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Anti-NMDAR Encephalitis Presenting as Memory Impairment - A Case Report

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Abstract: ***Background**: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is among the most common autoimmune encephalitides, typically presenting with psychiatric symptoms, movement disorders, seizures, and autonomic dysfunction. Early recognition and immunotherapy are crucial for optimal outcomes. **Case Presentation**: A 15-year-old female presented with a two-month history of progressive memory impairment and behavioral disturbances. Previously excelling academically with exceptional memorization abilities, she developed severe recent memory deficits, inability to recall learned concepts, and withdrawn behavior with angry outbursts. Two months prior, she experienced new-onset seizures characterized by head and eye deviation to the right, oral secretions, and tonic posturing. Examination revealed recent memory impairment, calculation difficulties, and subtle perioral hyperkinetic movements resembling chewing motions occurring multiple times daily. **Investigations**: Complete blood count, inflammatory markers, thyroid function tests, and autoimmune panels were unremarkable. Cerebrospinal fluid analysis showed normal biochemistry and cell counts with negative virology. However, both serum and CSF NMDAR antibodies were strongly positive on cell-based assays. Brain MRI, electroencephalography, and computed tomography screening for malignancy were normal. **Management and Outcome**: The patient received intravenous methylprednisolone pulse therapy for five days followed by tapering oral steroids. Significant clinical improvement was observed, with resolution of memory deficits, behavioral symptoms, and perioral movements. She resumed school attendance confidently without seizure recurrence. **Conclusion**: This case highlights an unusual presentation of anti-NMDAR encephalitis with predominant memory impairment as the initial feature, absent viral prodrome, and normal neuroimaging. High clinical suspicion is essential for diagnosis, particularly in adolescents presenting with subacute cognitive and behavioral changes with movement abnormalities, even when conventional investigations appear unremarkable.*

Keywords: anti-NMDAR encephalitis, autoimmune neurological disorder, adolescent memory impairment, immunotherapy recovery, cognitive and behavioral changes

1. Introduction

Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis, caused by immunoreactivity against the NMDA receptor 1 (NR1) subunit of the NMDA receptor, is one of the most common autoimmune encephalitides, first described in 2007 by Dalmau and colleagues in which psychiatric and neurologic symptoms were found in women with ovarian teratomas (1). The clinical presentation of NMDAr encephalitis encompasses psychiatric symptoms, including agitation and hyperkinetic movements, as well as autonomic dysfunction and seizures (2). It often occurs in young women, with a male to female ratio of approximately 1:3.The average age of onset of symptoms is 21 years, although patients have been described in patients ranging from 8 months to 85 years (3). The diagnosis of anti-NMDAR encephalitis is often difficult and requires exclusion of other similar conditions including; infectious, endocrine and other immune-mediated aetiologies (4). Forms of autoimmune encephalitis are more prevalent than infectious encephalitis and represent treatable neurologic syndromes for which early immunotherapies lead to the best outcomes (5).

2. Case Report

A fifteen years old teenage female was brought to us with complaints of memory and behaviour disturbances for the past two months. She is in her tenth grade, usually good at her scholastic performance and well socialising with her peers and family members. She started forgetting the concepts learned recently and could not reproduce the memorised topics in her exams. She usually recites all thousand five hundred and fifty kurals of Thirukural which she hardly remembers now. Her teachers complained that she is not answering the questions both in oral and written formats. However, she was able to do her activities of daily living and instrumental activities without any difficulty.

In this period, she also had behaviour disturbance in the form of being withdrawn, reduced interaction with friends and family members and angry outbursts. Two months prior to these complaints, she had new onset seizures. First episode was at school where the semiology was not known and on the same day evening she had second episode with head turn to right, eye deviation to right followed by oral secretions and tonic posturing of all four limbs that lasted for five minutes. Imaging was done, that was normal, and she was started on a single anti epileptic. She had no further seizures.

On examination, she had recent memory impairment. Her new learning ability was defective. She had difficulties with calculation.

She had subtle hyperkinetic movement around right perioral area, like a chewing movement. It occurred many times a day, lasting less than 10 seconds, which both the patient and her parents were not aware of. There were no other neurological deficits.

Fifteen-year-old girl with subacute onset memory and behaviour disturbance, history of new onset seizure and a perioral movement suggested a possibility of Autoimmune encephalitis as per Graus et al criteria and investigations were proceeded accordingly.

Investigations

Her blood investigations complete blood count, ESR, CRP, ENA profile, Thyroid function tests, TPO antibodies were negative. CSF biochemistry and cell counts were normal.CSF virology profile were negative. Serum and CSF NMDAR Antibodies done by cell-based assays were strongly positive. Her CT chest, abdomen and pelvis screening were normal. MRI Brain Plain and contrast studies were normal. EEG was normal.

Management

Based on clinical features, examination findings and investigations NMDAR Antibody positive autoimmune encephalitis was diagnosed. She was given pulse IV Methyprednisolone for five days and maintenance tapering course of oral steroids were prescribed. Upon follow up, her memory deficits improved, she could attend her school confidently and give her exams. Her withdrawn nature and anger outbursts improved. Her peri oral movements stopped and no further seizure episodes.

3. Discussion

Anti-NMDA receptor encephalitis is a neuroimmunologic disorder mediated by intrathecal autoantibodies against the GluN1 subunit of the NMDAr. It manifests with a range of neuropsychiatric symptoms, sometimes preceded by a viral-like prodromal syndrome(6). Patients will subsequently experience progressive behavioural and psychiatric symptoms that are later accompanied by neurological symptoms. These psychiatric and behavioural symptoms are typically what leads patients to seek medical evaluation (7). The onset of neurologic symptoms typically occurs within days to weeks following psychiatric symptoms and commonly involves hyperkinetic movement disorders, seizures, and cognitive dysfunction. Cognitive dysfunction typically occurs simultaneously with psychiatric symptoms and is the main contributor to long-term disability (8). Studies have revealed deficits across all cognitive domains, years after the acute phase. Deficits were identified in verbal and visual memory, executive function, attention and working memory, language, and visuospatial function. Particularly, deficits in the memory and executive function may persist long after diagnosis (9). According to the more widespread and diffuse cerebral lesion pattern in NMDAR + AE, patients presented with focal and frequent bilateral tonic-clonic seizures. Semiological features of focal seizures in the NMDAR+ subgroup were diverse regarding impaired awareness and motor or nonmotor onset. In motor-onset seizures, clonic and myoclonic features were characteristics for NMDAR+ patients (10). MDs are common in anti-NMDAR encephalitis with a certain specificity and can assist in the diagnosis of the disease (11).

In recent years, some scholars further explored the influence of age on the various MDs in anti-NMDAR encephalitis and found that hyperkinetic movements, such as chorea, were more often seen in younger patients, whereas hypokinetic movements, such as catatonia and bradykinesia, were more common in older patients (12).

Dyskinesia is observed in a majority of patients with anti-NMDAR encephalitis and frequently includes orofacial dyskinesia that is characteristic of the disease (13). Anti NMDAR IgG antibodies, detected by indirect immunofluorescence assay in the serum and the CSF, are diagnostic for the disease. Antibody titres are higher in the CSF, and in some cases, diagnosis is possible after CSF testing with concurrent negative serum reports. CSF also can have low-grade hypercellularity and oligoclonal bands (14).

Brain MRI can be normal, but nonspecific white and grey matter T2/FLAIR signal hyperintensity can be present, most commonly in the hippocampus. Diffusion restriction positivity has been reported, as well as cerebellar atrophy, as the only irreversible radiologic finding with this encephalitis (15).One specific interictal EEG finding is extreme delta brushes(bursts of beta activity superimposed on diffuse delta activities)- a finding commonly seen in healthy premature neonates. Other EEG abnormalities- generalized theta and delta slowing, subclinical seizures, nonconvulsive status epilepticus- are frequently present but nonspecific findings of encephalopathy or encephalitis. After confirmation of the diagnosis, a comprehensive evaluation should be done to detect underlying malignancy. Whole-body CT, MRI abdomen and transvaginal ultrasound are commonly employed to detect tumours (16).

The diagnosis of probable anti-NMDAr encephalitis can be made when all the following three criteria (17) have been met:1.Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms: Abnormal (psychiatric behaviour) or cognitive dysfunction, Speech dysfunction (pressured speech, verbal reduction, mutism),Seizures, Movement disorders, dyskinesias, or rigidity/abnormal postures, Decreased level of consciousness, Autonomic dysfunction or central hypoventilation. 2. At least one of the following laboratory study results: Abnormal EEG (focal or diffuse slow or disorganized activity; epileptic activity, or extreme delta brush), CSF with pleocytosis or oligoclonal bands. 3. Reasonable exclusion of other disorders: The diagnosis of probable anti-NMDAr encephalitis can also be made in the presence of three of the above group of symptoms and identification of a teratoma, the diagnosis of definite anti-NMDAr encephalitis can be made in the presence of three of the above group of symptoms and IgG anti-GluN1 NMDA receptor antibodies after reasonable exclusion of other disorders

With support from the Autoimmune Encephalitis Alliance, The international expert panel aimed to create a consensus recommendation for the treatment of paediatric NMDARE, which was pragmatic and relevant to a global community and could serve as a practical decision support tool for the clinician confronted with this rare and challenging condition (18). Factors associated with good functional outcome (mRS score of 0 to 2) were adolescent age and first-line treatment with either therapeutic apheresis alone, corticosteroids with IVIG, or corticosteroids with IVIG and therapeutic apheresis. Factors associated with poor functional outcome (mRS score of 3 to 6) were infant or older adult age, ICU admission, extreme delta brush pattern on EEG, lack of immunotherapy within 30 days of onset, and IVIG treatment for 6 months or more. By contrast, relapsing disease was associated with adolescent age, and monophasic disease was associated with rituximab use or IVIG for 6 months or more (18).

Empiric treatment with intravenous methylprednisolone at a dose of 1 g per day for 3–7 days is a common reasonable approach to achieve initial immunosuppressive and anti-inflammatory effect in AE patients (19). Intravenous Ig (IVIg) at a dose of 2 g/kg over 2–5 days is a relatively easy-to-use and timely option for fast immunomodulation when corticosteroids are contraindicated or when the clinical picture is suggestive of or known to be related to antibody-mediated disease (eg, probable or definite NMDAR-antibody encephalitis) (20). PLEX (5–10 sessions every other day) is an effective option for acute immunomodulation when corticosteroids are contraindicated or ineffective (21).If there is no meaningful clinical or radiological response to optimised first-line therapy after 2–4 weeks, the addition of a second-line agent with both rapid and sustained immunosuppressive effects can improve the outcome. Both rituximab and cyclophosphamide have been used as second-line agents for rescue therapy in AE with good results (20).

We report this case for some of its unusual presentation of Autoimmune encephalitis. First, there was no viral prodrome preceding the event. Second, the initial presentation was a new onset seizure, where MRI Brain and EEG were normal, giving no clues to the etiology. Third she presented with memory deficits and behaviour disturbance with subtle perioral dyskinesia. Only upon strong clinical suspicion, NMDAR antibodies were tested and found to be positive, and the patient was effectively managed.

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