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Minor and Trace Elements in Cerebrospinal Fluid of Parkinson's Patients – Suggestions After a Critical Review of the Analytical Data

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1. Introduction

Patients suffering from neurodegenerative diseases are known to present, in comparison to controls, variations on the contents of minor and trace elements in body tissues and fluids. For individuals affected by Parkinson's disease (PD), some findings, regarding brain and serum, are cited hereafter. BRAIN. Various brain areas were characterized for trace element levels and some alterations were observed in patients. Higher concentrations of aluminum were determined by Yasui et al. (1992) in different sites; increased levels of copper were detected by Riederer et al. (1989) in raphe plus reticular formation, whereas diminished amounts were found in substantia nigra by Rajput et al. (1985) and Dexter et al. (1989). Dexter et al. (1991) and Griffits et al. (1999) observed an iron enrichment in substantia nigra; regarding to zinc, Dexter et al. (1989) found more elevated amounts in a few areas, while Riederer et al. (1989) noticed lower contents in raphe formation. Variations of aluminum, copper, iron and zinc levels in definite brain sites of PD patients were reviewed by Speziali & Orvini (2003). SERUM. For PD patients, trace element changes were observed also in serum. Several studies were carried out at the Italian Istituto Superiore di Sanità (ISS) by Bocca et al. (2004, 2006), Forte et al. (2004, 2005), Alimonti et al. (2007a). A decreasing trend for aluminum was observed by Bocca et al. (2004) and Forte et al. (2004), as well as by Hedge et al. (2004) and Pande et al. (2005). Copper resulted elevated in these last two works and in a paper by Mindadse & Tschikowani (1967); in other investigations, by Bocca et al. (2006), Forte et al. (2004) and Tan et al. (2007), copper resulted diminished. Hedge et al. (2004), Pande et al. (2005), Forte et al. (2005), Alimonti et al. (2007a) detected lower iron concentrations, whereas Tan et al. (2007) reported a higher amount. In the case of zinc, a slight increase was noticed by Tan et al. (2007), whereas Hedge et al. (2004), Pande et al. (2005), Forte et al. (2005), Alimonti et al. (2007a) observed a significant decrease. A lower mercury content was found by Gellein et al. (2008).

From this survey, it emerges that disagreeing findings for the same element are quite frequent. In the case of brain, we can suppose that the discrepancies among the various trials are related to the different areas examined. The less expected controversial findings for serum stimulated us to examine the up to date knowledge about the CSF of PD subjects. We have already published a short review on this topic (Speziali & Di Casa, 2009). In this

Chapter we present in a series of tables, for the first time, all the original values retrieved, along with several parameters that can influence the results. Here we discuss more extensively the role of all the factors affecting the results, which are the parameters reported in the tables along with the criteria for the enrollment of subjects, the analytical procedures and the statistical tests used. Finally, we propose with wider completeness several suggestions useful for possible future studies.

C = Controls	Et-AAS = Electrothermal Atomic Absorption Spectrometry
PD = Parkinson's disease patients	ICP-AES = Inductively Coupled Plasma - Atomic Emission Spectometry
PD (On) = PD with positive response to the therapy	DCP-AES = Direct Current Plasma -AES
PD (On/Off) = PD without positive response to the therapy	SF-ICP-MS = Sector Field – Inductively Coupled Plasma – Mass Spectrometry
PDCN = PD cognitively normal patients	S = significant or highly significant difference
PDD = PD demented patients	NS = non-significant difference
SD = Standard Deviation	
M = male	
F = female	

Table 1. Captions for the tables

2. Aim

We performed an investigation on the minor and trace element amounts, available in the literature, regarding the CSF of PD patients and paired controls. Our purpose was to obtain a comprehensive picture of the element concentrations and to verify possible imbalances in the CSF of the diseased individuals.

3. Data presentation

We considered only studies where: a) both patients and controls were examined in the same investigation; b) the concentration values determined were reported as numbers; c) statistical tests were employed to verify the significance of potential changes of element amounts in the CSF of patients. The scientific publications were retrieved through the data bank Medline along with the Personal Alert Service of Thomson Reuters, Philadelphia, PA. From the bibliographies of the recruited papers further references were derived. The concentration data we recruited in the literature were published from 1987 to 2008. Values of Al, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Hg, Li, Mg, Mn, Mo, Ni, Pb, Sb, Se, Si, Sn, Sr, Tl, V, W, Zn and Zr were found. In Tab. 1 we set out the captions useful for all our tables. In Tab. 2 - 11 we report the mean concentration values, along with the standard deviations; we also show several parameters affecting the results: number, gender and age of the subjects enrolled, analytical technique employed, significance of possible differences between concentration values for patients and controls. The simultaneous availability of all these factors allows scientists to evaluate immediately the reliability of each trial findings. From the tables, indications can be also deducted on the possibility (or not) to compare directly the results of different trials; increasing or decreasing element trends in patients are evident right away. Finally, in Tab. 12 we sum up some indications recorded in other publications of interest.

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Ca	C	24.696	1.997	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
	PD	27.911	4.964	26 (24 M + 2 F)	64.9 ± 10.8			
	C	26.956 {median: 25.579}	5.515	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
	PD	27.312 {median: 27.301}	3.385	42 (36 M + 6 F)	64.5 ± 10.7			
Mg	C	21.229	3.160	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
	PD	20.913	2.024	26 (24 M + 2 F)	64.9 ± 10.8			
	C	21.868 {median: 22.665}	3.509	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
	PD	23.693 {median: 22.365}	4.263	42 (36 M + 6 F)	64.5 ± 10.7			

Table 2. Calcium and magnesium in Controls and Patients (mg/L)

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y* (Range)	Technique	Significance	References
C	75.9	153.6	22 (20 M + 2 F)	age-matched	Et-AAS		Gazzaniga et al., 1992
PD tot	181	75.1	11 (10 M + 1 F)	64.9 (49-78)		NS	
PD untreated	28.3 *	141.5*	6	63.1 (49-78)		NS	
PD treated	266.4	183.6	5	67 (59-77)		NS	
C	210	150	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS		Jiménez-Jiménez et al., 1998
PD	170	170	37 (14 M + 23 F)	65.7 ± 8.8		NS	
C	73.3	72.7	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES		Forte et al., 2004
PD	33.0	29.4	26 (24 M + 2 F)	64.9 ± 10.8		NS	
C	237	37	21 (13 M + 8 F)	62 ± 11	Et-AAS		Qureshi et al., 2005 and 2006
PD (On)	345	47	17 (10 M + 7 F)	70 ± 15		S >	
PD (On/Off)	397	50	19 (13 M + 6 F)	72 ± 17		S >	
C	45.0	30.2	18 (10 M + 8 F)	63.8 ± 13.8	ICP-AES		Bocca et al., 2006
PD	28.2	14.6	91 (64 M + 27 F)	65.5 ± 9.7		S <	
C	35.5 {median: 36.8}	5.03	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES		Alimonti et al., 2007b
PD	28.2 {median: 24.4}	14.6	42 (36 M + 6 F)	64.5 ± 10.7		S <	

* these two values are incoherent

Table 3. Iron in Controls and Patients (µg/L)

4. Considerations on factors influencing the results

As already pointed out in the **Introduction**, many factors affect the results, conditioning then the comparability among the findings of the various studies. We describe now in details the influence of each factor as it emerged in the examined publications.

4.1 Criteria for subject enrollment

4.1.1 Health conditions

In the subject enrollment, the criteria for inclusion/exclusion are fundamental and should absolutely include health conditions along with age and gender. Ideally, exposures due to environmental pollution or occupational activities and diet should also be considered.
In the reviewed papers, only a few teams give full details of the selection criteria used. The researchers of the Italian Istituto Superiore di Sanità (ISS), Bocca, Forte, Alimonti and coworkers, along with the Spanish scientists (Jiménez-Jiménez et al. 1998 and Aguilar et al. 1998) are among the few authors who describe extensively the criteria employed. The diseases affecting the individuals recruited as patients or controls are often not precisely described, mainly in the less recent works. In some publications, incongruities appear within the text or among the text and the data presented in the tables. It is not always clear whether the patients were affected by comorbidities. Due to the fact that severe illnesses of heart, liver, kidney and also tumors are known to affect the levels of trace elements in human fluids and tissues, an exhaustive health report is also necessary in the case of controls. For these subjects, very heterogeneous situations have been observed. In Bourrier-Guerin et al. (1985) - see Tab. 12 - controls were not enrolled at all. Mindadse & Tschikowani (1967) - see Tab. 12 - employed blood donors. In Qureshi et al. (2005, 2006) control individuals, simply defined "healthy", were affected by tension headache, ischemic cerebrovascular disease or polyneuropathy. The Spanish group selected "healthy" subjects with suspected subarachnoid hemorrhage or pseudotumor cerebri, oculomotor palsies, etc. The scientists of the ISS enrolled individuals not suffering from any central neurological disease. Kjellin (1967a and 1967b - see Tab. 12) assumed psychoneurotic outpatients as representative of the "normal" condition. It is evident that, in the diverse investigations, were enrolled as controls subjects in really different health conditions. It is worth considering that, differently from blood, the samples of CSF are not easily available; therefore, the control specimens are mostly withdrawn from subjects undergoing lumbar puncture for clinical analyses. In the case of patients, the differences among the groups enrolled in the diverse studies are amplified by some clinical variables, as duration and severity of the disease along with medical treatments and possible comorbidities. Regarding duration and severity of the disease, in the trial by Aguilar et al. (1998) Se and Cr levels showed no correlation with age at onset and duration of the illness. On the other hand, Alimonti et al. (2007b) detected in patients a negative association of Cr amount and severity and duration of the illness; in the same study, Pb appeared to be negatively related to the severity of the disorder, while Sn resulted to be negatively associated with the duration of the disease. The authors also found that age at onset did not affect the concentration of Fe and of the other elements that resulted significantly different between controls and patients (Co, Cr, Pb, Si, Sn). Bocca et al. (2006) observed that duration and severity of the disease appeared not to be correlated with Al, Ca, Cu, Fe, Mn, Si and Zn amounts; on the other hand, Mg level decreased with the duration and severity of the illness. Concerning medical treatments, the therapies followed by patients are described by

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y* (Range)	Technique	Signif-icance	References
C	19.2 (range: 10 – 33)	5.8	21		DCP-AES	NS	Belliveau et al., 1990
PD	18.7 (range: 7 – 30)	6.3	16				
C	64.9	14.4	22 (20 M + 2 F)	age-matched	Et-AAS	NS	Gazzaniga et al., 1992
PD tot	67.7	19.9	11 (10 M + 1 F)	64.9 (49 – 78)		NS	
PD untreated	63.2	11.5	6	63.1 (49 – 78)		NS	
PD treated	67.0	18.5	5	67 (59 – 77)			
C	109.1	88.2	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS	NS	Jiménez-Jiménez et al., 1998
PD	104.9	86.3	37 (14 M + 23 F)	65.7 ± 8.8			
C	22.5	4.76	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
PD	23.7	10.5	26 (24 M + 2 F)	64.9 ± 10.8			
C	132	17	21 (13 M + 8 F)	62 ± 11	Et-AAS	NS	Qureshi et al., 2005 and 2006
PD (On)	119	18	17 (10 M + 7 F)	70 ± 15		NS	
PD (On/Off)	109	19	19 (13 M + 6 F)	72 ± 17			
C	21.9 {median: 2.2}	4.77	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
PD	19.4 {median: 17.0}	7.97	42 (36 M + 6 F)	64.5 ± 10.7			
C	19.6	1.3	32	85.2 ± 1.0		NS	Sparks et al., 2008
PDCN	17.4	4.3	12	85.3 ± 1.4		NS	
PDD	10.0	1.1	5	78.6 ± 2.2			

Table 4. Copper in Controls and Patients (μg/L)

many authors, as Gazzaniga et al. (1992), Qureshi et al. (2005, 2006), Aguilar et al. (1998), Jimenez-Jimenez et al. (1998), Bocca et al. (2004, 2006), Forte et al. (2004), Alimonti et al. (2007b) along with Campanella et al. (1973) and Takahashi et al. (1994). Aguilar et al. (1998) carried out studies about the influence of antiparkinsonian treatment with various drugs on Se and Cr levels; in the entire group of PD patients, Se showed a non significant increase compared to controls, but the elevation attained the significance when only patients not treated with levodopa were considered. This interesting observation is just recorded in the article text. Jimenez-Jimenez et al. (1998) studied the effects of the same drugs on the concentrations of Fe, Cu, Zn and Mn; they did not observe any significant influence. Gazzaniga et al. (1992), confronting long-term levodopa treated and untreated patients, did not find any significant differences in the amounts of Cu, Fe and Mn. Qureshi et al. (2005, 2006) determined the amounts of Cu, Fe, Se and Zn in patients treated with levodopa, who were divided into two groups (PD On and PD On/Off), depending on the positive or negative response to the therapy. Fe and Se were found to be markedly higher than in controls in both kinds of patients; Zn resulted instead significantly reduced in both groups. Bocca et al. (2006) evaluated that the type of therapy did not influence the concentrations of all the elements studied (Al, Ca, Cu, Fe, Mg, Mn, Si, Zn). Alimonti et al. (2007b) observed that diverse drugs did not affect the concentration of Fe; on the contrary, they influenced the amounts of the elements which resulted significantly different between controls and patients (Co, Cr, Pb, Si, Sn). Takahashi et al. (1994 - see Tab. 12) found that the Mg concentration in both untreated and treated (with levodopa) patients was lower than in controls.

4.1.2 Age

The subject age is known to influence the amounts of some elements in tissues and fluids. In serum, it has been documented for Cu by Ghayour-Mobarhan et al. (2005) and Kouremenou-Dona et al. (2006); for Se by Lopes et al. (2004). In brain, Markesbery et al. (1984), Ongkana et al. (2010) and Tohno et al. (2010) found age-related changes for several

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Signif-icance	References
C	170	140	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS	S <	Jiménez-Jiménez et al., 1998
PD	100	60	37 (14 M + 23 F)	65.7 ± 8.8			
C	32.9	8.85	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
PD	27.3	10.5	26 (24 M + 2 F)	64.9 ± 10.8			
C	161	31	21 (13 M + 8 F)	62 ± 11	Et-AAS	S <	Qureshi et al., 2005 and 2006
PD (On)	117	19	17 (10 M + 7 F)	70 ± 15		S <	
PD (On/Off)	96	11	19 (13 M + 6 F)	72 ± 17			
C	32.3 {median: 33.5}	11.4	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
PD	27.7 {median: 27.8}	9.01	42 (36 M + 6 F)	64.5 ± 10.7			

Table 5. Zinc in Controls and Patients (µg/L)

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y* (Range)	Technique	Signif-icance	References
C	0.97 ♥	0.34 ♥	29		Et-AAS	NS	Pall et al., 1987
PD	0.96 ♥	0.36 ♥	9				
C	5.7	1.8	22 (20 M + 2 F)	age-matched	Et-AAS	NS	Gazzaniga et al., 1992
PD tot	5.4	3.9	11 (10 M + 1 F)	64.9 (49 - 78)		NS	
PD untreated	6.0	1.3	6	63.1 (49 - 78)		NS	
PD treated	5.4	2.4	5	67 (59 - 77)			
C	0.88	0.76	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS	NS	Jiménez-Jiménez et al., 1998
PD	1.20	0.98	37 (14 M + 23 F)	65.7 ± 8.8			
C	0.85 {median: 0.91}	0.36	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	NS	Bocca et al., 2004 and Forte et al., 2004
PD	0.63 {median: 0.54}	0.43	26 (24 M + 2 F)	64.9 ± 10.8			
C	0.95	0.39	18 (10 M + 8 F)	63.8 ± 13.8	SF-ICP-MS	NS	Bocca et al., 2006
PD	0.69	0.42	91 (64 M + 27 F)	65.5 ± 9.7			
C	0.95 {median: 1.02}	0.39	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
PD	0.69 {median: 0.58}	0.42	42 (36 M + 6 F)	64.5 ± 10.7			

♥ data converted from nmol/L

Table 6. Manganese in Controls and Patients (µg/L)

elements. All authors who studied CSF and published element concentration values also for patients reported the mean age of each subject group; Gazzaniga et al. (1992) specified also the age range. Regarding element changes with age, Aguilar et al. (1998) found that Se and Cr levels were not correlated with the age of PD patients. Bocca et al. (2006) found no Zn changes in patients (no data given); in controls, they observed a significant Zn increment in subjects elder than 70 years in comparison with younger individuals, but these differences disappeared in patients.

4.1.3 Gender

This parameter also influences trace element levels. For changes of Se, Cu and Zn in serum, see Lopes et al. (2004) and Ghayour-Mobarhan et al. (2005). For Zn variations in brain, see Ongkana et al. (2010). Regarding CSF, Bocca et al. (2006) noticed lesser Fe amounts in PD males than in females, whereas the opposite was found in controls. They also report that Si concentration resulted significantly lower in patients than in controls and that in PD females it was two-times lower than in males. This remarkable observation could come out because the authors calculated distinct values, not published, for the two genders.

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Cr	C	14.6	6.3	43 (19 M + 24 F)	65.2 ± 13.0	Et-AAS	NS	Aguilar et al., 1998
	PD	14.5	7.4	28 (11 M + 17 F)	65.5 ± 9.1			
	C	1.39 {median: 1.47}	0.64	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.60 {median: 0.54}	0.47	26 (24 M + 2 F)	64.9 ± 10.8			
	C	1.28 {median: 1.39}	0.59	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	S <	Alimonti et al., 2007b
	PD	0.65 {median: 0.55}	0.46	42 (36 M + 6 F)	64.5 ± 10.7			
Se	C	13.5	8.2	43 (19 M + 24 F)	65.2 ± 13.0	Et-AAS	NS	Aguilar et al., 1998
	PD	17.9	12.3	28 (11 M + 17 F)	65.5 ± 9.1			
	C	14.2	1.8	21 (13 M + 8 F)	62 ± 11	Et-AAS	S >	Qureshi et al., 2006
	PD (On)	19.7	1.9	17 (10 M + 7 F)	70 ± 15		S >	
	PD (On/Off)	22.7	2.1	19 (13 M + 6 F)	72 ± 17			

Table 7. Chromium and selenium in Controls and Patients (µg/L)

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Pb	C	1.06 {median: 1.0}	0.34	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.42 {median: 0.30}	0.38	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.91 {median: 0.84}	0.36	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	S <	Alimonti et al., 2007b
	PD	0.46 {median: 0.43}	0.24	42 (36 M + 6 F)	64.5 ± 10.7			
Si	C	105	39.3	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	S <	Forte et al., 2004
	PD	66.9	49.7	26 (24 M + 2 F)	64.9 ± 10.8			
	C	95.0	38.0	18 (10 M + 8 F)	63.8 ± 13.8	ICP-AES		Bocca et al., 2006
	"	92.5	44.3	1 F				
	PD	58.4 •	44.8	91 (64 M + 27 F)	65.5 ± 9.7		S <	
	"	63.9	46.5	1 M			S <	
	"	28.9	13.7	1 F			S <	
	C	95.0 {median: 96.3}	38.3	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	S <	Alimonti et al., 2007b
	PD	58.4 {median: 52.3}	44.8	42 (36 M + 6 F)	64.5 ± 10.7			

• For gender difference, see text (section 4.1.3 Gender)

Table 8. Lead and silicon in Controls and Patients (µg/L)

4.1.4 Number of subjects examined

In the reviewed papers, the authors usually publish the total number of controls and patients, and even the numbers of males and females; however, they frequently do not report the information actually needed, that is the number of individuals really tested for each element. In our review, we observed that Be, Cd, Hg, and V were determined in two investigations by the team of ISS (Bocca et al. 2004 and Alimonti et al. 2007b). In the previous one, where a lower number of individuals was considered, the element decrements in patients were evaluated as significant; in the second trial, where more subjects were enrolled, the variations came out to be not significant. Fe resulted decreased in patients at the limits of significance ($p = 0.052$) in a trial carried out by Forte et al. (2004); in two successive investigations by the same team (Bocca et al. 2006 and Alimonti et al. 2007b), with a higher number of individuals, Fe was found to be significantly reduced. The control and patient groups of successive trials by the same authors probably included the corresponding groups already examined in the previous ones; the disagreeing findings could be due to the

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Co	C	0.15 {median: 0.16}	0.04	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.04 {median: 0.03}	0.04	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.13 {median: 0.13}	0.05	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	S <	Alimonti et al., 2007b
	PD	0.09 {median: 0.06}	0.09	42 (36 M + 6 F)	64.5 ± 10.7			
Ni	C	8.01 {median: 7.54}	1.39	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	NS	Bocca et al., 2004
	PD	4.37 {median: 1.07}	5.61	26 (24 M + 2 F)	64.9 ± 10.8			
	C	5.40 {median: 6.44}	3.33	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	3.34 {median: 1.53}	3.61	42 (36 M + 6 F)	64.5 ± 10.7			

Table 9. Cobalt and nickel in Controls and Patients (µg/L)

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Be	C	0.87 {median: 0.85}	0.33	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.44 {median: 0.44}	0.13	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.70 {median: 0.55}	0.37	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.56 {median: 0.54}	0.21	42 (36 M + 6 F)	64.5 ± 10.7			
Cd	C	0.06 {median: 0.06}	0.02	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.03 {median: 0.03}	0.01	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.05 {median: 0.05}	0.03	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.04 {median: 0.4}	0.02	42 (36 M + 6 F)	64.5 ± 10.7			
Hg	C	1.20 {median: 1.19}	0.50	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.67 {median: 0.74}	0.32	26 (24 M + 2 F)	64.9 ± 10.8			
	C	1.05 {median: 0.85}	0.46	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.73 {median: 0.81}	0.32	42 (36 M + 6 F)	64.5 ± 10.7			
V	C	0.12 {median: 0.11}	0.06	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.07 {median: 0.08}	0.03	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.09 {median: 0.10}	0.03	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.07 {median: 0.07}	0.03	42 (36 M + 6 F)	64.5 ± 10.7			

Table 10. Berillium, cadmium, mercury and vanadium in Controls and Patients (µg/L)

different number of the considered subjects. In the case of Co, Cr, Pb and Si, the outcomes for significance are always the same when the number of subjects, in both control and patient groups, is either lower or higher. We wonder whether the changes in patients of these elements are so marked that result noticeable in every case. As a general consideration, it is obvious that the higher is the number of the subjects examined, the higher is the representativeness of the results obtained.

4.2 Analytical procedures

When determining elements at trace levels, the entire analytical process is critical. Sampling and storage should be carried out in an appropriate way to minimize contamination and losses, following the recognized requirements in the field. The chemical treatments needed by each method should be as standardized as possible. The analytical technique employed must assure high sensitivity and good reproducibility.

In the reviewed studies, the preanalytical steps were described with more or less details; the techniques employed were cited by all authors, except Sparks et al. (2008). A careful description of the method is generally available in the most recent papers, that sometimes refer

to previous publications. The techniques used for the most studied elements were principally electrothermal atomic absorption spectrometry (Et-AAS) and inductively coupled plasma atomic emission spectrometry (ICP-AES). For some elements, sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) was also employed by the team of ISS. All these analytical techniques are widely used for trace element determination in human samples.

Element	Subjects	Mean	SD	Median	Significance
Al	C	2.64	0.51	2.72	NS
	PD	2.15	1.03	2.05	
Ba	C	0.35	0.15	0.31	NS
	PD	0.26	0.13	0.24	
Bi	C	0.10	0.07	0.09	NS
	PD	0.08	0.05	0.06	
Li	C	0.52	0.13	0.52	NS
	PD	0.82	0.53	0.65	
Mo	C	0.45	0.27	0.43	NS
	PD	0.33	0.17	0.27	
Sb	C	0.08	0.02	0.09	NS
	PD	0.06	0.04	0.07	
Sn	C	0.32	0.07	0.31	S <
	PD	0.26	0.11	0.24	
Sr	C	30.0	8.69	27.7	NS
	PD	24.6	8.66	22.6	
Tl	C	0.01	0.01	0.01	NS
	PD	0.01	0.007	0.01	
W	C	0.04	0.02	0.04	NS
	PD	0.03	0.02	0.03	
Zr	C	0.06	0.05	0.06	NS
	PD	0.04	0.03	0.04	
N. of subjects (Gender)				Age, *y*	
C 20 (17 M + 3 F)				66.2 ± 14.7	
PD 42 (36 M + 6 F)				64.5 ± 10.7	
Technique: SF-ICP-MS					

Table 11. Other trace elements in Controls and Patients (μg/L); (modified from Alimonti et al., 2007b)

4.3 Statistical tests

In this kind of studies, statistical tests of various types are required for diverse appraisals. Within each study and for each element considered, tests are applied at first to evaluate whether the concentrations found for controls and patients are significantly different or not. In the same trial, other tests can reveal non negligible dissimilarities among the control and patient groups, regarding one or more factors affecting the results. When a significant

discrepancy is disclosed, the comparison between the mean concentration values for controls and those for patients results rather inappropriate.
A crucial point, worth of a close investigation by the scientists of the field, is to assess at what extent the outcomes for significance of the various tests applied are the same. When comparing the results of different investigations, the diversity of the statistical tests applied in each one causes an amplification of the general inhomogeneity.
In the reviewed papers, the statistical tests used to verify the difference between the results for controls and patients are generally indicated. Some authors checked also possible differences, for one or more variability factors, among the various subject groups; their information is therefore more accurate.

5. Summary of the retrieved data

The retrieved data are non numerous, being the withdrawal of the fluid unpleasant; the control samples are taken from individuals undergoing lumbar puncture for neurological exams. Some values have been found for Cu, Fe, Mn and Zn, whereas only few results have been retrieved for Cr and Si. As far as other elements are concerned, the data are absolutely scarce or determined only once, mainly by the scientists of ISS.
Examining the collected values, regarding **copper** - see Tab. 4 - no significant variations for patients as compared to controls were found in trials performed by diverse teams; nevertheless, in other papers (not showing analytical data for Cu), Pall et al. (1987) and Pan et al. (1997) - see Tab. 12 - assess to have observed a remarkable elevation. In the case of **manganese** too – see Tab. 6 - no changes were observed in the different investigations; of note, the levels determined by Gazzaniga et al. (1992) are higher than those found by the other author groups. Concerning **calcium** and **magnesium** - see Tab. 2 - no significant alterations are reported; however, Takahashi et al. (1994) - see Tab. 12 - assess to have found a lesser Mg level in patients. As for **zinc** - see Tab. 5 - Forte et al. (2004) and Alimonti et al. (2007b) observed in PD a slight diminution, which in the trials by Jiménez- Jiménez et al. (1998) and Qureshi et al. (2005 and 2006) attained the significance. Aguilar et al (1998) found for PD subjects a non significant **selenium** increment - see Tab. 7; a significant elevation resulted instead in all the patients, with both positive and negative response to the therapy, enrolled by Qureshi et al. (2006). **Lead** - see Tab. 8 - was found to be significantly reduced in patients by the team of ISS (Bocca et al. 2004 and Alimonti et al. 2007b), that obtained the same finding also for **silicon** (Forte et al. 2004, Bocca et al. 2006, Alimonti et al. 2007b) - see Table 8. In the case of **iron** - see Tab. 3 - the most interesting element for PD, discordant results were unfortunately recruited. A significant depletion was found by Bocca et al. 2006 and Alimonti et al. 2007b; for a detailed description, see the paragraph 4.1.4. An elevation, also significant, was seen by Qureshi et al. (2005 and 2006); other scientists as Gazzaniga et al. (1992) and Jiménez- Jiménez et al. (1998) did not observe noticeable variations. The values determined by the ISS team appear to be remarkably lower than those published by the other groups. Dealing with **chromium** - see Tab. 7 - Aguilar et al. (1998) found similar amounts in the CSF of patients and controls; differently, Bocca et al. (2004) and Alimonti et al. (2007b) obtained much lower values and noticed a significant decrement in patients. **Al**, **Ba**, **Be, Bi**, **Co**, **Li**, **Mo**, **Ni**, **Sb**, **Sn, Sr**, **Tl**, **V, W** and **Zr** were determined only by the scientists of ISS - see Tab. 9, 10, 11. No variations were observed, except significant decreases of Co and Sn. Regarding the results for Be and V, see the paragraph 4.1.4, where are described also the findings for **Cd** and **Hg**; the values for these last four elements are shown in Tab. 10.

Bourrier-Guerin et al. 1985 report values for 13 elements in 70 patients (34 M and 36 F) affected by different neurodegenerative diseases; patients were grouped all together. Si and Zn resulted to be significantly higher in men than in women.

Campanella et al. 1973 enrolled 18 individuals (5 controls; 7 untreated patients; 6 patients treated with dopaminergic drugs), age > 39 y, no gender given. They published the Cu mean amount found for each subject. For both patients groups, the range of the mean values was wider than for controls.

Kjellin 1967a and 1967b reported Cu and Fe amounts in the CSF of a female patient (69 y) suffering from parkinsonism.
Cu and Fe resulted respectively higher and lesser in comparison to a unique control, who was probably in both cases a male of 65 y.

Mindadse & Tschikowani 1967 found that Au amount in PD patients was 66 μg/g, about the double than in controls. The Au concentration in controls (blood donors) is however not reported.

Pall et al. 1987 found in patients (24) with untreated, idiopathic PD, a higher Cu concentration than in controls (34) with various other neurological diseases. For Fe, they did not observe a difference between patients (26) and controls (33).

Pan et al. 1997 observed that Cu increased significantly in PD patients; on the other hand, the amounts of Cd, Fe, Mn and Zn did not change.

Takahashi et al. 1994 evaluated Br, Cu, Fe, Se, Zn and Mg levels in 25 controls and 20 PD patients (13 untreated and 7 treated with L-dopa). The mean Mg concentration in both treated and untreated parkinsonians was found to be lower than in controls.

Woodbury et al. 1968 determined in one PD patient a Mg amount overlapping the mean value found for controls (11). Always in one patient, these authors determined a higher zinc concentration than in controls (2).

Table 12. Additional information

6. Conclusion

Regarding the matrix CSF, the first remark we make is that the element concentration values available in the literature are non numerous, probably due to the rareness of the

samples. Among the recruited papers, the range of values was recorded only in that by Belliveau et al. (1990). Knowing the ranges for controls and patients would allow to establish a range of normalcy for each element and, as a consequence, to individuate in patients a possible shift towards elevation or diminution. Examining the retrieved data, it is evident that for some elements the results obtained by the various research groups are of different levels. For Cu, the values published by the different teams vary from less than two decades to more than a hundred of μg/L. For Fe and Zn, the scientists of ISS determined concentrations much lesser than the other teams. For Cr, Aguilar et al. (1998) found values an order of magnitude higher than those reported by the team of ISS. The discrepancies regarding the element levels are difficult to explain. The mean values retrieved have often very large standard deviations. In the case of Be, Cd, Cr Hg, Se, Si, V, the SDs are sometimes as high as the half of the mean. A similar situation resulted for Mn and Cu in the study by Jiménez-Jiménez et al. (1998). Dealing with Fe, Jiménez-Jiménez et al. (1998) and Forte et al. (2004) detected SD values very close to the mean. SDs close to the mean were also found for Co and Pb by the researchers of ISS; they report, for Ni, SDs even higher. The large SDs can be due to the individual variability and/or to the low number of the subjects enrolled; they are not surprising also when the element concentration level is very low (a few μg/L or less). In the case of Cr and Se, and mostly in that of Fe and Si, high SDs are less expected. Obviously, they make it really difficult to evaluate the significance of the difference among the results.

In this review, we have verified the influence, on the results, of number, age, gender of the subjects enrolled; health conditions (with regard also to clinical variables as duration and severity of the disease and pharmacological therapies) were demonstrated to be other influencing factors. The importance of adequate analytical procedures and statistical tests has been previously described (see the respective paragraphs).

At this point, we can suggest that, in a trial, attention should be paid to match, as far as possible, age and health conditions of the subjects belonging to the same group; this is more difficult to obtain in the case of patients. Concerning gender, separate male and female groups could reveal possible unexpected information. A similar number of individuals in the various groups should be enrolled; anyway, we are aware that, in the clinical practice, the scarceness of the CSF control samples and the prevalent number of male PD patients (Alimonti et al. 2007b) make these requirements not always achievable. In addition, all the previously mentioned factors should be not too different when confronting the results of the various studies, to allow a proper comparison. It is evident that this is a truly unattainable task.

In our opinion, a real upgrading in this field could actually be achieved if many specific indications were recorded in the single studies. Regarding every subject enrolled, information as age, gender, health condition, lifestyle and environmental exposure should be clearly reported; for each individual, also the results obtained for every element should be published. A detailed description of the various steps of sampling and analytical procedures should also be given; the single steps should be performed according to the indications most recently standardized.

Following all these suggestions, a database useful for diverse kind of investigations would be obtained; retrospective studies as meta-analyses, based on single factors affecting the results, could be derived; even findings not detectable at the moment could arise.

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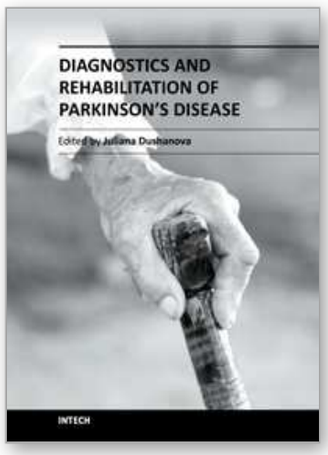

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Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

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