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Reversible transcortical motor aphasia induced by lithium

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Abstract

Transcortical motor aphasia is a unique form of aphasia characterized by an expressive aphasia with preservation of repetition; it is most classically associated with watershed infarcts of the Anterior Cerebral Artery (ACA) and Middle Cerebral Artery (MCA) territory. However, more recently, lithium toxicity has been reported as a cause of a transient, reversible transcortical motor aphasia which resolves with correction of the toxicity. We report a patient who presented with supratherapeutic lithium level of 2.8 mEq/L and typical systemic signs of toxicity including tremor and diaphoresis, with a transcortical motor aphasia despite no evidence of stroke on Magnetic Resonance Imaging (MRI). The aphasia and systemic toxicity completely resolved after the excess lithium was dialyzed. Though rare, language difficulties can be a manifestation of lithium toxicity and should be on the differential in patients taking lithium who develop these symptoms.

Keywords

lithium; aphasia; toxicology

Abbreviations

CHF: congestive heart failure; ACA: anterior cerebral artery; MCA: middle cerebral artery; CTA: computerized tomography angiography; MRI: magnetic resonance imaging

Introduction

A 59 yr old male presented by ambulance after having a four-day history of progressive worsening of his language noticed by his visiting nurse, described as “difficulty finding his words”. He also had noticed progressive worsening of tremor and was markedly diaphoretic. His past medical history was significant for Congestive Heart Failure (CHF), bipolar I disorder, and hyperlipidemia. He occasionally used recreational marijuana. His medications included lithium, quetiapine, trazodone, spironolactone, benztropine, simvastatin, and lisinopril.

The patient's vitals were unremarkable; he was afebrile, normotensive, and heart rate was 71. He was markedly diaphoretic and tremulous. His neurologic examination was significant for intact comprehension, impaired fluency, impaired naming, but spared repetition consistent with transcortical motor aphasia. Additionally, he had a postural and kinetic tremor bilaterally. The remainder of his

neurologic exam was intact, including cranial nerves, motor strength, sensory examination, and reflexes.

The patient's lab work revealed a markedly elevated lithium level of 2.81 mEq/L (therapeutic range: 0.5-1.2 mEq/L). His sodium level was 133 mEq/L and his creatinine, lactate and ammonia were within normal limits. Computerized Tomography Angiography (CTA) of the brain and neck revealed no acute hemorrhage, stroke, or large vessel occlusion. He was seen by nephrology and initially managed with intravenous fluids; however, due to his cardiac issues he was unable to tolerate the fluid load, and ultimately required hemodialysis. He underwent Magnetic Resonance Imaging (MRI) of the brain [Figure 1a,1b] to exclude stroke as an etiology of his presentation, which was negative for acute infarct or other causative lesion. His aphasia gradually improved over the subsequent days, and he was completely back to neurologic baseline within one week of presentation; lithium level at time of discharge was 0.13 mEq/L. The etiology of the lithium toxicity was not clear; he had no changes in renal function and had no intentional ingestion. Lithium was discontinued indefinitely and quetiapine was increased.

Discussion

Transcortical motor aphasia is a language disturbance which presents similar to a Broca's (expressive) aphasia in that patients have difficulty in expressive speech and impaired fluency, with relatively spared comprehension; however, in contrast to Broca's aphasia, repetition is completely intact. Transcortical motor aphasia has most classically been associated with watershed infarcts of the anterior cerebral artery and middle cerebral artery territory [1]. It has rarely been described in the context of lithium toxicity.

A fascinating element to this particular clinical presentation is the clearly focal nature of the patient's neurologic disturbance, in contrast to the well-known phenomenon of toxic-metabolic encephalopathy, which involves global disturbances of consciousness. Reversible focal neurologic deficits have been described in the past with both lithium toxicity and other toxic-metabolic derangements, most notoriously hyperglycemia, which has a predilection for causing hyperkinetic movement disorders; however, in these cases, MRI of the brain typically demonstrates abnormal signal in the basal ganglia [2]. It is unclear why a toxic disturbance would have a predilection to target such specific areas of the brain parenchyma, nevertheless, this phenomenon has been previously described despite the mechanism being unclear.

Lithium has been associated with reversible disorders of language in the past. In a case very similar to our patient, Katz and Packer described a patient with a transcortical motor aphasia in a patient with a bipolar disorder and a lithium level of 1.9 mEq/L [3]; the patient also had a history of CHF and was unable to obtain magnetic resonance imaging due to defibrillator, however, their patient also displayed a similar reversibility of symptoms. A reversible receptive (Wernicke's) aphasia, with impairment in comprehension and frequent paraphasic errors, has also been described in a patient with lithium toxicity and a level of 3.0 mEq/L [4]. Earlier cases have been described, without magnetic resonance imaging data, of patients with reversible aphasias with prominent word-finding difficulty and hesitancy in the context of lithium use [5,6]. In all the above cases, similar to our patient, the language deficits were completely reversible with the cessation of lithium and/or normalization of serum levels.

Lithium is a commonly used medication for the treatment of bipolar mania, and was FDA-pproved

Cavitary lesions appeared to be slightly increased, while a PET-CT excluded the presence of active infections, therefore the patients was not retreated. On the 23rd of August 2013 a CT images showed favorable evolution with presence of fibrosis (Fig 6).

Discussion

CPA designates a form of Aspergillosis that occurs frequently in patients with different respiratory pathologies (i.e. tuberculosis, sarcoidosis, COPD) [1]. Other conditions of immune deficiency can be associated with an increased CPA risk such as cirrhosis, diabetes and HIV infection [2]. CPA diagnosis can be difficult, particularly if neither a history of immune depression nor typical concomitant diseases are reported. In both cases here described, malnutrition was the mainly predisposing factor. Malnutrition-induced immune suppression is a major cause of morbidity and mortality in multiple susceptible patient populations. Apparently T dependent immune function was substantially normal in both patients, as evidenced the absolute CD4 and CD8+ cell count value in the normal range. Nevertheless malnourished patients may have altered T lymphocytes function, in particular malnutrition shifts the balance of pro-inflammatory Th1 versus anti-inflammatory Th2 cytokines and may therefore predispose to infection [3]. For example, malnutrition represents an independent risk factor for aspergillosis or other forms of zygomycosis in patients with hematological malignancy [4].

Diagnosis of CPA is often challenging, in particular in patients without classical risk factors for invasive fungal diseases and requires the combination of characteristics including radiological pattern (typically a new cavitary lesion), direct evidence of Aspergillus infection by culture (sputum and/or BAL) or an immunological response to Aspergillus [5]. BAL galactomannan is a reliable diagnostic marker with high sensitivity and specificity that should be routinely evaluated in the suspect of CPA, while serum galattomanan is typically negative [6]. In the first patient galactomannan on BAL was not performed and diagnosis was possible only on a repeated sputum culture, performed because of suspicious radiologic lesion. It is therefore suggested to request routinely both BAL cultures and galactomannan when suspicious lesions are observed otherwise diagnosis can be delayed.

Voriconazole is the treatment of choice of CPA, it is formulated as tablets or as a sulfobutyl-ether cyclodextrin solution for IV administration. The oral formulation has good bioavailability in the fed or fasted state and is preferred when it is possible. Voriconazole is effective [7] but has a narrow therapeutic range and displays multiple drug-drug interactions therefore requires expertise management. For all these reasons concomitant treatments should be carefully evaluated and periodic pharmacokinetic monitoring is advocated [8,9]. In the first patient here reported voriconazole was not effective due to an interaction with carbamazepine that led to significant reduction of voriconazole plasma levels. The duration of treatment is usually 4-6 months and it could be longer if the patient shows a slow response [2]. In the second case treatment with voriconazole was shorter than suggested by guidelines as the improvement of nutritional state was associated with disappearing of respiratory symptoms and radiological lesion.

In conclusion, patients with CPA can be admitted to internal medicine wards and diagnosis can be difficult for not expert clinicians, also management requires expertise due to possible drug-drug interactions and side effects.

in 1970. Although its mechanism of action is not clearly elucidated, it is known that lithium has multiple effects on signal transduction and gene expression in neural cells [7]. Lithium toxicity is a well-known and potentially serious complication of treatment; lithium has a narrow therapeutic index, and serum levels can be affected by multiple factors, including concomitant medications and renal function as well as volume status. Lithium is primarily excreted renally; dehydration, congestive heart failure, and certain medications such as Angiotensin-converting-enzyme (ACE) inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) can predispose patients to lithium toxicity [3,7,8]. Toxicity can be acute, acute-on-chronic, or chronic. The latter two forms occur in patients with prolonged lithium exposure and are associated with more severe symptoms due to decreased renal clearance [8]. At therapeutic levels, lithium can cause gastrointestinal symptoms, polydipsia, polyuria, weight gain, and hypothyroidism which may be clinical or subclinical [8]. Symptoms of acute toxicity include diarrhea, nausea, ataxia, tremor, and encephalopathy; more focal neurologic symptoms may also occur [9]. In many cases, neurologic symptoms are reversible, however a syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) syndrome has been reported in which patients do not recover [3]. In these cases, the cerebellum appears to be preferentially involved [7].

The management of lithium toxicity involves prompt cessation of the drug, and methods targeted towards enhancing its elimination. Administration of intravenous fluids can help enhance renal excretion of lithium, but severe cases may warrant hemodialysis [8]. Gastric lavage is typically not effective due to the rapid absorption of immediate-release lithium in the gut; whole-bowel irrigation has been described as a means of elimination but presents practical challenges [7,10]. Hemodialysis is another means of removal of the drug, and should be considered when there are severe neurologic symptoms such as seizures or coma, a concomitant renal disease preventing effective renal excretion of the drug, or a contraindication to volume repletion [7]. In the case of our patient, his congestive heart failure limited the safe administration of intravenous fluids, and he ultimately required dialysis to eliminate lithium.

Transcortical motor aphasia and other disturbances of language have been associated with lithium toxicity; in these cases, patients often present with other signs suggestive of lithium toxicity and neuroimaging fails to demonstrate a structural etiology of the symptoms. This is an important consideration in patients with language disorders and normal neuroimaging, as it can be reversible with prompt diagnosis and treatment.

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Figure

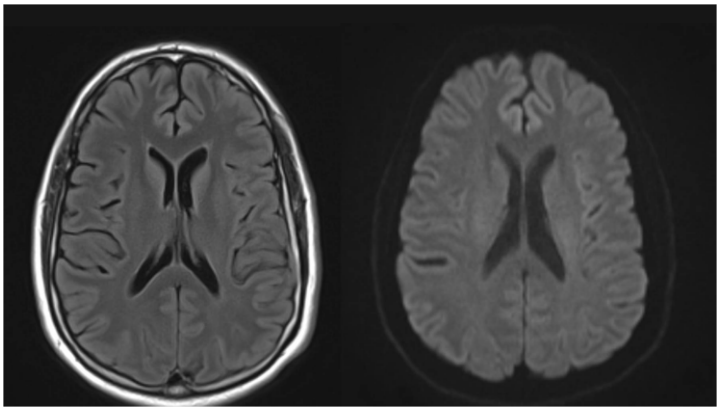

Figure 1: Demonstrates normal MRI of the brain

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