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Vascular Parkinsonism Is Not A Deployed Entity As Currently Considered: Links to Parkinson's disease Pathogenesis from New Retrospective and Comparative Cohort Studies

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Abstract

Aim: Vascular Parkinsonism has been considered along the time secondary to simple disruption of nigrostriatal pathways by variable vascular insult patterns, scarcely responsive to drug therapy and of minor interest to researchers. Nevertheless some recent studies have highlighted patients with Vascular Parkinsonism to be significantly responsive to dopaminergic therapy, while other studies showed the relevance of vascular damage in patients diagnosed with not-genetic Parkinson's disease, especially if compared with control subjects, or even other extrapyramidal diseases, like Essential Tremor. This retrospective study is inferring a possible continuity between cerebrovascular disease, vascular Parkinsonism and Parkinson's disease

Methods: firstly a statistical chi square calculation investigation between the incidence of cerebrovascular disease in a population of 116 patients affected by 'sporadic' Parkinson's disease and the incidence of cerebrovascular disease in a group of 68 subjects selected as control group was performed. Moreover, the same comparison was performed between Parkinson's disease group and 97 patients with Essential Tremor. This in order to confirm of the possible non-significance for the role of vascular damage in an extrapyramidal disease, not curable with dopaminergic therapy. Afterwards, the clinical case of a patient with multiple vascular risk factors and brain ictal events, who developed a PD with positive scintigraphy and good response to dopaminergic therapy is reported, as an example of correlation between Parkinson's disease diagnosis and vascular damage.

Results: The statistical significance of CVD comorbidity in PD compared to control population and ET have been confirmed by the values reported with the chi square calculations, with resulting p-value < 0.00001, as shown in previous studies.

Conclusions: On the basis of the present study, the pathogenic role of vascular damage on PD is further suggested. The damage could be more prominent in dopaminergic with respect to gabaergic receptors, and be on average susceptible to the duration of hypoxia along life. Even if a noticeable brain vascular damage load is shown in younger patients with idiopathic PD, increasing diagnosis of PD in aged populations endorse this hypothesis.

Keywords: Vascular Parkinsonism; Parkinson's disease; Cerebrovascular Disease; Essential tremor; Stroke; Dopaminergic therapy

Introduction

Vascular Parkinsonism (VP) is usually considered of little interest for the scientific community as well as for clinical practitioners, which include it in an ancillary position in the group of secondary parkinsonism's and describe its characteristics emphasizing the poor response to drug therapies. However recent studies have re-evaluated the role of Cerebrovascular Disease (CVD) in the genesis of Parkinson's Disease (PD) itself, as shown by the statistically significant incidence of CVD in PD, as well as the not random success of dopaminergic therapy (DT) in VP [1-5]. In those studies, it was also discussed a clinical overlapping between VP and PD in fairly large patients' populations which was not due to diagnostic bias (despite scintigraphic investigations had not been routinely carried out in tremor-free patients taken in charge

in the outpatient clinic) [2-5]. This fact accounts for the difficulty often found in clinical practice in making a distinct diagnosis of PD or VP, especially in patients without tremor [6-9]. This suggested some kind of continuity between VP and PD. Moreover, retrospective statistic comparison of PD population patients with other types of similar movement disorders showed a significant incidence of CVD in PD with respect to other conditions, such as Essential Tremor (ET), despite its common definition of senile tremor based on atherogenic damage [6]. Several other authors have described in recent articles both with single cases' odd episodic reports or in more extensive studies, the somewhat surprising efficacy of dopaminergic therapy in patients affected by parkinsonian symptoms after a stroke or in other types of diagnosed VP [7-10]. In a large age-range group of patients with PD, we demonstrated that CVD was more severe and extensive if compared to a control population fairly homogeneous for the age. These finding are coherent with a possible role of vascular impairment along the pathogenesis of PD in its large epidemiologic expression, and suggest possible strategies of prevention.

Materials and Methods

The present study consists of two parts: a retrospective investigation performed on a cohort of patients in charge in the outpatients' clinic Movement Disorders, which compared the incidence of CVD in a population of 116 (age range 54-95 yrs., 51 females, 65 males) subjects diagnosed with idiopathic PD, attending the clinic in the period from the beginning of 2013 to the end of 2021, with the incidence of CVD in a group of 68 selected subjects (age range38-94 yrs., 45 females, 23 males) attending the clinic in the same period for other diseases, considered as a control group. Moreover, 97 patients with diagnosed ET (age range 34-95 yrs., 49 females and 48 males) were taken into account to make a comparison with PD population for the CVD comorbidity. Among all groups, some subjects were finally excluded, due to lack of the results of the investigations requested in the various follow-ups. Particularly, the lost or missing MRI or TC scan reduced PD population to 108, the considered control group to 53, the ET group to 81. We conducted the comparison analysis of the incidence of CVD in the groups with the chi-square test calculator for a simple 2 x 2 contingency table. Similarly, the comparison between CVD incidences in the PD population vs the ET population was carried out with the same type of statistical analysis.

CVD Description

In this as in the previous studies of this Author, the CVD was morphologically diagnosed by MRI or CT-Scan studies, which defined ischemic vascular damage ranging from consistent leukoaraiosis to multiple micro-infarcts with various distribution, minor stroke and major stroke and hemorrhagic lesions [10-12]. These lesions have been mostly detected at the beginning of parkinsonian symptoms or earlier; the response to the dopaminergic therapy was monitored over time, both in VP and in PD. The assessed CVD consisted either in outcomes of acute cerebrovascular events, which had the random neuropathological cerebral distribution expected in a given population, as well as lacunar infarcts, multi-infarct lesions, or chronic signs of ischemic suffering classified like Fazekas' type leukoaraiosis of 2° or 3° degrees. The imaging of cerebral white matter leukoaraiosis is detected on axial T2 MRI.

Case Report

It is the clinical case of a patient who develops an extrapyramidal syndrome responsive to dopaminergic therapy, with a positive Iodine Ioflupane-123I scintigraphy (daTSCAN), after cerebral strokes involving -among other sites- the basal ganglia, resulting in a presumptive diagnosis of PD in a subject formerly suffering from multi-infarct vascular encephalopathy. At the time of coming to the first examination in our clinic for motor diseases (2019 September) the patient was a 74 yrs. old male, smoker, who had suffered since 2001 from polycythaemia Vera with myelodysplasia treated with oncocarbide. In 1999 he had myocardial infarction and afterwards an anticoagulant therapy (rivaroxaban) was introduced (2018). He had inoperable right carotid artery stenosis (close to occlusion). Finally, during the period of taking in charge, the cardiac PMK was applied (2021). Various cerebrovascular acute events resulted in the anamnesis, two of which were dated, respectively in 2013 and 2017 and documented with RM and TC imaging; moreover, he suffered from chronic obstructive pulmonary disease (OSAS) with severe obstructive sleep apnea syndrome treated with nocturnal CPAP. He had also developed vascular epilepsy after 2013 with focal onset seizures and secondary generalization, treated with a valproate and levetiracetam therapy, with seizure remission for some years. From 2017, due to the onset of extrapyramidal symptoms such as bradykinesia, hypomimia and plastic rigidity, he was examined in other clinic centers and placed on dopaminergic therapy. In addition, he underwent brain scintigraphy (daTSCAN) with the following report: "the investigation documents severe hypo fixation of the radiotracer in the right putamen, and moderate hypofixation in the ipsilateral caudate. Scintigraphic pattern compatible with severe hypofunction of the right nigro-striatal presynaptic endings". A cerebral TC scan of 2017 August showed:" CSF hypo density in the right frontal white matter, result of previous vascular ischemia. Small area of hypo density in the head of the left caudate nucleus. Oval area of hypo density posterior to the left Silvian fissure. Absence of perilesional edema of the areas described. Minimal increase in ex-vacuo size of the right lateral

ventricle. An RM cerebral scan with angiographic study on 2017 August shows: "Focal lesions are evident on the left hemisphere: one at the level of the caudate nucleus which causes slight compression on the anterior horn of the ipsilateral ventricle, others at the level of the occipital lobe and the temporal lobe. The study of the intracranial circulation shows absence of flow of the right internal carotid artery, with re-inhabitation of the flow of the Polygon of Willis from the contralateral carotid artery". The clinical examination showed the overlapping signs of the multiinfarct brain vascular disease with the parkinsonian signs like bradykinesia, hypomimic, rigidity. The lateral prevalence of parkinsonian symptoms was difficult to assess due to the complex -mixed symptomatology. However, the patient showed the need to take dopaminergic therapy, the dosages of which were increased over time (last session, l-dopa plus benserazide, 200 mg 4 times\die) as its suspension caused a clinical worsening.

Results

The statistical significance of CVD comorbidity in PD compared to control population and ET are shown in (Tables 1 and 2): in the first measure (Table 1: PD vs Controls) the chi-square statistic is 21.6193.

Table 1: *PD vs Controls.*

	CVD yes	**CVD no**	***Marginal Row Totals***
PD	92 (79.83) [1.86]	16 (28.17) [5.26]	108
Controls	27 (39.17) [3.78]	26 (13.83) [10.72]	53
Marginal Column Totals	119	42	161 (Grand Total)
(PD= Parkinson's disease; CVD =Cerebrovascular Disease)			

***Table** 2: PD vs ET.*

	CVD yes	**CVD no**	***Marginal Row Totals***
PD	92 (75.43) [3.64]	16 (32.57) [8.43]	108
ET	40 (56.57) [4.85]	41 (24.43) [11.24]	81
Marginal Column Totals	132	57	189 (Grand Total)
ET= Essential Tremor			

Table 3: *The inclusion of the three populations in the statistical analysis.*

Results			
	CVD yes	**CVD no**	**Row Totals**
PD	92 (70.96) [6.24]	16 (37.04) [11.95]	108
ET	40 (53.22) [3.28]	41 (27.78) [6.29]	81
controls	27 (34.82) [1.76]	26 (18.18) [3.37]	53
Column Totals	159	83	242 (Grand Total)

The p-value is < 0.00001 (Significant at p < .01). The chi-square statistic with Yates correction is 19.8799. The p-value is < 0.00001. (Significant at p < .01.). In the second measure (Table 2: PD vs ET) the chi-square statistic is 28.1675. The p-value is < 0.00001 (Significant at p < .01). The chi-square statistic with Yates correction is 26.4933. The p-value is < 0.00001 (Significant at p < .01). The Table 3 shows the inclusion of the three populations in the statistical analysis. The chi-square statistic is 32.8886. The p-value is < 0.00001. The result is significant at p < .01.

Discussion

In general, CVD is a definition used to describe a heterogeneous group of pathological conditions, the common feature of which is focal mismatch between oxygen supply and demand. This dysfunction has a remarkable heterogeneity of patterns. A considerable amount of clinical research on CVD in PD has focused on the presence of direct vascular disruption of the basal nuclei and or nigrostriatal array and projections as the cause of the onset of symptoms, mainly with a negative prognosis due to the lack of receptors and poor chance of pharmacological susceptibility. An indirect effect of vascular distress as a cause of Parkinsonian symptoms is admitted in the so called 'lower body parkinsonism' which is observed frequently in patients with white matter diffuse bilateral brain lacunar infarcts possibly associated with dementia and other disorders, such as dysphagia and dysarthria and with prevalent impairment of gait [7,8,10,12]. In other studies an inverse causal link between CVD and PD has even been hypothesized, as if PD was a questionable risk factor for vascular damage along lifetime in the patients affected: the latter hypothesis takes into account the detection of CVD by some researchers in clinical studies on patients who have a good and lasting response to DT and which represent an 'anomaly' in the panorama of so-called 'vascular parkinsonisms'; in fact, in the

standardized clinical model based on the 'ex juvantibus' diagnostic concept, the diagnosis of PD is conditioned by the response to DT. On the basis of the present statistical analyses as well as the clinical cases described in literature, the basic pathogenic role of vascular damage on the development of PD can be hypothesized. This hypothesis was also supported by the observation of a noticeable brain vascular damage load in younger patients diagnosed with idiopathic PD. In this regard it would be interesting to extend the statistical studies to a larger population selected for younger age and with non-familial PD. An attempt to deepen the relationship between PD and the long-lasting hypoxic damage has been performed with positive results in a study of statistical significance of CVD incidence in different age groups [3]. Moreover the previous studies and the present one demonstrate that the brain vascular damage is a pre-existing condition in these statistical samples. The statistical comparison with the group of patients affected by ET was chosen due to the good certainty of this diagnosis compared to other extrapyramidal diseases and to the greater relevance offered by the exclusion of the dopaminergic system, assuming that the hypoxic damage is more evident on dopaminergic receptors. The descripted clinical case was chosen as an example of the arguments reported in this and other articles [2,5]. In fact, it should be noted that the daTSCAN test was performed because of parkinsonian symptoms - including tremor - according to a diagnostic path independent from the concomitant CVD and from the numerous and severe Vascular Risk Factors (VRF), such as ipsilateral serrated carotid stenosis to the hemisphere with damage of the nigrostriatal system, polycythemia, hypertension; the positivity of the datSCAN in the examined patient demonstrates an impairment of the presynaptic dopaminergic system, -analogous to findings of common clinical practice in patients with consequent diagnosis of PD-, on the hemispheric side not involved in the main ischemic basal ganglia damage. Moreover, the patient was responsive to dopaminergic therapy. The presence of numerous cerebral vascular lesions not anatomically correlated with lack of pre-synaptic function, even affecting the basal nuclei contralateral to the hemisphere 'positive' at the daTSCAN, confirms that the pathogenic mechanism for PD regarding the ischemic damage of the pre-synaptic system is more linked to the effect exerted over time by the hypoxic suffering on the presynaptic endings instead of direct acute vascular insult. This is in favor of a long-term action of ischemic damage prior to the PD onset. In other cases, the ischemic damage is more likely to cause a disruption of nervous tissue array and seems to be responsible of a poor response to dopaminergic therapy, when extrapyramidal symptoms are evident; this may be one of the explanations for the lack of response to such therapy in many cases of VP. The role of blood perfusion impairment is a clear factor of Nervous System variety of dysfunction both at central and peripheral districts, and accounts for a recent trend towards a "unifying" vision of nervous system disorders which are ultimately attributable to alterations of membrane homeostasis and neuronal metabolism, similarly to what occurs in cellular aging processes. Various studies have shown that one of the factors responsible for neurodegeneration is oxidative stress resulting from an excessive production of oxygen free radicals (OFR) and/or the poor efficiency of antioxidant systems. Neurotransmission spaces and receptor systems could be particularly vulnerable to this mechanism, in addition to the accumulation of toxic substances (tau, synuclein). However vascular damage is not obviously the only cause in the processes. According to numerous research lines, idiopathic PD is a multifactorial pathology in which the incidence of predisposing genetic factors or the accumulation of metals play a crucial role in the clinical expression of the disease, while in other circumstances the oxidative agents are more influent and can be advocated as ‘modifiable risk factors’.

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Conflicts of Interest

The Author declares no conflicts of interest

Ethical Approval

Not applicable

Consent to Participate

Not applicable

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