

Case Report

Acute Motor Sensory Axonal Neuropathy with Preceding Herpes Zoster Infection

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ABSTRACT

ACUTE MOTOR SENSORY AXONAL NEUROPATHY WITH PRECEEDING HERPES ZOSTER INFECTION

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Introduction. Guillain-Barre syndrome (GBS) is an acute polyradiculopolyneuropathy with varying presentations. Approximately half of GBS patients can pinpoint a particular type of infection preceding their condition called antecedent infection that rarely caused by varicella zoster infection. Herpes zoster, commonly known as shingles, results from the spontaneous reactivation of the varicella-zoster virus (VZV). The incidence rate of GBS after herpes zoster was 0.02% with adjusted hazard ratio to be 18.37 times more likely compared to without.

Case 54 years old male Javanese patient came to neurology clinic because there was sudden bilateral leg weakness that was heavier on right leg with numbness in right leg and aching on left leg. He said one month before he was paralyzed there was vesicular skin lesions on his on the right chest to the right back as high as the top of the nipple which was diagnosed as herpes zooster. He had history of left sided weakness caused by stroke 9 years ago but there was no history of prior vaccination, immunotherapy, surgery, or infection aside from herpes zoster in this 6 weeks. There was no any neurological disease in his family history. He was a construction worker that was still working until he was paralyzed with no history of smoking and alcohol use. On neurological examination it was found he had bilateral flaccid leg weakness with medical research council (MRC) muscle strength of 112 on right leg and 322 on left leg with MRC sum score 36. Diagnosis was confirmed by albuminocytologic dissociation on CSF examination and acute motor sensory axonal neuropathy (AMSAN) subtype of GBS was identified with electroneurogram studies. The patient was treated with intravenous immunoglobulin with dosage of 0.4 mg/kg Body weight/day for 5 days. After treatment there was improvement on leg weakness with MRC 322 on right leg and 322 on left leg with MRC sum score of 51 and patient was discharged afterwards

Discussion. GBS is an acute polyradiculoneuropathy with immunological pathomechanism. There was subtypes of GBS including AMSAN. The diagnosis was based on clinical characteristic and supporting examination with CSF and electroneurography test. In half the patients of GBS antecedent infection can be identified mostly of *Campylobacter jejuni* infection but rarely VZV virus infection is the only identified infection. Herpes zoster was reactivation of VZV infection and it was found there is 5 per 10.000 cases of GBS in HZV patients. The subtype of GBS related to herpes zoster were predominantly acute inflamatory demyelinating polyradiculoneuropathy (AIDP). The management of GBS include assesment of high risk patient for intensive care unit (ICU) admission, immunotherapy, pain management, and physical rehabilitation.

Conclusion. We present case of GBS with AMSAN subtype that was preceded by only herpes zoster infection.

Keywords : Herpes zoster, Guillain-Barre Syndrome, Acute Motor Sensory Neuropathy

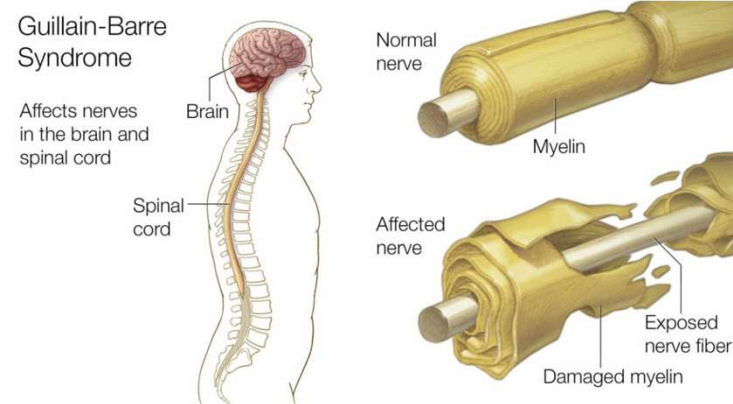


INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute polyradiculopolyneuropathy with varying presentations.

- GBS stands as the primary reason behind sudden flaccid paralysis, occurring at a rate of around 1–2 cases per 100,000 individuals annually across the globe. (100,000 individuals worldwide/year)
- Can affect individuals of any age (highest point between the ages of 50 and 70).
- Males are approximately 1.5 times more prone to GBS compared to females.
- GBS emerges as a disorder occurring after an infection. Two-thirds, of patients experience symptoms related to respiratory or gastrointestinal tract infections before GBS onset.
- The subtypes of GBS were motor-sensory type, which were further classified as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and, acute motor sensory axonal neuropathy (AMSAN), Miller Fisher syndrome, with Bickerstaff brainstem encephalitis as its more severe form, and other atypical form of GBS, such as pandysautonomia, pharyngel-cervical-brachial GBS, or pure sensory GBS

- Approximately half of GBS patients can pinpoint a particular type of infection preceding their condition, with *C. jejuni* accounting for at least one-third of these infections. In multivariate analysis, GBS patients exhibited significantly higher rates of infections with *Campylobacter jejuni* (32%), cytomegalovirus (13%), and Epstein-Barr virus (10%) compared to controls. Univariate analysis showed that *Mycoplasma pneumoniae* infections were more prevalent in GBS patients (5%) than in controls.
- Additionally, infections with *Haemophilus influenzae* (1%), parainfluenza 1 virus (1%), influenza A virus (1%), influenza B virus (1%), adenovirus (1%), herpes simplex virus (1%), and varicella-zoster virus (1%) were observed in GBS patients



- Herpes zoster, (shingles) results from the spontaneous reactivation of the varicella-zoster virus (VZV), presenting as distinct skin lesions featuring painful vesicles that spread across 1 to 3 dermatomes. While the precise pathomechanism remains incompletely understood, the reactivation of the virus and the onset of herpes zoster may be linked to alterations in the host's immune status due to factors such as aging, trauma, stress, or other illnesses.
- There was 0.02% of incident rate adjusted hazard of GBS in herpes zoster patients was found to be 18.37 times higher (with a 95% confidence interval ranging from 10.22 to 33.01 times higher, $P < .001$) compared to those without. Additionally, the study revealed that patients who experienced GBS subsequent to herpes zoster were more prone to prior infection, in contrast to herpetic patients who did not develop GBS

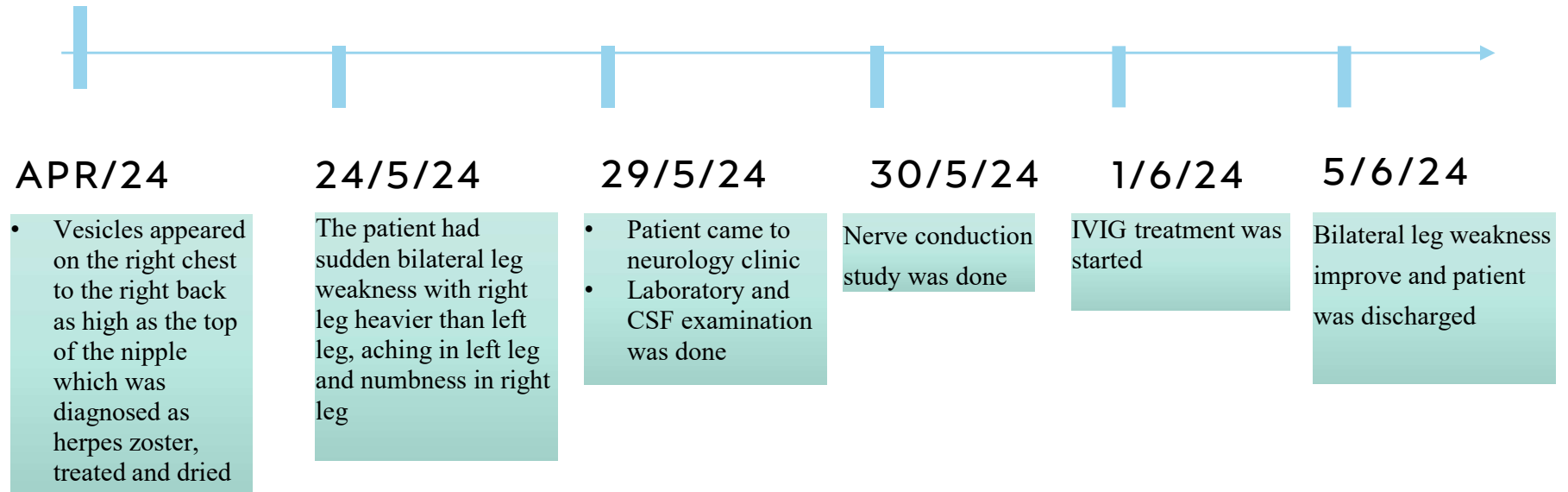


CASE REPORT

- 54 YO, Javanese, male, patient, came to neurology clinic with weakness of both legs felt since 5 days ago. The weakness was felt abruptly in the afternoon where the patient had difficulty walking and lifting his legs with electric shock sensation at first. The weakness was felt more severe in the right leg where the patient could not move his lower leg at all. On the left leg, the patient could still move but it was difficult to lift the lower leg, the patient also felt pain in the thigh and behind the knee of the left leg. In the morning of the attack, the patient could still walk and do activities as usual.
- numbness and dulled in the right leg at the level of the middle thigh which was felt simultaneously during weakness. The left leg also felt numb ,but not as heavy as the right, and more dominated by feeling of pain, especially when moved.

- One month ago, there were watery spots on the right chest to the right back as high as the top of the nipple which was diagnosed as herpes zoster, already treated and dried but after that the patient felt pain in the herpes marks but improved. Only analgetic that he still consumed
- No other fever, respiratory symptoms, gastorintestinal symptoms, vaccination, and surgical procedure in this 6 weeks before he was paralyzed.
- history stroke 9 years ago with left sided weakness, and improved after treatment in which the patient can walk and do activity normaly but no routine check up.
- no history of weakness or any neurological disease in the patient's family.
- The patient was a construction worker that often needed to lift heavy load for works.
- The patient does not smoke and consumed alcohol.

TIMELINE





Patient's multiple healed dry crusted skin lesion caused by healed herpetic zoster

Physical examination

- BP was slightly elevated (141/85 mmHg), other vital sign was normal
- numerical pain scale of 4-5/10 especially when moving left leg
- There was multiple healed dry crustae in his upper chest along T1 dermatome
- An initial neurological examination it was found the patient has seventh supranuclear cranial nerve palsy which was attributed to his history of stroke.
- slightly spastic weakness on left arm (with 4+ power in Medical Research Council (MRC) Muscle Power Scale), lower leg strength was, from proximal to distal muscle with MRC scale, 113 in right leg and 311 in left leg.
- muscle tone on left arm was elevated with slight spasticity and both legs' tone was decreased. There is absent of knee jerk reflex and ankle jerk reflex on both legs and hypesthesia on left leg.

Laboratory Examination



Patient's yellowish colored cerebrospinal fluid sample

- Lab 29/5/24

WBC 6.32/ NE% 58.10/ LY% 26.40/ RBC 5.05/ HGB 15.00/ HCT 44.0/ PLT 280.0 SGOT 28.0/ SGPT 28.0/ BUN 11.0/ Creatinin 0.59 L/ e-LFG 114.78 Natrium (Na) 138/ Chlorida (Cl) 100.9/ Calsium (Ca) 8.7/ **Magnesium (Mg) 2.79 H**/ Kalium (K) 3.55/ **PPT 14.7 H**/ INR 1.04/ APTT 30.1

- CSF 29/5/24

Macroscopic: yellowish colored, opening pressure 18cmH₂O, Queckenstedt (+).

Microscopic: Sel 3 / monosite dominance 100%/ protein 1589.70 H/ glucose CSF 69/ BS plasma 168/ CSF glucose ratio 0.41 / nonne +++/ pandy +++/ disosiation citoalbumin

Nerve Conduction Study

MNCS											
Nerve	Lat		Amp		Distance mm	CV		Stim Intens mA	Lat Diff		
	ms	NL	mV	NL		m/s	NL		ms	NL	
Medianus Motor Right											
Wrist - APB APB	4.26	< 4.2	0.98	> 3.5				57.4			
Elbow-Wrist APB	9.27		0.87	> 3.5	260	45.2	> 48.0	64.0	5.8		
Axilla-Elbow APB	11.1		0.67	> 3.5	120	65.6		63.6	1.83		
Peroneus Motor Left											
Ankle - EDB EDB	6.30	< 5.5	0.66	> 2.5				100			
Ab. fib. head-Ankle EDB	11.8	< 5.5	0.64	> 2.5	290	52.7		100	5.5		
Peroneus Motor Right											
Ankle - EDB EDB	4.57	< 5.5	0.036	> 2.5	0			100			
Ab. fib. head-Ankle EDB	10.0	< 5.5	0.50	> 2.5	290	53.4		100	5.4		
Radialis Motor Right											
Forearm - Eip Eip	2.08	< 2.5	2.6	> 2.0				52.2			
Upper arm-Forearm Eip	4.94		1.68	> 2.0	210	73.4	> 51.8	88.2	2.9		
Tibialis Motor Left											
Med. mal - Abd hal Abd hal	4.25	< 6.0	14.5	> 3.9				91.4			
Pop Fossa-Med. mal Abd hal	11.4		5.7	> 2.5	310	43.4	> 41.0	100	7.2		
Tibialis Motor Right											
Med. mal - Abd hal Abd hal	3.52	< 6.0	8.2	> 3.9				65.4			
Pop Fossa-Med. mal Abd hal	10.6		8.0	> 2.5	280	39.5	> 41.0	73.6	7.1		
Ulnaris Motor Right											
Wrist - ADM ADM	2.81	< 3.4	6.1	> 3.5				48.6			
Bl. elbow-Wrist ADM	6.81		5.6	> 2.7	240	60.0	> 51.0	50.6	4.0		
Ab. elbow-Bl. elbow ADM	8.85		5.5	> 2.7	100	49.0	> 45.7	54.2	2.0		

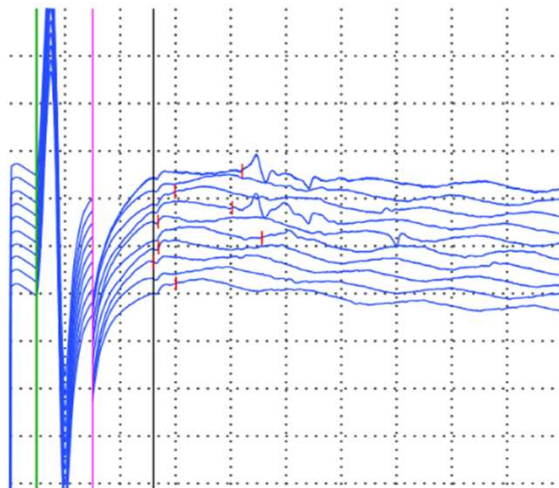
Table 1. Motor nerve conduction study results that shows reduced amplitude in right median nerve, right and left peroneus nerve

SNCS									
Nerve	Peak Lat		Amp		Distance	CV		Stim Intens	
	ms	NL	uV	NL	mm	m/s	NL	mA	
Medianus Sensory Right									
Wrist - Dig II	2.60		34.5		120	46.2		12.0	
Radialis Sensory Right									
Forearm - Web space I-II	2.19	< 2.1	10.6	> 15.0	140	63.9	> 44.3	26.2	
Suralis Sensory Left									
Mid. dorsal leg - Lat. Malleolus	1.33	< 3.5	3.6	> 10.0	140	105	> 40.0	21.2	
Suralis Sensory Right									
Mid. dorsal leg - Lat. Malleolus	1.86	< 3.5	2.4	> 10.0	140	75.3	> 40.0	23.4	
Ulnaris Sensory Right									
Wrist - Dig V	2.07		7.6		120	58.0		25.8	

Table 2. Sensory nerve conduction study results that shows reduced amplitude in right radialis nerve, right ulnaris nerve, and right and left sensory nerve

Left Tibialis

Med. mal-Abd hal
M:3mV/D 10ms/D
F:0.3mV/D 10ms/D



Right Tibialis

Med. mal-Abd hal
M:3mV/D 10ms/D
F:0.3mV/D 10ms/D

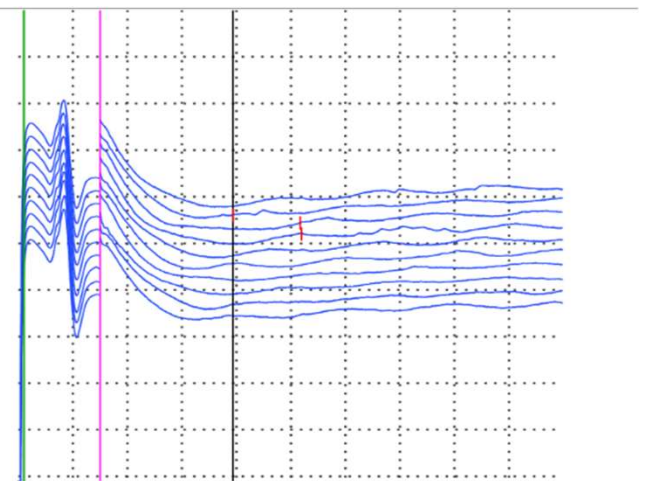


Image 3. F-response of left and right tibialis nerve. It shows reduced persistency of left tibialis nerve and no response in right tibialis nerve

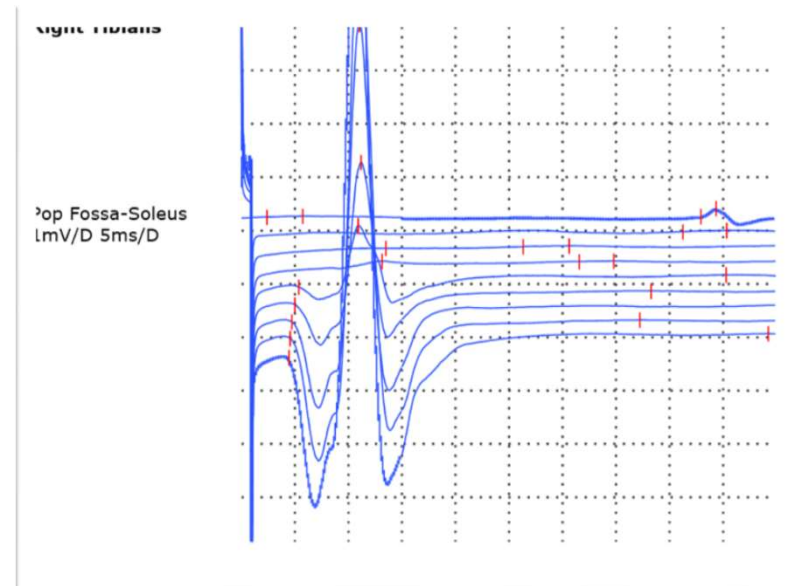
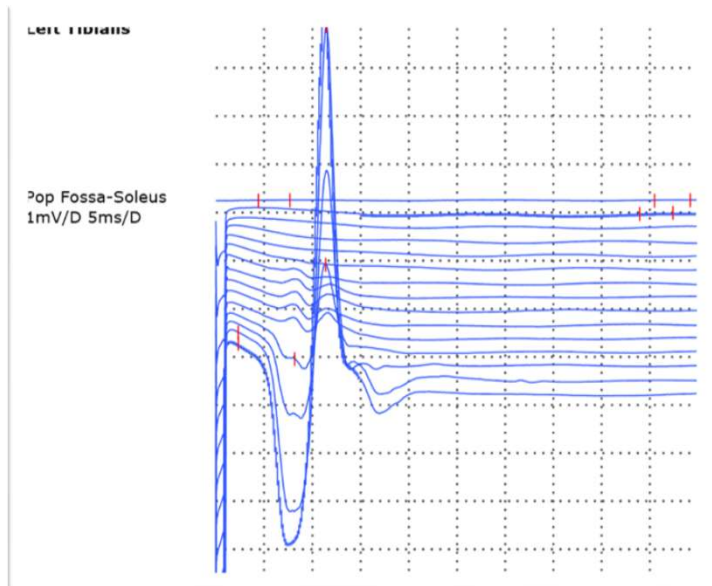


Image 4. H-reflex of left and right tibial nerve. It shows there is no response on H-reflex testing on both nerve

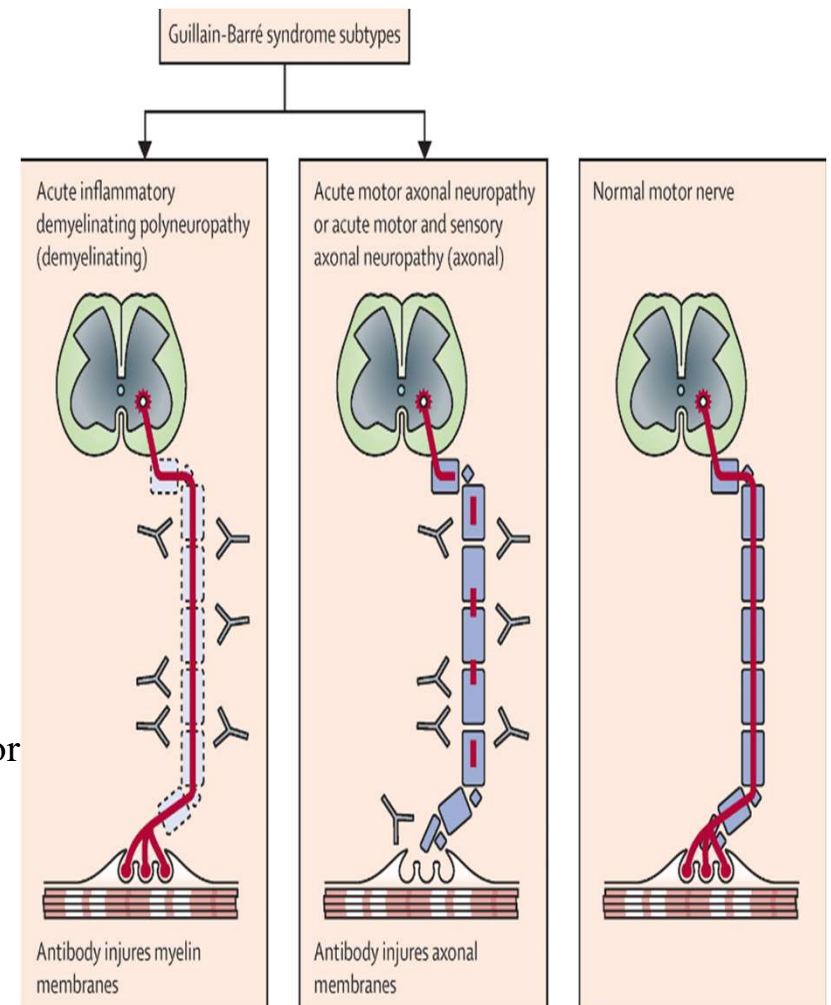
TREATMENT



- After the AMSAN diagnosis was confirmed, immunomodulatory therapy with intravenous immunoglobulin (IVIG) was given to the patient with dosage of 0,4 gr/kg of body weight/day for 5 days via infusion line
- therapy showed improvement in lower leg muscle strength that is 322 in right leg and 322 in left leg with MRC sum score of 51 and modified Erasmus Guillain-Barre outcome score (mEGOS) of 4 with 6% risk of being unable to walk 6 months after admission.

DISCUSSION

- GBS is an acute polyradiculoneuropathy that usually has antecedent infection 6 weeks prior of the onset of GBS.
- The subtypes of GBS encompass the motor-sensory type, further categorized as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN). Additionally, there's Miller Fisher syndrome, with Bickerstaff brainstem encephalitis representing its more severe manifestation, along with other atypical forms of GBS such as pandysautonomia, pharyngeal-cervical-brachial GBS, or pure sensory GBS
- Clinically, GBS is characterized by the sudden or gradual onset of varying degrees of weakness in the limbs or muscles innervated by cranial nerves. This weakness is typically accompanied by reduced or absent reflexes and presents a distinct profile in the cerebrospinal fluid (CSF).



- Patients commonly exhibit progressive weakness in the limbs, usually starting in the legs and advancing to the arms and muscles controlling swallowing and speaking.
- The weakness is often symmetrical and may be associated with sensations of tingling or numbness, particularly in the hands and feet.
- Can be rapid, within 2–4 week sometimes hours.
- respiratory failure due to involvement of the nerves controlling breathing, necessitating mechanical ventilation, which is linked to poorer outcomes.
- Cranial nerve deficits, such as facial weakness or difficulty moving the eyes, as well as autonomic dysfunction leading to symptoms like low blood pressure, constipation, and irregular heart rate, may also occur.
- In the case patients it was found there was sudden bilateral leg weakness with numbness in right leg and aching pain in left leg. The neurological examination suggest that the bilateral leg weakness of lower motor neuron type with flaccid muscle tone and absent of bilateral knee jerk reflex and ankle jerk reflex. The MRC score of right leg were 113 and 311 in left leg and sum of MRC score was 37.

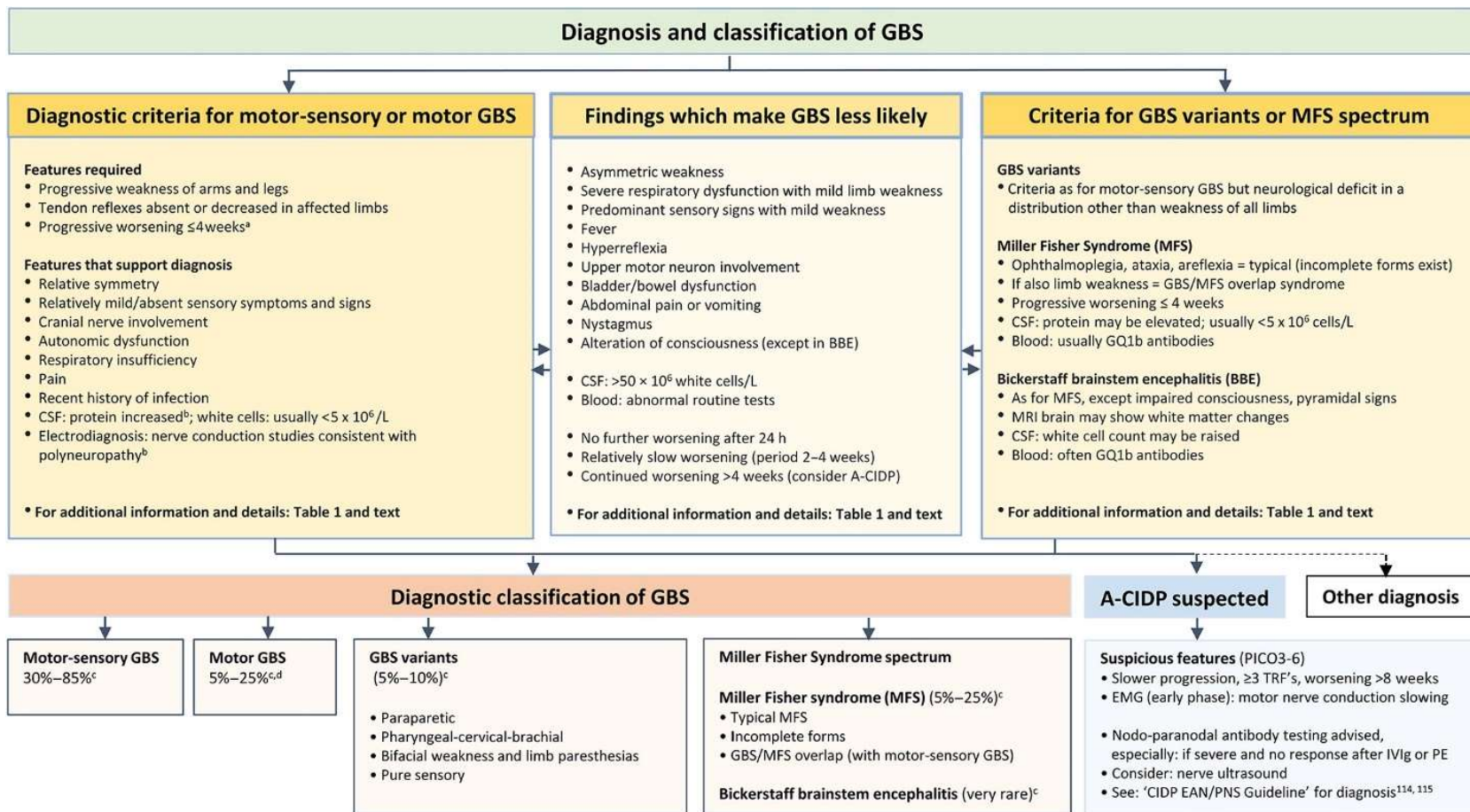


Image 5. Diagnosis and classification of GBS. A-CIDP, acute-onset CIDP; BBE, Bickerstaff brainstem encephalitis; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; MFS, Miller Fisher syndrome; PE, plasma exchange; TRF, treatment-related fluctuation. ^aOnly applies if duration of progression is known (e.g., to separate from CIDP). ^bCSF protein and electrodiagnostics may be normal early in the disease. ^cPercentages of motor-sensory GBS, motor GBS, GBS variants, MFS, BBE are estimated from various publications. ^dPercentage of motor GBS is strongly dependent on region of origin

- CSF analysis of GBS can help to further diagnose this condition. Cytoalbuminic dissociation which characterized as increased protein content of CSF with normal cell counts helps to further support the diagnosis of GBS. The CSF analysis can be normal in 1st week where 50% of patients had elevated CSF protein levels in fewer than 3 days of onset and 84% of patients had elevated CSF protein levels at more than 7 days of onset. The case patient had lumbal puncture and CSF examination at 5 days of onset. It was found that there was cytoalbuminic dissociation with elevated protein levels of 1589.7 and normal cell count of 3 cell.

Electrophysiology study through nerve conduction studies can help to diagnose GBS and further classify subtypes of GBS. In AIDP, at least one of the following in each of at least two nerves, or at least two of the following in one nerve if all others inexcitable and distal compound motor action potential (dCMAP) > 10% lower limit of normal (LLN):

1. Motor conduction velocity < 90% LLN (85% if dCMAP < 50% LLN)
2. Distal motor latency > 110% upper limit of normal (ULN) (>120% if dCMAP < 100% LLN)
3. Proximal CMAP/distal CMAP ratio < 0.5 and dCMAP > 20% LLN
4. F-response latency > 120% ULN

WHAT IS AMSAN?

- Is subtypes of GBS whereas there is axonal damage in ventral and dorsal root of nerve roots . In North America, Europe, and Australia, the majority of studies show a demyelinating polyradiculoneuropathy pattern in cases of GBS. However, in other regions of the world, axonal patterns are more commonly observed.
- The pathology observed in AMSAN shares similarities with that of Acute Motor Axonal Neuropathy AMAN, characterized by macrophage invasion of the perinodal space.
- However, in AMSAN, both the dorsal and ventral roots are affected. Additionally, there is a lack of lymphocytic inflammation, suggesting an antibody-mediated mechanism from infection.

- In AMSAN, none of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP<10% LLN with sensory action potential amplitudes < LLN.
- In AMAN,* none of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP<10% LLN and sensory action potential amplitudes normal
- In case patients there was no latency prolongation and there were reduced amplitude on motor nerve of right medianus nerve, and bilateral peroneal nerve and reduced amplitude on sensory nerve of right radialis, right ulnaris, and both sural nerve, that show that there was axonal neuropathy supporting acute motor and sensory axonal polyneuropathy

- There were typical gangliosides antibody that can be detected in some subtypes of GBS. Although the diagnostic sensitivity of this assay is low-moderate (32% to 64%) with test assay variability, it can be useful in some suspected motor GBS, GBS variants or some other cases with diagnostic uncertainty, except in Miller Fisher syndrome. In cases of Miller Fisher Syndrome, the sensitivity of detecting anti-GQ1b antibodies is notably high, ranging from 88% to 100%, with an exceptionally high specificity of 100%. Particularly in situations where clinical uncertainty exists and test results can be acquired promptly, testing for anti-GQ1b antibodies is deemed beneficial. Accordingly, we don't test for anti ganglioside in AMSAN cases like in our patients.

Antecedent events in GBS can be found in two third of patients and can help to support the diagnosis of GBS

infection	Non - infection
Campilobacter jejuni (32%)	Vaccination
Cytomegalovirus (13%)	Surgery
Epstein-Barr (10%)	Immune drug exposure (monoclonal antibodies)
Haemophilus influenzae (1%)	
Parainfluenzae (1%)	
Influenza A (1%)	
Influenza B (1%)	
Adenovirus (1%)	
Herpes simplex (1%)	
Herpes zoster (1%)	

- Herpes zoster as antecedent of GBS are rare, where the incidence rate of GBS in herpes zoster patients with herpes zoster as the only antecedent infection was 5 per 10.000 cases of herpes zosterpatients.
- It was found that patients with herpes zoster are more prone to other infection, especially with gastrointestinal and genitourinary infection, which incidence of GBS with antecedent infection.
- It was unknown whether anti viral therapy at acute onset of herpes zoster will influence the incidence GBS.
- The subtype of GBS that was identified in cases of herpes zoster related are AIDP with 1 cases repots of AMAN type of GBS. In our patients, there was no identifiende antecedent events except acute herpes zoster which happen 1 month before onset of weakness. The identified subtype of GBS in this patients is AMSAN.

- Management and therapy of GBS include monitoring and admission to intensive care unit (ICU) for high risk patients, immunotherapy, pain management, and physical therapy.
- modified Erasmus GBS Respiratory Insufficiency Score (mEGRIS) that can estimate the risk of requiring mechanical ventilation at any time during the first 2 months from disease onset (identifying high risk patient).
- Single breath counting test < 20 (inability to count in a single breath out loud from 1 to 20) is a useful bedside tool to assess the need for transfer to ICU.

	Categories	Score
Days between onset of weakness and hospital admission	> 7 days	0
	4 – 7 days	1
	≤ 3 days	2
Facial and/or bulbar weakness at hospital admission	Absence	0
	Presence	1
MRC sum score at hospital admission	60 – 51	0
	50 – 41	1
	40 – 31	2
	30 – 21	3
	≤ 20	4

- Regular assessment of risk factor requiring mechanical ventilation during hospital admission include: rapid progression of limb weakness during hospital admission; GBS Disability Score grade 4 (unable to walk 10 m even with aid); neck flexion, facial or bulbar weakness, and especially the inability to cough; autonomic instability such as fluctuations in blood pressure or heart rate. Other assesment that was needed was signs of decline in respiratory functions,with signs of declining respiratory function were a fall of the forced vital capacity (FVC) $> 30\%$ below the predicted baseline should alert concern, a fall of $>30\%$ in 24 h likely indicates immediate transfer to ICU, or a 50% decline in under 24 h likely indicates the need for ventilation. Elective ventilation should be considered when $FVC \leq 20$ mL/kg, and when the FVC is ≤ 10 mL/kg ventilation is almost inevitable.

- Immunotherapy that is recommended are IV immunoglobulin and therapeutic plasma exchange. Currently the guidelines was against using steroids as immunotherapy in GBS patients.

- In this patients we started immunotherapy after the diagnosis of AMSAN was confirmed. The immunotherapy that we give was intravenous immunoglobulin 0.4 mg/kg Body Weight/days for 5 days accordingly. After the treatment there was improvement in muscle strength with lower leg muscle strength are 322 in right leg and 322 in left leg with MRC sum score of 51

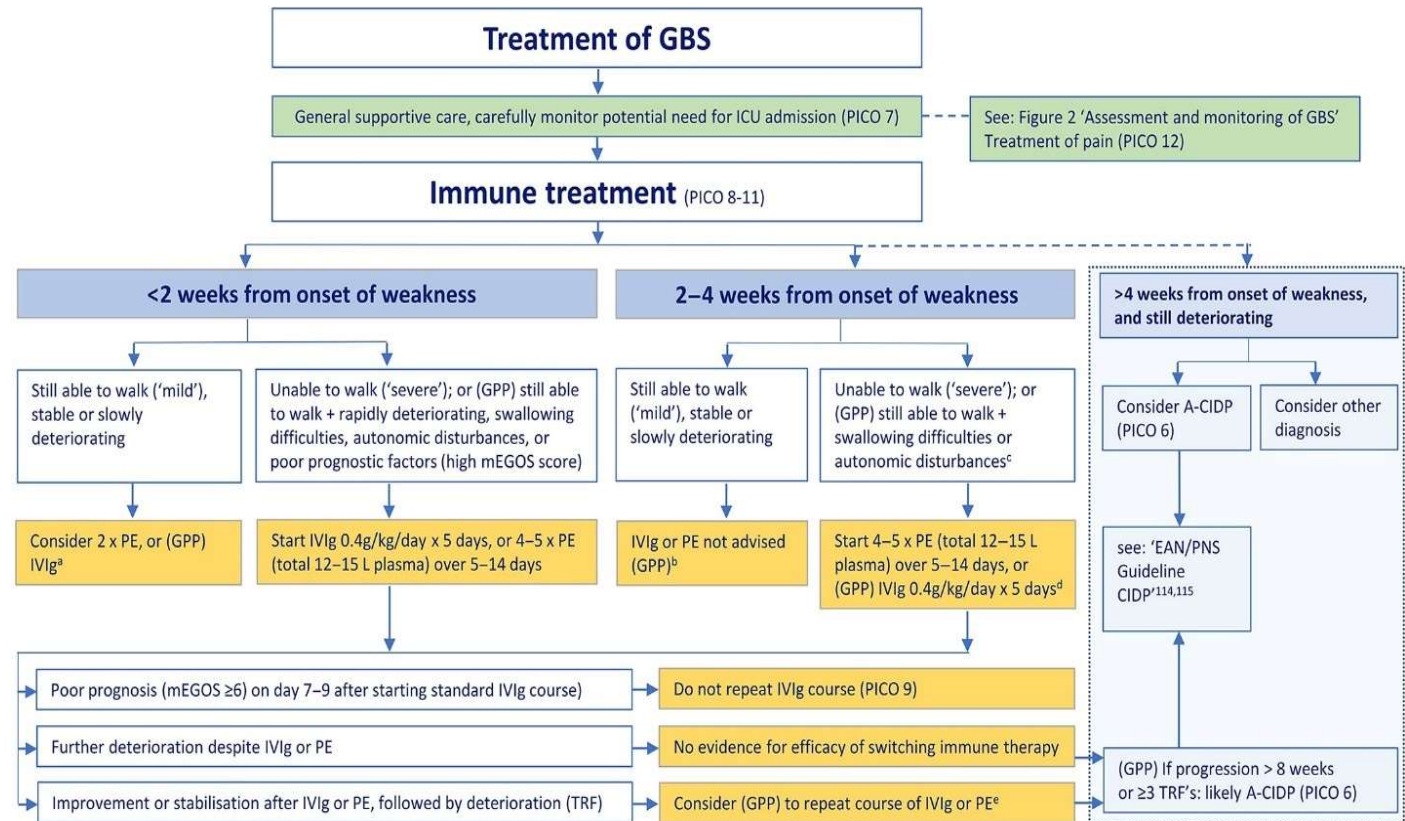


Image 6 . Treatment of GBS

- The probability of how the patients can walk in 6 months can be predicted with modified Erasmus GBS Outcome Score (mEGOS) which more accurately predict the prognosis of patients at 7 day of admission.
- This patients has mEGOS 4 with 6% risk of being unable to walk 6 months after admission.

Prognostic factors	Score	Prognostic factors	Score
Age at onset, y		Age at onset, y	
≤40	0	≤40	0
41-60	1	41-60	1
>60	2	>60	2
Preceding diarrhea ^a		Preceding diarrhea ^a	
Absent	0	Absent	0
Present	1	Present	1
MRC sumscore (at hospital admission)		MRC sumscore (at day 7 of admission)	
51-60	0	51-60	0
41-50	2	41-50	3
31-40	4	31-40	6
0-30	6	0-30	9
mEGOS	0-9	mEGOS	0-12

Table 3. modified Erasmus GBS Outcome Score (mEGOS)

CONCLUSION

Herpes zoster can be antecedent infection of GBS case and although usually the subtype that occur is AIDP subtype, we present rare cases of AMSAN cases related with Herpes Zoster that was confirmed by CSF examination and electrophysiology.





THANK YOU

