

Clinical and imaging analysis to evaluate the response of patients with anti-DPPX encephalitis to immunotherapy

Jun Xiao

Second Clinical Hospital of Tongji Medical University; Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Pei-cai Fu

Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Zhi-jun Li (✉ zjlhuazhong@163.com)

Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology <https://orcid.org/0000-0001-7198-8632>

Research article

Keywords: anti-DPPX encephalitis, clinical and imaging spectrum, immunotherapy

Posted Date: March 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-104470/v2>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at BMC Neurology on April 5th, 2022. See the published version at <https://doi.org/10.1186/s12883-022-02649-7>.

Abstract

Background: To report the main spectrum, new clinical and imaging characteristics of dipeptidyl-peptidase-like protein 6 (DPPX) antibody-associated encephalitis, and evaluate the effect of immunotherapy.

Methods: A retrospective analysis of nine patients reported describing the clinical and immunological features was performed, and all previously reported cases were reviewed. A cell-based indirect immunofluorescence assay with human embryonic kidney 293 cells transfected with DPPX was used.

Results: Nine patients were identified (median age, 51 years; range, 14–65 years) with prodromal fever, diarrhea, or weight loss, followed by a rapidly progressive encephalopathy characterized by cognitive disorder. One patient who received methylprednisolone therapy and a trail of tacrolimus showed substantial improvement and had no relapse in the six-month follow-up. Our comprehensive literature review demonstrated that a total of 53 cases were reported, of which more than half had prodromal weight loss (52.8%), and gastrointestinal disorders (58.5%). Cognitive (74.6%) and brainstem/spinal cord disorders (75.5%) were the most common major symptoms. Our study is the first to report three patients with anti-DPPX encephalitis who had sleep disorder of rapid eye movement sleep behavior disorder (RBD), limb paralysis (two), severe pleocytosis and elevated protein levels (two) in the cerebrospinal fluid, and increased T2/FLAIR signal abnormalities in the bilateral hippocampus, temporal lobe, amygdala, basal ganglia, thalamus, centrum semiovale, and frontal and parietal lobes in seven cases (77.8%).

Conclusion: Our study expanded the clinical and imaging phenotype of anti-DPPX- encephalitis. We also reported the use of tacrolimus for long-term immunosuppressant therapy in anti-DPPX encephalitis, with substantial improvement and no relapse during a follow-up period of 6 months. Further studies elucidating the entire clinical spectrum of anti-DPPX encephalitis, pathogenic roles, and prognosis under long-term immunosuppressive therapy are warranted.

Background

Autoimmune encephalitis, usually sensitive to immunotherapy, is a group of inflammatory diseases mediated by antibodies against neuronal surface and synaptic proteins, receptors, and ion channels [1]. Recently, newly identified antibodies for autoimmune encephalitis include metabotropic glutamate type 5 [2], gamma-aminobutyric acid receptors type A [3], and dipeptidyl-peptidase-like protein 6 (DPPX) antibody [4].

DPPX, a cell surface regulatory subunit of the voltage-gated A-type Kv4.2 potassium channel, is expressed in neuronal soma and dendrites. It is localized to the hippocampus, cerebellum, and myenteric plexus [5, 6], presenting a multi-regional neurological phenotype for autoimmunity. Anti-DPPX encephalitis is a rare type of autoimmune encephalitis, first described by Boronat et al. in 2013, caused by cell surface DPPX autoantigens [4]. Clinically, this disease is consistent with memory loss, agitation, confusion, psychiatric symptoms, seizures, tremors, myoclonus, ataxia, diarrhea, and weight loss [4, 7, 8]. Immunotherapies are widely used in the majority of patients with anti-DPPX encephalitis, and may be beneficial to most patients regardless of the duration of symptoms. To date, only a few patients with DPPX antibodies have been reported, with little known about the clinical spectrum and treatment outcomes of this disease. Thus, the diagnosis and therapy for anti-DPPX encephalitis remain challenging based on the variety of clinical symptoms and signs.

Here, we reported the clinical features and imaging characteristics of nine patients with anti-DPPX encephalitis and investigated their responses and outcomes to several immunotherapy strategies. We also reviewed all previously reported cases, to expand the clinical and imaging phenotype, aiming to offer new recommendations for immunologic treatment.

Methods

Patients

The study consisted of nine patients admitted to the Department of Neurology, Tongji Hospital, Wuhan, China from December 2018 to December 2019. Patient sera and cerebrospinal fluid (CSF) were found positive for the anti-DPPX antibodies with service testing. Cranial magnetic resonance imaging (MRI) was performed in all cases. Clinical information was obtained from certified neurologists through a structured written questionnaire (Supplementary data), and their clinical characteristics are described in detail below, and summarized in Table 1.

This study was approved by the Ethics Committee of Tongji Hospital, and written informed consent was obtained from all patients or their surrogates before enrollment, for the use of serum, CSF, and clinical information for research purposes.

Serologic and CSF studies

Sera were obtained from all nine patients, with paired CSF specimens obtained from six patients. Anti-DPPX antibodies were detected using a cell-based indirect immunofluorescence assay with human embryonic kidney 293 (HEK293) cells transfected with DPPX, as previously reported [4]. Biochips (Euroimmun, Lübeck, Germany) present the DPPX-antigen on fixed HEK 293 cells. HEK293 cells were transfected with plasmids containing pDNA3 and human DPPX gene using Lipo2000 (Invitrogen, California, US). After incubation for 2-3 days, the reactivity of the antibodies was detected with patients' sera or CSF (dilutions were 1:40/1:2), using a fluorescein isothiocyanate-conjugated antibody from goat (Sigma, St Louis, US) as per the manufacturer's instructions.

Review of reported patients with anti-DPPX antibodies

We reviewed all previously reported cases (44) until September 2020, where anti-DPPX antibodies were detected to evaluate the spectrum of the symptoms, responses to treatment, and imaging characteristics.

Results

Demographic and clinical features

The main clinical findings of the nine patients identified are summarized in Table 1. Six were female, and the median age at onset was 51 years (range, 14-65 years). Five patients had a prodromal headache, four had fever, three had severe diarrhea, and two had weight loss. The development of neurological disorder progressed for a median of 1 month (insidious in 4, subacute in 3, acute in 2). Patients develop a rapidly progressive encephalopathy characterized by cognitive disorder or memory loss (7), accompanied by sleep disorders, including insomnia and rapid eye movement sleep behavior disorder (RBD) (3) and limb paralysis (2). Examination revealed nystagmus and hyperreflexia. Tumor screening detected B-cell non-Hodgkin lymphoma in one patient (case 6), and micropapillary carcinoma of the thyroid was found during the course of the disease in another patient (case 3).

Routine blood work of all the nine patients was normal. CSF data were available for all patients; white cell counts were elevated in two patients (370 and $220 \times 10^6/L$, normal range, $0-8 \times 10^6/L$) and protein levels were elevated in four patients (549 mg/L, 2096 mg/L, 958 mg/L and 609 mg/L; normal range, $150-450$ mg/L), without evidence of any infectious agents. As shown in Figure 1, anti-DPPX antibodies were also detected by immunofluorescence in nine patients (nine serums and six CSF specimens). All patients showed anti-DPPX antibody seropositivity, whereas three CSF specimens were anti-DPPX antibody positive (1:3.2, 1:10, and 1:1, respectively). Tests for other antibodies associated with paraneoplastic syndromes and autoimmune inflammatory disorders were negative in all patients, except for Patient 5, where highly positive titers of autoantibodies against the glial fibrillary acidic protein (GFAP, serum: 1:320; CSF: 1:10) were noted.

Responses to treatment

When anti-DPPX antibodies were detected, all patients received multiple immunotherapies. Five patients were administered methylprednisolone intravenously (1 g for 3 days, 500 mg for 3 days, 240 mg for 3 days, and 120 mg for 3 days), followed by 80 mg prednisolone orally (slowly tapered over 6 months to 5 mg daily). All symptoms, such as memory loss, tremor, and ataxia, showed marked improvement. However, as prednisolone was slowly tapered over 6 months to 5 mg daily, two patients experienced a relapse of symptoms (patient 9, serum titer of 1:10 before immunotherapy, serum titer of 1:32 at follow-up after 10 months). Only one patient received oral steroids due to presentation of mild symptoms that subsequently resolved, except for very slight ataxia during the heel-to-toe test. A single treatment with intravenous (IV) methylprednisolone and a course of IV Ig (0.4 g/kg/dose * 5 days), however, produced only an incomplete effect. Patients 4 and 6 who received IV methylprednisolone therapy mentioned above and a trail of tacrolimus (3 mg, bid) or rituximab (2 cycles every 3 months, each of 375 mg/m²) had substantial recovery after 6 months of follow up.

Brain MRI changes in patients with anti-DPPX antibodies

Abnormalities were reported in brain MRIs of eight patients, of which seven had abnormalities specific for encephalitis. Only one patient showed nonspecific white matter changes. Fig 2A-2C shows increased T2/FLAIR signals in the bilateral hippocampus, temporal lobe, and amygdala. T2/FLAIR signals of the right basal ganglia, thalamus, and the left centrum semiovale and extensive abnormalities in the frontal lobe and parietal lobe were revealed (Fig. 2D-2F). Changes in the functional cortical and basal ganglia regions mentioned above were very common in encephalitis, which could lead to symptoms such as cognitive dysfunction, ataxia, nystagmus, sleep disorder, mood disorder, autonomic symptoms, limb paralysis, and extrapyramidal symptoms.

Summary of anti-DPPX encephalitis syndrome spectrum

Since the disorder of anti-DPPX encephalitis was discovered, till September 2020, the number of patients reported is 44 [4, 7-16]. Combining our nine patients (a total of 53), the median age was 52 years (range 13-76 years), and 34 (63%) were male. Only three patients were aged < 18 years (13, 14, and 15 years).

As shown in Table 2, prodromal headache occurred in six patients (11.3%), weight loss in 28 patients (52.8%), gastrointestinal disorders including diarrhea, gastroparesis, constipation, and abdominal pain in 31 patients (58.5%). Cognitive disorders (74.6%) and brainstem/spinal cord disorders including abnormal eye movement, dysphagia, stiffness, dysarthria, respiratory failure, vertigo, and hyperekplexia (75.5%) were the most common main symptoms of anti-DPPX encephalitis. Other common indications included myoclonus or tremor (49.1%), mood disorders (41.5%), sleep disorders (39.6%), disautonomia (37.7%), cerebellar ataxia (34%), and psychosis (28.3%). Seven patients (12.2%) had generalized seizure attacks and two (3.8%) had limb paralysis.

The presence of tumor was identified in eight patients (one Mantle-cell lymphoma, four B-cell non-Hodgkin lymphoma, one B cell chronic lymphocytic leukemia, one breast adenocarcinoma, and one micropapillary carcinoma of the thyroid).

Patients with anti-DPPX encephalitis might have elevated white cell count and protein levels in the CSF (42.9%), however, no evidence of infectious agents was found. Tests for other antibodies associated with autoimmune inflammatory disorders were negative in most, except for two cases. In one patient, highly positive titers of autoantibodies against GFAP (serum: 1:320; CSF: 1:10) were detected, while AQP4 antibodies were found in the serum (1:375) but not in the CSF of the other patients [14].

Multiple immunotherapies were used in 45 patients (81.1%). Follow-ups were observed in 47 patients, including 8 patients without immunotherapy: 23 (48.9%) had marked improvement, nine (19.1%) had incompletely resolved issues, nine (19.1%, 6 of them treated without immunotherapy) had no improvement, and six (12.8%, 2 of them treated with no immunotherapy) patients had died. Ten patients (21.3%) had clinical relapses, most of them occurred in steroid taper. Seven of them received immunosuppressants subsequently (rituximab, cyclophosphamide, or tacrolimus); all showed clinical improvement, whereas others had poor outcomes (two died, one had clinical progression).

Discussion

DPPX, a widely expressed cell surface neuronal auto-antigen, is a regulatory subunit of the voltage-gated Kv4.2 potassium channel complex [4, 17, 18]. DPPX proteins are distributed in both the nervous and enteric systems, including hippocampus, cerebellum, cortex, brainstem, and submucous plexus neurons [4, 8, 17], which may lead to prominent manifestations, including encephalopathy, sleep disturbance, and gastrointestinal symptoms [18]. Although 44 cases of anti-DPPX encephalitis have been reported and studied, the clinical and imaging characteristics, mechanism, and treatment strategy of this disease remain poorly understood. Here, we report nine new patients with anti-DPPX encephalitis, and review all the cases previously reported.

As shown in Table 2, the clinical presentation of our cases was dominated by cognitive disorders including memory loss (77.8%), and the majority of our patients had gastrointestinal symptoms (44.4%) and sleep disorders (44.4%), whose features were similar to those previously reported.

With the increasing number of new patients, the spectrum of anti-DPPX encephalitis is likely to expand further. First, a noteworthy clinical feature was limb paralysis in two of our nine patients (22.2%), while the trunk and limbs were never severely involved in the previously reported 44 patients. Moreover, increasing evidence indicates a strong association between RBD and Parkinson's disease, dementia with Lewy bodies (DLB), and voltage-gated potassium channel antibody-associated limbic encephalitis, principally against CASPR2 and LGI1 [19–22]. In our case series, we first report three patients with anti-DPPX encephalitis who had a sleep disorder with features characteristic of RBD. Second, previously reported cases showed only mild pleocytosis (130 cells/ μ L, maximum) and elevated protein levels (820 mg/L, maximum) in CSF. Contrastingly, changes were severe in our two cases (WBC count 220 and 370 cells/ μ L; protein level 2096 mg/L, maximum). Third, of 44 previously reported patients, only nine had abnormalities in brain MRI, mostly non-specific changes, including white matter changes and temporal lobe or hippocampus atrophy [23, 24]. Doherty suggested that FDG-PET showed increased FDG activity in the left medial, right lateral, and bilateral inferior recti, correlating with the slow phases of horizontal (LB) and vertical (UB) nystagmus [10]. Zhou showed markedly decreased metabolic activity in the bilateral mesial temporal lobes (especially the left side) on 18 F-FDG PET-MR [13]. Increased T2/FLAIR signal abnormalities in the bilateral hippocampus, temporal lobe, amygdala, basal ganglia, thalamus, centrum semiovale, frontal lobe, and parietal lobe were observed in seven cases (77.8%), which could explain the symptom of limb paralysis. These findings could enrich the understanding of the pattern of this relatively rare disease, enabling more comprehensive recognition of new cases. Therefore, in the context of unclear etiology and various manifestations, it should raise more concern for anti-DPPX encephalitis.

Paraneoplastic and autoimmune encephalitis may occur with antibodies against neural or glial antigens. Bien reported a case of paraneoplastic occurrence of antibodies against DPPX and AQP-4 in a patient with breast cancer and encephalitis [14]. Unlike the AQP-4 antibody, GFAP astrocytopathy is a meningoencephalomyelitis characterized by the detection of immunoglobulin G against GFAP in CSF, coexisting autoantibodies detected in the same patient, sometimes with paraneoplastic cause, called an overlapping syndrome [25–28]. We first report a 14-year-old patient with both autoantibodies against DPPX and GFAP, however, no tumor was detected within one year of follow-up. Further studies should be conducted.

Patients with anti-DPPX encephalitis appear to respond well to early initiated immunotherapy, including IVMP or oral steroids, and relapse accompanies steroid tapering, so long-term immunosuppressant therapy is needed to sustain optimal neurologic outcomes [4, 7, 8, 16]. Although rituximab alone or combined with other therapies (cyclophosphamide or azathioprine) have been reported to be highly effective in numerous autoimmune disorders [29–31], as occurred in our study and previous studies, the high costs or intolerable adverse events (deadly infections, granulocytopenia, and progressive multifocal leukoencephalopathy) interfere with their wide applications.

Tacrolimus, a calcineurin inhibitor, a first-line immunosuppressive drug, prevents organ and tissue rejection in transplantation [32–34] and promotes long-term safety and efficacy against myasthenia gravis [35] and neuromyelitis optica spectrum disorder [36]. Additionally, few reports describe tacrolimus therapy for autoimmune encephalitis, and we observed that most of the adverse events of tacrolimus were minor and well-managed [37]. Thus, we first demonstrated the possibility of sequential steroid treatment (IVMP) with tacrolimus for anti-DPPX encephalitis. The patient had no relapse within the six-month follow-up. Our research suggests that tacrolimus may be another promising immunosuppressant for anti-DPPX encephalitis. Further observations and investigation are required to assess and confirm this beneficial effect.

Conclusions

We conducted a retrospective study of patients with anti-DPPX encephalitis and reviewed all previously reported cases. Our study expands the clinical and imaging phenotype of anti-DPPX encephalitis, firstly reports symptoms of RBD and limb paralysis, severe pleocytosis and elevated protein levels in

CSF, and specific abnormalities in cerebral MRI. Moreover, it is the first to use tacrolimus for long-term immunosuppressant therapy in anti-DPPX encephalitis, with substantial improvement and no relapse during the follow-up. We believe that our study significantly contributes to improved understanding of anti-DPPX encephalitis and presents novel therapeutic strategies. There are still some limitations to this study. It is a single-center retrospective observational study, and due to a relatively low incidence of this disease, only one case uses the tacrolimus for therapy in our study, the conclusion is not solid enough. And the molecular mechanisms of anti-DPPX encephalitis are not elucidated in our study. Further studies elucidating the exact pathogenic roles and the associated clinical spectrum are warranted, to confirm the effect of this immunosuppressive therapy.

List Of Abbreviations

dipeptidyl-peptidase-like protein 6: DPPX

rapid eye movement sleep behavior disorder: RBD

cerebrospinal fluid : CSF

magnetic resonance imaging: MRI

human embryonic kidney 293: HEK293

glial fibrillary acidic protein: GFAP

intravenous: IV

Declarations

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing. We thank Wuhan Kindstar Diagnostics Co., Ltd, Wuhan, China, for technical support. All authors have no disclosures and no conflict of interest to declare.

Funding

This work was supported by the *Independent Innovation Research Fund of Huazhong University of Science and Technology* (No.2016YXMS109).

Availability of data and materials

All data generated or analysed during this study are included in this published article

Authors' Contributions

ZL designed this research. JX and PF were responsible for acquiring and analyzing the clinical data. JX was responsible for drafting the manuscript and figures. ZL revised the manuscript. All the authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tongji Hospital, and written informed consent was obtained from all patients or their surrogates before enrollment, for the use of serum, CSF, and clinical information for research purposes.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not Applicable

References

1. Posova H, Horakova D, Capek V, Uher T, Hruskova Z, Havrdova E. Peripheral blood lymphocytes immunophenotyping predicts disease activity in clinically isolated syndrome patients. *BMC Neurol.* 2017;17(1):145.
2. Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, McCracken L, Martinez-Hernandez E, Mason WP, Kruer MC, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol.* 2014;13(3):276–86.
3. Lancaster E, Martinez-Hernandez E, Titulaer MJ, Boulos M, Weaver S, Antoine JC, Liebers E, Kornblum C, Bien CG, Honnorat J, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology.* 2011;77(18):1698–701.

4. Boronat A, Gelfand JM, Gresa-Arribas N, Jeong HY, Walsh M, Roberts K, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R, Graus F, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol*. 2013;73(1):120–8.
5. Wada K, Yokotani N, Hunter C, Doi K, Wenthold RJ, Shimasaki S. Differential expression of two distinct forms of mRNA encoding members of a dipeptidyl aminopeptidase family. *Proc Natl Acad Sci U S A*. 1992;89(1):197–201.
6. Nadal MS, Ozaita A, Amarillo Y, Vega-Saenz de Miera E, Ma Y, Mo W, Goldberg EM, Misumi Y, Ikehara Y, Neubert TA, et al. The CD26-related dipeptidyl aminopeptidase-like protein DPPX is a critical component of neuronal A-type K⁺ channels. *Neuron*. 2003;37(3):449–61.
7. Hara M, Ariño H, Petit-Pedrol M, Sabater L, Titulaer MJ, Martinez-Hernandez E, Schreurs MW, Rosenfeld MR, Graus F, Dalmau J. DPPX antibody-associated encephalitis: Main syndrome and antibody effects. *Neurology*. 2017;88(14):1340–8.
8. Tobin WO, Lennon VA, Komorowski L, Probst C, Clardy SL, Aksamit AJ, Appendino JP, Lucchinetti CF, Matsumoto JY, Pittock SJ, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. *Neurology*. 2014;83(20):1797–803.
9. Stoek K, Carstens PO, Jarius S, Raddatz D, Stöcker W, Wildemann B, Schmidt J. Prednisolone and azathioprine are effective in DPPX antibody-positive autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e86.
10. Doherty L, Gold D, Solnes L, Probasco J, Venkatesan A. Anti-DPPX encephalitis: prominent nystagmus reflected by extraocular muscle FDG-PET avidity. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(4):e361.
11. Wijntjes J, Bechakra M, Schreurs MWJ, Jongen JLM, Koppelaar A, Titulaer MJ. Pruritus in anti-DPPX encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(3):e455.
12. Valero-Lopez G, Martin-Fernandez JJ, Hernandez-Clares R, Baidez-Guerrero AE, Martinez-Hernandez E. [Progressive encephalitis due to anti-DPPX antibodies: a case with good response to treatment with rituximab]. *Rev Neurol*. 2017;65(11):525–6.
13. Zhou Q, Zhu X, Meng H, Zhang M, Chen S. Anti-dipeptidyl-peptidase-like protein 6 encephalitis, a rare cause of reversible rapid progressive dementia and insomnia. *J Neuroimmunol*. 2020;339:577114.
14. Bien CG, Schanzer A, Dargvaine J, Dogan-Onugoren M, Woermann F, Strickler A. Co-occurrence of antibodies against dipeptidyl-peptidase-like protein-6 and aquaporin-4 during a case of paraneoplastic encephalitis. *Clin Neurol Neurosurg*. 2020;197:106093.
15. Balint B, Jarius S, Nagel S, Haberkorn U, Probst C, Blöcker IM, Bahtz R, Komorowski L, Stöcker W, Kastrup A, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. *Neurology*. 2014;82(17):1521–8.
16. Piepgras J, Hölte M, Michel K, Li Q, Otto C, Drenckhahn C, Probst C, Schemann M, Jarius S, Stöcker W, et al. Anti-DPPX encephalitis: pathogenic effects of antibodies on gut and brain neurons. *Neurology*. 2015;85(10):890–7.
17. Clark BD, Kwon E, Maffie J, Jeong HY, Nadal M, Strop P, Rudy B. DPP6 Localization in Brain Supports Function as a Kv4 Channel Associated Protein. *Front Mol Neurosci*. 2008;1:8.
18. Birnbaum SG, Varga AW, Yuan LL, Anderson AE, Sweatt JD, Schrader LA. Structure and function of Kv4-family transient potassium channels. *Physiol Rev*. 2004;84(3):803–33.
19. Iranzo A, Graus F, Clover L, Morera J, Bruna J, Vilar C, Martinez-Rodriguez JE, Vincent A, Santamaria J. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. *Ann Neurol*. 2006;59(1):178–81.
20. Silber MH. Autoimmune sleep disorders. *Handb Clin Neurol*. 2016;133:317–26.
21. Çoban A, Ismail Küçükali C, Bilgiç B, Yağcıncaya N, Haytural H, Ulusoy C, Turan S, Çakır S, Uçok A, Ünübol H, et al. Evaluation of incidence and clinical features of antibody-associated autoimmune encephalitis mimicking dementia. *Behavioural neurology*. 2014;2014:935379.
22. Lin YQ, Chen SD. RBD: a red flag for cognitive impairment in Parkinson's disease? *Sleep Med*. 2018;44:38–44.
23. Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C. Imaging of autoimmune encephalitis—Relevance for clinical practice and hippocampal function. *Neuroscience*. 2015;309:68–83.
24. Karim AR, Jacob S. Experience with newer central nervous system autoantibodies. *Ann Clin Biochem*. 2018;55(1):7–17.
25. Shan F, Long Y, Qiu W. Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy: A Review of the Literature. *Frontiers in Immunology* 2018, 9.
26. Fang B, McKeon A, Hinson SR, Kryzer TJ, Pittock SJ, Aksamit AJ, Lennon VA. Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy. *JAMA Neurology* 2016, 73(11).
27. Kimura A, Takemura M, Yamamoto Y, Hayashi Y, Saito K, Shimohata T. Cytokines and biological markers in autoimmune GFAP astrocytopathy: The potential role for pathogenesis and therapeutic implications. *Journal of Neuroimmunology* 2019, 334.
28. Flanagan EP, Hinson SR, Lennon VA, Fang B, Aksamit AJ, Morris PP, Basal E, Honorat JA, Alfugham NB, Linnoila JJ, et al. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. *Ann Neurol*. 2017;81(2):298–309.
29. Huijbers MG, Querol LA, Niks EH, Plomp JJ, van der Maarel SM, Graus F, Dalmau J, Illa I, Verschuuren JJ. The expanding field of IgG4-mediated neurological autoimmune disorders. *Eur J Neurol*. 2015;22(8):1151–61.
30. Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. *Annu Rev Pathol*. 2014;9:315–47.
31. Ariño H, Armangué T, Petit-Pedrol M, Sabater L, Martinez-Hernandez E, Hara M, Lancaster E, Saiz A, Dalmau J, Graus F. Anti-LGI1-associated cognitive impairment: Presentation and long-term outcome. *Neurology*. 2016;87(8):759–65.
32. Jouve T, Noble J, Rostaing L, Malvezzi P. An update on the safety of tacrolimus in kidney transplant recipients, with a focus on tacrolimus minimization. *Expert Opin Drug Saf*. 2019;18(4):285–94.

33. Yu M, Liu M, Zhang W, Ming Y. Pharmacokinetics, Pharmacodynamics and Pharmacogenetics of Tacrolimus in Kidney Transplantation. *Curr Drug Metab.* 2018;19(6):513–22.
34. Schutte-Nutgen K, Tholking G, Suwelack B, Reuter S. Tacrolimus - Pharmacokinetic Considerations for Clinicians. *Curr Drug Metab.* 2018;19(4):342–50.
35. Kim YH, Shin HY, Kim SM. Long-Term Safety and Efficacy of Tacrolimus in Myasthenia Gravis. *Yonsei Med J.* 2019;60(7):633–9.
36. Chen B, Wu Q, Ke G, Bu B. Efficacy and safety of tacrolimus treatment for neuromyelitis optica spectrum disorder. *Sci Rep.* 2017;7(1):831.
37. Spindel J, Heckroth M, Marsano L. Antibody-negative autoimmune encephalitis as a complication of long-term immune-suppression for liver transplantation. *BMJ Case Rep* 2020, 13(9).

Tables

Table 1 Demographic, clinical features, immunologic data and treatment of the patients with DPPX antibodies

	Patient 1	Patient 2	Patient 3 ^a	Patient 4	Patient 5	Patient 6 ^b	Patient 7	Patient 8	Patient 9
Demographic									
Sex	F	F	F	M	M	F	F	M	F
Age at onset, y	65	47	62	35	14	51	35	54	52
Months to onset	12	0.5	3	0.5	0.5	0.5	4	1	6
Clinical Features									
Prodromal symptoms	Headache	Fever, diarrhea	Weight loss (10 kg), diarrhea, headache;	Headache	Fever, gastroparesis and constipation	Fever, headache, weight loss (5 kg)	Vertigo, diarrhea	Headache	Fever
Main symptoms	Memory loss, executive dysfunction, delusions, hyperreflexia	Delirium in 11 days to cognitive disorder, aphasia, limb paralysis, RBD, vertigo	Bradykinesia, tremor, memory loss, RBD, hyperreflexia, nystagmus	Stiffness, sleep disorder (insomnia), generalized seizure	Confusion, cognitive disorder, limb paralysis, respiratory failure, hyperreflexia	Memory loss, insomnia, ataxia, nystagmus	Generalized seizure, insomnia, RBD	Somnolence, cognitive disorder, myoclonus, insomnia	Delirium, cognitive disorder, recurrent generalized seizures,
Brain MRI	Bilateral hippocampus T2/FLAIR increased signals	Bilateral temporal lobe and amygdala T2/FLAIR increased signals	Nonspecific white matter changes	Left hippocampus and basal ganglia T2/FLAIR increased signals	Extensive abnormal signals in the brainstem, basal ganglia and bilateral white matter	Extensive abnormal signals in the frontal lobe, basal ganglia, hippocampus and cerebellum	Normal	Nonspecific white matter changes	Bilateral temporal lobe, hippocampus and left frontal lobe T2/FLAIR increased signals
Immunologic data									
CSF	WBC: normal Protein: normal	WBC: normal Protein: normal	WBC: normal Protein: normal	December 2018 WBC: 370, Protein: 852 January 2019 WBC: 20, Protein 549	March 2019 WBC: 220, Protein:2096 May 2019 WBC: 10, Protein: 469	WBC: normal Protein: normal	WBC: normal Protein: normal	WBC: normal Protein: 958	November 2018 WBC (-), Protein: 609 December 2018 WBC (-), Protein (-)
DPPX antibody	Serum: 1:100 CSF: ND	Serum: 1:10 CSF: ND	Serum: 1:32 CSF: ND	Serum: 1:32 CSF: 1: 3.2	Serum: 1:320 CSF (-)	Serum: 1:100 CSF: 1:1	Serum: 1:10 CSF: (-)	Serum: 1:1000 CSF: 1:10	December 2018 Serum:1:10 CSF: (-) October 2019 Serum:1:32 CSF: ND
Treatment/response	IVMP, oral steroids/ marked improvement	IVMP, oral steroids/ marked improvement, but relapsed with steroid taper	Oral steroids/ marked improvement	IVMP, Tacrolimus/ mild, but steady improvement	IVMP, IVIg/ incomplete improvement	IVMP, Rituximab/ marked improvement	IVMP, oral steroids/ marked improvement	IVMP, oral steroids/ marked improvement	IVMP, oral steroids/ marked improvement, but relapsed with steroid taper

Abbreviations: DPPX= dipeptidyl-peptidase-like protein-6; ND= not done; IVMP= intravenous methylprednisolone; IVIg= intravenous immunoglobulins.

^a Micropapillary carcinoma of thyroid was found during the course of the disease.

^b Non-Hodgkin's lymphoma was found during the examinations.

Table 2: Neurologic characteristics of 53 patients with DPPX antibodies

Characteristics	No. (%)		
	Previous reported (n = 44)	Ours (n = 9)	Sum (n= 53)
Cognitive disorders	32 (72.7)	7 (77.8)	39 (73.6)
Brainstem or spinal cord disorders ^a	36 (81.8)	4 (44.4)	40 (75.5)
Cerebellar ataxia	16 (36.4)	2 (22.2)	18 (34.0)
Myoclonus or tremor	23 (52.3)	3 (33.3)	26 (49.1)
Limb paralysis	0 (0)	2 (22.2)	2 (3.8)
Psychosis ^b	14 (31.8)	1 (11.1)	15 (28.3)
Headache	1 (2.3)	5 (55.6)	6 (11.3)
Weight loss	25 (56.8)	3 (33.3)	28 (52.8)
Sleep disorders ^c	17 (38.6)	4 (44.4)	21 (39.6)
Mood disorders ^d	19 (43.2)	3 (33.3)	22 (41.5)
Gastrointestinal sytms ^e	27 (61.4)	4 (44.4)	31 (58.5)
Seizures	5 (11.4)	2 (22.2)	7 (12.2)
Dysautonomia ^f	17 (38.6)	3 (33.3)	20 (37.7)
CSF elevated white cell account	16/33 (48.5)	2 (22.2)	18/42 (42.9)
CSF elevated proteins	8/19 (42.1)	4 (44.4)	12/28 (42.9)
Brain MRI abnormalities	9 (20.5)	8 (88.9)	17 (32.1)
Brain MRI specific changes	1 (2.3)	7 (77.8)	8 (14.1)
Tumor Screening	5 (11.4)	2 (22.2)	7 (13.2)

Abbreviations: DPPX= dipeptidyl-peptidase-like protein-6; MRI= Magnetic Resonance Imaging.

^a Abnormal eye movement; dysphagia; stiffness; dysarthria; respiratory failure; vertigo; hyperekplexia

^b Delirium; hallucination; delusion

^c Insomnia; hypersomnia; RBD

^d Depression; anxiety; apathy; appetite loss

^e Diarrhea; gastroparesis; constipation; abdominal pain

^f Diaphoresis; temperature dysregulation; urinary symptoms

Figures

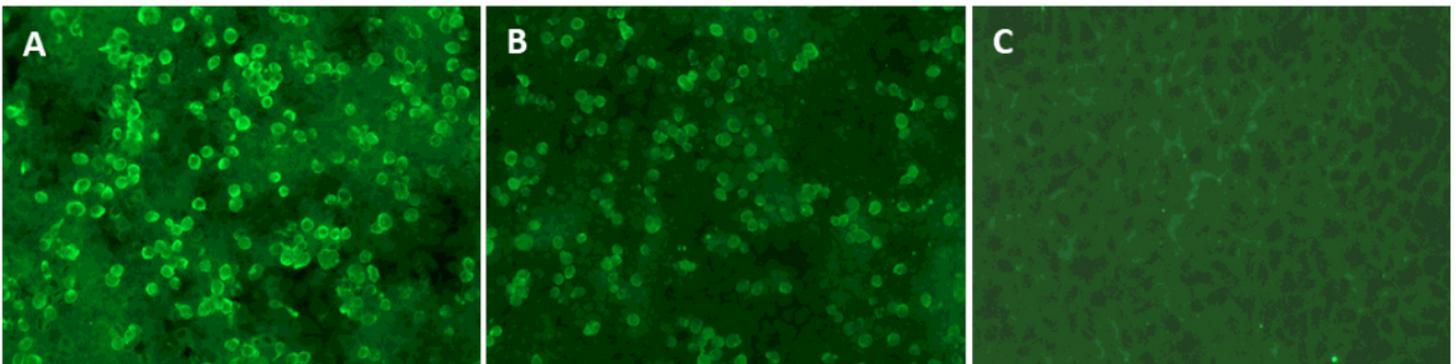


Figure 1

Immunofluorescence in serum and CSF in patient with anti-DPPX encephalitis Positive reaction with transfected HEK 293 cells expressing DPPX with serum (A) (titer: 1: 1000); and with CSF (B) (titer: 1:10). (C) A negative control

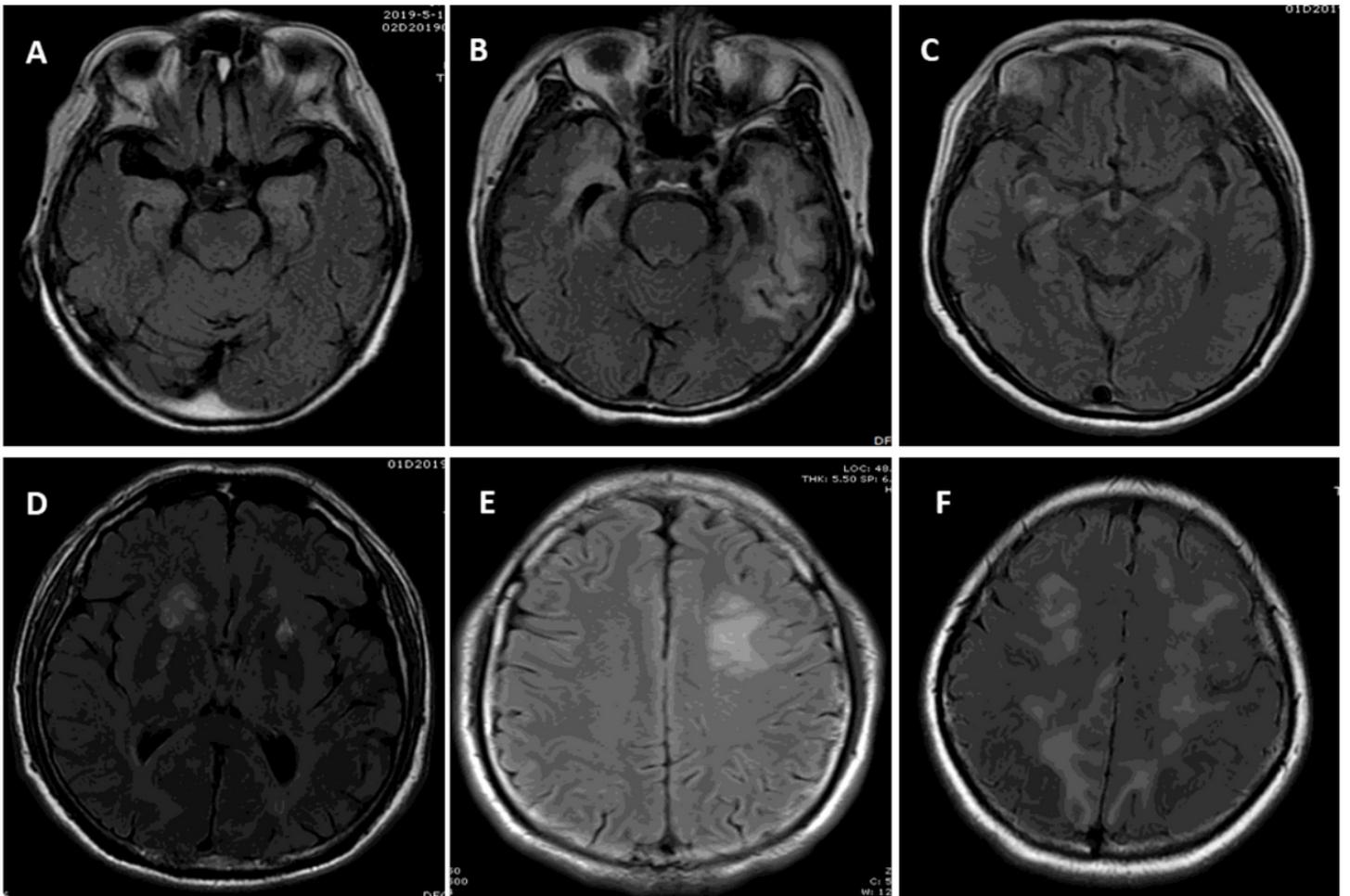


Figure 2

Brain T2/ FLAIR axial MRI specific changes of the patients with DPPX antibodies A Mild increased T2/FLAIR signals of the bilateral hippocampus; B T2/FLAIR increased signals of the bilateral temporal lobe and hippocampus; C Mild T2/FLAIR increased signals Of the bilateral amygdala; D Increased T2/FLAIR signals in the right basal ganglia and thalamus; E T2/FLAIR increased signals of the left centrum semiovale; F Extensive abnormal T2/FLAIR signals in the bilateral frontal lobe and parietal lobe

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.docx](#)