EDELWEISS PUBLICATIONS
OPEN ACCESS

https://doi.org/10.33805/2641-8991.120
Volume 2 Issue 1 | PDF 120 | Pages 5

Neurophysiology and Rehabilitation

Research Article ISSN: 2641-8991

Double Hit Theory for the Development of Vascular Parkinsonism

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Citation: Manosalva HA. Double hit theory for the development of Vascular Parkinsonism (2019) Neurophysio and Rehab 2: 42-46

Received: Mar 8, 2019
Accepted: Jun 10, 2019
Published: Jun 15, 2019

Abstract

Introduction: Identify the non-decoded network in Vascular Parkinsonism (VasP).

Objective: To determine what pattern of stroke lesions is responsible for VasP, as compared to those patients who had stroke, gait and balance problems, but absence of a hypokinetic rigid syndrome also called Vascular Pseudo Parkinsonism-V PSeuP.

Materials and Methods: Design: prospective cohort study. Participants were consecutively screened for parkinsonian symptoms during a year as according to our previous study. Validated questionnaire (Tanner Questionnaire-TQ) was used, and a new scale operationalizing the criteria for VasP (FMAS score). All participants in the original study had a clinical exam to identify if presence of a hypokinetic rigid syndrome. Lesion patterns were analyzed. Setting: tertiary care stroke prevention clinic at the University of Alberta Hospital. Participants: Eligible participants attained a score of ≥ 4 on the TQ, high risk for parkinsonism. Four groups were considered: V PseuP, VasP (onset of parkinsonism within a year of the stroke -FMAS score of 4), Pseudo Vascular Parkinsonism-PseuVP (hypokinetic rigid syndrome not related to stroke), and Pseudo Vascular Pseudo Parkinsonism-PseuV PseuP (no stroke and no extrapyramidal syndrome), but with gait and balance problems. Baseline demographic information and clinical characteristics were recorded including vascular risk factors, and stroke subtype. All participants had a Holter, CT head and/or brain MRI, and CTA. Medications that produce drug-induced-parkinsonism were recorded for every participant. The primary outcome was to find the pattern of anatomical lesions particularly involved in the VasP subgroup considering the Basal Ganglia Motor Output Circuit-BGMO, the Thalamo Cortical Drive Loop-TCD and connections to frontal cortex.

Results: 240 consecutive participants were screened during 12 months. We found 46 patients with potential Parkinsonism (TQ>4). VPseuP was found in 25/46 (54%), VasP in 8/46 (17%), PseuVP in 7/46 (15%), and PseuV PseuP in 6/46 (14%). VasP were older (p<0.0007) and had a higher risk for cardio embolism due to atrial fibrillation (p=0.02, odd ratio 6.6 CI 95% (1.2 – 35.2)). Neuro images showed that only the pattern involving the BGMO and frontal cortex was significantly associated to the group of VasP (X2 Fisher exact test p<0.0005 Odds ratio 32 CI 95% (9.6-108)); whereas the pattern TCD was not significantly different between the groups (X2 Fisher exact test p=0.828 Odds ratio 1.2 CI 95% (0.5-2.8)).

Discussion and Conclusion: A two strategic location hit within the BGMO circuit and frontal cortex is required, so a phenotype of VasP may occur.

Keywords: Pathophysiology, Vascular Parkinsonism, Vascular pseudo parkinsonism, Gait and balance problems, Neuroimaging, Basal ganglia network in Parkinsonian disorders.

Abbreviations: TQ-Tanner Questionnaire, VasP-Vascular Parkinsonism, V PSeuP-Vascular Pseudo Parkinsonism, PseuV PseuP-Pseudo Vascular Pseudo Parkinsonism, BGMO-Basal Ganglia Motor Output Circuit, TCD-Thalamo Cortical Drive Loop, STN-Subthalamic Nucleus.

Question: What pattern of stroke lesions is seen in patients with stroke who develop a vascular parkinsonism that is not found in patients with stroke who had gait and balance problems, but not a hypokinetic rigid syndrome (vascular pseudo parkinsonism) ?

Findings: Lesions involving the basal ganglia motor output circuit (lenticular nucleus and frontal cortex) were predominantly seen in patients with VasP (p<0.0005). Lesions in the thalamo cortical drive circuit (thalamus and frontal lobes) were not different between the groups (p=0.8)

Meaning: A double location hit in the basal ganglia (lenticular nucleus) and frontal lobe is required to develop a phenotype of vascular parkinsonism.

Introduction

Critchley described an "atherosclerotic parkinsonism" in patients with multiple strokes, gait and balance problems and cognitive decline [1]. Subsequently Yamanouchi described diffuse white matter lesions in the frontal lobes [2]. On 1989 FitzGerald and Jankovic utilized the term "lower body parkinsonism" noticing that the parkinsonian feature was more prominent in the lower limbs [3].

Zijlman and colleagues [4] identified based on autopsies pathological lesions that increased the Basal Ganglia Motor Output (BGMO) including substantia nigra and lenticular nucleus, and lesions that decreased the Thalamo Cortical Drive (TCD) involving the ventro lateral area of the thalamus and frontal lobes. Recently, Viscarra and colleagues have arguments against the previously defined syndrome, referring to the low probability that strokes may present as true Parkinsonism, and proposed 3 types of phenotypes. These phenotypes may differ according to presence or not of Parkinsonism on the clinical exam, and presence or absence of stroke. All these patients may present with gait and balance problems. Additionally, they schematized the clinical manifestations and differentiated the affected brain areas with patterns [5].

We had the hypothesis that the pattern of ischemic lesions and network might be different between those participants with Parkinsonism onset within 1 year from stroke(s) (VasP) versus those with stroke and gait and balance problems, but who never developed a hypokinetic rigid syndrome (V PseuP).

Materials and Methods

This study follows up our previous group of patients with stroke screened in a tertiary care stroke prevention clinic in Alberta. All participants in the original study had a clinical exam to identify if presence of a hypokinetic rigid syndrome. Further details about that first study may be found elsewhere [6]. We selected from that database those patients at high risk for Parkinsonism defined as those with high Tanner Questionnaire-TQ score (a screening validated questionnaire for the identification of participants with Parkinsonism) that had a cut off score of ≥ 4 which gave the highest sensitivity and specificity of this test, as confirmed in ours and other previous studies **(Table 1).**

Please answer the following questions by circling the correct response:			
1	Do you have trouble arising from a chair?	YES	NO
2	Is your hand writing smaller than it once was?	YES	NO
3	Do people tell you that your voice is softer than it once was?	YES	NO
4	Is your balance, when walking poor?	YES	NO
5	Do your feet suddenly seem to freeze in door-ways?	YES	NO
6	Does your face seem less expressive than it used to?	YES	NO
7	Do your arms and legs shake?	YES	NO
8	Do you have trouble buttoning buttons?	YES	NO
9	Do you shuffle your feet and take tiny steps when you walk?	YES	NO
Screening Questionnaire: instrument for possible detection of Parkinsonism.			

Table1: Tanner Questionnaire: Screening Questionnaire.

All participants were screened in our original study with a new scale operationalizing the most recent criteria for Vascular Parkinsonism the FMAS score [6] **(Table 2)**. It consisted of item 1 and 2 corresponding to clinical criteria for diagnosing and hypokinetic rigid syndrome, item 3 which considered a stroke(s) confirmed by neuroimaging in the locations and network proposed by Zijlman to be associated with onset of VasP. Item 4 correlated in time the onset of Parkinsonism with the occurrence of the stroke(s) symptoms. A score of 2 would be able to identify participants with Parkinsonism on clinical exam, and a score of 4 was necessary to consider a clinical diagnosis of VasP [6].

1	Parkinsonism	
a. Bradykinesia (Not due to Paresis)		YES_NO_ (1 point)
b. Rest tremor or rigidity or postural instability		YES_NO_ (1 point)
2	Stroke or cerebrovascular disease	YES_NO_ (1 point)
3	Parkinsonism onset within 1 year of the Stroke or cerebrovascular disease with bilateral onset of Parkinsonism and early Shuffling Gait	YES_NO_ (1 point)
FMAS SCORE: Diagnosis of Vascular Parkinsonism is attained with a total score of 4 points.		

Table 2: Five Minute Assessment Scale (FMAS).

The selection criteria for the prospective cohort of participants in this study were patients attaining a TQ score ≥ 4 from our previous original study. We classified the participants in four groups, according to presence or absence of Parkinsonism on clinical exam, and presence of stroke and relationship between the onset of Parkinsonism and the occurrence of the stroke **(Table 3)**. First subgroup: Pseudo Vascular Parkinsonism (PseuV P) in which patients may have parkinsonism, but there is no evidence of stroke in the neuroimaging or the location of the stroke and timing of the lesion does not explain the clinical picture of parkinsonism; the second subgroup or phenotype is Vascular Pseudo Parkinsonism (V PseuP) in which patients may have acute symptoms related to stroke and the ischemic lesion is confirmed by neuroimaging. These participants may present with gait and balance problems, but on clinical exam there is no evidence of a hypokinetic rigid syndrome. The third phenotype is Pseudo Vascular Pseudo Parkinsonism (PseuV PseuP) in which patients neither have acute symptoms related to stroke and no cerebrovascular event is seen on neuroimaging, or do they have and hypokinetic rigid syndrome on the exam. However, these patients may have gait and balance problems. Finally the subgroup with VasP in which the onset of Parkinsonism was present within 1 year from the stroke(s) occurrence.

Phenotype	**Stroke**	**Hypokinetic rigid syndrome**	**Onset of parkinsonism within 1 year from stroke (s)**	**Gait and balance problems**
Vascular Parkinsonism **VasP**	YES	YES	YES	YES
Vascular Pseudo Parkinsonism **V PseuP**	YES	NO	N/A	YES
Pseudo Vascular Parkinsonism **PseuV P**	YES or NO	YES	NO	YES
Pseudo Vascular Pseudo Parkinsonism **PseuV PseuP**	NO	NO	N/A	YES

Table 3: Different phenotypes found in stroke patients with gait and balance problems TQ ≥ 4.

Pseudo Vascular Parkinsonism (PseuVP) in which patients may have parkinsonism, but there is no evidence of stroke in the neuroimaging or the location of the stroke and timing of the lesion does not explain the clinical picture of parkinsonism; the second phenotype is Vascular Pseudo Parkinsonism (VPseuP) in which patients may have acute symptoms related to stroke and confirmed by neuroimaging with gait and balance problems, but on exam there is no evidence of a hypokinetic rigid syndrome. The third phenotype is Pseudo Vascular Pseudo Parkinsonism (PseuVPseuP) in which patients neither have acute symptoms related to stroke and no cerebrovascular event is seen on neuroimaging, or do they have and hypokinetic rigid syndrome on the exam. However, these patients may have gait and balance problems.

The study was approved by the Human Research Ethics Committee of the University of Alberta, and informed consent was obtained from all participants attending to the stroke prevention clinic.

Demographic information was obtained from all participants, and the subtype of stroke was assigned according to the TOAST classification [7] **(Table 4)**. All participants had a Holter, echo, CT head or brain MRI, and CTA. Neuroimaging were reviewed by a senior fellow in movement disorders. Images were reported initially by neuroradiology y unaware of the different subgroups in the study. Data was extracted from our previous study [6]. Stroke lesions were topographically identified, and patterns were analyzed including the BGMO, the TCD, and frontal cortex.

1	Large-artery artherosclerosis
2	Cardioembolism
3	Small-vessel occlusion
4	Stroke of other determined etiology
5	Stroke of undetermined etiology a. Two or more causes identified b. Negative evaluation c. Incomplete evaluation

Table 4: Subtypes of ischemic stroke-TOAST classification.

Sample size was calculated based on prevalence of Vascular Parkinsonism found previously in stroke care centers, and using the formula $n=Z^2\ P\ (1-P)/d^2$ [8]. Statistical analysis was done with the program SAS software (copyright the SAS institute, Cary, N.C.), including in the second study chi square, Fisher's exact test for categorical variables, p value less than 0.05 was consider of statistical significance, confidence intervals and odds ratio were calculated too.

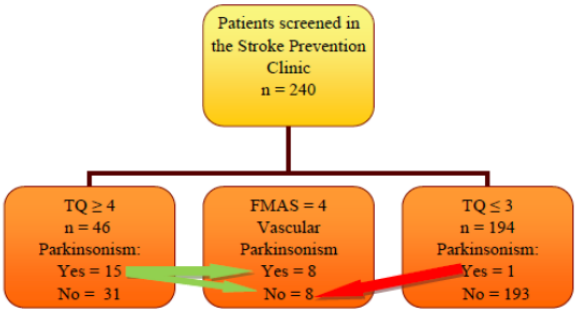

Figure 1: Flow Diagram. Patients' enrollment. Abbreviations: FMAS-Five-Minute Assessment Scale; TQ-Tanner Questionnaire. Modified with permission from the copyright holder, Elsevier Journals. The source has been acknowledged.

Results

From 240 patients screened, 16 were found to have Parkinsonism attaining at least a score of 2 in the FMAS, and 15 of them with TQ ≥ 4 **(Figure 1)**. The total group of TQ ≥ 4 was composed of 46 people. Demographic data is shown in **(Table 5).** Patients with VasP were older (p<0.0007), and had a higher risk for cardio embolism (odds ratio 8.5, 95% CI (1.5-47.9), p=0.01) due to atrial fibrillation (odds ratio 6.6, 95% CI (1.2-35.2), p=0.02).

We described in detail the different phenotypes found within the group weather they had an extrapyramidal syndrome, stroke syndrome, both or none accordingly **(Figure 2)**. More than half of the group (54%) had gait and balance disturbances due to stroke, but no extra pyramidal syndrome was found on them (sub group VPseuP). It was followed by the patients with VasP (17%), then PseuV P (15%) and the different diagnosis found in this group, and finally PseuV PseuP (14%).

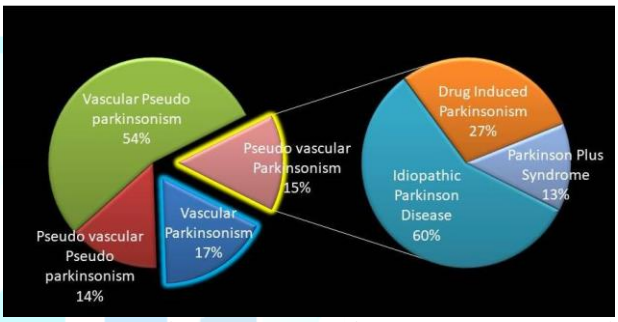

Figure 2: Group of patients at high risk for Parkinsonism TQ ≥ 4, total sample of 46 participants. Different phenotypes were found in this group: vascular, parkinsonian, both or none accordingly.

Characteristics	**Stroke patients**	**Vas P patients**	**Odds Ratio**	
Participants with TQ ≥ 4	**without Vas P** (N=38)	**FMAS=4** (N=8)	**(95% CI)**	**P value**
Age-years (standard deviation)	65.1 (3.5)	77.3 (11.9)		***0.0007**
Female sex - no. (%)	22 (58%)	5 (63%)	1.2 (0.2-5.8)	0.8
Vascular Risk Factors (%)				
Previous stroke	22 (58%)	6 (75%)	2.1 (0.3-12.2)	0.3
Hypertension	28 (74%)	7 (88%)	2.5 (0.2-22.9)	0.4
Diabetes Mellitus	14 (37%)	5 (63%)	2.8 (0.5-13.8)	0.1
Hyperlipidemia	31 (82%)	7 (88%)	1.5 (0.1-14.9)	0.6
Coronary disease	9 (24%)	3 (38%)	1.9 (0.3-9.7)	0.4
Atrial Fibrillation	5 (13%)	4 (50%)	**6.6 (1.2-35.2)**	***0.02**
Chronic Kidney Disease	8 (21%)	2 (25%)	1.2 (0.2-7.4)	0.8
Smoking	13 (34%)	2 (25%)	0.6 (0.1-3.6)	0.6
Type of Ischemic Stroke (TOAST classification)				
Large Artery Atherosclerosis	4 (11%)	1 (13%)	1.2 (0.1-12.5)	0.8
Small vessel occlusion	11 (29%)	2 (25%)	0.8 (0.1-4.6)	0.8
Cardio embolism	4 (11%)	4 (50%)	**8.5 (1.5-47.9)**	***0.01**
Undetermined				
Other				
TIA	11 (29%)	2 (25%)	0.8 (0.1-4.6)	0.8

TQ = Tanner Questionnaire score; Vas P = Vascular Parkinsonism; FMAS = Five Minute Assessment Scale; N = number of participants; TIA = Transient ischemic attack*= p<0.05 significant difference.

Table 5: Demographic Characteristics of Participants with TQ ≥ 4 with and without Vascular Parkinsonism.

We analyzed the pattern of ischemic brain lesions found in all participants (**Table 6)**. We analyzed ischemic lesion located at the BGMO and the TCD, and analyzed the most frequent patterns found. The pattern involving the Lenticular nucleus (BGMO) and frontal lobes was significantly associated to the group of VasP (X^2 Fisher exact test p<0.0005, odds ratio 32, 95% CI (9.6-108)); whereas the pattern Thalamus-Frontal Lobes (TCD) was not significantly different between the two groups (X^2 Fisher exact test p=0.828, odds ratio 1.2, 95% CI (0.5-2.8)).

Discussion

The prevalence of VasP in a tertiary care stroke prevention clinic was of 3%, similar to what has been reported in other European, and American studies [9]. Other groups have made the observation that VasP patients are older than patients with idiopathic Parkinson disease when comparing the onset of the extra pyramidal syndrome [10]. In our

cohort we found similar results, participants with VasP were older than patients with Parkinsonism due to other cause, or those who had a stroke(s) without an extrapyramidal syndrome. Also, the high prevalence of A. Fib and cardio embolism was related to the older age in this group of VasP. According to the Framingham study, there is an exponential increase in the prevalence of A. Fib. With aging our patients may also have decreased brain plasticity due to aging [11,12].

Ischemic lesions location	Vascular Parkinsonism FMAS = 4 (N = 8)	Vascular Pseudo parkinsonism (N = 25)	Odds ratio (95% CI)	X2 Fisher test p value
Putamen	4 (50%)	3 (7.8%)		
Caudate	1 (12.5%)	2 (5.2%)		
Globus Pallidus	1 (12.5%)	0		
Thalamus	2 (25%)	5 (13.1%)		
Frontal lobe	6 (75%)	13 (34.2%)		
PWML	3 (37.5%)	6 (15.7%)		
Lesion patterns according to stroke location				
BGMO: (lenticular nucleus)+Frontal lobes	4 (50%)	1 (2.6%)	32 (9.6-108)	*p<0.0005
TCD: Thalamus +Frontal lobes	1 (12.5%)	4 (10.5%)	1.2 (0.5-2.8)	p=0.828
PWML-Periventricular White Matter Lesions, * = statistically significant. BGMO-Basal Ganglia Motor Output, TCD-Thalamo Cortical Drive Circuit.				

Table 6: Group of participants at high risk for Parkinsonism (TQ ≥ 4) comparing Stroke location and network pattern between patients with Vascular Parkinsonism versus Vascular Pseudo Parkinsonism seen in a Tertiary Care Stroke Prevention clinic.

We propose a double hit theory in which the network that increase the basal ganglia motor output is damaged from the lenticular nucleus\ substantia nigra to the cortical frontal connections. Having a decreased output from the Globus Pallidus externus (Lenticular nucleus) to the Subthalamic Nucleus (STN), may preferentially favored the excitatory neurotransmitter effect from the STN over the Globus Pallidus Internus and Substantia nigra pars reticulate, consequently favoring the inhibitory output towards the thalamus & cortex loop. This would be expressed clinically as limited movement with bradykinesia [13].

Perforant arteries typically perfuse the deep structure of the basal ganglia (lenticulo striate arteries), and frequently hypertension and diabetes mellitus are the underlying risk factors. On the other hand, cortical strokes including frontal lobes are frequently involved in cardio embolism, and in a smaller percentage may also affect the deep structures of the basal ganglia too [14]. It is important to point out that the most frequent vascular risk factors in our cohort of patients with VasP were Diabetes Mellitus and Atrial Fibrillation. Our study suggested the need for a double hit ischemic injury at these brain locations (deep basal ganglia structures, and frontal cortex), so consequently the phenotype of an extrapyramidal syndrome may appear. The yield of involving both locations may become higher when combining different mechanisms. Lipohyalinosis related to small vessel occlusion applicable to the first location, also reported by other investigators in VasP [15], and cardio embolism particularly due to A. Fib in elderly population involving the frontal lobe applicable to the second location [16].

Interestingly, we found that when the pattern of ischemic lesion involved the frontal lobe and thalamus connections, participants had gait and balance problems, but no Parkinsonism.

Some of the weakness is that our previous study was a cross sectional study, so new onset of a hypokinetic rigid syndrome could not be identified prospectively. On the other hand, participants with lower TQ scores<4 were unlikely to have Parkinsonism (1out of 193 participants) as data from our previous investigation.

Future neuroimaging studies including Dopamine receptors/transporters and neuroimmune modulatory molecules involved in this network are required to confirm our findings: a double location hit within the BGMO and Lenticular nucleus, and the frontal cortex, so a phenotype of VasP may occur.

Funding

The original study on which this article is based was funded through a grant from the Toupin foundation at the University of Alberta.

Permission

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