Hepatitis A Virus Infection in Guillain-Barré Syndrome

Neneng Ratnasari, Siti Nurdjanah

Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Gadjah Mada/Dr. Sarjito Public General Hospital, Yogyakarta

ABSTRACT

Background

Prodromal factors of Guillain-Barré syndrome (GBS) are often associated with previous viral infection (60%). The ailment supported by the acquired immunomediated disorder concept. Viral hepatitis is very rarely found in GBS, preceded by cytomegalovirus (15-18%), Campylobacter jejuni *(28%), and Epstein-Barr virus (5%). There is no specific etiology of GBS because those viruses usually appear sporadically (subclinically). All hepatitis virus infection can cause neurological complications, including GBS.*

Case Report

We report two cases of hepatitis A virus infection (HAV) in GBS patients in Dr. Sardjito General Hospital during 5 years of observation (1996-2000) from 92 GBS patients. The diagnosis of HAV was based on more than 2 times increment of transaminase enzyme, positive IgM anti HAV, negative HbsAg, and negative IgM anti HCV. The diagnosis of GBS was based on clinical symptoms of acute generalized paralysis, cerebrospinal fluid examination, and electromyelography. In both cases, sub-clinical and sporadic symptoms appeared several days before paralysis, which makes it more likely that the prodromal period of GBS occurred at the same time of HAV incubation period.

Discussion

The incidence of HAV in GBS patients during 5 years of observation was 2%. This corresponds with the case reported by Verona et al, 1996 and Pelletier et al, 1985, i.e. the presence of peripheral neuropathy (n. facialis and n. occulomotorius). Possible alternative pathways for hepatitis virus complicating as GBS are perivascular and endometrial peripheral nerve infiltration by mononuclear cells, T cell sensitization, stimulation of IL-2 growth factor surface receptor, and B cell stimulation. All of the conditions mentioned above causes necrotizing arteritis, vascular occlusion, and at the end, segmental demyelinization. Hepatitis virus may replicate in the central nervous system or peripheral nervous system, subsequently developing into multiple neuropathy disorder and polyarteritis.

Conclusion

The diagnoses of HAV and GBS in both cases were established. HAV is one of several viruses that may trigger GBS. In both cases, HAV infection was sub-clinical and sporadic. Symptoms of hepatitis infection subsided along with improvements in the patient's neurological status.

Acute viral hepatitis has a wide clinical spectrum and laboratory manifestation that is in accordance with the severity, varying from unclear symptom (anicteric) to jaundice. Acute hepatitis A, B, C infections have the same symptoms in general. However, hepatitis B and C tend to be more severe. The mildest symptoms are transaminase enzyme level increment, no jaundice, gastrointestinal symptoms, flu-like symptoms, and sometimes it can not be diagnosed. The more severe symptoms are jaundice with obvious generalized symptoms.[1] The incidence of hepatitis A is difficult to be determined accurately because of its characters, i.e. sporadic, endemic, and has a high rate of asymptomatic infection.[2,3,4]

Guillain-Barré syndrome (GBS) is a disorder of the peripheral nervous system, occurring as a clinical

syndrome with unknown etiology. The syndrome is characterized by acute onset, generalized, involving the radix and peripheral nerve, and sometimes central nervous system. GBS is one of the nerve disorders with peripheral nerve demyelinization (demyelinating motor neuropathy) and usually occur very discreet. The disease can be accompanied by HIV, Campylobacter jejuni*, hepatitis, mononucleosis, and Mycoplasma pneumoniae infections, vaccination, surgery, lymphoma, or systemic lupus erythematosus.[5] Acute hepatitis infection is rare in GBS patient, MacLeod (1987) reported 3 GBS patients as complication of acute hepatitis, and quoting a report by Berger* et al *(1981) between year 1944-1980, 26 GBS patients were related with viral hepatitis,[6] with incidence of 1-2 per 100,000 per year, ranging from young adult to 55 years old, occurring more in males than females (2:1).[5,7]*

The objective of this case report is to present 2 cases of hepatitis A virus in GBS patients who were hospitalized in RSUP Dr. Sardjito, during 5 years observation (1996-2000). The problem found was that such cases were rare.

CASE REPORT

Case 1

A 19 year-old, male student , was hospitalized for 34 days in the neurology ward. The patient was admitted to the hospital due to high fever for 2 days, headache, nausea, and epigastric pain since 3 weeks prior to admission. The patient went to a physician and the fever subsided, while the nausea and headache remained. His stomach was distended, his urine was tea-like in color, and he had an irregular frequency of defecation. Five days prior to admission both of the patient's legs became weak and heavy, while the color of his urine still resembled the color of tea, but there was no longer any fever. Three days prior to admission, the patient's complaints worsened. He became unable to walk, and could not feel either arms, particularly the fingertips. Since one day prior to admission, he was unable to urinate. There was no past history of disease, and he had had no surgery or vaccination recently. There was no familial history of disease.

During physical examination the patient was found to be generally weak, fully conscious, with a blood pressure of 170/100 mmHg, a pulse rate of 80x/minute, a respiration rate of 20x/minute, and a body temperature of 37ºC. His conjunctivae were not pale, and his sclerae were not jaundiced. There was no neck stiffness. There were no palpable lymph nodes. Heart and lungs were within normal range. His liver and spleen were not palpable. Peristalsis was within normal range. There was flaccid tetra-paresis, and no edema.

Neurological state: there was no abnormality of the cranial nerves, abdominal wall reflex was decreased.

Extremities: movement was limited, motor strength scale 4, physiologic reflexes were decreased. There were no pathologic reflexes. Muscle tone was normal, eutrophy, no clonus. Sensibility: acral paresthesia. Vegetative function: urine retention.

The results of laboratory examination were as follows: Hemoglobin level 12.1 g/dL; leukocyte count 8,500/mm^3; segmental leukocyte composition 71%, lymphocyte 29%; platelet count 337,000/mm^3; hematocryte 36.0; SGOT 140 iu/L; SGPT 197 iu/L; total bilirubin 2.10 mg/dL; direct bilirubin 1.13 mg/dL; total protein 7.4 g/dL; albumin 4.4 g/dL; cholesterol 256 g/dL; triglyceride 348 mg/dL; HDL 26 mg/dL; LDL 160 mg/dL; Ca 2.14; cito blood glucose 141 mg/dL, ureum level 37 mg/dL; creatinine level 1.0 mg/dL; Na^+ 133 mmol/L; K^+ 4.3 mmol/L; Cl^- 95 mmol/L. Results of blood gas analysis were as follows: pH 7.45; pCO_2 36; pO_2 85; HCO_3 23.8; TCO_2 24.8; BE 0.7; Sat 96%.

Seromarkers for viral disease were as follows: negative HBsAg, positive anti HAV IgM (1.20), negative anti HCV IgM. Evaluation of anti CMV IgM/IgG was not performed due to financial reasons, and other means for viral disease examinations were not available.

Cerebrospinal fluid analysis (on the 16th day of hospitalization) demonstrated: no cells; erythrocyte +; glucose 62 mg%; Na^+ 141; K^+ 2.6; Cl^- 118; protein 53%; NaCl 694 mg%; no CRP; no albumin; negative pandy test. The neuropathological evaluation of cerebrospinal fluid found 1-5 cells, consisting of lymphocytes and monocytes. These findings suggested post-myelitis, recovery stage.

The results of electroneuromyelography were as follows: prolonged distal motor latency of the right and left tibial nerves; delayed nerve conduction velocity of right and left tibial nerves; grave neuropathy of right and left peronei nerves; positive M and H waves; no reflexes.

During hospitalization, the patient suffered from skin infection i.e. crystalized miliaria (on the 4th day of hospitalization) and urinary tract infection with 10^7 citrobacter (on the 15th day of hospitalization).

Case 2

A 43 year-old, male civil servant , was hospitalized at Dr. Sardjito hospital for 12 days. The patient came to the hospital with complaints of weakness in the lower extremities for about 10 days prior to admission, preceded by fever 1 week before.

Weakness of the extremities aggravated to the point where he found it hard to walk. There were also nausea, vomiting, bloating, stomachache, and the color of the patient's urine resembled the color of tea. The patient was hospitalized at Klaten hospital for 1 week and then referred to Dr. Sardjito hospital. Neither the patient nor any family member had ever suffered from the same disease before.

The results of the physical examination were as follows: the patient's general condition was weak. He was fully conscious and had a good nutritional status. Vital signs were as follows: blood pressure 120/80 mmHg, pulse rate 88x/minute, respiration rate 20x/minute, and body temperature 37ºC. His conjunctivae were not pale, his sclerae were not jaundiced, and his pupils were isochor. There was no neck stiffness. His lymph nodes were not palpable. Heart and lung findings were within normal range. His liver and spleen were not palpable. Peristalsis was within normal range. There was flaccid tetraparesis, and no edema.

Neurological evaluation findings were as follows: there was no cranial nerve abnormality; there was L1 (right) and L2 (left) dermatomal hypestesia; the motor strength of the upper extremities were 4, the lower extremities 0; physiologic reflexes of both extremities were decreased; muscle tone was normal, eutrophy; there were no pathologic reflexes; negative clonus; vegetative function was within normal range.

Laboratory examination results were as follows: Hemoglobin 14.9 g/dL; leukocyte count 19,200/mm^3, segment composition 76.6%, lymphocyte 16.1%, monocyte 4.7%, eosinophil 2.5%, basophil 0.1%; platelet count 238,000/mm^3; hematocryte 45.5%; SGOT 163 iu/L; SGPT 342 iu/L; blood glucose 70 mg/dL, ureum level 70 mg/dL; creatinine level 1.72mg/dL; Na^+ 135 mmol/L; K^+ 4.8 mmol/L; Cl^- 95 mmol/L. A week later, laboratory examinations were repeated, resulting in the following findings: SGOT 154 iu/L; SGPT 195 iu/L; total bilirubin 0.4 mg/dL; direct bilirubin 0.2 mg/dL, alkaline phosphatase 323 iu/L, gamma GT 81 iu/L, total protein 7.4 mg/dL, albumin 4.5 mg/dL.

Seromarkers for viral infection were as follows: negative HBsAg, positive anti HAV IgM (1.40), negative anti HCV IgM. Results of TORCH examination: anti toxoplasma IgM 0.229 (cov 0.513), antitoxoplasma IgG 11.4 (<45: (-)), anti Rubella IgM 0.241 (cov 0.290), anti Rubella IgG 31.7 (moderate immunity protection), anti CMV IgM 0.290 (cov 0.291), anti CMV IgG 31.7 (>115 : latent infection), anti HSV1 1/80 (+), and anti HSV1 IgM 1/20 (-).

Findings of cerebropinal fluid analysis (on the 1st day of hospitalization) were as follows: there were no cells; no erythrocytes, negative rivalta; glucose 70 mg%; protein 19%; NaCl 694 mg%; no albumin; no globulin; no CRP; negative pandy. Conclusion: suspected Guillain-Barré syndrome.

Results of electroneuromyelography (ENMG) were as follows: prolonged distal motor latency of right and left tibial nerves; delayed nerve conduction velocity of right and left tibial nerves; grave neuropathy of right and left peronei nerves; positive M and H waves; and no reflexes. During hospitalization there were no other infection, the patient's general condition improved, and subsequent liver function testing demonstrated progress. The patient left the hospital by his own choice on the 12th day.

In both cases the premiere diagnoses were (1) observation of flaccid tetraparesis with the following differential diagnosis: Guillain-Barré syndrome, myelitis, spinal medulla tumor; (2) acute hepatitis.

The therapy given were: intravenous fluid drop using Ringer Lactate, liver diet III, oxygen 2l/minute (when needed), injection of roborantia, hepatoprotective agents, antibiotics in the presence of infection was proven (in case 1), urine catheterization in case 1, and physiotherapy.

Based on the physical examination, laboratory findings and auxiliary examination, the final diagnosis of both cases was Guillain-Barré syndrome with acute hepatitis A virus infection (sporadic).

DISCUSSION

Prodromal factors leading to GBS are associated with preceding viral diseases (virus-like illness). GBS is supported by acquired immunomediated disorder concept. The viral diseases stated before include upper respiratory tract infection (CMV titer 15-18%), gastrointestinal tract infection (*Campylobacter jejuni* titer of 28%), Epstein-Barr virus infection (5%), HIV, Hepatitis, Mycoplasma (5%), post vaccination (tetanus toxoid, influenza, rabies, polio), and post surgery (10%).[5,7,8,9] Viral infections as the main prodromal of GBS (40-60%), usually occur in the first to fourth week since the appearance of viral infection symptoms until

the neuropathy symptoms. There is no specific etiology that can be implemented to most of the GBS patient because the virus usually appears sporadically based on the clinical diagnosis, antibody response, or virus isolation.[6,8,10] All types of viral hepatitis might lead to neurological complications including GBS.[4]

The pathogenesis and the pathophysiology of the GBS are based on findings of perivascular and endometrial peripheral nerve infiltration by the mononuclear cells, an immune component related with segmental demyelinization, which clinically mimics allergic neuritis in laboratory animals. In the acute phase of GBS, there is T cell sensitization towards P_0 protein, P_2 protein and peripheral nerve myelin, which shows the existence of cellular immunity disorder. The T cell will anonymously present growth factor IL-2 surface receptors when stimulated by antigen or mitogen. Serum IL-2 (soluble IL-2 receptors) concentration increment indicates T cell activity. T cell activation can be triggered by B cells through several ways: production of anti-myelin antibody, activation of the complement system or action as effectors using the cytotoxic activity against myelin or schwann cells.[5,10,11,12]

Based on the findings and the validity of the immune-mediated demyelinization existence, researcher suggests the use of plasmapheresis to reduce clinical symptoms.[10,13]

Only a small number of literature states the relation between hepatitis and GBS, though the viral hepatitis infections are common. As reported by Berger *et al* (1981) who collected data since 1944-1980, only 26 of viral hepatitis cases were correlated with GBS. Macleod (1987) reported 3 cases of non-A and non-B viral hepatitis-correlated GBS out of 26 GBS cases.[6] Kippel, (1993) reported 1 case of viral hepatitis type C in a GBS patient.[14] Liver function disorder in GBS might occur in conjunction with viral hepatitis and other virus infection during the prodromal phase of GBS, or during the acute phase with negative serologic test (CMV, EBV, HAV, HBV). The last could be explained by the synchronization between immune mediated regulation disorder of the liver and peripheral nervous system, proven by the administration of intravenous immunoglobulin preventing the development of hepatitis.

In approximately 10 recent years, sub-clinical hepatitis B virus infections are reported as the prodromal factor of GBS, which occur during the incubation period and pre-jaundice phase of hepatitis B virus infection. The cerebrospinal fluid is normal or in other words there is no protein increment and pleocytosis. HBV infection is related with acute arteritis (30% of positive HbsAg in patient with periarteritis). Research on immunofluorescence demonstrated the existence of antigen, immunoglobulin, and complement on the inflamed blood vessel wall. This suggests that antigen-antibody complexes are accumulated in the blood vessel or formed on the blood vessel wall, and conversely the activation of complement might be represented by acute tissue damage. The antigen-antibody complexes might reach the small vessels of the central nervous system and peripheral nervous system, which causes necrotizing arteritis and vascular occlusion, resulting in central nervous system focal disorder, and multiple mononeuritis. Based on the above, HBV virus infection in GBS have no relation with arteritis, but it is more likely that HBV replicates in the central nervous system, proven by the existence of HBV in the cerebrospinal fluid and the absence of in the serum.[6,8,12,14]

Verona *et al*, 1996,[16] reported a case of acute HAV infection involving peripheral neuropathy (n. facialis and n.occulomotorius), that improved without residual symptoms in four weeks time. Verona *et al* quoted a research by Pelletier *et al* (1985) that only four out of 10,000 viral hepatitis patient experienced facial nerve neuropathy, two of them being viral hepatitis type A patients. Symptoms of neuropathy were subtotal and improved completely, appearing before and after the liver function disorders. Temb *et al*, 1999,[17] reported nine viral hepatitis type C patients with neurological complications, seven of them suffering from chronic sensory polineuropathy, multi-neuropathy and encephalopathy associated with cryoglobulinemia.

Based on the observation of the hospitalized GBS patients in Dr. Sardjito General Hospital in five years time (January 1996-Desember 2000), there were only 92 GBS patients recorded. More than twofolds increment from the normal transaminase enzyme level was found in only 21 cases (22.82%). Three patients suffered from hepatitis (3.26%) and two of them was proven to be infected by HAV (HbsAg (+); TORCH (-) while no serological tests for either HAV or HCV were performed on the second patient. Infection of other viruses besides hepatitis virus were CMV in four patients (4.35%), two of them were in the acute phase of infection (IgM (+), while the others were in the latent period of infection. In addition, there were two patients (2.17%) with IgG HSV1 (+) and one patient with IgG HSV2 (+). Mortality was found in three cases with respiratory failure as the cause of death.

SUMMARY

Two hospitalized patients at Dr. Sardjito General Hospital were reported to suffer from viral hepatitis type A accompanying Guillain-Barré syndrome in five years observation (1996-2000). Hepatitis virus infection is the prodromal factor in GBS, which occurs during the first to fourth week since the first appearance of viral infection symptoms until neuropathy appears. There is no specific etiology to prove the cause of GBS due to sporadic virus appearance, based on the clinical diagnosis, antibody responses or viral isolation.

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