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Atypical parkinsonism in Guadeloupe: a common risk factor for two closely related phenotypes?

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In Guadeloupe, there is an abnormally high frequency of atypical parkinsonism. Only one-third of the patients that develop parkinsonian symptoms were reported to present the classical features of idiopathic Parkinson disease and one-third a syndrome resembling progressive supranuclear palsy (PSP). The others were unclassifiable, according to established criteria. We carried out a cross-sectional study of 160 parkinsonian patients to: (i) define more precisely the clinical phenotypes of the PSP-like syndrome and the parkinsonism that was considered unclassifiable in comparison with previously known disorders; (ii) define the neuropsychological and brain imaging features of these patients; (iii) evaluate to what extent a candidate aetiological factor, the mitochondrial complex I inhibitor annonacin contained in the fruit and leaves of the tropical plant *Annona muricata* (soursop) plays a role in the neurological syndrome. Neuropsychological tests and MRI were used to classify the patients into those with Parkinson's disease (31%), Guadeloupean PSP-like syndrome (32%), Guadeloupean parkinsonism–dementia complex (PDC, 31%) and other parkinsonism-related disorders (6%). Patients with a PSP-like syndrome developed levodopa-resistant parkinsonism, associated with early postural instability and supranuclear oculomotor dysfunction. They differed, however, from classical PSP patients by the frequency of tremor (>50%), dysautonomia (50%) and the occurrence of hallucinations (59%). PDC patients had levodopa-resistant parkinsonism associated with frontosubcortical dementia, 52% of these patients had hallucinations, but, importantly, none had oculomotor dysfunction. The pattern of neuropsychological deficits was similar in both subgroups. Cerebral atrophy was seen in the majority of the PSP-like and PDC patients, with enlargement of the third ventricle and marked T_2-hypointensity in the basal ganglia, particularly the substantia nigra. Consumption of soursop was significantly greater in both PSP-like and PDC patients than in controls and Parkinson's disease patients. In conclusion, atypical Guadeloupean parkinsonism comprises two forms of parkinsonism and dementia that differ clinically by the presence of oculomotor signs, but have similar cognitive profiles and neuroimaging features, suggesting that they may constitute a single disease entity, and both were similarly exposed to annonaceous neurotoxins, notably annonacin.

Keywords: Annonaceae; annonacin; atypical parkinsonism; dementia; MRI; PSP

Abbreviations: DLB = dementia with Lewy bodies; FAB = frontal assessment battery; FTDP = frontotemporal dementia with parkinsonism; Gd-PDC = guadeloupean parkinsonism-dementia-complex; Gd-PSP = guadeloupean progressive supranuclear palsy; I-PD = idiopathic Parkinson disease; Mattis DRS = Mattis Dementia Rating Scale; MMSE = Mini-Mental Status Examination; PSP = progressive supranuclear palsy; PDC = parkinsonism-dementia complex; UPDRS = Unified Parkinson's Disease Rating Scale

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Introduction

It was previously shown that there is an abnormally high frequency of atypical parkinsonism in Guadeloupe, a French Caribbean island with 422 000 inhabitants (Caparros-Lefebvre *et al.*, 1999, 2002). Only one-third of the patients had idiopathic Parkinson's disease, compared with 70% in European or North American populations, one-third had a PSP-like disease and one-third an undetermined form of parkinsonism (Caparros-Lefebvre *et al.*, 1999, 2002). In addition, a greater number of patients with atypical parkinsonism consumed fruit and infusions of leaves of *Annona muricata* (soursop, corossol), suggesting that the disease might be related to a toxin in the plant. *A. muricata* contains acetogenins that are potentially toxic inhibitors of the mitochondrial respiratory chain (Cavé *et al.*, 1997). Experimental studies *in vitro* (Lannuzel *et al.*, 2003) and *in vivo* (Champy *et al.*, 2004) on the effects of annonacin, the major acetogenin in *A. muricata*, have confirmed its toxicity at concentrations compatible with those contained in the fruit and infusions consumed by patients (Champy *et al.*, 2005).

Since Annonaceae are widely used in alimentation by populations living in or originating from tropical areas, it is important to confirm the implication of annonaceous neurotoxins in atypical parkinsonism. Indeed, associations between the consumption of Annonaceae and atypical parkinsonism have been reported in New Caledonia (Angibaud *et al.*, 2004) and in patients of Caribbean origin in London (Chaudhuri *et al.*, 2000).

To establish correlations between the patients and possible epidemiological and genetic factors, it is necessary to clearly define the clinical characteristics of the patients or subgroups of patients that may be affected. Whereas the PSP-like patients might form a homogeneous group, the 'undetermined' atypical patients need to be analysed in greater detail to determine their characteristics. In particular, the neuropsychological deficits of the patients, PSP-like or undetermined, have never been analysed, although dementia is a salient feature of atypical parkinsonism in Guadeloupe. Furthermore, none of the patients have undergone neuroimaging examinations to determine whether the same brain structures are involved in all. Finally, the consumption of annonaceous products by the individual patients needs to be quantified.

Therefore, to fully characterize the patients with atypical parkinsonism, we undertook a cross-sectional study with prospective inclusion of patients with parkinsonism, seen successively between September 2003 and September 2005, in the Neurology Department of the University Hospital in Pointe-à-Pitre, which is the referral centre for movement disorders in Guadeloupe. They underwent detailed clinical investigations to determine the characteristics of their parkinsonism, as well as detailed neuropsychological examinations and magnetic resonance brain imaging. In addition, the consumption of fruit and infusions of *A. muricata* by the patients was quantified.

Material and methods

Patients

One hundred and sixty consecutive patients with parkinsonism [defined as a combination of bradykinesia and at least one of the following: muscular rigidity, 4–6 Hz rest tremor, or postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction (Calne *et al.*, 1992)] were examined during the 2 years of the study. Only patients that were born in the Caribbean and resided in Guadeloupe at the time of examination were included. Most patients were Afro-Caribbeans from Guadeloupe ($n = 145$) or Haïti ($n = 3$), others were of Indian ($n = 10$) or Caucasian ($n = 2$) descent. Seven temporary residents, born in metropolitan France, all Caucasian, were diagnosed as having Parkinson's disease and were not included in the study. We also excluded patients with symptomatic parkinsonism, i.e. treated with neuroleptics during the 2 years prior to examination or with histories of severe or repeated head trauma, encephalitis, stroke, vascular parkinsonism or evidence of such on brain images. The excluded patients represented about 10% of all parkinsonian patients seen. When parkinsonism started before the age of 50 years, Wilson's disease was excluded by measuring copper and ceruloplasmin levels in blood and urine. To exclude symptomatic dementia, serum levels of thyroxine, TSH, vitamin B12 and folic acid were measured. The patients were also tested for HIV and syphilis. All patients had standard blood tests. Of the 160 patients, 31 (12 Parkinson's disease, 19 atypical parkinsonism) were prevalent cases, whereas 129 were incident.

Clinical examinations

Demographic data, family history, presenting symptom and disease onset were recorded. When the patient was unable to respond because of cognitive or speech disorders the main caregiver was requested to provide information. Each patient was examined clinically by two neurologists with expertise in movement disorders (A.L. and G.H. or S.V.). Parkinsonian symptoms were scored with part III of the Unified Parkinson's Disease Rating Scale (UPDRS III) and the Hoehn and Yahr (H&Y) scale. The response to levodopa was defined as improvement of the UPDRS III score by 0–30% (minimal response), 31–50% (moderate response), 51–100% (good response) after acute (200–300 mg levodopa in a single dose) or chronic (up to 1000 mg levodopa per day for 3 months when response was minimal or moderate) treatment. Acute levodopa tests were performed in 48 patients (40 atypical parkinsonian and 8 with Parkinson's disease patients). To assess autonomic dysfunction, orthostatic falls in blood pressure (a decrease in systolic pressure of at least 30 mmHg or a decrease in diastolic pressure of 15 mmHg were considered to be pathological (Gilman *et al.*, 1999), urinary incontinence (persistent involuntary partial or total bladder emptying) and erectile dysfunction in men were recorded.

Diagnostic criteria

The patients were classified according to accepted criteria. The diagnosis of Parkinson's disease (Gibb and Lees, 1988) was based on unilateral onset, good response to levodopa (>50%) and levodopa-induced dyskinesias. The diagnosis was excluded if there

were additional features, such as supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, early severe dementia, Babinski sign (Gibb and Lees, 1988). Possible or probable PSP was defined according to the NINDS-SPSP criteria (Litvan *et al.*, 1996a). The presence of vertical supranuclear gaze palsy affecting downward gaze or slowing of vertical saccades was essential for the diagnosis. Possible PSP was diagnosed in the presence of a gradually progressive disorder with onset at age 40 years or later, either vertical supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of onset. Probable PSP required vertical supranuclear palsy, prominent postural instability and falls in the first year of onset. The diagnosis of possible or probable PSP was excluded if there were hallucinations or delusions, severe autonomic dysfunction, cortical sensory deficit or alien limb phenomena (Litvan *et al.*, 1996*a*). Multiple system atrophy (Gilman *et al.*, 1999) was diagnosed if a poor response to levodopa was associated with autonomic, cerebellar or pyramidal symptoms. Marked asymmetry of parkinsonism and signs of cortical dysfunction (focal apraxia, alien limb phenomena, cortical sensory loss, hemineglect, focal or asymmetric myoclonus) were suggestive of corticobasal degeneration (Boeve *et al.*, 1999). Dementia with Lewy bodies (DLB) was diagnosed according to McKeith *et al.* (1996, 2005), as a progressive cognitive impairment with at least two of the following features: fluctuating cognition with pronounced variations in attention and alertness, recurrent well-formed visual hallucinations and parkinsonism.

Neuropsychiatric and neuropsychological ratings

Neuropsychiatic symptoms were assessed in all patients with the Mini-Mental Status Examination (MMSE) and the Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000). The Mattis Dementia Rating Scale (DRS) (Mattis, 1988) was used to evaluate 44 patients recruited from January to September 2005. Frontal behaviours were noted in all 44 patients. Visuoconstructive abilities were evaluated by the Rey figure copying test when possible or the Clock test and pentagonal reproduction in the MMSE.

Dementia was diagnosed when the FAB score was $\leq$12/18 and the MMSE score $\leq$24/30. In patients with borderline MMSE or FAB scores, dementia was diagnosed if the Mattis DRS score was $\leq$130. For patients unable to read or write ($n = 32$, 20% of the total cohort), phonemic fluency was replaced by category fluency on the FAB test. The total MMSE score could not be taken into account in these patients, since not all the subscores were evaluated.

Brain imaging

All patients had CT scans, brain MRI or both. MRI was performed with a neuro-optimized 1.5-T scanner with a standard quadrature head coil (Philipps 'Brillance'). Sagittal T_1, coronal T_2 and 3-mm-thick axial T_2, FLAIR and T_2^*-weighted gradient echo sequences were acquired. The presence of abnormal signals (hypo- and hypersignal) were noted and atrophy was rated (none, moderate or severe), in comparison with reference templates, in the cerebral cortex (frontal, temporal, parietal, occipital lobes), subcortical areas, midbrain and cerebellum. Mesencephalic atrophy was analysed, as recommended by Righini *et al.* (2004) on the superior profile of the midbrain on the midsagittal T_1-weighted images. The profile, represented by an imaginary line connecting a point immediately posterior to the mammillary body to a point on the upper opening of the aqueduct, was considered normal when convex, moderately atrophied (rated 1) when flat, or severely atrophied (rated 2) when concave. Enlargement of the lateral and the third and fourth ventricles was rated from 0 (none) to 3 (severe). Abnormal signals in the basal ganglia, midbrain and white matter were rated according to location, type (punctiform, linear, surface area) number and side. The scans were analysed independently by two neuroradiologists (PP, LG) who were blind to the clinical data. If the raters disagreed, they re-evaluated the images together until they reached consensus.

Quantification of consumption of annonaceous products

The consumption of annonaceous products of 69 patients and 88 controls matched for age and sex was quantified on the basis of a questionnaire that recorded birthplace, place of residence, educational attainment (years of schooling), professional occupation and consumption of the fruit and infusions of the leaves of *A. muricata* and other alimentary habits (data not shown). Controls were selected from patients on the waiting list for consultations in ophthalmology or traumatology (80%) or from associations of retired persons (20%). The control population first answered a list of nine questions that were previously validated for the detection of parkinsonism (Duarte *et al.*, 1995; Pramstaller *et al.*, 1999) and that we have validated, in French, in the Guadeloupean population (unpublished data). Subjects giving three or more positive responses were excluded.

Consumption of fruit (or fruit juice) and infusions was evaluated separately for successive 10-year periods over the life of the patient, and was expressed as fruit-years and cup-years, defined as the number of fruits and glasses of fruit juice (one glass of juice = 1 fruit) or cups of infusion consumed per day multiplied by the number of years of consumption (for example, a person who has eaten two fruits a day for 10 years, one fruit a day for 20 years or four fruits a day for 5 years all have a cumulative consumption of 20 fruit-years). The consumers were finally classified into two groups according to the amount of fruits or infusions they had consumed: low consumers (nul or occasional, <10 fruits or cups per day for 1 year); high consumers ($\geq$10 fruits or cups per day for 1 year). Fruit-years and cup-years were also converted into milligrams of annonacin, as determined by mass spectroscopy (Champy *et al.*, 2005). One average fruit or glass of juice was estimated to contain 15 mg of annonacin and one cup of infusion 0.14 mg. Fruit-years were thus multiplied by 15 mg and cup years by 0.14 mg. To obtain the total amount of annonacin ingested during the patient's life, these values were then multiplied by 365 days. For comparison with the neurotoxic dose in rats treated with annonacin, the total amount of annonacin was then divided by the weight of an average person (estimated to be 70 kg).

Statistical analysis

Statistical comparisons were performed using the STATVIEW 4.51.1 package for PC. Results are presented as the percentage or mean $\pm$ SEM. Normal parametric variables were compared in two groups of patients by one-way ANOVA followed by the Student–Newman–Keuls test. For non-parametric variables, the χ^2 test was used. It was replaced by the Fisher exact test when over 20% of the values were <5. A P-value <0.05 was considered significant.

Results

Patient classification

According to the criteria described in the Material and Methods, 50 patients (31%) fulfilled the diagnostic criteria for Parkinson's disease, 3 (2%) for multiple system atrophy with predominant parkinsonism and 3 (2%) for corticobasal degeneration (CBD). The remaining 104 patients (63%) had atypical forms of parkinsonism, and could be divided into two major groups. Half ($n = 51$) had a supranuclear ocular motor dysfunction. Twelve of these fulfilled the NINDS-SPSP diagnostic criteria for possible ($n = 10$) or probable ($n = 2$) PSP (Litvan *et al.*, 1996a), but the majority ($n = 39$, 76%) had at least one mandatory exclusion criterion [hallucinations and/or delusions ($n = 21$), severe autonomic dysfunction ($n = 6$) or both ($n = 12$)]. These 51 atypical patients with oculomotor dysfunction were grouped together and will be referred to as Guadeloupean PSP (Gd-PSP). Another 50 patients had a rather homogeneous clinical syndrome characterized by the presence of both levodopa-unresponsive parkinsonism and dementia, but no oculomotor problems. This group was designated Guadeloupean parkinsonism–dementia complex (Gd-PDC). Three patients with atypical parkinsonism could not be classified and were referred to as undetermined parkinsonism. The demographic data for all the patient groups are shown in Table 1.

Initial symptoms

Tremor was the most frequent initial symptom at onset of the disease in 73% of Parkinson's disease, 45% of Gd-PSP and 43% Gd-PDC patients. Bradykinesia (6% of Parkinson's disease, 12% of Gd-PSP and 9% of Gd-PDC) and rigidity (4% in all three groups) were less frequent initial symptoms. In Parkinson's disease patients, parkinsonian symptoms were either strictly unilateral or asymmetric at onset (92%), whereas they were symmetric in 39% Gd-PSP patients and 47% of those with Gd-PDC. Postural instability and falls as well as dysarthria and dysphagia were almost exclusively reported as presenting symptoms in the Gd-PSP group (12%). Cognitive or psychiatric dysfunction was a frequent initial symptom in Gd-PDC (27%, $n = 12$), less often in Gd-PSP (6%) and never in Parkinson's disease. Initial cognitive deficits in Gd-PDC patients were memory impairment ($n = 8$), personality changes ($n = 2$) or hallucinations ($n = 2$) and preceded the onset of parkinsonism on the average by 1.1 ± 0.2 (range 0.25–3) years.

Parkinsonian symptoms

The UPDRS III scores OFF levodopa were higher in Gd-PSP patients than in those with Gd-PDC, suggesting a more rapid disease progression (Table 2). They were also higher than in patients with Parkinson's disease, who have significantly longer disease durations, which would make the difference between the progression of Gd-PSP and Parkinson's disease even greater. The H&Y and UPDRS III scores, assessed when the ON response was best, were higher in Gd-PSP and Gd-PDC. The response to levodopa was good to excellent in Parkinson's disease patients, but absent or minimal in 96% of those with Gd-PSP and 76% of Gd-PDC (Table 2). Almost all patients had bradykinesia and rigidity. Rigidity predominated in axial muscles in 51% of Gd-PSP patients, but was more pronounced in limb muscles in 72% of Gd-PDC patients and in 100% of Parkinson's disease patients. Tremor was also frequently observed in the three groups, but its characteristics were different. In Parkinson's disease patients, it was an asymmetric, low frequency, rest tremor (90%). In Gd-PSP and Gd-PDC patients, it was usually a bilateral and irregular postural tremor (56 and 44%, respectively), associated with a fine, fast rest tremor (27 and 16%, respectively) or a low frequency, high amplitude rest tremor (20 and 34%, respectively). Four Gd-PSP (8%) and nine Gd-PDC (18%) patients also had intention tremor. Parkinsonian symptoms were most often symmetrical in Gd-PSP (67%) and Gd-PDC (60%) patients, whereas they were asymmetrical in 76% of those with Parkinson's disease. Postural instability was common in Gd-PSP (82%) and Gd-PDC (70%) patients

Table 1 Distribution and demographic characteristics of parkinsonian syndromes in Guadeloupe

Patient group	I-PD ($n = 50$)	Gd-PSP ($n = 51$)	Gd-PDC ($n = 50$)	MSA ($n = 3$)	CBD ($n = 3$)	UP ($n = 3$)
Total cohort (%)	31	32	31	2	2	2
Sex ratio (M/F)	1.5 (30/20)	2.6 (37/14)	1.5 (30/20)	0 (0/3)	3 (3/0)	2 (2/1)
Age (years ± SEM)	65.8 ± 1.7	73.9 ± 1.2***	73.2 ± 1.2***	66.0 ± 3.5	73.0 ± 1.7	59.6 ± 6
Age at onset (years ± SEM)	59.6 ± 1.6	71.1 ± 1.3***	69.5 ± 1.2***	61.0 ± 2.0	69.0 ± 1.5	54.6 ± 5.0
Afro-Caribbean, *n* (%)	48 (96)	48 (94)	47 (94)	1 (33)	3 (100)	0
Indian[a], *n* (%)	2 (4)	3 (6)	3 (6)	2 (67)	0	1 (30)
Caucasian[a], *n* (%)	0	0	0	0	0	2 (70)
Family history[a,b], *n* (%)	11 (22)	3 (6)*	4 (8)	0	0	0

I-PD, idiopathic Parkinson's disease; Gd-PSP, Guadeloupean progressive supranuclear palsy; Gd-PDC, Guadeloupean parkinsonism-dementia complex; MSA, multiple system atrophy; CBD, corticobasal degeneration; UP, undetermined parkinsonism. *$P < 0.05$ versus I-PD, ***$P < 0.001$ versus I-PD. Statistical analysis: one-way ANOVA followed by the Student–Newman–Keuls test for age and age at onset; χ^2 test, replaced by Fisher's exact test when over 20% of the values were <5. [a]For other variables. [b]First or second degree relatives with a history of parkinsonism and/or dementia.

Table 2 Main clinical features of patients with I-PD, Gd-PSP and Gd-PDC

Patient group	I-PD ($n = 50$)	Gd-PSP ($n = 51$)	Gd-PDC ($n = 50$)
Disease duration, years ± SEM (range)	6.4 ± 0.8 (0.4–23)	4.0 ± 0.5 (1–16)**	3.9 ± 0.4 (0.5–10)**
Hoehn and Yahr score, mean ± SEM	2.4 ± 0.1	3.5 ± 0.2***	3.0 ± 0.2**
UPDRS III OFF, mean ± SEM	30.4 ± 3.4	38.7 ± 2.4*	27.7 ± 2.0##
UPDRS III best ON, mean ± SEM	15.0 ± 1.7	38.3 ± 2.3***	21.6 ± 2.0***
Response to levodopa[a]			
0–30%: *n* (% of patients)	1 (2)	49 (96)***	38 (76)***,##
30–50%: *n* (% of patients)	8 (16)	2 (4)	7 (14)
50–100%: *n* (% of patients)	41 (82)	0***	5 (10)***

[a]Response to levodopa = % improvement on UPDRS III evaluated in 50 I-PD, 40 Gd-PSP and 39 Gd-PDC patients by chronic or acute levodopa tests performed in 8 I-PD, 21 Gd-PSP, 19 Gd-PDC patients; 10 Gd-PSP and 11 Gd-PDC patients were not treated because they were too severely affected or, inversely, their parkinsonian syndromes were not severe enough to warrant treatment. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus I-PD; ##$P < 0.01$ Gd-PSP versus Gd-PDC. Statistical analysis: one-way ANOVA followed by the Student–Newman–Keuls test for disease duration; χ^2 test for other variables.

Table 3 Non-parkinsonian clinical signs and symptoms in I-PD, Gd-PSP and Gd-PDC

Patient group		I-PD ($n = 50$)	Gd-PSP ($n = 51$)	Gd-PDC ($n = 50$)
Oculomotor dysfunction	Supranuclear palsy, *n* (%)	0 (0)	47 (92)***	0 (0)###
	Slowing of vertical saccades¶, *n* (%)	0 (0)	4 (8)	0 (0)
Dysarthria/dysphagia, *n* (%)		1 (2)	21 (41)***	7 (14)##
Motor symptoms	Pyramidal dysfunction, *n* (%)	0 (0)	12 (23)**	9 (18)*
	Myoclonus, *n* (%)	0 (0)	7 (14)***	7 (14)***
	Cerebellar dysfunction¶, *n* (%)	0 (0)	2 (4)	3 (6)
	Dystonia, *n* (%)	6 (12)	8 (16)	5 (10)
	Gait apraxia¶, *n* (%)	0 (0)	2 (4)	0 (0)
Dysautonomia	Urinary incontinence, *n* (%)	7 (14)	27 (53)***	25 (50)***
	Orthostatic hypotension[a], *n* (%)	8 (16)	15 (41)*	10 (24)
	Male erectile dysfunction[b], *n* (%)	10 (38)	10 (62)	8 (50)
Epilepsy¶, *n* (%)		1 (2)	6 (12)	2 (4)
Clinical RBD[c], *n* (%)		11 (22)	10 (20)	14 (28)
Psychiatric symptoms	Hallucinations, *n* (%)	3 (6)	30 (59)***	26 (52)***
	Delusions¶, *n* (%)	1 (2)	3 (6)	4 (8)
	Episodic confusion¶, *n* (%)	1 (2)	3 (6)	7 (14)
	Fluctuating alertness¶, *n* (%)	0 (0)	0 (0)	2 (4)
	Illusions¶, *n* (%)	2 (4)	0 (0)	0 (0)
	Dementia, *n* (%)	5 (10)	47 (92)***	50 (100)***

[a]Evaluated on the basis of data available data for 48 I-PD, 36 Gd-PSP and 42 Gd-PDC patients. [b]Evaluated on the basis of data available for the male population: 26 I-PD, 16 Gd-PSP, 16 Gd-PDC. [c]REM sleep behaviour disorder, diagnosed on the basis of reports by the patients and their spouses. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus I-PD; ##$P < 0.01$, ###$P < 0.001$ Gd-PSP versus Gd-PDC. Statistical analysis: χ^2 test, replaced by Fisher's exact test when over 20% of the values were <5¶.

and induced falls in significantly more Gd-PSP (69%) than Gd-PDC (40%) patients ($P < 0.01$). The delay between disease onset and the first fall was significantly shorter in Gd-PSP (2.5 ± 0.5 years) and Gd-PDC (3.4 ± 0.6 years) than in Parkinson's disease patients (9.6 ± 1.6 years) ($P < 0.001$). Falls occurred during the first year of the disease in 27% of Gd-PSP and 12% of Gd-PDC patients.

Additional symptoms

Other neurological and psychiatric signs and symptoms are summarized in Table 3. By definition, oculomotor dysfunction was observed only in Gd-PSP patients. Supranuclear gaze palsy was partial in 41 (80%) and complete in 6 (12%) Gd-PSP patients. Four (8%) Gd-PSP patients only had slowing of vertical saccades. Ten (20%) Gd-PSP patients reported diplopia or blurred vision as well. None of the Gd-PDC patients had supranuclear gaze palsy or slowing of vertical saccades. Two of them (4%) had limited up gaze pursuit and saccades, but in a range compatible with normal aging.

Signs of bulbar dysfunction, such as dysarthria and dysphagia, were more frequent in Gd-PSP (41%) than Gd-PDC patients (14%) ($P < 0.01$). Dysphagia was severe enough to warrant insertion of a gastrostomy tube in seven Gd-PSP patients. Dystonic extension of the neck, a common clinical feature of PSP, was observed in only two Gd-PSP

patients. Dysautonomia occurred earlier in the course of the disease in Gd-PSP and Gd-PDC patients than in those with Parkinson's disease. Urinary incontinence was reported after 5 ± 1 years of evolution in Gd-PSP patients and 3.6 ± 0.4 years in Gd-PDC, compared with 11 ± 3 years in Parkinson's disease. Fifteen (41%) Gd-PSP patients developed orthostatic hypotension at 4 ± 0.8 years after disease onset, and 10 (24%) Gd-PDC patients at 3 ± 0.5 years compared with a delay of 13.3 ± 2.8 years in Parkinson's disease patients ($n = 8$, 16%). It was unrelated to dopaminergic treatments and required treatment with midodrine in eight cases (4 PSP, 2 PDC and 2 Parkinson's disease). One Gd-PSP patient had blue hands in a context of severe autonomic dysfunction. Erectile dysfunction was reported by about half of the male patients in all three groups. Six (12%) Gd-PSP and two (4%) Gd-PDC patients also had epilepsy. The first crisis occurred early in the disease course, during the first year in three cases, and evolved to partial motor status epilepticus in two Gd-PSP cases. One-fifth of Parkinson's disease and Gd-PSP patients and 28% of Gd-PDC patients had clinical REM sleep behaviour disorder, diagnosed on the basis of reports by the patients and their spouses (Schenck *et al.*, 1986).

Many Gd-PSP (59%) and Gd-PDC patients (52%) experienced hallucinations. They were predominantly well-formed visual hallucinations (vivid animals, faces, people who were deceased), less often auditory. Only one Gd-PDC patient reported olfactory hallucinations. Hallucinations were the initial symptom in two patients with Gd-PDC and one with Gd-PSP, and were observed in 20 patients (8 Gd-PSP, 12 Gd PDC) in the absence of dopaminergic medication or any other hallucinogenic medication. Other psychiatric symptoms (delusions, illusions, episodes of acute confusion) were rare in all three groups.

Dementia was observed in only five patients with Parkinson's disease (10%), but in 92% of Gd-PSP patients and in 100% of Gd-PDC patients. Three of the four non-demented Gd-PSP patients fulfilled the criteria of possible PSP according to NINDS-SPSP criteria. The appearance of cognitive symptoms usually followed parkinsonism in both the Gd-PSP and Gd-PDC patients, with a mean delay of 1.45 ± 0.2 (range 0.25–3) years in the Gd-PSP group and 1.52 ± 0.2 (0.25–3) years in the Gd-PDC group, compared with 17 ± 1.8 (13–23) years for idiopathic Parkinson disease (I-PD) patients. At the time of examination, the MMSE (maximal score = 30, mean score after exclusion of patients unable to perform all the subscore tests because they were unable to read and write or were too severely affected to be tested) showed similar degrees of cognitive dysfunction in Gd-PSP (18.7 ± 1.6; $n = 28$) and Gd-PDC patients (18.3 ± 1.4; $n = 29$); both groups were more severely affected ($P < 0.001$) than Parkinson's disease patients (26.5 ± 1; $n = 20$). The global FAB score (maximum 18 points, mean score after exclusion of patients too severely affected to be tested) was also significantly lower ($P < 0.001$) in Gd-PSP (8.9 ± 0.7; $n = 37$) and in Gd-PDC (8.2 ± 0.8; $n = 42$) patients, compared to those with Parkinson's disease (14.6 ± 1; $n = 20$).

Neuropsychological assessment

Because dementia was the most prevalent symptom that distinguished both Gd-PSP and Gd-PDC from Parkinson's disease, we studied in greater detail the neuropsychological deficits in 44 consecutive patients (25 Gd-PSP and 19 Gd-PDC) seen between January and September 2005, after exclusion of patients unable to perform the neuropsychological tests due to severe speech or cognitive problems. The subset of assessed Gd-PSP and Gd-PDC patients was representative of the entire group, in terms of age, disease duration and degree of cognitive impairment. The neuropsychological data concerning the Gd-PSP and Gd-PDC patients are shown in Table 4.

Visuoconstructive abilities were impaired in less than half of the patients in both groups. Frontal lobe dysfunction was systematically seen in both Gd-PSP and Gd-PDC patients, whereas temporoparietal signs, such as aphasia, gestural apraxia and agnosia, were rarely present. The most frequent frontal signs in both Gd-PSP and Gd-PDC were slowness of thought, perseveration, primitive reflexes (grasping/palmomental reflex) and apathy. Abnormal frontal behaviours (prehension/imitation, disinhibition) were significantly more frequent in Gd-PDC than in Gd-PSP patients ($P < 0.05$). Formal testing for frontal lobe executive dysfunction showed severe impairment. The global FAB score (maximum score 18, Gd-PSP: 9.7 ± 0.9; Gd-PDC: 9.6 ± 0.7) and the global Mattis DRS (maximum score 144; Gd-PSP: 95.3 ± 4.5; Gd-PDC: 106 ± 4.5) were below normal in both Gd-PSP and Gd-PDC patients. The Mattis subscores for attention, initiation, construction, conceptualization and memory showed homogeneous impairment. The FAB and Mattis scores showed clear evidence of a dysexecutive syndrome in virtually all Gd-PSP (87.5%) and Gd-PDC (100%) patients.

Neuroimaging

The MRI characteristics of 23 I-PD, 31 Gd-PSP and 30 Gd-PDC patients seen between January and September 2005, are shown in Table 5. The MRI scans were abnormal in all patients with atypical parkinsonism, except for one Gd-PDC patient, but were strictly normal in 50% of I-PD patients. Brains of both Gd-PSP and Gd-PDC patients showed widespread atrophy of both the cerebral cortex and the brainstem. When atrophy was observed in Parkinson's disease patients, it was minimal in comparison with patients with Gd-PSP or Gd-PDC. Cortical atrophy was most pronounced in the frontal and temporal lobes in Gd-PSP patients and in the frontal and parietal lobes in Gd-PDC patients. Supratentorial atrophy was symmetrical in 87% of Gd-PSP and 70% of Gd-PDC patients. Tectal atrophy was observed in about one-third of both Gd-PSP

Table 4 Neuropsychological features of Gd-PSP and Gd-PDC

Patient group		Gd-PSP ($n = 25$)	Gd-PDC ($n = 19$)
Age, years ± SEM		72.1 ± 1.5	72.7 ± 1.3
Sex ratio, M/F		20/5, 4	11/8, 1.4
Disease duration, years ± SEM		3.8 ± 1.0	4.3 ± 0.6
Education, years ± SEM		6.7 ± 0.7	6.0 ± 0.7
MMSE, maximum score 30 (range)		18.1 ± 0.9 (8–27)	20.0 ± 1.0 (11–28)
Impaired visuoconstructive abilities, *n* (%)		10 (43)	7 (35)
Temporoparietal signs, *n* (%)	Aphasia¶	1 (4)	1 (6)
	Gestual apraxia	5 (21)	2 (12)
	Agnosia¶	2 (9)	4 (23)
Frontal signs, *n* (%)	Slowness of thought	21 (88)	15 (79)
	Apathy	8 (33)	4 (24)
	Disinhibition¶	3 (12.5)	5 (26)
	Perseverations	14 (60)	11 (58)
	Pallilalia/echolalia¶	1 (4)	0 (0)
	Prehension/imitation	2 (9)	8 (42)*
	Grasping/palmomental reflex	10 (42)	11 (60)
FAB, maximum score 18 (range)		9.7 ± 0.9 (1–17)	9.6 ± 0.7 (4–15)
Mattis total score, maximum 144 (range)		95.3 ± 4.5 (55–136)	106 ± 4.5 (59–130)
Attention (maximum 37)		28.7 ± 1.2	31 ± 1.2
Initiation (maximum 37)		23.3 ± 1.3	26.3 ± 1.3
Construction (maximum 6)		3.3 ± 0.5	4.3 ± 0.5
Conceptualization (maximum 39)		25 ± 1.7	27.4 ± 1.6
Memory (maximum 25)		14.5 ± 1.1	17 ± 1.3

Data are mean ± SEM unless indicated otherwise. *$P < 0.05$ versus Gd-PSP. Statistical analysis: one-way ANOVA, followed by the Student–Newman–Keuls test for age, disease duration, education and mean MMSE, FAB and Mattis score; χ^2 test, replaced by Fisher's exact test when over 20% of the values were <5¶, for other variables.

Table 5 MRI characteristics of I-PD, Gd-PSP and Gd-PDC

Patient group		I-PD ($n = 23$)	Gd-PSP ($n = 31$)	Gd-PDC ($n = 30$)
Age, years ± SEM		64.5 ± 3.3	72 ± 1.5*	71 ± 1.4*
Atrophy, *n* (%)	Cortical atrophy	3 (13)	27 (87)***	21 (70)***
	Subcortical atrophy	3 (13)	25 (81)***	21 (70)***
	Mesencephalic atrophy	4 (17)	21 (68)***	13 (43)
	Stage 1 (flat upper profile)	4 (17)	11 (36)	9 (30)
	Stage 2 (concave upper profile)¶	0 (0)	10 (32)**	4 (13)
	Tectal atrophy	0 (0)	10 (32)**	8 (27)**
	Cerebellar atrophy	4 (17)	19 (61)**	14 (47)
	Corpus callosum atrophy	0 (0)	14 (45)***	13 (43)***
Enlarged ventricles, *n* (%)	Lateral ventricles	5 (22)	22 (71)***	21 (70)***
	Third ventricle	5 (22)	25 (85)***	23 (77)***
	Fourth ventricle¶	0 (0)	6 (19)***	3 (10)***
T2-T2* hyposignal, *n* (%)	Putamen	0 (0)	7 (23)*	6 (20)**
	Pallidum	2 (9)	16 (52)**	13 (43)*
	Substantia nigra	0 (0)	12 (39)**	16 (53)***
	Red nucleus	0 (0)	9 (29)**	7 (23)*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus I-PD. Statistical analysis: one-way ANOVA followed by the Student–Newman–Keuls test for age; χ^2 test, replaced by Fisher's exact test when over 20% of the values were <5, for other variables¶.

and Gd-PDC patients. In contrast, the frequency of mesencephalic or cerebellar atrophy was elevated only in Gd-PSP, but not in Gd-PDC patients. Severe mesencephalic atrophy was significantly more frequent in Gd-PSP (Fig. 1). It was observed in 10 patients, four of whom fulfilled the NINDS-SPSP criteria for possible and probable PSP, whereas six had additional symptoms, hallucinations or autonomic dysfunction. Mesencephalic atrophy in Gd-PSP was not correlated with disease duration. It was absent in two patients with 12 years of evolution and only moderate in one patient after 16 years of evolution, the longest disease duration in the Gd-PSP patients studied. The lateral and third ventricles were frequently enlarged in both Gd-PSP and Gd-PDC patients.

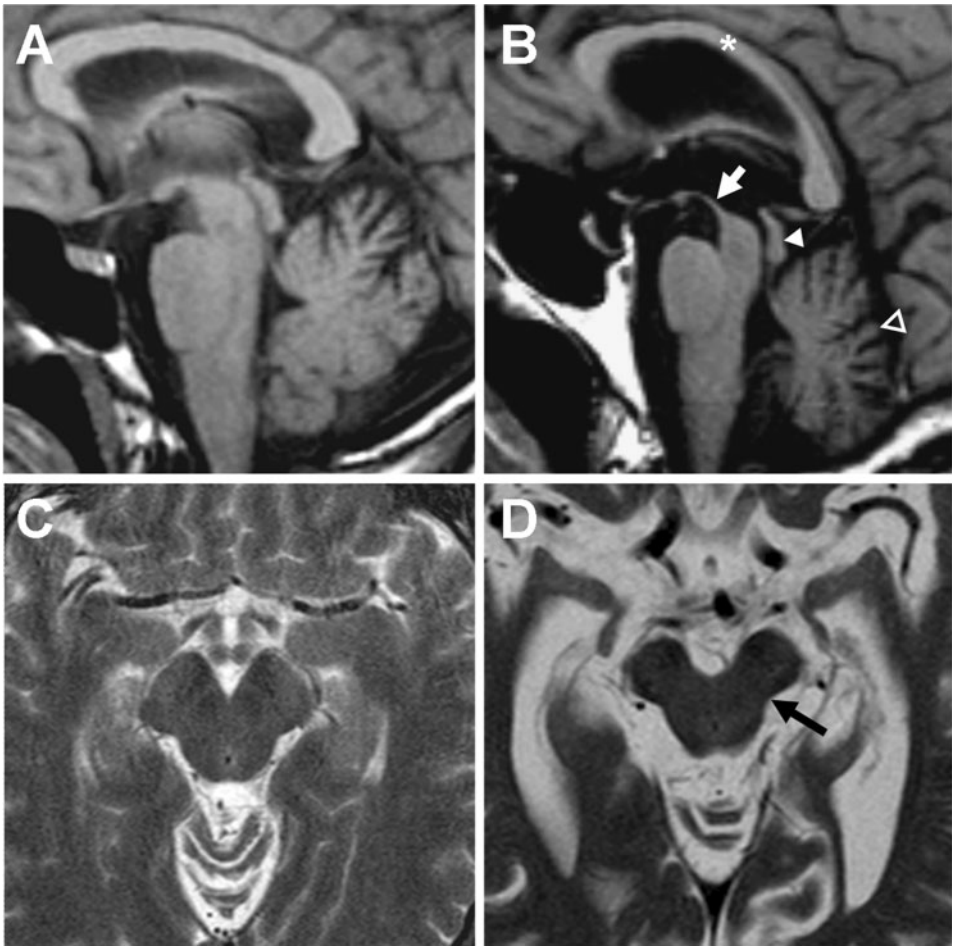

Fig. 1 Mesencephalic atrophy in Gd-PSP. Sagittal T_1-weighted sequence of a normal mesencephalon in a Parkinson's disease patient (**A**) compared with the severe mesencephalic atrophy (arrow) associated with atrophy of the tectum (white arrowhead), cerebellum (empty arrowhead) and corpus collosum (asterisk) in a Gd-PSP patient (**B**). Axial T_2 sequences showing a normal mesencephalon in a Parkinson's disease patient (**C**) and stage 2 atrophy (arrow) in a Gd-PSP patient (**D**).

Hyperintense signals in the T_2-weighted images were seen infrequently in all three patient groups, but in most cases resembled unspecific changes related to age. No characteristic pattern of hyperintense signals distinguished any of the three patient groups. However, a large centromesencephalic hypersignal observed in three Gd-PSP patients and three Gd-PDC patients might have disease-specific significance. None of these patients had mesencephalic atrophy and one had probable PSP according to NINDS-SPSP criteria. In contrast, hypointense signals were frequently present on the T_2- and T_2^*-weighted images in both Gd-PSP and Gd-PDC patients, but rarely in I-PD patients (Table 5). These abnormal signals were most often observed in basal ganglia nuclei, such as the globus pallidus, the putamen, the red nucleus, and particularly the substantia nigra (Fig. 2). Hypointense signals in the putamen, red nucleus and the substantia nigra were never observed in I-PD patients. Two patients with possible and one with probable PSP according to NINDS-SPSP criteria had both mesencephalic atrophy and T_2 and T_2^* hyposignals in the red nucleus and the substantia nigra. Hyposignals in the substantia nigra, observed less than 1 year after disease onset, were the only MRI abnormalities in two Gd-PDC patients.

Consumption of annonaceous products by patients with parkinsonism in Guadeloupe

The consumption of fruit and infusions of leaves of *A. muricata* was evaluated in patients with Parkinson's disease [$n = 26$, age $= 63.9 \pm 2.48$ (years $\pm$ SEM)], Gd-PSP ($n = 21$, age $= 72.3 \pm 0.99$) and Gd-PDC ($n = 23$, age $= 72.5 \pm 1.4$), compared with 88 control subjects matched by age to the patient groups ($n = 50$, age $= 63.1 \pm 0.8$ for comparison with Parkinson's disease patients; $n = 75$, age $= 72.9 \pm 0.99$ for Gd-PSP and Gd-PDC). The results are presented in Fig. 3.

In the control groups, 14% reported high consumption of fruits and 19% a high consumption of infusions ($n = 23$). The consumption of fruit was not correlated with age, but 78% of the high consumers of herbal teas were more than 70 years old. Their mean age (77.8 ± 2.4 years) was significantly higher than the mean age of the

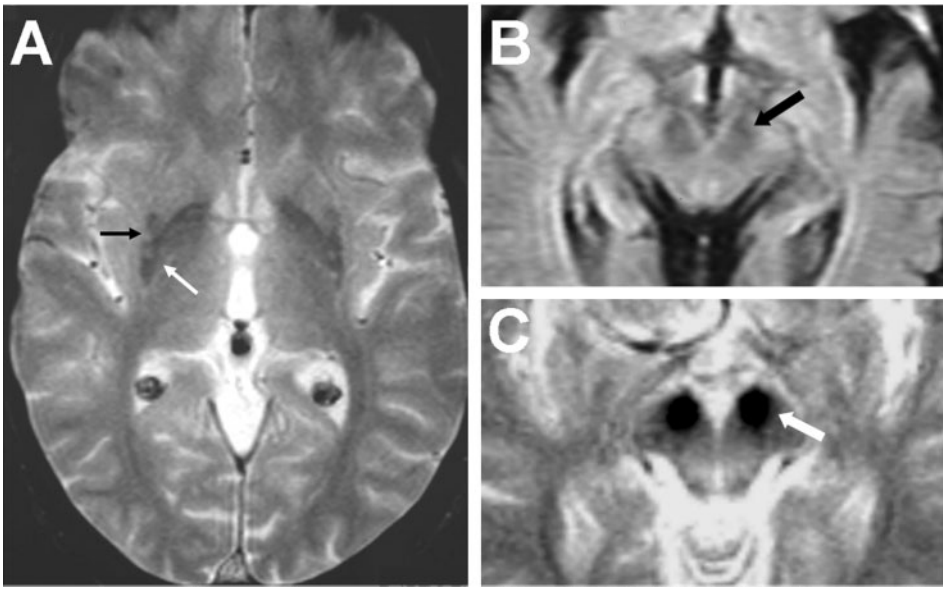

Fig. 2 Hypointense signals in basal ganglia nuclei in Guadeloupean atypical parkinsonism. T_2^* sequence showing a hyposignal in the globus pallidus (white arrow) and the inferolateral part of the putamen (black arrow) in a patient with Gd-PDC (**A**). Hypointense signal in the substantia nigra on axial T_2 FLAIR (black arrow) (**B**) and T_2^* (white arrow) (**C**) sequences associated with mesencephalic atrophy in patients with Gd-PSP.

total control population (70.4 ± 1, $P = 0.017$). In the Parkinson's disease group, five patients (20%) reported high consumption of annonaceous products (herbal teas in four, herbal teas and fruits in one), whereas 76% of Gd-PSP patients and 74% of Gd-PDC patients were high consumers. Parkinson's disease patients and their age-matched controls did not differ in their consumption of either fruit or infusions. Gd-PSP and Gd-PDC patients, however, consumed significantly more fruit ($P < 0.001$), but not more infusions, than their age-matched controls. However the percentage of high consumers of herbal teas was significantly higher in Gd-PSP ($P < 0.001$) or Gd-PDC patients ($P = 0.005$) than in controls. The Gd-PSP and Gd-PDC groups did not differ significantly. When converted to milligrams of annonacin, the estimated amount ingested during the patient's life were 148 ± 40 g for Gd-PSP patients, 156 ± 48 g for Gd-PDC, 22 ± 5 g for Parkinson's disease and 33 ± 6 g for controls, which corresponds to cumulative dose for an average adult (70 kg) of 2 ± 0.6 g/kg for Gd-PSP patients, 2.2 ± 0.7 g/kg for Gd-PDC, 0.3 ± 0.1 g/kg for Parkinson's disease and 0.5 ± 0.1 g/kg for controls. The estimated amounts of annonacin ingested were significantly higher in Gd-PSP and Gd-PDC subgroups than in controls and Parkinson's disease patients ($P < 0.001$) and about 20-fold above the dose of 106 mg/kg that induced widespread neurodegeneration in the basal ganglia and mesencephalon of rats when infused intravenously over a period of 28 days. However, in the absence of any knowledge of the bioavailability of annonacin after oral or intravenous administration, this comparison is only indicative (Champy *et al.*, 2004, 2005).

Discussion

In this study, three parkinsonian phenotypes, with equal frequencies, were distinguished: Parkinson's disease, a PSP-like syndrome designated Gd-PSP and a parkinsonism–dementia syndrome designated Gd-PDC. The two groups were initially constituted on the basis of the presence of PSP-like oculomotor signs in the Gd-PSP group and dementia in the Gd-PDC group. However, our detailed analysis showed that, aside from the oculomotor signs, there were few statistically significant clinical differences between these two groups. Gd-PSP and Gd-PCD patients had the classic parkinsonian symptoms, rigidity, akinesia and tremor, but these symptoms were not responsive to levodopa and they only rarely developed dopa-induced dyskinesias. They also had early postural instability and falls and autonomic dysfunction, and almost all were demented. Furthermore, aside from the oculomotor signs, the Gd-PSP patients differed markedly from patients with classical PSP. The major sign that differentiated Gd-PSP from classical PSP was the presence of hallucinations, mainly visual and unrelated to medication, in 59% of patients in the present study and in all three previously reported PSP-like patients that had been examined neuropathologically (Caparros-Lefebvre *et al.*, 2002). Gd-PSP patients frequently had autonomic dysfunction, including orthostatic hypotension (41%) and urinary incontinence (53%). According to the NINDS-SPSP diagnostic criteria, unexplained autonomic dysfunction is a mandatory criterion for exclusion. However, in individual reports of patients with pathologically proven PSP, orthostatic hypotension (45%) and urinary incontinence (75%) were as frequent as in our patients (Wenning *et al.*, 1999). The Gd-PSP patients also

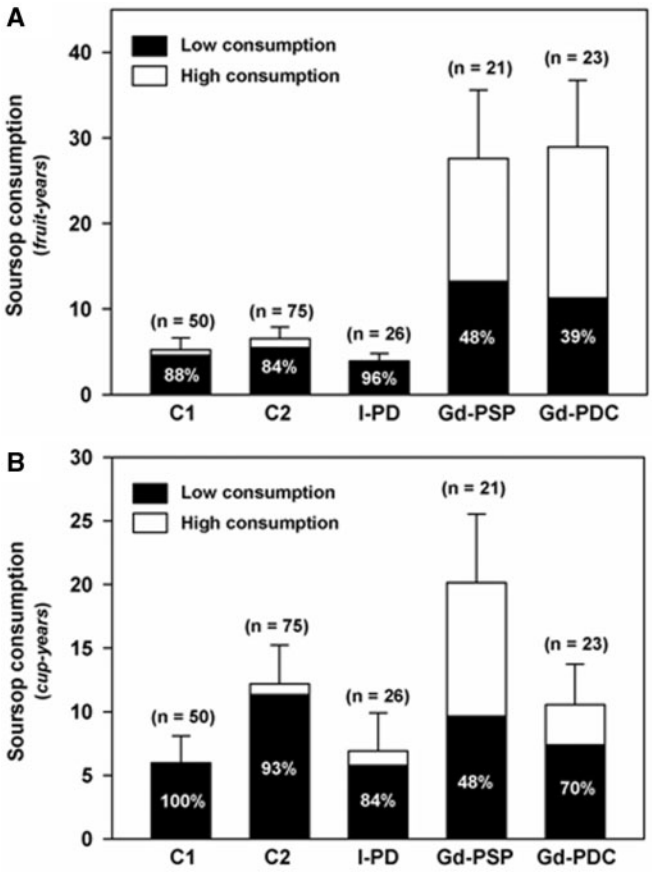

Fig. 3 Consumption of *A. muricata* (soursop) by patients with parkinsonism in Guadeloupe. Evaluation of fruit (**A**) and herbal tea (**B**) consumption by Parkinson's disease, Gd-PSP and Gd-PDC patients compared with age-matched controls of 63.1 ± 0.8 years for Parkinson's disease (**C1**) and 72.9 ± 0.99 years for atypical forms of parkinsonism (**C2**). The bars as a whole represent cumulative consumption expressed in fruit-years or cup-years; i.e. the number of fruit or cups of infusion consumed per day multiplied by the number of years of consumption (see Material and Methods). The filled and open portions of the bars represent the percentage of low and heavy consumers, respectively. Note that heavy consumers were defined as having more than 10 fruit-years or cup-years, in each group. As a point of reference, it should be noted that the pulp of an average fruit has been shown to contain on average 15 mg of annonacin and one cup of leaf infusion 0.14 ± 0.05 mg (Champy *et al.*, 2005).

differed from PSP patients, by a higher frequency of tremor [56% versus 17–37% (Litvan *et al.*, 1996*b*)] and particularly by the presence of a low-frequency and high-amplitude rest tremor in 20% of them, a relatively mild postural instability and the late occurrence of falls (a mean 2.5 years after disease onset). Postural instability and falls were rarely initial symptoms in our patients (7%) compared with 63% in classical forms of PSP (Litvan *et al.*, 1996*b*). A larger proportion of Gd-PSP patients (92%) were demented, compared with 52–74% in PSP patients (Menza *et al.*, 1995; Williams *et al.*, 2005).

A common pattern of cognitive dysfunction was found in both Gd-PSP and Gd-PDC patients. Both Gd-PSP and Gd-PDC patients performed poorly on tests of executive functions involved in behavioural planning and adaptation (Pillon *et al.*, 1995). This is typical of fronto-subcortical dementia, which was diagnosed in virtually all of the Gd-PSP and Gd-PDC patients (Pillon *et al.*, 1991). The degree of global impairment, as measured by the MMSE, was similar in both groups. The performance of Gd-PSP patients (MMSE score 19) was worse than that of a previously studied series of PSP patients (MMSE score 27) with comparable disease durations (3.8 years in our group versus 4.4 years in PSP patients) (Pillon *et al.*, 1995). The Gd-PSP patients had a lower educational level (6.2 years) than PSP patients (9.1 years), which might partially explain this difference, but a difference in the distribution or in the nature of the neuropathological lesions might also be responsible. Interestingly, the majority of non-demented Gd-PSP patients (3 on 4) fulfilled the NINDS-SPSP criteria, suggesting that the presence of additional neurological signs, hallucinations and autonomic dysfunction contributes to the severity of cognitive impairment. The pattern of dementia was similar in both Gd-PSP and Gd-PDC patients, although frontal type behaviours were more frequent in the Gd-PSP group.

Other parkinsonism–dementia syndromes have also been described, notably Parkinson's disease with dementia, Alzheimer's disease with parkinsonism, dementia with Lewy bodies and frontotemporal dementia with parkinsonism (FTDP) (McKeith *et al.*, 1996, 2005; Neary *et al.*, 1998 McKhann *et al.*, 2001). The Gd-PSP and Gd-PDC patients, however, do not seem to correspond to any of these clinical entities. Parkinson's disease with dementia can be excluded because, although deficits in memory, visuospatial and executive functions have been described in the early stages of Parkinson's disease, frank dementia is only observed after a mean disease duration of 10 ± 4 years (Biggins *et al.*, 1992; Emre, 2003; Aarsland *et al.*, 2005), whereas we excluded patients in whom dementia occurred more than 3 years after the beginning of parkinsonism. Alzheimer-type temporoparietal dementia can also be excluded, since the Guadeloupean patients showed little evidence of temporoparietal dysfunction, such as aphasia, gestural apraxia or agnosia, arguing against an Alzkeimer's-like type of dementia. The presence of hallucinations in a majority of Gd-PDC patients, as well as in Gd-PSP patients, is evocative of dementia with Lewy bodies (DLB) (McKeith *et al.*, 1996, 2004). However, the Guadeloupean patients, unlike those with DLB (McKeith *et al.*, 2005), did not have the fluctuations in cognition, attention and alertness that are characteristic of DLB [38]. Delusions were reported in 57% of patients with neuropathologically proven DLB, but were present in only 8% of our Gd-PDC patients and no Gd-PSP patients (Aarsland *et al.*, 2001). However, to confirm that Gd-PDC is not DLB, post-mortem neuropathological examinations will be needed. The clinical course of dementia in the Guadeloupean atypical parkinsonians differed from FTDP in that a majority of patients

(61% of Gd-PSP and 67% of Gd-PDC) had the typical parkinsonian triad, rigidity akinesia or tremor, as initial symptoms. When cognitive symptoms occurred first, it was mainly memory loss, not changes in personality and behaviour as observed in FTDP (McKhann *et al.*, 2001; Neary *et al.*, 2005).

The neuroradiological profiles of the Gd-PSP and Gd-PDC patients also largely overlapped. Widespread supratentorial atrophy and enlargement of the ventricles, particularly the third, were observed in both groups. Upper mesencephalic atrophy was severe in a large percentage of Gd-PSP patients, as in classical PSP (Savoiardo *et al.*, 1989; Stern *et al.*, 1989), but was found in only a small number of patients with Gd-PDC. The hyposignals on T_2 sequences observed in the substantia nigra, red nucleus, putamen and pallidum of half of the Gd-PSP and Gd-PDC patients are similar to what has been frequently described in the putamen of multiple system atrophy patients, more rarely in PSP and exceptionally (9%) in Parkinson's disease patients (Kraft *et al.*, 1999), but this is the first observation of such signals in the mesencephalon. The hypointensities in the substantia nigra and red nucleus, observed in about half of Gd-PSP and Gd-PDC patients, sometimes in the early stages of the disease, can be helpful for the diagnosis. Decreased signals in brain nuclei on T_2 and T_2^* sequences have been reported in other diseases, such as the advanced stages of multiple sclerosis, in relation to the presence of iron deposits (Drayer *et al.*, 1987). In conclusion, except for the greater severity of mesencephalic atrophy in Gd-PSP patients, the MRI patterns of Gd-PSP and Gd-PDC are alike. Signal abnormalities in the substantia nigra and red nucleus may, therefore, be considered as a specific sign of atypical parkinsonism–dementia syndromes in Guadeloupe.

The clinical, neuropsychological and neuroradiological analysis of Gd-PSP and Gd-PDC patients suggests that these two groups cannot be confounded with Parkinson's disease and, except for the oculomotor signs, cannot be distinguished from each other. This is confirmed by correlation with the consumption of annonaceous products, which is as low in Parkinson's disease patients as in controls, but equally high in the Gd-PSP and Gd-PDC groups, although there was a tendency for Gd-PDC patients to have consumed more than the Gd-PSP patients. It should be noted, however, that about 50% of the atypical patients were not heavy consumers of annonaceaous products, suggesting that other factors, environmental or genetic, might affect the vulnerability of patients to the neurotoxins in Annonaceae. In addition, a certain number of control patients ($n = 22$) fell into the category of high consumers, and might constitute a group at risk for the development of atypical parkinsonism. This study has reinforced the hypothesis that atypical parkinsonism in Guadeloupe may be related to an alimentary toxin, but prospective longitudinal studies are needed to clarify this point, which is very important not only for scientific reasons, but also for public health. Our detailed clinical, neuropsychological and neuroradiological analysis of this form of parkinsonism provides criteria for the diagnosis of this disease in other populations potentially at risk.

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