Young girl with abnormal behavior: Anti-N-Methyl-D-Aspartate receptor immune encephalitis

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Abstract

Anti N Methyl D Aspartate receptor immune encephalitis (Anti NMDARE) is a recently defined, under-recognized and often misdiagnosed disease, which typically occurs in young females and may be associated with an underlying tumor, usually ovarian teratoma. If diagnosed early, initiation of immunotherapy and tumor removal (if present) may result in recovery. We report a case of a 17 years old girl with Anti NMDARE who was initially misdiagnosed as Functional psychosis, Neuroleptic Malignant Syndrome and Sepsis syndrome. To the best of our knowledge, this is only the second case of anti NMDARE being reported from India. This case report underscores the need for a greater awareness of this entity across multiple specialties, e.g., general medicine, psychiatry and neurology, to ensure a heightened diagnostic suspicion, which can lead to timely diagnosis and adequate therapy of this treatable disease.

Key Words

Immune encephalitis, N-Methyl-D-Aspartate, psychosis, neuroleptic malignant syndrome

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Ann Indian Acad Neurol 2013;16:169-71

Introduction

Anti-N-Methyl-D-Aspartate receptor immune encephalitis (Anti-NMDARE) is an immune-mediated syndrome that remains under-recognized despite a growing body of literature. We describe an interesting case of a young girl with anti-NMDARE who was initially misdiagnosed as functional psychosis, Neuroleptic Malignant syndrome (NMS), and Sepsis syndrome.

Case Report

A 17-year-old, school-going girl developed acute onset of behavioral change, initially manifested as extreme politeness and obedience (as against her pre-morbid gregarious personality), progressing within a few days to excessive and irrelevant talks accompanied with features of disinhibition. Frank psychotic features emerged within 10 days, including verbal and physical aggression, muttering to herself, and marked delusional thoughts with a tendency to run amok.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.112456

A diagnosis of acute functional psychosis was made by a psychiatrist and oleanzapine was started. The behavioral syndrome persisted, albeit with mild reduction of psychomotor activity. After a few days, she developed stiffness of whole body along with akinesia and mutism. She was evaluated further by neurologist and psychiatrist. Magnetic resonance imaging (MRI) Brain revealed few scattered, non-diffusion restricted, non-contrast-enhancing T2 and Fluid Attenuated Inversion Recovery sequence (FLAIR) hyper intensities in periventricular and centrum semi-ovale region. Cerebrospinal fluid (CSF) examination revealed no cells, normal protein, and normal glucose levels. CSF viral markers, Venereal Diseases Research Laboratory test, gram stain, acid fast bacillus stain, India ink, cryptococcal antigen, and bacterial, mycobacterial and fungal cultures were negative. Electroencephalogram showed a non-specific diffuse theta delta slowing. She had low grade fever and serum Creatinine Phosphokinase was raised to 1800 U/dl. A diagnosis of NMS due to oleanzapine was considered and dantrolene and hydration were started. Other than a slight reduction of rigidity, no other improvement was noticed. Clinical worsening continued over next 2 weeks, with increasing mental obtundation and persistent akinetic mute state. About 4 weeks after disease onset, frequent bouts of tachypnea, tachycardia, hypotension, and sweating were noticed, which deteriorated over next 48 h to gasping for breath, associated with oxygen desaturation in blood, necessitating endotracheal intubation, and mechanical ventilation. At this stage, patient was brought to our center. Widely fluctuating heart rate and blood pressure were noted, with stimulus-induced sinus tachycardia,

tachypnea, and diaphoresis, necessitating sedative infusion. A provisional diagnosis of sepsis syndrome due to bilateral aspiration pneumonia was considered by the treating physician. She received critical care and medical support and was re-evaluated by neurology team for her underlying progressive illness. A possibility of immune encephalitis was considered at this stage. MRI Brain was repeated; similar changes as noted before were found [Figure 1]. Besides work up for infectious meningoencephalitis (which turned out normal again), CSF samples were also sent for anti-NMDA receptor antibody, anti-Voltage gated potassium channel VGKC, and anti-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antibody levels. Vasculitic work up (anti nuclear antibody, anti-double stranded DNA, anti phospholipid antibody, lupus anti-coagulant, cytoplasmic and perinuclear anti neutrophilic cytoplasmic antibody) was normal. Anti-thyroid peroxidase antibody and anti-thyroglobulin antibody were negative. Computed tomography (CT) scan of chest, abdomen, and pelvis revealed neither ovarian teratoma nor any other malignancy. Patient had two episodes of tonic-clonic seizures, unrelated to any transient metabolic abnormality. While the immune CSF markers were still awaited, it was thought prudent to empirically treat her with immunomodution. She received intravenous immunoglobulin (IVIG), 20 g/day, for 5 days. Within a few days, first signs of improvement of sensorium were noticed with ability to spontaneously open eyes and fixate gaze. The clinical course was further complicated by sequential development of ventilator-associated bilateral pneumothorax, on right side followed by left, necessitating bilateral intercostal tube drainage. During the stage of improvement of sensorium, she developed severe oro-lingual dyskinesias which subsided over next 10 days. Patient was gradually weaned off the ventilator within 2 weeks after receiving IVIG. The anti-NMDA antibody in CSF was meanwhile reported to be positive, whereas anti-VGKC and anti-AMPA antibodies were negative, thus confirming the diagnosis of anti-NMDARE. The patient had a remarkable and quick neurological recovery, with full recovery of sensorium with normal higher mental functions, within 4 weeks of receiving IVIG, with subtle, steadily resolving distal acral lower motor neuron deficit due to overlap of critical illness polyneuropathy. The need for follow-up and periodic screening for teratoma has been explained to the patient and her parents.

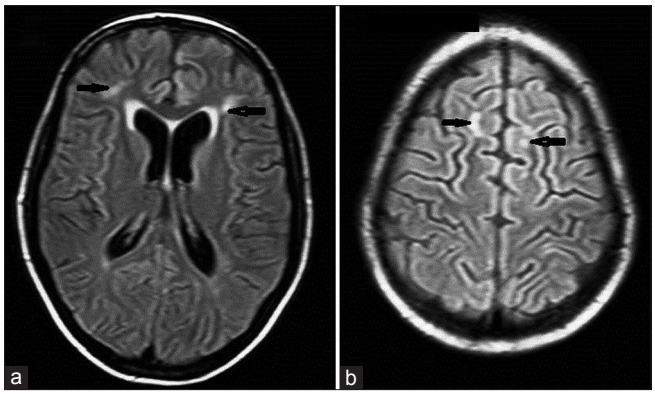

Figure 1: FLAIR magnetic resonance imaging brain revealing few periventricular (a, arrows) and centrum semiovale (b, arrows) white matter hyper intensities

Discussion

Anti-NMDAR encephalitis, first defined in 2007 by Dalmau J *et al*., has been reported from India only once, in 2010.[1,2] Predominantly described in young females with a constellation of symptoms, including personality changes, autonomic dysfunction, extra pyramidal features, and seizures, it may be either an idiopathic or a paraneoplastic syndrome, the latter being associated commonly with ovarian teratomas (in about 60% of young females) and rarely with other neoplasms, e.g., mediastinal teratoma, hodgkin's lymphoma, testicular tumor or small cell lung carcinoma (in 1-2% of patients, mainly in males).[3]

Clinical syndrome follows well-defined phases. Following a prodromal flu-like illness, neuropsychiatric symptoms such as agitation, psychotic symptoms, behavioral changes, and progressive unresponsiveness occur. Next, a dysautonomic phase ensues, with central hypoventilation, cardiac arrhythmias, hypo or hyperthermia, apneic spells, blood pressure fluctuations, and seizures. This is followed by a hyperkinetic phase with dyskinesias, bruxism, lip and tongue biting, dystonia, complex stereotyped movements, and ophisthotonus and oculogyric crisis, in various combinations. Next follows the phase of gradual recovery wherein the neurological syndrome gradually subsides, sometimes leaving behind its sequelae.[2,4,5] The clinical course in our patient conformed well to these typically described phases of clinical evolution.

Pathogenesis wise, antibodies against NR1-NR2 subunits of NMDA receptors, present in serum and CSF, predominantly block gamma amino butyric acid containing neurons, leading to disinhibition of excitatory pathways and increased extracellular glutamate. Resultant fronto-striatal syndrome is characterized by psychosis, catatonia, mutism, and dystonia. Disinhibition of brainstem central pattern generator accounts for orofacial dyskinesias and involuntary movements of the limbs and trunk. Blockade of NMDAR in the dopaminergic, cholinergic, and noradrenergic systems may explain the dysautonomia whereas a direct effect of the antibodies on the ponto-medullary respiratory network may lead to respiratory dysfunction. Since ovarian teratomas express NR1; immune cross-reactivity probably accounts for association with anti-NMDARE.[6]

Cranial CT scan is usually normal. MRI brain may be normal or may demonstrate non-specific, non-contrast-enhancing white matter hyper intensitiesin the T2-weighted or FLAIR sequences (as seen in our patient). CSF may be initially abnormal, with moderate lymphocytic pleocytosis and normal or mildly increased protein concentration in up to 80% of patients. CSF anti-NMDAR antibodies are highly positive and titers correlate with disease process.[3,6,7]

Although no standard of care exists, experts recommend eradication of associated malignancy and immunomodulation. Immunotherapies include corticosteroids, IVIG, plasmapheresis, rituximab, cyclophosphamide, and azathioprine, of which corticosteroids, IVIG, or plasmapheresis constitute the first line approach.[3,8,9] Since plasmapheresis is not without risks, especially in dysautonomic state, and

corticosteroids carry the risk of aggravation of usually co-existing infection, IVIG appears to be a safer option. However, systematic comparisons between the three first line modalities are not yet available.[9] Decision to choose one modality or the other may therefore be made on a case-to-case basis, keeping the clinical condition of patient, cost, and availability factors in mind.

Relapses may occur in 20-25% of patients, especially in those without teratoma; in such patients continued immunosuppressants (mycophenolate mofetil or azathioprine) for at least 1 year after discontinuation of initial immunotherapies is recommended.[3] Besides, periodic screening for tumor is recommended if it is not found on first presentation. The extent and frequency of screening depends on patient's age and sex. In female patients aged 12 years or older, approach similar to that of paraneoplastic syndromes is appropriate (e.g., MRI of the abdomen and pelvis every 6 months for 4 years), but in young children (<12 years) and male patients the need for repeat screening is not clear. If detected, the tumor should be promptly removed to speed up improvement and decrease relapses.[3,9]

The important outcome determinants, identified in a recently published observational cohort study, include stay in an intensive care unit (a marker for the severity of disease) and the time from symptom onset to initiation of treatment.[9] Latter underscores the need for early diagnosis and prompt treatment.

In conclusion, this case report highlights several important issues. Since most of the initial manifestations are likely to mimic functional psychosis, neurologists and psychiatrist should be aware of this entity. Intensivists and internists diagnosing NMS in patients on anti-psychotic medications should also have a high index of suspicion for this entity. Absence of hyperpyrexia and lack of good response to dantrolene should alert towards an alternate possibility, other than NMS. A greater awareness of auto-immune encephalitis, including NMDARE across various specialties would prevent potential diagnostic pitfalls which lead to non-diagnosis and misdiagnosis of this disease which probably is more under-recognized than rare.

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How to cite this article: Suri V, Sharma S, Gupta R, Jadhao N, Suri K. Young girl with abnormal behavior: Anti-N-Methyl-D-Aspartate receptor immune encephalitis. Ann Indian Acad Neurol 2013;16:169-71.

Received: 01-01-13, **Revised:** 20-01-13, **Accepted:** 21-01-13

Source of Support: Nil, **Conflict of Interest:** Nil