Parkinsonism is a Late, Not Rare, Feature of CADASIL
A Study on Italian Patients Carrying the R1006C Mutation

Michele Ragno, MD; Alfonso Berbellini, MD; Gabriella Cacchiò, MD; Antonio Manca, MD; Fabio Di Marzio, MD; Luigi Pianese, MSC, PhD; Anna De Rosa, MD, PhD; Serena Silvestri, MSC; Maria Scarchella, MD; Giuseppe De Michele, MD

Background and Purpose—To describe parkinsonism as a clinical manifestation of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Methods—We report 5 patients carrying the R1006C mutation in the exon 19 of NOTCH3 gene. All cases presented late onset, slowly progressive parkinsonism, not responsive to l-dopa. We performed brain MRI and 123I-FP-CIT SPECT in all and in 3 additional patients carrying the same mutation but without parkinsonism. Four patients with parkinsonism underwent myocardial 123I-meta-iodobenzylguanidine scintigraphy.

Results—In all patients, brain MRI showed widespread ischemic lesions in the periventricular white matter, the internal and external capsules, the basal ganglia, and thalami. 123I-FP-CIT SPECT showed symmetrical or asymmetrical reduction of tracer uptake in the putamen, with inconstant caudate involvement. Myocardial 123I-meta-iodobenzylguanidine scintigraphy resulted normal. Nigrostriatal denervation was also demonstrated in 2 patients without parkinsonism.

Conclusions—In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, parkinsonism may be a not rare, late onset manifestation. The clinical picture, the lack of response to dopaminergic treatment, and MRI findings suggest a vascular parkinsonism, which may be preceded by a protracted presymptomatic phase.

Key Words: CADASIL syndrome ▪ imaging ▪ Parkinson disease

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-vessel disease caused by mutations in the NOTCH3 gene. The clinical spectrum includes migraine, recurrent transient ischemic attacks or stroke, cognitive decline, psychiatric manifestations, epileptic seizures, and cognitive impairment. Parkinsonian features are not viewed as typical of the CADASIL phenotype and, so far, a clear parkinsonian syndrome has been rarely described. Here, we report 5 CADASIL patients carrying the R1006C mutation affected by parkinsonism.

Methods

Since 1995, we observed 45 individuals belonging to 20 families sharing the R1006C mutation in the exon 19 of NOTCH3 gene and originating from the district of Ascoli Piceno, Central Italy. Among them, 5 presented parkinsonism and were included in the study. We also included, for comparison, 3 CADASIL patients with the same mutation and without parkinsonism.

Brain MRI and 123I-FP-CIT SPECT studies were performed in all subjects and myocardial 123I-meta-iodobenzylguanidine (MIBG) scintigraphy in 4 patients with parkinsonism. Details of methodology of clinical and imaging studies are in the online-only Data Supplement.

Results

Clinical features of the patients are shown in Table 1, and imaging data are shown in Table 2 and the Figure in the online-only Data Supplement. Four patients were male and 1 was female; mean age±SD was 63.0±9.3 years, mean age at onset of CADASIL manifestations was 47.6±14.3 years, and that of parkinsonism 61.6±8.7 years. The severity of the parkinsonian syndrome was moderate in 4 patients and severe in case 3. Median Hoehn and Yahr stage was 3, median Unified Parkinson’s Disease Rating Scale—Motor Section (UPDRS-III) score 19, median Rankin Scale score 2, and median Global Deterioration Scale score 5. Akinesia, rigidity, and postural instability were present in all patients, whereas rest tremor was always absent. Asymmetry of signs was observed only in case 1. Levodopa response was tested in 4 patients without benefit.

In all patients, MRI showed widespread areas of increased signal in the periventricular white matter extended down to involve the external and internal capsules, consistent with ischemic lesions, detected on T2-weighted images or FLAIR sequences and associated with focal gliotic hyperintensities or lacunar lesions in the basal ganglia and thalami.

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Table 1. Clinical Features of the Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Patients With Parkinsonism</th>
<th>Patients Without Parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sex/age</td>
<td>M/59</td>
<td>M/50</td>
</tr>
<tr>
<td>Age at onset (CADASIL/PARK)</td>
<td>30/58</td>
<td>45/49</td>
</tr>
<tr>
<td>RS/GDS</td>
<td>2/4</td>
<td>2/5</td>
</tr>
<tr>
<td>Akinesia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rigidity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tremor</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Asymmetry of parkinsonism</td>
<td>Right</td>
<td>No</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Levodopa response</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Apraxia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Increased tendon reflexes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>No</td>
<td>Left</td>
</tr>
<tr>
<td>Pseudobulbar signs</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Onset age is given for both cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and parkinsonism (PARK). GDS indicates Global Deterioration Scale; H–Y, Hohen–Yahr Staging; NA, not applicable; RS, Rankin Scale; and UPDRS-III, Unified Parkinson’s Disease Rating Scale—Motor Section.

123I-FP-CIT SPECT showed reduction of putamen tracer uptake, bilateral in all patients except case 1. The caudate uptake was normal in 3 cases, unilaterally reduced in case 5, and bilaterally decreased in case 3, the most severely affected patient. Meta-iodobenzylguanidine uptake was normal in the 4 investigated patients. Clinical and imaging findings of 3 CADASIL patients without clinical signs of parkinsonism are shown for comparison in Tables 1 and 2.

Discussion

The pathological hallmarks of CADASIL are deposits of granular osmiophilic material,1 loss of vascular smooth muscular cells, and fibrosis of tunica media in small and medium-size penetrating arteries. The intimal thickening, vessel stenosis, and reduced blood flow presumably cause lacunar infarcts, mainly in the basal ganglia and fronto-temporal white matter.

CADASIL progresses in a stepwise fashion, and pseudobulbar signs tend to occur late in the disease. Parkinsonian features, such as rigidity or akinesia, have been reported,2 but only a few patients showed a clear parkinsonian syndrome,4,5 and one showed a clinical picture mimicking progressive supranuclear palsy.3

Here, we describe 5 patients carrying the R1006C NOTCH3 mutation, presenting with parkinsonism, originating from a population of 45 patients presently followed by us (11%). The overall clinical presentation and the neuroimaging investigations are consistent with vascular parkinsonism (VP). Proposed diagnostic criteria for VP require the presence of bradykinesia and ≥1 of rest tremor, rigidity, or postural instability, and cerebrovascular disease, defined radiologically or by the presence of focal signs or symptoms consistent with stroke.7 VP may have acute or delayed progressive onset after stroke or, more frequently, an insidious onset. Our patients showed an insidious onset and, except for case 5, a prolonged delay between onset of CADASIL and parkinsonian features. VP is characterized clinically by bilateral symptoms at onset with early shuffling of gait, postural instability, rare presence of rest tremor, cognitive impairment, corticospinal or pseudobulbar signs, and urinary incontinence, an overall clinical picture that matches well with that found in our patients.

The main neuroimaging abnormalities in VP include extensive periventricular and subcortical white matter lesions and basal ganglia infarcts. In patients with acute onset, there is evidence of infarcts in or near areas that increase the basal ganglia motor output or decrease the thalamocortical drive.7 In our patients, the insidious onset of parkinsonism and the absence of focal infarcts in strategic areas altering the basal ganglia motor output are consistent with a more diffuse small-vessel disease affecting the striatonigral or the thalamocortical pathways.

Although 123I-FP-CIT SPECT studies in our patients gave evidence of presynaptic dopaminergic deficit, the absence of response to levodopa suggests that dysfunction of the striatal dopamine receptors or of the nondopaminergic thalamocortical pathway also contribute to the pathophysiology of CADASIL-related parkinsonism.123I-meta-iodobenzylguanidine myocardial scintigraphy resulted to be normal in the 4 investigated patients, contributing to rule out the diagnosis of idiopathic Parkinson disease.8

We also investigated 3 CADASIL patients without parkinsonism. They were younger, less severely affected, and did not show pseudobulbar signs or urinary incontinence (Table 1).
Although they had no clinical signs of parkinsonism, 123I-FP-CIT SPECT showed clear nigrostriatal denervation in case 6, which also showed a right putaminal infarct, and slight uptake reduction in case 8. Their total and basal ganglia MRI lesion scores were similar to CADASIL parkinsonian patients. It is conceivable that a diffuse small-vessel disease, such as CADASIL, could damage the substantia nigra, the putamen, the caudate, and the basal ganglia–thalamocortical circuit and that after a protracted presymptomatic phase, some patients could show clinical features of parkinsonism, which progress slowly in the course of the disease. A limitation of our study is that only patients with R1006C mutation have been examined, leaving open the hypothesis that parkinsonism is a peculiar feature of this genotype. However, a clear genotype–phenotype correlation is not evident in CADASIL, cases with parkinsonism carrying a different mutation have previously been reported, and we found putaminal reduction of tracer uptake in a non-parkinsonian CADASIL patient carrying the R141C mutation (not included here because the study was conducted with a different SPECT methodology).

Furthermore, a study on a large sample of 102 CADASIL patients showed an age-dependent increase of basal ganglia symptoms (akinesia, rigidity, and psychomotor slowing) in up to 48% in patients >60 years of age.

In conclusion, parkinsonism may not be a rare feature of the CADASIL spectrum. 123I-FP-CIT SPECT shows symmetrical or asymmetrical reduction of tracer uptake in the putamen, with inconstant caudate involvement. Parkinsonism in CADASIL is not an early disease manifestation and may be preceded by a presymptomatic phase. Onset of symptoms is insidious and progression slow. It is likely related to disconnection between the basal ganglia and the cortex or trans-synaptic degeneration of nigral dopaminergic neurons subsequent to subtle striatal vascular lesions. Because early and even presymptomatic diagnosis is possible in CADASIL, this disease may represent a model for investigating the pathogenesis and the evolution of parkinsonism related to cerebral small-vessel disease.

Disclosures

None.

References

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Supplemental Material

Supplemental Methods

In all subjects the following clinical features were recorded: presence of parkinsonism assessed by Hoehn and Yahr Staging and Unified Parkinson’s Disease Rating Scale Motor Section (UPDRS - part III; range 0-108) (1); functional ability at the time of investigation, assessed by the modified Rankin Scale (RS, range 0-6) (2); overall cognitive functioning, rated on Global Deterioration Scale (GDS; range 1-7) (3).

Brain MRI (1.5 T MRI system Symphony, Siemens) was performed in all subjects. Distribution of brain lesions was assessed by a semi-quantitative scale which assigns a score from 0 to 6 to each region (4). A total of 15 individual regions were scored separately, and the total score (range 0-90) was calculated as an index of overall severity of lesion load. MR images were also examined for abnormal signal intensities in the deep brain nuclei to calculate a basal ganglia score.

To investigate nigrostriatal function SPECT studies were performed 3 hours after IV injection of about 185 MBq of $^{123}$I-FP-CIT (DaTscan, GE Healthcare). The studies were processed using the Basal Ganglia Matching Tools ver. 2 software to obtain a semiquantitative striatal DAT uptake evaluation by measurement of \( \frac{(\text{Caudate-Background})}{\text{Background}} \) and \( \frac{(\text{Putamen-Background})}{\text{Background}} \) ratios, and left-to-right side uptake percent asymmetry \( \frac{100 \times (\text{Left-Right})}{\frac{1}{2} \times (\text{Left+Right})} \). This method is operator-independent, based on 3D template of the striatum derived from Talairach and Tournoux’s anatomical atlas. The normal values (mean ± SD) obtained for caudate-to-background and putamen-to-background are: 4.21 ± 0.67 and 3.59 ± 0.66 (5). The software compared the proband patient vs. an Italian population of 96 normal subjects. Caudate and putamen background-normalized values for each patient were graphically plotted vs healthy subjects at two C.I. levels: 90% and 97%. Values below these levels were considered slightly or definitely abnormal (6). Finally, each study was scored according a visual scale (range: 0-3) specifically designed for vascular parkinsonism (7).
Myocardial $^{123}$I-meta-iodobenzylguanidine (MIBG) scintigraphy was performed in four patients with parkinsonism to investigate myocardial sympathetic denervation for differential diagnosis with idiopathic PD. $^{123}$I MIBG (AdreView, GE Healthcare, 185 MBq) was injected intravenously and two anterior planar studies of thorax were acquired after 10 minutes and after 4 hours. Regions of interest (ROI) were drawn over left heart ventricle (H) and mediastinum (M) and H/M ratios were calculated for early (H/M$_{10m}$) and late study (H/M$_{4h}$) (8). In our laboratory, we use a late ratio cut-off value $<$1.39 to suggest the diagnosis of a myocardial sympathetic impairment as found in idiopathic PD.

Analysis of MRI, $^{123}$I- FP-CIT SPECT, and $^{123}$I-MIBG scintigraphy was done by an investigator (AM for MRI, AB for molecular imaging studies) blinded to the patients’ clinical status in relation to parkinsonism.

All subjects gave their informed consent to participate in the present study according to the principles of the Declaration of Helsinki as revised in 2000. The study was approved by ethics committee.
Supplemental Figure
Legend to Supplementary Figure.

Upper row. Axial brain MRI showing: multiple lacunae of the basal ganglia, more evident on the right pallidus and left caudate head on T2-weighted images in Case 1 (a); small basal ganglia lacunae and ischemic lesions of the left ventral thalamus and right globus pallidus on T2-weighted spin echo image in Case 2 (b); cortical infarct in the left temporo-occipital region and lacunae in the left pallidus and right thalamus on T2-weighted images in Case 3 (c); ischemic infarction of the right lentiform nucleus on T2-weighted spin echo images in Case 5 (d).

Lower row. [123I]-FP-CIT showing: slight reduction of left putamen uptake in Case 1 (e); bilateral low putaminal uptake in Case 2 (f); bilaterally reduced uptake in the caudate and putamen in Case 3 (g); moderate low uptake at the right caudate and bilaterally reduced putaminal uptake in Case 5 (h).
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**Supplementary Files**

**Methodological details**

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