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Pure psychiatric presentation of the Lewy body disease is depression– an analysis of 60 cases verified with myocardial meta-iodobenzylguanidine study –

Katsuji Kobayashi,*1, 2, Hiroyuki Nakano1, Noriko Akiyama1, Takashi Maeda1, 2, Sanae Yamamori3

1. Department of Psychiatry, Awazu Neuropsychiatric Sanatorium, 88 Yatano-machi, Komatsu, Ishikawa, 923-0342, Japan +81-761-44-2545, +81-761-44-8050

2. Department of Psychiatry and Neurobiology, Kanazawa University Graduate School of Medical Sciences, 13-1, Takara-machi, Kanazawa, Ishikawa, 920-8641, Japan +81-76-265-2000, +81-76-234-4254

3. Department of Nuclear Medicine, Yawata Medical Center Hospital, 12-7, Yawata, Komatsu, Ishikawa, 923-8551, Japan

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* Corresponding author: Katsuji Kobayashi, MD., PhD. Department of Psychiatry, Awazu Neuropsychiatric Sanatorium, 88 Yatano-machi, Komatsu, Ishikawa, 923-0342, Japan

Tel +81-761-44-2545, Fax +81-761-44-8050, E-Mail: k-koba@ta2.so-net.ne.jp

Katsuji Kobayashi; k-koba@ta2.so-net.ne.jp

Hiroyuki Nakano; hiro-naka-kanaz@ezweb.ne.jp

Noriko Akiyama; ogen@tvk.ne.jp

Takashi Maeda; hwtmd086@yahoo.co.jp

Sanae Yamamori; s.yam@katsuki-g.com

Abstract

Background: Parkinson's disease (PD), Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) were collectively termed Lewy body disease (LBD). Pure psychiatric presentation (PPP) of the LBD may be the fourth subtype in which psychiatric symptoms without definite parkinsonism and cognitive disturbance lasted for many years. The aim of this study is to localize the presence of the PPP in subjects with low uptake of myocardial meta-iodobenzylguanidine (MIBG).

Methods: Sixty MIBG-verified patients (28 women and 32 men) were classified into three psychiatric pictures; depression (Group D: 27 patients), isolated visual hallucinations (Group V: 16 patients) and psychosis (Group P: 17 patients). Fifty six cases were examined with single photon emission tomography (SPECT) study of the brains in which hypoperfusion lobes were identified in 37 cases and 19 cases showed no abnormality. After that, we determined final diagnoses; PD, PDD, DLB and PPP with an aid of the DSM-IV, the unified Parkinson's disease rating scale (UPDRS), and Mini-mental state examination (MMSE).

Results: Of Group D patients 40% remained depressive without parkinsonism and about 50% had or developed typical parkinsonism. Most Group P patients developed clinical pictures of PDD or DLB. Statistics provided four combinations: Group V-DLB-occipital lobe hypoperfusion, Group D-PD without SPECT abnormality, Group P-PDD with temporal lobe hypoperfusion, and Group D-PPP without SPECT abnormality.

Conclusions: PPP featured major depressive disorder and can be preparative of incidental LBD and prodromal depression of PD. Psychosis and dementia were of the same quality that characterizes the PDD.

Introduction

A non-demented, non-parkinsonian psychosis of Lewy body disease (LBD) was designated as pure psychiatric presentation (PPP) (McShane, 1995; Lennox et al., 1998). As LBD includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and Parkinson's disease with dementia (PDD), this isolated psychosis may be the fourth subtype of LBD and has been noted in association with incidental DLB because incidental LBD was defined as the presence of Lewy bodies or Lewy neurites in non-demented and non-parkinsonian individuals (Forno and Alvard, 1971; Fearnley and Lees, 1991). Low uptake of meta-iodobenzylguanidine (MIBG) is presently being considered to be a reliable marker for LBD irrespective of the duration of disease and autonomic failure, and neuropathological studies have confirmed the morphological basis of this mechanism in which Lewy bodies and Lewy neurites affected the cardiac sympathetic nerves early in the course of LBD (Courbon et al., 2003; Yoshita et al., 2006; Orimo et al., 2008; Dickson, 2008; Tateno et al., 2011).

The frequency of incidental LBD cases have been reported to be several percent in neuropathological settings (Adler et al., 2010; Jellinger and Attems 2012), and 7.7% in biopsied epicardial fat tissues (Navarro-Otano et al., 2013). Frequency of low uptake of MIBG was reported to be 5% in outpatients with mild cognitive impairment and such patients were presumed to be amnesic

type of DLB (Sakakibara et al., 2012). Thus, pre-motor LBD has three phenotypic variations: non-motor symptoms, amnesic symptoms and apparent normality.

Psychiatric condition is still unclear in individuals with incidental LBD and PPP. In our previous study psychiatric features could be classified into three groups and each of them had clinical distinctive characteristics in MIBG-verified patients (Kobayashi et al., 2010). The purpose of the present study is to examine whether PPP can be identified or not in setting of psychiatric clinic with more numbers of patients.

Patients and methods

Sixty patients (22 women and 28 men, aged 51 to 95 years) who visited our hospital with psychiatric and neurological complaints and with significantly low uptake of cardiac MIBG were studied. Diagnosis of PD was performed according to the criteria (Hughes et al., 1992) and PDD was defined dementia after one year or more from the onset PD (Dubois et al., 2007). DLB was diagnosed with an aid of the criteria (McKeith et al., 2005). Psychiatric picture was diagnosed with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR (American Psychiatric Association, 2000). In terms of predominant psychiatric pictures patients were grouped into three (Kobayashi et al., 2010); isolated visual hallucinations (Group V, 12 cases), depressive and anxious symptoms relevant to major depressive disorder (Group D, 22 cases) and psychosis (Group P, 26 cases) (Table 1a). When a patient showed at least one of symptoms relevant to the diagnostic criteria of DLB and PD or when a patient had no previous history of depression and psychosis, MIBG study was performed. All patients were subjected to blood chemistry and electrocardiogram study prior to MIBG study to confirm the absence of diseases that influence the MIBG data, and patients with diabetes mellitus or cardiac diseases were excluded from the present study. These MIBG-verified patients were diagnosed as PD, DLB and PDD according to each diagnostic criterion, and patients who did not fit these criteria were tentatively diagnosed with PPP (Table 1b).

Motor symptoms were evaluated with the the Movement Disorder Society-sponsored new version of the unified Parkinson's disease rating scale (MDS-UPDRS) Part III (Goetz et al., 2008), and were scored. Cognitive impairment was evaluated with Mini-mental state examination (MMSE). Motor examination items of UPDRS were employed for evaluation of the parkinsonism in which rigidity (item 3.3), hand tremor (item 3.5), freezing of gait (item 3.11) as akinesia, and postural stability (item 3.12) were selected and scored from 0 to 4.

A decrease in MIBG uptake was evaluated with careful inspection of cardiac contour, and early and late phase heart-to-mediastinum (HM) ratios were estimated and utilized for diagnosis of LBD. A cutoff value of HM ratio was set at 1.78 in early phase or 1.68 in late phase (Yoshita et al., 2006). Out of 60 patients, 12 were medicated with anti-depressants, 10 with antipsychotics, 5 with Levodopa-carbidopa and 33 were non-medicated at the time of myocardial MIBG study.

Regional cerebral blood flow (rCBF), obtained 56 out of 60 patients, evaluated with brain perfusion SPECT imaging with technetium-99m Tc, Tc-99m, and 2-ethylene diylbis-L-cysteine diethyl ester

dihydrochloride (99mTc-ECD). SPECT data was expressed as hemispheric blood flow (ml/100g/min) and the cerebral hypoperfusion region was estimated by Z-score map.

Statistics employed ANOVA followed by non-parametric Kruskal-Wallis test and the correspondence analysis with JMP (Version 10.0.2, SAS Institute Inc. NC, USA, 2012). Statistical significance was available at $p < 0.05$. Consent to publish clinical data was obtained in writing from all patients and their close relatives.

Results

Demographic data of the patients are shown in two ways; by three psychiatric pictures (Table 1a) and by four final diagnoses (Table 1b). Difference in male-female ratio was insignificant across both tables (the psychiatric pictures: $\chi^2 = 0.377$, $p = 0.8283$, the final diagnosis: $\chi^2 = 3.266$, $p = 0.3524$). In the psychiatric picture, the average age of the Group V patients were the highest and Group D showed the highest average MMSE score. The average MDS-UPDRS III score was the highest in Group P and the lowest in Group D. In the Group D patients, parkinsonism was found only one case out of 27 cases and mean score of the MDS-UPDRS III was the lowest. Average value of the hemispheric rCBF was lower in the Group V and Group P than in the Group D.

In the final diagnosis table, average age at onset was oldest in DLB and the youngest in PPP. Average MMSE score was the lowest in the PDD and the highest in the PPP. Similarly PPP had the highest average rCBF and the lowest MDS-UPDRS score. Statistical difference in the Hoehn and Yahr stages was available with the χ^2 test in the psychiatric pictures and the final diagnosis, but it was hard to specify the relationship of clinical picture with the Hoehn and Yahr stages because of insufficient number of the cases.

Relationship between the psychiatric pictures and the final diagnosis were examined with χ^2 -test and correspondence analysis in terms of nominal variable. Figures 1a and 1b are mosaic diagrams of three psychiatric pictures and four final diagnoses. In figure 1a horizontal axis stands for psychiatric pictures and vertical axis does final diagnoses. Figure 1b interchanges these two axes. Four factors of the final diagnoses and three factors of the psychiatric pictures showed significant differences ($\chi^2 = 64.828$, $P < 0.0001$). Of 27 patients of group D, 13 were diagnosed as PD, 2 were as DLB, one was as PDD and 11 were as PPP. In contrast, 15 out of 16 patients of Group V were diagnosed as DLB. Correspondence analysis provided 4 combinations of psychiatric picture and final diagnosis shown in figure 2, i.e., PPP and Group D, PD and Group D, DLB and Group V, and PDD and Group P. The H/M ratio among medicated and non-medicated subjects with ANOVA showed no significant difference in early ($p = 0.3991$) and late ($p = 0.5345$).

Fifty six cases out of the 60 cases were examined with cerebral SPECT study. Thirty-seven cases had hypoperfusion lobes and 19 cases showed no abnormality. Their SPECT profiles were shown in two ways; by psychiatric picture (Figure 2a) and by final diagnosis (Figure 2b). Cases with frontal hypoperfusion and with normal perfusion showed depression, and most of Group D patients were diagnosed as PD and PPP. Cases with temporal lobe hypoperfusion showed psychosis and they were

mostly diagnosed as PDD and DLB. Correspondence analysis showed that there were three significant combinations; the temporal lobe hypoperfusion and Group P, the occipital lobe hypoperfusion and Group V, and no hypoperfusion lobe and Group D.

Discussion

In the present study, depression was found in form of either isolated depression or symptomatic depression in which about 40% of the Group D patients were lack of parkinsonism and about 90% of the PD patients were suffering from depression. Isolated visual hallucinations and psychotic symptoms, on the other hand, predominated our DLB and PDD cases. Therefore depression is significantly attributable to PD, and isolated depression is considered to correspond with the PPP. Depression sometimes occurs prior to clinical symptoms of PD and DLB (Lieberman, 2006; Pfeiffer, 2007; Borroni et al., 2008). Clinical course of depression of PD and DLB was studied in a few studies. A one-year follow-up study reported that 20% of DLB patients newly developed depression and two third of them remained depressive after one year (Fritze et al., 2011). Thus, depression can last for at least a few years prior to the onset of PD and DLB, as Lieberman speculated (Lieberman, 2006). Although pathogenesis of the isolated depression of PD and DLB is not known, the present study confirmed the presence of isolated depression in MIBG-verified patients.

The frequency of incidental LBD is similar to that of MIBG-verified patients, and incidental LBD has been frequently reported in patients with late-onset depression in autopsy studies (Ballard et al., 2004; Iritani et al., 2008; Adler et al., 2010; Jellinger and Attems, 2012; Navarro-Otano et al., 2013). Clinicopathological study reported that amounts of alpha-synuclein deposits bore no relationship with Hoehn & Yahr stage in incidental LBD (Dijkstra et al., 2014). The absence of motor disturbance may be due to variable severity of pathological lesions, which suggests that psychosis without motor disturbance can be found in patients with LBD. The PPP presented here is assumed to be incidental LBD, but it is not determined how long the isolated depression continues.

Apathy is one of symptoms of the major depressive disorder and is also a non-motor symptom in LBD. Apathy was shown to predominate in akinetic-rigid form compared with the tremor-dominant form of PD, and motor disturbance was closely correlated with severity of dementia (Alves et al., 2006; Lemke, 2008; Reijnders et al., 2009; Moretti et al., 2012). Thus, apathy should be included into dementia rather than depression. In our study motor disturbance was related with cognitive disturbance. Thus depression of LBD is unrelated to cognitive disturbance. These findings indicate that PPP is independent from motor disability and cognitive disturbance.

In the present SPECT study, localization of hypoperfusion lobes was associated with the psychiatric pictures rather than final diagnose. The occipital lobe hypoperfusion was shown to be representative finding for visual hallucination in DLB (Lobotesis et al., 2001). However DLB shows a diversity of symptoms. On the diagnostic accuracy of DLB, Huang and Halliday (Huang and Halliday, 2013) pointed that supportive features were more sensitive than the central and core features in , in which DLB cases without visual hallucination and consciousness fluctuation might not be correctly

diagnosed. Thus, the psychiatric pictures exert a great influence on diagnostic processes of LBD. As the changes in rCBF were much more remarkable in our PDD and DLB patients than PPP and PD patients, psychosis and dementia may be same in quality. Thus LBD and its preparative have the multitudinous conditions in terms of SPECT abnormality and psychiatric picture. Longitudinal follow-up study is necessary to localize the PPP.

Conclusions

The isolated depression of LBD can be outlined as preparative of PD.

Conflict of interest statement

There is no financial or personal relationship.

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Table 1a

Demographic data of 60 patients by visual hallucination (Group V), depression (Group D) and psychosis (Group P). Average age at onset and age at the first visit were the oldest in the Group D and the highest in the Group V. Average of rCBF value was normal in Group D and low in the Group V and Group P. Similarly average score of MMSE was normal value in Group D. Average MDS-UPDRS III score was graded as Group P > Group V > Group D. The probability value, p, indicates ANOVA. Statistical significance of non-parametric Kruskal-Wallis test was marked with $p < 0.05$ * and $p < 0.001$ **. H/M ratio: heart-to-mediastinum ratio; MMSE: Mini-mental state examination; MDS-UPDRS III: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale Part III; rCBF: regional cerebral blood flow.

Table 1b.

Demographic data of 60 patients by final diagnosis. Average age at onset and age at the first visit were the oldest in the Group D and the highest in the Group V. Average of rCBF was a normal value in Group D and low in the Group V and Group P. Similarly average score of MMSE was normal value in Group D. Average MDS-UPDRS III score was graded as Group P > Group V > Group D. Hoehn-Yahr stage, from 0 to 5, was low in PPP but high in DLB, PD and PDD. The probability value, p, indicates ANOVA. Statistical significance of non-parametric Kruskal-Wallis test was marked with $p < 0.05$ * and $p < 0.001$ **. H/M ratio: heart-to-mediastinum ratio; MMSE: Mini-mental state examination; MDS-UPDRS III: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale Part III; rCBF: regional cerebral blood flow.

Figure 1a shows mosaic diagram of three psychiatric pictures (the horizontal axis) and four final diagnose (the vertical axis). Figure 1b interchanges these two axes. Most patients with PPP and PD were suffering from depression and patients with psychosis corresponded with PDD. Isolated visuals hallucination was contributed to DLB. D: depression as Group D; P: psychosis as Group P; V: visual hallucination as Group V; DLB: dementia of Lewy body; PD: Parkinson's disease; PPP: pure psychiatric presentation of Lewy body disease; PDD: Parkinson's disease with dementia.

Figures 2a and 2b show relationship between hypoperfusion lobe and psychiatric picture (2a) and between hypoperfusion lobe and final diagnosis (2b). Patients with PD and PPP had no hypoperfusion lobe. Patients with DLB and PDD had temporal lobe hypoperfusion. D: depression as Group D; P: psychosis as Group P; V: visual hallucination as Group V; DLB: dementia of Lewy bodies; PD: Parkinson's disease; PPP: pure psychiatric presentation of Lewy body disease; PDD: Parkinson's disease with dementia; T: temporal lobe hypoperfusion; O: occipital lobe hypoperfusion; F: frontal lobe hypoperfusion; None: no hypoperfusion lobe.

Table 1a

Psychiatric pictures	Group V 16 cases	Group D 27 cases	Group P 17 cases
Male / Female	9/7	15/12	8/9
Age at onset (year)	78.6*	67.9**	74.1
Age at the first visit (year)	79.3**	70.1**	75.9
Duration between onset and visit	0.8	2.3	1.9
H/M ratio early	1.4	1.4	1.4
H/M ratio late	1.3	1.2	1.2
MMSE score	21.1	28.0*	19.8
Right rCBF (ml/100g/min)	37.2	40.7*	38.3
Left rCBF (ml/100g/min)	36.8	40.4*	37.8
MDS-UPDRS III	10.6*	5.5*	15.9*
Presence / absence of Parkinsonism	10/6	1/26	13/4
Number of cases corresponding to the Hoehn and Yahr stage 0/1/2/3/4/5	6/8/2/0/0/0	9/17/1/0/0/0	0/7/9/1/0/0

p value
0.8283
0.0001
0.0002
0.0725
0.9881
0.7118
<0.0001
0.0005
0.0009
<0.0001
<0.0001

0.0002

Table 1b

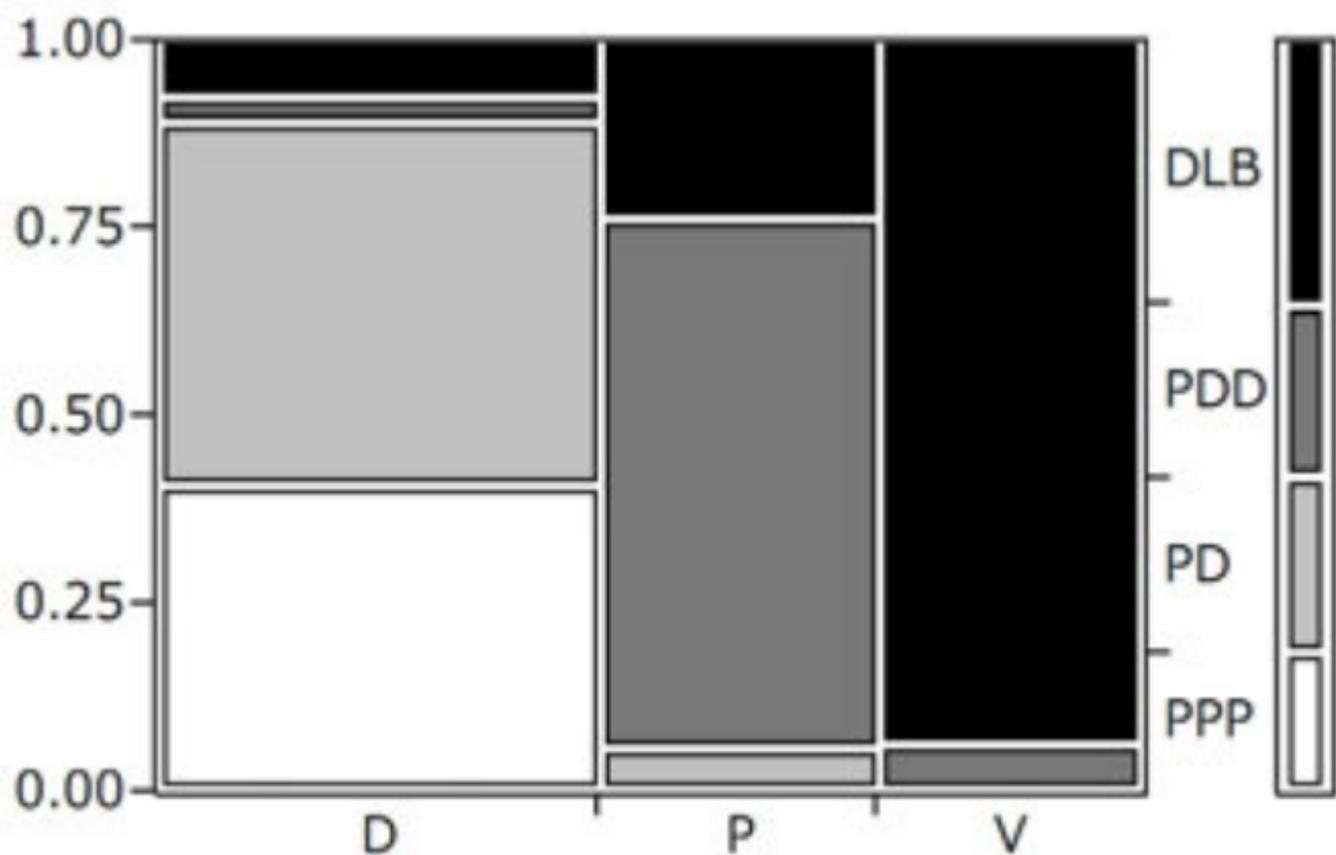
Final diagnosis	DLB 21 cases	PD 14 cases	PDD 14 cases
Male/Female	11/10	10/4	7/7
Age at onset (year)	76.9**	69	74.7
Age at the first visit (year)	77.7	71.6	76.7
Duration between onset and visit	0.8	2.3	2.1
H/M ratio early	1.4	1.5	1.4
H/M ratio late	1.2	1.3	1.3
MMSE score	22	27.1	19.1**
Right rCBF (ml/100g/min)	37.7	40.3	38.2
Left rCBF (ml/100g/min)	37.2	39.9	37.7
MDS-UPDRS III	10.2	6.9	18.4
Presence / absence of Parkinsonism	11/10	14/0	14/0
Number of cases corresponding to the Hoehn and Yahr stage	6/13/2/0/0/0 0/1/2/3/4/5	3/11/0/0/0/0	0/3/10/1/0/0

PPP		最終診断	DLB
11 cases	p value	症例数	21
4/7	0.3524	男/女	11/10
65.2*	0.008	発症年齢	76.9**
67.8*	0.0008	受診年齢	77.7
2.5	0.0818	発症から受診までの年数	0.8
1.4	0.8793	H/M ratio 初期	1.4
1.2	0.5958	H/M ratio 後期	1.2
29.2*	<0.0001	MMSE スコア	22
41.5	0.0026	右大脳血流 (ml/100g/min)	37.7
41.6	0.0015	左大脳血流 (ml/100g/min)	37.2
1.9	<0.0001	MDS-UPDRS III	10.2
0/11	0.0001	パーキンソン症候の有/無	11/10
6/5/0/0/0/0	<0.0001	Hoehn and Yahr stage 0/1/2/3/4/5症 例数	6/13/2/0/0/0

PD	PDD	PPP	p value
14	14	11	
10/4	7/7	4/7	0.3524
69	74.7	65.2*	0.008
71.6	76.7	67.8*	0.0008
2.3	2.1	2.5	0.0818
1.5	1.4	1.4	0.8793
1.3	1.3	1.2	0.5958
27.1	19.1**	29.2*	<0.0001
40.3	38.2	41.5	0.0026
39.9	37.7	41.6	0.0015
6.9	18.4	1.9	<0.0001
14/0	14/0	0/11	0.0001
3/11/0/0/0/0	0/3/10/1/0/0	6/5/0/0/0/0	<0.0001

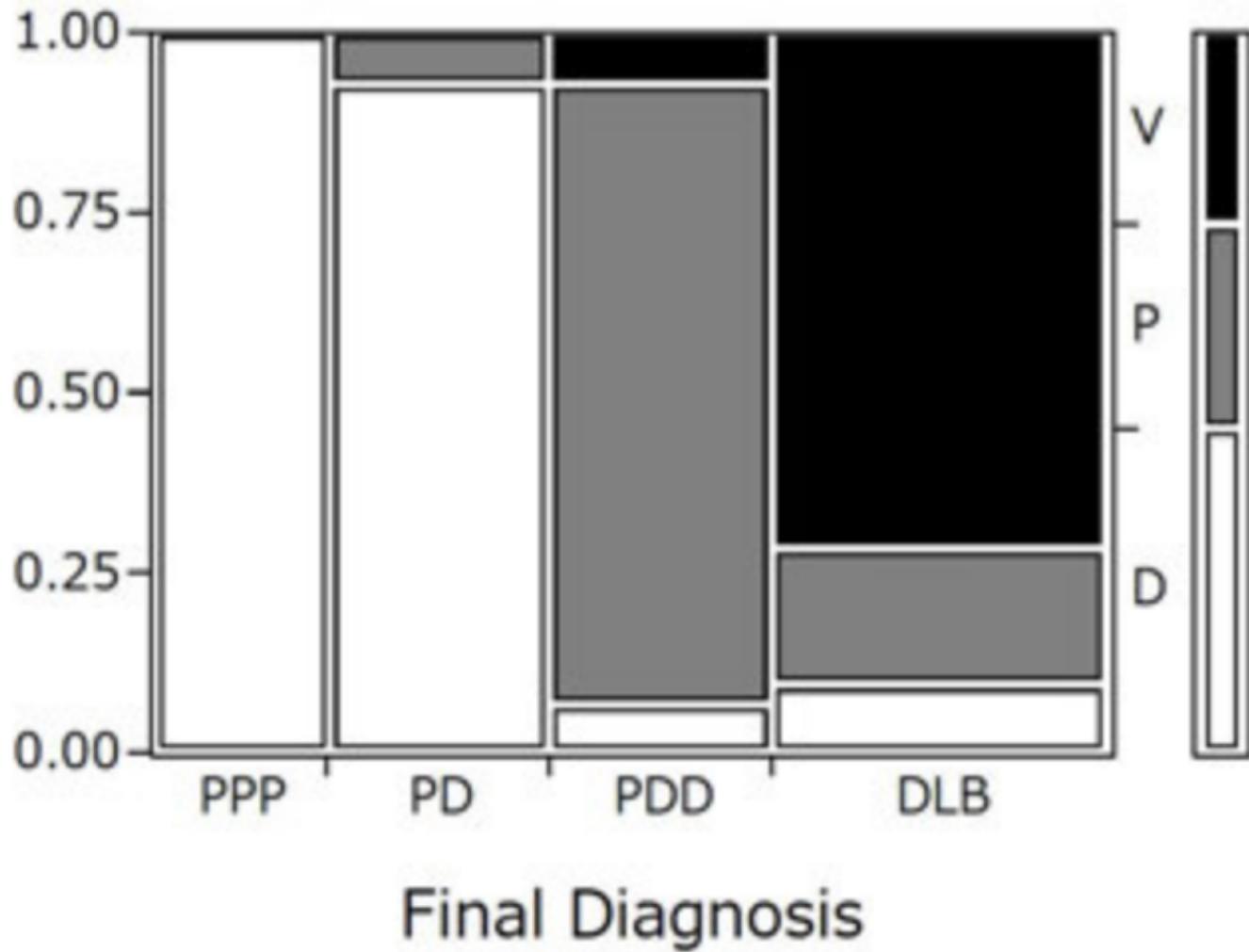
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Final Diagnosis



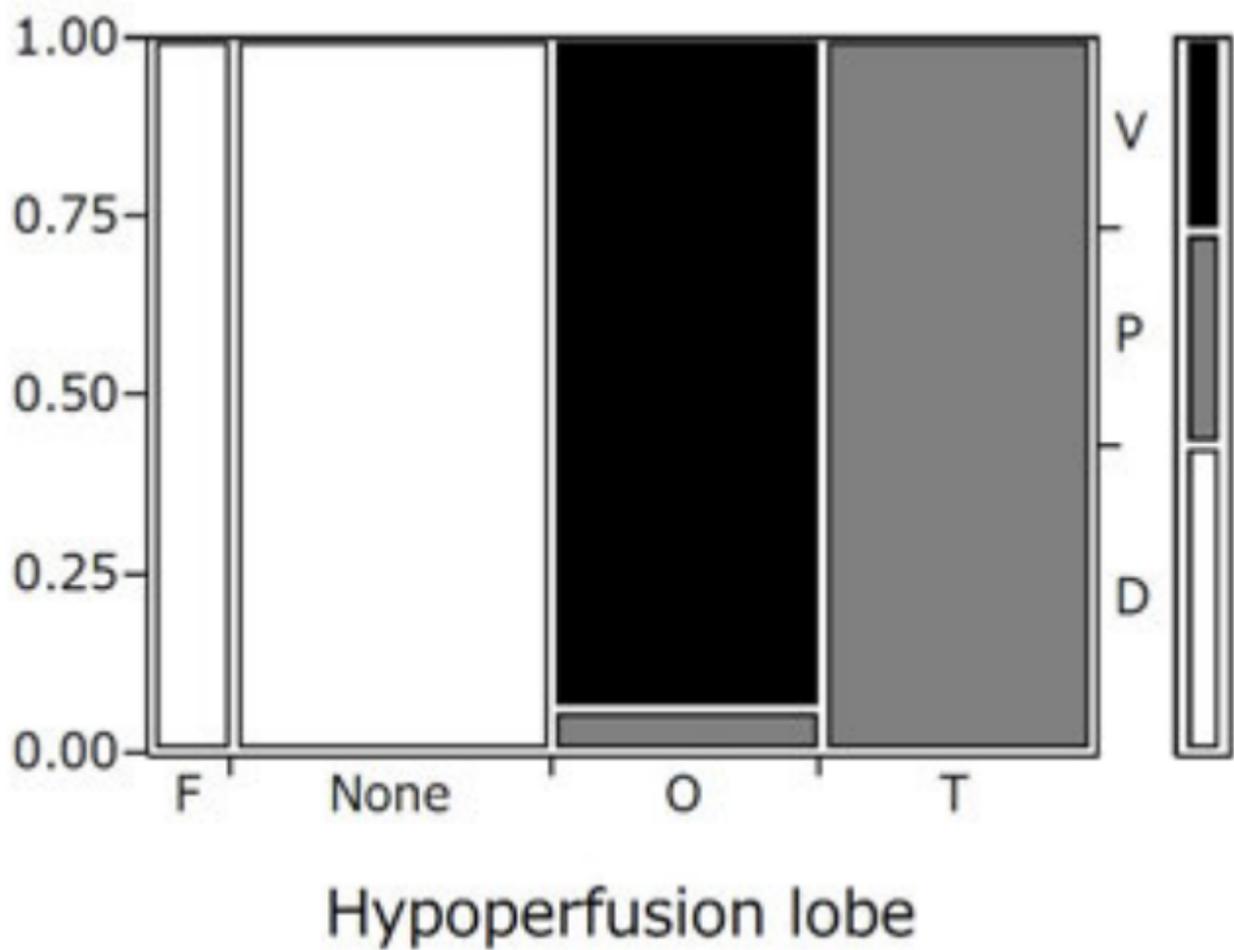
Psychiatric picture

Psychiatric picture



Figures 2a and 2b show relationship between hypoperfusion lobe and psychiatric picture (2a) and between hypoperfusion lobe and final diagnosis (2b). Patients with PD and PPP had no hypoperfusion lobe. Patients with DLB and PDD had temporal lobe hypoperfusion. D: depression as Group D; P: psychosis as Group P; V: visual hallucination as Group V; DLB: dementia of Lewy bodies; PD: Parkinson's disease; PPP: pure psychiatric presentation of Lewy body disease; PDD: Parkinson's disease with dementia; T: temporal lobe hypoperfusion; O: occipital lobe hypoperfusion; F: frontal lobe hypoperfusion; None: no hypoperfusion lobe.

Psychiatric picture



Final Diagnosis

