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Erythrocyte superoxide dismutase activity differs in clinical subgroups of Parkinson's disease patients

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Abstract

There is controversy as to whether there are clinical subgroups in Parkinson's disease (PD). Six tremor-dominant and six bradykinesia-dominant patients identified among 29 cases with PD were compared in terms of erythrocyte superoxide dismutase (SOD) activity and several clinical variables. Erythrocyte SOD activity in tremor-dominant patients was higher than in bradykinesia-dominant patients. According to our preliminary results obtained from small number of patients, the difference of SOD activity in clinically distinct subgroups suggests there may be separate clinical subgroups of PD which can be differentiated by a biological marker.

Keywords : Clinical subgroups; erythrocyte superoxide dismutase activity; Parkinson's disease.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease with preferential loss of the dopaminergic neurons of the substantia nigra pars compacta (SNc), presenting with resting tremor, bradykinesia, rigidity, and postural instability as the major clinical manifestations (Jankovic *et al*., 1990).

Despite an enormous amount of research, the etiology of PD is unknown. There is substantial evidence that antioxidant defence mechanisms (ADM) are aberrant, based on the abnormal activities of related enzymes and increased levels of lipid peroxidation products (Jenner *et al*., 1992).
Superoxide dismutase (SOD) is a metalloenzyme that exists in cytosolic (Cu, Zn-SOD) and mitochondrial (Mn-SOD) forms, and erythrocyte SOD activity is exclusively due to Cu, Zn SOD (Kushleika *et al*., 1996). It converts superoxide radical ($O_2^{\cdot}$) to hydrogen peroxide (H_2O_2), which is than converted to water by catalase or glutathione peroxidase. With insufficient activity of latter enzyme systems or with the increased activity of SOD and with the presence of iron, which is abundant in parkinsonian SNc, H_2O_2 leads to generation of highly reactive hydroxyl radical ($OH^{\cdot}$) (Jenner *et al*., 1992). The activity of SOD havs uniformly been found high in parkinsonian SNc (Olanow *et al*., 1998). While this might be the reflection of the primary pathology, it may be an epiphenomenon due to cellular degeneration or inefficient mitochondrial respiration.

The clinical expression of PD is highly variable, and this variability suggests that there may be different subgroups within PD with distinct clinical patterns and perhaps different pathogenic mechanisms (Jankovic *et al*., 1990; Graham and Sagar 1999). Zetusky *et al*. (1985) and Graham and Sagar (1999) reviewed studies that distinguished subgroups of patients with PD by patterns of motor symptoms (tremor dominant vs. akinetic-rigid), age at onset (early vs. late-onset), presence or absence of dementia, or family history of PD.

We previously compared erythrocyte SOD activity of PD patients with a control group and found a higher activity level in the patients with PD (Kocaturk *et al*., 2000). In an attempt to identify further evidence for the presence of subgroups within PD, we reanalysed our previously published data to compare different clinical subgroups of PD in terms of erythrocyte SOD activity.

Methods and Materials

There were 29 cases (13 females, 16 males) with PD with a mean age of 62.1 ± 9.9 (range 40-78). Subjects with other diagnoses or on drug therapy (other than the drugs that are used in the treatment of PD) that may affect the ADM were excluded (like vitamins, coenzyme Q10 or ginko biloba extract). The patients were considered to have PD when at least two of the following were detected: levodopa responsive and asymmetrical bradykinesia, rigidity, and resting tremor. Special care was given to uncover the signs that might indicate another cause for parkinsonism (like gaze paresis, levodopa unresponsiveness, apparent autonomic, cognitive, pyramidal or cerebellar dysfunction). Patients with dementia and a family history of parkinsonism were excluded.

Table 1

Classification of patients into tremor- and bradykinesia-dominant subtypes

Bradykinesia Subscore	Tremor Subscore	Clinical Subgroup	No of Patients
Lower than median BS	Higher than median TS	TG	6
Higher than median BS	Lower than median TS	BG	6
Higher than median BS	Higher than median TS	None	6
Lower than median BS	Lower than median TS	None	7
Either BS or TS at median value			4
Total			**29**

BG : Bradykinesia-dominant group, BS : Bradykinesia score, TG : Tremor-dominant group, TS : Tremor score.

Parkinsonian signs were rated by the Unified Parkinson's Disease Rating Scale (UPDRS), which enables the quantification of type, number, and severity of extrapyramidal symptoms and signs and is widely used for the clinical evaluation of PD. For each sign or symptom, a five-step severity gradation is employed, with 0 representing absence and 4 representing the maximum severity (Fahn *et al*., 1987). In order to evaluate different manifestations of PD the subscore for bradykinesia is obtained by adding the scores of the items 23, 24, 25, 26, and 31 ; for tremor 20 and 21; for postural instability 28 and 30, and the score of item 22 for rigidity.

Cases with tremor subscore higher than the median tremor subscore and with bradykinesia subscore lower than the median bradykinesia subscore formed the tremor-dominant group (TG), and cases with bradykinesia subscore higher than the median bradykinesia subscore and with tremor subscore lower than the median tremor subscore formed the bradykinesia-dominant group (BG). Cases with both high bradykinesia and tremor subscores, and cases with both low bradykinesia and tremor subscores were included neither in TG nor in BG (Table 1). Other signs of PD were also processed to compose clinical subgroups (like BG versus rigidity dominant group, postural instability dominant group versus rigidity dominant group, etc.) with the same method. A similar method was used by Jankovic *et al.* (1990) to divide PD patients into clinical subgroups. Early-onset patients were defined as the patients who noticed their first symptom before or at age 40.

The association of the erythrocyte SOD activity with age at the time of study, sex, duration of disease, age at disease onset, and the type of drugs patients were using for PD was also evaluated.

For the determination of erythrocyte SOD activity the blood samples of the patients were always drawn in the morning at the same time and were put in heparinised tubes. The plasma was kept in polypropylene tubes and each sample was studied within an hour. The activities of red-cell SOD were determined by spectrophotometry (Winterbouin *et al*., 1975). Principle of method was based on percent inhibition of nitro blue tetrazolium reduction in the presence of SOD activity.

Table 2

Erythrocyte superoxide dismutase activities of patients, controls, and clinical subgroups. The activity difference both between patient and control groups, and between tremor-dominant and bradykinesia-dominant groups are statistically significant.

	Number of Cases	Mean SOD Activity ± SD
Controls	24	4983.1 ± 544.4
Patients	29	5344.6 ± 758.8
Tremor-dominant Group	6	5586.8 ± 720.8
Bradykinesia-dominant Group	6	4688.8 ± 797.7

SD: Standard deviation, SOD: Superoxide dismutase.

Results

Among the clinical subgroups of PD patients, the only significant association was found between TG and BG. The erythrocyte SOD activity of TG was found to be higher than BG (Mann Whitney U, $p = 0.04$) (Table 2). Both TG and BG consisted of six patients. Seventeen patients were included neither in TG nor in BG.

Among the analyses we conducted to see whether there were any other differences besides SOD activity between TG and BG, Fisher's exact test revealed, but only in trend level, that the number of patients within BG is higher in the early-onset patients ($p = 0.07$). There were no patients below age 40 in TG, while there were four patients below age 40 in BG.

There was not a significant association between erythrocyte SOD activity and age at the time of study, sex, duration of disease, age at disease onset, or the type of drugs patients were using for the treatment of PD. We also could not find a significant correlation between drug doses and SOD activity.

Discussion

Even in the landmark clinical studies about the natural history of PD, Schwab *et al.* (1959) and Hoehn and Yahr (1967) observed that PD patients

with tremor as the dominant symptom had less functional impairment and more benign progression than their bradykinesia-dominant counterparts. Later studies associated tremor-dominant patients, when compared with bradykinesia-dominant patients, with infrequent and less severe cognitive impairment, frequent family history of PD, less disability, slower progression of disease, better levodopa response, and longer survival (Zetusky *et al.*, 1985 ; Bernheimer *et al*., 1973 ; Barbeau and Porcher, 1982 ; Mortimer *et al*., 1982 ; Roy *et al*., 1983 ; Goetz *et al*., 1988 ; Hershey *et al*., 1991 ; Rajput *et al*., 1993 ; Roos *et al*., 1996 ; Gomez *et al*., 1997). Jankovic *et al*. (1990) analysed the DATATOP database including clinical information on 800 patients so as to evaluate clinical heterogeneity of PD. Their results suggested that older age at onset and presentation with postural instability and gait disorder (PIGD) and with bradykinesia were predictive of a more aggressive course than the early-onset of symptoms and presentation with tremor. They stated the need for new studies correlating the clinical characteristics and neurobiologic markers to understand whether tremor-dominant PD is pathogenically different from the PD with PIGD and bradykinesia (Jankovic *et al*., 1990). Average erythrocyte SOD activity of our tremor-dominant subgroup of patients was higher than bradykinesia-dominant subgroup. The only histopathologic correlation of clinical subtypes of PD came from Rajput *et al*. (1993) who reported diagnoses other than PD more frequently in PIGD than in tremor-dominant patients. Depending on this finding, we suggest that the reason for difference in SOD activity revealed in this study, and in other clinical variables reported before, between TG and BG is that the bradykinesia-dominant patients might constitute a heterogeneous diagnostic group. This suggestion might be supported by Ihara *et al*. (1999) who reported similar levels of plasma SOD activity between patients with multisystem atrophy and controls, while the activity in PD was found to be increased.

High frequency of patients in BG among early-onset patients is one finding that does not reach statistical significance which emphasises the importance of performing studies with greater number of patients that might better delineate different clinical subgroups of PD.

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