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CASE REPORT

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# Anti-dopamine receptor 2 antibody encephalitis in adults: a case report

Xiaoke Wu[1†], Mengmeng Shi[1†] and Haifeng Zhang[1*]

## Abstract

**Background** Anti-dopamine receptor 2 (D2R) antibody encephalitis (D2R encephalitis) is a subtype of autoimmune encephalitis (AE). Lesions in affected patients primarily involve the basal ganglia, resulting in a range of psychiatric and movement disorders. A majority of cases reported to date have impacted children or adolescents, whereas we here describe a case of adult-onset D2R encephalitis.

**Case presentation** A 30-year-old female patient affected by insomnia, recent memory impairment, bradykinesia, decreased responsivity, increased muscular tone of the extremities, and involuntary shaking of the right limb. Magnetic resonance imaging (MRI) of the basal ganglia did not reveal any notable findings, and both serum and cerebrospinal fluid were positive for antibodies specific for D2R. D2R encephalitis was diagnosed following the exclusion of other diseases. The patient's symptoms improved significantly with immunotherapeutic treatment, and she recovered fully over a 6-month follow-up period.

**Conclusions** D2R is a new form of AE that can develop in adults and can be effectively treated via immunotherapy.

**Keywords** D2R encephalitis, Autoimmune encephalitis, MRI negative, Adult, Case report

## Background

Autoimmune encephalitis (AE) is a disease of the central nervous system (CNS) in which immune-mediated inflammation results in the development of a range of acute or subacute psychobehavioral abnormalities and related symptoms including seizures, sleep disorders, and movement disorders [1–3]. Anti-neuronal antibodies detected in AE patients are broadly classified into antibodies specific for intracellular antigens, antibodies specific for synaptic antigens and ion channels, and antibodies specific for cell surface antigens. Each of these autoantibody classes can result in distinct symptoms in affected AE patients [4, 5]. D2R is a synaptic channel antigen that is an autoantibody target in some AE cases and that is expressed at high levels in the basal ganglia where it functions through interactions with specific ligands. A potential diagnosis of D2R encephalitis should be considered when patients exhibit symptoms of basal ganglia involvement including motor, mental, and sleep disorders [6, 7].

D2R encephalitis is a form of AE driven by autoantibodies specific for the N-terminal domain of neuronal D2R, resulting in basal ganglia encephalitis characterized by basal ganglia abnormalities detectable by magnetic resonance imaging (MRI), anti-D2R positivity in serum and/or cerebrospinal fluid (CSF) samples, together

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**New & noteworthy** A majority of cases of D2R encephalitis reported to date have impacted children or adolescents. In this article, we describe a case of anti-D2R encephalitis in an adult woman.

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with movement disorders and psychiatric symptoms [8, 9]. In addition to being present in most patients suffering from basal ganglia encephalitis, D2R antibodies are also detectable in a significant minority of patients with Sydenham chorea (SC, an autoimmune syndrome that develops following streptococcal infection), PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; a neuropsychiatric and autoimmune disease in children associated with streptococcal infection), Tourette's syndrome (TS), and acute onset psychosis. There have also been reports of D2R antibodies have also been identified in cases of relapse with chorea after the resolution of herpes simplex encephalitis [10–13]. As is evident from these studies, the use of cell-based neuronal antibody testing has improved the accuracy of the results as the level of testing has increased. Cell-based assays (CBAs) rely on indirect immunofluorescence based on cell transfection. The introduction of antigen genes into mammalian cells results in the specific expression of large quantities of antigen by the cells, and allowing antibodies from patient specimens to bind specifically to the antigen. This is followed by the use of fluorescently labeled secondary antibodies to bind to the patient's antibodies, with the intensity of fluorescence indicating the antibody levels. Therefore, the CBA method maintains the structure of the antigen, retaining its natural conformation, modifications, and other characteristics, and thus provide a more realistic reflection of the natural characteristics of the epitope for effective antibody binding; the sensitivity and specificity of these assays have been recognized [14–16].

D2R encephalitis is a rare subtype of AE that has primarily been reported in pediatric and adolescent patients to date. Few such cases have been described in adults, and below, we describe the case of an adult D2R encephalitis patient.

## Case presentation

A 30-year-old Chinese female without any clear predisposing factors developed impulsive behaviors including irritability and a tendency to throw objects that had been present for 6 months, together with insomnia and the involuntary shaking of the right limb that had been present for over 40 days. These symptoms were relieved through the gradual introduction of psychotropic drug maintenance therapy consisting of venlafaxine hydrochloride sustained-release tablets (75 mg/day) and risperidone orally disintegrating tablets (4 mg/day). She was ultimately admitted to the hospital with the abovementioned symptoms and with new-onset memory impairment, depression, bradykinesia, decreased responsivity, and increased muscle tone of the extremities. She was additionally unable to walk independently and presented with a modified Rankin scale (mRS) score of 4. Physical examination revealed enhanced tension of the limbs with cogwheel rigidity. Dystonic akinesia due to risperidone-related side effects was not considered because of the relatively small dose and the fact that it had been discontinued for about one month. Based on the patient's history and clinical presentation, pathology of the basal ganglia was suspected. Routine blood tests, cranial MRI, long-term video-electroencephalogram (VEEG), CSF analyses, and AE-related antibodies in the serum and CSF were analyzed soon after hospital admission.

Routine bloodwork and MRI scans did not reveal any significant abnormalities (Fig. 1. Brain magnetic resonance imaging. (a) No positive results were found in the T1 sequence; (b) No positive results were found in the T2 sequence; (c) No positive results were found in the DWI, and VEEG results were normal. The CSF pressure was 105 mm$H_2O$, and CSF samples were negative for pathogenic microorganisms. Analysis of the CSF indicated that her white blood cell levels were normal ($4\times10^6$/L), but she exhibited an increased neutrophil percentage (47%),

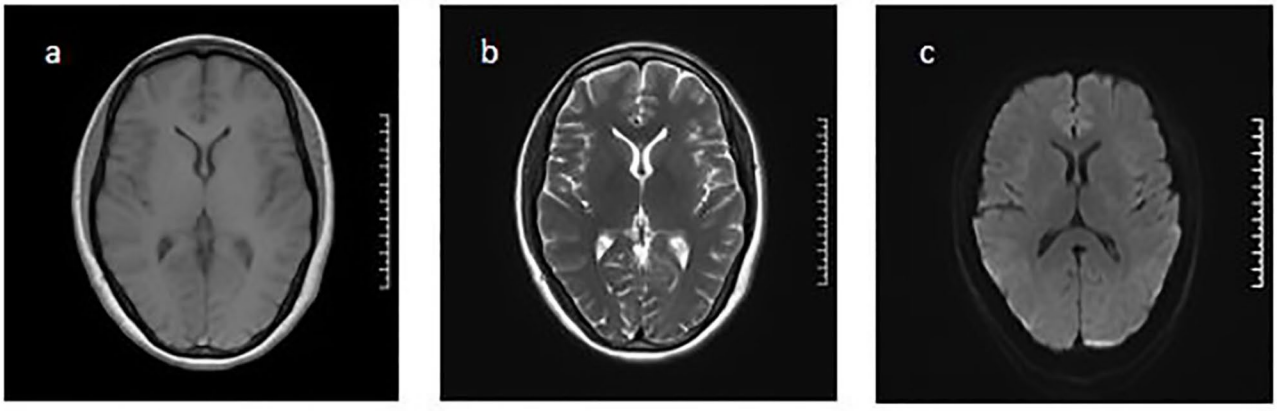


**Fig. 1** Brain magnetic resonance imaging. (**a**) No positive results were found in the T1 sequence; (**b**) no positive results were found in the T2 sequence; (**c**) no positive results were found in the DWI

high albumin levels (325.30 mg/L), elevated protein (577 mg/L), high IgG production index (Index 0.95), and high 24-hour IgG synthesis rate (12.26). The commercial kits of CBA (Euroimmun, Lübeck, Germany) confirmed the presence of anti-D2R IgG (1:1) in the CSF and anti-D2R IgG (1:100) in the serum (Fig. 2. Serum and CSF samples with detection of anti-D2R antibodies by CBA. (a) Cell surface IgG binding of the patient serum diluted 1:100 against D2R transfected cell line; (b) cell surface IgG binding of control serum diluted 1:100 against D2R transfected cell line; (c) cell surface IgG binding of the patient CSF diluted 1:1 against D2R transfected cell line; (d) cell surface IgG binding of control CSF diluted 1:1 against D2R transfected cell line). The detection of other autoimmune encephalitis-associated antibodies, including antibodies against NMDAR, LGI1, CASPR2, GABAB, AMPA1, AMPA2, IgLON5, DPPX, GAD65, mGluR5, GlyR, MOG, and neurexin-3, and anti-neuronal IgG antibodies, including amphiphysin, CV2, PNMA2, Ri, Yo, and Hu, in both serum and CSF samples were negative.

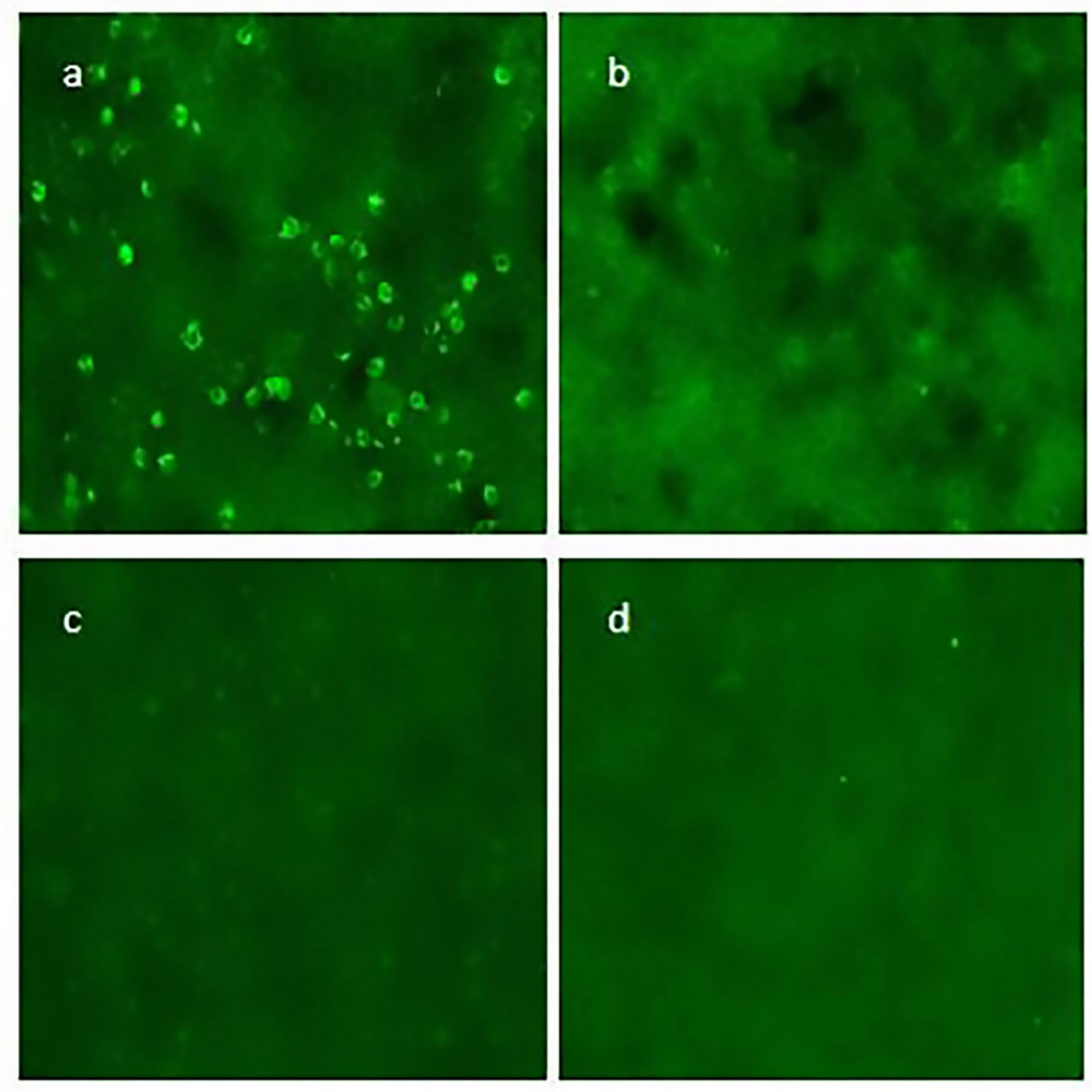


**Fig. 2** Serum and CSF samples with detection of anti-D2R antibodies by CBA. (**a**) Cell surface IgG binding of the patient serum diluted 1:100 against D2R transfected cell line; (**b**) cell surface IgG binding of control serum diluted 1:100 against D2R transfected cell line; (**c**) cell surface IgG binding of the patient CSF diluted 1:1 against D2R transfected cell line; (**d**) cell surface IgG binding of control CSF diluted 1:1 against D2R transfected cell line

The patient was diagnosed with D2R encephalitis based on her medical history and the antibody testing results. Following five days of immunotherapeutic treatment with immunoglobulin (0.4 g/kg/day) and methylprednisolone (500 mg/day) delivered via intravenous infusion, the patient's motor and psychiatric symptoms went into remission and her memory and sleep began to improve, accompanied by increased responsivity and reduced dystonic akinesia. The methylprednisolone dose was halved every 3 days, with treatment for 12 total days, and the patient's symptoms continued to improve. She was able to communicate simply and the score on the mRS scale was 3. Upon hospital discharge, the patient was given oral prednisone tablets (60 mg/day), with the dose being reduced by 10 mg every week and maintained at 10 mg/day after 5 weeks for an extended period.

Follow-up examination at 6 months after hospital discharge revealed that the patient exhibited proper memory, a markedly improved mental state, smooth communication, no shaking of the right limb, and that she was free of any neuropsychological or psychiatric sequelae such that she could live and function independently. Her mRS score at follow-up was 0, and she continues to undergo treatment with oral prednisone (10 mg/day). Her recovery was thus complete after discharge and free of any significant sequelae.

## Discussion and conclusion

### AE-related clinical progress

The steady advancement of medical techniques and diagnostic technologies has spurred gradual increases in the number of AE reports and the reported subtypes of this condition [5, 17]. In patients with AE, autoantibodies may target the basal ganglia, limbic system, or brainstem, contributing to either localized or global inflammation and consequent cognitive dysfunction [3]. For example, when antibodies target D2R, which is expressed at high levels in the basal ganglia, this can contribute to the onset of psychiatric, motor, and autonomic symptoms of dysfunction consistent with D2R encephalitis or other diseases of the basal ganglia diseases [9]. Japanese encephalitis (JE) is a potentially fatal viral infection with a wide range of manifestations that can involve the basal ganglia, resulting in the development of characteristic clinical manifestations related to basal ganglion encephalitis [18]. Even when antibody positivity is not detected, other criteria including a characteristic presentation, imaging results, VEEG results, and outcomes from other pertinent tests can guide AE diagnosis, and patients can be administered appropriate immunotherapeutic regimens that can confer early benefit [4, 19].

### Possible diagnostic criteria

Based on reports to date of cases exhibiting anti-D2R antibody positivity, we propose the following preliminary diagnostic standard for D2R encephalitis: patients meeting essential prerequisite conditions and meeting at least one and one non-core symptom simultaneously can be considered for the diagnosis of D2R encephalitis.

Core symptoms: motor impairment (including dystonia, chorea, bradykinesia) and psychiatric disorders (including depression, anxiety, or other subacute neurological/psychiatric abnormalities).

Non-core symptoms: symptoms consistent with damage to the basal ganglia (including increased tongue extension, tongue biting symptoms in TS), sleep disorders (hypersomnia or insomnia), epilepsy, and cognitive impairment (such as recent declines in memory function).

Prerequisite: positive D2R antibodies titers in the serum and/or CSF (note that these titers may change dynamically such that a negative titer during the early stages of disease does not necessarily exclude a potential D2R diagnosis).

Auxiliary examinations: patients may exhibit other signs such as abnormal basal ganglia signal on MRI evaluation, EEG results exhibiting either normal activity or a lack of specific slow-wave activity may be observed, and patients should undergo routine CSF, cytology, and paraneoplastic antibody analyses to exclude other potential diseases.

### Clinical manifestations of D2R encephalitis

D2R encephalitis generally presents with dystonia and dystonic tremor, a range of movement disorders such as chorea and Parkinson's disease, and pronounced psychosocial abnormalities including memory loss, impaired sleep, cognitive deficits, and other symptoms associated with basal ganglia involvement. These symptoms can be highly heterogeneous among patients [9]. While seizures are a key manifestation of AE, they impact just 20% of D2R encephalitis patients as compared to 73% of NMDAR encephalitis patients [20].

### D2R antibody-positive disease

SC, PANDAS, and TS may all exhibit basal involvement and exhibit anti-D2R antibody positivity [9]. Immune responses resulting in PANDAS and SC can result from streptococcal infections, and some SC patients exhibit D2R serum and/or CSF positivity. However, such positivity is relatively rare, suggesting that anti-DR2 antibody production is not dependent on the streptococcal-triggered immune response. PANDAS is an atypical autoantibody-related disease of the CNS that occurs in children and progresses rapidly, resulting in motor, verbal, and obsessive-compulsive symptoms for which appropriate

antibiotic treatment can be effective [21]. D2R seropositivity is not specifically related to PANDAS diagnosis, and some patients may be positive for anti-D2R whereas others are negative for these autoantibodies [22]. Some herpes simplex encephalitis (HSE) patients also develop serum D2R antibody positivity following relapse together with chorea, which can be relieved by immunotherapeutic treatment [11].

### Auxiliary examinations for D2R encephalitis patients

MRI scanning is a key auxiliary examination used to diagnose a wide range of neurological conditions. MRI scans from D2R encephalitis patients may exhibit an abnormal basal segment signal consistent with encephalitis primarily impacting this region. However, in some patients, these MRI findings may initially be normal during the onset of the disease, as has been reported in 40% of the 22 D2R antibody-positive encephalitis reported to date [9–11, 23–26]. VEEG examination results are generally routine and can exhibit nonspecific findings in ~22% of cases, providing further support for a model in which D2R antibody encephalitis primarily impacts the subcortical regions of the basal ganglia, with scalp EEG failing to detect any abnormal seizures [9–11, 23–26].

### D2R autoantibody detection

The diagnosis of AE is highly dependent on the CBA-mediated detection of relevant serum and CSF antibodies, although AE cannot be definitively excluded if these assay results are negative [10]. In reported D2R encephalitis cases, serum and CSF samples are initially negative for D2R autoantibodies, with anti-D2R positivity only developing with the dynamic progression of the disease [23]. The rate of serum anti-D2R positivity is higher than in CSF samples, with detection rates of up to 90% in published D2R encephalitis cases, potentially suggesting that these antibodies may enter the brain parenchyma directly from the bloodstream, although this remains to be definitively demonstrated. It may also be a consequence of the lack of test sensitivity or insufficient intrathecal immunoglobulin synthesis [9–11, 23–26]. CBA has higher sensitivity and specificity and thus increased confidence in the results, and can also avoid false positives caused by signal distortions seen in enzyme-linked immunosorbent assay (ELISA), which is currently the most commonly used method for the detection of neuronal antibodies. As such, in cases of suspected CNS inflammation it is important that both serum and CSF autoantibody profiles be evaluated in affected patients.

### The treatment and prognosis of D2R encephalitis patients

The most effective available treatment option for AE patients, including those with D2R encephalitis, is an immunotherapeutic regimen. In cases of suspected AE, when serum and CSF antibody testing have not been conducted, first-line immune drug treatment can be administered as appropriate to provide patients with maximal clinical benefit, particularly for the early treatment of patients positive for neuronal surface-specific autoantibodies [27]. The choice of the most appropriate immunotherapy regimen is ultimately dependent on disease severity and clinical classification. First-line treatment options include glucocorticoids, immunoglobulin, and plasma exchange. Second-line treatments can include rituximab and cyclophosphamide, which are primarily administered to tumor antibody-negative NMDAR encephalitis patients exhibiting poor responses to first-line treatment options [28].

#### Abbreviations

| | |
|---|---|
| AE | Autoimmune encephalitis |
| CBA | Cell-based assay |
| CNS | Central nervous system |
| CSF | Cerebrospinal fluid |
| D2R encephalitis | Anti-dopamine receptor 2 antibody encephalitis |
| D2R | Dopamine receptor 2 |
| ELISA | Enzyme-linked immunosorbent assay |
| HSE | Herpes simplex encephalitis |
| JE | Japanese encephalitis |
| MRI | Magnetic resonance imaging |
| mRS | Modified rankin scale |
| PANDAS | Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections |
| SC | Sydenham chorea |
| TS | Tourette syndrome |
| VEEG | Video-electroencephalogram |

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#### Author contributions

XKW and MMS contributed equally to this work. HFZ conceived the idea of this study and revised the article. XKW and MMS contributed to the data extraction and wrote the article. All authors contributed to the article and approved the final manuscript.

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#### Data availability

Data is provided within the manuscript.

## Declarations

#### Ethics approval and consent to participate

The studies involving humans were approved by Ethics Committee of The First Affiliated Hospital of Zhengzhou University (2021-KY-0779). The related information obtained the patient and her legal guardian the informed consent.

#### Competing interests

The authors declare no competing interests.

#### Conflict of interest

The authors declare that they have no conflict of interest.

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