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 (O2•−) to hydrogen peroxide (H2O2), which is then 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, H2O2 leads to generation of highly reactive hydroxyl radical (OH•) (Jenner et al., 1992). The activity of SOD has 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.
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 grading 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).

<table>
<thead>
<tr>
<th>Bradykinesia Subscore</th>
<th>Tremor Subscore</th>
<th>Clinical Subgroup</th>
<th>No of Patients</th>
</tr>
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<tbody>
<tr>
<td>Lower than median BS</td>
<td>Higher than median TS</td>
<td>TG</td>
<td>6</td>
</tr>
<tr>
<td>Higher than median BS</td>
<td>Lower than median TS</td>
<td>BG</td>
<td>6</td>
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<tr>
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<td>None</td>
<td>6</td>
</tr>
<tr>
<td>Lower than median BS</td>
<td>Lower than median TS</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Either BS or TS at median value</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>29</strong></td>
</tr>
</tbody>
</table>

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

Table 1

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.

Table 2

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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 (Zetisky 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 pathogenetically 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.

REFERENCES


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