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Short Communication

Bilateral thalamic changes in anti-NMDAR encephalitis presenting with hemichorea and dystonia and acute transient psychotic disorder

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is one of the most common causes of autoimmune encephalitis. Both movement disorders and neuropsychiatric manifestations are considered core features of anti-NMDAR encephalitis. Strong clinical suspicion, along with NMDAR antibody positivity in paired sample of serum and cerebrospinal fluid, with supportive MRI changes clinch diagnosis in majority. We herein report a case of a middle-aged woman with subacute behavioral abnormalities, which were so severe that forced her to attempt suicide. Hemichorea and dystonia, which appeared later in course, are not previously reported movement disorders in combination in anti-NMDAR encephalitis. Further, magnetic resonance imaging showed bilateral thalamic hyperintensities with diffusion restriction, which are in turn not described in this entity. After amalgamation of history, especially the presence of neuropsychiatric symptoms, clinical features, physical examination, and investigations, the diagnosis of anti-NMDAR encephalitis could be established. Our case not only highlights that the combination of hemichorea and dystonia can be features of anti-NMDAR encephalitis, but adds novelty by bilateral symmetric thalamic changes.

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common anti-neuronal antibody mediated autoimmune encephalitis. (Gable et al., 2012) The most frequent modes of presentation are behavioral changes, psychiatric problems, seizures, cognitive disabilities, movement disorders and dysautonomia. (Dalmau et al., 2011) This is truly a heterogeneous disease in terms of affected age group, being more frequent in young women with ovarian neoplasms. (Dalmau et al., 2011) Both movement disorders and neuropsychiatric manifestations are considered core features of anti-NMDAR encephalitis. (Bai-yabal-Carvallo et al., 2013; Dalmau et al., 2011) In the initial stages, the subtle personality changes and behavioral alteration closely mimic true psychiatric illness and can therefore be delusive to even expert clinicians. (Dalmau et al., 2019) In a large study including 544 diagnosed cases of anti-NMDAR encephalitis, 77% of patients presented with neuropsychiatric complaints, most of them were agitation and psychotic symptoms, especially disorganized behavior and visual-auditory hallucinations as well as persecutory delusions. (Sarkis et al., 2019).

Amidst the array of prevalent movement disorders in anti-NMDAR encephalitis, dyskinesia (particularly orofacial) is most common (van de Riet et al., 2015) followed by limb and oromandibular dystonia, choreoathetosis, myorhythmia, blepharospasm, opisthotonos and tremor. (Bai-yabal-Carvallo et al., 2013; Dalmau et al., 2011; Mohammad et al., 2014; van de Riet et al., 2015) The combination of hemichorea and dystonia associated with anti-NMDAR encephalitis has not been published previously.

Magnetic resonance imaging (MRI) of brain reveals no discernable abnormal signal in the parenchyma in near about 50% cases of anti-NMDAR encephalitis. (Wang et al., 2018; Zhang et al., 2018) Even when it reveals abnormal intensities, there is a clinic-radiological paradox.
isolated thalamus involvement is very rare in lobes, insular cortices, basal ganglia, parietal lobes, brainstem, periventricular white matter, internal capsules, and thalami. Isolated thalamus involvement is very rare in anti-NMDAR encephalitis and bilateral symmetric thalamic changes is novel. We herein report a case of a middle-aged woman who initially had a psychiatric diagnosis of acute transient psychotic disorder, which was so severe that she tried to commit suicide. Lately she developed a peculiar hyperkinetic movement disorder with bilateral thalamic hyperintensities with diffusion restriction. She was finally diagnosed with anti-NMDAR encephalitis. The response to combination of intravenous corticosteroids and intravenous immunoglobulin (IVIG) was excellent.

2. Case report

A 34-year-old previously healthy woman was referred to emergency with history of attempted hanging and with complaint of new onset involuntary, uncontrollable, dance-like movements involving right half of her body for last four days. Her relatives gave history that she had gradual onset, progressive behavioral abnormality for last three months for which she was getting treatment (quetiapine 100 mg/day, valproate 1200 mg/day, escitalopram 15 mg/day, and clonazepam 1 mg/day) from a psychiatrist without any improvement. Her husband had noticed rather abrupt change in her wife's behavior since she returned from visit to her parents three months ago. Initially, she was more anxious, poorly attentive, indecisive, restless, and was not able to keep conversations for a longer period in a concentrated manner. She complained of hearing singing voices. In addition, she started nurturing a delusional belief that she had been impregnated with a baby from an evil force. She was also bursting into tears every now and then, particularly in front of her husband. With this feeling of extreme guilt, she attempted suicide by hanging herself ten days back. Her relatives were nearby and responded with utmost promptness. She was hospitalized in a nearby rural health facility and discharged after 48 hours of observation as she had no demonstrable neurological deficit other than the pre-existing behavioral abnormality. She was finally referred to tertiary center.

She had no history of previous psychiatric illness and addiction and none of her family members were suffering from any neuropsychiatric illness. Her mood was depressed, often associated with intermittent aggression, agitation, and intermittent loosening of track of conversation. Her Mini-Mental State Examination (MMSE) total score was 21/30 with problems in registration, recall and following three-step-command, suggestive of attention, recent memory, and executive domain involvement. She was having right hemichorea and dystonia (predominantly right upper limb) and cervical dystonia. Other systemic examination revealed no abnormality.

Serum electrolytes, hepatic, renal and thyroid function tests, including anti-thyroid peroxidase antibody levels, were within normal range. Serum thiamine and B12 vitamin levels were normal. Urinalysis for toxic screening and pregnancy test were also negative. Serologies for hepatitis B, C, HIV, malaria, and syphilis were also negative. MRI of brain displayed symmetrical hyperintensities in both thalami in T2 and FLAIR with diffusion restriction in DWI and ADC (Fig. 1). Cerebrospinal fluid (CSF) analysis was unremarkable except mildly increased protein content. CSF and serum lactate-pyruvate ratios were normal. CSF cultures and polymerase chain reaction assays for the detection of neurotropic viruses (herpes simplex virus 1 and 2, human herpes virus 6 and 7, Epstein Barr virus, cytomegalovirus, enterovirus, parvovirus B19, varicella zoster virus, human parechovirus, adenovirus, and severe acute respiratory syndrome coronavirus-2) were negative as well as Japanese encephalitis and dengue serology testing. 1-70 Hz conventional electroencephalography did not reveal any evidence of epileptiform discharges. Primary demyelinating disorders (multiple sclerosis, acute demyelinating encephalomyelitis, neuromyelitis optica spectrum disorder, and anti-myelin oligodendrocyte glycoprotein encephalomyelitis) were excluded as CSF oligoclonal bands, IgG index, anti-aquaporin-4 antibodies, and anti-myelin oligodendrocyte glycoprotein antibodies were normal or negative. In addition, criteria for anti-aquaporin-4 IgG-negative neuromyelitis optica spectrum disorder were not fulfilled. Anti-Nuclear Antibody (ANA) screening using HEP-2 cells and ANA profile were otherwise normal. Paired sera for autoimmune encephalitis panel were sent. Anti-NMDAR antibodies came out to be positive in high titers. Further extensive investigations failed to demonstrate any associated concealed neoplastic process. Clinical assessment scale in autoimmune encephalitis (Lim et al., 2019) and anti-NMDAR encephalitis one-year functional status scores (Balu et al., 2019) were 9/27 and 2/5, respectively.

On day 5 of hospital stay, intravenous methylprednisolone (1 g/day) was initiated for consecutive 5 days. Her movement disorders were abolished, but cognitive and behavioral problems persisted. Hence, on day 15 of hospital stay she was put on IVIG for 5 days. With this therapy, her behavioral problems abated, and psychotic symptoms disappeared. She was again evaluated by a panel of neurologists and psychiatrists and had no depressive symptoms. There was significant improvement in MMSE with a total score of 27/30 (1 point was deducted from each in registration, recall and the last three-step-command). She was discharged in a stable condition with minor cognitive impairment and oral steroids in tapering doses. Repeat MRI showed decreased hyperintensities as compared to the previous scan in the corresponding areas.

3. Discussion

Our patient presented with subacute onset behavioral abnormality, cognitive difficulties, and psychiatric symptoms, followed by hemichorea and dystonia, a constellation of clinical features germane to diagnosis of anti-NMDAR encephalitis. In about 70% of patients with anti-NMDAR encephalitis, there is a prodromal phase characterized by headache, fever, gastrointestinal symptoms and upper respiratory tract illness. In patients who presented with anti-NMDAR encephalitis, there is a prodromal phase characterized by headache, fever, gastrointestinal symptoms and upper respiratory tract illness (Dalmau et al., 2011; Dalmau et al., 2019; Sarkis et al., 2019) which was not reported in our patient. Credible explanations are prodromal symptoms were there, but her relatives probably ignored them, as she was not with her at that time and the patient herself could not give proper account of the initial illness. She did not develop severe encephalopathy, seizures and dysautonomia traits requiring intensive care admission fortunately because she was diagnosed relatively earlier. (Dalmau et al., 2011)

Suicidality is more common than it was thought of in backdrop of anti-NMDAR encephalitis associated neuropsychiatric issues. Zhang et al. (Zhang et al., 2017) reported that almost 13% of their study population (N = 133) had suicidality. Only 6-7% had attempted a suicidal attempt unsuccessfully. (Zhang et al., 2017) In patients who presented a psychiatric disorder, suicidality was more common. (Zhang et al., 2017) like in our patient.

Our patient had several manifestations deviant from anti-NMDAR encephalitis. Most striking of them was obviously the bilateral thalamic hyperintensities with diffusion restriction. Literature search and clinical experience divulge that thalamic involvement in anti-NMDAR encephalitis is exceptional. (Dalmau et al., 2008; Kelley et al., 2017; Kim et al., 2020; Wang et al., 2018) Symmetrical bilateral thalamic involvement with diffusion restriction propelled the treating physicians to look for other etiologies rather than anti-NMDAR encephalitis or overlapping on it. (Kim et al., 2020) Radiological differential diagnosis, which were considered, are shown in Table 1. (Hegde et al., 2011; Özgür et al., 2017; Renard et al., 2014; Smith et al., 2009; Tuttle et al., 2019) After amalgamation of history, especially the presence of neuropsychiatric symptoms, clinical features, physical examination, and investigations, the diagnosis of anti-NMDAR encephalitis stood tall.
The neuropsychiatric and cognitive symptoms in our patient could be, at least partially, explained by bilateral thalamic involvement. Emerging data support novel views of thalamic functions that emphasize integrative roles in cognition. (Anticevic et al., 2014; Pinault, 2011; Uhlhaas et al., 2013; Wolff and Vann, 2019) In addition, damage to the thalamus, causing the phenomenon of diaschisis, can be manifested as various neuropsychiatric symptoms. (Anticevic et al., 2014; Pinault, 2011; Uhlhaas et al., 2013; Wolff and Vann, 2019) Specifically, damage to the dorsomedial nucleus of thalamus, particularly on the right side, results in disruption of the thalamus from thalamo-cortical-limbic networks. (Julayanont et al., 2017) This disrupted network may cause mania, which is secondary to the dysregulation of emotion, motivation, social conducts, reward seeking behaviors, and personality. (Julayanont et al., 2017) Similarly, damage to pulvinar nucleus decreases thalamic suppression to the occipital and temporal cortices, known as release phenomenon, which results in visual and auditory hallucinations. (Julayanont et al., 2017)

Movement disorders, particularly the hyperkinetic ones, usually appear after the onset of prodromal and neuropsychiatric phases in adults. Nevertheless, a specific movement disorder may well be the index symptom of undermined anti-NMDAR encephalitis. (Baizabal-Carvallo et al., 2013; Dalmau et al., 2011; Mohammad et al., 2014; van de Riet et al., 2015). Clinicians often find it problematic to differentiate movement disorders from seizures in these cases. Stereotypies, motor perseveration, reproduction of acquired complex motor activities and orofacial dyskinesias are the classic phenotypic of movement disorders found in anti-NMDAR encephalitis. (Florance et al., 2009; Granata et al., 2018; Mohammad et al., 2014) Rather than a single pure movement, a composite of various movement disorders is common presentation. (Mohammad et al., 2014) Oral stereotypies are quite specific for anti-NMDAR encephalitis. (Florance et al., 2009; Mohammad et al., 2014) Ferioli et al. (Ferioli et al., 2010) reported a case of paraneoplastic anti-
resulting in such bizarre movements, (Dalmau et al., 2011; Jucaite et al., 2010) hypothesised that in patients aged more than 18 years, choreoathetoid myorhythmia with “Smooch Sign”. Duan et al. (Duan et al., 2016) reported a case of anti-NMDAR encephalitis with prominent bulbar and limb myorhythmia. Neiman et al. (Neiman et al., 2015) and Vivin et al. (Vivin et al., 2010; Stamelou et al., 2012) mentioned that in patients aged more than 18 years, choreoathetoid movements are rarely seen in comparison to the age group below 10 years. Hacohen et al. (Hacohen et al., 2014) reported three patients with pure hemichorea and dystonia, where hemichorea with dystonia can be features of anti-NMDAR encephalitis, but adds novelty by bilateral symmetric thalamic changes.

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### Table 1

Differential diagnosis bearing in mind the symmetrical bilateral thalamic involvement.

| Differential diagnosis                                                | Odds                                                                 |
|-----------------------------------------------------------------------|----------------------------------------------------------------------|
| Osmotic demyelination syndrome, extrapontine myelinolysis variety     | > No history suggestive of metabolic perturbations.                  |
|                                                                       | > Normal electrolytes and osmolarity values throughout hospital stay. |
|                                                                       | > No therapeutic misadventure.                                       |
| Wernicke's encephalopathy                                             | > None of the typical clinical features (ataxia, ophthalmoparesis, encephalopathy). |
|                                                                       | > No traditional risk factors.                                       |
|                                                                       | > Normal serum thiamine level.                                       |
|                                                                       | > Peri-aqueductal grey, mammillary bodies, and basal ganglia unaffected. |
| Leigh's disease                                                        | > None of the clinical features and age group fitted with mitochondrial disease. |
|                                                                       | > CSF and serum lactate: pyruvate ratios were normal.                |
|                                                                       | > Basal ganglia, brainstem and diencephalon not involved.            |
|                                                                       | > No putaminal involvement.                                          |
| Japanese encephalitis                                                 | > No clinical feature of infective encephalitis.                    |
|                                                                       | > CSF was not suggestive of infective etiology.                     |
|                                                                       | > Paired sera were negative.                                         |
| Dengue encephalitis                                                   | > No clinical feature of infective encephalitis.                    |
|                                                                       | > CSF was not suggestive of infective etiology.                     |
|                                                                       | > Paired sera were negative.                                         |
| Malaria                                                               | > No clinical feature suggestive of cerebral malaria.                |
|                                                                       | > Thin and thick smear tested negative for trophozoites.             |
|                                                                       | > Rapid diagnostic kit test for Plasmodium falciparum and vivax were negative. |
| Creutzfeldt-Jacob disease                                             | > Clinical features not matching.                                    |
|                                                                       | > No family history.                                                 |
|                                                                       | > No pulvinar sign.                                                  |
|                                                                       | > No cortical ribbon pattern.                                        |
|                                                                       | > Improvement with treatment.                                        |
| Arterial occlusion                                                    | > No vascular risk factor.                                           |
|                                                                       | > Normal prothrombotic screening.                                    |
|                                                                       | > Did not follow typical territory of arterial occlusion stroke.     |
|                                                                       | > Contrast magnetic resonance angiography and digital subtraction angiography were normal. |
|                                                                       | > Improvement with immunomodulators.                                 |
| Deep cerebral venous infarct/thrombosis                               | > No traditional risk factors.                                       |
|                                                                       | > Negative thrombophilia screen.                                     |
|                                                                       | > No T1-hyperintensity.                                              |
|                                                                       | > Normal CT brain and contrast MR venography.                       |
| Posterior reversible encephalopathy syndrome                         | > No traditional risk factors.                                       |
|                                                                       | > Not a typical site of involvement.                                 |
|                                                                       | > Cytotoxic edema > > > vasogenic edema.                             |
|                                                                       | > The watershed zones were unaffected                                |
|                                                                       | > Cerebral cortex, basal ganglia, and hippocampi unaffected.         |
|                                                                       | > No “reversal sign”.                                                |
|                                                                       | > No white cerebellum sign.                                          |
|                                                                       | > Hanging duration and attempt was not enough severe to cause asphyxia related hypoxic ischemic encephalopathy. |
| Hyponic ischemic encephalopathy                                       | > Not fitting with typical acute disseminated encephalomyelitis age group. Clinical features and CSF were not either suggestive. |
|                                                                       | > Paired sera for anti-myelin oligodendrocyte glycoprotein encephalitis antibody and anti- aquaporin4 antibody were negative. |
| Demyelinating disorders                                               | > Clinically not suggestive.                                        |
|                                                                       | > No T1-hyperintense pulvinar sign.                                  |
|                                                                       | > Corresponding T2 hypointensity.                                    |
| Wilson's disease                                                      | > No history suggestive of metabolic perturbations.                  |
|                                                                       | > No therapeutic misadventure.                                       |
|                                                                       | > Normal biochemical parameters.                                    |
|                                                                       | > No Kayser-Fleischer ring.                                          |
| Fahr's disease                                                        | > CT scan did not reveal hyperdense signal of calcification.         |
| Fabry's disease                                                       | > Age group and clinical features did not corroborate.              |
|                                                                       | > No T1-hyperintense pulvinar sign.                                  |
|                                                                       | > Corresponding T2 hypointensity.                                    |
