The Egyptian Journal of Internal Medicine

CASE REPORT Open Access

A case report of anti-NMDA receptor encephalitis in a young Egyptian female patient presenting with hyperreligiosity

Hamdi Ibrahim[1*], Attaa Ali[1], Safwat Abdel Maksod[1], Magdy Khorshed[1], Mona Wassef[1], Mostafa Alfishawy[1], Hanan Rady[1], Adel Mohamed[1], Mohamed Mahmod[1], Khaled Ismael[1], Marwa Haron[1], Suzan Said[1], Riham Adel[1] and Noha Mohamed[1]

Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a form of autoimmune encephalitis that remains underrecognized due to the variability of the initial symptoms and can be misdiagnosed as viral encephalitis or other pathogens. This syndrome has been predominantly described in young females including personality changes, autonomic dysfunctions, and neurologic decompensation.

About half of the cases have tumors, most commonly teratomas of the ovaries; another established trigger is herpes viral encephalitis, while the cause in other cases is unclear. In case of clinical suspicion, electroencephalogram and brain magnetic resonance imaging are useful, but lumbar puncture for cerebrospinal fluid analysis is used to confirm the diagnosis. Treatment for this disease includes immunosuppression, plasmapheresis, and tumor resection when indicated. In this case report, we present a case that presented with hyperreligiosity and proved to have autoimmune encephalitis.

The main purpose of our case is to increase awareness regarding immune-mediated encephalitis, especially the anti-NMDAR encephalitis.

Keywords Anti-NMDA receptor encephalitis, Hyperreligiosity

Background

Anti-NMDAR encephalitis is a relatively rare diagnosis with just a few hundred cases reported in medical literature, but its true prevalence especially in individuals with purely psychiatric manifestations is yet to be determined as a large majority present to a psychiatrist first. Herein, we report a case that presented with hyperreligiosity and proved to have autoimmune encephalitis.

*Correspondence:
Hamdi Ibrahim
hamdi1962.hi@gmail.com
[1] Egypt Ministry of Health and Population Giza, Cairo, Egypt

We found only one case of the hyper-religious theme in the context of delirium after extensive web search (PubMed, Medline, Google).

Case presentation

A 21-year-old female, student, previously healthy with no past medical history and no past psychiatric illness or drug abuse presented to our emergency department in Embaba Fever Hospital with a fever and altered mental status (Tables 1, 2, 3, and 4).

The history dated back 2 weeks before admission when she started to suffer from fever and headache followed by prominent psychiatric changes in the form of anxiety, delusions, hallucinations, and hyperreligiosity. She had developed abnormal behavior in the form of talking

Table 1 Biochemical, immunologic, metabolic, and serological investigations

Test	Result	Unit	Reference range
Complete blood count			
WBC	3×10^3	U/L	4–11
Hemoglobin	10.5	g/dl	11–16
Hematocrit	31.2	%	33–44
Red cell count	3.41×10^6	UL	3.8–5.4
MCV	91.5	Fl	78–96
MCH	30.8	Pg	26–32
MCHC	33.7	g/dl	31–36
RDW	13.4	%	11.5–14.5
Platelets	140 × 103	U/L	150–450
Differential count			
Basophils	1	%	0–1
Eosinophils	0	%	0–3
Stab	0	%	0–7
Segmented	66	%	40–75
Lymphocytes	29	%	20–40
Monocytes	4	%	1–10
Potassium	3.4	mmol/l	3.5–5
Sodium	14	mEq/	135–145
Calcium ionized	1.10	mmol/l	1.2–1.4
ALT	68	u/l	14–63
AST	54	u/l	15–37
S. ammonia	0.3	mg/dl	0.17–0.8
S. creatinine	0.4	mg/dl	0.55–1.3
RBS	118	mg/dl	74–106
BUN	17	mg/dl	7–18
Total bilirubin	0.239	mg/dl	0.20–1.00
CRP	2	mg/l	> 5
S. troponin	Zero	ng/ml	> 0.02
CK-MB	15	IU/L	20–200
Free T3	2.47	pg/ml	1.58–6.91
Free T4	1.09	ng/dl	0.7–1.48
TSH	1.747	u/Uml	0.55–4.78
S.PTH	32.0	Pg/ml	15–68
Anti-nuclear Ab (ANA)			
Nuclear pattern	Negative		
Cytoplasmic pattern	Negative		
Mitotic pattern	Negative		
HSV-1 IgG	15.8		< 9 negative 9–11 equivocal > 11 positive
HSV-1 V IgM	1.2		< 9 negative 9–11 equivocal > 11 positive
HSV-2 IgG	1.3		< 9 negative 9–11 equivocal > 11 positive
HSV-2 IgM	1.7		< 9 negative 9–11 equivocal > 11 positive
CMV Ab IgG	37.2		Negative up to 6
CMV Ab IgM	3.2		Negative < 18 Intermediate < 22 Positive > 22
EBV VCA IgM	55.6		Up to 150 negative 150–180 cutoff > 180 positive
EBV-VCA-IgG	118 µ/ml		Up to 150 negative 150–180 cutoff Over 180 positive

Table 2 CSF analysis, oligoclonal bands, and NMDA receptor antibodies

Color	Colorless	Colorless
Aspect	Clear	Clear
Cell count	15 cu mm	(0–5 lymphocytes)
Differential count		
Neutrophils	Zero %	Zero
Lymphocytes	100%	< 5
Gram stain	No bacteria	No microorganisms
Ziehl–Neelsen stain	No acid fast bacilli	No TB bacilli
Sugar	58 mg%	50–80 mg/dl
Protein	30 mg%	15–45 mg/dl
Oligoclonal bands in CSF by isoelectric focusing		
Serum	Zero band	Zero band
CSF	8 band	Less than 2 bands
Oligoclonal band	Positive	
Immunology		
NMDA receptor Ab		
NMDA receptor Ab	Positive 1/100	Negative < 1/10

excessively about religious matters as no God except Allah. She had also expressed her desire to die in Ramadan while she is fasting; she got easily confused and even paranoid; she could not focus, could not sleep, and could not sit still. During the same time period, there was a fluctuation in the level of orientation to time, place, and person.

This acute confusional state was initially diagnosed by psychiatrists as acute psychosis and received antipsychotic medications; as the symptoms worsened, she received one session of electroconvulsive therapy; the fever persisted, and the consciousness level deteriorated

Table 3 Meningitis/encephalitis panel by Biofire Film Array (Multiplex PCR)

Bacteria	Result	Viruses	Result
Escherichia coli	Not detected	CMV	Not detected
H. influenza	Not detected	Enteroviruses	Not detected
Listeria monocytogenes	Not detected	HSV1	Not detected
Neisseria meningitidis	Not detected	HSV2	Not detected
Streptococcus agalactiae	Not detected	Human herpes virus 8	Not detected
Streptococcus pneumoniae	Not detected	Human parechovirus	Not detected
		Varicella zoster virus	Not detected
Yeast: *Cryptococcus neoformans*	Not detected		

Table 4 Patient management

Therapy and dosage for anti-NMDAR encephalitis
Intravenous immunoglobulins (IVIG:0.4 g/kg + methylprednisolone 1 gm iv daily for 5 days followed by:
Prednisolone 1 mg/kg/day in a tapering dose
Agitation
Haloperidol 5 mg iv stat dose
Clonazepam: 0.5 mg once daily
Convulsions and abnormal movements: levetiracetam: 500 mg iv twice daily
Additional consideration
Ryle feeding replaced after 4 weeks by gastric tube placement
Gastric tube placement for 2 weeks
Early physical therapy

more; she was referred to the fever hospital as suspected encephalitis.

On examination

The patient was febrile with generalized spasticity; pupils were rounded, regular, and reactive 10/15 (E5V1M4). There was unilateral abnormal slow movement on the right hand and right side of the face mimicking focal fits. Systemic examination was within normal.

CBC: mild normocytic normochromic anemia.

CRP: 2 mg/l, normal metabolic panel, and normal ANA.

Urine analysis: normal.

CSF analysis shows lymphocytic pleocytosis: 15 cells/cu mm, no pathogen seen by gram stain, no acid-fast bacilli by Ziehl–Neelsen stain, sugar: 58 mg%, protein: 30 mg%, negative CSF culture.

CSF viral meningitis panel (Biofire Film Array®) was negative.

CSF and serum electrophoresis (by isoelectric focusing): oligoclonal band.

Normal abdominopelvic ultrasound examination.

EEG: diffuse slowing with no epileptiform activities (diffuse encephalopathy).

Brain CT examination without contrast was normal.

Brain MRI with gadolinium and MRV: normal.

A thorough workup for neoplasms was negative including a body PET CT scan.

Given the concern for viral encephalitis, acyclovir was started empirically, but after the meningitis panel, the viral causes were excluded, and we had to think about non-infectious causes of encephalitis, so as regards initial presentation and the neuropsychiatric manifestations, and the MRI result, anti-NMDA antibodies in CSF was requested. She had started intravenous immunoglobulins (IVIG) for presumed autoimmune encephalitis.

CSF result was positive for anti-NMDA antibodies (1/100), and then, the diagnosis was confirmed as anti-NMDA receptor encephalitis.

Intravenous immunoglobulins IV Ig and methylprednisolone were started together with the antiepileptics to control the abnormal movements that mimic the fits.

After a few days, the patient started to show clinical improvement, and their consciousness level improved. Although her recovery was slow, follow-up of the patient was excellent; there were no anxiety or panic attacks, and no hallucinations or paranoid thoughts after 1 month; she was referred for plasmapheresis. After 5 sessions of plasmapheresis, the patient improved more and was discharged home for follow-up.

Discussion

Anti-NMDAR encephalitis patients are usually picked up by psychiatrists [1] since anti-NMDARs play a central role in synaptic transmission helping to modulate human memory and cognition and explain common psychiatric signs and symptoms in this disease including decreased cognition and personality changes [2]. The psychiatric manifestations of anti-NMDAR encephalitis syndrome is preceded by a non-specific prodromal stage that can

include headaches, low-grade fevers, diarrhea, or upper respiratory infection symptoms [1–7].

About half of the cases are associated with tumors, most commonly teratomas of the ovaries [3–5].

Another established trigger is herpes viral encephalitis, while the cause in other cases is unclear [1–3].

The focus issue in this patient is the clinical presentation of delirium caused by autoimmune encephalitis where hyperreligiosity and increased flow of speech leading to excessive talkativeness were the presenting features before she had gone into the state of stupor.

Getting a hyper-religious theme in the context of delirium may not have an impact on the outcome or management, but it may nurture diagnostic confusion as delirious mania, and acute manic episodes with psychiatric symptoms may also have a similar presentation [8, 9].

Diagnosis is typically based on finding specific antibodies in the cerebral spinal fluid [1], MRI of the brain is often normal [2], and misdiagnosis is common [7]. The current diagnosis is based on finding anti-NMDAR antibodies in the CSF or serum. CSF studies show lymphocytic pleocytosis and normal to a mild elevation of protein. The oligoclonal band may be present in 60% of patients [10].

Differential diagnosis

The differential diagnosis often includes a primary psychiatric disorder, drug abuse, neuroleptic malignant syndrome, or infectious encephalitis [11].

In some instances, the diagnosis of rabies has been considered due to the presence of extreme agitation, prominent sialorrhea, and abnormal movements. In contrast to anti-NMDAR encephalitis in which the brain MRI is frequently normal [12], the MRI of patients with rabies often shows symmetric involvement of the gray matter of dorsal brainstem, thalamus, basal ganglia, or central region of the spinal cord [13].

Prognosis is as follows: the recovery process from anti-NMDAR encephalitis can take many months, the symptoms may reappear in reverse order, and the patient may experience psychosis again leading many people to falsely believe the patient is not recovering. As the recovery process continues, the psychosis fades. Lastly, the person's social behavior and executive functions begin to improve.

Conclusion

Autoimmune encephalitis is an important consideration in patients presenting with new onset of the altered mental status of unknown etiology. Emergency physicians are not familiar with this disease.

It can be assumed that hyper-religious thought content can be a part of excited delirium; the presence of hyper-religious thinking does not rule out delirium.

In case of a patient with a suggestive clinical picture of anti-NMDAR encephalitis presenting to the emergency room, lumbar puncture should be performed as soon as possible to look for CSF pleocytosis, oligoclonal bands, and anti-NMDAR in the CSF. Identification of AE is important because it facilitates prompt use of immunotherapy, and triggering malignancy screening as well as detection of any occult neoplasm is critical.

Abbreviations

AE	Autoimmune encephalitis
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptors
EEG	Electroencephalogram
CSF	Cerebrospinal fluid
GCS	Glasgow Coma Scale
CBC	Complete blood count
ANA	Anti-nuclear antibody
CRP	C-reactive protein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CK-MB	Creatine kinase myoglobin binding
S.PTH	Serum parathyroid hormone
HSV	Herpes simplex virus
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
Brain CT	Brain computed tomography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
PET CT	Positron emission tomography
IVIG	Intravenous immunoglobulins

Acknowledgements
Not applicable.

Authors' contributions
AS collected the patient data and wrote the manuscript, H. Ibrahim was the major contributor in writing the manuscript, RA and NM were the clinical pharmacists responsible for reviewing medications regarding doses and drug interactions. Hamdy Ibrahim is the corresponding author, Email address: hamdi1962.hi@gmail.com, All authors read and approved the final manuscript.

Funding
No funding sources; not applicable.

Declarations

Ethics approval and consent to participate
Not applicable for this section.

Consent for publication
Written and signed consent to publish the information is available from the parent of the patient for publication of this case report. Informed consent was received by the authors as part of the submission process.

Competing interests
The author declares that they have no competing interests.

Received: 2 November 2022 Accepted: 7 March 2023
Published online: 06 April 2023

References

1. Kayser MS, Dalmau J (2011) ant-NMDA receptor encephalitis in psychiatry. Current psychiatry Rev 7(3):189–183
2. Wang D, Fries B (2014) Anti-NMDAR encephalitis, a mimicker of acute infectious encephalitis and a review of the literature. ID cases 1(4):66–67
3. Barry H, Byrne S, Barret E et al (2015) anti-N-methyl-D-aspartate –receptor encephalitis: a review of clinical presentation, diagnosis, and treatment. BJ Psych Bull 39(1):19–23
4. Kayser MS, Dalmau J (2016) Anti-NMDA receptor encephalitis , autoimmunity and psychosis https://www.ncbi.nlm.nih.gov/PMC4409922. Schizophr Res 176(1):3640. https://doi.org/10.1016/j.schres.2014.10.007(10.1016%2Fj.schres.2014.10,00
5. Venkatesan A, Adatia K (2017) Anti-NMDA-receptor encephalitis from bench to clinic. ACS Chem Neurosci 8(12):2586–2595
6. Dalmau J, Armangue T, Planagumg J, Radosevic M, Mannara F, LeypddtF Geis C, Lancaster E, Titulaer MJ, Rose field MR, Graus F. (2019) An n update on anti-NMDA receptor encephalitis for neurologist and psychiatrist mechanisms and models. Lancet Neurol 18(11):1045–1057
7. Minagar, Alireza, Alexander J. Steven (2017). Inflammatory disorders of the nervous system pathogenesis, immunology, and clinical management (https //books?id=FoZtD gAAQBAJA pg=PA 177) Humana Press. P.177-ISBN9783319512204. Retrieved 14 July 2018
8. RosenzWeig I, Earl H, Wai C, Girling D, Thompson F (2011) Geriatric manic delirium with no previous history of mania. J Neuropsychiatry Clin Neuro Sci 23:39–41
9. Karmacharya R, England ML, Ongur D (2008) Delirious mania: clinical features and treatment response. J affect Disord 109:312–6
10. DalmauJ L (2011) E, Martinez – Hernandez E et al Clinical experience and laboratory investigations in patients with anti NMDAR encephalitis. Lancet Neurol 10:63–74
11. Gable MS, Gavali S, Radner A et al (2009) Anti NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis 28:1421–1429 {PMC free article } {Pub Med} {Google Scholar}
12. Dalmau J, Gleichman AJ, Hughes EG et al (2008) Anti-NMDA–receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7:10091–10098
13. Laothamatas J, Sungkarat W, Hemachudha T (2011) Neuroimaging in rabies. Adv Virus Res 79:309–327 ({Pub Med} {Google Scholar})

Publisher's Note