Neuropsychiatric presentation of anti-DPPX progressive encephalomyelitis with rigidity and myoclonus

Ray Jen Neo, MBBS, MRCP(UK),[1,2] Arpan R. Mehta, BM BCh, MA, MRCP(UK), PhD,[1] Mikail Weston, MB BCh BaO, MRCP(UK),[4] Francesca Magrinelli, MD, PhD,[1] Andrea Quattrone, MD, PhD[1,3] Sonia Gandhi, MD, PhD,[1] Eileen M. Joyce, MA, PhD, MRCP, FRCPsych,[1] Kailash P. Bhatia, MD, DM, FRCP[1]

1. Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom

2. Department of Neurology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

3. Institute of Neurology, Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Italy

4. Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom

Corresponding author

Prof. Kailash P. Bhatia

Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology

University College London, Queen Square, London WC1N 3BG, United Kingdom

Telephone: +44 (0)2034488756

E-mail: k.bhatia@ucl.ac.uk

Word count

Abstract: N/A

Text: 802 words

References: 8

Graphics (Tables/Figures): 1/1

Supplementary file: 1 video

Running title

Neuropsychiatric presentation in anti-DPPX PERM

Key words

Ataxia; autoimmunity; Dipeptidyl-peptidase-like protein-6; Hyperekplexia; Stiff person spectrum disorder.

Progressive encephalomyelitis with rigidity and myoclonus (PERM) falls at the severe end of stiff-person-syndrome spectrum disorders, being characterised by brainstem and autonomic involvement in addition to axial and limb rigidity, and CNS hyperexcitability.[1] Autoantibodies against glycine receptor (GlyR) are associated with 70% of PERM cases.[2] Other PERM-associated autoantibodies encompass antibodies against glutamic acid decarboxylase (GAD), dipeptidyl peptidase-like-protein-6 (DPPX), and amphiphysin.[3] Here, we report an atypical case of anti-DPPX-associated PERM with prominent neuropsychiatric prodrome.

Case report

A 17-year-old male presented to a neuropsychiatry clinic with an 18-month history of behavioural change, loss of appetites, significant weight loss, and a possible functional movement disorder.

He was born after an uncomplicated pregnancy and delivery with normal neurodevelopmental milestones. At primary school, he had features of hyperactivity and poor concentration. At 12-years, his behaviour improved, and he achieved a good academic performance and was described as outgoing and popular. At 14-years, his behaviour changed suddenly in that he became aggressive. He began to take illicit drugs, which he stole, engaged in risky behaviour involving the police, and impulsively self-harmed. He was diagnosed with attention-deficit hyperactivity disorder (ADHD) by child and adolescent mental health services. At 16-years, his memory deteriorated, and his behaviour changed to one of apathy, low mood, self-neglect, and social isolation. In addition, he developed difficulty walking, recurrent falls, legs tremor, disabling urinary frequency, sleep disruption, and double vision.

Examination revealed an undernourished (BMI: 15.3 kg/m^2), withdrawn, irritable, and uncooperative adolescent with a preference to remain shirtless and lie in a dark room because of extreme skin sensitivity and photophobia. He had persistent sinus tachycardia. Eye examination showed left exophoria, macro square-wave jerks, horizontal gaze-evoked nystagmus, downbeating nystagmus, saccadic intrusions, and saccadic dysmetria. He had

allodynia, stimulus-sensitive generalized myoclonus, upper limb postural tremor, limb ataxia (worse on the left), hyperekplexia on tactile and acoustic stimulation, head-retraction jerks on forehead stimuli with poor habituation, and stimulus-sensitive axial rigidity. His reflexes were brisk, with bilateral Babinski's sign. There was intermittently visible paraspinal muscle contraction with hypertrophy. He walked with an ataxic and bouncy gait with negative myoclonus on standing. (Video 1)

Neuropsychological testing showed slow processing speed, attentional/executive dysfunction, and poor memory. Naming, visuo-perceptual, and visuo-spatial skills were intact. This pattern of cognitive deficits indicated dysfunction of anterior, subcortical, and medial-temporal brain areas.

A diagnosis of PERM was made. His serum and CSF DPPX antibodies were positive. Antibodies against GlyR, GAD, amphiphysin, NMDA receptor, LGI1, CASPR2, IgLON5, Purkinje, other cerebellar cells, Tr, myelin, Hu, Yo, Ri, Ma-1, Ma-2, CV2, Zic-4, SOX-1, recoverin, titin, thyroid peroxidase, and tissue transglutaminase were negative. He had unmatched CSF oligoclonal bands, normal CSF protein (0.37 g/L, 0.13 - 0.45 g/L), and normal CSF:serum glucose ratio (0.6), with no pleocytosis. Serial brain MRI one year apart showed mild generalised cerebellar atrophy (Fig 1). Whole-body FDG-PET showed no indication of neoplasm. EEG showed an excess of slow activity, suggesting a mild cortical dysfunction. Nerve conduction studies were normal. Electromyography was not tolerated over paraspinal muscles.

The myoclonus improved with levetiracetam. He received 3-day of IV methylprednisolone followed by oral prednisolone and 4 cycles of plasma exchange. Soon, his irritability and hostility diminished. There was early significant improvement of his gait, myoclonus, stimulus-sensitivity, and delayed improvement of his eye movement abnormalities, urinary dysfunction, and tachycardia. He then received intravenous immunoglobulin 2g/kg over 5 days, with little additional benefit. Solifenacin and mirabegron had little response for his bladder symptoms. Subsequently, he underwent rehabilitation and received rituximab

maintenance therapy. Five months after starting immunotherapies, his mobility had improved, and he had gained ~20kg, but bladder issues, cerebellar signs, and stimulus-sensitivity partially persisted. (Video 1)

Discussion

DPPX is a cell-surface regulatory subunit of the neuronal voltage-gated A-type Kv4.2 potassium channel.[4,5] It is expressed in the hippocampus, striatum, cerebellum, and myenteric plexus.[6,7] Our patient presented with the triad of weight loss, cognitive dysfunction, and CNS hyperexcitability (myoclonus, stimulus-sensitivity, hyperekplexia, tremor, and axial rigidity) with ataxia, pyramidal signs, eye movement abnormalities, urinary dysfunction, dysautonomia, allodynia, and sleep disruption.

When he developed motor symptoms, he showed cognitive impairment and became apathetic and withdrawn, neuropsychiatric symptoms which have been described in some cases.[8] However, for several years before, he showed uncharacteristic antisocial behaviour including extreme violence against others and towards himself. This could be an exacerbation of ADHD or neuropsychiatric manifestation of this disorder. His neuropsychiatric symptoms improved following treatment support the latter. Interestingly, he had severe weight loss due to anorexia without diarrhoea and prominent bladder dysfunction. His clinical characteristics are compared with published cases of anti-DPPX-associated PERM in table 1.[3]

Most PERM cases with positive antibodies other than anti-GlyR hitherto reported showed some response to immunotherapy.[2] Our patient has had a good but partial response to immunotherapies. High index of suspicion is required to recognise this potentially treatable condition early. Our report further expands the phenotypes of anti-DPPX-associated PERM.

Acknowledgment

The authors thank the patient and his family for permitting the publication of this case report.

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Data Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

RJN: 1A, 1B, 1C, 3A

ARM: 1A, 1B, 1C, 3B

MW: 1B, 1C, 3B

FM: 1B, 3B

AQ: 1B, 3B

SG: 1B, 3B

EMJ: 1B, 3B

KPB: 1A, 1B, 3B

Disclosures

Funding Sources and Conflict of Interest:

No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months:

RJN, ARM, MW, and EMJ have no disclosures to declare. FM is supported by the Michael J. Fox Foundation Edmond J. Safra fellowship in movement disorders. AQ has received grant support not related to this study from the Italian Society for Parkinson and movement disorders LIMPE-DISMOV. SG is funded by MRC Clinician Scientist Fellowship. KPB has received grant support from Welcome/MRC, NIHR, Parkinsons's UK and EU Horizon 2020. He receives royalties from publication of the Oxford Specialist Handbook Parkinson's Disease and Other Movement Disorders (Oxford University Press, 2008), of Marsden's Book of Movement Disorders (Oxford University Press, 2012), and of Case Studies in Movement Disorders–Common and uncommon presentations (Cambridge University Press, 2017). He has received honoraria/personal compensation for participating as consultant/scientific board member from Ipsen, Allergan, Merz and honoraria for speaking at meetings and from Allergan, Ipsen, Merz, Sun Pharma, Teva, UCB Pharmaceuticals and from the American Academy of Neurology and the International Parkinson's Disease and Movement Disorders Society. The University College London (UCL) Queen Square Movement Disorders Centre (MDC) acknowledges the National Institute of Health and Care Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC).

Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. Patient consent was obtained for video recording and publication.

Legends

Table 1. Clinical, CSF characteristics, and treatment response of the patients with anti-DPPX-associated PERM.

Fig. 1. Sagittal view of brain magnetic resonance imaging (MRI) performed 18 months after motor manifestations showing mild cerebellar atrophy.

Video 1. Segment 1: Baseline clinical features prior to treatment. He had stimulus-sensitive generalized myoclonus, upper limb postural tremor, limb ataxia (worse on the left), hyperekplexia on acoustic stimulation, and chin tremor. Eye movement examination showed left exophoria, square-wave jerks, saccadic intrusions, and saccadic dysmetria. He walked with an ataxic and bouncy gait. **Segment 2: 3 weeks post treatment.** He had improvement in stimulus-sensitive myoclonus with less hyperekplexia. He had an upper limb postural tremor and limb ataxia. Stimulus sensitive paraspinal contraction was demonstrated. He walked with a broad-based gait with a tendency to veer to the left. **Segment 3: 5 months post treatment.** He had minimal upper limb postural tremor, mild upper limb ataxia, and mild stimulus-sensitive myoclonus. He had horizontal gaze-evoked nystagmus. Gait had improved with mild ataxia.

References

1. Meinck HM, Thompson PD. Stiff man syndrome and related conditions, *Mov Disord* 2002; 17:853-866.

2. Chang A, Lin KY, Chuang KJ, et al. Progressive encephalomyelitis with rigidity: A Taiwanese case and review of literature. Clinical Neurology and Neurosurgery 2021; 208:106807.

3. Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology 2014; 82:1521–1528.

4. Wada K, Yokotani N, Hunter C, et al. Differential expression of two distinct forms of mRNA encoding members of a dipeptidyl aminopeptidase family. Proc Natl Acad Sci USA 1992; 89:197–201.

5. Nadal MS, Ozaita A, Amarillo Y, et al. The CD26-related dipeptidyl aminopeptidase-like protein DPPX is a critical component of neuronal A-type K1 channels. Neuron 2003; 37:449-461.

6. Clark BD, Kwon E, Maffie J, et al. DPP6 localization in brain supports function as a Kv4 channel associated protein. Front Mol Neurosci 2008; 1:8.

7. Boronat A, Gelfand JM, Gresa-Arribas N, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. Ann Neurol 2013; 73:120–128.

206 8. Jun Xiao, Pei-cai Fu, Zhi-Jun Li. Clinical and imaging analysis to evaluate the response of
207 patients with anti-DPPX encephalitis to immunotherapy. BMC Neurology 2022; 22:129
208

209

Table 1. Clinical, CSF characteristics, and treatment response of the patients with anti-DPPX-associated PERM.

	Patient 1*	**Patient 2***	**Patient 3***	**Our Patient**
Demographics				
Sex	**M**	**M**	**M**	**M**
Age at onset, y	**15**	**27**	**26**	**16**
Total disease duration, y	**5**	**8**	**18**	**1.5**
Signs and symptoms				
Neuropsychiatric prodrome	**-**	**-**	**-**	**+++**
Hyperekplexia	**+++**	**+++**	**+++**	**+++**
Cerebellar ataxia	**++**	**+**	**++**	**+++**
Stiffness	**++**	**+**	**++**	**++**
Pyramidal signs	**+**	**-**	**+**	**++**
Eye movement abnormalities	**++**	**+**	**++**	**++**
Cognitive impairment	**+**	**-**	**++**	**++**
Dysautonomia	**-**	**++**	**+++**	**++**
Gastrointestinal symptoms	**-**	**+**	**+++**	**-**
Bladder symptoms	**-**	**-**	**+**	**+++**

Allodynia	**-**	**+**	**++**	**++**
Neurogenic pruritus	**-**	**+**	**+**	**-**
CSF				
Lymphocytosis	**+**	**+**	**+**	**-**
Intrathecal IgG/OCB	**+**	**+**	**+**	**+**
Therapy response				
Corticosteroids	**Poor**	**Good**	**Good**	**Good**
PLEX	**Poor**	**ND**	**None**	**Good**
IVIG	**Poor**	**Poor**	**Good**	**Poor**
Rituximab	**Good**	**ND**	**ND**	**Good**

Abbreviations: DPPX = dipeptidyl peptidase-like protein 6; IgG = immunoglobulin G; IVIg = IV immunoglobulin; ND = not done; OCB = oligoclonal bands; PLEX = plasma exchange.

Symbols: - = none; + = mild; ++ = moderate; +++ = prominent.

*Cases are obtained from Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology 2014[3]