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Pearls & Oy-sters: Delayed Diagnosis of Acute Motor Axonal Neuropathy With Cardiac Arrest

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Abstract

We present the case of a 53-year-old female who presented with right lower extremity weakness with preceding systemic symptoms including fever and chest pain. She developed rapid quadriparesis over 24 hours and had ventricular fibrillation with cardiac arrest. Examination demonstrated tetraplegia, facial diplegia with spared extra-ocular movements and areflexia. Electrodiagnostic studies including nerve conduction studies and electromyography were consistent with Acute Motor Axonal Neuropathy (AMAN). This case highlights an atypical asymmetric presentation with initially preserved reflexes, rapid progression and cardiac dysfunction that can occur independent of dysautonomia. Treatment options include intravenous immunoglobulin (IVIg) or plasmapheresis as well as supportive care and long term multidisciplinary rehabilitation and communication strategies.

Data Availability Statement: All data presented or referenced in the report below can be provided in full upon request.

Pearls

- Asymmetric onset and rapidly progressive weakness should raise the suspicion for Guillain-Barré Syndrome (GBS) and its variants.
- Although uncommon, AMAN can be complicated by dysautonomia, requiring close monitoring for cardiac arrhythmia and rarely ventricular fibrillation.

Oysters

- Preserved reflexes do not exclude the possibility of AMAN, where areflexia can occur later on.
- While cerebrospinal fluid albuminocytologic dissociation is a classic finding in GBS, mild pleocytosis may also occur.

Case

A 53-year-old woman presented to hospital for sudden onset of right leg weakness. After dropping her children to school, she was unable to support her body on her right leg with difficulty walking back to her car. She was able to get into the car and ankle strength was sufficient to operate the pedals. Upon getting out of the car her right leg buckled again. She was unable to stand and called an ambulance. She endorsed some low back pain without any radiating pattern. Her past medical history was significant for hypothyroidism and dyslipidemia, treated with levothyroxine and rosuvastatin accordingly.

On initial examination, she was afebrile with normal vital signs. She was alert, oriented, with normal language testing. Pupils were equal and reactive to light. Visual fields and extraocular movements were full. She had full facial sensation and strength. Tongue and palate were midline. Shoulders and neck were strong. Upper extremities and left leg demonstrated normal strength, sensation, deep tendon reflexes, and coordination. Right leg demonstrated grade 2/5 strength in hip flexion, 3/5 in knee flexion and extension, but otherwise 5/5 in ankle movements with normal sensation. Her Achilles reflexes were present bilaterally but patellar reflexes were absent. Plantar response was flexor bilaterally.

An urgent CT head and angiography did not reveal early ischemic changes or occlusion. ECG showed normal sinus rhythm. Serum creatine kinase and TSH were normal. On serial assessments in the emergency department, there were fluctuations in the motor strength of the

right leg, prompting speculation that she may have functional weakness. The patient was admitted to hospital for further investigations, namely an MRI of the lumbar spine. Within the next 24 hours, she developed rapid quadriparesis and dysphagia to liquids and solids. She was found unresponsive without a pulse with ventricular fibrillation and CPR was initiated. She achieved return of spontaneous circulation after one shock and 6 minutes of CPR. She was intubated and was transferred to the intensive care unit. Repeat ECG showed sinus rhythm with T-wave inversions, mildly prolonged QTc at 500 msec; troponin and B-type natriuretic peptide were unremarkable. The cardiology team was not able to identify a specific cause or trigger for the ventricular fibrillation including no significant electrolyte imbalances, toxic exposure, or structural cardiac abnormalities.

After discontinuation of anesthetics, she remained ventilator-dependent with absent cough and gag. She was alert with spontaneous eye movements and blinking. Her pupils remained equal and reactive to light. Extraocular movements remained full and she had clear bifacial weakness with incomplete eye closure and scleral show left more than right, and no frontalis or orbicularis oris activation. She had flaccid tone and no motor activity or response throughout the extremities. Deep tendon reflexes were globally absent. She was able to reliably answer yes/no questions with eye movements, and she reported preservation of light touch, pain, and vibration sensation in all extremities. Lumbar puncture revealed elevated protein (0.70 g/L; ref 0.15-0.45) and lymphocytic (69%) pleocytosis (9×10^6 /L; ref 0-5), with otherwise normal cytology and negative viral testing. Plasma porphyrin and urinary porphobilinogen were normal. MRI brain and spine were unremarkable. Nerve conduction studies performed 8 days after presentation revealed normal sensory responses for the superficial radial, ulnar dorsal cutaneous and sural sensory nerves with absent median, ulnar, fibular and tibial motor responses, and electromyography showed no spontaneous activity or motor unit activation (Table 1).

She was treated with intravenous immunoglobulin (IVIG) 2 g/kg over five days and had minimal response. Four weeks after her last dose of IVIG she received five sessions of plasma exchange. Over the next several weeks she had some improvement in terms of neck flexion and extension strength. Examined at 7-month follow-up she has also made improvements with regards to extraocular movements, lateral head movements and full strength at the trapezius bilaterally. She is now also able to speak with a flaccid dysarthria.

Discussion

Guillain-Barré Syndrome (GBS) is a demyelinating immune-mediated polyneuropathy, an important cause of acquired neuromuscular weakness¹. It encompasses several subtypes, most commonly acute inflammatory demyelinating polyneuropathy (AIDP)¹. Another variant of GBS is Acute Motor Axonal Neuropathy (AMAN). AMAN is characterized as a pure motor axonal subtype of GBS with a more rapid progression and earlier nadir than demyelinating GBS. Unlike the typical form of AIDP, reflexes in AMAN can be preserved and autonomic manifestations are relatively rare^{1,3}.

²The pathophysiology is mediated by molecular mimicry with findings in the serum of patients to various antiganglioside antibodies. Most commonly, anti-GM1, anti-GD1a, and anti-GD1b⁴. In comparison to AIDP, patients with AMAN less commonly involve the cranial nerves and sensory deficits. In addition, recovery from axonal regeneration takes much longer compared with recovery from demyelinating processes. Two patterns of recovery are typically seen in patients with AMAN: a subset of patients that recover within days whereas others have a very prolonged time of recovery⁵.

Electrodiagnostic studies play a critical role in the diagnosis of AMAN, as they do in AIDP.

While the latter is characterized by slowing of conduction velocity, conduction block or temporal dispersion indicative of demyelination in two or more motor nerves, AMAN is characterized by

reduced amplitudes of distally evoked compound muscle action potentials without significant reduction in conduction velocity, with normal sensory nerve conduction studies^{1,6}. Axonal damage is typically associated with positive sharp waves and fibrillations but can take up to 3 weeks to appear. Given that nerve conduction studies and electromyography were done 8 days after presentation in our case, this may explain the absence of spontaneous activity seen on electromyography.

Autonomic dysfunction in GBS has a wide spectrum of manifestations. Most commonly sinus arrhythmias, labile blood pressure, urinary retention, pupillary abnormalities and sudomotor dysfunction⁶. In contrast with other variants of GBS, patients with AMAN rarely have the autonomic dysfunction¹. Dysautonomia is more common in patients with more severe disease such as those with quadriplegia, neck flexor and bulbar weakness and on mechanical ventilation⁷. Patients with dysautonomia have been found to have more major complications that have not been necessarily related to the dysautonomia this includes cardiac arrhythmias with ventricular tachycardia, atrial fibrillation with rapid ventricular response, neurogenic stunned myocardium, cardiomyopathy, syndrome of inappropriate antidiuretic hormone secretion and posterior reversible encephalopathy syndrome^{7,8}. CSF evaluation in GBS can reveal albuminocytologic dissociation, mild pleocytosis or normal CSF studies, particularly during the first few weeks of presentation for both classic AIDP and variants such as AMAN while demyelinating forms may show higher levels of protein⁹.

We present a case of AMAN with several educational features for clinicians. For one, the presence or even exaggeration of reflexes should not rule out a diagnosis of AMAN as about ten percent of patients have preserved reflexes throughout the disease course⁴. In addition, initial physical exam features of our case may have appeared as functional weakness including knee “buckling” and give-way weakness on initial strength examination. This highlights the

importance of serial physical examination and careful observation of the patient moving around their environment.

Another learning point is the significance of autonomic manifestations. Our case illustrates that patients with AMAN can have cardiac complications that may or may not be directly related to dysautonomia, for instance the cardiac arrest and post arrest atrial fibrillation. Consequently, close monitoring with telemetry is indicated in these patients.

With regards to treatment, IVIG and plasma exchange have proved in numerous clinical trials to be efficacious for AIDP⁸. However, as most of these trials were conducted in North America and Europe, most of the patients included were likely AIDP rather than patients with the axonal variant and it is unclear if these therapies are efficacious for AMAN. There have been two studies that suggest that IVIG may be better for AMAN as compared with plasma exchange although the findings have not been consistent¹. Given the lack of evidence for either treatment or both treatments in AMAN, our team had a discussion with the patient's family and ultimately decided to treat with plasma exchange in addition to IVIG approximately 4 weeks after the course of IVIG was finished. Treatment decisions for AMAN must be done on a case by case basis given the lack of large randomized trials with supporting evidence.

Finally, communication was a significant challenge given the severity of our patient's weakness, she initially only had ability to control her extraocular muscles. As such, finding strategies to help patients communicate (Figure 1) as well as keeping them engaged through entertainment , cognitive activities and social interaction can be a critical part of patient care. In addition, this case highlights that reliable non-verbal communication provided confirmation of preserved sensory function on clinical examination, allowing a presumptive diagnosis of AMAN before electrodiagnostic testing.

References:

1. Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: Concepts and controversies [online]. *Lancet Neurol*. Elsevier; 2013. p. 1180–1188. Accessed at: <http://www.thelancet.com/article/S1474442213702151/fulltext>. Accessed May 5, 2021.
2. McKhann GM, Cornblath DR, Ho T, et al. Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. *Lancet* [online serial]. *Lancet*; 1991;338:593–597. Accessed at: <https://pubmed.ncbi.nlm.nih.gov/1679153/>. Accessed May 5, 2021.
3. Yuki N, Kokubun N, Kuwabara S, et al. Guillain-Barré syndrome associated with normal or exaggerated tendon reflexes. *J Neurol* [online serial]. *J Neurol*; 2012;259:1181–1190. Accessed at: <https://pubmed.ncbi.nlm.nih.gov/22143612/>. Accessed May 5, 2021.
4. Magid-Bernstein J, Al-Mufti F, Merkler AE, et al. Unexpected rapid improvement and neurogenic stunned myocardium in a patient with acute motor axonal neuropathy: A case report and literature review [online]. *J. Clin. Neuromuscul. Dis.* Lippincott Williams and Wilkins; 2016. p. 135–141. Accessed at: <https://pubmed.ncbi.nlm.nih.gov/26905914/>. Accessed June 13, 2021.
5. Hiraga A, Mori M, Ogawara K, Hattori T, Kuwabara S. Differences in patterns of progression in demyelinating and axonal Guillain-Barré syndromes. *Neurology* [online serial]. Lippincott Williams and Wilkins; 2003;61:471–474. Accessed at: <https://pubmed.ncbi.nlm.nih.gov/12939419/>. Accessed May 5, 2021.
6. Sheikh KA. Guillain-Barré Syndrome. *Continuum (Minneapolis)* [online serial]. NLM (Medline); 2020;26:1184–1204. Accessed at: https://journals.lww.com/continuum/Fulltext/2020/10000/Guillain_Barr__Syndrome.6.aspx. Accessed June 13, 2021.
7. Chakraborty T, Kramer CL, Wijedicks EFM, Rabinstein AA. Dysautonomia in Guillain-Barré Syndrome: Prevalence, Clinical Spectrum, and Outcomes. *Neurocrit Care* [online serial]. Springer; 2020;32:113–120. Accessed at: <https://link.springer.com/article/10.1007/s12028-019-00781-w>. Accessed June 13, 2021.
8. Zaeem Z, Siddiqi ZA, Zochodne DW. Autonomic involvement in Guillain-Barré syndrome: an update [online]. *Clin. Auton. Res.* Dr. Dietrich Steinkopff Verlag GmbH and Co. KG; 2019. p. 289–299. Accessed at: <https://doi.org/10.1007/s10286-018-0542-y>. Accessed June 13, 2021.
9. Dimachkie MM, Barohn RJ. Guillain-Barré Syndrome and Variants. *Neurol Clin* [online serial]. NIH Public Access; 2013;31:491. Accessed at: </pmc/articles/PMC3939842/>. Accessed September 29, 2021.
9. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, van Doorn PA, Dourado ME, Hughes RAC, Islam B, Kusunoki S, Pardo CA, Reisin R, Sejvar JJ, Shahrizaila N, Soares C, Umapathi T, Wang Y, Yiu EM, Willison HJ, Jacobs BC. Diagnosis and management of Guillain-Barré syndrome in ten steps. *Nat Rev Neurol*. 2019 Nov;15(11):671–683. doi: 10.1038/s41582-019-0250-9. Epub 2019 Sep 20. PMID: 31541214; PMCID: PMC6821638. Accessed September 25, 2021.

Table 1. Nerve conduction study and electromyography (EMG) demonstrating findings consistent with a severe motor axonal variant of Guillain-Barre syndrome. This was done approximately 1-week after the presentation presented to hospital. *APB: Abductor pollicis brevis, EDB: Extensor Digitorum Brevis.

Sensory Nerve Conduction Studies		
	Patient Values	Normal Values
Sural Sensory (Left) - Antidromic		
Latency, ms	1.73	≤3.0
Distance, mm	120	120
Amplitude, uV	6.2	≥6
Conduction Velocity, m/s	69.4	≥40
Ulnar Dorsal Cutaneous Sensory (Right)		
Latency, ms	1	<1.8
Distance, mm	60	80
Amplitude, uV	15.3	>12
Conduction Velocity, m/s	60	≥50
Superficial Radial Sensory (Right)		
Latency, ms	1.31	≤2.0
Distance, mm	100	100
Amplitude, uV	35.5	≥15
Conduction Velocity, m/s	76.3	≥50
Motor Nerve Conduction Studies		
Median Motor (Right) Wrist-APB**		
Latency, ms	Absent	≤4.4
Distance, mm	70	70
Amplitude P-P, mV	Absent	>4.0
Conduction Velocity, m/s	Absent	>49
Fibular Motor (Right) Ankle – EDB**		
Latency, ms	Absent	≤4.4
Distance, mm	90	90
Amplitude P-P, mV	Absent	>4.0
Conduction Velocity, m/s	Absent	>49
Tibial Motor (left) Ankle - Abductor hallucis		
Latency, ms	Absent	<5.8
Distance, mm	90	90
Amplitude P-P, mV	Absent	>4.0
Conduction Velocity, m/s	Absent	>41
EMG Findings		

Biceps (right)		
Spontaneous activity	None	
Interpretation	Unable to activate	
Tibialis anterior (right)		
Spontaneous activity	None	
Interpretation	Unable to activate	

Figure 1. Illustration of the method used to communicate with our patient given only intact extraocular movements. To use this tool, the patient was asked which letter she is indicating by clarifying which box (“is it 1? 2? 3?...”) for which the patient would look up for “yes” and down for “no”. To proceed, she was then asked to clarify which letter in that box by being asked one at a time (“is it A? B? ...”)

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