Double Trouble: Neuroleptic Malignant Syndrome (NMS) Clouding Initial Presentation of Anti- NMDA-Receptor Encephalitis (ANRE)

Mohamad Chmayssani,M.D. [1]; Venkata Bandi, M.D. [2] ; Deborah Forst, M.D[2].; Joseph Kass, M.D. [1]; David Friedman M.D. [1]; Yogeshwar Kalkonde, M.D., M.Sc[1]

[1]Department of Neurology, Baylor College of Medicine, Houston, TX and
[2]Department of Medicine, Baylor College of Medicine, Houston, TX

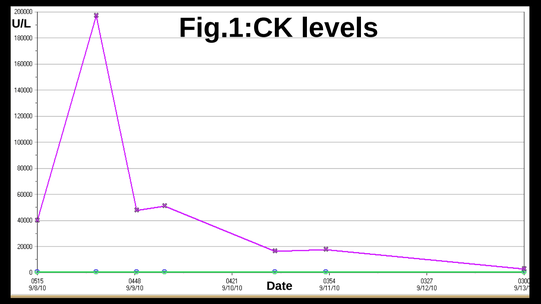
OBJECTIVE: To report a unique case of anti-N-methyl-D-aspartate encephalitis (ANRE) where the initial presentation of encephalitis was clouded by neuroleptic malignant syndrome (NMS).

BACKGROUND: Encephalitis is one of the most challenging syndromes for physicians to manage. Disease onset is acute, symptoms progress rapidly, and previously healthy individuals become quickly, and possibly permanently, disabled. ANRE is a potentially life threatening but reversible autoimmune disorder associated with antibodies to NR1/NR2 heteromers of the NMDA receptor [1]. The disease is commonly seen in females and is associated with tumors in up to 60% of patients, mostly ovarian teratomas [1]. The presence of atypical clinical features and psychiatric symptoms often pose diagnostic difficulties. The patients have altered mental status, rigidity, autonomic instability and fevers thus clinical presentation of ANRE can mimic (NMS) [1,2,3].

DESIGN/METHODS: We describe a 27 year old African American woman with no history of psychiatric disorders who presented with acute onset of bizarre behavior at the workplace.

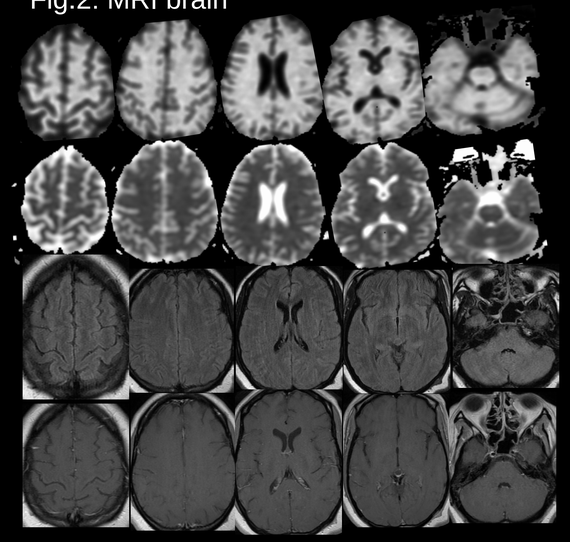
RESULTS: She was admitted to the county psychiatric facility and was diagnosed with bipolar disorder. She was started on valproate and received haloperidol (09/06/10) for agitation. After receiving haloperidol she was noted to have rigidity, delirium and seizure-like activity. She was found to have creatine kinase (CK) 14,470 (09/07/10), and became delirious. Afterwards, patient was transferred to the local county hospital with the diagnosis of rhabdomyolysis and possible NMS (09/08/10). Her urine toxicology screen was unremarkable except the presence of cannabinoids. Her creatinine was 1.6mg/dL. The patient was admitted to the internal medicine service and received intravenous fluids with improvement in CK levels and creatinine. She subsequently developed two generalized tonic-clonic seizures, and a neurology consultation was obtained. On initial neurological exam, the patient was awake but incoherent and had a temperature of 101.3° F and heart rate in 150s. Her blood pressure was labile with fluctuating heart rate. Her pupils were normal in size and reactivity. Strength in extremities was noted to be normal with generalized rigidity. She did not withdraw to painful stimulus. She had hyperreflexia. Laboratory workup showed mild leukocytosis (11,600/μl), significantly elevated CK (>150,000U/L, Fig.1) and deranged liver functions (AST- 769 U/L, ALT-109 U/L) suggestive of NMS. CSF findings were as shown in Table 1 and were remarkable for lymphocytic pleocytosis. Computerized tomography (CT) scan of the brain without contrast was unremarkable. The patient developed increased agitation and seizures, was transferred to the medical intensive care unit (MICU) and was intubated . Haloperidol was discontinued, and bromocriptine and benzodiazepines were used instead of dantrolene due to abnormal liver dysfunction. Subsequent improvement in metabolic derangements and rigidity was not coupled to improvement in mental status. She also developed intermittent generalized dystonia and facial dyskinesias. These episodes consisted of myoclonic facial twitching, forceful turning of head to one side, and sudden sitting up in the bed. Magnetic resonance imaging (MRI) of the brain with and without contrast was unremarkable (Fig. 2). Multiple EEGs, including several hours of continuous EEG monitoring, showed diffuse slowing consistent with moderate to severe encephalopathy without any epileptiform activity . The patient was treated for clinical seizures with anti-epileptic medications.

Given the presence of new onset psychosis in a female patient without prior psychiatric history and a clinical presentation resembling encephalitis, ANRE was suspected. A repeat lumbar puncture was obtained, and CSF was sent for anti-NMDA receptor antibodies to the University of Pennsylvania. The patient was treated empirically with high-dose IV methylprednisolone (1g/d for 5 days) followed by intravenous immunoglobulins (IVIg) due to a lack of clinical response to steroids. CT scan of the pelvis with contrast did not show any ovarian teratoma and CT scan of chest and abdomen did not reveal any malignancy. Anti-thyroperoxidase, anti-thyroglobulin, anti-CV2 and anti-Hu antibodies were negative. CSF returned positive for antibodies against the NR1/NR2B heteromer of the NMDA receptor and she was treated with rituximab (1000mg on day 1 and day 15), as her condition did not improve after IVIg. Given these CSF findings, a pelvic MRI with contrast was obtained to evaluate for ovarian teratoma which could have been missed on the CT scan. The MRI was negative for ovarian teratoma.



Fig,1Evolution of the CK levels U/L over time.

Fig.2: MRI brain



RBC/μl	15	St. Louis encephalitis IgM/IgG	Neg
WBC/μl	25	HSV PCR	Neg
Lymphocytes	98%	HHV-6	Neg
Protein (mg/dL)	22.1	Adenovirus PCR	Neg
Glucose (mg/dL)	71	VDRL	Neg
West Nile encephalitis IgM/IgG	Neg	Cryptococcal antigen	Neg
California encephalitis IgM/IgG	Neg	Gram stain/culture	Neg
Western encephalitis IgM/IgG	Neg	AFB stain/culture	Neg
Eastern encephalitis IgM/IgG	Neg	Fungal stain/culture	Neg
EBV PCR	Neg	IgG synthesis rate * (normal: -9.9 to 3.3)	8.3
CMV PCR	Neg	IgG index *	2.2

* repeat CSF study

The patient had a prolonged MICU stay and underwent tracheostomy as well as gastrostomy tube placement. She was then transferred a step down facility followed by a rehabilitation facility and her condition gradually improved.

Six months after discharge the patient has a near normal neurological exam. She is living at home with parents and independent in all activities of daily living. Her neurological examination is mostly unremarkable with a score of 26/30 on Montreal Cognitive Assessment (-1 cube, -1 language, -2 delayed recall). A repeat pelvic MRI remains negative.

CONCLUSIONS/RELEVANCE:

- Altered mental status, muscle rigidity, elevated CK as well as dysautonomia which are seen in NMS have also been described with ANRE [1,2]
- A close temporal association of worsening of clinical features and laboratory parameters after haloperidol, very high levels of CK and elevation of transaminases not previously described with ANRE makes us suspect that this patient had NMS in addition to the ANRE
- While clinical and laboratory features of ANRE can mimic NMS, patients with ANRE are also at risk of developing concurrent NMS as they may be treated with neuroleptics for behavioral abnormalities
- Presence of NMS in patients with ANRE can mislead clinicians resulting in delayed diagnosis and treatment of ANRE
- Clinicians need to have a high degree of suspicion for ANRE when female patients with no psychiatric history present with new onset psychiatric symptoms

Acknowledgement:
We thank Dr Josep Dalmau's lab at the University of Pennsylvania for testing the CSF for anti-NMDA receptor antibodies.

References:

1.Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008 Dec;7(12):1091-8
2.Sansing LH, Tüzün E, Ko MW, Baccon J, Lynch DR, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. Nat Clin Pract Neurol. 2007 May;3(5):291-6.
3.Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry. 2007 Jun;164(6):870-6.