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Cerebellar ataxia as a presenting symptom in a patient with anti-NMDA receptor encephalitis

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Anti-NMDA receptor (anti-NMDAR) encephalitis is a treatment-responsive autoimmune encephalitis, first described in 2007.[1] Ovarian teratomas are found in one-third of the patients.[2] The clinical features of this disorder vary between patients and age groups and usually include abnormal (psychiatric) behavior or cognitive dysfunction, speech dysfunction (pressured speech, verbal reduction, and mutism), seizures, movement disorders, dyskinesias, or rigidity/abnormal postures, decreased level of consciousness, autonomic dysfunction, or central hypoventilation.[2] Cerebellar ataxia has been described as a symptom during the first months of the disease, especially in young children, in combination with other symptoms.[2,3] It is extremely rare as the initial symptom, especially in adults. We report a case of a female adult with anti-NMDAR encephalitis presenting with cerebellar ataxia associated with recurrent mature ovarian teratomas.

Case report

A 32-year-old woman, born in South Korea and adopted at age 4 months, presented with vertigo, nausea, and vomiting for 4 days. Her medical history consisted of bilateral cystectomy revealing mature teratomas, discovered by ultrasound examination after a missed abortion at age 26 years. During cesarean sections afterward (ages 29 and 31 years), no macroscopic abnormalities were seen. Furthermore, she had had depressive symptoms, treated with venlafaxine for years.

Neurologic examination showed a horizontal gaze-evoked nystagmus to the right without other neurologic signs or symptoms. Laboratory investigations on admission were normal, and brain CT showed no abnormalities.

Initially, she improved after treatment with antiemetic drugs, but after 3 days, she deteriorated quickly, also complaining of headache. Neurologic examination showed nystagmus in all directions and dysarthric speech (cerebellar) that further worsened to impaired speech restricted to one-word sentences. She showed bilateral dysmetria of the lower and especially the upper limbs, truncal ataxia, and inability to stand and walk. Psychiatric evaluation showed rapid progression of depressive symptoms with suicidal ideation and labile affect.

Brain MRI and MRV were normal. CSF analysis and extensive laboratory investigations showed pleocytosis (table). Anti-NMDAR antibodies were negative in serum, but positive in CSF,[4] confirming the diagnosis of definite anti-NMDAR encephalitis.[3]

The patient was treated with IV methylprednisolone 1,000 mg (day 13, 5 days) and IV immunoglobulins 0.4 g/kg (day 16, 5 days). Thorax/abdomen CT and transvaginal ultrasound revealed 2 lesions in the pelvic area with fat tissue and calcifications, suspect for teratomas. Bilateral laparotomic ovariectomy was performed (day 19). Pathologic examination showed mature cystic

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Table Overview of investigations

CSF analysis	
White blood cells	*30 × 10^6/L* (100% mononuclear cells) [ref: <5 × 10^6/L]
Protein	31 [ref: 24–49] mg/dL
Glucose	3.6 [serum: 6.4] mmol/L
Erythrocytes	<5,000 × 10^6/L
Oligoclonal bands	*Present*
IgG index	0.59
IgG quotient	*3.1* [ref: <2.8]
PCR in liquor	
HSV-1, HSV-2, VZV, EBV, enteroviruses, parechoviruses, and *Borrelia*	Negative
Extensive laboratory investigations, among these:	
TSH, anti-TPO, and vitamin E	Normal
Ceruloplasmin, anti-tissue transglutaminase, anti-endomysium, and anti-GQ1b	Negative
Antibodies in serum and CSF	
Anti-NMDAR in serum	Negative
Anti-NMDAR in CSF (cell-based assay and immunohistochemistry)	*Positive*
Anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-amphiphysine, anti-CV2 (CRMP5), anti-Ma1, anti-Ma2, anti-GAD65, anti-LGII, anti-Caspr2, anti-GABA$_B$R, anti-GABA$_A$R, anti-AMPAR, and anti-DPPX	Negative
Urine analysis	
Dipstick test and pregnancy test	Negative

Abbreviations: anti-NMDAR = anti-NMDA receptor; anti-TPO = anti–thyroid peroxidase; EBV = Epstein-Barr virus; HSV = herpes simplex virus; TSH = thyroid-stimulating hormone; VZV = varicella zoster virus.
Abnormal values are shown in italic font.

teratomas, without immature components, containing nervous tissue. Hormone replacement therapy was started.

Her neurologic condition improved within a week, but the depressive mood remained. Recovery was hampered by urosepsis, treated with cefuroxime/amoxicillin. She was treated with a second course of methylprednisolone 4 weeks after the initial treatment and immunoglobulins at 8 weeks for remaining speech impairments and severe depression. This resulted in further improvement of both. After 6 weeks, the patient was transferred to a rehabilitation unit.

After 6 months, the patient returned home. She was able to perform activities of daily living independently, but needed walking aids outside due to residual ataxia and had not returned to work (yet).

Discussion

This case with cerebellar ataxia as an initial symptom highlights an unusual presentation of anti-NMDAR encephalitis. If cerebellar ataxia is present in patients with anti-NMDAR encephalitis, it is almost exclusively found in (young) children, and most frequently, it appears later in the disease in combination with other symptoms.[2] Different brainstem-cerebellar symptoms have been described, such as opsoclonus-myoclonus syndrome, ocular movement abnormalities, and low cranial nerve involvement in patients with ovarian teratomas, but these symptoms have more frequently been described in whom no NMDAR antibodies could be identified.[5] Although 2 simultaneously occurring paraneoplastic neurologic syndromes, due to an ovarian teratoma, cannot be fully excluded, this is considered unlikely. The development of multiple symptoms quickly into diseases compatible with anti-NMDAR encephalitis (psychiatric symptoms and mutism), the confirmation of NMDAR antibodies by different tests,[4] and the identification of an ovarian teratoma are suitable with a diagnosis of "definite anti-NMDAR encephalitis."[3]

Although it is known that anti-NMDAR IgG antibodies bind to granular cells in the cerebellum (but not to Purkinje cells),[6] it is unknown why only approximately 5% of patients show cerebellar complaints. MRI abnormalities of the cerebellum have been described in 6% of patients.[7] A small study showed

progressive cerebellar atrophy by follow-up MRI in 2 of 15 patients with anti-NMDAR encephalitis.[6]

In conclusion, cerebellar ataxia is unusual in adult patients and an extremely rare presenting symptom of anti-NMDAR encephalitis. This case shows that anti-NMDAR encephalitis should be considered in the differential diagnosis of cerebellar ataxia, especially in patients with previous teratomas and those developing other symptoms shortly afterward.

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