BAHAN AJAR VI

GUILLAIN BARRE SYNDROME (GBS)

Nama Mata Kuliah/Bobot SKS	: Sistem Neuropsikiatri / 8 SKS
Standar Kompetensi	: area kompetensi 5: landasan ilmiah kedokteran
Kompetensi Dasar	: menerapkan ilmu kedokteran klinik pada sistem neuropsikiatri
Indikator	: menegakkan diagnosis dan melakukan penatalaksanaan awal sebelum dirujuk sebagai kasus emergensi
Level Kompetensi	: 3B
Alokasi Waktu	: 2 x 50 menit

1. Tujuan Instruksional Umum (TIU) :

Mampu mengenali dan mendiagnosis penyakit-penyakit neuromuskular dan neuopati serta melakukan penangan sesuai dengan tingkat kompetensi yang ditentukan, dan melakukan rujukan bila perlu.

2. Tujuan Instruksional Khusus (TIK) :

a. Mampu menyebutkan patogenesis terjadinya GBS
b. Mampu melakukan penapisan / penegakan diagnosis GBS
c. Mampu melakukan manajemen / terapi awal
d. Mampu melakukan promosi kesehatan dan pencegahan GBS

Isi Materi;

Introduction

Guillain-Barre´ syndrome (GBS) is the major cause of acute neuromuscular. (Hughes RAC, 2007) Guillain–Barré syndrome (GBS) is an acute onset, usually monophasic immune-mediated (autoimmune) disorder of the peripheral nervous system usually characterized by a progressive flaccid paralysis with areflexia In general, the diagnosis is based on clinical criteria; nevertheless, the presence of suggestive findings in the complementary test as demyelinating changes in the nerve conduction studies (NCS) or albuminocytological dissociation in the cerebrospinal fluid (CSF), help to confirm the diagnosis. (Gonzales-Suarez I, 2013)

The worldwide incidence of GBS is reported to be 0.6-2.4 cases per 100,000 per year. GBS common to all races and ages between ages 30-50; male is more common than female. No apparent genetic susceptibility to developing GBS. Risk of GBS after vaccination may be slightly higher (1-2 additional cases per one million flue vaccinated persons) than general population. The classic form, the acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is the most frequent subtype in Europe, which accounts for 90% of GBS cases. Other subtypes like the axonal forms or the Miller-Fisher syndrome (MFS) are less common. (Gonzales-Suarez I, 2013)

Main Features of GBS

The main features of GBS are rapid progressive bilateral and relative symmetrical weakness of the limbs with or without involvement of respiratory or cranial nerve-innervated muscles or sensory disturbances. Patients have decreased or absent tendon reflexes. Cerebrospinal fluid examination typically shows an increased protein level with a normal white cell count. Pain frequently occurs and may cause severe complaints. It often starts before the onset of weakness and therefore can lead to diagnostic difficulties.

Electromyography (EMG) can be helpful in confirming the diagnosis in clinically difficult cases such as in patients with extreme pain. EMG is especially useful for subclassifying GBS into subgroups such as acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP).

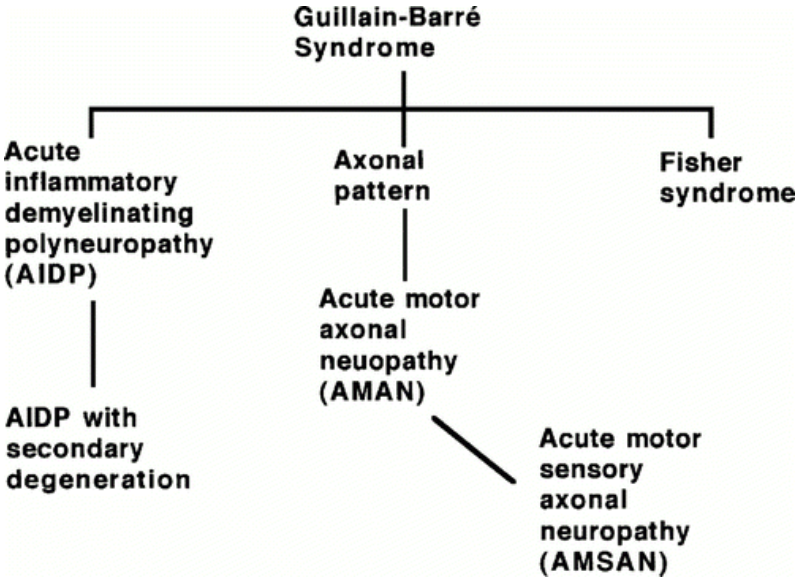

Fig.1 Classification of GBS

Etiology

Prior infection (1-4weeks before in 75% cases) is well established as a precipitating event in the development of GBS. GBS may **rarely develop within a day or two, or after 4-6** weeks, of an acute illness. Most antecedent illnesses associated with GBS affect the upper respiratory or GI tracts. Upper respiratory tract infection may precede GBS in 50% of cases. The presence of an antecedent illness is more often determined by serologic evidence, than the presence of systemic symptoms.

1. Cytomegalovirus (CMV) is the most common viral antecedent infection with serologic evidence in up to 15% of cases. CMV induced GBS tends to occur in younger patients and is often severe with respiratory failure, marked sensory and cranial nerve dysfunction, and elevated antibodies against ganglioside GM2.
2. Epstein Barr (EBV) infection may precede GBS in about 10% of cases; preceding clinical signs include mononucleosis, hepatitis, or pharyngitis.
3. GBS may occur with HIV seroconversion. Aside from a CSF pleocytosis, HIV-GBS is clinically and EDX indistinguishable from non-HIV GBS.
4. Camplylobacter jejuni (*C. jejuni) is, overall, the most* common antecedent infection and has been reported in up to 32% of cases. C. jejuni enteritis is characterized by watery diarrhea and abdominal cramping. Clinical enteritis may be absent in 30% of *C. jejuni associated GBS. In these cases there is* only serologic evidence of the prior bacterial infection. *C. jejuni-GBS has marked motor axon* degeneration, an elevated anti-GM1 antibodies, and a delayed and often incomplete recovery. There appears to be an over-representaton of certain strains of *C. jejuni* suggesting that the lipopolysaccharides of these organisms share ganglioside-like epitopes with peripheral nerves. This molecular mimicry appears to confuse the immune system resulting in mistaken attack against neural antigens. Other potential antecedent conditions include mycoplasma pneumoniae (5%); possibly Lyme disease, Hodgkin's disease, lung cancer, thyroid disease, SLE, paraproteinemia, and sarcoidosis.
5. GBS may possibly occur after surgery, trauma, and in the post-partum period.

Clinical Course of GBS

Rapidly progressive weakness is the core clinical feature of GBS. By definition, maximal weakness is reached within 4 weeks, but most patients reach it within 2 to 3 weeks. Thereafter, patients enter a plateau phase that ranges from days to several weeks or months. This phase is followed by a usually much slower and variable recovery phase. In Europe, about one-third of GBS patients remain able to walk ("mild patients"); about 25% of the GBS patients who are unable to walk ("severe patients") need artificial ventilation. This is predominantly due to weakness of the respiratory muscles. Despite standard treatment with intravenous immunoglobulin (IVIG) or plasma exchange (PE) treatment, about 20% of severely affected patients remain unable to walk after 6 months. Moreover, many patients remain otherwise disabled or severely fatigued. Even 3 to 6 years after onset, GBS has a great impact on social life and the ability to perform activities of daily life. Therefore, GBS remains a severe disease for which better treatments are required. (van Doorn PA, Ruts L, Jacobs BC, 2008)

Table 1. Disability Scale for GBS (Hughes RAC, 2007)

Table 1 Guillain-Barré syndrome disability scale

0.	Healthy
1.	Minor symptoms or signs of neuropathy but capable of manual work/*capable of running*
2.	Able to walk without support of a stick (*5 m across an open space*) but incapable of manual work/*running*
3.	Able to walk with a stick, appliance or support (*5 m across an open space*)
4.	Confined to bed or chair bound
5.	Requiring assisted ventilation (*for any part of the day or night*)
6.	Death

The original scale is shown in regular print (Hughes *et al.*, 1978) and subsequent modifications in *italics* (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997).

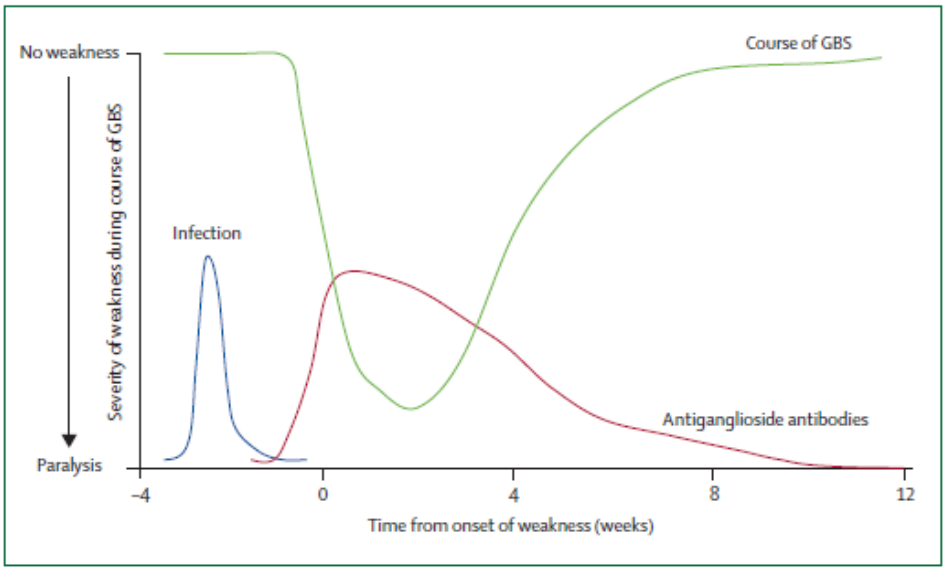

Figure 1: **Relation between infections, antiganglioside antibodies, and clinical course of GBS**

Immunobiology

AIDP is much more common than axonal forms in the Western world. Experimental evidence implicates autoantibodies to gangliosides as the cause of the axonal subgroups of GBS and of Fisher syndrome. These autoantibodies may be generated by the immune response to an infective organism, such as Campylobacter jejuni, cross-reacting with epitopes on the axon. The resemblance of AIDP to experimental autoimmune neuritis suggests pathogenetic mechanisms involving T-cell induced macrophageassociated demyelination. This proposed autoimmune aetiology led to the introduction of immunotherapy. Before its introduction, 10% of patients died and 20% were left seriously disabled. Plasma exchange (PE) was introduced as a possible treatment in 1978 and was shown to offer significant benefit by a randomized trial published in 1985. It became the gold standard against which other treatments were measured. (Hughes RAC, 2007)

There is convincing evidence that GBS at least in some patients is caused by an infection-induced aberrant immune response that damages the peripheral nerves. Four key factors were identified that control this process: (van Doorn PA, Ruts L, Jacobs BC, 2008)

1. Anti-ganglioside antibodies

   In up to 50% of patients, serum antibodies to various gangliosides present in human peripheral nerves, including GM1, GD1a, GalNAc-GD1a, and GQ1b, can be demonstrated. Other antibodies may bind to mixtures or complexes of different gangliosides instead of individual ones. Interestingly, most of these antibodies are related to defined clinical subgroups of GBS.

2. Molecular mimicry and cross-reactivity

   C. jejuni isolates from GBS patients express lipooligosaccharides (LOS) that mimic the carbohydrates of gangliosides. The type of ganglioside mimic in C. jejuni seems to determine the specificity of the anti-ganglioside antibodies and the associated variant of GBS. Antibodies in these patients usually are cross-reactive; they recognize LOS as well as gangliosides or ganglioside complexes. GBS after Campylobacter infection in anti-GM1/GD1a/GQ1b antibody-related cases is considered to be true example of molecular mimicry-related disease.

3. Complement activation

   Postmortem studies demonstrated that local complement activation occurs at the side of nerve damage. A mice model for GBS showed that some anti-ganglioside antibodies are toxic for peripheral nerves and can cause blockade of nerve transmission and paralysis of the nerve-muscle preparation. Additionally, there is destruction of the nerve terminal and perisynaptic Schwann cells. Antibodies to GM1 affect the sodium channels

at the nodes of Ranvier of rabbit peripheral nerves. All of these effects appear to be dependent on complement activation and formation of the membrane attack complex. The neurotoxic effects of these antibodies can be inhibited by IVIG and the complement inhibitor eculizumab.

4. Host factors

Less than 1:1,000 patients with a C. jejuni infection will develop GBS. Host factors may influence this susceptibility to develop GBS or the extent of nerve damage and outcome. Single nucleotide polymorphisms (SNPs) showed no consistent association with the susceptibility to develop GBS. Evidence indicates, however, that these SNPs may be important as disease-modifying factors. An association has been demonstrated between disease severity or outcome and SNPs in genes encoding for mannose-binding lectin, FcγRIII, MMP9, and TNF-α. However, confirmation in more extensive studies is required.

Table 2. Spectrum of GBS subtypes and serum antiganglioside antibodies

(van Doorn PA, Ruts L, Jacobs BC, 2008)

	Antibodies
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)[34,36,44,55]	Unknown
Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)[34,36,38,45,46,48,49,55,56]	GM1, GM1b, GD1a, GalNAc-GD1a
MFS and GBS overlapping syndrome[34,36,49,44,45,55]	GD3, GT1a, GQ1b

Table: Spectrum of GBS subtypes and serum antiganglioside antibodies

DIAGNOSIS

Features required for diagnosis of GBS:

- Progressive weakness in both arms and legs
- Areflexia (or decreased tendon reflexes)
- Features strongly supporting the diagnosis
- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain (often present)
- High concentration of protein in cerebrospinal fluid (CSF)
- Typical electrodiagnostic features (EMNG examination)

Features that should raise doubt about the diagnosis of GBS:

- Severe pulmonary dysfunction with limited limb weakness at onset
- Severe sensory signs with limited weakness at onset
- Bladder or bowel dysfunction at onset
- Fever at onset
- Sharp sensory level
- Slow progression with limited weakness without respiratory involvement
- (consider subacute inflammatory demyelinating polyneuropathy or CIDP)
- Marked persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- Increased number of mononuclear cells in CSF (>50×106/L)
- Polymorphonuclear cells in CSF
- Central nervous system involvement

Treatment of GBS

Treatment of GBS has two components: supportive care and specific therapy. Supportive care remains the cornerstone of therapy. If patients advance past the acute phase of illness, most will recover function. However, the neuropathy can advance so rapidly that endotracheal intubation and mechanical ventilation may be necessary within 24 hours of symptom onset. For this reason, all patients who have GBS should be admitted to a hospital for close observation for respiratory compromise, cranial nerve dysfunction, and autonomic instability. Autonomic nervous system dysfunction may manifest as fluctuations in blood pressure, cardiac dysrhythmias, gastrointestinal pseudo-obstruction, and urinary retention. Prophylaxis for deep venous thrombosis should be provided because patients frequently are immobilized for many weeks. As respiratory muscles weaken, elective endotracheal intubation should be considered. Progression to respiratory failure can be predicted using measurable respiratory parameters. Patients who are unable to demonstrate this minimal lung function require intubation. Frequent reassessment with serial lung function testing for rapid progression is critical. Additional predictors of subsequent mechanical ventilation include the following:

1. time from GBS onset to hospital admission of less than seven days,
2. inability to lift the elbows or head above the bed
3. inability to stand
4. ineffective coughing
5. increased liver enzyme levels

Table I Guillain-Barré syndrome disability scale

0.	Healthy
1.	Minor symptoms or signs of neuropathy but capable of manual work/*capable of running*
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Predictors of mechanical ventilation in patients who had a previously determined vital capacity included time from GBS onset to admission of less than seven days, an inability to lift the head, and a vital capacity less than 60 percent predicted. One retrospective study demonstrated a 40 percent decrease from predicted vital capacity, compared with a 60 percent decrease reported in another study. This discrepancy may be related to different study methods and the larger number of patients enrolled in the latter study. Pain and psychologic stress should be treated. Narcotics should be used with caution because risk of ileus is already increased. Physical therapy, including gentle massage, passive range-of-motion exercises, and frequent position changes may provide pain relief. Carbamazepine and gabapentin have been used as adjuncts in pain management in GBS. Patients who were treated with these medications required less narcotic analgesia with fewer narcotic side effects and minimal sedation compared with those who received placebo. Patients are paralyzed by the illness, but mentally alert and fearful. Reassurance and discussion about the phases of illness and recovery can help reduce psychologic stress.

The value of corticosteroids alone in the treatment of GBS has been disputed for decades. Many clinicians were persuaded of their benefit; however, two randomized controlled trials, one with conventional-dose

prednisolone and the other with high-dose methylprednisolone, have failed to demonstrate beneficial effect. Although corticosteroids can no longer be recommended as routine treatment for acute GBS, we have observed a few instances in which the administration of intravenous high-dose corticosteroids seemingly halted the progress of an acute case.

Specific treatment should be initiated soon after diagnosis. High-dose intravenous immunoglobulin (IVIg; 400 mg per kg daily for five days) or plasmapheresis/plasma exchange (five exchanges over five to eight days) can be initiated. To determine whether IVIg was as effective as plasma exchange in treating patients with GBS, a large multicenter trial was designed to compare plasma exchange and IVIg and the combination of both treatments for GBS. The study followed 150 patients over four weeks. There were no statistically significant differences in the disability rating between the two treatment groups. IVIg and plasmapheresis were found to be equally effective therapies.

Prognosis

Approximately 85 percent of patients with GBS achieve a full and functional recovery within 6 to 12 months. Recovery is maximal by 18 months past onset. However, some patients have persistent minor weakness, areflexia, and paresthesia. Approximately 7 to 15 percent of patients have permanent neurologic sequelae including bilateral footdrop, intrinsic hand muscle wasting, sensory ataxia, and dysesthesia. (Newswanger DL, Warren CR, 2004)

Death rate is described to be between 1-18%. (González-Suárez I et al, 2013) The mortality rate is less than 5 percent in tertiary care centers with a team of medical professionals who are familiar with GBS management. Causes of death include adult respiratory distress syndrome, sepsis,

pulmonary emboli, and cardiac arrest. Several factors during the acute phase of illness predict subsequent poor recovery. These factors include age older than 60 years; severe, rapidly progressive disease; and low nerve conduction amplitudes on distal stimulation, which suggests axonal loss.

In addition, prolonged mechanical ventilation for more than one month and preexisting pulmonary disease predict a poor outcome. In general, a poor long-term prognosis is directly related to the severity of the acute episode and delay in onset of specific treatment. Relapse occurs in a small percentage of patients. One multicenter trial18 of 229 patients showed a relapse rate of 3 to 5 percent. In that study, the relapse rate was not significantly affected by treatment type or any other factor tested.

References

Brenner B. Clinical Experience with Octagam, a solvent detergent (SD) virus inactivated intravenous gammaglobulin. In: Clinical and Experimental Rheumatology 14 (Suppl.15): S115-S119, 1996.

González-Suárez I et al. Guillain-Barré Syndrome: Natural history and prognostic factors: a retrospective review of 106 cases. In: BMC Neurology 2013, 13: 95. http://www.biomedcentral. com/1471-2377/13/95

Hughes RAC et al. Immunotherapy for Guillain-Barre¤ syndrome: a systematic review. In: Brain (2007), 130, 2245-2257.

Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. In: British Society for Immunology, *Clinical and Experimental Immunology*, 2005, 142: 1–11

Newswanger DL, Warren CR. Guillain-Barré Syndrome. In: American Family Physician. Volume 69, Number 10 / May 15, 2004.

Sederholm BH. Treatment of Acute Immune-mediated Neuropathies: Guillain-Barré Syndrome and Clinical Variants. In: Semin Neurol. 2010;30(4):365-372.

van Doorn P et al. IVIG Treatment and Prognosis in Guillain–Barré Syndrome. In: J Clin Immunol (2010) 30 (Suppl 1):S74–S78

van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. In: Lancet Neurol 2008; 7: 939–50

Wiles CM et al. Intravenous immunoglobulin in neurological disease: a specialist review. In: J Neurol Neurosurg Psychiatry 2002;72:440–448.

Yuki N, Hartung HP. Guillain–Barré Syndrome. In: N Engl J Med 2012;366:2294-304.