The L-dopa response in vascular parkinsonism

J C M Zijlmans, R Katzenschlager, S E Daniel, A J L Lees

METHODS

Subjects

All seventeen patients with pathologically confirmed VP from the pathological collection held at the Queen Square Brain Bank for Neurological Disorders (QSBBND) were selected.

Methods: Seventeen patients with pathologically confirmed VP were selected from the pathological collection of the Queen Square Brain Bank for Neurological Disorders, and their L-dopa response during life was compared with the presence of macroscopic vascular damage in the nigrostriatal pathway and microscopic substantia nigra cell loss.

RESULTS: Ten of the twelve patients with a good or excellent response had macroscopic infarcts or lacunae caused by enlarged perivascular spaces in the basal ganglia or microscopic neuronal cell loss in the substantia nigra. In contrast, only one of the five patients with a moderate or no response had lacunae in the putamen, and none had lacunar infarcts or substantia nigra cell loss.

Conclusion: These results suggest that a substantial number of patients with clinically suspected VP may respond with benefit to dopaminergic therapy, especially those with lesions in or close to the nigrostriatal pathway.

Objective: To determine whether a positive L-dopa response in vascular parkinsonism (VP) is correlated with the presence of nigrostriatal pathology due to either vascular damage or neuronal cell loss.

Vascular parkinsonism (VP) has generally been considered to respond poorly or not at all to L-dopa treatment. However, we recently reported that different types of vascular damage—that is, macroscopic lacunar infarcts in the basal ganglia and diffuse microscopic small vessel disease (SVD), can cause VP. The L-dopa response has never been examined systematically in relation to these different pathological lesions. In the only systematic clinico-pathological study up to now in which the L-dopa response was described, VP was characterised by a negative response to L-dopa. However, these authors only examined patients whose parkinsonism was caused by SVD that interrupted the thalamocortical pathways and not by macroscopic lacunar infarcts in the basal ganglia. We wish to report more encouraging results based on the first published study in pathologically confirmed cases that takes different anatomical lesions and pathomechanisms of VP into account.

METHODS

Subjects

All seventeen patients with pathologically confirmed VP from the pathological collection held at the Queen Square Brain Bank for Neurological Disorders (QSBBND) were selected.

They had parkinsonism but with no pathological evidence of either idiopathic Parkinson's disease or any Parkinson plus syndrome. Parkinsonism was defined by the presence of bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions in either upper or lower limb, including the presence of reduced step length) and at least one of the following: rest tremor, muscular rigidity, or postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. Patients with neuroleptic therapy or severe head injury in the year before onset of parkinsonism were excluded. All patient brains were collected in the QSBBND over the last 10 years. Six hundred parkinsonian brains were screened to find the cases. Seven of the patients had been prospectively assessed annually by neurologists in the United Kingdom Parkinson’s Disease Group (UKPDRG) using standardised clinical information sheets. The other patients had all been diagnosed as having parkinsonism by consultant neurologists or geriatricians with a particular interest in Parkinson’s disease.

Methods

The clinical features and the L-dopa response during life of all patients identified were abstracted from the clinical records, and from the QSBBND prospective annual assessment data that were available for seven patients. The L-dopa response was classified into four different categories by investigators blinded to the pathology parameters. The seven patients for whom QSBBND prospective annual assessment data were available and one of the others rated their response as excellent (70–100% improvement of motor symptoms), good (50–70% improvement), moderate (25–50%), or absent (less than 25%). In the rest the response was scored as excellent if in the notes it was described as “dramatic”, “spectacular”, or “excellent” for at least 1 year; good if motor symptoms improved substantially and were sustained for at least 1 year; moderate where the terms “modest” or “moderate” were used but giving nevertheless a clear cut response, and absent when there was a statement to the fact that no useful response had occurred at the end of 1 year.

Half brains contralateral to the more symptomatic side of the body, fixed in 10% neutral formalin, were examined using standard neuropathological techniques. Tissue for paraffin embedding was taken from frontal, temporal, parietal, and occipital grey and white matter, and all deep grey nuclei including four levels through the striatum, midbrain, pons, medulla oblongata, and cerebellum. Sections were stained with haematoxylin and eosin, luxol fast blue/cresyl violet, and modified Bielschowsky silver impregnation. On selected regions, immunocytochemistry was performed using the biotin–streptavidin method and antibodies to ubiquitin (Dako, polyclonal 1:150), alpha-synuclein (a gift from Professor B Anderton, 1:500), tau (Dako, polyclonal 1:150) and GFAP (Dako, polyclonal 1:400).

Abbreviations: SVD, small vessel disease; QSBBND, Queen Square Brain Bank for Neurological Disorders; UKPDRG, United Kingdom Parkinson’s Disease Group; VP, vascular parkinsonism
In all identified cases the diagnosis of Parkinson’s disease and other parkinsonian syndromes including progressive supranuclear palsy, multiple system atrophy, post-encephalic parkinsonism, corticobasal degeneration, and dementia with Lewy bodies was excluded.

Data relating to the presence of macroscopically visible lacunar infarcts (type 1 lacunae), lacunae caused by enlarged perivascular spaces (type 2 lacunae), and large infarcts in main cerebral arterial areas were extracted from neuropathological reports. The number of lacunar lesions was recorded at brain cutting (by SED) and subsequently confirmed microscopically (by SED and JZ). The degree of microscopic nigral neuronal cell loss was also extracted from the neuropathological reports and subsequently confirmed blindly microscopically (by SED and JZ). Nigral cell loss was considered severe if more than 50% of the melanin containing cells in the substantia nigra were absent.

Statistics

The L-dopa responses of patients and their relation to the pathology and clinical features are described, as group sizes did not allow statistical tests.

RESULTS

Patients mean (SD) age at death was 81.4 (5.7) years. Among the patients there were 10 males and 7 females. Age at onset of symptoms was 70.5 (7.0) years and duration of the disease was 10.9 (5.5) years. The cause of death was known in 12 patients: bronchopneumonia (8), heart failure (2), hepatic failure (1) and brainstem stroke (1). The mean Hoehn and Yahr score was 1.9 (0.8) at presentation and 4.4 (0.9) before death. Clinical features are reported elsewhere. A sustained excellent L-dopa response was seen in three patients, and nine others had a good response, with only two of these experiencing a severe diminution in benefit as treatment continued. A moderate improvement in the first year was seen in two patients. The remaining three showed no response to L-dopa doses of 300–400 mg/day. Fifteen of the seventeen patients were still on L-dopa (mean dose 450 mg/day, range 100–1000 mg/day) up to the time of death. Five of the twelve patients with a good or excellent response developed motor response complications. Two patients complained of diminishing effects that started 2–4 years after the initiation of L-dopa; they were on a daily L-dopa dose of 450 and 1000 mg respectively. Three other patients developed dyskinesias. In one of them, “bizarre movements occurred directly after bromocriptine to a daily L-dopa dose of 1000 mg. A second patient became “dyskinetic” within 1 month of starting low dose L-dopa (100 mg/day). “Lip smacking” was noticed in the other patient within a year of starting 400 mg/day of L-dopa.

Only one VP case had an infarct in a main cerebral arterial supply territory, the middle cerebral artery territory. Macroscopically visible lacunar infarcts (type 1 lacunae) or lacunae caused by enlarged perivascular spaces (type 3 lacunae) were seen in the caudate, putamen, and globus pallidus in 10 of the parkinsonian brains. Their distribution could be seen on the luxol fast blue/cresyl violet stained slices in the putamen and caudate nucleus. The putamen only, and the external segment of the globus pallidus. Six of the nine good responders had lacunar infarcts or type 3 lacunae in the putamen or globus pallidus. Two of the good responders had severe neuronal cell loss in the substantia nigra with severe microscopic ischaemic damage in the putamen and globus pallidus. One also had a macroscopic lacunar infarct in this area. In contrast, only one of the five patients with a moderate or absent response had type 3 lacunae in the putamen, and none had lacunar infarcts in the nigrostriatal pathway or severe neuronal cell loss in the substantia nigra. All patients with motor response complications showed vascular damage in the basal ganglia or nigrostriatal neuronal cell loss.

DISCUSSION

A good response to L-dopa in our patients could not be predicted by onset type (acute or insidious), or by localisation (unilateral or bilateral, upper or lower limbs), or by any of the dominant features (tremor, hypokinetic rigidity, or shuffling gait). However, it was related to the presence of lesions in or near the nigrostriatal pathway—that is, macroscopically visible lacunar infarcts or lacunae caused by enlarged perivascular spaces in the putamen, caudate nucleus, and globus pallidus, or microscopic substantia nigra cell loss. This is in agreement with the outcome of individual L-dopa responses (positive or negative) in the only 34 reported VP patients in whom the presence or absence of a macroscopic lesion in the nigrostriatal pathway, found with imaging or on pathological examination, was described. All 14 VP patients who did not have macroscopic lesions in the basal ganglia showed a negative response to L-dopa (patient 1 of Fitzgerald and Jankovic, patients 2 and 3 of Winikates and Jankovic, patients 2 and 3 of Mark et al., and all nine patients without basal ganglia lesions of Zijlmans et al.). Of the other 20 VP patients who had macroscopic lesions in the nigrostriatal pathway, 15 showed a positive response to L-dopa (patient 1 of Dubinsky and Jankovic, patient 1 of Tison et al., patient 1 of Mark et al., Remy et al., Boecker et al., Jellinger, Leduc et al., and only 5 showed a negative response (patient 3 of Tolosa and Santamaría, patient 3 of Fitzgerald and Jankovic, Ikekua et al., Fénelon and Houéto). A positive response in VP patients can be explained by the presence of a remaining pool of striatal dopaminergic nerve terminals in a dysfunctional nigrostriatal pathway that remains adequate to convert exogenous L-dopa into dopamine and thus restore the intrinsic dopaminergic drive. The absence of an L-dopa response in other patients with a nigrostriatal lesion may be because the increase of basal ganglia output by L-dopa was unable to compensate for the dysfunctional thalamocortical drive.

Motor response complications have been seen in only three VP patients in the literature. A temporary increase to eight tablets of 250 mg L-dopa with 25 mg carbidopa caused severe dyskinesia without fluctuations in one patient. Another patient showed foot dystonia and motor fluctuations when on 125/500 mg carbidopa/levodopa daily. The third patient demonstrated episodes of hyperkinetic movements resembling chorea following 700 mg L-dopa plus 175 mg carbidopa daily in combination with selegiline 5 mg/day. Similar to our study, these previously reported patients demonstrated vascular lesions in striatum or substantia nigra. Our results confirm that the presence of motor response complications (dyskinesias and diminishing drug effect) is not a specific diagnostic marker of a primary neurodegenerative condition involving the nigrostriatal system and that in clinical practice, they do not help to reliably distinguish Parkinson’s disease from other causes of parkinsonism.

Both cases with severe nigral cell loss had extensive vascular damage in the putamen or globus pallidus in
absence of Lewy bodies. This may represent examples of transneuronal degeneration, as the vascular damage appears to have resulted in degeneration of substantia nigra neurons. Forno noted slight to moderate nerve cell loss in the ipsilateral substantia nigra of ten patients with massive unilateral infarction of the basal ganglia at post-mortem. In common with Parkinson’s disease, medial cell groups of the rostral portion of the substantia nigra in our patients were only slightly involved compared with the severe damage in the ventrolateral tiers.

There are potential weaknesses inherent in all clinico-pathological series. The patients in the present study were from the QSBBD, which recruits donors with either Parkinson’s disease or a related parkinsonian disorder. Therefore, the clinical picture of the studied patients may be biased toward a more “Lewy body PD type” presentation. Furthermore, the three non-responders were only on doses of 300–400 mg of L-dopa daily, and it is conceivable that if they were on higher doses, they might have had a good or substantial response. Another weakness of the study is that the ascertainment of L-dopa responsiveness was not uniform. Seven patients rated their own responsiveness, while ten ratings were abstracted from physician notes. Physicians and patients may have differing opinions regarding the degree of L-dopa responsiveness, which potentially is a source of bias. Therefore, the clinical picture of the studied patients may be biased towards a more “Lewy body PD type” presentation.

In view of our findings, we recommend that all patients with clinically suspected VP should receive an adequate trial of L-dopa. Patients found to have macroscopically visible lacunae caused by perivascular dilatations or lacunar infarcts predominating in the nigrostriatal pathway are most likely to respond well. However, one case with only microscopic substantia nigra cell loss and extensive microscopic vascular damage in the absence of macroscopic lesions also showed a positive L-dopa response. This is the first systematic clinico-pathological study that takes different anatomical lesions and pathomechanisms of VP into account. We suggest that a good therapeutic response in VP is related to the presence of lesions in or nearby the nigrostriatal pathway—that is, vascular damage in the putamen or globus pallidus area, or substantia nigra cell loss.

Authors’ affiliations
J C M Zijlmans, R Katzenschlagor, S E Daniel, A J L Lees, Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, Queen Square, London, UK
J C M Zijlmans, Department of Neurology, VU Medical Centre, Graduate School for Neurosciences, Amsterdam, the Netherlands

R Katzenschlagor, Department of Neurology, Donauplau/SMZ-Ost, Vienna, Austria

Competing interests: A J L Lees has received honoraria from Roche in 2002–03 for talks on L-dopa treatments in Parkinson’s disease (but not vascular Parkinson’s)

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