Clinical Case Reports

Case Report Open Access

# Clostridium Difficile-induced Delirium: The Great Neurologic Mimicker

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**Abstract**

We present a 85-year-old male with acute onset of agitation, left sided weakness and bowel and bladder incontinence, who was found to be *Clostridium difficile* positive where an extensive neurological work up ruled out stroke, seizure- and sleep disorders, leaving an atypical type of delirium, secondary to *Clostridium difficile* infection, as a rare complication of his *Clostridium difficile* infection.

## Introduction

*Clostridium difficile* infection is an infectious process of the large intestine resulting from the ingestion of bacterial spores that adventitiously colonize the bowel microenvironment following a change in the colonic flora by antibiotics or chemotherapeutic agents [1]. The bacterial spores release one of two toxins, *Clostridium difficile* toxins A/B, resulting in colonic mucosal necrosis, inflammation and pseudomembranes. The most common risk factor for *Clostridium difficile* colitis is the use of antibiotics, particularly clindamycin, ampicillin, amoxicillin and cephalosporins [2]. Other risk factors include patients >65-years of age, nursing home residents, patients with IBD and patients on proton pump inhibitor therapy [3]. Clinical manifestations include acute watery diarrhea that may or may not include blood or mucus; lower abdominal pain, fever, and leukocytosis [4]. Pseudomembranous colitis can also occur, manifesting as pseudomembranes and bowel wall thickening [5,6]. Fulminant colitis occurs in close to 2-3% of patients, presenting with a picture of toxic megacolon with significant colonic dilatation, atony and systemic toxicity [7]. However, a neurological symptom such as delerium and weakness has been rarely described especially as an initial presenting feature of *Clostridium difficile* infection.

## Case Presentation

An 85-year-old male with a past medical history significant for mild Parkinson's disease, hypertension, and Type II Diabetes, presents to the emergency department with acute onset of altered mental status with agitation and left sided weakness. Per the patient's wife, the patient reportedly began to exhibit violent movements of all extremities in the early morning while he was reportedly asleep; these movements were associated with loss of bladder and bowel incontinence with loose stools. The patient was unresponsive but did not experience any loss of consciousness. The entire episode lasted 10-15 minutes.

The patient had been admitted a month prior to this hospitalization for cellulitis and was treated with IV Cefazolin and Vancomycin. At that point, the patient was alert and oriented, cooperative with a normal neurological physical exam.

Family history was significant for Type II Diabetes Mellitus and Hypertension in the mother. Social History was significant for previous tobacco use, last use in 1984. The patient denied any use of alcohol or illicit drug use. Medications include Glipezide XL 10 mg PO BID, sitagliptin50 mg PO daily, Losartan 100 mg PO daily, Baclofen 10 mg PO TID, Carvedilol 25 mg PO BID and Latanoprost 1 drop right eye daily.

Upon presenting to the ED, his vitals showed a temperature of 97.7 F, blood pressure 158/84, pulse 74, respiratory rate 20 and oxygen saturation of 100% on room air. Initial laboratory values revealed WBC count of 6.3 k/µl, hemoglobin of 11.7 g/dl, hematocrit of 33.6%, and glucose of 147 mg/dl. A basic metabolic profile, including magnesium, calcium, phosphate, potassium and sodium were within normal limits.

Physical exam was significant for mild diffuse abdominal pain, normal CN I-XII, except for CN XI, with reduced left trapezius muscle strength (3/5). Strength 4/5 on right upper and lower extremities; 3/5 on left upper and lower extremities; decreased vibration and proprioception in bilateral lower extremities; no Babinski sign or hyperreflexia present; normal knee and ankle reflexes. Intact sensation bilaterally in upper and lower extremities.

Initial CXR in the ED showed mild left basilar atelectasis, however no pleural effusions, infiltrates or cardiomegaly. A non-contrast CT head was negative for hemorrhagic stroke (Figure 1). However, due to the patient's neurological deficits and risk factors, suspicions for stroke remain heightened. The patient was admitted to the medicine service and started on ASA 325 mg×1 dose, Atorvastatin 80 mg daily and IV fluids with normal saline at 100 cc/hr. Given that the onset of symptoms exceeded 4.5 hours, tPA was not given. Stool toxin assay and cultures were collected given the patient's history of previous antibiotic use loose stools upon presentation.

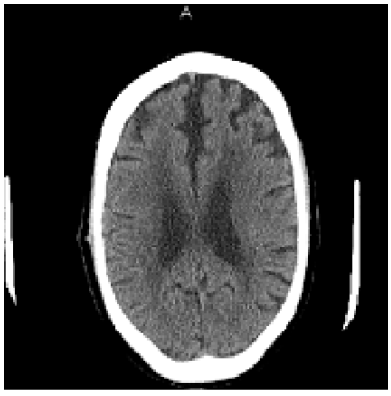

**Figure 1:** Head-CT without contrast, ruling out hemorrhagic stroke.

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**Received** October 21, 2013; **Accepted** January 23, 2014; **Published** January 25, 2014

**Citation:** Mehrzad R, Bravoco J, Mehrzad M (2014) Clostridium Difficile-induced Delirium: The Great Neurologic Mimicker. J Clin Case Rep 4: 338. doi:10.4172/2165-7920.1000338

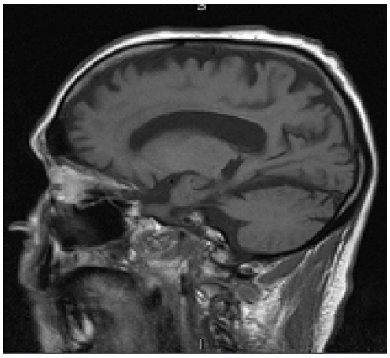

**Figure 2:** Brain MRI showed mild volume loss and microangiopathy, but no stroke, mass lesions or anyotherabnormalities.

An EEG was performed and showed diffuse theta background slowing with no epileptiform discharges, thus, not consistent with seizures. Brain MRI showed mild volume loss and micro angiopathy, but no stroke, mass lesions or any other abnormalities (Figure 2). *PCR for Clostridium difficile* toxin was found to be positive on the second hospital day.

The differential diagnosis included lacunar stroke secondary to cerebral angiopathy, other ischemic strokes, Transient Ischemic Attach (TIA), primary seizure disorder of tonic-clonic, septic encephalopathy, CNS vasculitis, hydrocephalus, dural sinus venous thrombus, epidural hematoma/expanding subdural hematoma, and classification or REM sleep behaviour disorder.

## Outcome

During the first two hospital days the patient's mental status was altered. He had wandering attention, difficulty speaking and recalling word, rambling with nonsense speech, restless and agitated. He was afebrile, but expressed mild abdominal pain and diarrhoea. Patient was found to be *Clostridium difficile* positive on stool cultures on hospital day two, and treatment with Flagyl 500 mg PO three times daily was started. After antibiotic treatment was started, particularly on hospital day three, there was a rapid improvement of the patient's mental status. He was more alert, cooperative and speech was profoundly more intelligible. The patient's agitation resolved completely. His left sided weakness improved and the patient was able to ambulate. The patient was discharged home with antibiotic treatment for a total of 10 days. Per recommendations of neurology, patient is scheduled follow up with an outpatient sleep study, which did not show any evidence of REM sleep behaviour disorder.

## Discussion

*Clostridium difficile* infection is an infectious process of the large intestine [8]. Clinical manifestations typically include acute watery diarrhoea that may or may not include blood or mucus; lower abdominal pain, fever, and leukocytosis [8]. Pseudomembranous colitis can also occur, manifesting as pseudomembranes and bowel wall thickening [9]. Fulminant colitis occurs in close to 2-3% of patients, presenting with a picture of toxic megacolon with significant colonic dilatation, atony and systemic toxicity [10]. Our patient presented with neurological symptoms secondary to his *Clostridium difficile* infection.

Delirium, which is described as a clinical phenomenon consisting of a constellation of symptoms, in conjunction with an underlying acute mental status change, is frequently discovered in hospitalized patients with acute illness [10]. It is a clinical syndrome with typically acute onset. The elderly are particularly affected, with nearly 11-25% affected during their respective hospital course [11]. The mechanism behind *Clostridium difficile* infection inducing delirium is complex and not fully understood. The presence of an infectious colitis induces the production of inflammatory cells, particularly chemotactic cytokines, such as IL-1, TNF-alpha, IL-6 and IL-8, which, acting as endogenous pyrogens, in turn lead to a pyrexic state, through the activation of receptors concentrated in the hypothalamus that activate downstream production of arachnidonic acid and finally prostaglandins, namely PGE2 [12]. Within the milieu of elevated basal body temperature, there is a disruption of neuronal cell signalling and dysregulation of neurohumoral homeostatic mechanisms, leading to an altered mental status [13]. In the setting of elderly patients, with an underlying baseline state of dementia quite possible, this can trigger the onset of delirium and present in an acute fashion [14]. Also, the presentation may be atypical, and can masquerade other neurological conditions such as TIA or stroke, with the presence of focal neurological deficits and acute onset of mental status changes [14].

Although confusion has been reported as a manifestation of any severe infection, including *Clostridium difficile* colitis [15], delirium and other neurological symptoms are unusual complications. Our case validates the difficulties of instituting an appropriate plan of medical management when these complications occur, given that the symptoms are often vague and could be misleading. Although few in number, there are studies that have described the association of changes in mental status and *Clostridium difficile* colitis. One particular study, reported altered mental status, similar to that of Thrombotic thrombocytopenic purpura (TTP) [16], associated with systemic infections such as *Clostridium difficile* colitis; other neurologic changes included aphasia, visual disturbances and paresthesias. In our case, the initial differential diagnosis was extensive, stroke and primary seizure disorder claiming the top spots in the lost of most likely causes of the patient's symptoms. As a result, this could have potentially resulted in treatment with tPA and/or anti-epileptic medications with possible adverse outcomes due to side effects affiliated with these interventions.

It is known that complications of this enteric bacterial infection are more substantial in patients with advanced age and underlying cognitive impairment and can serve as relative predictors for worse outcomes requiring increased level of care, more aggressive treatment and earlier surgical intervention [17]. Furthermore, a fulminant *Clostridium difficile* colitis could ultimately "trigger" a microangiopathic haemolytic anaemia and induce a significant decompensation in the mental status of the patient, particularly in those with co-existing cognitive dysfunction and neurological and psychiatric co-morbidities. However, anaemia was not identified as a complication in our patient and his mental state could therefore not be explained by this. Along the same vein, a separate study reported cognitive impairment as one of the risk factors for severity of *Clostridium difficile* associated disease (odds ratio 11.0, $P<0.01$), and that anticipating these signs may limit morbidity and mortality in these patients [18].

Given the acute presentation of mental status changes, along with a history of vasculopathy, TIA was considered as part of the differential diagnosis; however, the clinical course lasted beyond 24 hours from onset of symptoms, making this potential etiology less likely. In addition, an investigation was performed looking into other possible causes for this patient's acute altered mental status, including, but not limited to, hypomagnesemia, thiamine deficiency, hypothyroidism or trace element deficiency, but laboratory results were normal for

each of these possible etiologies. Furthermore, septic encephalopathy would have been a likely diagnosis, however the patient never met SIRS criteria, nor was a source of infection, except for *Clostridium difficile*, identified. However, this was an elderly patient with other comorbidities, so there is a possibility that this presentation was by chance and caused by another etiology than a hitherto described manifestation of *Clostridium difficile*.

Despite the high prevalence of *Clostridium difficile*-associated diarrhea in hospitalized patients, the utilization of isolation wards, in concert with proper antimicrobial technique on behalf of medical practitioners, have demonstrated significant benefit in reducing the incidence of *Clostridium difficile* infection and preventing possible complications. Furthermore, the implementation of antimicrobial stewardship is increasingly important as it pertains to care and treatment of the geriatric community and must be strictly adhered to [19]. However, despite the presence of guidelines that have been instituted for care and medical oversight of patients with documented *Clostridium difficile* infection and associated delirium, outcomes have not shown significant improvement and further demonstrate the need for proper prevention of this condition to avoid neurologic sequelae [20].

Fortunately, by identifying the *Clostridium difficile* infection and initiating appropriate antibiotic treatment, the neurological symptoms seem to be reversible, as observed in our patient. The aforementioned studies have provided some ancillary corroboration of similar clinical presentations and served as a springboard for future investigation [20]; however, there remains at the present time a paucity of evidence on this topic. This can be attributed to the purported rarity of neurologic findings that are associated with, and a consequence of, *Clostridium difficile* infection and its systemic nature.

Consequently, we believe it is important for clinicians to be aware and identify these rare but potential neurological complications of *Clostridium difficile* infection. We advocate the necessity of further investigations germane to this topic and stress the importance of obtaining a comprehensive history of recent antibiotic use, sick contacts and nursing home visits in elderly patients who present with symptoms of diarrhoea and altered mental status.

## Take Home Messages

- *Clostridium difficile* infection can present with a delirium-type clinical picture that shares many of the same features as purely neurologic diagnoses.
- By identifying the *Clostridium difficile* infection and initiating appropriate antibiotic treatment, the neurological symptoms seem to be reversible.
- Prognosis for patients with *Clostridium difficile*-associated disease is worse in the context of associated neurocognitive decline and acute mental status changes.
- The presentation of *Clostridium difficile* infection can be multisystem and must be diagnosed and treated promptly to obviate potential neurologic sequelae and poorer outcomes.

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