Immune factors or depression? Fatigue correlates in Parkinson's disease

Z. Katsarou [a], S. Bostantjopoulou [b], O. Hatzizisi [c], E. Giza [a], A. Soler-Cardona [a], G. Kyriazis [c]

IMMUNE FACTORS OR DEPRESSION? FATIGUE CORRELATES IN PARKINSON'S DISEASE

Summary. Introduction. *Fatigue is a frequent symptom in Parkinson disease (PD), but its pathogenesis remains obscure. Fatigue may be influenced by depression and motor disability, but immunological factors have been also implicated. The purpose of the study was to assess fatigue in PD patients in relation to depression and various immunological factors.* Subjects and methods. *Forty PD patients and 26 normal matched controls were studied. Fatigue was assessed by the Fatigue Severity Scale (FSS). The Beck Depression Inventory (BDI) was employed for depression screening. The following immunological factors were estimated: a) T- and B-lymphocytes, T-lymphocyte subsets (helper/suppressor cells) as well as natural killer cells (NK); b) circulating levels of interleukins IL-1alpha, IL-1beta, IL-6, IL-1 receptor antagonist (IL-1Ra) and tumor necrosis factor-alpha.* Results. *FSS mean score was higher in PD patients compared to controls (*$p < 0.01$*). Significant differences between patients and controls were found in the following immunological parameters. In PD patients: a) mean percentage of NK cells was higher,* $p < 0.01$*); b) IL-1beta levels were significantly increased (*$p < 0.01$*) and IL-1Ra levels were decreased (*$p < 0.001$*). FSS correlated significantly to BDI (*$p < 0.008$*). Circulating Il-1Ra levels correlated to fatigue severity (*$p < 0.01$*), but after exclusion of depressed PD subjects this correlation significance level dropped to* $p = 0.055$*.* Conclusions. *Our results indicate that fatigue is a common non motor symptom in PD. Immunological differences between PD patients and controls were observed in percentages of NK cells, IL-1beta and IL-1Ra blood levels. Fatigue correlated to depression and IL-Ra levels. However after exclusion of depressed subjects IL-1Ra levels showed only a tendency to significance, leaving depression as the principle correlate of fatigue. [REV NEUROL 2007; 45: 725-8]*

Key words. *Cytokyines. Depression. Fatigue. FSS. Parkinson's disease. T- B-lymphocytes.*

INTRODUCTION

Fatigue is a major non-specific symptom presenting in a number of systemic and neurological disorders such as cancer, multiple sclerosis, Parkinson's disease (PD), amyotrophic lateral sclerosis etc. [1-4]. Particularly in PD fatigue has been reported by the patients themselves as one of the three most serious symptoms having a severe impact on their health related quality of life [1,5]. Nevertheless fatigue evaluation is frequently neglected during the clinical assessment of PD patients. This attitude may be responsible for our limited knowledge regarding the epidemiology, aetiology, distinctive clinical characteristics of fatigue and its relationship to other disease related conditions e.g. depression [1,4].

The pathogenesis of PD is unknown, however there are certain lines of evidence implicating neuroinflammatory factors to the dopamine neuron damage in the substantia nigra [6]. A number of studies have shown central or peripheral humoral and cellular immune changes in patients with PD [6-8]. On the other hand, it is well known that fatigue has been related to immune dysregulation in various systemic disorders such as cancer, systemic lupus erythymatosus, chronic fatigue syndrome etc. [1].

The purpose of the study was to assess fatigue in PD patients in relation to various immunological factors, depression and the pertinent clinical characteristics of the disease.

Accepted: 26.11.07.

[a] Department of Neurology. Hippokration Hospital. [b] Department of Neurology. [c] Laboratory of Immunology. Department of Pulmonology. G. Papanicolaou Hospital. Thessaloniki, Greece.

Corresponding author: Evangelia Giza, MD. Armenopoulou 14. 54635 Thessaloniki (Greece). E-mail: evgiza@the.forthnet.gr

Versión española disponible en www.neurologia.com

SUBJECTS AND METHODS

Subject selection

Forty patients (26 men, 14 women) with idiopathic PD, according to the U.K. Brain Bank criteria were studied [9].These patients were selected from the population of two outpatient clinics for movement disorders by means of the following criteria:

- Satisfactory cognitive function (Mini Mental State Examination score > 24) [10].
- No report of severe motor fluctuations.
- Absence of systemic diseases such as heart failure, thyroid dysfunction, autoimmune disorders, anemia, diabetes, kidney, pulmonary and hepatic insufficiency as well as cancer.
- Absence of a recent infection.
- Negative history of current treatment with tranquilizers or amantadine.

Twenty six normal subjects (14 men, 12 women) matched for age, education and socioeconomic status served as controls. Controls were recruited from the population of PD patients' relatives and visitors to the hospital. They were not formally tested for cognitive impairment, but they were questioned for the presence of memory and reasoning problems as well as for depression. The study was approved by the hospital ethical committee. All subjects gave their informed consent for participation in the study.

Evaluation

Fatigue was evaluated in all subjects by means of the Greek version of the Fatigue Severity Scale (FSS) [11,12].

FSS is nine item scale, covering the most pertinent symptoms of fatigue and their impact on everyday activities during the past two weeks. Each item is rated by the examiner on an analogue scale ranging from 1 'completely disagree' (e.g. absence of fatigue related symptoms) to 7 'completely agree', with 4 being the neutral point. The total score is derived from the average score of all items. The neutral point 4 is the highest possible score to exclude the absence of clinically relevant fatigue.

Motor disability in PD patients was clinically evaluated by means of the motor score of Unified Parkinson's Disease Rating Scale (UPDRS, part III) [13]. PD patients were classified in stages according to the Hoehn and Yahr (H&Y) classification scale [14]. PD patients were also assessed for depression by the Greek version of the Beck Depression Inventory (BDI) [15].

Their sleep quality was measured on an 7 point analogue scale ranging from 0 (bad quality of sleep) to 7 (best quality of sleep) [16]. All patients were under levodopa plus a dopamine agonist treatment.

Clinical characteristics of PD patients are presented in table I.

The following immunological factors were estimated:

– T- and B-lymphocytes, T-lymphocyte subsets (CD4/helper and CD8/suppressor cells) as well as natural killer cells ($CD3/CD16^{+}56$, NK).
– Serum levels of interleukines IL-1α, IL-1β, IL-6, IL-1 receptor antagonist (IL-1Ra) and tumor necrosis factor α (TNF-α).

All blood samples were collected fasting in the morning. T and B lymphocytes and T-lymphocytes subsets (by percentage) were evaluated by direct two-color immunofluorescence on a FACS scan flow cytometer (Becton Dickinson), immediately after blood collection. Serum for circulating cytokine assessment was frozen and preserved at –70 ºC. Cytokines levels were measured by means of enzyme linked immunosorbent assay (ELISA) kits.

Statistical analysis was performed by means of the Mann-Whitney test for two independent samples for comparisons between PD patients and controls. Spearman's rho correlation coefficient was employed for bivariate correlations between FSS score, BDI and immunological factors in PD patients. Finally multiple associations between FSS score (dependent variable) and significant immunological parameters as well as BDI score (independent variables) were explored by means of the weighted least squares procedure.

Significance was set to $p < 0.05$. However, since multiple test comparisons in lymphocyte subsets and circulating cytokine levels may lead to type I error we applied a Bonferroni correction, thus setting the statistically significant level at $p = 0.01$ for lymphocyte subsets and cytokine levels comparisons between PD patients and controls. Higher p levels were interpreted as a tendency for statistical significance. The SPSS for Windows software, v. 12.0, was used for all statistical analysis calculations.

RESULTS

Mean FSS score in PD patients was higher than controls (4.8 ± 1.5 versus 3.4 ± 1.6; $p < 0.01$). Sixty two percent of PD patients reported FSS levels above the neutral point of the scale. Correlation between FSS score and clinical parameters of the disease such as duration, stage, UPDRS score and levodopa dose was not significant. However, stage of the disease showed a tendency for statistical significance ($\rho = 0.239$; $p = 0.06$). Fatigue was also not related to sleep quality ($\rho = 0.09$; $p > 0.1$). On the other hand, BDI correlated strongly to FSS score ($\rho = 0.412$; $p = 0.008$).

Mean percentage of T- and B-leukocytes in PD patients and controls are presented in table II. Briefly, comparisons between PD patients and controls yielded the following findings: a) Mean percentage of T-lymphocytes was lower in PD patients, but this difference did not reach statistical significance after Bonferroni correction ($p < 0.05$); b) mean percentage of NK cells was higher in patients ($p < 0.01$). Correlation between percentages of T- and B-leukocytes in PD patients and FSS score was not significant. Mean cytokine blood levels in PD patients and controls are presented in table III. IL-1β levels were significantly increased ($p = 0.01$) and IL-1Ra levels were decreased ($p = 0.001$) in PD patients. Correlation between cytokine levels and FSS score was significant for IL-1Ra ($\rho = –0.396$; $p = 0.01$) only. Correlation between BDI score and immunological parameters was not significant.

Multiple associations between FSS score and the statistically associated parameters e.g. IL-1Ra and BDI, showed a marginal relationship to IL-1Ra (β coefficients for IL-1Ra = 0.335; $p = 0.023$) and significant correlation for BDI (β coefficients = 0.354; $p = 0.01$). After excluding patients with considerably high BDI scores we tested differences in IL-lRa levels in a subgroup of patients with a high (above neutral point) FSS score and in PD patients with a low FSS score. Mean IL-1Ra levels in the first subgroup were 721.8 ± 479.2 pg/mL and in the second one 528.0 ± 173.7 pg/mL. A comparison showed a tendency for statistically significant difference between the two subgroups ($p = 0.055$).

Table I. Clinical characteristics of Parkinson's disease patients (mean ± SD).

Age (years)	56.4 ± 9.8
Disease duration (years)	9.6 ± 6.6
Stage (Hoehn & Yahr)	2.7 ± 0.9
UPDRS (part III)	29.4 ± 12.6
Beck Depression Inventory score	11.1 ± 7.0

SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Table II. Mean percentage of T- and B-leucocytes in Parkinson's disease (PD) patients and controls.

	PD patients	Normal controls	*p*
T cells	68.3 ± 6.5	73.7 ± 8.1	< 0.05 [a]
B cells	9.3 ± 2.6	10.1 ± 4.1	NS
CD4/helper	44.7 ± 5.8	45.2 ± 8.3	NS
CD8/suppressor	25.0 ± 7.5	29.2 ± 9.1	NS
NK lymphocytes	21.5 ± 6.8	15.3 ± 8.1	< 0.01

Values are expressed as mean percentage ± standard deviation (pg/mL). [a] Tendency for statistical significance (Bonferroni correction). NS: not significant.

Table III. Mean blood levels of cytokines in Parkinson's disease (PD) patients and controls.

	PD patients	Normal controls	*p*
IL-1α	0.64 ± 2.04	0.0 ± 0.0	NS
IL-1β	3.1 ± 3.0	1.05 ± 0.5	< 0.01
IL-6	0.84 ± 1.48	0.3 ± 1.2	NS
IL-1Ra	648.85 ± 372.94	807.7 ± 216.8	< 0.001
TNF-α	1.15 ± 2.53	0.63 ± 2.2	NS

Values are expressed as mean percentage ± standard deviation (pg/mL). NS: not significant.

DISCUSSION

Our results are in consistence with other literature reports that consider fatigue as a major non-specific symptom in PD [1,4,5]. Our group of patients had significantly higher FSS scores in comparison to controls and 62 % of them scored above the neutral point of the scale. Fatigue did not correlate to motor symptoms of the disease although a subtle relationship to stage was observed, but this failed to reach statistical significance. Other investigators have reported controversial associations between fatigue and motor impairment in PD [1,4,16-19].

Depression and sleep disturbances are regarded as important contributors to fatigue, but in PD patients this issue remains controversial, too [1,17,18]. Depression is common in PD and sometimes its somatic symptoms overlap with those of parkinsonism [4,20]. Fatigue has been related to depression by some authors [1,17,19], while others could not prove any association [21,22]. In our group of patients depression correlated significantly to FSS score and emerged as a major correlate of fatigue in these patients. A point of argument however in this case is that there is a considerable overlap of symptoms between fatigue and depression. Besides fatigue is listed as one of the symptoms of major depression in the DSM-IV [23]. The pathophysiology of

fatigue in PD is unknown. It has been hypothesized that it may be linked to peripheral as well as central factors. Muscle stiffness, tremor, difficulties in everyday activities can lead to muscle fatigue. One report has found evidence for muscle mitochondrial dysfunction to be related to fatigue [1,4,24]. Central mechanisms are of paramount importance. Dopaminergic deficiency affecting the frontal lobe-basal ganglia circuits may be a possible substrate for fatigue [1]. However although Abe et al [22] using ^{99m}Tc-HMPAO SPECT showed frontal lobe hypometabolism in relation to fatigue in PD patients, the direct relationship to dopamine loss was not supported by DaT-Scan measurements [25,26]. Thus the problem of the pathogenesis of fatigue in terms of brain localization remains unsolved.

Immunological factors have been implicated in the pathophysiology of fatigue in patients with multiple sclerosis, cancer and autoimmune disorders [1-3,27-30]. Several lines of evidence converge to the fact that cytokine release due to tissue damage triggering an inflammatory response can have a significant impact on neurotransmitters, neuroendocrine function and behavior. Products of immune cells also mediate non-specific symptoms of sickness such as malaise, fatigue, anorexia, apathy or sleepiness. This type of behavior has been also induced in animals and humans by administration of pro-inflammatory cytokines [31,32].

PD is a neurodegenerative brain disorder of unknown etiology. Several reports imply the presence of immunological abnormalities in PD patients, such as impaired T cell responses or cytokine production by the peripheral immune system as well by activated microglia intrathecally [6-8,33-39]. Microglia activation has been regarded as an immune response to neuron degeneration and death, but abnormal peripheral immune responses are of unknown etiology [7,36-40].

More specifically marked increase of cytokine levels, especially TNF-α, IL-1β, IL-6 and IL-2 were found in the substantia nigra and in the striatum of parkinsonian patients [7,8]. Furthermore the density of glial cells in the substantia nigra expressing TNF-α, IL-1β and IFN-γ were elevated in PD patients compared with age-matched controls [6]. TNF-α, IL1β, IL-2, IL-4 and IL-6 were also significantly increased in the CSF in PD [7,8,41]. An inverse correlation between IL-6 levels in CSF and disease severity has been reported by Müller et al [42]. Studies about cytokine blood levels in PD are controversial. Blum-Degen [41] found no alteration of the cytokine levels while Dobbs et al [33] reported increased serum TNF-α in patients with abnormal postural and psychomotor responses. Alterations of T-lymphocyte populations are also present in the peripheral blood of parkinsonian patients. These alterations include decrease of CD4+CD45RA+ naïve T cells and increase of CD4+CD45RO+ memory T cells, TCRγδ+, and CD4 bright+ CD8 dull+ T cells [34,35,38].

A further support to the possible implication of cytokine in PD comes from genetic studies. A polymorphism of IL-1β encoding gene has been associated with an increased risk of developing PD thereby indirectly incriminating inflammatory responses in the development of the disease [43].

In our study significant increase in NK cells in PD was observed, but the most interesting findings concern the circulating cytokines. Proinflammatory IL-1 levels were elevated and anti inflammatory IL-1Ra levels were significantly decreased. These finding are in line with the hypothesis of inflammatory factors involvement in PD pathogenesis. There are arguments about the correct interpretation of circulating cytokine levels and their relationship to intracerebral processes. It is possible that circulating levels of cytokines reflect systemic inflammation, but may not adequately mirror intracerebral inflammatory responses due to the presence of the blood brain barrier [39,44]. In this context, it is noteworthy that perivascular macrophages and microglia in the brain that participate in intraparenchymal inflammation are derived from circulating macrophages. Therefore, measurement of the peripheral cytokines may better reflect their potential to contribute to intracerebral inflammation [7,44].

Exploring the relation of the circulating cytokines studied and fatigue severity, we observed a positive correlation between IL-1Ra and fatigue severity. However, this correlation did not stand vigorous statistical testing and was confounded by depression.

To the best of our knowledge there are no other published studies that address the topic of immune related factors and fatigue in PD. There are a number of interesting studies in cancer patients linking IL-1Ra to fatigue, but it does not sound reasonable to make any direct associations to our patients [30].

It is obvious that the pathophysiology of fatigue in PD is a complex phenomenon. Various mechanisms must be taken into consideration simultaneously [1,4]. The complex interplay between brain function and immune mechanisms cannot be so easily conceptualized. The present study is a preliminary, exploratory attempt to address the problem of a possible relation between fatigue and immune factors in PD. More studies are required to replicate these data and to explore this hypothesis further.

REFERENCES

1. Krupp LB. Fatigue. Philadelphia: Butterworth-Heinemann; 2003.
2. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult Scler 2003; 9: 219-27.
3. Sood A, Moynihan TJ. Cancer-related fatigue: an update. Curr Oncol Rep 2005; 7: 277-82.
4. Friedman JH, Brown RG, Comella C, Garber CE, Krupp LB, Lou JS, et al. Working Group on Fatigue in Parkinson's Disease. Fatigue in Parkinson's disease: a review. Mov Disord 2007; 22: 297-308.
5. Herlofson K. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand 2003; 107: 1-6.
6. Hunot S, Hirsch E. Neuroinflammatory processes in Parkinson's disease. Ann Neurol 2003; 53 (Suppl 3): S49-60.
7. McGeer P, McGeer E. Inflammation and neurodegeneration in Parkinson's disease. Parkinsonism Relat Disord 2004; 10 (Suppl 1): S3-7.
8. Nagatsu T, Sawada M. Inflammatory process in Parkinson's disease: role of cytokines. Curr Pharm Des 2005; 11: 999-1016.
9. Hughes AJ, Daniel SE, Kilford I, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181-4.
10. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the mental state of patients for the clinicians. J Psychiatr Res 1975; 12: 189-98.
11. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46: 1121-3.
12. Katsarou Z, Bostantjopoulou S, Peitsidou E, Kourtesi G, Tsipropoulou, V, Kafantari A. Fatigue assessment in Parkinson's disease. Encephalos 2007; 44: 150-7.
13. Fahn S, Elton RL, and members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease, II. Florham Park: MacMillan Headcare; 1987. p. 293-304.
14. Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427-42.
15. Donias S, Demertzis I. Standardized assessment of depression by means of the Beck Depression Inventory. Proceedings of the 5th Greek Conference for Neurology and Psychiatry 1983; 1: 486-92.

16. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology 1993; 43: 2016-8.
17. Alves G, Wentzel-Larsen T, Larsen JP. Is fatigue an independent and persistent symptom in patients with Parkinson disease? Neurology 2004; 63: 1908-11.
18. Larsen JP, Karlsen K, Tandberg E. Clinical problems in non-fluctuating patients with Parkinson's disease: a community-based study. Mov Disord 2000; 15: 826-9.
19. Lou J, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord 2001; 16: 190-6.
20. Starkstein SE, Merello M. Psychiatric and cognitive disorders in Parkinson's disease. Cambridge: Cambridge University Press; 2002.
21. Herlofson K, Larsen JP. Measuring fatigue in patients with Parkinson's disease –the Fatigue Severity Scale. Eur J Neurol 2002; 9: 595-600.
22. Abe K, Takanashi M, Yanagihara T. Fatigue in patients with Parkinson's disease. Behav Neurol 2000; 12: 103-6.
23. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4 ed (DSM-IV). Washington DC: APA; 1994.
24. Schapira AH. Evidence for mitochondrial dysfunction in Parkinson's disease: a critical appraisal. Mov Disord 1994; 9: 125-38.
25. Weintraub D, Newberg AB, Cary MS, Siderowf AD, Moberg PJ, Kleiner-Fisman G, et al. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. J Nucl Med 2005; 46: 227-32.
26. Katsarou Z, Bostantjopoulou S, Gerasimou G, Kafantari A, Peitsidou E, Kourtesi G. Fatigue in Parkinson's disease: relation to clinical parameters and 123 I-FP-CIT SPECT data. Parkinsonism Relat Disord 2005; 11 (Suppl 2): S150.
27. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002; 64: 604-11.
28. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 2005; 104: 788-93.
29. Kozora E. Fatigue in systemic lupus erythematosus and related immune disorders. In DeLuca J, ed. Fatigue as a window to the brain. Cambridge, Mass: MIT Press; 2005. p. 243-64.
30. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. Brain Behav Immun 2007; 21: 413-27.
31. Kelley KW, Bluthé RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, et al. Cytokine-induced sickness behavior. Brain Behav Immun 2003; 17 (Suppl 1): S112-8.
32. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007; 21: 153-60.
33. Dobbs RJ, Charlett A, Purkiss AG, Dobbs SM, Weller C, Peterson DW. Association of circulating TNF-α and IL-6 with ageing and parkinsonism. Acta Neurol Scand 1999; 100: 34-41.
34. Hisanaga K, Asagi M, Itoyama Y, Iwasaki Y. Increase in peripheral CD4 Bright+ CD8 Dull+T cells in Parkinson disease. Arch Neurol 2001; 58: 1580-3.
35. Bas J, Calopa M, Mestre M, Molleví DG, Cutillas B, Ambrosio S, et al. Lymphocyte populations in Parkinson's disease and in rat models of Parkinsonism. J Neuroimmunol 2001; 113: 146-52.
36. Selikhova M, Kushlinskii N, Lyubimova N, Gusev E. Impaired production of plasma interleukin-6 in patients with Parkinson's disease. Bull Exp Biol Med 2002; 33: 81-3.
37. Orr CF, Rowe DB, Mizuno Y, Mori H, Halliday GM. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. Brain 2005; 128: 2665-74.
38. Baba Y, Kuroiwa A, Uitti RJ, Wszolek ZK, Yamada T. Alterations of T-lymphocyte populations in Parkinson disease. Parkinsonism Relat Disord 2005; 11: 493-498.
39. Sawada M, Imamura K, Nagatsu T. Role of cytokines in inflammatory process in Parkinson's disease. J Neural Transm (Suppl) 2006; 70: 373-81.
40. Perry VH. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain Behav Immun 2004; 18: 407-13.
41. Blum-Degen D, Müller T, Kuhn W, Gerlach M, Przuntek H, Riederer P, et al. Interleukin-1β and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. Neurosci Lett 1995; 202: 17-20.
42. Müller T, Blum-Degen D, Przuntek H, Kuhn W. Interleukin-6 levels in cerebrospinal fluid inversely correlate to severity of Parkinson's disease. Acta Neurol Scand 1998; 98: 142-4.
43. Mattila KM, Rinne JO, Lehtimäki T, Röyttä M, Ahonen JP, Hurme M. Association of an interleukin 1β gene polymorphism (-511) with Parkinson's disease in Finnish patients. J Med Genet 2002; 39; 400-2.
44. Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, et al. Inflammatory markers and the risk of Alzheimer disease. The Framingham Study. Neurology 2007; 68: 1902-8.

¿FACTORES INMUNES O DEPRESIÓN? LA FATIGA RELACIONADA CON LA ENFERMEDAD DE PARKINSON

Resumen. Introducción. *La fatiga es un síntoma frecuente en la enfermedad de Parkinson (EP), pero su patogénesis permanece sin aclarar. El propósito de este estudio fue evaluar la fatiga de pacientes con EP en relación con los factores inmunológicos.* Sujetos y métodos. *Se estudiaron 40 pacientes con EP y 26 sujetos control. La fatiga se evaluó con la* Fatigue Severity Scale *(FSS). Se empleó el* Beck Depression Inventory *(BDI) para examinar la depresión. Como factores inmunológicos se estudiaron los linfocitos T y B, subclases de linfocitos T (*helper *y* supressor*), así como las células* natural killer *(NK), y los niveles sanguíneos de interleucinas IL-1alfa, IL-1beta, IL-6, el antagonista del receptor de IL-1 (IL-1Ra) y el factor de necrosis tumoral alfa.* Resultados. *Se encontró significación estadística (*$p < 0,01$*) entre los niveles sanguíneos de IL-1Ra y la gravedad de la fatiga, pero tras excluir los pacientes con depresión y EP, el nivel de significación disminuyó a* $p = 0,055$. Conclusiones. *Se hallaron diferencias inmunológicas en los niveles sanguíneos de pacientes con EP y sujetos control en los porcentajes de células NK, IL-1beta e IL-1Ra. La fatiga correlacionaba con la depresión y los niveles de IL-1Ra. Sin embargo, tras la exclusión de los pacientes con depresión, los niveles de IL-1Ra mostraron sólo una tendencia hacia la significación, y situaron a la depresión como el principal factor correlacionado con la fatiga. [REV NEUROL 2007; 45: 725-8]*
Palabras clave. *Citocinas. Depresión. Enfermedad de Parkinson. Fatiga. FSS. Linfocitos T y B.*