Look like Miller Fisher’s Syndrome but not: A Case of Bilateral Cranial Nerves Paralyze as The Clinical Manifestation of Rhino-Orbital-Cerebral Mucormycosis

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1. Abstract
Rhino-orbito-cerebral mucormycosis (ROCM) as a rare but life-threatening fungal infection always resulted in unilateral clinical signs, which included ptosis, proptosis, periorbital swelling, facial swelling and dysesthesia. However, we described a rare bilateral invasive ROCM in a young male with newly diagnosed diabetic mellitus accompanying diabetic ketoacidosis. The patient at first was misdiagnosed as Miller Fisher’s Syndrome because of bilateral cranial nerves paralysis (including II, III, VI) involved. We realized the presence of ROCM until next-generation sequencing (NGS) and fungal smear and fluorescence staining confirmed the presence of Rhizopus arrhizu in cerebral spinal fluid (CSF). Although the effective anti-fungal therapy was early initiated, the patient rapidly progressed into cerebral hemorrhage secondary to cerebral infarction, which resulted into brain herniation. This case indicated that the clinicians should consider the presence of ROCM when the bilateral cranial nerves paralysis and cerebral hemorrhage were the first clinical presentations.

2. Introduction
Mucormycosis is a rare and opportunistic fungal infection with high mortality rate, which is the next commonest fungal pathogens to Aspergillus [1]. Since the emergence of Coronavirus Disease 2019 (COVID-19) pandemic, the prevalence of mucormycosis was becoming more and more high, especially in India, who witnessed the mucormycosis superinfection among COVID-19[2]. Rhino-orbito-cerebral mucormycosis (ROCM) was still the most common form of mucor infection in patients without [1, 3, 4] or with COVID-19[2]. The most common manifestations of ROCM included ptosis, proptosis, periorbital swelling, facial swelling and dysesthesia and black necrotic area, especially for unilateral signs [5]. Although there was once a case report about bilateral central retinal artery occlusion in a post-COVID ROCM [6], the most visual manifestations of COVID-associated ROCM were unilateral light perception accompanying with ophthalmoplegia because of its angio-invasive ability and subsequent thrombosis [7].

To our limited knowledge, to date, there was no case report about bilateral cranial nerves involved in non-post-COVID ROCM. Here, we described an unusual case of invasive ROCM in newly diagnosed diabetic patient with diabetic ketoacidosis where bilateral cranial nerves paralysis were the first presentations of the disease. In addition, the patient rapidly suffered from cerebral hemorrhage secondary to cerebral infarction and rapidly progressed and deteriorated into brain herniation.
### 3. Case Presentation

A 25-year-old man without any medical history, was admitted to the critical care department of Shandong Province Hospital, complaining about diarrhea and general fatigue of 10 days’ duration and sudden painless loss of vision in his both eyes with drooping of both upper eyelid for 2 days. However, he denied the presence of headache, fever and facial pain during the whole process. On the admission to our department, he was conscious. His vital signs were stable without any mechanical and medical supports. Physical examinations of cardiovascular, respiratory as well as abdominal systems were normal. There was no light perception in both eyes. And extraocular motility in both eyes were restricted in all directions with complete bilateral ptosis. Pupils of both eyes were mid diluted and fixed as well as nonreactive to direct and indirect light reflex. Fundus examination was not performed. There were other positive neurological examinations, which included dysarthria, dysphagia and bilateral hyporeflexia. All these positive neurological examinations indicated that bilateral cranial nerves (II, III, VI) were involved. Babinski sign, stiff neck and meningeal irritation were not elicited.

Lab examination showed white blood cells (WBC) count of $7.89 \times 10^9/l$ (3.5-9.5109/l), neutrophils percent 80% (40-75), hemoglobin A1c (HbA1c) of 11.7 (4-6), random blood sugar of 14.2mmol/l (3.9-6.1), and procalcitonin (PCT) 0.42ng/ml (0-0.05). Blood culture was negative. T2-weighted magnetic resonance imaging (T2WI) and diffusion weighted imaging (DWI) of brain showed hyperintense lesions in cerebral pons (Figure 1B) (indicating central pontine myelinolysis (CPM) exclude from brain stem encephalitis), bilateral frontal lobes (Figure 1A) (indicating acute cerebral infarction) as well as the thickening mucosa of bilateral maxillary sinus (Figure 1C), ethmoid sinus and sphenoid sinus (indicating nasosinusitis) (Figure 1D). A magnetic resonance angiography scan of the brain was normal (Figure 1E). Thus, the empiric treatments with acyclovir, immunoglobulin and piperacillin/tazobactam were initiated, which covered the presumption of CPM, possible bacterial infection and Guillain-Barré syndrome (GBS).

On 3rd day of admission to our department, lumber puncture revealed clear fluid with an opening pressure 195 mmH2O (80-180 mmH2O), glucose of 8 mmol/l (2.8-4.5mmol/l), WBC count of 270/ml (0-5/ml) (60% monocytes) and protein content of 0.9g/l (0.15-0.45g/l). The routine infectious disease screen of CNS using CSF included PCR against viruses (EBV (Epstein-Barr virus), HSV- 1 (herpes simplex virus type1), HSV-2 (herpes simplex virus type 2), CMV (Cytomegalovirus), Gram and acid-fast staining, bacterial and fungal culture and next-generation sequencing (NGS). But above those results except for NGS were negative. The autoantibody screen in blood and CSF for GBS were negative. At the midnight of 3rd day to our department, he was intubated and mechanically ventilated because of acute respiratory failure while he was still conscious. On 5th day, NGS results just demonstrated 233 unique sequence reads of Rhizopus arrhizus in CSF, covering 91.76% of the nucleotide sequences. According to the results of NGS, acyclovir and immunoglobulin were discontinued. Liposomal amphotericin B and Posaconazole were immediately initiated. Lumber puncture was performed again to obtain CSF for immediately fungal smear and fluorescence staining. At the same time, nasal swab was also performed for fungal smear and fluorescence staining. Fortunately, wide angle of non-dichotomous branching (nearly 90 degree) and greater diameter hyphae were detected in nasal swab (Figure 2A) and CSF (Figure 2B) smear under microscope by fluorescence staining, indicating mucormycosis. On 8th day of admission to our department, his condition suddenly deteriorated, which included no spontaneous respiration, deep coma (Glasgow Coma Score, GCS 3) and enlarged pupil diameter (7mm) than first admission to hospital. Plain CT (computer tomography) brain imaging showed right frontal lobe hemorrhage (Figure 3A&C) broken into the ventricles (Figure 3C) and subarachnoid space (Figure 3B). His parents refused to receive any further treatment and strongly requested to voluntary discharge after trepanation and drainage. The patient died eventually after 3 hours of discharge.
Figure 1: MRI and MRA image of brain

A&B: DWI image showing hyperintense in brainstem (A) and bilateral frontal lobe (B).

C&D: T2W image showing mucosal thickening in bilateral maxillary sinus (C, white arrow), bilateral ethmoid sinuses (D, white arrow) sphenoid sinus (D, white arrow), and air-fluid level (C, blue arrow) in the left maxillary sinus and sphenoid sinus (D, blue arrow)

E: MRA of brain showing the intracranial vessels was normal.

Figure 2: Hyphal morphology in Rhizopus arrhizus from nasal swab (A) and CSF (B) detected via fluorescence staining.

A: The picture illustrated the wide, non-septate and 90° branching angle of hyphae from nasal swab.

B: The picture illustrated the wide, non-septate and 90° branching angle of hyphae from CSF

Figure 3: The plain computed tomography finding of brain on 8th day of admission to our department

A &B: The plain CT image showed hyperintense in left frontal lobe (A) and subarachnoid space (B)

C: The plain CT image showed hyperintense in left frontal lobe (black arrow), subarachnoid space (white arrow) and ventricles (blue arrow).
4. Discussion

At first, Miller Fisher’s syndrome (MFS), Bickerstaff brainstem encephalitis (BBE) and botulism were suspected according to the presentations as well as medical history. MFS as the variant of GBS (Guillain-Barré syndrome) presented with bilateral ophthalmoplegia, areflexia and ataxia [8]. Bilateral dilated (fixed) pupils, ptosis, and ocular motor dysfunction occasionally occurred to MFS at first, according to his clinical presentations as well as neurological physical examinations. But, the results of CSF questioned the possible diagnosis of MFS because of the absence of albumin-cytological dissociation in CSF. The results of CSF revealed the elevated levels of WBC and protein. In addition, the image of brain MRI, including bilateral frontal lobe infarction and CPM, suggested the involvement of central nervous system, which further questioned the diagnosis of MFS. There was a case report that acute bilateral ophthalmoplegia was an unusual presentation of BBE [10]. Now, BBE and MFS were considered to be part of the disease spectrum, which share some same features, including antibody against GQ1b in the serum and albumin-cytological dissociation in CSF [11]. But, BBE affected central nervous system. Thus, the results of CSF denied the diagnosis of BBE. Acute bilateral ophthalmoplegia occasionally occurred to the patient with botulism [12]. However, CSF in botulism was normal [12], which excluded the diagnosis of botulism.

The elevated levels of WBC and protein in CSF indicated the presence of central nervous system infection. But, we did not conclude the possible infectious pathogen. Until the results of NGS as well as fungal smear and fluorescence staining (Figure 2A &B), we just realized the possible diagnosis of ROCM. To date, uncontrolled diabetes with or without diabetic ketoacidosis is still the most common predisposing factor for ROCM with or without post-COVID-19[2, 5]. Rhizopus arrhizus was the most frequently isolated causative Mucorales organisms of ROCM [4]. Consistent with previous reviews [3, 5], this patient had the predisposing factor (diabetes with diabetic ketoacidosis). Multiple reviews suggested that the most common presentations of ROCM included ophthalmoplegia, ptosis, as well as facial and ocular involvements [3, 5]. But these presentations were unilateral not bilateral. Thus, we did not consider the presence of mucormycosis before the NGS results.

Except for angio-invasive ability [1], Mucorales fungi also has the ability of direct tissue invasion or spreading beyond the paranasal sinuses [13]. Vascular invasion of Mucorales fungi indicated that fungus penetrated into the internal elastic lamina of vessel, then breach the endothelium, which resulted into infarction, hemorrhage, and tissue necrosis [4]. Direct tissue invasion referred to fugal spores depositing on the mucosa of the nasal turbinates, with subsequent invasion and progression to involve the paranasal sinuses, orbits, and intracranial structures [13]. It was accepted that Mucorales infection started in the nose and spread to the paranasal sinuses and orbit, and after invading the orbit, finally reached the central nervous system tissue [14]. MRI image (Figure: 1A-D) performed on admission to our department indicated bilateral frontal cerebral infarction and bilateral nasosinusitis, which included bilateral maxillary sinus, ethmoid sinus and sphenoid sinus. Thus, we speculated that bilateral frontal infarction was caused by the angio-invasive ability of Mucorales fungi. And bilateral acute ptosis, ophthalmoplegia and visual loss, which was also called orbital apex syndrome, could be explained by the ability of direct tissue invasion or spreading beyond the paranasal sinuses from Mucorales fungi. In addition, later cerebral hemorrhage further supports the diagnosis of ROCM because of angio-invasive ability of Mucorales organisms. Thus, ROCM need to be considered for a patient with predisposing factors, whose nasosinus and central nervous system were affected. Although early diagnosis and systemic antifungal therapy were initiated, the patient rapidly deteriorated and died.

5. Conclusion

Although bilateral cranial nerve paralysis as the manifestations of invasive ROCM rarely occurred, the clinicians should keep in mind for the presence of bilateral invasive ROCM for the patients in the status of diabetes mellitus with diabetic ketoacidosis, especially for the patients whose neurological dysfunctions could not be explained by other common diseases. In addition, the clinicians should be especially aware that cerebral hemorrhage occurred to the patient with ROCM, whose condition was rapidly deteriorated into brain herniation.

6. Acknowledgment

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7. Conflict of Interest Statement

All the authors declared that there were no conflicts of interest.

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