Türk Psikiyatri Dergisi

Turkish Journal of Psychiatry

Letter to the Editor

ANTI-NMDA RECEPTOR ENCEPHALITIS MIMICKING A PRIMARY PSYCHIATRIC DISORDER IN A 13-YEAR-OLD GIRL

Dear Editor,

Anti-NMDA receptor (NMDAR) encephalitis has only recently been described as a cause of paraneoplastic and autoimmune encephalitis (Dalmau et al. 2008). Herein we present a 13-year-old girl with NMDAR encephalitis characterized by acute mania at onset, which was initially misdiagnosed as a primary psychiatric disorder. No evidence of a tumor was found. Intravenous immunoglobulin (IVIG) was administrated (table) and full recovery occurred 19 months after onset.

A 13-year-old previously healthy girl was hospitalized in our department (Department of Child and Adolescent Neurology of the National Institute of Neurology (Tunisia)) on the 5th of March , 2010 due to fluctuating behavioral disturbances. Her family reported that she had had been experiencing sudden changes in mood and was becoming increasingly irritable. Then, she exhibited acute manic symptoms (logorrhea, euphoric state, insomnia, inappropriate sexual behavior agitation, and extreme irritability alternating with a state of unresponsiveness). Neurological examination and brain MRI were normal. A primary psychiatric disorder was suspected. The patient developed tonic jerks of the right hemibody 3 d after onset of manic symptoms. Electroencephalography (EEG) showed a theta rhythm of 4-6 Hz. CSF analysis showed mild lymphocytic pleocytosis (WBC: 17 mL^{-1}). Acyclovir and valproic acid were initiated on the 10th of March, 2010 due to suspected viral encephalitis, and 9 d later she developed high-grade persistent fever and disturbed consciousness with complex abnormal movements (stereotyped episodes of brief repetitive dystonic posturing of the left hemiface and left upper extremity, orofacial dyskinesias, hypersalivation, and chewing movements).

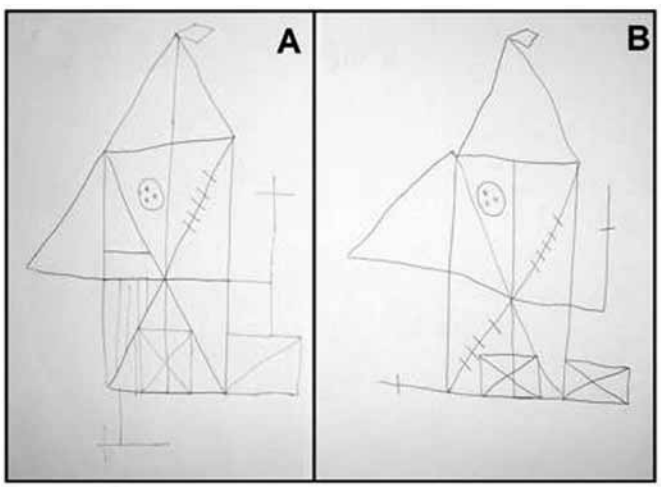
Complex partial status epilepticus was suspected and as such, the patient was given intravenous clonazepam, but improvement was not achieved. Video-EEG showed that EEG activity and polymorphous dyskinesias were not correlated. On the 21st of March, 2010, the patient developed autonomic imbalance and was given midazolam (0.1 mg/Kg/d) for 5 d. Viral serological findings were negative, as were the findings of extensive screening for systemic diseases. During the following 2 weeks, the patient had visual and auditory hallucinations, echolalia, echopraxia, and mutism. She was treated with neuroleptics without improvement. Autoimmune encephalitis was suspected and tests for onconeural antibodies (Hu, Yo, Ri, CV2/CRMP5, amphiphysin, Ma1, and Ma2) were negative. CSF screening for NMDA receptor antibodies (NR1-NR2) was positive. Following the diagnosis of NMDAR encephalitis, pelvic US and thoracic-abdominopelvic CT were performed, but provided no evidence of a tumor. IVIG (0.4 $g{\cdot}kg^{-1}{\cdot}d^{-1}$) was administrated for 5 d on the 4th of April 2010 (Table).

Table 1. The course of cognitive assessment following immunoglobulin treatment

Time (months)	1	2	3	4	5	6	10	14→17	18	19
Immunoglobulin (number of cure)	0	2	1	1	1	1	0	4	1	1
WISC-III										
Immediate shortw-term memory: Digit span forward (standard = 6)	Impossible	Impossible	2	4	4	4	4	4	5	6
Working memory: Digit span backward (standard = 4)	Impossible	Impossible	2	2	2	2	3	3	4	4
Intellectual quotient (PM 38)	Impossible	Impossible	Impossible	80	85	85	85	85	90	100
Executive dysfunction	Impossible	Impossible	+++	+++	+++	+++	++	++	+	–
Mood disturbances	++	++	+++	++	++	+	+	+	–	–
Behavioral disturbances	+++	++	+	+	+	–	–	–	–	–

WISC-III : Wechsler Intelligence Scale for Children, 3rd Edition.
–: Absent; +: mild; ++: moderate; +++: severe.

Figure. Simple **Rey**-Osterrieth Complex Figure **Test**.



A. Rey figure copy (type 1: time = 4 min).
B. Rey figure immediate recall (type 1: time = 3min28s).

During the next 10 d, the patient did not exhibit any movement disorder and was not febrile, although she still appeared perseverative. She was given 5 additional monthly IVIG trials from April to August 2010 (table). On December 2010, neuropsychological tests showed improvement in memory and executive function (Table). Follow-up CSF screening for NMDA receptor antibodies performed on January 2011, showed low-level positivity. As such, 6 additional IVIG trials were administrated from April to August 2011(table) and 19 months after onset of manic symptoms, the patient had normal neuropsychological test results and had resumed attending school (Table and Figure).

The present patient presented with a non-paraneoplastic form of NMDAR encephalitis, with improvement after immunotherapy. NMDAR encephalitis is a newly described limbic encephalitis that has been primarily observed in young women with ovarian tumors (Irani et. al. 2011; de Broucker and Martinez-Almoyna 2010; Dalmau et. al. 2008); however, it is increasingly seen in females without tumors, in men, and in children (Florance et. al. 2009). A high incidence (25 to 48%) of prodromal flu-like symptoms has been described (Irani et. al. 2011; Dalmau et. al. 2008). Psychiatric features associated with NMDAR encephalitis include catatonia, confusion, hallucinations, and memory deficit (Irani et. al. 2011; de Broucker and Martinez-Almoyna 2010). In the presented patient, psychiatric disturbances were the initial presenting feature and were initially misdiagnosed as a psychiatric disorder. They included such manic symptoms as logorrhea, insomnia, inappropriate sexual behavior and irritability, which were followed by visual and auditory hallucinations, echolalia, echopraxia, and mutism.

Recently, cases of NMDAR encephalitis with pure psychiatric features, including late onset autism or childhood disintegrative disorder, have been reported in children (Creten et al. 2011). Additional research is needed to more clearly define the range of clinical presentation in children, because the impact of psychiatric symptoms may be especially challenging in the pediatric population (Creten et. al. 2011). The psychiatric features, seizures, and abnormal movement disorders in the present case led to the suspected diagnosis of NMDAR encephalitis, which was confirmed via screening for specific an-

tibodies. No evidence of a tumor was noted in the presented patient.

Because of the severity of the disease, NMDAR encephalitis patients are usually referred to an ICU (Wandinger et al. 2011). The treatment protocol is fairly well codified and usually consists of immunotherapy and tumor treatment (in the presence of a tumor). Interestingly, patients with non-paraneoplastic NMDAR encephalitis do not respond as well to immunotherapy as do patients with paraneoplastic encephalitis (Kuo et al. 2012). In the presented patient 12 IVIG trials given during a period of 19 months (table) led to recovery. As relapses can occur, neurological follow-up and periodic screening for ovarian teratoma for at least 2 years are strongly recommended.

NMDAR encephalitis is a complex immune-mediated disorder with polymorphous symptoms, including psychiatric features that may lead clinicians to misdiagnose a psychiatric disease. Despite its severe spontaneous course, NMDAR encephalitis has a good prognosis. Early recognition of this entity prevents cognitive sequelae; therefore, we think it essential that all clinicians be aware of NMDAR encephalitis.

Conflict of interest

The authors declare they have no conflicts of interest relevant to the materials presented herein.

Keywords: Anti-NMDA receptor encephalitis, acute mania.

REFERENCES

Creten C, van der Zwaan S, Blankespoor RJ et al. (2011) Late onset autism and anti-NMDA-receptor encephalitis. Lancet, 378:98.

Dalmau J, Gleichman AJ, Hughes EG et al. (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol, 7:1091-8.

de Broucker T, Martinez-Almoyna L (2010) Anti-NMDA-receptor encephalitis. Med Mal Infect, 40:1-5.

Florance NR, Davis RL, Lam C et al. (2009) Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol, 66:11-8.

Irani SR, Bera K, Waters P et al. (2011) N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain, 133:1655-67.

Kuo YL, Tsai HF, Lai MC et al. (2012) Anti-NMDA Receptor Encephalitis with the initial presentation of psychotic mania. J Clin Neurosci.,19: 896-8.

Wandinger KP, Saschenbrecker S, Stoecker W et al.(2011) Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. J Neuroimmunol 231:86-91.

Nedia Ben Achour, *MD, Resident, UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.* ***DOI:*** *10.5080/u7147*

Ilhem Ben Youssef-Turki, *MD, Assoc. Prof., UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Meriem Messelmani, *MD, Resident, UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Ichraf Kraoua, *MD, Assist. Prof., UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Jihene Yaacoubi, *MD, UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Hedia Klaa, *MD, UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Aida Rouissi, *MD, UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Hanen Benrhouma, *MD, Assist. Prof., UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*

Malika Ben Ahmed, *MD, Assoc. Prof., Department of Clinical Immunology. Pasteur Institute, Immunology, Tunis.*

Adrien Didelot, *MD, Prof., Center of Reference For Diagnosis and Treatment of Neurological Paraneoplastic Syndrome, Neurology, Lyon.*

François Ducray, *MD, Prof., Center of Reference For Diagnosis and Treatment of Neurological Paraneoplastic Syndrome, Neurology, Lyon.*

Neziha Gouider-Khouja, *MD, Prof., UR 06 /11 and Department of Child and Adolescent Neurology. National Institute of Neurology, Tunis.*