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ANTI-NMDA RECEPTOR ENCEPHALITIS PRESENTING WITH SEVERE EPISODIC HYPERTENSION: A CASE REPORT

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis is one of the most commonly emerging autoimmune encephalitis in children and young adults in recent years. Clinical manifestations range from prodromal symptoms to seizures, movement disorder, psychiatric manifestations, cognitive/speech impairment, and autonomic dysfunction. Our case presented with initial symptoms of severe episodic hypertension, sweating, agitation, and tachycardia. She received early care for pheochromocytoma and panic disorder in Qatar, but there was no relief. Three weeks later, she presented in our emergency room with seizures, cognitive/speech impairment, and orofacial dyskinesia. Electroencephalography (EEG) revealed right hemispheric delta activity and cerebrospinal fluid CSF anti-NMDA Receptor IgG was positive. Magnetic resonance imaging MRI brain and CSF studies were normal. She was treated symptomatically for hypertension and psychiatric manifestations. She received high dosage pulse intravenous methylprednisolone, followed by intravenous immunoglobulin, which significantly alleviated her cognitive, neuropsychiatric, and autonomic features. Severe hypertension is an uncommon presentation of Anti- NMDAR encephalitis. Early recognition and prompt management improves prognosis and long term sequelae.

Key Words: Anti-NMDAR Encephalitis; Hypertension; Case report; Autonomic Dysfunction; Intravenous Immunoglobulins

INTRODUCTION

Anti-NMDAR encephalitis is a recently identified autoimmune disorder by Dalmau and colleagues in 2007, first found in women with neuropsychiatric symptoms associated with ovarian teratomas.[1] However, in recent years, a wide spectrum of clinical manifestations in children and young adults has been reported. Antibodies against the NR1 subunit of the N-methyl-D-aspartate receptor (NMDAR) are thought to be involved, causing reversible receptor internalisation in neurons.[2] It mimics diseases like schizophrenia, anxiety disorders, eating disorders, major depressive disorder, and autism as well as Alzheimer's disease and spinocerebellar degeneration.[3] Diagnostic test for this disorder is detection of Anti-NMDAR antibodies in the serum and CSF.[1] Our case presented with autonomic dysfunction manifesting as severe episodic hypertension, tachycardia and sweating, which is a poorly researched domain in anti-NMDAR encephalitis.

CASE REPORT

A 14 year old girl, with no known comorbids reported having generalised headaches of varying intensity, nausea, and episodic palpitations for three weeks. At a hospital in Qatar, she was initially suspected and treated for pheochromocytoma, but her symptoms persisted. Later, she experienced multiple episodes of palpitations, sweating, and elevated blood pressure. Sertraline, lorazepam, and atenolol were started as treatment for her panic attacks; however there was no significant improvement in her panic episodes. She travelled to Pakistan and reported to our emergency with tonic fits, new-onset unexplained panic episodes and hypertension. She had another tonic seizure in the emergency room, along with altered consciousness and excessive sweating. She was treated with intravenous levetiracetam.

She was admitted in Paediatric Intensive care unit (ICU) for workup to rule out meningoencephalitis, autoimmune encephalitis, and lupus cerebritis. ANA/ENA profile, an anti-neuronal profile, CSF routine exam were reported negative and MRI Flair and T1 with contrast images (Figure 1a, b) showed no lesion of the brain. Pheochromocytoma workup was likewise normal. Initial EEG showed predominant higher voltage delta activity over the right hemisphere (Figure 1c). On examination, her GCS was 15/15, she was following commands but was slow to respond. Her speech was

slow and slurred, she had orofacial dyskinesias. Cranial nerve examination and muscle power was normal. Deep tendon reflexes were +1 and symmetrical, plantars were bilateral flexor.

Her heart rate and blood pressure frequently elevated to 190 beats per minute and 220/120 mmHg, accompanying agitation and aggression, leading her to bite her lower lip in one episode. Repeat EEG showed diffuse low voltage Theta and delta activity with superimposed beta activity, suggestive of moderate diffuse encephalopathy. There were no epileptiform discharges seen on EEG. A Psychiatric evaluation was sought to control her agitation. She was advised clonazepam 0.5mg six hourly per oral, and midazolam 5 mg intravenous for her agitation but intermittent hypertensive episodes persisted. Four hourly Blood pressure monitoring was done (Figure 2), labetalol and hydralazine were administered.

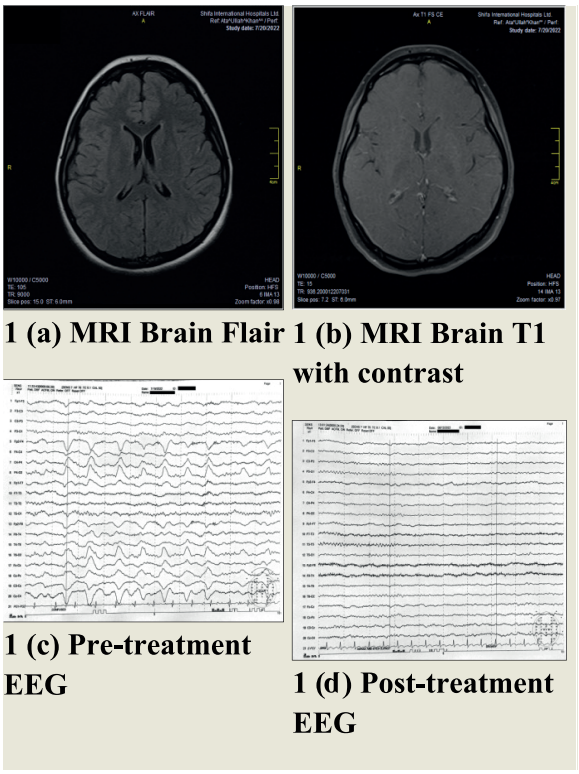

Figure 1 (a) and **(b)**: No acute intracranial haemorrhage, ischemic infarct or midline shift. No intraparenchymal or abnormal nodular leptomeningeal enhancement. **(c)** Predominant higher voltage delta activity over the right hemisphere, **(d)** 8-9 Hz symmetrical alpha rhythm.

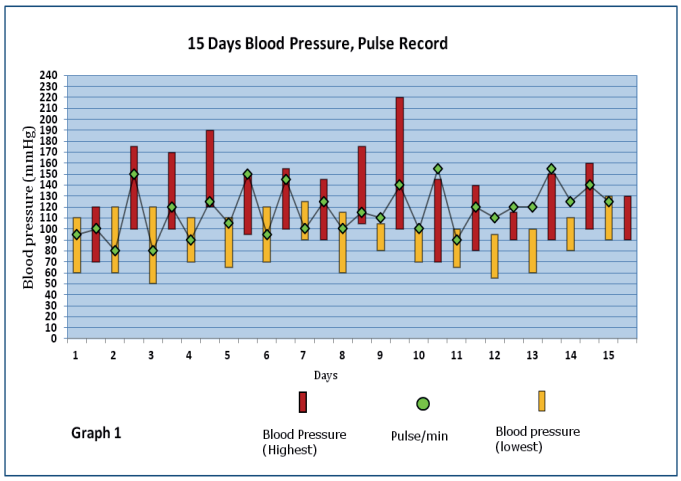

Figure 2: Highest (Red) and lowest (Yellow) Blood pressure and pulse (Green) record of patient during 15 day stay at hospital. IVIG was administered at day 10 for 5 days

CSF and Serum for anti-NMDA Receptor IgG by Indirect immunofluorescence was reported positive two days later. She was started on a high dose pulse intravenous methylprednisolone 1 gram/day for 5 days. Subsequently, CSF HSV DNA by PCR was also reported negative and antivirals (acyclovir) were discontinued.

Follow up EEG showed mild diffuse encephalopathy. Computed tomography CT scan pelvis and abdomen was done to rule out ovarian teratoma, however, the result was unremarkable. Pertinent laboratory diagnostics are listed in Table 1.

TABLE 1: Tests done during the course of admission and their results.

Test	Result	Range
Cortisol	31.49	5:00 To 6:00 PM: 2.3 - 11.9 Ug/dL
Prolactin	18.01	Female: 4.79-23.30 ng/mL, Male:4.04-15.20 ng/mL
Aldosterone	249	140-830 pmol/L (Seated)
Renin	6.25	8-35 uIU/ml (Seated)
Vanillylmandelic acid	7.3	1.0 - 11.0 mg/24 Hr
Meningitis serology	Normal	
CSF gram stain, CSF Routine Exam	Negative	
ENA Profile	Negative	5 Negative 5 - 10 Equivocal >10 Positive
CSF HSV DNA by PCR	Not detected	
Autoimmune encephalitis antibody profile Serum (indirect immunofluorescence)	**NMDAR antibody Positive**	
NMDA R IgG IN CSF Indirect immunofluorescence using EU 90	**Positive**	

cells		
Echocardiography	Normal Study	
IgA	2.1	12-13 years 0.58-3.58 g/L 14-15 years 0.47-2.49 g/L
Anti- Neuronal Antibodies	Negative	Negative 0-5 AU Borderline(+) 6-10 AU Positive(+) 11-25 AU Positive(++) 26-50 AU Strong Positive(+++) >50AU
Alpha Fetoprotein	1.6	For Male and Non-pregnant Female:=7.0 ng/mL
Beta- human chorionic gonadotropin	< 0.10	Pregnant Females > 25.0 mIU/mL, Non pregnant Females 5.0 mIU/mL,
Lactate dehydrogenase	169	Female:135-214 U/L, Male:135-225 U/L
CT Chest, Abdomen and Pelvis	Mild hepatomegaly. No other significant abnormality.	

CSF cerebrospinal Fluid, ENA Extractable Nuclear Antigen

After receiving Intravenous methylprednisolone for five days, dyskinesias did not improve significantly. She was then administered intravenous immunoglobulins (IVIG) 0.4 gm/day/kg for five days, along with baclofen 5 mg 12 hourly and amantadine 50 mg 12 hourly. She responded within two days, started following simple commands and communicated in short sentences. However, she had one episode of agitation with increased heart rate. Risperidone was discontinued and haloperidol was tapered off due to lack of effectiveness, as advised by psychiatry.

The patient had improvements in motor, autonomic, and cognitive/speech function after five doses of IVIG and multidisciplinary rehabilitation. Clonazepam dose was decreased, antihypertensives were adjusted accordingly. She was discharged with home medication; family was counselled regarding patient care and follow up plan. In clinic follow up after a week, EEG was done and was normal (fig 1d) she was responding well, blood pressures were stable. A video follow up from Qatar 6 weeks later showed she was alert and off medication and had resumed her studies.

DISCUSSION

Anti-NMDAR encephalitis is becoming well recognised in our population in recent years, it is important to recognise variations in symptomatology. Patients with anti-NMDAR encephalitis experience a multiphase illness that progresses from prodromal features such as fever, fatigue, headache, nausea, and vomiting to

seizures, memory Problems and language difficulty, unresponsiveness, psychosis, along with abnormal movements, autonomic and breathing dysfunction.[4] Variation in presentation can frequently cause delays in accurate diagnosis and treatment. A case series by Sheikh et al in 2019 showed that psychiatric features were prominent in adults while younger patients suffered from hyperactivity and irritability.[5] According to one clinical study, early symptoms in children include seizures, abnormal movements, behavioural and speech difficulty. However, breathing instability and autonomic dysfunction is not often seen or severe in children.[8]

Clinical symptoms of Autonomic dysfunction in anti-NMDAR encephalitis include tachycardia, bradycardia, central respiratory depression, hypotension , hypertension, hypersalivation, sweating, constipation, urinary retention, and Hyperthermia.[6] A retrospective study by Yan et al in 2021 showed that epilepsy, involuntary movements, and diminished consciousness were common in individuals with anti-NMDAR encephalitis with autonomic dysfunction. Moreover, the gravity of the disease was greater; requiring ICU admission and mechanical ventilation, and their prognosis was worse.[6] Therefore, early management with immunotherapy (corticosteroids, IVIG, or plasma exchange) is beneficial in prognosis of this disease.[7]

Autoimmune encephalitis is a potentially curable disease, underreported from Pakistan. It has a likelihood of being incorrectly identified as a panic disorder, endocrine problem, or psychiatric illness if not thoroughly probed. Initial presentation with autonomic dysfunction might be more serious and necessitates close observation and care. Patients with episodic hypertension and neuropsychiatric symptoms should not be disregarded. Early detection and prompt management can slow the progression of the disease and prevent patients from long term complications. A clinical study showed that two or more kinds of immunotherapy were needed in the patients with autonomic dysfunction than without autonomic dysfunction, which implies that patients with autonomic dysfunction have a substantially severe condition and need to undergo aggressive treatment.[6] Nevertheless, regardless of their antibody status, two thirds of the patients demonstrate a satisfactory response after immunotherapy. Furthermore, first-line immunotherapy helps the majority of patients.[9]

Literature review showed few publications on Anti-NMDAR encephalitis from Pakistan.[5, 10, 11] This case report adds to the literature and opens a future prospect for further research regarding different manifestations of autonomic dysfunction in Anti-NMDAR encephalitis. In a retrospective study by Byun et al cardiovascular autonomic dysfunction in anti-NMDAR encephalitis was shown by heart rate variability study, in which patients had prominently reduced sympathetic function.[7] However, long-term follow up with laboratory workup including antibody titres, CSF analysis and brain imaging is needed to determine the long-term efficacy of treatment.

CONCLUSION

Our case highlights autonomic dysfunction as a presentation of Anti-NMDAR encephalitis manifesting as severe episodic hypertension, tachycardia and sweating.

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Arsalan Ahmed; concept, case management, manuscript review