Risperidone-induced tardive dystonia and psychosis

L Vercueil, J Foucher

We read with great interest the recent paper from Brown and Marsden introducing new perspectives on basal ganglia functioning.[1] One of the outstanding fields in research opened up is the possible opposite linkage between psychosis and movement disorders through γ synchronisation dysfunction dependent on basal ganglia influence. We would like to report a clinical observation that could be regarded as a strong illustration of their hypothesis.

A 49-year-old-man, without family history of psychosis or neurological disorder, developed at the age of 25 years a recurrent brief psychotic disorder, according to the Diagnostic and Statistical Manual (DSM). After his last episode, which was followed by complete remission of the psychiatric manifestations under antipsychotic drugs, risperidone was introduced as monotherapy in June, 1997, because of extrapyramidal symptoms. Unfortunately, 3 months after introduction, tardive dystonia did appear consisting of rapid tonic movements involving mouth and neck muscles. Those movements were continuous but disappeared during sleep and while chewing gum. These symptoms persisted despite discontinuation of the drug and introduction of various therapeutic measures including anticholinergics, tetrabenazine, clozapine, NMDA blockers, and botulinum toxin.

After a 1-year course of tardive dystonia, the condition rapidly disappeared 2–3 days preceding a psychiatric relapse consisting of cosmic delusions and auditory hallucinations. 15 days after olanzapine introduction, psychiatric symptoms disappeared while the dystonic manifestations reoccurred. The patient recovered his previous mental status which allowed professional activity as a drum teacher. Brain imaging and plasma metabolic investigations remained normal.

This case is, so far as we know, the first report of risperidone-induced tardive dystonia. In a recent study,[2] focal tardive dystonia was considered as the prominent presentation with craniocervical involvement occuring in 87% of cases. Moreover, to our knowledge it is the first time that such an alternation between tardive dystonia and psychosis has been described.

For the following discussion, it should be underscored that tardive dystonia remained quite different from tardive dyskinesia (clinical manifestations, pharmacological response). Dystonia can be regarded as the manifestation of acute dopamine depletion (MPTP monkey,[3] drug induced acute dystonia, early morning dystonia in Parkinson's disease). Clinical history in our patient seemed to show a balance between tardive dystonia and psychotic states. A way to model this could be deduced from the hypothesis by Brown and Marsden, who pointed out that dystonia could be regarded as a deficit in γ synchronisation whereas psychotic manifestations would be ascribed to a hypersynchronisation due to non-linearity of the dopaminergic modulation.

However, other researchers have demonstrated an abnormal frontotemporal interaction in psychotic symptoms, leading to the possibility of a lack of synchrony,[4] which can be understood as a failure of large-scale synchronisation in the γ band (sometimes referred as the conscience rhythm) while local synchronisation is enhanced. This could fit well with the bi-modal effect of dopaminergic drugs favouring γ synchronisation: enhancing concentration at low doses (methylphenidate) while inducing psychosis in high dosage (cocaine) because of an excessive local synchrony as opposed to the large scale one.

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2 Kiriakakis V, Bhatia KP, Quinn NP, Marsden CD. The natural history of tardive dystonia: a long-term follow-up study of 107 cases. *Brain* 1998; **121:** 2053–66.
3 Perlmutter JS, Tempel LW, Black KJ, Parkinson D, Todd RD. MPTP induces dystonia and parkinsonism: clues to the pathophysiology of dystonia. *Neurology* 1997; **49:** 1432–38.
4 Frith CD, Friston KJ, Herold S, et al. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br J Psychiatry* 1995; **167:** 343–49.

Clinique neurologique, Hopitaux universitaires de Strasbourg, 1 pl de l'hôpital, 67000 Strasbourg, France
(J Foucher e-mail: jfouc@calva.net)

Blood vessels change in the mesencephalon of patients with Parkinson's disease

Baptiste A Faucheux, Anne-Marie Bonnet, Yves Agid, Etienne C Hirsch

The proportion of dopaminergic neurons that degenerates in Parkinson's disease varies between sub-populations of dopaminergic neurons in the mesencephalon.[1] Neurotrophic and neurotoxic factors could be involved in neurodegeneration, and local factors such as changes in the vascular system and blood supply might be associated with the differential vulnerability of nigral dopaminergic neurons.

We have compared the numbers of nuclei of blood vessel endothelial cells, melanised neurons, non-melanised neurons, and glial cells[2] in mesencephalon sections from six patients with Parkinson's disease (mean age 74 years [SE 5, range 62–94], mean necropsy delay 21 [4] hours) and ten control patients (mean age 84 [3, range 65–94] years, mean necropsy delay 20 [2] hours). Frozen tissue sections (20 μm) mounted on gelatin-coated glass slides were fixed for 7 weeks in 4% paraformaldehyde and processed for Nissl's staining. Endothelial cell nuclei were identified by both their shapes and location in blood vessels. Quantifications were done in 20 circular fields (125 μm in diameter; randomly distributed throughout the analysed regions and recorded by a computerised plotting system [Histo200 program, Biocom, France]) within four midbrain subregions containing dopaminergic neurons and identified from acetylcholinesterase histochemistry:[1] SNpc, medioventral part of ventral tegmental area (VTA-Mv, A10 cell group), retrorubral area containing A8 cell group (A8), and central grey substance (CGS).[1]

42752 cell nuclei were counted. Mean numbers of nuclei located in the four midbrain subregions were very close in patients with Parkinson's disease and controls (SNpc: 433 [SE 27] *vs* 427 [38] nuclei per 0·25 mm^2; VTA-Mv: 443 [21] *vs* 427 [36]; A8: 523 [28] *vs* 557 [47]; CGS: 518 [23] *vs* 531 [47]). Mean numbers of identified non-melanised neurons were nearly identical in the two groups, whereas those of melanised neurons were decreased in the VTA (–19%) and SNpc (–68%) of patients with Parkinson's disease (table) together with a slight increase for glial cells. Mean numbers of nuclei of blood vessel endothelial cells were very similar in the four subregions for control subjects, both for their mean values and variabilities. In patients with Parkinson's disease, they were multiplied by a