usage of thimerosal in vaccines given to infants. Since 1990, 88 cases of patients developing Kawasaki's disease have been reported to the Centers of Disease Control in the United States shortly after vaccination [18]. Early thimerosal exposure was recorded in a large cohort of 1047 children aged 7 to 10 years. In 42 of them, vaccine (thimerosal-containing)-induced neuropsychological outcomes were suspected. However, only in a few were significant associations with exposure to mercury from thimerosal determined, not supporting a causal association between early exposure to this vaccine and deficits in neuropsychological status [19]. Other studies also pointed to the efficacy and safety of thimerosal-containing vaccines. In a study of 770 healthy adults the immunogenicity and safety of both thimerosal-free recombinant hepatitis B virus vaccine and a

vaccine containing trace amounts of thiomersal were found to be comparably safe and effective [20]. Thus, it appears that over the years immunizations become more effective and safe, although there is still room for improvement.

In summary, the clinical symptoms of bilateral optic neuritis described in this issue of *IMAJ* occurring 14 days after the trivalent influenza vaccination in an otherwise healthy male strongly support a causal relationship. Although attention should be drawn to the possibility of post-vaccination neuropathy and other side effects, we must continue to uphold vaccination as one of the most important prevention tools in medicine. New adjuvant avenues with respect to both safety and efficacy should be investigated.

**Corresponding author:**

**Dr. E. Toubi**

Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, Haifa 31048, Israel

**email:** elias.toubi@b-zion.org.il

**References**

1. Frigui M, Frikha F, Sellemi D, Chouayakh F, Feki J, Bahloul Z. Optic neuropathy as a presenting feature of systemic lupus erythematosus. *Lupus* 2011; 20: 1214-18.
2. Siddiqui J, Rouleau J, Lee AG, Sato Y, Voigt MD. Bilateral optic neuritis in acute hepatitis C. *J Neuroophthalmol* 2009; 29: 128-33.
3. Koga M, Takahashi T, Kawai M, Fujihara K, Kanda T. A serological analysis of viral and bacterial infections associated with neuromyelitis optica. *J Neurol Sci* 2011; 300: 19-22.
4. Pavlovik M, Kats A, Cavallo M, Shoenfeld Y. Clinical and molecular evidence for association of SLE with parvovirus B19. *Lupus* 2010; 19: 783-92.
5. Nahum A, Dadi H, Bates A, Roifman CM. The biological significance of TLR3 variant L412F, in conferring susceptibility to cutaneous candidiasis, CMV and autoimmunity. *Autoimmun Rev* 2012; 11: 341-7.
6. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y.

Adjuvants and autoimmunity. *Lupus* 2009; 18: 1217-25.

7. Toubi E. ASIA – Autoimmune syndromes induced by adjuvants: rare, but worth considering. *IMAJ Isr Med Assoc J* 2012; 14: 121-4.
8. Shoenfeld Y, Agmon-Levin N. ASIA – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36: 4-8.
9. Bhat A, Naguwa S, Cheema G, Gershwin ME. The epidemiology of transverse myelitis. *Autoimmun Rev* 2010; 9: A395-9.
10. Zafir Y, Agmon-Levin N, Paz N, Shilton T, Shoenfeld Y. Autoimmunity following hepatitis B vaccine as part of the spectrum of ASIA: analysis of 93 cases. *Lupus* 2012; 21: 146-52.
11. Santoro D, Vita G, Vita R, et al. HLA haplotype in a patient with systemic lupus erythematosus triggered by hepatitis B vaccine. *Clin Nephrol* 2010; 74: 150-3.
12. Agmon-Levin N, Raz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. *Nat Rev Rheumatol* 2009; 5: 648-52.
13. DiMario FJ Jr, Hajjar M, Clesielski T. A 16-year-old girl with bilateral visual loss and left hemiparesis following an immunization against human papilloma virus. *J Child Neurol* 2010; 25: 321-7.
14. Erguven M, Guven S, Akyuz U, Bilgic O, Laloglu F. Optic neuritis following hepatitis B vaccination in a 9-year-old girl. *J Clin Med Assoc* 2009; 72: 594-7.
15. Lapphra K, Huh L, Scheifele DW. Adverse neurologic reactions after both doses of pandemic H1N1 influenza vaccine, with optic neuritis and demyelination. *Pediatr Infect Dis J* 2011; 30: 84-6.
16. Mittrakrishnan S, Ranjanie G, Thirunavakarasu T, Manjula C, Nayananjani K. Seizures and retrograde amnesia with cerebrospinal fluid changes following H1N1 influenza vaccination. *Vaccine* 2011; 29: 6369-70.
17. Rubinov A, Beiran I, Krasnitz I, Miller B. Bilateral optic neuritis after inactivated influenza vaccination. *IMAJ Isr Med Assoc J* 2012; 14: 705-7.
18. Mutter J, Yeter D. Kawasaki's disease, acro-dynia, and mercury. *Curr Med Chem* 2008; 15: 3000-10.
19. Thompson WW, Price C, Goodson B, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *N Engl J Med* 2007; 357: 1281-92.
20. Rebedea I, Diaconescu IG, Bach D, Bartelsen O, Arndtz N. Comparison of thiomersal-free and thiomersal-containing formulations of a recombinant hepatitis B vaccine in healthy adults. *Vaccine* 2006; 24: 5320-6.

**If you don't like something, change it. If you can't change it, change your attitude. Don't complain**

Maya Angelou (1928- ), African-American author and poet, best known for her series of autobiographies. Her list of occupations includes pimp, prostitute, night-club dancer and performer, cast member of *Porgy and Bess*, journalist in Egypt and Ghana during decolonization, and actor, writer, director, and producer of plays, movies, and public television programs. She was active in the Civil Rights movement and worked with both Martin Luther King and Malcolm X. In 1993, Angelou recited her poem "On the Pulse of Morning" at President Bill Clinton's inauguration. She is respected as a spokesperson of Black people and women, and her works have been considered a defense of Black culture