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Doon-off variations cause discrepancies in the historical items of the UPDRS?

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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.1-3 In some cases, environmental factors have been suspected, including the consumption of tropical fruits of the Annonaceae family containing alkaloids with possible neurotoxicity.1,4,5 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 from the present survey.3 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 from Annona muricata.6,12

References


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,1 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.2 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.4

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.3 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.3 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,1 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.”1

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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References

On behalf of the Movement Disorder Society Task Force for Rating Scales for Parkinson’s Disease.

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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),1 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 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.2 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.1

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

<table>
<thead>
<tr>
<th></th>
<th>On score</th>
<th>Off score</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia score</td>
<td>2.72 ± 1.2</td>
<td>3.61 ± 1.2</td>
<td>0.011</td>
</tr>
<tr>
<td>(q 32–34)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Complications (Part IV)</td>
<td>6.71 ± 1.5</td>
<td>8.00 ± 1.5</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Scores are means ± standard error.