Parkinsonism and Related Disorders xxx (2015) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: A critical review of the literature

Branislav Veselý [a], Ivan Rektor [b, *]

[a] Department of Neurology, Hospital Nitra, Slovak Republic
[b] Masaryk University, Central European Institute of Technology (CEITEC), Centre of Neuroscience, Brno Czech Republic

ARTICLE INFO

Article history:
Received 28 August 2015
Received in revised form
2 September 2015
Accepted 3 September 2015

Keywords:
White matter lesions
Cerebrovascular disease
Parkinson's disease
Mild cognitive impairment
Dementia

ABSTRACT

We reviewed the impact of white matter lesions (WML) of cerebrovascular origin on cognitive impairment in Parkinson's disease (PD) patients. A search of PUBMED and Googlescholar.com revealed eleven studies that met the inclusion criteria: diagnosis based on the United Kingdom Brain Bank criteria (UK BBC); cognitive assessment; WML assessed on magnetic resonance imaging (MRI) by semiquantitative visual scales or automated method.

Eight studies described the negative impact of WML on cognition in PD. Patients with mild cognitive impairment (MCI) and dementia had significantly more WML than the group without MCI and dementia. There was significant relationship between increasing total WML volume and worse performance on executive function, memory and language. Patients with vascular parkinsonism and dopaminergic denervation had more severe frontal lobe dysfunctions than patients with PD. In contrast in three studies there was no negative correlation between WML and cognition. Although the progression of neurodegenerative process in advanced stage of PD has been recognized as being mainly responsible for cognitive impairment in PD, WML may also be a contributing factor. It is possible that by reducing the vascular risk factors that cause WML cognitive impairment could be prevented or slowed down.

1. Introduction

White matter lesions (WML) contribute to cognitive impairment in the elderly, in Alzheimer's disease (AD) and in vascular dementia. The objective of our review was to assess the impact of WML resulting from cerebrovascular disease (CVD) on cognition in patients with PD. We performed a search in PUBMED and at Googlescholar.com using following key words: vascular pathology and PD; WML and PD; CVD and PD; PD and cognition. The browser identified 2422 articles which were reviewed by titles and by abstracts. The criteria for inclusion in the review were: patients met the UK BBC for PD; had undergone cognitive assessment; underwent an MRI brain scan; WML were assessed by either a semiquantitative visual rating scale [1–3] or automated method [4]. We excluded studies investigating the secondary parkinsonism, Parkinson-plus syndromes and WML from other than a vascular origin. Eleven studies met the inclusion criteria and were reviewed: three case–control, eight cross-sectional from which was one with longitudinal extension. See Table 1 for demographical data and WML assessment and Table 2 for cognitive assessment.

2. Evidence of negative influence of wml on cognitive status of PD patients

Choi et al. reviewed and compared medical records and autopsy findings of 51 patients with PD confirmed by histopathology [5]. The extent of WML of patients with dementia (PDD) was compared with patients without dementia (PDND). The results adjusted for

List of abbreviations: AD, Alzheimer's disease; BFCSR, Buschke Free and Cued Selective Reminding Test-verbal episodic memory test; CC, case control; CS, cross sectional; CVD, cerebrovascular disease; DD, dopaminergic denervation; DSM-IV, criteria for the diagnosis of dementia; HC, healthy controls; LONG, longitudinal; MMSE, mini mental state examination; MOCA, Montreal Cognitive Assessment; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; N-MCI, neurodegenerative mild cognitive impairment; PDND, non-demented patients; PD, Parkinson' disease; PDD, patients with dementia; PLB-MCI, Parkinson-Lewy body mild cognitive impairment; PLBD, Parkinson-Lewy body dementia; SPM, statistical parametric maping; V-MCI, vascular mild cognitive impairment; VD, vascular dementia; VP, vascular parkinsonism; UK BBC, United Kingdom Brain Bank criteria; UPDRS, unified Parkinson's disease rating scale; WML, White Matter Lesions.

* Corresponding author. Pekařská 664/53, 656 91 Brno, Czech Republic.
E-mail addresses: brano.vesely@yahoo.com (B. Veselý), irektor@med.muni.cz (I. Rektor).

http://dx.doi.org/10.1016/j.parkreldis.2015.09.019
1353-8020/

Table 1
Demographic data and WML assessment in reviewed studies.

Authors	Design	Patients	Mean age	MRI	WML assessment
Choi et al., 2010	CS	26 PDD	74.4	X	autopsy
		25 PDND	82.7	X	
Beyer et al., 2006	CC	16 PDD	73.9	1.5 T	Scheltens scale
		20 PDND	71.3		
		20 HC	73.6		
Meyer et al., 2007	CS	52 PD	65.6	1.5 T	automathed volumetric assessment, Wahlund scale
		30 N-MCI	77.2		
		35 V-MCI	72.4		
		8 PLB-MCI	78.75		
		19 AD	78.74		
		17VD	77.47		
		5 PLBD	76.2		
Slawek et al., 2008	CS	17 PD	64.47	1.5 T	Wahlund scale
		25 MCI	68.64		
		18 PDD	71.67		
Dalaker et al., 2009	CC	155 PD	67.5		brain volume-SIENAX
		101 HC	65.6		
Santangelo et al., 2009	CS	12 not demented VP	72.2	1.5 T	Scheltens scale
		12 not demented with VP and DD	71.2		
		12 PD	68.7		
Lee et al., 2010	CS	35 PD	65.2	1.5 T	Scheltens scale
		36 PDD	67.2		
Ng et al., 2010	CS	33 PD with low WML	63.58	3 T	Fazekas's scale
		33 PD with high WML	66.64		
Gonzalez-Redondo et al., 2012	CS	39 PD	68	1.5 T	Scheltens scale
	LONG	46 PD with MCI	72		
		26 PDD	74		
Slawek et al., 2013	CC	135 PDND	63.7	1.5 T	Wahlund,Scheltens
		57 PDD	63.7		
		184 HC	65.35		
Kandiah et al., 2013	CS	24 PD with MCI	68.99	3 T	SPM
		67 PD without MCI	63.34		

AD- Alzheimer's disease, CC- case control, CS- cross sectional, DD-dopaminergic denervation, HC- healthy controls, LONG-longitudiinal, MCI-mild cognitive impairment, N-MCI neurodegenerative mild cognitive impairment, PDND-non–demented patients, PD- Parkinson' disease, PDD-patients with dementia, PLB- MCI Parkinson-Lewy body mild cognitive impairment, PLBD- Parkinson-Lewy body dementia, SPM, statistical parametric maping, -MCI vascular mild cognitive impairment, VD — vascular dementia, VP-vascular parkinsonism.

age at onset of PD, age at death, and duration of PD, showed greater WML burden in PDD. It was not clear whether other causes of dementia were excluded and the duration of dementia was taken into account. Beyer et al. compared patients with PDD, PDND and healthy controls (HC), the PDD group had significantly more WML in deep white matter and periventricular areas than the PDND group. Deep WML was significantly associated with a lower mini mental state examination (MMSE) score. On the other hand PDND patients had significantly less WML than HC [6]. The cohort of patients was small; the patients were assessed only by MMSE instead of complex battery of neuropsychological tests. A merit of this study was case control design and fact that the diagnosis of PD was confirmed at autopsy in 22 patients. In Meyer et al.'s study MRI assessment correlated with cognitive status in seven groups of patients with: normal cognition, neurodegenerative MCI (N-MCI), vascular MCI (V-MCI), Parkinson-Lewy Body MCI (PLB-MCI), AD, vascular dementia (VD), Parkinson-Lewy body dementia (PLBD). PLB-MCI and PLBD subjects displayed less severe white matter lesions compared to the V-MCI and VD groups. When divided into two subgroups according to the presence or absence of vascular risk factors, the results showed that PLB-MCI with vascular risk factors displayed significantly more extensive subcortical WML and basal ganglia lacunar infarcts and greater bilateral frontal horn enlargement than those without vascular risk factors [7]. A limitation was the small number of patients in the PLB-MCI and dementia groups and that patients did not undergo comprehensive neuropsychological testing (see in Table 2). Santangelo et al. studied patients with parkinsonism without dementia who were divided into 3 groups; with pure vascular parkinsonism (VP), VP and dopaminergic denervation and PD. They tested executive functions and memory. The results showed that patients with VP and VP plus dopaminergic denervation had more severe frontal lobe dysfunction as assessed by means of verbal fluency tasks than patients with PD. Impairment of frontal lobe functions including cognitive flexibility, selective attention and logical abstract thinking was more severe in patients with VP plus dopaminergic denervation than with PD. The patients underwent comprehensive neuropsychological testing. The numbers of patients in each cohort were small [8]. Lee et al. showed that patients with PDND had less extensive WML in the supratentorial regions than patients with PDD. The association between WML burden and cognitive impairment remained significant even after correction for age and duration of PD [9]. Ng et al. showed that PD patients with a higher burden of WML had lower cognitive scores, particularly for executive functions. Periventricular WML appeared adversely to influence cognition in PD [10]. Slawek et al. explored the role of cortical, subcortical and basal ganglia WML and hippocampal atrophy in PDD, in relation to vascular risk factors and homocysteine blood levels in particular. The WML and hippocampal atrophy were more advanced in the PDD group than in the PDND group [11]. Kandiah et al. compared early stage PD patients with MCI and patients with PD without MCI with respect to total volume and distribution of WML [12]. PD-MCI patients had significantly higher total WML volume, periventricular WML and deep subcortical WML compared to PD patients with no MCI. PD-MCI patients had significantly greater WML load in the frontal, parietal and occipital regions. Total WML, periventricular WML and deep subcortical WML remained significantly higher in the PD-MCI group after correction for age

Please cite this article in press as: B. Veselý, I. Rektor, The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: A critical review of the literature, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.019

Table 2
PD and cognitive assessment used in reviewed studies.

Assessment/author	Beyer et al., 2006	Meyer et al., 2007	Slawek et al., 2008	Dalaker et al., 2009	Santangelo et al., 2009	Lee et al., 2010	Ng et al., 2010	Gonzalez-Redondo et al., 2012	Slawek et al., 2013	Kandiah et al., 2013	Choi et al., 2010
PD assessment											UK BBC
UPDRS total	X		X	X		X	X	X	X		
Hoehn- Yahr	X		X	X	X		X	X	X		
Schwab-England			X						X		
UPDRS III					X						
Cognitive assessment											DSM IV
MMSE	X	X	X	X		X	X	X	X	X	criteria for
10-point clock drawing test					X					X	dementia
20 point naming test										X	
Activity of daily living											
Auditory verbal learning test			X								
Benton Visual Retention									X		
BFCSR								X			
Blessed dementia scale								X			
Boston naming test								X			
California verbal learning test				X							
Cognitive Capacity Screening Examination		X									
Colour trails 2										X	
Digit span							X			X	
Figure copy test											
Frontal Assessment Battery					X		X			X	
Hamilton Depresion Rating Scale		X			X						
Interview for Deterioration in Daily Living in Dementia								X		X	
Maze test											
MOCA							X			X	
Montogomery-Asberg Scale				X							
Raven progresive matrices					X			X			
Rey auditory 15-word learning test					X						
Rey–Osterrieth Complex Figure Test					X				X		
Stroop test				X				X			
Trail Making Test					X						
Visual Object and Space Perception Batery				X							
Wechsler-Bellevue scale									X		
Wisconsin Card Sorting Test			X		X				X		
Yesavage Geriatric Depresion Scale								X			

BFCSR- Buschke Free and Cued Selective Reminding Test-verbal episodic memory test, DSM-IV criteria for the diagnosis of dementia, MMSE-mini mental state examination, MOCA- Montreal Cognitive Assessment, UPDRS- unified Parkinson's disease rating scale.

and vascular risk factors (diabetes mellitus, arterial hypertension, hyperlipedemia, smoking). There was a significant relationship between an increase in WML volume and lower performance in executive function, memory and language: This significance persisted after correction for age, education and vascular risk factors. A limitation of the study was that the majority of study patients were in the early stages of PD. A strength was that the study used an automated method to quantify the WML on a 3 T MRI machine that is more accurate than semiquantitative visual scales; on the other hand it is difficult to compare this study with those in which examiners used visual scales.

3. Evidence againts the negative influence of wml on cognitive status of PD patients

Slawek et al assessed PD patients using comprehensive neuropsychological testing and according to the results they were divided into 3 groups; normal cognitive status, MCI and with dementia [13]. Some of the test results showed that there was no significant difference between the three groups and the burden of WML on Wahlund scale [3]. Dalaker et al. assessed WML and global brain atrophy and the relationship of cognitive status in patients with PD-MCI and PDD, compared to HC [14]. There were no significant differences between PD and controls in whole brain atrophy, total WML volume, regional WML distribution, spatial distribution of WML. None of the MRI variables was retained as a significant predictor of global or specific cognitive domain functions (attention-executive, memory, and visuospatial). The strengths of this study were the large cohort of patients, case control design and recruitment of newly diagnosed treatment naive patients. In González-Redondo'et al. cross-sectional study with 111 patients and a longitudinal study with 36 patients from the same cohort, patients were divided in groups as did Slaweks et al. [13]. Vascular risk factors were equally present in all groups. In the cross-sectional arm there were no significant differences in Schelten's score among the groups [2]. The relationship between the subscores for the distinct lobar regions (frontal, temporal, and parieto-occipital) and the neuropsychological test scores derived from testing each cognitive domain was assessed by nonparametric correlations. There was a negative correlation between semantic fluency and frontal WML burden. In the longitudinal arm 36 patients were assessed from 12 to 48 months after the base-line evaluation, there was no association between the progression of WML on MRI and progression to a higher category of cognitive

Please cite this article in press as: B. Veselý, I. Rektor, The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: A critical review of the literature, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.019

impairment (from normal to MCI, and from MCI to dementia) [15]. However follow-up cohort was small so that these results should be interpreted with caution.

4. Discussion

Eight studies supported the negative impact of WML due to CVD on cognitive symptoms in PD [5–12]; three studies did not [13–15]. WML has also been associated with postural impairment and gait disorder (PIGD) in PD (nine studies were reviewed by Veselý et al., submitted). Kelly's cross-sectional study of 783 PD patients showed that deficits in global cognition were associated with more severe PIGD. Deficits in executive function were associated with impairments of gait, freezing, and postural instability; visuospatial deficits were associated with freezing, and poorer memory function was associated with greater postural instability [16]. Cognitive decline in PD is considered to be a continuous process driven by deposition and accumulation of limbic and neocortical Lewy body pathology [17], and possibly also neurofibrillary tangles and senile plaques [18]. Loss of neurotransmitters, in particular dopamine and acetylcholine [19], due to Lewy and Alzheimer type pathologies [17] was described as possibly contributing to cognitive impairment. It is not clear to what extent progression of PD pathology to cortical regions according to Braak et al. [20] and to what extent AD pathology contributes to cognitive decline [21]. WML due to CVD might aggravate the already defective neuronal connectivity and therefore increase cognitive dysfunction. WML in the deep white matter of the frontal lobe may cause dysfunction of frontostriatal circuits and contribute to executive dysfunction [22]. WML might also affect connections important for attention and working memory [23]. The exact mechanism by which vascular pathology contributes to impairment in cognitive functions in PD is putative. Two mechanisms are possible. There may be an additive effect of two independent but convergent disease processes, neurodegenerative and vascular. This possibility cannot be excluded, but an argument against is the absence of significant CVD in many PD patients. The alternative and more probable mechanism is a synergic effect of both conditions, a deleterious effect of an otherwise subclinical hypoperfusion on regions made vulnerable by the degenerative process [24,25]. The impairment of brain vessels was identified as a factor contributing to mortality in PD [25]. A relation between impairment of brain vessels and cognitive impairment in PD was demonstrated in one of our earlier studies [24]. Guan performed a histopathological case–control study of PD brain [26]. The results showed vessel degeneration in multiple brain regions. When compared to controls, the capillaries in PD were fewer in number, shorter in length, larger in diameter with damaged capillary network with less branching and lost capillary connection. These data suggest that vessel degeneration in PD was primarily at the level of capillaries, which may themselves be more vulnerable to degeneration than the small arteries or veins. WML as a result of repeated hypoxic and ischeamic episodes due to CVD may lead to an inflammatory response which induces proteases and to the generation of free radicals and consequent myelin breakdown [27]. On the other hand the relationship between cognitive functions in PD and WML are complex, for example in the Scigliano's study with no evidence of CVD contribution to PD related dementia [28]. It was proposed that levodopa-derived dopamine modulates sympathetic overactivity. This may lead to reduction of blood pressure and may counter-balance the role of hyperhomocysteinaemia due to levodopa therapy. The authors concluded that autonomic hyperactivity may be involved in the pathogenesis of vascular disorders, and levodopa therapy may be protective. Although the progression of neurodegenerative process in advanced PD has been recognized as primarily responsible for cognitive impairment in PD,WML may also be a contributing factor. In a longitudinal study, WML was demonstrated to be a factor determining the progression of cognitive impairment in PD in addition to hippocampal volume [29].

The contradictory results of reviewed studies might be due to differences in the methods of assessing WML on MRI [1–4] as well as using different MRI machines (1.5 T and 3 T magnet). It appears that WML is not a unitary phenomenon. The pathological substrates of WML, e.g. the lacunes and microbleeds, as well as the spatial distribution of WML should be further investigated [30]. Difference in assessments of cogniton is another important factor.

It is probable that by reducing the vascular risk factors that cause WML cognitive impairment could be prevented or slowed down. The hypothesis of negative impact of WML on cognition was confirmed in eight studies however further confirmation by longitudinal studies with sufficient number of patients, using high-field MR and comprehensive battery of neuropsychological tests is needed. The contribution of vascular risk factors to cognitive impairment may be more important in the stage of MCI rather than dementia. There is a need for clinicians to screen for and treat vascular risk factors among their PD patients. As recommended by Kandiah et al. [12], clinicians should perform cognitive screening regularly for their PD patients with coexistingWML in order to detect and intervene at the earliest phase of cognitive impairment.

Acknowledgments

This work was supported by the “CEITEC – Central European Institute of Technology” project (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund.

References

[1] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MRI signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (1987) 351–356.
[2] P. Scheltens, F. Barkhof, D. Leys, J.P. Pruvo, J.J. Nauta, P. Vermersch, M. Steinling, J. Valk, A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging, J. Neurol. Sci. 114 (1993) 7–12.
[3] L.O. Wahlund, F. Barkhof, F. Fazekas, L. Bronge, M. Augustin, M. Sjogren, A. Wallin, H. Ader, D. Leys, L. Pantoni, F. Pasquier, T. Erkinjuntti, P. Scheltens, European task force on age-related white matter changes. A new rating scale for age-related white matter changes applicable to MRI and CT, Stroke 32 (2001) 1318–1322.
[4] R. de Boer, H.A. Vrooman, F. van der Lijn, M.W. Vernooij, M.A. Ikram, A. van der Lugt, M.M. Breteler, W.J. Niessen, White matter lesion extension to automatic brain tissue segmentation on MRI, Neuroimage 45 (2009) 1151–1161.
[5] S.A. Choi, V.G. Evidente, J.N. Caviness, H.A. Shill, M.N. Sabbagh, D.J. Connor, J.G. Hentz, C.H. Adler, T.G. Beah, Are there differences in cerebral white matter lesion burdens between Parkinson's disease patients with or without dementia? Acta Neuropathol. 119 (2010) 147–149.
[6] M.K. Beyer, D. Aarsland, O.J. Greve, J.P. Larsen, Visual rating of white matter hyperintensities in Parkinson's disease, Mov. Disord. 21 (2006) 223–229.
[7] J.S. Meyer, J. Huang, M.H. Chowdhury, MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias, J. Neurol. Sci. 257 (2007) 97–104.
[8] G. Santangelo, C. Vitale, L. Trojano, D. De Gaspari, L. Bilo, A. Antonini, P. Barone, Differential neuropsychological profiles in Parkinsonian patients with or without vascular lesions, Mov. Disord. 25 (2010) 50–56.
[9] S.J. Lee, J.S. Kim, J.Y. Yoo, I.U. Song, B.S. Kim, S.L. Jung, D.W. Yang, Y.I. Kim, D.S. Jeong, K.S. Lee, Influence of white matter hyperintensities on the cognition of patients with Parkinson disease, Alzheimer Dis. Assoc. Disord. 24 (2010) 227–233.
[10] A. Ng, I. Chew, K.Y. Tay, W.L. Au, L. Tan, N. Kandiah, White matter disease adversely influences cognition in idiopathic Parkinson's disease, Alzheimer's Dementia 8 (2012) 171–172.
[11] J. Sławek, A. Roszmann, P. Robowski, M. Dubaniewicz, E.J. Sitek, K. Honczarenko, A. Gorzkowska, S. Budrewicz, M. Mak, M. Golab-Janowska, E. Koziorowska-Gawron, M. Drozdik, M. Kurzawski, T. Bandurski, M. Bialecka, The impact of MRI white matter hyperintensities on dementia in Parkinson's disease in relation to the homocysteine level and other vascular risk factors, Neurodegener. Dis. 12 (1) (2013) 1–12.
[12] N. Kandiah, E. Mak, A. Ng, S. Huang, W.L. Au, Y.Y. Sitoh, L.C. Tan, Cerebral white matter hyperintensity in Parkinson's disease: a major risk factor for

Please cite this article in press as: B. Veselý, I. Rektor, The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: A critical review of the literature, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.019

mild cognitive impairment, Park. Relat. Disord. 19 (2013) 680–683.
[13] J. Sławek, D. Wieczorek, M. Derejko, M. Dubaniewicz, B. Brockhuis, E. Sitek, L. Wilczewska, A. Roszmann, P. Lass, The influence of vascular risk factors and white matter hyperintensities on the degree of cognitive impairment in Parkinson's disease, Neurol. Neurochir. Pol. 42 (2008) 505–512.
[14] T.O. Dalaker, J.P. Larsen, M.G. Dwyer, D. Aarsland, M.K. Beyer, G. Alves, K. Bronnick, O.B. Tysnes, R. Zivadinov, White matter hyperintensities do not impact cognitive function in patients with newly diagnosed Parkinson's disease, Neuroimage 47 (2009) 2083–2089.
[15] R. González-Redondo, J. Toledo, P. Clavero, I. Lamet, D. Garcia-Garcia, R. Garcia-Eulate, P. Martinez-Lage, M.C. Rodriguez-Oroz, The impact of silent vascular brain burden in cognitive impairment in Parkinson's disease, Eur. J. Neurol. 19 (2012) 1100–1107.
[16] V.E. Kelly, C.O. Johnson, E.L. McGough, A. Shumway-Cook, F.B. Horak, K.A. Chung, A.J. Espay, F.J. Revilla, J. Devoto, C. Wood-Siverio, S.A. Factor, B. Cholerton, K.L. Edwards, A.L. Peterson, J.F. Quinn, T.J. Montine, C.P. Zabetian, J.B. Leverenz, Association of cognitive domains with postural instability/gait disturbance in Parkinson's disease, Park. Relat. Disord. 21 (2015) 692–697.
[17] D. Aarsland, R. Perry, A. Brown, J.P. Larsen, C. Ballard, Neuropathology of dementia in Parkinson's disease: a prospective, community- based study, Ann. Neurol. 58 (2005) 773–776.
[18] K.A. Jellinger, The morphological basis of mental dysfunction in Parkinson's disease, J. Neurol. Sci. 248 (2006) 167–172.
[19] N.I. Bohnen, K.A. Frey, Imaging of cholinergic and monoaminergic neurochemical changes in neurodegenerative disorders, Mol. Imaging Biol. 9 (2007) 243–257.
[20] H. Braak, K. Del Tredici, U. Rüb, R.A. de Vos, E.N. Jansen Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2003) 197–211.
[21] K.A. Jellinger, K. Seppi, G.K. Wenning, W. Poewe, Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease, J. Neural Transm. 109 (2002) 329–339.
[22] R.J. Theilmann, J.D. Reed, D.D. Song, M.X. Huang, R.R. Lee, I. Litvan, D.L. Harrington, White-matter changes correlate with cognitive functioning in Parkinson's disease, Front. Neurol. 4 (2013) 1–8.
[23] R. Au, J.M. Massaro, P.A. Wolf, M.E. Young, A. Beiser, S. Seshadri, R.B. D'Agostino, C. DeCarli, Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study, Arch. Neurol. 63 (2006) 246–250.
[24] I. Rektor, D. Goldemund, K. Sheardová, I. Rektorová, Z. Michálková, M. Dufek, Vascular pathology in patients with idiopathic Parkinson's disease, Park. Relat. Disord. 15 (2009) 24–29.
[25] I. Rektor, D. Goldemund, P. Bednařík, K. Sheardová, Z. Michálková, S. Telecká, M. Dufek, I. Rektorová, Impairment of brain vessels may contribute to mortality in patients with Parkinson's disease, Mov. Disord. 27 (2012) 1169–1172.
[26] J. Guan, D. Pavlovic, N. Dalkie, H.J. Waldvogel, S.J. O'Carroll, C.R. Green, L.F. Nicholson, Vascular degeneration in Parkinson's disease, Brain Pathol. 23 (2013) 154–164.
[27] G.A. Rosenberg, M. Bjerke, A. Wallin, Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment, Stroke 45 (2014) 1531–1538.
[28] G. Scigliano, M. Musicco, P. Soliveri, I. Piccolo, G. Ronchetti, F. Girotti, Reduced risk factors for vascular disorders in Parkinson disease patients: a case control study, Stroke 37 (2006) 1184–1188.
[29] N. Kandiah, K. Hani Zainal N,Narasimhalu, R.J. Chander, A. Ng, E. Mak, Y.Y. Au WL,Sitoh, N. Nadkarni, L.C.S. Tan, Hippocampal volume and white matter disease in the prediction of dementia in Parkinson's disease, Park. Relat. Disord. 20 (2014) 1203–1208.
[30] A.A. Gouw, A. Seewann, W.M. van der Flier, F. Barkhof, A.M. Rozemuller, P. Scheltens, J.J. Geurts, Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations, J. Neurol. Neurosurg. Psychiatry 82 (2) (2011) 126–135.

Please cite this article in press as: B. Veselý, I. Rektor, The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: A critical review of the literature, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.019