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| **TITLE OF CASE** |
| Severe stridor and profound weakness after Cerebral Malaria |
| **AUTHORS OF CASE *Please indicate corresponding author by \*(after the author’s name)*** |
| Charlotte Fuller, Gavin Wooldridge\*, Alice Liomba, Stephen Ray |
| **SUMMARY *Up to 150 words summarising the case presentation and outcome*** |
| Cerebral malaria (CM) is defined by the World Health Organisation as coma (Blantyre Coma Score (BCS) 2 or less) in a patient with *Plasmodium falciparum* parasitaemia and no alternative cause of coma identified. Mortality is approximately 15 - 30% in African children[1] and up to a third of survivors have neurological sequelae[2]. We present a patient with severe stridor and prolonged profound weakness during an intensive care admission with CM. These complications initially presented a diagnostic dilemma in our limited resourced setting. The stridor failed to improve with empiric steroids and a subsequent opportunistic ENT consult diagnosed dystonic vocal cords. The weakness was so profound that the patient was unable to lift his head during the acute illness. The child received intensive physiotherapy, and at one month follow up, the stridor and weakness had resolved. |
| **BACKGROUND *Why you think this case is important – why you decided to write it up*** |
| Cerebral malaria (CM) carries a huge global disease burden, with 500,000 children affected annually despite significant reduction in incidence over the last 20 years[3]. CM is diagnosed by *Plasmodium falciparum* parasitaemia on peripheral blood film in patients with unrousable coma not attributable to any other cause. Sequestration of parasitised erythrocytes in the cerebral microvasculature can cause severe brain swelling in CM. If persistent, this leads to midbrain compression, respiratory arrest and death[4]. As access to intensive care in resource-limited settings increases[5,6], more children may survive severe cerebral oedema with resultant sequelae, as mechanical ventilation could theoretically support failing respiratory function until oedema resolves[4]. We present a patient with severe stridor post-extubation and profound weakness during an intensive care unit (ICU) admission with CM. These complications initially presented a diagnostic dilemma in our low resource setting. However, our case was recruited into an ongoing interventional clinical trial investigating whether ventilation or hypertonic saline reduces mortality from CM, therefore we had unique access to a broad range of investigatory modalities to aid diagnosis. We report the first case of dystonic vocal cords and prolonged central hypotonia following CM in a Malawian child. |
| **CASE PRESENTATION *Presenting features, medical/social/family history*** |
| A 6-year-old Malawian boy presented to his local health clinic with a two-day history of fever and generalised tonic-clonic seizures. Malaria was diagnosed by rapid diagnostic test and he received intramuscular artesunate, ceftriaxone and diazepam. As seizures persisted he was taken to another clinic and given a further dose of diazepam, along with intravenous artesunate, benzylpenicillin and gentamicin. He remained deeply unconscious (BCS 0) and was referred to the local mission hospital. He received 3 days of intravenous artesunate and ceftriaxone before transfer to the tertiary paediatric centre.  Upon arrival, BCS was 1/5, with no posturing and regular respiration. Pupils were normal and cranial nerves intact, apart from a left conjugate gaze deviation on passive head movement. Tone and deep tendon reflexes were normal throughout, except plantars were upgoing bilaterally. Malaria parasites were present on blood film, glucose was normal, packed cell volume was 23% and lactate 4 mmol/L. Retinopathy-positive CM was confirmed, and he was recruited into the interventional trial. The MRI brain (see figure 1) revealed significant cerebral oedema which persisted on MRI over the subsequent 48 hours. He was then randomised to immediate ventilation. Intubation with an age-appropriate sized endotracheal tube (5.0mm, cuffed) was uneventful and he was sedated. Lumefantrine-artemether and intravenous fluids (5% dextrose and Ringer’s Lactate) were continued, including ceftriaxone to complete a 7 day course. A blood culture was taken and Amikacin introduced on Day 4 during a febrile episode, suspected to be linked to a local ICU outbreak of multi-resistant *Klebsiella Pneumoniae.* This was confirmed by its growth on serial peripheral blood cultures and Amikacin was continued for 9 days until the bloodstream was sterilised (see investigations).  He was extubated on day 4, but immediately developed severe biphasic stridor. Despite intravenous dexamethasone and adrenaline nebulisers, he required emergent re-intubation 4 hours later. The same size endotracheal tube passed easily through the cords, with no significant erythema or oedema visualised upon laryngoscopy. After 24 hours of dexamethasone, extubation was once again trialled. The stridor was present at rest, occasionally severe and biphasic, but a second re-intubation was avoided. |
| **INVESTIGATIONS *If relevant*** |
| **Blood results on admission to tertiary centre (Day 1)**  **Electrolytes:** Sodium 145mmol/L, Calcium 1.99mmol/L, Potassium 2.9 mmol/L,  Magnesium 0.75 mmol/L, Urea 4.9 mmol/L  **FBC:** WBC 2.1 x 109/litre, Hb 6.8g/dl, Platelets 170 x 109/litre, MCV 82.4 dL/red cell  **Malaria Parasites**: 1+, cleared parasites at 18 hours  **Blood Gas** (after first intubation):pH 7.54, pCO2 25.8mmHg, pO2 74mmHg, HCO3 22.1mmol/L, lactate 0.6mmol/L  **Microbiology**  **Blood cultures** – Day 1: no growth. Day 4 and 5: *Klebsiella Pneumoniae* resistant to ceftriaxone, sensitive to Amikacin and Meropenem. Day 10: No growth  **LP** (Day 1) – CSF: WBC 0 x 106 cells/L, RBC 1 x 106 cells/L, Protein 4.3 mg/dL, Glucose 0.49 mmol/L. No Growth  **HIV** RDT (Day 6) - Negative  **Imaging and electrophysiology**  **EEG** – Day 1: Moderate to severe non-specific encephalopathy with epileptiform discharges  Day 2 & 3: Diffusely slow EEG associated with encephalopathy. No epileptiform discharges.  **Transcranial Doppler**: Day 1: Bilateral middle cerebral artery flow velocities 3-4 SD below age and gender normal values.  **MRI**: Day 1-3: Moderate brain swelling (see figure 1)[7]. Day 4: improvement of oedema.  Day 28: resolution of swelling with mild cerebral atrophy. |
| **DIFFERENTIAL DIAGNOSIS *If relevant*** |
| Post-extubation stridor is commonly suspected; often due to local inflammation and laryngeal oedema secondary to the endotracheal tube or suctioning [8]. Flexible nasolaryngoscopy ruled out supraglottic pathology e.g. oedema.While the subglottic region could not be visualized here, the ease in which serial endotracheal tubes of equal, age-appropriate, size were inserted during intubation makes subglottic pathology (e.g. oedema, stenosis) less likely. Although rare, recurrent laryngeal nerve (RLN) palsy is a well described complication of intubation resulting from direct nerve injury via arytenoid joint subluxation, tube compression of RLN blood supply or neck hyperextension [9,10]. However, this is nearly always unilateral, and laryngoscopy here revealed fixed bilateral vocal cord adduction. Peripheral nerve damage was also considered but gross cranial nerve examination (central uvula) was normal. Underlying anatomical variations, such as laryngomalacia and vocal cord papillomas were excluded via endoscopy.  Weakness is a common presenting manifestation of severe malaria[11]. This patient’s weakness, however, was profound and persistent leading to consideration of other diagnoses.  Poor oral intake before presentation, coupled with increased ADH production from brain injury, can cause electrolyte imbalance, however this patient had a mild hypokalaemia only. Infections such aspolio, enterovirus and botulism cause profound weakness and do occur in areas of Malawi due to poor vaccination uptake. However, the natural history was not suggestive of polio or botulinism. Relevant diagnostics were unavailable in real-time, but blood and CSF underwent PCR analysis for 13 pathogens, including Enterovirus, HSV1 and HSV2, CMV, VZV, *S.pneumoniae, H.influenzae, N.meningitidis, M.tuberculosis, E.coli, S.agalactiae, K.pneumoniae, Salmonella spps.* at a later date as part of a parallel aetiological study, all of which were negative. Inflammatory causes including acute disseminated encephalomyelitis, transverse myelitis and Guillain-Barre syndrome (GBS) were considered. Features of demyelination were not present on MRI, and although a raised CSF protein might support a GBS diagnosis, there was no ascending weakness.  This patient was critically unwell for a prolonged period due to CM complicated by Klebsiella pneumoniae bacteraemia - likely hospital-acquired in light of a sterile blood culture on admission and a known klebsiella outbreak on ICU during the patient’s stay. Prostration following CM is common, particularly with a superadded bacteraemia. However, persistent critical weakness leading to poor head and shoulder girdle control, greater than two weeks after acute illness, is not described in such a profound nor prolonged fashion. |
| **TREATMENT *If relevant*** |
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| **OUTCOME AND FOLLOW-UP** |
| Stridor and profound global weakness persisted during this patient’s early convalescence. Whilst in ICU, BCS remained 3/5 with minimal spontaneous and antigravity movements. Post extubation, he was hypotonic, unable to lift his head and power was 1/5 and 3/5 in his lower and upper limbs, respectively. Reflexes were normal with down-going plantars and no clonus. A neurology review noted a normal cranial nerve examination with a central uvula. Due to the presence of leak before each extubation (without laryngeal oedema), an ENT opinion was opportunely sought from a visiting consultant. A flexible nasal endoscopy revealed bilateral vocal cord adduction dystonia.  He was transferred to the ward on Day 9 for daily physiotherapy. The stridor resolved on day 11 but he was unable to vocalise until day 13. He was discharged on Day 14 with significant neurological sequelae. He was alert but partially blind, with an expressive aphasia although able to swallow. He remained hypotonic with poor head control and gross generalised weakness, rendering him unable to sit unsupported or feed independently. Weekly physiotherapy continued in the community, and at one month follow up he had fully recovered, with an entirely normal neurological examination including vision, hearing, speech, cranial nerves, tone, power, reflexes, co-ordination and gait. |
| **DISCUSSION *including very brief review of similar published cases (how many similar cases have been published?)*** |
| CM is a leading known infectious cause of neurodisability in African children. Sequelae are varied, from paresis, cranial nerve palsies and blindness, through to cognitive, behavioural and seizure disorders[12]. To our knowledge, this is the first formal description of vocal cord dystonia and stridor, in conjunction with profound and prolonged central hypotonia, complicating cerebral malaria.  While failed extubation is often attributed to local airway pathology, neurological impairment is an important consideration. Up to 70% of children who fail extubation have either an acute, or a history of, brain injury; only a small proportion of these have an identifiable airway pathology on diagnostic laryngoscopy [12]. CNS injury, coupled with pharyngeal hypotonia, can cause unpredictable physiological responses to the airway leading to extubation failure [13- 15]. Neurogenic inspiratory stridor can result from vocal cord abductor paralysis, laryngospasm or laryngeal muscle dystonia[16]. In our case, direct laryngoscopy revealed vocal cord adductor dystonia. Nasal endoscopy is limited to supra-glottic assessment, and in the absence of tracheoscopy we cannot definitively exclude subglottic pathology. However, the ease in which serial endotracheal tubes of equal, age-appropriate, size were inserted during intubation makes subglottic pathology (e.g. oedema, stenosis) less likely. This valuable information adds further weight to our postulated diagnosis; that vocal cord dystonia, as directly visualized, was the cause of this child’s severe stridor. Laryngeal dystonia is usually a chronic presentation described in conditions such as Cerebral Palsy and Multiple System Atrophy[17-19]. Acutely, it can be medication induced [20]. The most likely pathogenesis in our case is acute brain injury from CM.  Profound weakness is a hallmark of severe malaria[11], but the pathogenesis of this is poorly understood. We know that sequestration of parasitised erythrocytes within the cerebral vasculature and the associated brain swelling contribute to the comatose state in CM[6]. This is likely to have led to acute brain injury in our case, with profound weakness as a key consequence. However, sequestration has been demonstrated in other organs such as the heart, lungs and gut[21]. One could speculate that generalised weakness may be due to sequestration within the vasculature supplying muscles involved in central motor functions such as swallowing and airway maintenance; though this is not described in the literature. Although prostration is common in CM, persistent critical weakness leading to poor head and shoulder girdle control for such a long period following the acute illness, without resultant spasticity, has not been described before. This child also had a concurrent *Klebsiella Pneumoniae* bacteraemia. It remains possible that enterovirus, a known cause of acute flaccid paralysis, could have caused this child’s weakness. While systematic PCR pathogen detection was undertaken for 13 organisms, this was only completed on CSF and blood samples. Enterovirus may have been below the limit of detection for the CSF PCR. Respiratory PCR, where diagnostic yield is greater, was not undertaken. We therefore cannot definitively exclude co-infection as an explanation of these symptoms. However, MRI evidence of significant cerebral oedema with brain stem compression would be in keeping with a neurological origin.  In summary, we suspect that CM and associated acute brain injury led to vocal cord adductor dystonia and profound weakness in our case. First-line management of post-extubation stridor often includes steroid administration due to its success in viral laryngotracheobronchitis[22-25]. Yet, this did not achieve resolution in our case, triggering further investigation. Fortuitously, an ad hoc laryngoscopy formally diagnosed the vocal cord abnormality In the absence of a laryngoscopy, as is more typical in the resource limited setting, one must systematically consider a wide spectrum of causes for acute stridor. In our case, the stridor resolved two weeks into acute illness and the persistent profound weakness resolved with regular outpatient physiotherapy. This is the first description, to our knowledge, of both stridor and profound weakness as sequelae of cerebral malaria. |
| **LEARNING POINTS/TAKE HOME MESSAGES *3*** ***to 5 bullet points*** |
| * Cerebral Malaria (CM) carries a high rate of neurological sequelae, including a wide spectrum of manifestations. * Laryngeal dystonia and profound weakness can occur after acute CNS injury, but to our knowledge, this is the first described case after CM. * Intensive physiotherapy led to a full recovery of profound weakness in our case and should be offered to similar cases in the tropics. * Pragmatic guidance for the diagnostic approach to post-extubation stridor in the resource-limited setting is required. |
| **REFERENCES *Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)*** |
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| **Figure captions** |
| Figure 1. MRI Brain showing significant brain swelling secondary to cerebral malaria |
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