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CASE REPORT

Rare cause of acute psychiatric manifestation in children: a case report of anti-NMDA receptor encephalitis

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ABSTRACT

Background: NMDA (N-methyl-D-aspartate, a glutamate receptor) receptor is involved in higher brain functions including learning and memory. Anti-NMDA receptor encephalitis is an autoimmune disorder with complex presentations that includes psychiatric symptoms, memory deficits and autonomic instability. It has been recognized as an important differential diagnosis in patients presented initially with psychiatric manifestations. Patients present variant signs that range from anxiety symptoms and seizure to unresponsive states, which may mislead diagnosis towards psychosis in the emergency department as this disease is a neurological disorder in psychiatric disguise.

Case presentation: We present a case of a 6 years old girl with psychiatric manifestations in terms of change in behavioral aspects like being fearful, restless and anxious, which progressed to autonomic instability and decreased level of consciousness within days. EEG was carried out beside anti-NMDA receptor antibodies, and the patient was diagnosed with anti-NMDA receptor encephalitis, which was treated with monoclonal antibody (rituximab) and psychotropic medication, all symptoms subsided and full recovery was obtained after a few months.

Conclusion: This case describes a treatable medical condition that may be missed in emergency settings. Hence, the awareness of this disorder is important for diagnosis as acute psychotic episodes. Correct diagnosis and right evaluation can lead to early intervention and better prognosis.

Keywords: Childhood psychosis, anti-NMDA receptor encephalitis, Autoimmune encephalitis, Paraneoplastic neurological syndromes, acute psychosis, case report.

Background

Psychotic disorders are defined by having neuropsychological abnormalities like delusions, hallucinations, disorganized thinking (speech),grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms of psychotic disorders such as: diminished emotional expression and avolition, alogia, anhedonia, and asociality [1]. Acute psychotic disorders in childhood especially school-going can be either of primary psychiatric disorder or secondary psychiatric illnesses.

The prevalence of childhood psychosis is difficult to establish [1]. The estimated prevalence of psychosis is 17% in children aged between 9-12 years while it drops to 7% among 13 to 18 years old [2]. However, this is the age group that constitute the early onset psychosis that is defined by psychosis presented in age group (12-17 years) while the very early onset psychosis is defined by psychosis onset before age of 12. Still, there is lack of evidence for the psychosis onset before the age of 18 years [3]. It is difficult to diagnose psychosis in children due to many reasons; the difficulty in distinguishing between the real delusions or other psychotic symptoms and the immature responses in children such as thinking

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about magic, secondly, the insidious onset of childhood psychosis and lastly, high percentage of prodromal psychotic symptoms among children and adolescents [4].

There are two main reasons of psychosis: Primary like schizophrenia, brief psychotic disorder and schizoaffective disorder. Secondary causes such as psychotic disorder secondary to: general medical condition, medications or substances, one of the general medical conditions that might present with psychotic features is autoimmune encephalitis.

Autoimmune encephalitis is a neurological disorder caused by antibodies against neuronal cell surface or synaptic proteins. It has been recognized recently over the past 10 years as infectious causes were commonly recognized reasons for encephalitis before this discovery. Its neurological manifestations present the same as the infectious encephalitis but in addition to that it has psychiatric manifestations and lacks fever and CSF pleocytosis [5]. The absence of dysmorphic features, intellectual disability or family history of psychosis increases suspicion of an acquired medical or neurologic cause [6]. The existing diagnostic criteria relies a lot on the antibody testing and response to immunotherapy which is not the case always and because a substantial number of patients who were diagnosed with autoimmune encephalitis were not presented initially with well-defined syndrome, some comorbidities in the initial period might suggest the presence of this disorder. There are many identified types of autoimmune encephalitis and one of recently recognized type is Anti N- methyl-D aspartate receptor encephalitis (anti-NMDA encephalitis) in which there are autoantibodies against theGluN1 subunit of the NMDA receptor [5]. This receptor is involved in higher brain functions such as learning and memory besides its importance in the normal neuronal network in which the hyper activation of this receptor mediates acute neuronal death and chronic neuro-degeneration while hypo activation of NMDA is involved in psychotic manifestations as it is widely distributed in limbic system [7]. Diagnosis of this disorder includes rapid onset of four out of six groups of symptoms which are; Abnormal (psychiatric) behavior or cognitive dysfunction, Speech dysfunction (pressured speech, verbal reduction, mutism) Seizures, Movement disorder, dyskinesias, or rigidity/ abnormal postures, Decreased level of consciousness and Autonomic dysfunction or central hypoventilation, And one of laboratory tests: abnormal EEG or CSF with pleocytosis or oligoclonal bands [5].

This paper describes a case of a 6 year old child who was presented initially with psychiatric manifestations and later was discovered with Anti-NMDA receptor encephalitis. Due to its new recognition, it is often misdiagnosed with early onset psychosis especially in young children forgetting the treatable but rare syndromes this paper emphasizes this disorder in the case described below.

Case presentation

A previously healthy 6 year old girl was presented to emergency department with five days history of change in her behavior in the form of screaming, being restless, and fear of the unknown. She was afraid that something bad would happen to her mother. During those days, she was noticed to be anxious most of the time, her sleep got interrupted, and she frequently woke up frightened. She was noticed to have stereotyped movements on the left side of the body (both upper and lower limbs) which increased during sleep. A day later, she developed fever, two episodes of vomiting and loss of urinary sphincter control (urine) while being aware of it. She stopped going to school and continued to be aggressive towards her family, giving irritable stares that lasted for seconds and became disoriented to people around her. She was then seen in the emergency department by psychiatry on call team and was diagnosed with anxiety disorder (school refusal) and later on she was referred to child psychiatry team to be re-evaluated after she was admitted.

While in the emergency department, she vomited twice and had a spike of fever, and was admitted to general pediatric ward. On the fourth day of admission, she had frequent episodes of bradycardia (documented by electrocardiogram (ECG) that showed sinus bradycardia), accompanied with deterioration in her level of consciousness which necessitated transfer to the pediatric intensive care unit (PICU). Glasgow Coma Scale (GCS) at that time was 11 out of 15 and her muscle power in left side of the body was between 2 and 3 over 5. Pupils were normal in size but had sluggish reflexes and vital signs were stable. While in PICU, she was still having bouts of agitation, fluctuating level of consciousness and the abnormal movements of left upper and lower limbs increased, the assessment was delirium but the cause was not revealed. She was sedated by midazolam and Risperidone syrup was used only for few days aiming to control her agitation. Her GCS dropped to 10 over 15 on 2nd day in PICU and nasogastric tube (NGT) was inserted. Throughout the course of illness, she never had any convulsion or any manifestation of seizure. On the fourth day in PICU her renal function got impaired, she was still agitated, disoriented to family members and others, stopped communicating verbally and became completely silent. Lorazepam was added to control her behavior and amlodipine to reach sinus rhythm. The initial assessment showed almost normal results of blood tests, CSF, CT and MRI of the brain, but electroencephalogram (EEG) showed mild slowness over the right frontal area.

After 17 days in PICU with static neurological findings (while waiting for anti-NMDA receptor antibodies results both from blood and CSF), Rituximab (which is a monoclonal antibody) was initiated as the working diagnosis was anti-NMDA receptor encephalitis. While before that, as anti-NMDAR encephalitis is a rare disorder, management was initiated for viral or bacterial encephalitis for which IV antibiotics (acyclovir &

ceftriaxone) were started then IVIG followed by pulse therapy with methyl prednisone. Then test results were also found to be positive and she was shifted to general pediatric ward. During that time, although she was on Rituximab, psychiatric manifestations were still present: agitation (which was more at the end of the day and towards unfamiliar people), selective mutism, teeth grinding and change of sleep pattern. She was reviewed again by child psychiatry team for assessment of those symptoms.

The patient was still having choreo-athetoid movements, at that point Risperidone syrup was discontinued and Olanzapine was initiated with dose of 2.5 mg once daily then increased gradually to reach 2.5 mg (morning dose) A.M. and 5 mg at bedtime and Trihexyphenidyl in dose of 2.5 mg orally once per day was given to overcome extra pyramidal side effects of Risperdal that would be confusing with the choreoathetoid movements. With these medications patient started to settle, responded to family members and slept well. Then lorazepam was decreased gradually by treating team of general pediatrics. During this time, physiotherapist together with swallowing team became involved to enhance mobility and to prepare for extubation which was done successfully after four months since the admission. By the end of the fourth month, the patient was able to eat a small amount of food, walk with assistance for few meters without falling and was discharged home after a hospital stay of four months & three weeks.

Six months later, she was seen in psychiatric outpatient clinic with full recovery. She was ambulatory, communicating very well and returned to school again and her Olanzapine was reduced gradually and discontinued within few months.

Discussion

Anti-NMDA receptor encephalitis is an autoimmune disorder that has been recognized recently (during the last decade) and only a few publications have focused on the psychiatric manifestations of anti-NMDA receptor encephalitis. Most of the patients have psychiatric symptoms initially as well as neurological ones, which mislead physicians about its diagnosis to include schizophrenia, anxiety and drug toxicity [7,8].

As reported in the literature for similar cases with a diagnosis of anti-NMDA encephalitis, there is progress in the stages from prodromal phase, psychiatric manifestation and seizure followed by autonomic instability and dyskinesia, however most of the cases were in adolescents (as reported they constitute 40% of them) [9] and adults but rarely seen in young children as in this case. Beside that the presentation itself started with psychiatric symptoms that did not reach the stage of bizarre behavior until after a few days from having the fever which made the diagnosis of anti NMDA encephalitis at the bottom of the list and worked on primary psychiatric illness which is anxiety disorder (school refusal) as incidental co-morbid disorder with her medical condition at that time till she started to have rapid progress to autonomic stage and dyskinesia after one day of admission to investigate her fever and sudden loss of sphincter control with disorientation later on the differential diagnosis at that time was mainly towards encephalitis (viral or bacterial) or drug toxicity. Diagnosis of anti NMDAR encephalitis later on was made by confirmation of both blood and CSF presence of autoantibodies.

The treatment of patients with anti-NMDA encephalitis without tumor is challenging. Some cases of anti-NMDA encephalitis can present with tumor, in this case it is called Paraneoplastic Neurological Syndromes (PNS).

In this syndrome, an immune response occurs against neuronal proteins that are directly involved in encephalitis and they have ovarian tumor, mainly occur in young women [10]. Treatment of anti-NMDA encephalitis with resection of the tumor, if present, still has a high positive outcome and up to 80% of them return to near baseline [11].

As the exact incidence for this disorder is not known yet due to new discovery of this disorder, the increase number of case reports for it shows that it is more frequent that other known paraneoplastic encephalitis. It has to be suspected in any patient younger than 50 years who presents with rapid change in behavior, autonomic instability or abnormal movement. The antibody test should be done in both serum and CFS to ensure diagnosis. It is also important to have periodic screening to assess effectiveness of treatment. Examination for the presence of tumor should be also done for all patients to exclude ovarian teratoma in females and testicular germ-cell tumor in males and the recommendation is to do periodic screening for ovarian teratoma mainly for two years even if the patient has recovered from encephalitis.

Although there is no standard care, a proposal of treatment guidelines states that concurrent IVIg in dose of 0.4 g/kg per day and methylprednisolone in dose of 1 g/day for 5 days or plasma exchange with removal of tumor if present is preferable as first line therapy. It is difficult to choose plasma exchange in children generally. If there is no response after 10 days, a second line therapy suggested as guide line which is combination of rituximab in dose of 375 mg/m² every week for 4 weeks and cyclophophamide in dose 750 mg/m² (to be given with the first dose of rituximab), and then monthly cycles of cyclophosphamide till clinical features subsides that is usually accompanied with a decrease in both serum and CSF antibodies [12].

The anti-psychotic treatment should be used with caution (especially typical anti-psychotics) such as haloperidol, because it can exacerbate autonomic instability and it becomes very difficult to differentiate related illness from NMS and catatonia [13]. In the case presented above, olanzapine was used with great

effect on both behavior and sleep. Some authors reviewed treatment of psychiatric manifestation of anti-NMDAR encephalitis and ensured that the choice of treatment should not worsen the disease symptoms nor hide the disease revolution. They advised to use atypical antipsychotics for sedation and sleep, while advised valproic acid for mood symptoms, sedation and to control seizure. There isn't significant change with Lithium and benzodiazepines unless there is catatonic symptoms [14]. In literature, many case reports about anti-NMDA encephalitis in adults can be found but very few cases have been reported in children as early recognition and diagnosis is often missed because of its presentation that mimics acute psychotic episode [15].

The importance of early diagnosis of this disorder is to control symptoms and focus on optimal treatment. For such a case, a multidisciplinary approach is required because of the risk of neurological complications (seizure, decreased level of consciousness), the risk of associated pelvic neoplasms and psychiatric manifestations, which could be present with catatonia as described in the literature [8]. Awareness of this disorder as an important differential diagnosis of acute psychotic episode can lead to early intervention and better prognosis.

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List of Abbreviations

ECG	Electrocardiogram
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
IgG	Immunoglobulin G
IV	Intravenous
IVIG	Intravenous Immunoglobulin
NG	nasogastric tube
NMDA	N-methyl-D-aspartate receptor
PICU	Pediatric intensive care unit
PNS	Paraneoplastic Neurological Syndromes

Competing interests
None

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Authors' contribution
Noor Adnan Almodihesh is the sole author of this case report. She drafted, revised, edited and approved the final version of the manuscript.

Consent for publication
Informed consent was obtained from the parents of the subject to present and publish this case.

Ethical approval
No ethical approval is required at our institution for a case report involving a single patient while not disclosing the patient's identity.

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Summary of the case

Patient (gender, age)	1	6 year old, female
Final Diagnosis	2	Anti NMDAR encephalitis
Symptoms	3	Prodromal symptoms followed by disturbed behavior, autonomic instability and choreo-athetoid movements
Medications (Generic)	4	midazolam, Risperdal syrup,Rituximab = monoclonal antibody, olanzapine, Trihexyphenidyl, lorazepam, IVIG, IV acyclovir & ceftriaxone, methyl prednisone
Clinical Procedure	5	EEG, auto-NMDA antibodies screening, CT and MRI brain, CSF testing
Specialty	6	Pediatrics and child psychiatry
Objective	7	Recognition of disorder in acute physical & behavioral changes with rapid deterioration of course of symptoms
Background	8	Not to miss this autoimmune disorder even in very young age group patients
Case Report	9	Anti NMDAR encephalitis
Conclusions	10	Awareness of this disorder as an important differential diagnosis of acute psychotic episode can lead to early intervention and better prognosis.
MeSH Keywords	11	Childhood psychosis, anti-NMDA receptor encephalitis, Encephalitis, acute psychosis, case report