Delayed Onset Wound Botulism: A rare Post-Traumatic Presentation

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Abstract:

A 41-year-old male presented with rapidly progressive cranial neuropathies and muscle weakness followed by respiratory failure, which required ventilation support. On examination, there was marked bilateral ptosis and ophthalmoplegia with bulbar, neck, and proximal upper limb weakness. He had a recent open left humeral fracture that eventually required amputation. Despite immunoglobulin therapy, he continued to develop progressive weakness. Multiple investigative results were inconclusive. Eventually, Botulinum type A toxin was found positive, yet he had already passed the therapeutic window for antitoxin. He was continued on supportive management and treated for concomitant infections and nosocomial illnesses. He was subsequently weaned from respiratory support and made a good neurological recovery.

Keywords:
Botulism, cranial neuropathy, respiratory failure, bulbar weakness, muscle weakness, descending paralysis, Botulinum toxin, Botulinum antitoxin.

Background:

Rarely, respiratory failure requiring prolonged ventilation and nursing care can develop as a result of severe descending muscle paralysis caused by *Clostridium botulinum* neurotoxin **(1).** Major soil contamination through compound fractures, severe trauma, lacerations, puncture wounds, and hematomas have been linked to wound botulism **(2).**, in addition to its association with subcutaneous injecting drug **(3).**

Although the course of paralysis in patients with botulism is described as distinctive and recognisable the neurologic symptoms and the manner and rate of progression may be misinterpreted when a patient is initially examined by the healthcare professional (4).

Antitoxin administration should begin as soon as a definitive clinical diagnosis of botulism has been made since early targeted treatment is crucial (4).

We describe a complex case of bulbar weakness and acute cranial neuropathy following limb trauma. There was a complex evolving differential diagnosis and the cause was ultimately determined to be neurotoxicity caused by botulinum toxin.

Case:

A 41-year-old male with no previous medical history, presented to a local hospital with a 2-week history of progressive dysphagia associated with fluctuating ptosis and diplopia. 5 days later due to worsening unexplained symptoms, he was transferred to our hospital.

Six weeks before the admission, he was involved in a road traffic accident in Jordan and sustained a left humeral fracture with a degloving injury. There was a delay in wound washout and external fixation due to interhospital transfer. Upon returning to the United Kingdom (UK), he was hospitalised for internal fixation, which was unsuccessful due to neurovascular compromise. He underwent an above-elbow amputation three weeks after the initial injury. At the time of patient presentation to our hospital, we did not have clear history regarding the nature of his accident/injury, wound contamination during injury, or underlying cause of arm amputation. He did not receive a course of antibiotics apart from perioperative prophylaxis, and he was discharged well after 8 days.

On examination (day 14 of symptoms), he had marked bilateral ptosis, ophthalmoplegia, bulbar, neck, and proximal upper limb weakness, Medical Research Council (MRC) Scale grade 2/5, with preserved distal power. His upper limbs were relatively weaker than his lower limbs (proximal weakness grade 4/5). Reflexes were normal, and there was no sensory deficit. His pupils were normal initially; he was alert and able to communicate using handwriting and hand gestures. Of note, he displayed several autonomic features including labile blood pressure and heart rate and significant excess respiratory secretion. His gag reflex was reduced, and he did not have any dryness of mouth or throat.

Due to significantly worsening dysphagia, a nasogastric tube was inserted. Endoscopy and computerised tomography (CT) scans of the neck did not show any causative abnormalities. He rapidly deteriorated within the next 5 days, with worsening bulbar impairment, prominent ptosis, and muscle weakness leading to type 2 respiratory failure requiring intubation and mechanical ventilation. CT head did not show any acute intracranial pathology.

He was found to have fever during the first few days of admission, for that he was screened for systemic infections.

The initial differential diagnosis included myasthenia gravis, and he was therefore given a trial of pyridostigmine with no noticeable improvement. A 5-day course of intravenous immunoglobulin (IVIg) therapy was then commenced. Despite the therapy, he progressively developed complete bilateral total ptosis, an unreactive left pupil, worsening of limb weaknesses, and absence of upper limb reflexes. Pupillary changes started on the 4^{th} day of admission and lasted only for around only 4 days. Reflexes were also normal on the first few days, became reduced afterwards for few days then started to improve back later. Muscle weakness was much worse on the upper limbs reached grade 1/5 proximally and grade 4/5 distally compared to lower libs power of 3/5 proximally and preserved distal power.

Nerve conduction studies demonstrated normal sensory responses. Motor studies showed generally low amplitude compound muscle action potentials (CMAPs) with otherwise normal conduction parameters. F wave studies showed absent tibial response with normal right median and ulnar responses.

Repetitive nerve stimulation (RNS) studies at slow (3Hz) stimulation rates demonstrate a mild degree of decrement, (Anconeus 10%, Abductor Pollicis Brevis 9%). No facilitation of responses was seen at fast (30Hz) stimulation rates.

Electromyography (EMG) examination demonstrated prominent fibrillation potentials. Motor unit analysis demonstrated an excess of relatively low amplitude brief duration motor unit potentials of simple and complex morphology. Motor unit recruitment was early although very poorly sustained.

His cerebrospinal fluid (CSF) taken on day 4 of IVIg had a raised white blood cell (WBC) of 66 with no negative Gram stain; protein was 0.50 g/L and CSF glucose was 3.1mmol/L (plasma glucose 5.6mmol/L). A repeat CSF sample after 24 hours of IVIg completion showed a WBC of 15, CSF protein 0.52 g/L and CSF glucose was 3.2 mmol/l (plasma glucose was 5.2mmol/L). CSF Culture and extended viral panel were later reported negative.

During the intensive care unit (ICU) stay, he received multiple courses of antibiotics, including cefiderocol for multiresistant *Acinetobacter* pneumonia, intravenous Vancomycin for suspected line-related infection with coagulase-negative *Staphylococcus* in the blood culture, empirical meropenem for a possible central nervous system infection, and empirical metronidazole for a possible tetanus infection.

Magnetic Resonance Imaging (MRI) with contrast of the brain did not demonstrate characteristic features of intracranial infection but unexpectedly revealed subacute multifocal infarctions, including the left posterior inferior cerebellar artery (PICA) territory. Intracranial and carotid CT angiograms did not show evidence of vasculitis. CT thorax, abdomen, and pelvis did not show evidence of malignancy to suggest paraneoplastic syndrome but revealed left residual pulmonary embolus (PE), left lower lung base infarction, and small renal infarcts. There was no evidence of endocarditis, thrombus, or patent foramen ovale on the transoesophageal echocardiogram to suggest a cardiac embolic source. The ultrasound (US) Doppler of the lower limbs revealed right lower limb deep venous thrombosis (DVT). He was started on therapeutic anticoagulation for pulmonary embolism and DVT. Nevertheless, none of these findings led to a definite diagnosis, raising a serious consideration of botulism.
MRI Left upper arm stump showed collection at the tip/inferior aspect of the stump, with areas of cortical erosion, intramedullary oedema, and soft tissue collection, suggestive of subacute osteomyelitis. He was started on Co-amoxiclav, switched to Piperacillin -Tazobactam as US guided left arm stump aspirate grew Pseudomonas aeruginosa. This was later switched to oral Levofloxacin on discharge. The L arm stump aspirate that was sent to reference lab for Clostridium botulism polymerase chain reaction (PCR) came back negative.

The initial differential diagnosis included myasthenia gravis, Miller Fisher syndrome and botulism, although at the time of original assessment we did not identify any clear wound infection that would have caused the latter. Neurophysiology examination did not show clear features of myasthenia nor neuropathy. Review of his notes from other hospitals identified that a swab from the wound had

grown *Pseudomonas* sp. and *Clostridium perfringens*, raising the diagnostic suspicion of wound botulism as a cause for his clinical presentation.

The results for acetylcholine receptor antibody and Anti Muscle Specific Kinase (MuSK) were both negative. Anti Glycolipid antibodies and Anti Myelin oligodendrocyte glycoprotein (MOG) antibodies were also negative. Serum screening tests for connective tissue disease, vasculitis, antiphospholipid syndrome, and paraneoplastic autoantibodies were negative.

After 2 weeks in the ICU, the UK Health Security Agency informed the team that a mouse bioassay showed delayed but significant physiological changes at 4 to 5 days, which could relate to the late sampling time of the serum after symptom onset or a weaker toxin-producing strain. Subsequently, Botulinum type A toxin was found positive via in-vivo inhibition of mouse symptoms with specific anti-toxin; however, the patient had already started to show slow gradual improvement in muscle weakness after 10 days of ICU admission. He underwent a percutaneous tracheostomy on day 15 of the ICU to assist with ventilatory weaning. The tracheostomy was finally decannulated on day 35 of ICU admission, and he was transferred to the ward the day after. Timeline of our patient's clinical manifestations are summarized in **table 1**.

TIME (DAYS)	**manifestations**
1	Car accident.
20	Amputation.
29	Diplopia/ophthalmoplegia.
29	Dysphagia.
39	progressive upper limbs weakness.
42	respiratory failure/ventilation.
44	lower limbs weakness.
46	absent reflexes.
48	pupillary changes.
52	Re-reactivity of pupils.
58	Tracheostomy.
68	botulism confirmation.
68	improvement of reflexes.
69	Trials of ventilation weaning
70	Beginning of improvement of ophthalmoplegia.
71	Beginning of improvement of ptosis.
75	weakness improvement in Lower limbs.
84	total weaning of ventilation.
88	Tracheostomy decannulation.
95	weakness improvement in upper limbs.

Table (1): timeline of clinical manifestation since time of care accident.

He underwent further respiratory weaning and had a successful tracheostomy decannulation on day 35. He was gradually started on oral fluid within 24 hours of tracheostomy decannulation. He continued to have physiotherapy, neurorehabilitation, occupational therapy, and swallow therapy on the ward. He was discharged on day 67 of hospital admission with an oral antibiotic course for an infected collection in the region of the humeral stump, and a direct oral anticoagulant (DOAC). Upon discharge, he was independently mobile and able to steadily climb up and go down the stairs.

Discussion and conclusion:

This case underscores the importance of considering wound botulism as a potential diagnosis when encountering patients with neuromuscular paralysis, particularly in the context of recent fractures. The wound can look benign, with minimal erythema or discharge, but the organism and toxin may still be present [5]. Our patient did not have any signs of wound infection, from his previous history; however, botulinum toxin was detected on his serum later on and swab results from other hospitals and imaging of his upper limb stump also supported chronic infection.

Fever is reported in wound botulism, not on foodborne botulism [6], but was not present at initial presentation. We could attribute our patient fever to either botulism itself or other causes of bacteraemia as detected later in his blood cultures.

Generally, incubation period is 4-14 days for wound botulism, this patient presented around 6 weeks after his initial road traffic accident which lowered the suspicion of botulism given the prolonged time and suggested that the condition may have presented following his amputation, acquiring this after his left arm amputation at local hospital. However, cases of prolonged latency to clinical onset in wound botulism have been described, perhaps reflecting slow release of toxin from an infective focus [7].

Botulism typically manifests as a distinctive syndrome characterized by cranial nerve palsies, which can progress to bilateral, symmetric, descending flaccid paralysis. This paralysis initially affects proximal muscle groups before extending to distal limb musculature, potentially leading to respiratory failure and, in severe cases, death [4]. The pattern of symptoms presentation is reported not to follow the classical descending paralysis pattern in some cases which can impact on the diagnostic process.

In our case, pupillary unreactivity occurred around 20 days from symptom onset and were transient, improving after four days. The cause for pupillary inequality in a presumably systemic process is unclear. However sluggish reactive pupils were reported in some cases of botulism. We excluded central causes for this by MRI brain imaging.

At the time of presentation, reflexes were preserved which favoured myasthenia over botulism. Later on, reflexes diminished on upper limbs, making botulism more likely clinically. Loss of reflexes in the peak period of the illness can correlate with the severity of upper limbs weakness. Reflexes started to improve followed by gradual muscle power improvement.

Autonomic involvement is common in botulism, although can be seen in other acute neuromuscular conditions such as GBS. Our patient had fluctuation in blood pressure and heart rate, but he did not have dryness of mouth or throat which are typical of botulism. Gag reflex tend to be reduced in some cases of botulism [7].

Lack of sensory involvement highlighted the possibility of neuromuscular junction abnormality rather than GBS, as a high percentage of those patients with GBS described sensory abnormalities. Furthermore, the degree of weakness in relation to respiratory failure did not support the diagnosis of GBS in which muscle weakness is marked especially in the LLs before the stage of respiratory involvement.

The pharyngeal-cervical-brachial (PCB) variant of Guillain–Barré syndrome, which comprises rapidly progressive oropharyngeal and cervicobrachial weakness with upper limb areflexia, can be confused with botulism. However, with absence of CSF albuminocytological dissociation, negative IgG anti-

GT1a or anti-GQ1b antibodies and absent neurophysiological features of neuropathy, this condition was excluded.

It is noteworthy that physicians often consider a range of other diagnoses along with botulism. For 274 out of 332 botulism cases (83%), physicians explored alternative possibilities at the time of public health consultation. The most common misdiagnoses included Guillain-Barré syndrome (GBS) in 99 cases and myasthenia gravis in 76 cases [8]. Our main differential diagnosis and correlation with the patient's manifestations are summarized in table (2).

	Wound botulism	myasthenia	GBS with variants
history			
injury/wound	yes (however wound was clean)	No	No
early fluctuating symptoms	Atypical	Yes, however no diurnal variation	No
clinical manifestation			
ptosis	yes	yes	In Miller Fischer variant
ophthalmoplegia	yes	yes	yes
facial weakness	yes	yes	yes
proximal UL weakness	yes, descending pattern	yes, but LL would be affected to almost same degree	In Pharyngo-cervical-brachial variant
reflexes	Diminished or normal	normal	Diminished/absent
respiratory failure	yes	yes, but early RF is atypical	yes, but here is disproportionate to weakness
bulbar weakness	yes	yes, but early symptoms are atypical	yes, but here is disproportionate to weakness
pupillary changes	yes	no	no
normal sensations	yes	yes	Variable
fever	yes	No	no

Table (2): main differential diagnosis in our case with highlighting the patient's manifestations which were in favour of or against these conditions.

All botulinum toxin serotypes disrupt neuromuscular transmission by inhibiting the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction. The administration of botulinum toxin via intramuscular injection weakens muscles via chemo denervation. Botulinum toxins can affect different sites in the body, including the neuromuscular junction, autonomic ganglia, postganglionic parasympathetic nerve endings, and postganglionic sympathetic nerve endings that release acetylcholine [9].

Electrophysiological studies did not show the typical pattern of abnormality seen in botulism, but it helped in exclusion of other causes as myasthenia and neuropathies. Notably no facilitation of

responses was seen with fast RNS. This is most probably explained by the severity of neuromuscular junction blocking present. However, the study did show low amplitude motor responses, a mild degree of decrement at slow RNS rates while EMG examination demonstrated prominent fibrillation and myopathic-type features. These findings while not specific findings are certainly consistent with a diagnosis of botulism **(table 3).**

Neurophysiology test	**Findings in our patient**	**Comment and explanation**
nerve conduction study	normal sensory responses.	Makes acute inflammatory neuropathy unlikely
	Motor studies showed generally low amplitude compound muscle action potentials (CMAPs)	Typical feature of presynaptic neuromuscular junction (NMJ) disorders, once CMAPs are of normal duration and normal distal motor latency.
	F wave studies showed absent tibial response with normal right median and ulnar responses	Absence of F wave responses may be seen in profoundly weak muscles due to reduced excitability of the relevant anterior horn cells (AHCs). Their absence does not necessarily indicate peripheral nerve demyelinating pathology
repetitive nerve stimulation:	a mild degree of decrement, (Anconeus 10%, APB 9%).	Decrement at low stimulation rate (2-5hz) can be seen in both pre and post synaptic NMJ disorders
	No facilitation of responses was seen at fast (30Hz) stimulation rates.	Post tetanic facilitation or high frequency (20-30Hz) facilitation is a feature of presynaptic NMJ disorders but not invariably seen.
EMG	prominent fibrillation potentials	Fibrillation potentials and positive sharp waves, signs of denervation, are common in botulism but not in other NMJ disorders. Botulinum toxin is a potent NMJ blocker and effectively causes functional chemo-denervation.
	Motor unit analysis demonstrated an excess of relatively low amplitude brief duration motor unit potentials of simple and complex morphology.	Motor unit analysis can demonstrate relatively low amplitude, brief duration potentials. These features are typically referred to as “myopathic”. However, they may be seen in botulism but not in other acute NMJ

		disorders.
	Motor unit recruitment was early although very poorly sustained.	Early or increased motor unit recruitment is a typical feature of myopathy but may also be seen in Botulism.

Table (3): neurophysiological results and interpretation in our patient.

Patients with botulism often have normal outcomes from routine laboratory testing, such as complete blood counts, CSF analysis, and radiologic examinations [(4).] Elevated CSF protein has occasionally been reported. The initial CSF WBC was elevated, but this was during IVIG treatment, and we suspected that this could be due to IVIG induced aseptic meningitis. Drug induced aseptic meningitis is a diagnosis of exclusion and with normal cultures and viral panel, absence of clinical or radiological features suggesting meningitis and improvement of results in the second lumbar puncture, we were able to attribute the CSF pleocytosis with IVIG induced aseptic meningitis. Normal CSF protein also was against the diagnosis of GBS.

Specimens should be collected for diagnostic testing as soon as possible because toxin levels decrease over time. This patient serum that was sent to reference lab (prior to IVIG) was approximately 10 days after the start of his symptoms and the delayed onset in the mouse could relate to the late sample time of the serum after symptom onset, or the presence of a more weak toxin producing strain.

The mouse bioassay (MBA) remains the most widely used test to confirm levels of active Botulinum neurotoxins (BoNTs). It does, however, have several disadvantages, including the cost and ethical issues of live animal research, as well as the amount of time taken to conduct the assay. Isolation of Clostridium botulinum from pus or detection of toxin in serum remain insensitive.

Culture of wound specimens may not be positive, particularly if antibiotics had already been administered. This patient had antibiotics prior to US guided aspiration of L arm stump collection. Due to lack of some information at time of admission regarding the nature of injury and cause of amputation, Tetanus (as a part for management of any possible wound infection) was considered in his antibiotic's prescription at time of admission to our hospital despite not having clear clinical manifestations of tetanus; cranial tetanus would present with hyperkinetic movement disorder rather than muscle weakness. It was excluded on the following few days after recalling the patient's previous hospitals' data.

Detection of stroke on brain imaging did not explain the clinical presentation in our patient. We investigated him for causes of young stroke, however we could not find any evidence of an underlying cause. One of the main concerns to exclude septic emboli as he had large artery infarction with multifocal areas in DWI. However, we could not find any supportive evidence in our investigations. The possibility of meningitis with septic emboli through the meningeal artery was unlikely due to the involvement of different vascular territories and the lack of a clinical picture of meningitis or systemic features of this. Potentially, systemic sepsis could result in a prothrombotic state which can explain both the brain and renal infarctions. His PE can be explained by prolonged immobility and prolonged ICU stay.

It is recommended to initiate treatment with botulinum antitoxin (BAT), promptly for patients with suspected botulism based on clinical findings without waiting for laboratory confirmation. This is because test results may take several days and can sometimes yield false negatives in patients with

botulism. Botulinum antitoxin cannot reverse paralysis, so prompt administration early in the course of disease is critical. Authors recommended to be given as early as within 48 hours from manifestations, however there are some reports with better outcome with late administration in the first 7 days. [4] There is no current recommendation regarding the maximum time of BAT administration, and we recommend this to be subjected to clinical evaluation. We informed Public Health England (PHE) regarding possibility of botulism, but due to the mechanism of the wound and possibility of other pathologies including CSF pleocytosis, their advice was that botulism was unlikely. At time of confirmation of botulism, our patient was already starting to improve. Given this and the long latency to confirmation, PHE colleagues did not feel that BAT administration was indicated.

Supportive care, intubation, mechanical ventilation when required, and the delivery of an equine-derived botulinum antitoxin are all part of the treatment. Botulism can cause paralysis that lasts for weeks or months and ventilatory support is usually required for 2 to 8 weeks, and may be needed up to 7 months for some, since recovery from botulism depends upon breakdown of toxin as well as compensatory sprouting of new presynaptic terminals and new synapse formation. Early respiratory failure is often the cause of death in the acute stage, but complications including ventilator-associated pneumonia and deep vein thrombosis (DVT) become the main causes of death later in the course of the illness **[(4).]**

Patients presenting with wound botulism should undergo wound debridement to reduce bacterial burden and remove tissue contaminated with toxin, even if there are few gross markers of wound infection. It is crucial to rule out any ongoing possible source of clostridial infection as there is a risk of relapse if not dealt with.

Appropriate supportive care plays a crucial role in the survival and recovery of botulism patients. A significant proportion of these patients experience respiratory compromise, even with prompt diagnosis and early antitoxin treatment. Therefore, excellent critical care support is essential for the survival of all botulism patients, whether they received antitoxin treatment or not **[(10).]**

Although our patient's diagnosis came too late for BAT treatment, there was a dramatic improvement in their condition, albeit after a delay, particularly in respiratory function, following appropriate intervention.

Mortality rates are notably higher in patients who are far from hospitals or emergency care facilities. Early recognition and adherence to best intensive care unit practices are essential components of comprehensive botulism patient care. In situations with limited antitoxin availability, the availability of critical supportive care is pivotal in determining the survival of patients facing respiratory compromise **[(10).]**

Conclusion:

In our case study, we presented a patient who exhibited descending paralysis and neuromuscular weakness as a result of wound botulism secondary to trauma. Due to the rarity of botulism and its complex presentation, the diagnosis was delayed. The diagnostic process was further complicated by the presence of multiple systemic infections, non-diagnostic neurophysiological findings, and neuroradiological findings which required further investigation. Wound botulism should be considered in the differential diagnosis of acute neuromuscular weakness, especially with a history of recent open fractures, wound infection or subcutaneous drug injection. Excellent functional recovery can be seen with appropriate supportive case even if antitoxin treatment is not possible.

Key points:

- Wound botulism should be suspected in cases of neuromuscular paralysis, cranial neuropathies, and bulbar failure with history of trauma as well as injecting. A high index of suspicion is required in cases without clear infective focus.
- Treatment with botulinum anti- toxin should be administered as early as possible, best within 48hours from manifestations without waiting for laboratory confirmation.

Further reading:

- Rao AK, Sobel J, Chatham-Stephens K, Luquez C. Clinical guidelines for diagnosis and treatment of botulism, 2021. MMWR Recommendations and Reports. 2021 May 5;70(2):1.
- Brett MM, Hallas G, Mpamugo O. Wound botulism in the UK and Ireland. Journal of medical microbiology. 2004 Jun;53(6):555-61.

Competing interests:

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All authors provided clinical care for the patient. **ME** took the lead in writing the manuscript, gathering most data, and obtaining the patient's consent. **CK** provided critical revision of the manuscript. **JH** helped in clinical data collection. **RM** reviewed the neurophysiology part. **AP** and **SK** reviewed the microbiological part.

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