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Short communication

Parkinsonian axial signs in schizophrenia

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List of abbreviations:
APs
antipsychotic drugs
DDD
defined daily dose
DIP
Drug-induced parkinsonism
DRBA
dopamine receptor blocking agents
123I-FP-CIT SPECT
single photon emission computed tomography of dopamine transporter
PD
Parkinson's disease
PDD
prescribed daily dose
Schiz- Axial
schizophrenia with axial parkinsonian signs
Schiz-NO-Axial
schizophrenia without axial parkinsonian signs
UPDRS
Unified Parkinson's Disease Rating Scale

ABSTRACT

Introduction: We have recently demonstrated evidence of nigro-striatal denervation, disease progression and response to levodopa in a subgroup of patients with schizophrenia who developed parkinsonism.
Objective: In the present study, we investigated whether axial parkinsonian signs might be an early manifestation of parkinsonism in schizophrenia not necessarily related to chronic administration of antipsychotic drugs (AP) drugs.
Methods: From a baseline cohort of 299 schizophrenic patients who did not satisfy the diagnostic criteria for parkinsonism (presence of at least two of the following appendicular signs: bradykinesia, tremor, rigidity), we identified a group of patients who manifested two out of three axial parkinsonian signs (abnormality of trunk posture, hypomimia and short-step gait). Accordingly, we obtained two sub-groups of patients with schizophrenia, with (*Schiz-Axial*, N = 26), and without parkinsonian axial signs (*Schiz-NO-Axial*, N = 273). Clinical and demographical variables were compared between groups. The motor section of the Unified Parkinson's disease rating scale (UPDRS) was employed to measure motor disability.
Results: *Schiz-Axial* patients were significantly older ($p = 0.007$) and had longer disease duration ($p = 0.04$) compared to *Schiz-NO-Axial*. The two groups did not differ for variables related to AP treatment. Total UPDRS motor score ($p < 0.0001$) as well as limb ($p < 0.0001$) and axial ($p < 0.0001$) UPDRS sub-scores were increased in *Schiz-Axial* patients compared to *Schiz-NO-Axial*.
Conclusions: Our findings provide evidence that axial parkinsonian signs might be an early manifestation of parkinsonism in schizophrenia associated to older age and longer disease duration.

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1. Introduction

Patients with schizophrenia may develop parkinsonism, likely as result of chronic administration of antipsychotic (AP) drugs. Nevertheless, we have recently suggested that parkinsonism associated to schizophrenia recognizes a multifactorial pathogenesis, not being entirely due to post-synaptic D2-receptors blockade by dopamine receptor blocking agents (DRBA) [1,2]. Indeed, a subgroup of patients with schizophrenia, exhibit abnormalities of single photon emission computed tomography of dopamine transporter (^{123}I-FP-CIT SPECT) [2], progression of motor disability over 2-years follow-up and response to levodopa [1]; these findings are in line with the hypothesis that neurodegenerative changes in the nigro-striatal pathway may occur in schizophrenia and may be partly responsible of parkinsonian signs [3]. Using unpublished data from our previous cross-sectional study that investigated parkinsonism in patients with schizophrenia, we identified subjects who did not satisfy the criteria for parkinsonism diagnosis, but who manifested two out of three parkinsonian axial signs among gait impairment, hypomimia, trunk postural abnormalities. In this cohort of patients, we investigated whether axial parkinsonian signs might represent an early manifestation of parkinsonism in schizophrenia not necessarily related to chronic administration of AP drugs.

2. Methods

An extensive description of the enrollment methodology is described elsewhere [2]. Briefly, outpatients fulfilling DSM-IV criteria for schizophrenia were consecutively enrolled by trained psychiatrists in eight recruiting centers. Patients were only included in the study if they gave written, informed consent to participate. All study sites gained full approval for the study from the local research Ethics Committee. Patients were informed by the treating psychiatrist about the nature of the study and underwent clinical neurological assessment performed by a neurologist trained in movement disorders. Patients treated with anticholinergic drugs (orphenadrine, biperidene) were examined by the neurologist after a wash-out period lasting at least 3 days, after which the treatment could be restored.

We selected patients receiving pharmacological treatment with one or more AP drugs for at least 6 months and older than 40 years old. From a baseline cohort of 448 patients with schizophrenia, we diagnosed parkinsonism in 149 patients according to presence of two out of three cardinal parkinsonian signs (rest tremor, rigidity, bradykinesia) [2,4]. Among the remaining 299 patients who did not satisfy the criteria for parkinsonism diagnosis, we identified a group of patients who manifested two out of three axial parkinsonian signs (abnormality of trunk posture, hypomimia and short-step gait). Accordingly, we obtained two sub-groups of patients with schizophrenia, with and without parkinsonian axial signs (*Schiz-Axial*, *Schiz-NO-Axial*) which were the focus of this post-hoc analysis.

Socio-demographic and clinical data including age, sex, onset of schizophrenic symptoms, medical and family history of psychiatric or neurological diseases, and a detailed history of pharmacological treatment - including type, dosage and duration of current antipsychotic treatment and other psychotropic drugs (benzodiazepines, antiepileptic drugs, tricyclic antidepressants) - were obtained. Motor disability was evaluated by means of the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part III), which represents the most widely used instrument for measuring severity of parkinsonian symptoms and have excellent inter-rater and test-retest reliability. A difference $\geq$4 points in items 20–26 of the UPDRS III between the more and less affected sides was considered indicative of clinical asymmetry. The axial-UPDRS and limb-UPDRS motor scores were respectively calculated as sum of items 19, 27–29 and items 20–26 of motor UPDRS. Patients were included after giving written, informed consent to participate. Approval for the study was obtained at all local Ethics Committee of the participating centers.

Categorical data were analysed by chi-square statistics. Mann-Whitney two-sample statistics were used to analyse continuous data which were not normally distributed.

AP doses prescribed at discharge were converted into multiples of the defined daily dose (DDD) for each drug by dividing the prescribed daily dose (PDD) by the DDD [PDD/DDD]. The DDD is a theoretical unit of measurement of drug usage approved by the World Health Organisation for drug use studies. Expression of drug use in terms of multiples of DDDs makes it possible to calculate a cumulative measure of drug consumption for each patient, taking into account the concurrent use of more than one agent. A PDD/DDD ratio of one indicates that the dose prescribed is equal to the DDD of that drug; similarly to our previous studies, a ratio greater than two was defined as a high AP dose and was entered in the analysis. Significance level was set at $p \leq 0.05$.

3. Results

Out of 299 patients without parkinsonism originally enrolled in our cross-sectional analysis, 26 patients (8.7%) met the study criteria to be defined *Schiz-Axial* and were compared with 273 patients *Schiz-NO-Axial*. The Table 1 shows group comparisons for all socio-demographic and clinical variables. *Schiz-Axial* patients were significantly older and had longer disease duration compared to *Schiz-NO-Axial*. The two groups of patients did not differ for gender distribution, duration of AP treatment, frequency of family history for parkinsonism. Moreover, distribution of patients currently treated with two or more AP drugs was similar, as those treated with a high AP dose and with depot AP. Interestingly, *Schiz-Axial* patients were less likely to have been treated with two or more AP in the past compared to *Schiz-NO-Axial*. Finally, total UPDRS motor score as well as limb and axial UPDRS sub-scores were significantly increased in *Schiz-Axial* patients compared to *Schiz-NO-Axial* (Fig. 1).

4. Discussion

The present study showed that parkinsonian axial signs occur in those patients with schizophrenia who are older and have longer disease duration. No other clinical variable was different compared to patients without parkinsonian axial signs, including duration of exposure and current treatment with AP drugs, either in terms of number of AP prescribed or as overall cumulative dose.

Previously, we have demonstrated that parkinsonism in schizophrenia was related to older age and use of long-acting AP [2,5]. In the present study, older age and longer disease duration were related to development of axial parkinsonian signs in a cohort of schizophrenic patients without evidence of clear limb bradykinesia. Nevertheless, they had some degree of motor impairment, as pointed out by higher UPDRS motor scores. These data support the hypothesis that parkinsonism occurring over the clinical course of

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