Brainstem Midline Assessed by Transcranial Sonography in Parkinson's Disease: Further Evidence of a Different Etiopathogenesis of Alexithymia and Depression

Roberta Di Giacomo[1,2*], Vincenzo D'Agostino[3], Maria Vittoria De Angelis[2], Francesco Cerritelli[1], Luciano Paolo Marchionno[2], Maria Chiara D'Amico[1], Astrid Thomas[1], Marco Onofrj[1,2], Laura Bonanni[1,2]

[1]Department of Neuroscience, Imaging and Clinical Sciences, University G.d'Annunzio of Chieti-Pescara, Italy

[2]Neurology Clinic, SS Annunziata Hospital, Chieti, Italy

[3]University of Tor Vergata, Faculty of Letters and Philosophy, Department of History, Roma, Italy

*Corresponding author: Roberta Di Giacomo, Department of Neuroscience, Imaging and Clinical Sciences, University G.d'Annunzio of Chieti-Pescara, Italy, Tel: 390871562019; E-mail: roberta.digiacomo84@gmail.com

Abstract

Objective: Parkinson's disease (PD) is often characterized by altered emotional processing, such as depression and alexithymia. Alexithymic and depressive symptoms may be partially overlapping and the relative independence of these two disorders is strongly debated. Reduced echogenicity of midbrain raphe, evaluated with transcranial sonography (TCS), is a characteristic finding in depression associated with PD. No data are available on brainstem's echogenicity in alexithymic PD patients. We assessed, by means of transcranial sonography, possible differences between PD patient with or without alexithymia and/or depression.

Methods: We recruited 22 PD patients among our local cohort of 200 patients referred to our Movement Disorder Center during 2014. All patients were treated with optimal dose of dopaminomimetic (L-DOPA EQ mg 499.7 ± 256.3) and underwent neuropsychological tests including Beck Depression Inventory (BDI) and Toronto Alexithymia Scale-20 (TAS-20). Motor symptoms were assessed with Unified Parkinson's Disease Rating Scale (UPDRS III) and modified Hoehn and Yahr scale (H&Y). TCS was performed, through temporal window, using a color-coded phased-array ultrasound system (SONOS 7500), to evaluate midbrain raphe (0=absent, 1=discontinuous, 2=continuous).

Results: TAS-20 and BDI identified 4 patients with depression without alexithymic symptoms (18.18%), 7 alexithymic patients without depression (31.82%), 5 PD patients with depression and alexithymia (22.73%) and 6 PD patients without any of the two disorders (27.27%). At statistical analysis hypoechogenicity correlated with BDI score and the presence of alexithymia was not significantly correlated with absent or discontinuous raphe.

Conclusion: The study evidenced the presence of hypoechogenicity in the midbrain raphe in PD patient with depression. No alteration of midbrain raphe was found in PD patients with alexithymia. These findings suggest that while depression in PD may involve central component of brainstem midline, constituting the basal limbic system, called mesocorticolimbic pathway, alteration in alexithymia does not affect the midbrain. This study provides further evidence that depression and alexithymia are independent affective disorder.

Abbreviations PD: Parkinson's Disease; TCS: Transcranial Sonography; BDI: Beck Depression Inventory; TAS-20: Toronto Alexithymia Scale-20; UPDRS: Unified Parkinson's Disease Rating Scale; mH&Y: Modified Hoehn and Yahr Scale; MMSE: Mini-Mental State Examination; LED: L-Dopa Equivalent Dose; D: Depression, A: Alexithymia

Introduction

Parkinson's disease (PD) is often characterized by altered emotional processing. Depression occurs with a prevalence of 30-35% in medicated PD patients and alexithymia with a prevalence of 21% in PD patients [1,2].

Salient features of alexithymia are the inability to distinguish one's feelings from the associated bodily sensations with a tendency to amplify the somatic sensations accompanying emotional arousal, the inability to communicate feelings to others and an externally oriented cognitive style, reflecting reduced inner thoughts and fantasies [3].

Alexithymic and depressive symptoms may be partially overlapping and the relative independence of the two disorders is strongly debated [2-5]. Previous studies show that alexithymic features may be relevant in PD patients and may be associated with the severity of depression [2], but depressive symptoms do not completely explain the difficulty in describing and communicating emotions in this group of patients.

Both depression and alexithymia seem to find their pathophysiological correlate in limbic system dysfunction.

Depression has been associated to morphological alterations of the midbrain raphe [6,7].

A tool to assess the anatomy of the midbrain raphe is transcranial sonography (TCS). This allows a 2D visualization of brain parenchyma [6].

Reduced echogenicity of midbrain raphe, evaluated with TCS, is a characteristic finding in depression associated with PD [7-10]. No data are available on brainstem's echogenicity in alexithymic patients.

In the present study, we aimed to disentangle the possible pathogenetic background of alexithymia and depression, by evaluating, by means of TCS, a group of PD patients with depression in comparison with a group of PD patients with alexithymia and with a group of PD patients without any of the two symptoms.

Materials and Methods

We recruited 22 consecutive PD patients, among a local cohort of 200 patients referred to our institution during 2014. All patients gave their written informed consent to participate and fulfilled research diagnostic criteria for idiopathic PD (UK Brain Bank Criteria [11]).

All the patients were treated with optimal dose of dopaminomimetics. The global cognitive status was assessed with the Mini-Mental State Examination (MMSE). The presence and severity of depression was assessed by Beck Depression Inventory (BDI) which classifies depressive symptoms as mild mood disturbance (score from 11 to 16), borderline clinical depression (score 17-20), moderate depression (score 21-30), severe depression (score 31-40), extreme depression (score over 40).

The Toronto Alexithymia Scale-20 (TAS-20) was also administered. TAS-20 is the most widely used and validated self-administered alexithymia scale [12]. It includes three subscales (F1 difficulty identifying feelings, F2 difficulty describing feelings and F3 difficulty focusing on inner affective experience). Total scores categorize patients as non alexithymic (scores<51), borderline alexithymic (scores from 51 to 60) and alexithymic (scores>=61) [12].

Motor symptoms were assessed with Unified Parkinson's Disease Rating Scale (UPDRS III) [13] and modified Hoehn and Yahr scale (mH&Y) [14].

TCS was performed by an experienced and certified ultrasound physician (RDG) using a color-coded phased-array ultrasound system (SONOS 7500). Patient lied in supine position; the ultrasound probe was pressed on the temporal window, at the temporal squama before the ear as recommended else-where [15]. Axial plane on orbitomeatal line was assessed to evaluate midbrain raphe [16]. A dynamic range of 45 dB, image brightness and time-gain compensation were adapted as needed for each examination. Echogenicity of the brainstem midline was rated in comparison with the echogenicity of the tectum of the mesencephalus and classified as grade 0=absent, 1=discontinuous, 2=continuous [8,15] (Figure 1A example of absent raphe, Figure 1B example of continuous raphe). Grade 0 and grade 1 are classified as hypoechogenic. Continuous echogenicity of the raphe is the normal finding in the general population [8-10]. Neuropsychological tests and TCS were performed and analysed in different settings and by examiners blind to diagnosis of depression/alexithymia.
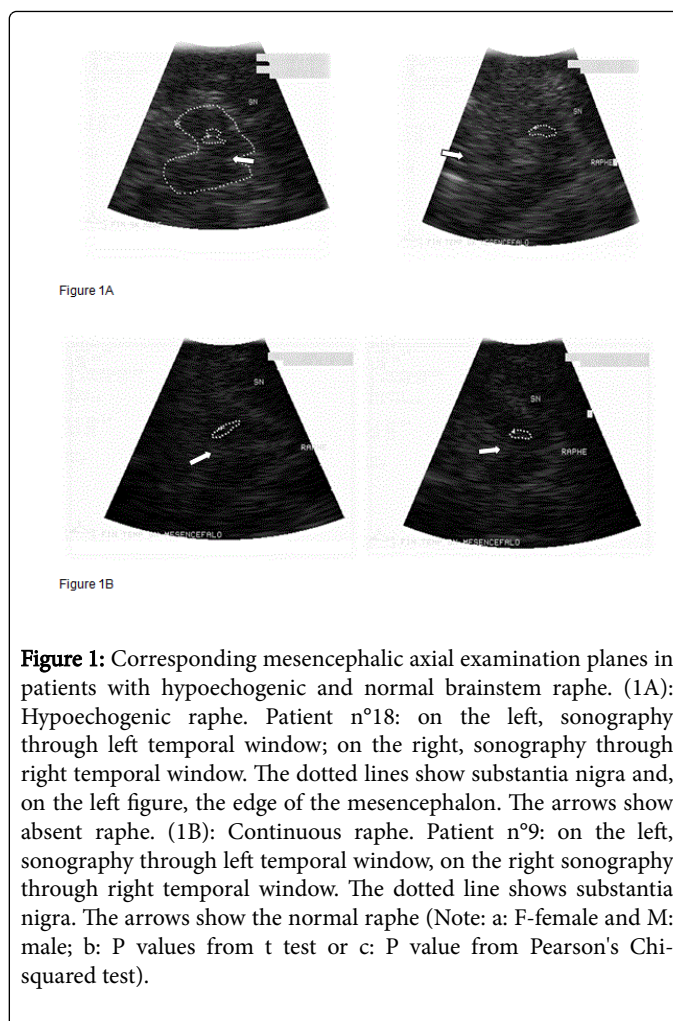

Figure 1A

Figure 1B

Figure 1: Corresponding mesencephalic axial examination planes in patients with hypoechogenic and normal brainstem raphe. (1A): Hypoechogenic raphe. Patient n°18: on the left, sonography through left temporal window; on the right, sonography through right temporal window. The dotted lines show substantia nigra and, on the left figure, the edge of the mesencephalon. The arrows show absent raphe. (1B): Continuous raphe. Patient n°9: on the left, sonography through left temporal window, on the right sonography through right temporal window. The dotted line shows substantia nigra. The arrows show the normal raphe (Note: a: F-female and M: male; b: P values from t test or c: P value from Pearson's Chi-squared test).

Exclusion criteria included cognitive impairment suspected on the basis of MMSE ≤ 25 and clinical examination, evidence of severe psychotic symptoms or systemic diseases, features suggestive of atypical Parkinsonism, modifications of the antiparkinsonian pharmacological treatment in the last 3 months and insufficient quality of the bone windows.

Statistical Analysis

Arithmetic mean, standard deviation, percentage, range were used. Binary data was compared using the X^2 test. One-factorial analysis of variance (ANOVA) with the main factors group was conducted to test the difference in variance among the four groups having defined an alfa level less than 0.05. Ordinal data were analyzed using Kruskall-Wallis test with post hoc Bonferroni-Dunn correction was used to manage multiple comparisons. In addition, bivariate Pearson's Correlation was used to explore correlation between echogenicity and neuropsychological results (TAS-20 and BDI).

The statistical software used was R (v. 3.3.2). Results were expressed in terms of point estimate and 95% of confidence interval (CI). Statistical significance was set at p<0.05.

Results

Demographic, clinical and pharmacological findings, neuropsychological and TCS results are reported in Table 1 and compared in Table 2.

Patient	Gender	aLED(mg)	bUPDRS (III)	Antipsicotic/ Antidepressant Drugs	Age (years)	Education (years)	Disease Duration (years)	cmH&Y	dMMSE	eBDI	fTAS20	Raphe	Disease-Group (PD-A,PD-DA,PD-D,PD)
1	M	300	13	NO	76	13	1	2.5	28,3	4	54	2	PD-A
2	M	550	15	NO	78	5	6	2.5	25,7	6	52	2	PD-A
3	M	352	16	NO	66	13	1	1.5	26,2	5	55	2	PD-A
4	F	300	11	NO	52	13	3	1	30	8	56	2	PD-A
5	F	105	11	NO	64	5	1	1	30	3	51	2	PD-A
6	M	100	26	NO	69	18	2	2	27,2	2	56	1	PD-A
7	F	675	19	NO	73	5	5	2	26,3	7	65	2	PD-A
8	F	575	31	NO	76	4	5	2.5	27,7	7	35	0	PD
9	F	510	18	NO	58	13	5	2	28	9	46	2	PD
10	M	715	24	NO	62	13	10	2	30	7	46	2	PD
11	F	507	9	NO	58	16	4	2	30	10	47	0	PD
12	F	400	17	NO	61	8	5	2	30	8	45	2	PD
13	M	885	13	NO	64	13	14	2	29	5	46	2	PD
14	F	510	15	NO	56	16	2	1	30	23	50	0	PD-D
15	M	750	27	YES	80	5	6	2	25,4	15	50	1	PD-D
16	F	785	33	NO	76	4	24	3	27	13	43	1	PD-D
17	M	400	16	YES	70	5	14	2	26,3	12	37	2	PD-D
18	M	415	47	NO	55	18	4	2.5	30	23	53	0	PD-DA
19	M	1180	23	NO	58	8	9	2	30	12	54	0	PD-DA
20	M	380	33	YES	57	13	1	2.5	30	15	63	1	PD-DA
21	F	300	10	YES	48	8	3	2.5	28	21	81	0	PD-DA
22	M	300	22	NO	68	8	1	2	25	16	57	1	PD-DA

Table 1: Demographic and clinical findings. Neuropsychological and transcranial sonography results (Note: a: L-DOPA equivalent dose; b: Unified Parkinson's Disease Rating Scale motor section III; c: modified Hoehn and Yahr scale; d: Mini-Mental State Examination; e: Beck Depression Inventory; f: Toronto Alexithymia Scale-20; g: PD-A: PD patients with alexithymia; h: PD-DA: PD patients with depression and alexithymia; i: PD-D: PD patients with depression; l: PD: PD patients without depression and/oralexithymia).

	PD (n=6)	PD-D (n=4)	PD-A (n=7)	PD-DA (n=5)	p-value b	f-value
Age (Mean ± SD)	63.17 ± 6.71	70.50 ± 10.50	68.29 ± 8.81	57.20 ± 7.19	0.09	2.54
Gender (M:F)a	02:04	02:02	04:03	04:01	0.15c	-
Disease duration (Mean ± SD)	7.17 ± 3.97	11.50 ± 9.71	2.71 ± 2.06	3.60 ± 3.29	0.05	3.232

LED (Mean ± SD)	598.67 ± 174.25	611.25 ± 186.47	340.29 ± 213.11	515.00 ± 375.13	0.23	1.581
Education (Mean ± SD)	11.17 ± 4.36	7.50 ± 5.69	10.29 ± 5.25	11.00 ± 4.47	0.67	0.522
UPDRS (Mean ± SD)	18.67 ± 7.87	22.75 ± 8.73	15.86 ± 5.30	27.00 ± 13.84	0.21	1.639
mH&Y (Mean ± SD)	2.08 ± 0.20	2.00 ± 0.82	1.79 ± 0.64	2.30 ± 0.27	0.43	0.974
MMSE (Mean ± SD)	29.12 ± 1.06	27.18 ± 1.99	27.67 ± 1.80	28.60 ± 2.19	0.31	1.282

Table 2: Comparison of demographic and clinical characteristics among different disease groups.

Among 22 patients, TAS-20 (cut-off value 51) and BDI (cut-off value 11) identified 4 patients with depression without alexithymic symptoms (PD-D) (18.18%), 7 alexithymic patients without depression (PD-A) (31.82%), 5 PD patients with depression and alexithymia (PD-DA) (22.73%) and 6 PD patients without any of the two disorders (PD) (27.27%).

Three PD-D and 5 PD-DA patients showed the presence of hypoechogenicity in the midbrain raphe: hypoechogenicity correlated with BDI score (Pearson's Correlation: t=-3.9103, df=20, p<0.001). Among 7 PD-A patient's only one showed discontinuous raphe and no one showed absent raphe. At statistical analysis, the presence of alexithymia was not significantly correlated with absent or discontinuous raphe (Pearson's Correlation: t=-0.67542, df=20, p=0.507). Two patients of 6 PD patients without depression or alexithymia had absent raphe, one of these showed BDI score equal to 10 and clinical features of depression.

Among demographic characteristics, only disease duration was different between PD-D and PD-A groups. This finding should not affect our observation, because age, disease severity (mH&Y, LED) and clinical features (UPDRS) of the patients were no different. In addition, echogenicity of midbrain structures seems to remain constant over time [17].

Discussion and Conclusion

In the present study, we found a different TCS pattern in PD patients with depression as compared to PD patients with Alexithymia.

We confirmed the presence of hypoechogenicity in the midbrain raphe in PD patient with depression. This alteration may be due to a distinct disruption of fibre tracts and raphe nuclei of the brainstem in depressed patients, as highlighted by neuropathological [18] and MRI findings [6].

In contrast, no alterations of midbrain raphe were found in alexithymic PD patients.

Previous research has generated controversy as to whether alexithymia and depression are distinct or overlapping constructs [4,19,20]. The disentanglement of the two disorders is important because alexithymic patients do not seem to respond satisfactorily to antidepressants and should be directed to psychotherapies involving specific techniques to enhance emotional awareness and integrate symbolic and subsymbolic elements of emotion schemas [21,22]. On the other hand, patients with hypoechogenic raphe seem to respond better to selective serotonin reuptake inhibitor (SSRI) therapy than those with normal echogenicity [23].

Our findings confirmed that depression and alexithymia in PD may recognize different mechanisms. Depression seems to involve central component of brainstem midline, constituting the mesocorticolimbic pathway and involving, mainly, serotoninergic system. On the other hand, the presence of alexithymia is not associated with midbrain alterations. This latter result found a significant positive confirmation in several studies, which showed that alexithymia may involve mainly cortical dysfunctions [24-26]. In a recent work evaluating the default mode network (DMN) in alexithymic patients, a higher connectivity was found within right prefrontal and sensory areas. These areas have been associated with emotion suppression and a more action-oriented behavior. Furthermore, the alexithymic group showed reduced connectivity within the frontal areas of the DMN, which could be related to the reduced emotional awareness of alexithymic patients [27].

Furthermore, we note that depressed mood occurs with a prevalence of 40% and alexithymic symptoms were present with a prevalence of 54.55% in our sample. These values were higher than reported in the literature [1,2]. This can be due to the small sample size or to the fact that, at difference with previous reports [2], we included, in the prevalence evaluation, also slightly symptomatic patients (borderline alexithymic patients and mild depressed mood).

The main limitations of our study are the small sample size of patients tested and the semi-quantitative analysis of signal intensity. Moreover, despite we are supported by the abundant literature about consistency of TCS technique [6-8,28], the reliability of this technique is dependent on the quality of the ultrasonography system and on the qualification of the investigator.

In conclusion, the brainstem midline echogenicity would be highly interesting to perform in the future to disentangle these two disorders and, toward this aim, study on non-parkinsonian subjects with and without alexithymia is advisable.

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