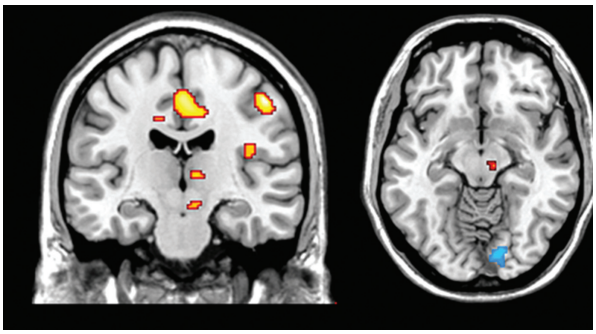

FIG. 1. Representative regions of increased (red to yellow color) and decreased (dark blue to light blue) fMRI activation during visual hallucination periods relative to periods of no hallucinations in a single subject. The regions are projected onto a canonical brain where the right side of the image represents the right side of the brain.

integration perhaps leading to self-referential visual perceptions.[6] Most remarkably, the relative deactivation of the primary visual system during the hallucinations, suggests a feedback suppression of posterior function during the visual hallucinations directly or indirectly from the aberrantly active frontally mediated circuits.

In one other report using single photon emission computed tomography (SPECT) to study a demented PD patient with frequent hallucinations, increased cerebral blood flow was documented during a visual hallucination in the left superior and middle temporal and inferior frontal gyri as well as in the apex of the right temporal lobe.[7] Their patient, however, differed from ours in that our patient was not demented. The differences between their study and ours may lie in the difference between imaging techniques with blood flow, as measured by SPECT, and blood oxygenation, as measured by fMRI as well as the differences in the patients' cognitive status.

Visual hallucinations are typical of PD, but other sensory modalities can become involved, especially among patients with long-standing hallucinations. In 1 longitudinal report that monitored hallucinations over a decade, multisensory hallucinations became the predominant form of hallucinations late in PD and involved visual plus olfactory, auditory, and tactile forms.[8] Our patient had only pure visual hallucinations during his scan, and thus the activation patterns of other sensory modality hallucinations may well be different than the pattern we observed. ■

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Herpes Simplex Encephalitis Relapse With Chorea Is Associated With Autoantibodies to *N*-Methyl-*D*-Aspartate Receptor or Dopamine-2 Receptor

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ABSTRACT

Background: Movement disorder relapses after herpes simplex virus 1 (HSV1) encephalitis have been hypothesized to be secondary to postviral autoimmunity. Recently, a proportion of patients with HSV1 encephalitis (HSE) were shown to produce autoantibodies against *N*-methyl-*D*-aspartate receptor (NMDAR).

Methods: We measured autoantibodies against NMDAR and dopamine-2 receptor (D2R) expressed at the cell surface in the stored acute serum of 9 children with HSE, 3 of whom had a relapsing course with chorea.

Results: The 3 patients with chorea had elevated autoantibodies against NMDAR (n = 1), D2R (n = 1), or both (n = 1), whereas patients without chorea were negative

(n = 6). The prospectively identified patient with chorea and NMDAR autoantibodies improved after early treatment with steroids, intravenous immunoglobulin, and cyclophosphamide, with reduction in serum NMDAR antibody titers.

Conclusions: These autoantibody findings lend support to the autoimmune hypothesis and the early use of immune suppression in post-HSE chorea. © 2013 International Parkinson and Movement Disorder Society

Key Words: herpes simplex encephalitis; NMDA receptor; dopamine-2 receptor; chorea; autoantibody

Herpes simplex virus 1 (HSV1) encephalitis (HSE) is an uncommon but serious condition in adults and children. Complications after HSE can be severe and include chorea or epileptic encephalopathy. Some of these complications have been proposed to be secondary to postviral autoimmunity due to benefit from immunosuppression[1-3] and the absence of HSV replication. Recently, it has been shown that a minority of adult patients with HSE have immunoglobulin G (IgG) autoantibodies against the *N*-methyl *D*-aspartate receptor (NMDAR),[4] although their clinical phenotype did not differ from antibody-negative patients. NMDAR antibodies have been used to define an autoimmune encephalitis characterized by seizures, encephalopathy, psychosis, dyskinesia, and autonomic dysfunction.[5] Armangue et al.[6] recently reported 1 case of post-HSE chorea who had NMDAR antibodies. We have recently shown that NMDAR antibody-negative patients with autoimmune encephalitis complicated by movement disorders can instead have autoantibodies that bind to the extracellular domain of the dopamine-2 receptor (D2R).[7] We tested the stored acute serum of 9 children with HSE for NMDAR and D2R autoantibodies. Only patients with chorea had positive autoantibodies. We provide clinical and immunological evidence to support the benefit of early immune suppression in these cases.

Patients and Methods

We included 9 children with a clinical and radiological syndrome compatible with HSE, with investigation support (confirmed, n = 6; possible, n = 3) using the criteria of Granerod et al.[8] The demographics, clinical presentation, magnetic resonance imaging (MRI), and outcome are presented in Table 1. Eight of the cases were retrospectively tested for autoantibodies using stored acute serum (from the first 6 weeks of admission), and 1 patient was prospectively investigated (case 1). NMDAR IgG antibodies were measured using an in-house flow cytometry cell-based assay as described.[7] The threshold of positivity was defined using the mean of 22 healthy controls + 3 SD, as described. Positive NMDAR antibody sera were confirmed at the national referral center for NMDAR autoantibodies using a commercially available kit (Euroimmun, Lubeck, Germany). D2R IgG autoantibodies were measured using an in-house flow cytometry cell-based assay against the long isoform of D2R expressed at the cell surface, as described.[7] The threshold of positivity was defined using the mean of 24 healthy controls + 3 SD. Assays were repeated a minimum of 3 times and representative data is shown. Brain sections and HEK293 cells were immunostained as reported,[7] and were visualized through ×40 and ×60 1.4 numerical aperture (NA) (with an auxiliary magnification of ×1.5) oil immersion lenses with an inverted Olympus IX-70 microscope (DeltaVision Core; Applied Precision, Issaquah, WA, USA) and a photometric CoolSnap QE camera. Images were acquired as thirty-five 0.2-μm-thick serial optical sections, then deconvolved, and volume projections of the entire *Z*-series were generated using DeltaVision SoftWoRx software, version 5.0.0 (Applied Precision) and ImageJ software version 1.44o (NIH, Bethesda, MD, USA). Representative images are shown.

Results

Three patients had a relapse with chorea and encephalopathy with onset 15, 42, and 15 days after HSE onset, respectively (Table 1). Serum autoantibodies were positive in these patients but were negative in the other 6 patients without chorea (Table 1). One patient had NMDAR IgG autoantibodies only (case 1), 1 had D2R IgG autoantibodies only (case 2), and 1 had both NMDAR and D2R IgG autoantibodies (case 3) (Fig. 1A). D2R antibody-positive sera co-immunolabeled microtubule-associated protein 2 (MAP2)-positive striatal neurons in wild-type mouse brains (Fig. 1B, case 2 shown), whereas the immunolabeling was decreased in D2R knockout striata (Fig. 1B, case 2 shown). D2R antibody-positive sera, but not controls, also immunolabeled D2R-expressing HEK293 cells (Fig. 1C).

Additional Supporting Information may be found in the Acknowledgments section online.

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Relevant conflicts of interest/financial disclosures: A patent has been filed by FB and RCD (University of Sydney) claiming D2R as target for autoantibodies.

Full financial disclosures and author roles may be found in the online version of this article.

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TABLE 1. Demographics, clinical presentation, magnetic resonance neuroimaging, autoantibody profile, and outcome of 9 patients with herpes encephalitis (n = 3 with chorea and 6 without a movement disorder)

Age and sex	Clinical syndrome at onset	HSV result	Magnetic resonance neuroimaging	Clinical syndrome at relapse	Serum antibody finding[a]	Length of follow-up and outcome
7-year-old male (case 1)	Fever, encephalopathy, focal Sx	CSF PCR positive	Unilateral temporal cortical and white matter lesions	Encephalopathy, chorea, dystonia, dysautonomia	NMDAR Ab positive[b]	9 months; developmental delay
12-month-old female (case 2)	Fever, encephalopathy, focal seizures	CSF PCR positive	Unilateral temporal cortical and white matter lesions	Encephalopathy, chorea	D2R Ab positive[b]	14 years; refractory epilepsy, intellectual disability, behavioral problems
8-month-old female (case 3)	Fever, encephalopathy, focal and general Sx, pyramidal signs	Intrathecal HSV1 IgG synthesis, IgM positive	Unilateral parietal cortical, and white matter, basal ganglia and thalamic lesions	Encephalopathy, chorea	NMDAR and D2R Ab positive[b]	13 years; refractory epilepsy, dystonic cerebral palsy, intellectual disability
8-month-old male	Fever, encephalopathy, focal and gen Sx	IgM positive	Unilateral parietal cortical and bilateral basal ganglia lesions with hemorrhagic changes	No relapse	Negative	3 years and 11 months; epilepsy
5-month-old female	Fever, encephalopathy, gen Sx	CSF PCR positive	Unilateral temporal-parietal cortical lesions with hemorrhage, necrosis and diffusion restriction	No relapse	Negative	5 years and 6 months; intellectual disability, behavioral problems
2-month-old female	Fever, encephalopathy, focal Sx	CSF PCR positive	Bilateral fronto-temporo-parietal cortical with white matter, basal ganglia and thalamic lesions plus hemorrhagic changes	No relapse	Negative	5 years and 10 months; refractory epilepsy, cerebral palsy, intellectual disability, behavioral problems, visual impairment
8-month-old female	Fever, encephalopathy, focal Sx	CSF PCR positive	Unilateral temporal cortical with white matter lesions plus diffusion restriction	No relapse	Negative	2 years and 4 months; normal
4-year-old male	Fever, encephalopathy, generalized Sx	IgM and IgG positive	Bilateral fronto-parietal cortical with white matter and thalamic lesions plus diffusion restriction and cerebral edema	No relapse	Negative	5 years and 4 months; epilepsy, intellectual disability, behavioral problems
3-year-old female	Fever, encephalopathy, focal and general Sx	IgM and IgG positive	Bilateral fronto-temporo-parietal cortical and basal ganglia lesions	No relapse	Negative	8 years and 1 month; normal

[a]All serum samples taken from first 6 weeks of admission.
[b]Serum from relapse at 15, 42, and 15 days, respectively.
HSV, herpes simplex virus; Sx, seizures; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; NMDAR, N-methyl-D-aspartic acid receptor; Ab, antibody; D2R, Dopamine-2 receptor; IgG, immunoglobulin G; IgM, immunoglobulin M.

Case 1

A 7-year-old boy was admitted with an episode of generalized tonic-clonic status epilepticus following 4 days of fatigue, vomiting, and fever. Polymerase chain reaction (PCR) for HSV1 was positive on cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) of the brain showed right temporal lobe changes. He was treated with intravenous acyclovir at a dose of 10 mg/kg every 8 hours for 14 days. He had mild left hemiparesis and oro-motor dysfunction requiring nasogastric feeding. Ten days after starting acyclovir, he improved significantly, and started walking with minimal support and speaking in short sentences. Fifteen days into his illness he deteriorated, with emotional lability, irritability, incontinence of urine, visual hallucinations, and left hand tremor. The next day he developed episodic flailing movements of the limbs, which evolved over the following week with incessant generalized chorea, intermittent dystonic posturing, and ballismic limb and body movements (Video 1). T2-weighted MRI sequences at this time showed persisting right temporal lobe changes with symmetric hyperintensity in both putamen. HSV1 PCR on CSF tested on day 16 and over the following 2 months remained negative. The clinical syndrome of encephalopathy and

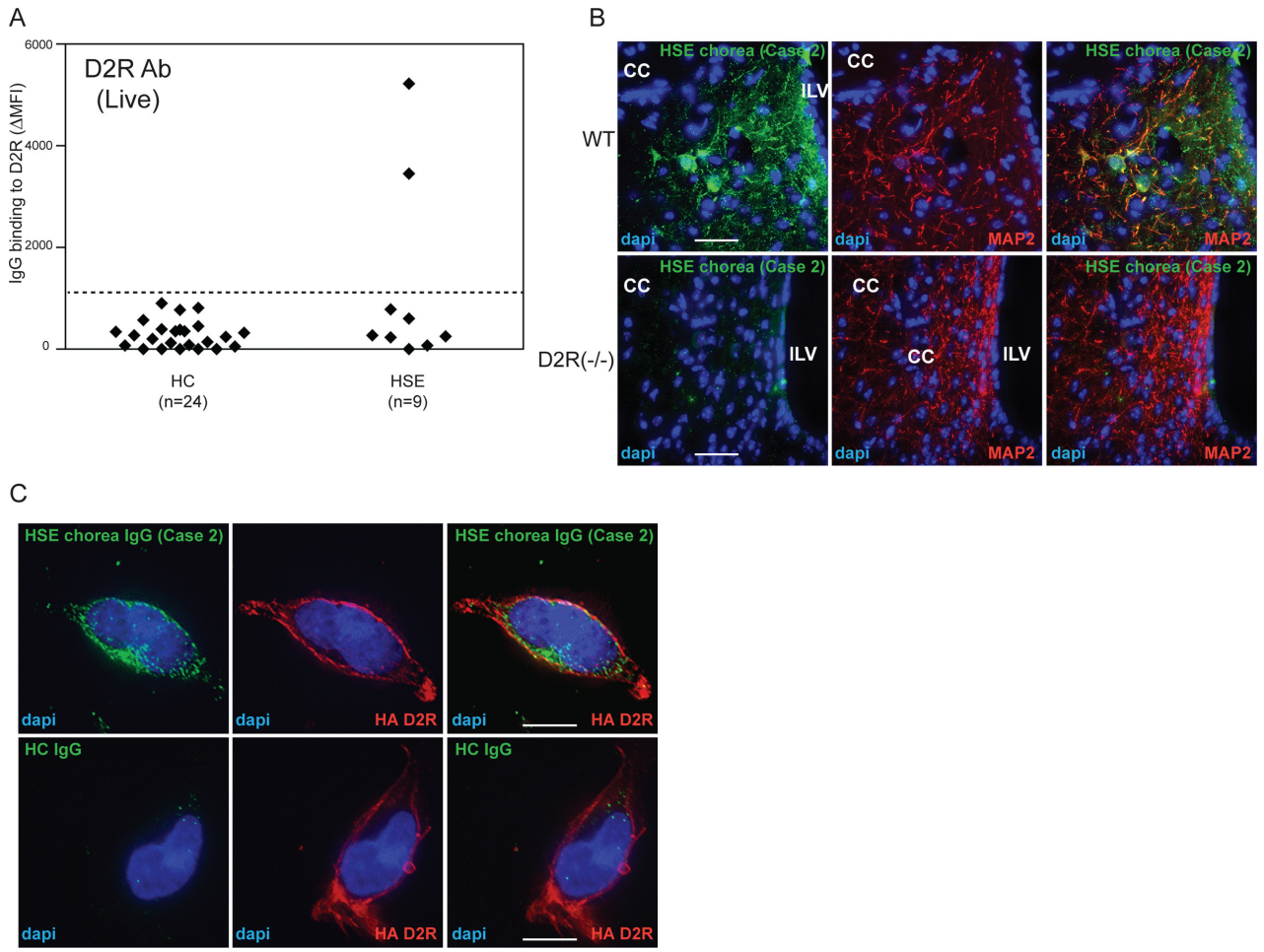

FIG. 1. A: Human surface D2R IgG was detected in serum in 2 HSE patients with chorea. Dotted line represents positivity threshold (control mean + 3 SD). **B:** Immunoreactivity of HSE patient serum in the striatum of wild-type and D2R knockout ($D2R^{-/-}$) mice. Case 2 serum (green) immunolabeled dendrites and cell bodies of $MAP2^{+}$ neurons (red) in striatum of wild-type mice (upper row), whereas the immunolabeling was significantly decreased in $D2R^{-/-}$ striatum (lower row). Nuclei stained with DAPI (blue). Scale bar = 40 μm. **C:** Immunocytochemistry on fixed nonpermeabilized stable HEK^{D2R+} transfectants confirmed HSE patient (case 2) co-immunolabeled HA-D2R positive cells (red, upper row). Cells were labeled with protein G-purified 8 μg IgG from the serum of case 2 followed by Alexa Fluor 647-conjugated anti-human IgG secondary antibody and anti-HA antibody followed by Alexa Fluor 555-conjugated anti-mouse IgG secondary antibody. Purified IgG from HC (8 μg) showed a significantly reduced immunolabeling (lower row). Nuclei stained with DAPI. Scale bar = 24 μm. D2R, dopamine-2 receptor; IgG, immunoglobulin G; HSE, herpes simplex virus 1 encephalitis; MAP2, microtubule-associated protein 2; DAPI, 4′,6-diamidino-2-phenylindole; HA, hemagglutinin; HC, healthy control; CC, corpus callosum; ILV, left lateral ventricle.

dyskinesia was reminiscent of NMDAR encephalitis, and CSF and serum NMDAR antibodies were positive, although antibodies against D2R were negative. The patient received intravenous steroids and 2 g/kg human intravenous immunoglobulin (IVIg) followed by 3 doses of 750 mg/m^2 cyclophosphamide with Mesna cover over a 5-month period.[5] Oral valacyclovir was continued during this period. One month after the third dose of cyclophosphamide, the patient was visually interactive and could stand without support (Video 1). Subtle chorea was restricted to periods of emotional agitation. Sleep and autonomic dysfunction had reverted to normal. Serum NMDAR IgG antibodies were significantly elevated at chorea onset, but declined on convalescent testing and during therapy (data not shown).

Case 2

A previously well 12-month-old female presented with drowsiness, irritability, and focal seizures. Initial electroencephalography (EEG) showed left temporal lobe epileptic activity with slowing, and brain MRI showed hyperintensity in the left temporal lobe cortex and white matter. PCR for HSV1 was positive on CSF with 6 monocytes and 8 red cells. The patient was treated with phenytoin and 3 weeks of intravenous acyclovir. Her encephalopathy initially improved; however, 6 weeks after onset she developed generalized chorea with feeding difficulty. She was given a further 3 weeks of intravenous acyclovir and 2 years of oral valacyclovir. The chorea resolved within 2 months but the patient has had epilepsy

since then, with daily seizures refractory to multiple antiepileptic drugs and the ketogenic diet. She also suffered an epileptic encephalopathy with pronounced developmental delay, intellectual disability, and challenging behavior. Due to the refractory nature of the epilepsy, a left temporal lobectomy was performed at 7 years of age. The temporal lobe revealed destructive architecture, cystic changes, foamy macrophages, extensive gliosis, and neuronal loss. In addition, there were perivascular lymphocytic aggregates demonstrating chronic active encephalitis. HSV1 testing on the brain tissue using viral culture and PCR was negative. Lobectomy and subsequent callosotomy performed at 8 years of age did not improve seizure control although modest benefit in cognition and behavior was seen after the callosotomy. Serum taken during the episode of chorea showed elevated autoantibodies against D2R, but it was negative for antibodies to NMDAR (no CSF was available). At 9 years of age, the patient received an immune therapy trial of oral prednisolone (2 mg/kg/day for 1 month) and 2 g/kg of IVIg without apparent benefit. At the age of 18 years, she has ongoing epilepsy, intellectual disability, and is mobile but with multiple falls.

Case 3

A previously well 8-month-old girl presented with fever, drowsiness, vomiting, and focal motor seizures. MRI showed pronounced left parietal cortical changes with associated white matter hyperintensity, and bilateral basal ganglia and thalamic lesions. Ten days after onset, CSF showed 19 monocytes, 4 red cells, and negative HSV1 PCR, although there was intrathecal synthesis of HSV1 IgG compatible with definite HSE.[8] After 15 days of intravenous acyclovir and antiepileptic drugs, seizures and encephalopathy initially improved. On stopping the acyclovir, however, she deteriorated with increasing encephalopathy and chorea. MRI showed further evolution of previous changes. She was treated with a further 2 weeks of acyclovir and 3 days of intravenous methylprednisolone with 2 g/kg of IVIg. The movement disorder resolved after 2 months, but the patient has been left with a significant brain injury, and convalescent MRI has shown pronounced bilateral encephalomalacia with gliosis. At 14 years of age, she has dystonic quadriplegic cerebral palsy requiring a wheelchair for mobility, intellectual disability, and refractory epilepsy. Testing the serum 2 weeks into the illness revealed elevated autoantibodies against both NMDAR and D2R. No CSF was available for testing.

Discussion

The 3 chorea patients had a typical clinical syndrome and investigation findings of HSE associated with an initial positive response to acyclovir, but then a relapse with chorea. A secondary worsening with abnormal movements has been described in a minority of patients with HSE, and we found over 20 cases reported in the literature with a similar clinical course.[1,2,6,9-14] All reports and a review from 1998[1] suggest that relapse of HSE with abnormal movements carries a poorer prognosis with ~20% mortality and ~50% patients left with severe neurological deficits.[15,16] Most relapses with chorea occur 1.5 to 4 weeks after the initial illness, and the lack of HSV replication has led to the hypothesis that postinfectious autoimmunity is operating.[1,2,6,13,15,17] Authors have reported varying benefits from immunosuppressive therapy in such patients.[2,17]

Recently, a series of 44 patients with HSE was reported by Prüss et al.[4] This retrospective analysis found NMDAR IgG, IgA, or IgM antibodies in the serum or CSF in 13 of 44 patients with HSE. However only 4 of them had IgG antibodies against the NR1 subunit, and 3 of the patients had intrathecal production of IgG antibody. No clinical difference nor movement disorders were noted in the patients who were positive for NMDAR antibodies. In a recent cohort of 20 children with NMDAR encephalitis, 1 child had preceding HSE and the authors proposed a possible link between HSE and NMDAR encephalitis.[6] The relapsing phase in case 1 was clinically suggestive of NMDAR encephalitis with encephalopathy, agitation, autonomic dysfunction, dyskinesia, and disruption of the sleep-wake cycle. In view of the evidence of postviral autoimmunity, we treated our patient with steroid and IVIg, and due to poor initial response, we escalated immunosuppression with cyclophosphamide as has been used in the treatment of NMDAR encephalitis.[5,6,18] Our patient appeared to respond to the therapy, and the encephalopathy and movement disorder markedly improved. Our laboratory work echoed the clinical improvement and showed a clear decline in NMDAR antibodies after therapy. Case 2 also had a relapse with chorea and was negative for NMDAR antibodies, but had positive autoantibodies against D2R. Only serum was tested for NMDAR antibodies, which has lower sensitivity than CSF.[18] We have recently described autoantibodies against D2R in patients with movement and psychiatric disorders of autoimmune origin.[7] This autoantibody finding was made retrospectively using stored serum from the relapsing phase of the illness, and the patient was not given immune therapy during the early stages of the illness. Case 2 had a chronic active encephalitis in the absence of active HSV1 infection 6 years after the acute illness. In view of the ongoing CNS inflammation, a modest trial of immune therapy was given 8 years after the acute illness, but this was ineffective. Case 3 had a relapse with chorea after partial recovery from HSE. The chorea subsided after immune

suppression but has been replaced by refractory epilepsy and severe neurological impairment. This patient's serum from the time of relapse had positive autoantibodies against both NMDAR and D2R.

In conclusion, because both NMDAR and D2R are important receptors involved in the control of movements, we believe that the presence of autoantibodies against these receptors expressed in their conformational state at the cell surface supports the hypothesis that chorea after HSE is an example of postviral autoimmunity. Although further studies are required to test the association and pathogenicity of autoantibodies in post HSE chorea, these findings lend support to the use of immune suppression in relapses of HSE.

Legend to the Video

Video 1. Before immunosuppression, the patient has severe generalized chorea and involuntary stereotyped movements associated with agitation. Two months after the third dose of cyclophosphamide, the patient is able to stand although is unstable. Three months after the third dose of cyclophosphamide, the patient is able to make some steps with support. His mobility is markedly improved and hemiparesis and movement disorder have resolved by 1 year from disease onset. ■

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Cortical Gyrification Reductions and Subcortical Atrophy in Parkinson's Disease

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ABSTRACT

Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor and nonmotor symptoms. Previous morphometric studies of PD were mainly conducted by measuring gray matter volume and cortical thickness, and little attention has been paid to the morphology of the cortical surface.

Methods: Using a surface-based local gyrification index (lGI), this study compared the cortical gyrification patterns of 37 PD patients and 34 matched healthy controls. Volumetric analyses also were performed on the subcortical structures.