Progressive supranuclear palsy–like parkinsonism ensuing from anti–N-methyl-D-aspartate receptor encephalitis

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An 18-year-old male postencephalitic patient was admitted with a 2-year history of staggering gait, bradykinesia, limb tremor, and memory decline (online supplementary Fig). Two years previously, he developed continuous fever, headache, psychosis, and generalised seizures. Magnetic resonance imaging scan at the time revealed remarkably high signals in the bilateral thalamus, midbrain and hippocampus (Fig 1). Electroencephalography showed diffuse slow waves, spikes and sharp waves. Immunoelectrophoresis test determined a type II oligoclonal band in the cerebrospinal fluid (CSF). Antigen-specific cell-based assay detected anti–N-methyl-D-aspartate receptor (NMDAR) autoantibodies in the CSF (Fig 2). After exclusion of potential pathogenic microbes and carcinomas, a diagnosis of anti-NMDAR encephalitis was made. The patient was prescribed immediate intravenous immunoglobulin (0.4 g/kg/d for 5 days) and methylprednisolone (500 mg/d, halved every 5 days). Perampanel (8 mg/d) was also administered to control seizure attacks. His symptoms gradually resolved and he was discharged 1 month later.

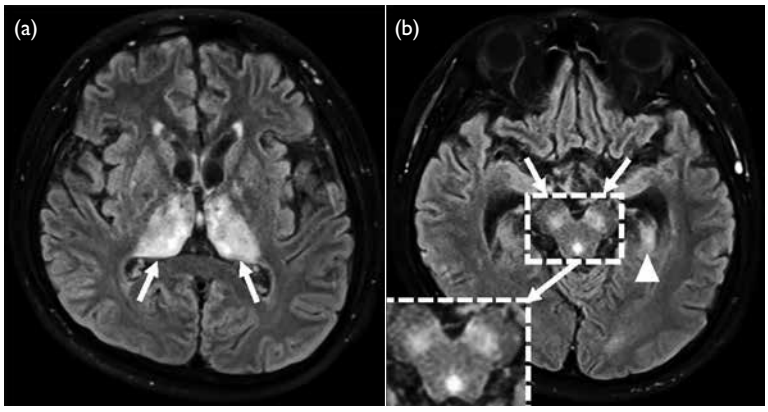

FIG 1. Identification of the cerebral liability foci in this patient with encephalitis. Magnetic resonance imaging scan revealed liability foci in bilateral thalamus (arrows in [a]), mesencephalic substantia nigra (arrows in [b]) and hippocampus (triangle in [b]) on axial T2 fluid-attenuated inversion recovery sequence. (a) Basal ganglia. (b) Midbrain

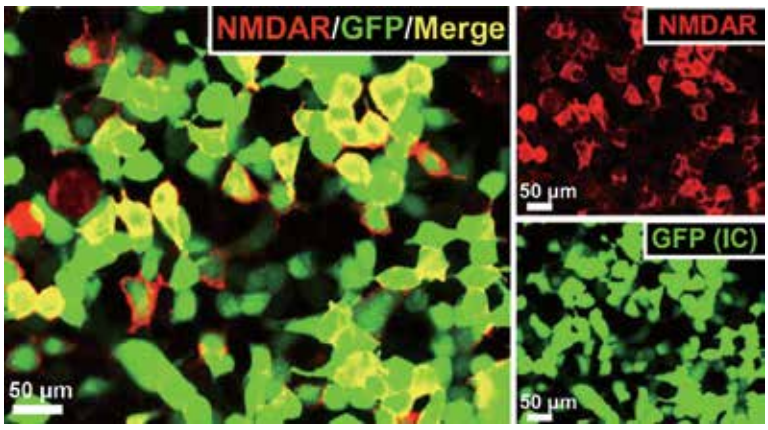

FIG 2. Determination of anti–N-methyl-D-aspartate receptor autoantibodies in the cerebrospinal fluid sample (titre, 1:1000) by cell-based assay
Abbreviations: GFP = green fluorescence protein; IC = internal positive control; NMDAR = N-methyl-D-aspartate receptor

During the rehabilitation period, the patient reported no relapse of encephalitis but presented with insidious bradykinesia, limb tremor, unsteady gait, and memory decline. These symptoms had gradually worsened over the 2-year period and contributed to frequent falls. He was wheelchair-bound at admission. Physical examination revealed limb tremor, hyperreflexia, patellar clonus, a positive Babinski sign, and vertical supranuclear gaze palsy (Fig 3). Mental status examination revealed space-time disorientation. Magnetic resonance imaging scan indicated remarkable midbrain atrophy (Fig 4). In contrast with the 'convex' contour before the encephalitis (Fig 4a), the magnetic resonance imaing scan in the postencephalitic stage revealed a 'concave' mesencephalic tegmental superior margin and a decreased midbrain-to-pons axis ratio (Fig 4b), mimicking the characteristic 'hummingbird sign' seen in progressive supranuclear palsy. Antigen-specific cell-based assay of the CSF sample determined a modest titre (in the ratio of 1:10) of anti-NMDAR autoantibodies. A compound therapeutic regimen of levodopa (750 mg/d), memantine (20 mg/d) and prednisone (60 mg/d) was initiated. At 3-month follow-up, the patient's hypokinetic-rigid and cognitive deficits had gradually resolved, and he no longer required a wheelchair.

Movement disorders are the third most frequently observed symptom in anti-NMDAR encephalitis.[1] We reported the first case of progressive supranuclear palsy–like parkinsonism consequent to anti-NMDAR encephalitis. Intriguingly, the brain regions implicated in this case coincided with the

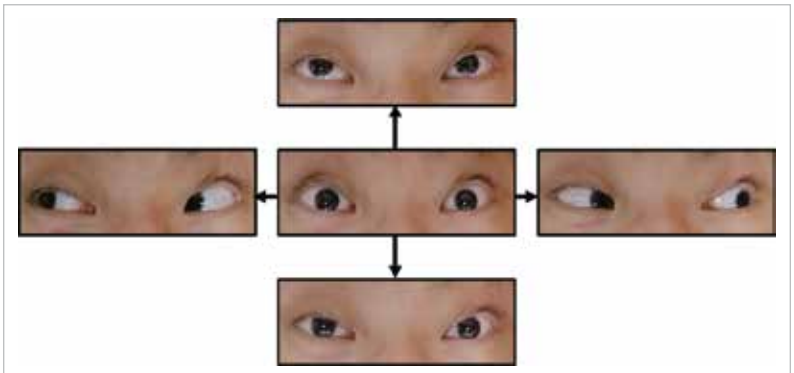

FIG 3. Vertical supranuclear gaze palsy in this patient with anti–N-methyl-D-aspartate receptor encephalitis. Eye movement test indicated vertical gaze palsy at the secondary ocular position, especially when gazing downward

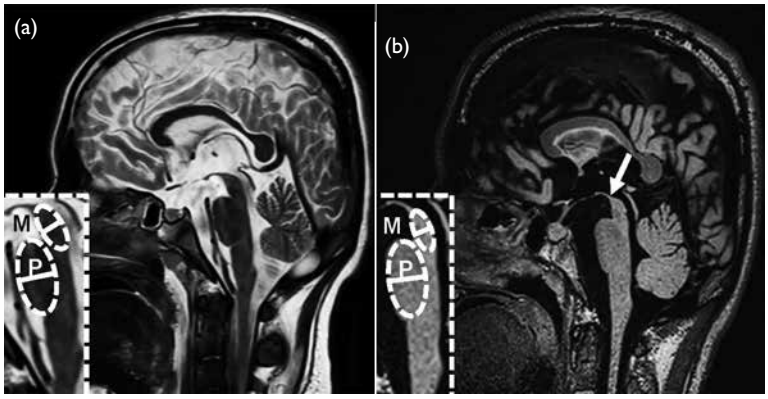

FIG 4. Morphological comparison of the midbrain of the patient (a) before and (b) after anti–N-methyl-D-aspartate receptor (NMDAR) autoimmune encephalitis (AE). After the anti-NMDAR AE, magnetic resonance imaging scan revealed that the mesencephalic tegmental superior margin had atrophied downwards to display the 'hummingbird sign' (arrow in [b]), and the major axis ratio of the midbrain and pons decreased from 0.65 in pre-AE (a) to 0.44 in post-AE stage (b)
Abbreviations: M = midbrain; P = pons

susceptible nuclei identified in parkinsonism.

Excitatory glutamatergic NMDAR subunits are abundantly expressed on postsynaptic nigrostriatal projection neurons, and are simultaneously under the feedback modulation by dopaminergic afferents.[2] Excessive glutamatergic activation, such as that seen in anti-NMDAR encephalitis, can drive excitotoxic neuronal death and contribute to progressive Parkinsonian motor and cognitive deficits.[3] A previous study reported that co-morbidity of anti-NMDAR encephalitis in Parkinson's disease worsens the existing extrapyramidal syndrome, resulting in severe bradykinesia or even akinesia.[4] Another recent study indicated that anti-NMDAR autoantibodies correlated with worsening cognitive deficits in Parkinson's disease patients.[5]

Similarly, the modest titre of anti-NMDAR antibody and amelioration of symptoms in this case following prednisone treatment suggest that persistent low-concentration autoantibody-mediated excitotoxicity might underlie the postencephalitic Parkinsonian and cognitive deficits, although not induce clinical relapse of autoimmune encephalitis. Nevertheless a proposed causal relationship between autoimmune encephalitis and postencephalitic neurodegeneration requires clarification in future follow-up cohort studies.

Author contributions

Concept or design: Y Shen.
Acquisition of data: N Wang, C Wang.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: Y Shen.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient for all treatments and procedures, and for publication of this article (including the clinical images).

Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2512884).

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