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Case Report

Complex ophthalmoplegia as the first manifestation of Gram-negative endocarditis by *Enterobacter cloacae*: A case report

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Introduction

Bilateral WEBINO (Wall-eyed Bilateral Internuclear Ophthalmoplegia) and third nerve palsy as the first manifestation endocarditis is an extremely rare presentation. The occurrence of neurological signs in the absence of a prodrome of fever and other constitutional symptoms must still prompt consideration of infective endocarditis, as early initiation of antibiotics is associated with a better outcome. The case report aims to draw attention to the possible differentials for bilateral ptosis, diplopia and drowsiness in a 53-year-old male, three days after an alcohol binge, and raise awareness about the clinical characteristics of this uncommon gram-negative non-HACEK endocarditis.

Septic emboli, a dreaded complication of infective endocarditis, is seen in up to 46% of cases, mostly associated with *Staphylococcus aureus* [1]. It usually occurs prior to the initiation of antibiotics or within a week of initiation [2] However, it is the presenting feature in less than 17% of cases [3]. This presentation of multiple brainstem embolic strokes in the absence of a febrile prodrome is rare for Gram negative endocarditis which commonly presents with fever. This case also highlights the challenges that exist with the standard stroke management protocol when a stroke is the first manifestation of occult endocarditis.

Case presentation

A 53-year-old man was transferred from a local hospital with an acute onset, bilateral, drooping of eyelids, double vision and altered consciousness. He was a woodcutter by

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profession, a heavy alcohol consumer and a smoker. He was last seen well by his family three days prior, when he had taken a binge of alcohol after which he had not left his room.

According to his family, there had been no history of fever, headache, trauma to the head, vomiting, chest pain, shortness of breath, cough or constitutional symptoms. They were uncertain about the possibility of a snake bite. There was no history of chronic diarrhoea, arthralgia, recent pigmentation or memory lapses. There were no previous similar episodes. He was a regular alcohol consumer and took a quarter bottle of illicit alcohol brew daily and smoked ten rolled tobacco per day for thirty years. He denied use of intravenous drugs or high-risk sexual behavior.

On examination, his GCS was 9/15 (E3V2M4). He had a bilateral partial ptosis with primary gaze exotropia of both eyes with dilated pupils (+3) which were non-reactive. On passive movements of his head, there was incomplete adduction, bilaterally, suggestive of ~~a~~ bilateral third neve palsy. He was not pale or icteric but had ~~with~~ inadequate oral hygiene. There were no oral ulcers, lymphadenopathy, clubbing, pedal oedema, skin rashes or stigmata of hyperlipidemia. His pulse was 76/min and regular; blood pressure was 110/80mmHg. His cardiac apex was not displaced. No palpable thrills or heart sounds were detected. A faint pansystolic murmur was heard at the apex with radiation to the axilla, suggestive of a grade 1 mitral regurgitation His respiratory rate was 21/min, SPO_2 98% on air. His abdomen was soft and non-tender. There was no organomegaly.

Table 1: Examination findings of the Nervous System

Upper limb	**Right**	**Left**
Tone	Normal	Normal
Power	Grade 4	Grade 4
Reflexes	++	++
Lower limb		
Tone	Normal	Normal
Power	Grade 4	Grade 4
Reflexes	++	++
Plantar	Down-going	Down-going

His random capillary blood sugar was 185mg/dL and his whole blood clotting time was less than 20 minutes. His ABG showed respiratory alkalosis – pH 7.474, PCO2 27.5mmHg, P02 98.5mmHg, HCO3 23.5mmol/L, Lac 0.7. His NCCT Brain excluded an intracranial hemorrhage.

Wernicke's encephalopathy was considered and he was started on intravenous thiamine and hydrated with Hartmann solution.

He improved the next day morning to a GCS of 15/15 which enabled a proper eye examination. He had bilateral internuclear ophthalmoplegia with vertical gaze palsy, loss of convergence and loss of intorsion illustrated in Figure 1: (1) - (6). This suggested

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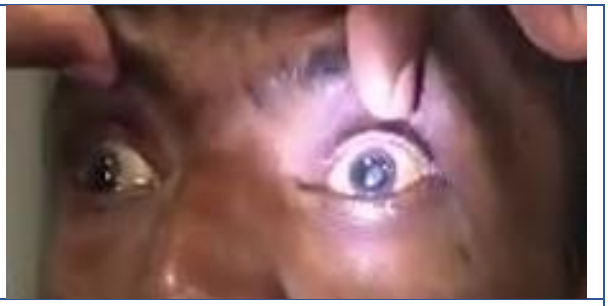
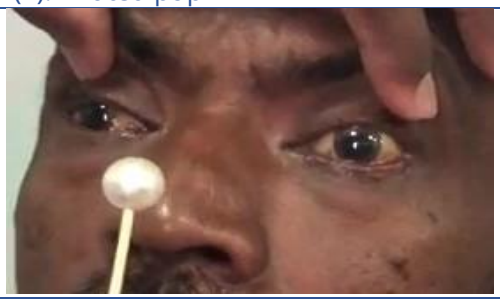
bilateral third and fourth nerve palsy with a WEBINO (Wall-eyed Bilateral Internuclear Ophthalmoplegia), His visual acuity and fundoscopy were normal. The rest of his cranial nerves were normal. He had truncal ataxia, falling to the right side while walking. He had bilateral past-pointing and dysdiadochokinesia, as well. His power was Grade 5 in all four limbs.

(1): Bilateral ptosis (3rd nerve nucleus)



(2): Dilated pupil

(3): Primary gaze exotropia



(4): Failure of convergence & intorsion (4th nerve)

(5): Failure of adduction of right eye with abduction nystagmus of left eye (Right INO)

(6): Failure of adduction of left eye with abduction nystagmus of right eye (Left INO)

Figure 1: (1) – (6) Bilateral internuclear ophthalmoplegia with vertical gaze palsy, loss of convergence and loss of intorsion

He had a normal full blood count with white blood cells being 6.25 x 10^3 /uL, haemoglobin 11.1 g/dL and platelets 214 x 10^3 /uL. He had an elevated ESR of 40mm/1st hour and a CRP of 60 mg/L. His chest X-ray was normal. HIV screening and melioidosis antibody tests were negative.

He was started on aspirin, clopidogrel and atorvastatin. His MRI brain confirmed multiple infarcts of the brainstem, bilaterally, with hemorrhagic transformation of a left thalamic infarct and clopidogrel was omitted while aspirin was continued.

MRI Brain (Figure 2) showed patchy areas of T2/FLAIR high signal intensity demonstrating restricted diffusion in DWI/ADC images in the left dorsomedial thalamus involving

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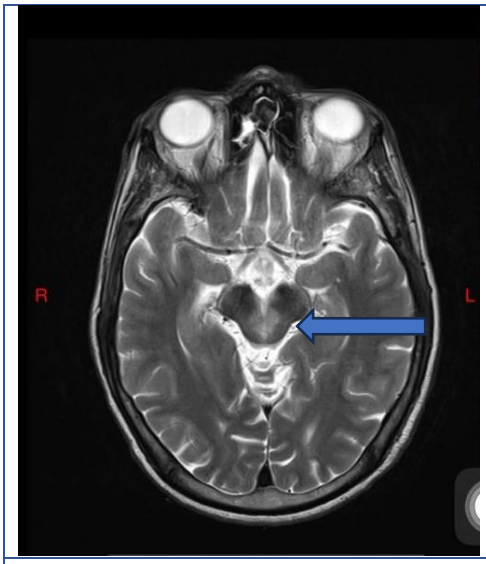
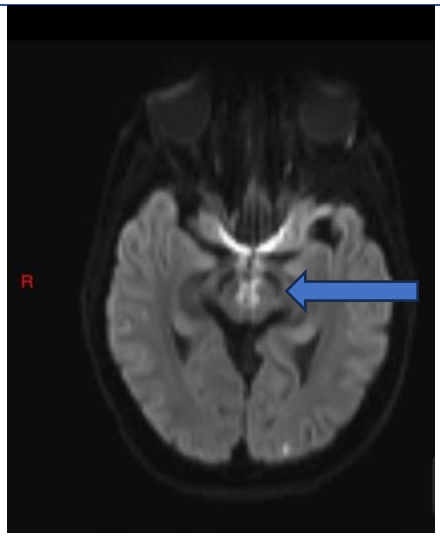
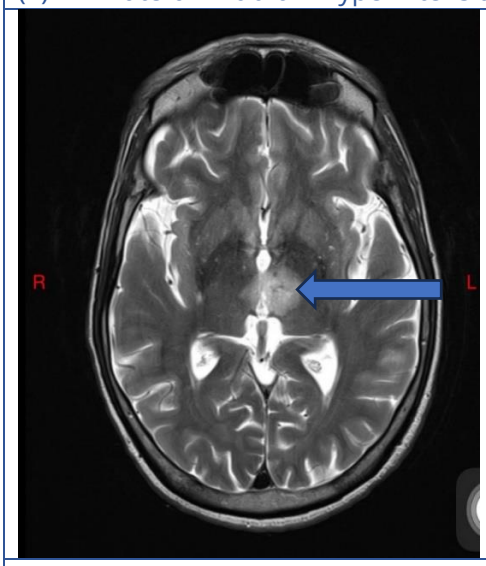
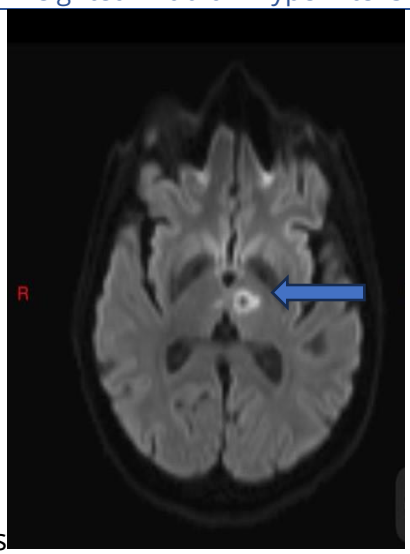
bilateral peri-aqueduct grey matter (left>right) extending to the midbrain. Blooming artefacts in SWI were seen in left thalamus suggestive of a haemorrhage. Similar areas were seen in the left occipital lobe and bilateral cerebellar hemispheres demonstrating a diffusion restriction. MRA and MRV failed to show AV malformations, aneurysms or venous sinus thrombosis.





(1) T2 Bilateral midbrain hyperintensities Diffusion weighted midbrain hyperintensities





(2) T2 Bilateral thalamic hyperintensities DWI – Acute thalamic infarction with left hemorrhagic transformation

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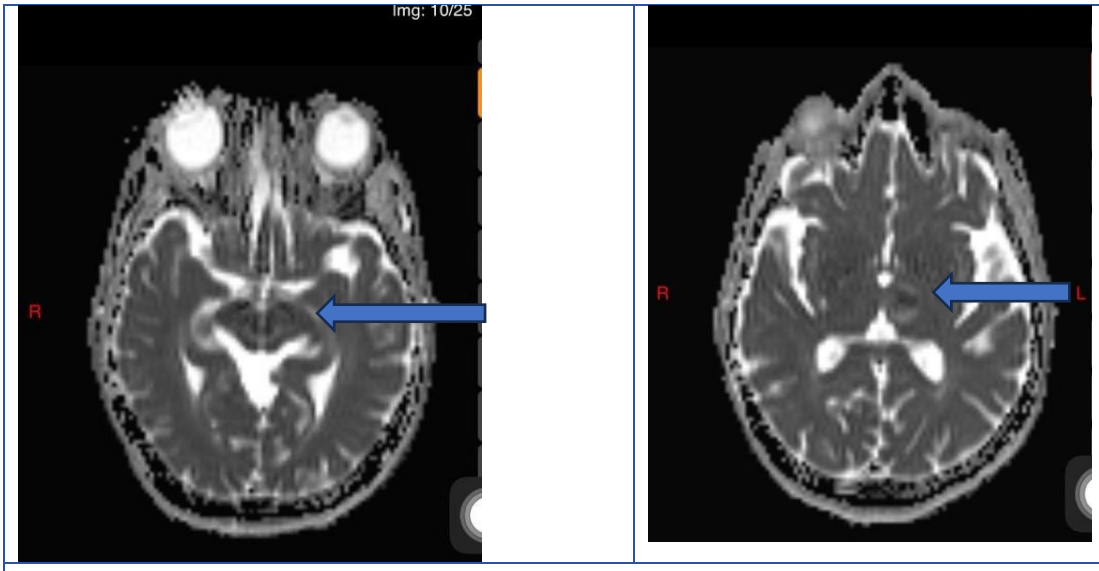

(3) ADC signal drop over midbrain and thalami – indicative of stroke

Figure 2: (1) – (3) MRI Brain

Three days later, while in the ward, he developed a fever spike of 100.8 F with chills and rigors. His blood culture became positive for the Gram-negative bacillus, *Enterobacter cloacae*, within 11 hours of incubation. He was commenced on intravenous meropenem. Subsequent echocardiogram showed an 8 X 9 mm vegetation attached to the anterior mitral valve leaflet (Figure 3). He fulfilled Duke's criteria for a definite diagnosis of infective endocarditis.

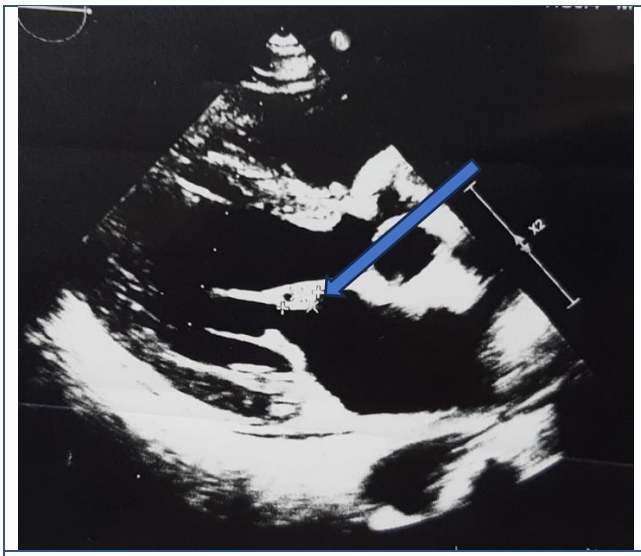

Figure 3: 2D ECHO showing an AMVL vegetation.

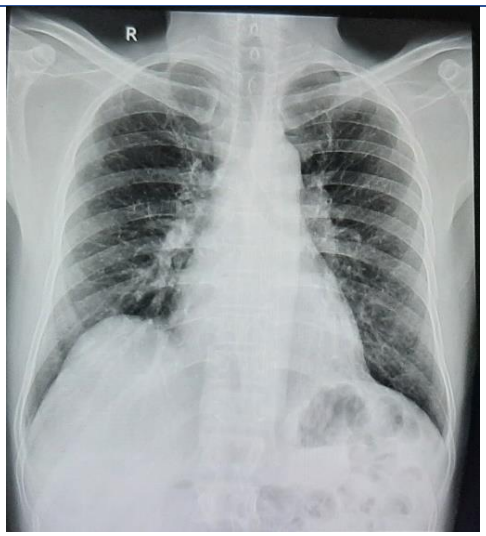

Figure 4: Chest-X ray of the patient

He made good progress and by the end of the second week his fever subsided and the size of the vegetation reduced to 2.6 X 3.5 mm, hence he was not considered for surgery. He was treated with IV antibiotics for six weeks. There were no further embolic phenomena.

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Discussion

When trying to localize the lesion in our patient who had bilateral ptosis, the presence of dilated pupils made ocular myopathies and neuromuscular junction disorders like myasthenia gravis unlikely. Although botulism and Krait bite were close considerations, he did not have a progressive descending paralysis with involvement of bulbar or respiratory muscles or abdominal pain.

The presence of complex ophthalmoplegia was suggestive of brainstem syndrome. Wernicke's encephalopathy was a possibility given the low level of consciousness and history of heavy alcohol consumption. Other differentials were brainstem stroke, demyelination including Bickerstaff encephalitis or a tumor. The absence of pyramidal signs was against Bickerstaff encephalitis. The intact reflexes were against Miller-Fischer Syndrome.

Once the MRI revealed multiple infarcts, an embolic stroke was suspected. WEBINO was due to infarcts involving the bilateral medial longitudinal fasciculus and pre-tectum supplied by perforating branches of the posterior cerebral artery [4]. The bilateral ptosis, dilated pupil and loss of intorsion were attributed to infarcts of the third and fourth nerve nucleus in the upper and middle part of the midbrain [5].

His only risk factor for atherosclerosis was heavy smoking. His heart rate on admission was regular. However, a 24 Hour Holter was planned to exclude paroxysmal atrial fibrillation. He did not have a displaced apex to suggest dilated cardiomyopathy with intracardiac clot formation. With the absence of a constitutional prodrome and only a soft grade 1 mitral regurgitation murmur, infective endocarditis was considered a less likely possibility.

It was only after three days of inward stay that he developed his first fever spike with chills and rigors. The other notable fact was that his blood culture became positive for an uncommon microbe – *Enterobacter cloacae.* Due to its rarity, evidence for its management was lacking. This non-HACEK variety of Gram-negative endocarditis is usually seen in intravenous drug users, recent hospital admission and prosthetic intracardiac devices, none of which were applicable in our patient [6]. *E. cloacae* endocarditis commonly presented with fever, sepsis, shock and immunologic phenomena, followed by heart failure [7]. Compared to *Staphylococcus aureus*, gram negative bacteria are less frequently implicated in septic emboli [8]. However, our patient had an embolic phenomenon on presentation.

Gram negative endocarditis is associated with grave sequelae such as valvular perforation or destruction, atrial thrombi, pericarditis, and myocarditis [9]. A prolonged course of antibiotics in combination with cardiac surgery is recommended in Gram negative endocarditis, particularly with left sided involvement [9]. Neurologic complications are seen in up to 40% of patients with infective endocarditis [9].

Intracranial mycotic aneurysms (ICMA) involving the distal middle cerebral artery are those most frequently seen in endocarditis. Clinical features are variable and include

headache, altered sensorium and focal neurologic deficits. Symptomatic cerebral emboli often, but not always, precede the discovery of an ICMA. (9) CT or MR angiography are recommended in such situations. MRA in our patient revealed multiple emboli confined to the posterior circulation in the absence of an aneurysm. Medical therapy is adequate for resolution of an ICMA [9]. Complications of embolization into the cerebral arteries include concomitant meningitis, intracerebral abscess formation and hemorrhagic transformation [10].

Vegetations are a mass of fibrin, platelets, and bacteria. The fibrin protects the bacteria from innate immune defenses hence requires prolonged treatment. This may be overcome by antiplatelets and fibrinolytics. However, as embolic infarcts are at increased risk of hemorrhagic transformation, there is a therapeutic dilemma to use antiplatelets or anti fibrinolytics. Reliable evidence for the use of these agents in endocarditis is still lacking [10]. A clinical conundrum exists when stroke is the presenting feature of occult infective endocarditis as thrombolytic therapy with r-tPA and anticoagulation increases the risk of hemorrhagic transformation and mortality [2].

The greatest risk for embolic phenomena is seen with large vegetations (>10mm) and involvement of the anterior mitral valve leaflet [11]. The persistence of a vegetation after systemic embolization may be considered an indication for surgery. In this patient, medical management with intravenous antibiotics resulted in clinical improvement and reduction in the size of the vegetation after two weeks of intravenous antibiotics.

In a review of patients' prognosis in *E. cloacae* endocarditis, clinical cure was noted in 75% while overall mortality was 30% [7]. Mortality is higher in those with neurologic complications than those without [12].

Conclusion

Our report aims to raise awareness about this rare clinical presentation of endocarditis without febrile prodrome or constitutional symptoms. We highlight the fact that we need to exercise caution with thrombolytic and antiplatelet therapy in strokes due to a higher risk of haemorrhagic transformation and mortality when associated with endocarditis. It also aims to revisit the characteristics and prognosis of non-HACEK Gram-negative endocarditis.

Consent for publication

Consent was obtained from the patient and family.

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