

## Letters to the Editors

### Atypical Parkinsonism and Annonaceae Consumption in New Caledonia

Recent studies have suggested a high incidence of atypical parkinsonism in patients living in or coming from different “exotic” areas.<sup>1–3</sup> In some cases, environmental factors have been suspected, including the consumption of tropical fruits of the Annonaceae family containing alkaloids with possible neurological toxicity.<sup>1,4,5</sup> Three Annonaceae fruits (*Annona muricata*, *A. squamosa*, and *A. reticulata*) are consumed traditionally in a French South Pacific island, New Caledonia. The aim of the present survey was to assess the proportion of typical versus atypical parkinsonism and Annonaceae consumption in this island.

We undertook a 1-year study that included all patients with parkinsonism seen consecutively at the neurology department of the Noumea General Hospital. Secondary parkinsonism, such as drug-induced and vascular parkinsonism, was excluded by careful history taking, neurological examination, and brain computed tomography (CT) scan. Each patient was examined by a neurologist and classified according to international diagnostic criteria for idiopathic Parkinson’s disease (PD),<sup>6</sup> progressive supranuclear palsy (PSP),<sup>7</sup> Lewy body dementia (LBD),<sup>8</sup> multiple system atrophy (MSA),<sup>9</sup> and corticobasal ganglionic degeneration (CBD)<sup>10</sup> or frontotemporal lobar degeneration.<sup>11</sup> Patients who did not fulfill operational criteria for such disorders were considered as undetermined parkinsonism (UP), according to previous reports.<sup>3</sup> Annonaceae consumption was assessed according to the following questionnaire: My consumption of sugar apple is (a) very regular (more than once a day); (b) regular (once a day); (c) quite regular (once or more a week); (d) occasional (less than once a week); and (e) rare or absent. For statistical analysis, regular (a + b + c) versus nonregular (d + e) consumers were compared.

All of 33 parkinsonian patients who attended the department were included (23 men, 10 women). Ethnic distribution was: 14 Caucasian, 9 Melanesian, 4 Wallisian (from Wallis and Futuna islands) and 6 Other. Of 33 patients, 18 were diagnosed as typical PD (54%), whereas 15 (46%) had clinical signs suggestive of atypical parkinsonism (2 probable MSA, 2 probable PSP, 1 LBD, and 10 UP). The typical/atypical parkinsonism ratio was comparable in the three main ethnic groups: Melanesian (4/9), Caucasian (7/14) and Wallisian (2/4). Eighteen subjects were regular Annonaceae consumers: 39% of the patients with typical PD (7/18) as compared with 73% of those with atypical parkinsonism (11/15,  $P = 0.048$ ,  $\chi^2$  test). All consumers had such a dietary habit for many years.

Diagnosis in this study was based solely on clinical grounds, and misdiagnosis cannot be excluded in the absence of pathological confirmation. Moreover, the studied population is small and selection bias may have occurred. Nevertheless, it is interesting to note that, like in the French Western Indies,<sup>1,3</sup> we observed an unusually high percentage of atypical cases among New Caledonian patients with parkinsonism. Some patients fulfilled diagnostic criteria for PSP, MSA, or LBD, but most (10/15) could only be classified as UP. Such patients had a clinical syndrome combining a relatively symmetrical akinetic-rigid syndrome unresponsive to levodopa with early dementia with prominent frontal lobe signs and postural instability. This is reminiscent of what has also been reported previously in Guadeloupean parkinsonism.<sup>3</sup> Pseudobulbar and motoneuron signs, however, were rare or absent in patients from south Caledonia (1 and 0/10 UP patients, respectively). The small size of this population does not allow definite conclusions on causal factors such as genetic susceptibility or environmental factors. Nevertheless, as in Guadeloupe, heavy Annonaceae consumers were more frequent among patients with atypical parkinsonism. This is compatible with a putative toxicity of such fruits, as suggested by experimental data with the alkaloid totum from *Annona muricata*.<sup>12</sup>

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### Atypical Parkinsonism in New Caledonia: Comparison With Guadeloupe and Association With Annonaceae Consumption

The clinical analysis of parkinsonism on New Caledonia Island, a French territory, is of great scientific interest. Dr. G. Angibaud, who worked on this island for several years (1994–1999) studying patients with local colleagues, invited Dr. O. Rascol, an expert in the field of parkinsonism, to review 33 patients referred to the Noumea General Hospital, the major medical centre of the island. They used operational criteria to classify patients as having Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and dementia with Lewy bodies (LBD). As proposed on Guadeloupe,<sup>1</sup> they defined an alternate subgroup of patients who did not fulfill the criteria of well-known atypical parkinsonian syndromes. This subgroup of patients might be reminiscent of Guamanian Parkinson–Dementia Complex (PDC), an unclassifiable parkinsonism sharing several similarities with unclassifiable Guadeloupean parkinsonism.<sup>2</sup> Interestingly, New Caledonia is close (~1,000 miles) to the Pacific islands where PDC has been described (Guam and Rota). The population of

New Caledonia (Melanesian “black” people with different origins from Africans) is clearly different from that of Guam (Asians, with complex admixed origins). The development of a similar disease in such different populations suggests that a genetic origin of this disease is improbable. All these locations are tropical, and botanical studies have demonstrated that these islands share several plants, such as Annonaceae, particularly *Annona muricata* and *A. squamosa*.<sup>4</sup>

These plants contain two different types of neurotoxins: benzyl-tetra-isoquinolines, probably acting as antidopaminergic agents, and acetogenins, a new class of polyketide whose primary mode of action is the inhibition of NADH-ubiquinone oxidoreductase.<sup>3</sup> Administration of Annonaceae acetogenins in vivo may induce significant neuronal death. To date, the possible synergistic effect of benzyl-tetra-hydro-isoquinolines and acetogenins has not been evaluated.

This is the first model of an environmental neurotoxin possibly producing atypical parkinsonism in several foci, demonstrated by epidemiological and experimental studies in vitro and in vivo. On Guam, however, the relationship between PDC and *Annona* consumption has not been tested up to now and another hypothesis has emerged, suggesting flying foxes on Guam biomagnify cycad toxins when they feed on the seeds and could then be toxic to humans when consumed.<sup>5</sup>

Atypical parkinsonism seems to be concentrated in some tropical areas, and the description of these foci has become possible when neurologists trained in parkinsonism and movement disorders moved from France to the French West Indies and New Caledonia in the 1980s and 1990s. On these islands, the health care system has developed during the last 30 years and is now more or less similar to that of Europe. We cannot exclude that atypical parkinsonism might be highly prevalent in other tropical areas, because most African and Asian countries probably do not have a way to assess precisely the respective representation of each subgroup of parkinsonism. Moreover, life expectancy is approximately 60 years in most of these countries, thus, the major part of the population may die before developing signs of neurodegenerative diseases.

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## Re: UPDRS: Status and Recommendations

In the July, 2003 issue of *Movement Disorders*,<sup>1</sup> the *Movement Disorder Society Task Force for Rating Scales for Parkinson's Disease* prepared a critique of the Unified Parkinson's Disease Rating Scale (UPDRS). They cited weaknesses such as "several ambiguities in the written text, inadequate instructions for raters, some metric flaws, and the absence of screening questions on several important nonmotor aspects of Parkinson's disease."<sup>1</sup>

These observations are of interest and emphasise the importance of standardisation in rating scale applications. Based on the published criteria of the UPDRS, the *Movement Disorder Society* has initiated a re-writing of the scale and this process is currently in progress. A number of testing protocols will be developed to establish clinometric properties of the new scale and its relationship to the currently available UPDRS 3.0. The observations on state dependence for historical sections of the scale will need to be incorporated into such testing.

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## Do On-Off Variations Cause Discrepancies in the Historical Items of the UPDRS?

In the recent critique of the Unified Parkinson's Disease Rating Scale (UPDRS),<sup>1</sup> it was commented that time of administration of the scale could be shortened by self-administration of the Mentation and Activities of Daily Living (ADL) sections by patients in the waiting room. We have collected recently data highlighting the importance of documenting whether these scores are collected when the patient is in the *on* or *off* state, as this can significantly alter the score achieved.

We have conducted a study of the use of cannabis oil extract (Cannador) for the treatment of levodopa (L-dopa)-induced

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**TABLE 1.** Difference in UPDRS Part IV scores when assessed in on and off states

	On score	Off score	P
Dyskinesia score (q 32–34)	2.72 ± 1.2	3.61 ± 1.2	0.011
Complications (Part IV)	6.71 ± 1.5	8.00 ± 1.5	0.013

Scores are means ± standard error.

dyskinesia in Parkinson's disease (C.B.C. and P.G.B., personal communication). A dyskinesia score was derived from the UPDRS questions 32 to 34. Within the trial protocol, baseline Parts II, III, and IV of the UPDRS were carried out with the patient in both the *on* and *off* state, before and after an L-dopa challenge. Data were collected by three raters from 19 patients. Analysis showed that obtaining a Part IV score when the patient was *off* resulted in a significantly higher score than when the patient was *on*, despite the score being derived from purely historical information (Table 1, significance assessed by paired *t* test). We assume that this difference results from alteration in patient perception.

These findings suggest that note should be made as to whether the historical aspects of the UPDRS are completed when the patient is *on* or *off*. Although not assessed in our study, it would seem inappropriate that patients be asked to provide *off* scores for mentation (Part I) and ADL (Part III) when in the *on* state and vice versa. Our findings also suggest that alteration in perception can artificially increase the difference between *on* and *off* scores. A low test–retest reliability of the mentation section of the UPDRS has been found previously in patients not treated with dopaminergic medications.<sup>2</sup> The impact of *on-off* fluctuations on this subsection of the UPDRS is likely to reduce reliability further. Finally, these considerations will further complicate the derivation of a Minimal Clinically Relevant Difference (MCRD) in the UPDRS discussed in the Task Force critique.<sup>1</sup>

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