

## Guillain-Barré syndrome following hepatitis B vaccination

M. Khamaisi<sup>1</sup>, Y. Shoenfeld<sup>2,3</sup>,  
H. Orbach<sup>4</sup>

<sup>1</sup>Department of Internal Medicine B and the Diabetes Center, Hadassah University Hospital, Jerusalem; <sup>2</sup>Department of Medicine "B" and Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer and Sackler Faculty of Medicine, Tel Aviv University; <sup>3</sup>Incumbent of the Laura-Schwartz-Kipp Chair for Research on Autoimmune Diseases, Tel Aviv University, Tel Aviv; <sup>4</sup>Department of Internal Medicine B, Wolfson Medical Center, Holon, Israel.

The authors do not have a commercial or other association that might pose a conflict of interest.

Please address correspondence to:  
Mogher Khamaisi, MD, PhD, Internal  
Medicine B Department, Hadassah  
University Hospital, POB 12000,  
Ein Kerem, Jerusalem, Israel.  
E-mail: mogher@bgumail.bgu.ac.il,  
murir@hadassah.org.il

Received on June 25, 2004; accepted in  
revised form on September 15, 2004.

© Copyright CLINICAL AND EXPERIMENTAL  
RHEUMATOLOGY 2004.

**Key words:** Immunization, vaccination, polyradiculoneuropathy, Guillain Barre syndrome, Engerix, recombinant vaccine.

### ABSTRACT

A 52-year-old woman developed Guillain-Barré syndrome 10 weeks after immunization with recombinant hepatitis B vaccine. Common infectious causes of GBS were ruled out. The temporal relationship between GBS and hepatitis B virus (HBV) vaccination was suggestive of a vaccine-induced cause. The possible mechanisms of this very rare complication are discussed.

### Introduction

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy, usually manifested by a rapidly evolving symmetric and ascending motor paralysis, with loss of tendon reflexes. The cerebrospinal fluid protein level is elevated without pleocytosis. In two-thirds of patients with GBS, acute infection precedes the neurological symptoms by 1 to 3 weeks (1). Several vaccines are suspected to mildly increase the susceptibility to GBS (2,3). We report a 52-year-old woman who developed GBS after her second injection of hepatitis B vaccine. The possibility and the mechanisms of hepatitis B vaccine-induced GBS is discussed with a review of 19 previous cases.

### Case report

A 52-year-old woman presented with abdominal pain and a 2-week history of progressive muscle weakness and limb tenderness particularly in her legs. She received the second dose of a recombinant hepatitis B vaccine (Engerix) ten weeks before admission and 3 weeks later the level of hepatitis B surface antibody was 105 IU/ml. Her past history included polycystic kidney disease with chronic renal failure which had been treated for with chronic hemodialysis for 8 months preceding the admission, and Barrett's esophagus with *Helicobacter pylori* found and treated a year earlier. She denied any infections in the previous ten weeks. Current medications included folic acid, atorvastatin, calcium and levcarnidipine. One day following her admission the patient's legs were sore and too weak to support her and she was confined to bed. She suffered from headache and mild photophobia. On admission her

temperature was 37.9°C, blood pressure 140/90 mm Hg, pulse 120/minute, and respiratory rate 20/minute.

The patient appeared ill. There was no rash, lymphadenopathy or icterus. An ear, nose and throat examination was interpreted as normal. Heart and breathing sounds were normal. An abdominal examination disclosed diffuse sensitivity without hepatosplenomegaly. Pelvic examination revealed no abnormalities. The arms and legs were unremarkable. There was no neck rigidity and the cranial nerve examination was interpreted as normal. The limbs showed a generalized hypotonia with grade 2-3/5, power in most muscle groups in the arms and 1-2/5 in most muscle groups in the legs. Normal sensation to light touch and pain was found. Biceps and triceps reflexes were diminished with absent knee and ankle reflexes. All the muscle groups were tender.

The blood count was WBC  $9.0 \times 10^9/L$  with a normal differential; hemoglobin was 12.2 g/dl and the platelet count was normal. ESR was 60 mm 1 h. Biochemistry values were within the normal range except for creatinine 529 (mmol/L) and urea 12.6 (mmol/L). Muscle enzyme assays were within the normal range and excluded myopathy. The cerebrospinal fluid (CSF) was acellular with elevated total protein (0.83 g/L) compatible with the diagnosis of GBS. Stool cultures were negative for *Salmonella*, *Shigella* and *Campylobacter* with no leukocytes observed by microscopy. On serology, antibodies to cytomegalovirus (CMV), Epstein-Barr virus (EBV) and West Nile fever were not found, anti-nuclear antibody titer was borderline and anti-double stranded-DNA negative,  $C_3$ -1.1 g/l and  $C_4$ -0.42 g/l, *Clostridium difficile* toxin (CDT) was not detected.

An abdominal and pelvic computed tomography scan revealed renal and liver cysts compatible with polycystic kidney disease. The patient was treated for GBS with 2 courses of intravenous immunoglobulin 0.4 g/kg/day for 5 days, 7 weeks apart. Four days after admission, the weakness progressed, and a neurological examination revealed symmetrical areflexic paralysis in 4 limbs. Her respiratory function deteriorated

and she was mechanically ventilated. EMG and nerve conduction velocity were not performed because of her deteriorating condition. Seven weeks later, there was only minor improvement in the cranial nerves and mechanical ventilation was continued via a tracheostomy, along with hemodialysis and supportive therapy. Five months after admission, Acinetobacter pneumonia developed followed by septic shock and she died.

**Discussion**

There is increasing evidence that GBS is an autoimmune disease. Various autoantibodies to gangliosides were described in GBS patients (4,5), and T cells with cross-reactivity to nerve-sheath components (4). The disease is related in most cases to respiratory or

gastrointestinal infections and vaccines, resulting in demyelination or axonal degeneration (2). The target of the immune attack differs with the clinical subtypes of GBS (3). Rarely is GBS related to Hodgkin’s lymphoma (6) or autoimmune disease such as systemic lupus erythematosus (7).

Infection with the following microorganisms can cause GBS: *Campylobacter jejuni*, in 25-41% of GBS patients, Epstein-Barr virus, cytomegalovirus (2), HIV infection, *Mycoplasma pneumoniae*, shigella, clostridium (8), and *Haemophilus influenzae* (9).

Vaccines reportedly related to the appearance of GBS include influenza, tetanus toxoid, BCG, rabies, smallpox, mumps, rubella, oral poliovirus vaccine, hepatitis B vaccines, either plasma-derived or recombinant vaccine and

diphtheria vaccine (10). The influenza vaccine in 1976 (“swine flue” or New Jersey 76) caused a 4- to 8-fold increase in the rate of GBS occurring 6-8 weeks after vaccination (11,12). Subsequent studies of influenza-vaccinated patients showed no increase in the GBS rate (13).

In a review of the English literature another 19 cases of hepatitis B vaccination were reported to precede the symptoms of GBS (14-22) (Table I). The plasma-derived hepatitis B vaccine became commercially available in June 1982. Shaw *et al.* (15) documented the first 3 years of postmarketing surveillance for neurologic adverse events after vaccination among 850,000 persons, mostly health workers, who received the HBV vaccine. Nine cases of GBS were reported up to 7 weeks after

**Table I.** Literature summary regarding Guillain-Barré syndrome related to hepatitis B virus vaccine.

Report no.	Reference	Year of publication	Number of patients	Age/sex	No. of HBV vaccine injections	Onset of symptoms §
1	MMWR [14]	1983	2	Not described	1	< 4 weeks
2	Shaw <i>et al.</i> [15]	1988	9	6 at age 25-44 2 at age 45-64 1 at age > 65 5M and 4F	5 received 1 4 received 2	< 7 weeks
3	Tuohy <i>et al.</i> [16]	1989	1	7/F	1	3 weeks
4	MacMahon <i>et al.</i> [17]	1992	2	-/M -/M	2 3	9 months 3 months
5	Kakar <i>et al.</i> [18]	1997	1	3/F	1	1 day
6*	Creange <i>et al.</i> [19]	1999	1	45/F	2	1 month
7*	Sinsawaiwong <i>et al.</i> [20]	2000	1	17/F	1	3 days
8	Sindern <i>et al.</i> [21]	2001	1	36/M	4	9 days
9*	Seti <i>et al.</i> [22]	2002	1	14/F	3	1.5 months
10*	Khamaisi <i>et al.</i> 2004	1	52/F	2	8 weeks	
Total			20	8 males 10 females 2 #		

M=male; F=female

§ Time difference between last vaccine and beginning of symptoms; \*recombinant HBV vaccine (Engerix); # not defined.

vaccination. One case was reported as atypical and 5 cases were compatible with a viral infection before the appearance of the neurological symptoms. GBS was reported as occurring significantly more often than expected when compared with the Center of Disease Control GBS background rate (11), but not when compared with the Olmsted County rate (23). The authors calculated that, taking into account age, sex and under-reporting, the rate of GBS was slightly higher in the vaccinated group, but concluded that no definite epidemiologic association could be made.

McMahon *et al.* (17) determined the incidence of adverse reactions from the plasma-derived hepatitis B vaccine in Alaska. Out of 43,618 subjects who received 101,360 injections, 2 patients developed GBS 3 and 9 months after the last injection. Their conclusion was that the vaccine was safe and that the incidence of GBS was not increased. The authors claimed that the adverse events caused by the plasma-derived HBV vaccine are due to the preservative material thimerosal, a mercurial compound that was found to be neurotoxic and is not included in the HBV vaccines since 1999 and to aluminium hydroxide, used as an adjuvant. Both compounds were also used in the recombinant vaccine.

In addition to our patient, 8 case reports of GBS after hepatitis B vaccine have been reported (14,16,18-22), 3 of them after receiving the yeast derived recombinant DNA hepatitis B vaccine. One of the patients died after a multiorgan failure, septic shock and adult respiratory distress syndrome. A neuropathologic examination revealed an inflammatory cell infiltrate in the gray matter especially in the anterior horn of the spinal cord, and small foci of macrophages in the long tracts. Most of the cells appeared around blood vessels, but were also found in the parenchyma, close to nerve cells (21). The pathogenesis of hepatitis B vaccine associated with GBS is not clear. The following mechanisms are suggested:

1) Molecular mimicry: As in other autoimmune disorders appearing after

vaccination, molecular mimicry is suspected. Hepatitis B surface protein may provoke an autoimmune attack on a similar protein present in the nerve cells. In molecular mimicry involving T lymphocytes these cells recognize their antigen as peptide-bound to MHC molecule. The microbial antigen has the same shape as a self antigenic epitope bound to the same MHC molecule. The DNA sequence of HBV was found to be homologous to myelin basic protein (23).

2) Another coincidental infection: Most of the vaccine recipients are at high risk for infection with EBV, CMV and HTLV 3, that also can cause demyelinating disease (18).

3) Immune complex disease: Five cases of GBS have been reported in patients suffering from infection with HBV. In the acute phase of GBS, immune complexes containing hepatitis B surface antigen were found in the serum and cerebrospinal fluid, but not in the sural nerve. Those immune complexes were not present when the hepatitis was first detected, but only after the appearance of neurological symptoms, and disappeared when the inflammatory phase of the disease had ended (24, 25).

Immune complexes without a known antigen were found in other cases of GBS in various organs. The immune complexes can transfer through the blood-nerve barrier and may be deposited in the endoneurium and injure nerve fibers (25). Treatment with plasmapheresis or IVIG may eliminate those immune complexes.

Recently, the presence of glycolipid (ganglioside) specific antibodies has been found to be associated with neurological disease, in particular with GBS. The pathogenic potential of these antibodies has remained unclear. Several mechanisms by which anti-ganglioside antibodies may exert their potential pathogenic effect have been proposed. Direct binding of anti-ganglioside antibodies to axon or Schwann cells might disturb ion fluxes and cause partial nerve conduction block (26). Naturally occurring antibodies crossreacting with gangliosides may become

pathogenic after affinity maturation and class switching initiated by preceding infection.

The hepatitis B vaccine has been used routinely for almost 20 years. Most of the side effects are local or transient minor reactions. The rate of the adverse events is 1 in 15,500 doses. Major reactions are rare and include variable autoimmune phenomena: erythema nodosum, lichen planus, acute urticaria, polyarthritis, including rheumatoid arthritis and reactive arthritis, vasculitis, glomerulonephritis, Evan's syndrome and thrombocytopenic purpura.

Neurological complications include acute cerebellar ataxia and autoimmune demyelinating disorders including multiple sclerosis, transverse myelitis and GBS (27). These reactions are sporadic and there is no clear evidence that the rate of GBS or multiple sclerosis is more common among the vaccinated population.

Hepatitis B vaccine is important and, according to the available data, the prevention of hepatitis B outweighs the rare incidence of diseases reported after vaccination. Further animal studies and evaluation of the risk factors for these adverse effects are indicated.

## References

- MELNICK SC, FLEWETT TH: Role of infection in Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 1964; 27: 395-407.
- HAHN AF: Guillain Barre's syndrome. *Lancet* 1998; 352: 635-41.
- YUKI N: Infectious origin of, and the molecular mimicry in, Guillain-Barré and Fisher's syndromes. *Lancet Infectious Diseases* 2001; 1: 26-37.
- TERRYBERRY JS, SHOENFELD Y, GILBURD B *et al.*: Myelin and microbe-specific antibodies in Guillain-Barré syndrome. *J Clin Lab Anal* 1995; 9: 308-19.
- SCHWERER B: Antibodies against gangliosides: a link between preceding infection and immunopathogenesis of Guillain Barré syndrome. *Microbes Infect* 2002; 4: 373-84.
- LISAK RP, MITCHELL M, ZWEIMAN B, ORRECHIO E, ASBURY AK: Guillain-Barré syndrome and Hodgkin's disease: three cases with immunological studies. *Ann Neurol* 1977; 1: 72-8.
- ROBSON MG, WALPORT MJ, DAVIES KA: Systemic lupus erythematosus and acute demyelinating polyneuropathy. *Br J Rheumatol* 1994; 33: 1074-7.
- ROPPER AH, VICTOR M: Influenza vaccination and Guillain-Barré syndrome. *N Engl J Med* 1998; 339: 1845-6.
- MORI M, KUWABARA S, MIYAKE M *et al.*:

- Haemophilus influenzae infection and Guillain-Barré syndrome. *Brain* 2000; 128: 2171-8.
10. SHOENFELD Y, ARON-MAOR A: Vaccination and autoimmunity-'vaccinosis': a dangerous liaison? *J Autoimmun* 2000; 14: 1-10.
  11. SCORBERGER LB, BREGMAN DJ, SULIVAN-BOLYAI JZ *et al.*: Guillain-Barré syndrome following vaccination in the national influenza immunization program, United-States, 1976-1977. *Am J Epidemiol* 1979; 110: 105-23.
  12. SAFRANEK TJ, LAWRENCE DN, KURLAND LT *et al.*: Reassessment of the association between Guillain-Barré syndrome and receipt of swine influenza vaccine in 1976-1977: results of a two state study: Expert neurology group. *Am J Epidemiol* 1991; 133: 940-51.
  13. LASKY T, TERRACCIANO GJ, MAGDER L *et al.*: The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med* 1998; 339: 1797-802.
  14. CENTERS FOR DISEASE CONTROL AND PREVENTION: The safety of hepatitis B virus vaccine. *MMWR* 1983; 32: 134-6.
  15. SHAW FE JR, GRAHAM DJ, GUESS HA *et al.*: Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. *Am J Epidemiol* 1988; 127: 337-52.
  16. TUOHY PG: Guillain-Barré syndrome following immunisation with synthetic hepatitis B vaccine. *N Z Med J* 1989; 102: 114-5.
  17. MCMAHON BJ, HELMINIAK C, WAINWRIGHT RB, BULKOW L, WAINWRIGHT K: Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; 92: 254-7.
  18. KAKAR A, SETHI PK: Guillain Barré syndrome associated with hepatitis B vaccination. *Indian J Pediatr* 1997; 64: 710-2.
  19. CREANGE A, TEMAM G, LEFAUCHEUR JP: Lumbosacral acute demyelinating polyneuropathy following hepatitis B vaccination. *Autoimmunity* 1999; 30: 143-6.
  20. SINSAWAIWONG S, THAMPANITCHAWONG P: Guillain-Barré syndrome following recombinant hepatitis B vaccine and literature review. *J Med Assoc Thai* 2000; 83: 1124-6.
  21. SINDERN E, SCHRODER JM, KRISMANN M, MALIN JP: Inflammatory polyradiculoneuropathy with spinal cord involvement and letal outcome after hepatitis B vaccination. *J Neurol Sci* 2001; 186: 81-5.
  22. SETI NK, REDDI R, ANAND I, SETHI PK: Guillain Barré syndrome following vaccination with hepatitis B vaccine. *JAPI* 2002; 50: 989.
  23. WRAITH DC, GOLDMAN M, LAMBERT PH: Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003; 362:1659-66.
  24. PENNER E, MAIDA E, NAMOLI B, GANGL A: Serum and cerebrospinal fluid immune complexes containing hepatitis B surface antigen in Guillain-Barré syndrome. *Gastroenterology* 1982; 82: 576-80.
  25. TSUKADA N, KOH CS, INOUE A, YANAGISAWA N: Demyelinating neuropathy associated with hepatitis B virus infection. Detection of immune complexes composed of hepatitis B virus surface antigen. *J Neurol Sci* 1987; 77: 203-16.
  26. VAN SORGE NM, VAN DER POL WL, JANSEN MD, VAN DEN BERG LH: Pathogenicity of anti-ganglioside antibodies in the Guillain-Barré syndrome. *Autoimmunity Review* 2004; 3: 61-68.
  27. GROTTI I, MANDEL Y, EPHROS M, ASHKENAZI I, SHEMER J: Major adverse reactions to yeast-derived hepatitis B vaccines – a review. *Vaccine* 1998; 16:329-34.