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Dementia Prevalence in Idiopathic Parkinson's Disease *Vs.* Vascular Parkinsonism: Retrospective Study in a 10-Year Clinical Cohort and the Role of Cerebrovascular Disease in Parkinson's Disease Dementia

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Abstract

Dementia in Parkinson's Disease (PDD) occurs with different clinical expressions, variable frequency and onset time, worsening the prognostic expectation. Since previous studies by this Author showed a significant comorbidity of Cerebro-Vascular Disease (CVD) in PD, we tried to investigate the statistical relationship between the incidence of CVD and dementia in a PD population taken in charge in a time frame from 2014 to 2023. A cross-analysis was carried out between the PD group and a group of patients with Vascular Parkinsonism (VP), and performed by means of the chi square calculation system, in different steps. In particular, the comparison was carried out between PD population and VP population, between the two subgroups of PD patients, with and without CVD, and between PD subgroup's patients with CVD and the group of VP patients, with respect to frequency of Dementia. A statistically significant difference was found between the whole PD population and the VP population, in favor of prevalence of Dementia in VP, while there was not difference ($p>.05$) when comparing the PD population's subgroups with or without CVD; a slight positive p value was obtained between the PD subgroup with CVD and the VP group (in favor of Dementia's prevalence in VP), which was cancelled with Yates correction. These findings support the hypothesis that, in contrast with what was previously found about the possible CVD influence on PD pre-synaptic system impairment, the mechanisms underlying the pathogenesis of Dementia in PD are driven by other independent variables involving multiple receptor systems, with a questionable role of CVD as a cofactor.

Keywords: Parkinson's disease; Vascular parkinsonism; Dementia; L-Dopa; Cerebrovascular disease; Stroke; Brain Vascular damage; Vascular dementia

Introduction

Numerous studies have described the coexistence of non-motor symptoms in Parkinson's Disease (PD), including a syndromic constellation of cognitive skills impairments defined in synthesis PDD [1-6]. The onset time and severity of dementia show a large range of intersubjective variability, but according to researchers' and clinicians' statistics they can occur 5 to 20 years after the onset of the disease and begin with variable and initially unrecognized symptoms. Many studies have shown different percentages of incidence and morbidity of PDD, not mentioning the early dementia of the Lewy Bodies Disease (LBD) and the Mild Cognitive Impairment (MCI) of PD [7]. However, the latter two conditions, as well as other Atypical Parkinsonisms (AP) have been excluded and not taken into consideration in this study, which focused on a definite PD pool of patients taken in charge in the Movement Disorder Center. The diagnosis had been expressed in the phase of taking in charge with particular care to avoid possible mix-up with respect to other parkinsonisms, but an extra caution in the data re-evaluation of the clinical cases selected for the purpose of this retrospection was applied, with particular warning about possible bias. As widely known, the onset of dementia drastically

worsens the prognosis of PD. In previous studies many clinicians focused their attention on the PD patients' comorbidity with brain vascular disease (i.e. CVD), with different levels of damage, ranging from ischemic diffuse spotting (without a definite pattern of cerebral tissue distribution, but with a relevant lesion load), to minor or major strokes involving either anatomically known brain areas, described as 'typical', or 'atypical' sites' strokes [8-15]. This observation led to hypothesize that there was a non-random relationship between vascular damage and the common variant (idiopathic) PD, and that oxidative stress could play a relevant role in the pathogenesis of the disease, in addition to other coexisting or consequent factors, such as synucleopathy and other neurotoxic factors. Furthermore, the finding that dopaminergic therapy was consistently effective on motor symptoms of many patients with vascular parkinsonism, led to the belief that oxidative damage could directly affect the presynaptic dopaminergic nigro-striatal system. PD is, however, a syndromic complex that includes multiple aspects in addition to motor symptoms; these are still extensively under study and require multidisciplinary investigations to clarify their biological bases, in which oxidative damage is uncertain and little explored. This study aims to explore the potential influence of vascular damage on the cognitive impairment generally defined as dementia of PD. The heterogeneity of symptoms described in the syndromes' frame of PDD, not always all coexisting, makes the statistical investigation difficult, especially in a retrospective study: the group under study include outpatients in charge to the movement disorders clinic over a 10-year period. Therefore, we had to manage parameters stored "off-line" and extract data suitable for statistical application, i.e. the standardized diagnostic tests used in clinical routine practice. The present study has anyway taken into consideration in its conclusions any limitation connected to the adopted methodological features.

Materials and Methods

Two populations were selected respectively with a definite diagnosis of PD and VP within the pool of patients taken in charge in the Movement Disorders Outpatients' clinic between 2014 and 2023, equal to 129 and 25 respectively (age range of PD patients 54 to 92 yrs, and of VP patients 63 to 96 yrs). The diagnosis of PD had been ascertained on the basis of clinical and instrumental data (clinical history, objective examination, efficacy of dopaminergic therapy, outcome of receptor scintigraphic imaging-Iodine Ioflupane-123I scintigraphy, DaTscan) and the patients taken in charge had been followed for a minimum period of 3 years to 11 years. The VP diagnosis was assessed by means of the clinical criteria internationally accepted according to the guidelines, that is: sudden or subacute onset of extrapyramidal symptoms after a stroke, presence of cerebral vascular lesions consistent with the affected side, presence of radiological signs of brain vascular damage and prevalent impairment of the lower limbs, as in "lower limb parkinsonism", prominent gait impairment with frequent early falls, reduced or uncertain or short-term efficacy of dopaminergic therapy, absence of olfactory disorders, presence of concomitant signs of pyramidal tract involvement, like after a stroke, non-specificity of the DaTscan, when performed. The Movement Disorders Clinic is supported by a computerized database that allows the recording of data concerning symptoms and other informations through a grid containing default items in both short verbal format and as a positive/negative (yes or no) response. Among the descriptive parameters included in the computerized database, carried out with a dedicated computer program, there is an item labelled 'dementia' recordable as « yes or no », based on the outcome of the Mini-Mental State Examination (MMSE) test used for routine global assessment of patients (regardless if existing at the first examination or subsequently ascertained diagnosis). The "yes" value for the dementia parameter was based on the clinical cut-off score of 23, which was considered the limit score below which defining the subject as suffering from dementia, in accordance with the general clinical consensus. In addition, patients had been routinely subjected to the Unified Parkinson's Disease Rating Scale (UPDRS). The statistical test used in the investigation was the chi-square calculator for a contingency table; in the first step the comparison was carried out between the independent parameters PD and VP groups, with respect to the incidence of dementia (total amount numbers of yes\no). Subsequently the PD population was divided into two subgroups, with and without CVD, (CVD yes and CVD no), which information was extracted from a parameters' item of the computer program labeled as yes-or-no: the CVD recognition labeled as yes was on the basis of the presence of neuro-radiological signs of vascular lesion and any history of stroke: the cerebral tomographic pattern (MRI and/or CT) classified within the CVD flag included multiple lesions according to the Fazekas' classification of grade 2 to 3 or more and major ischemic or hemorrhagic stroke, in line with previous studies on the incidence of CVD in PD [12,13]. Thereafter the two subgroups were compared, as independent variables, with respect to the incidence of dementia, using the chi-square test, as previously described. Finally, the comparison was applied between the group of PD patients with CVD and the VP group, with respect to the incidence of dementia. Notice that we calculated in the three steps a chi-square statistic also with the popular Yates correction, even if there is probably a consensus now that the correction is over-cautious in its desire to avoid a type 1 error, but considering the different size of the groups. Moreover there is a mismatch of total populations' numbers in the different satistical analysis, due to missing or lack of some registered parameters during patients' monitoring times (Tables 1-3).

Table 1: *Prevalence of Dementia: Parkinson's Disease (PD) vs. Vascular Parkinsonism (VP).*

Patient Group	Dementia (Yes)	Dementia (No)	Total	Statistical Analysis
Parkinson's Disease (PD)	41 (46.07) [0.56]	88 (82.93) [0.31]	129*	χ^2 = 5.349
Vascular Parkinsonism (VP)	14 (8.93) [2.88]	11 (16.07) [1.6]	25	p = .020
Total	55	99	154	Yates corr. p = .037*
*Note: Significant at p < .05. Sample sizes may vary slightly due to missing data in retrospective records.				

Table 2: *Comparison of Dementia Prevalence between PD Subgroups (with and without CVD).*

Group	Dementia (Yes)	Dementia (No)	Total	Chi-Square (p-value)
PD with CVD	34 (31.97) [0.13]	66 (68.03) [0.06]	100	1.0537 (p = .304)
PD without CVD	5 (7.03) [0.59]	17 (14.97) [0.28]	22	*Yates corr. (p = .438)*
Total	39	83	[N]	Not Significant
Note: N values may vary between analyses due to missing data in retrospective records				

Table 3: *Comparison of Dementia Prevalence: PD with CVD Comorbidity vs. Vascular Parkinsonism (VP).*

Patient Group	Dementia (Yes)	Dementia (No)	Total	Statistical Analysis
PD with CVD	34 (38.4) [0.5]	66 (61.6) [0.31]	100	χ^2 = 4.092
Vascular Parkinsonism (VP)	14 (9.6) [2.02]	11 (15.4) [1.26]	25	p = .043
Total	48	77	125	Yates corr. p = .072 (NS)*
*NS = Not Significant (p > .05).				

Results

The results of the statistical comparisons described are shown in tables 1, 2 and 3. As you can see, the absolute numbers indicate a prevalence of patients with dementia in the VP population. In particular, the comparison between patients with PD and VP demonstrates a significant difference with respect to the incidence of dementia (Table1): the chi-square statistic is 5.3493; the p-value is .020731, significant at p < .05; the chi-square statistic with Yates correction is 4.3465, with p-value =.037085, significant at p < .05. On the contrary, the statistical comparison between PD subgroups with and without CVD does not display significant differences regarding the incidence of dementia (Table 2): the chi-square statistic is 1.0537; the p-value is .304667, not significant at p < .05; with Yates correction the chi-square statistic is 0.5991, p-value = .438933, not significant at p < .05. Finally, the comparison between the group of PD patients with CVD comorbidity and the group of patients with VP showed significant differences with respect to the incidence of dementia with the standard chi square calculation (the chi-square statistic is 4.0923, the p-value is .04308: significant at p <.05), with a prevalence in VP group, but the Yates correction removes the difference's significance (chi-square statistic with Yates correction = 3.215; p-value =.072964, not significant at p < .05.) (Table 3). Note that the total marginal columns and rows numbers do not coincide in the different tables, despite the same populations under study, because some of the parameters considered in every analysis have not been recorded in different patients, who are therefore excluded from the single calculations.

Discussion

Among the non-motor symptoms of PD there is an extensive description of cognitive-affective and cognitive-behavioral disorders, which are widely investigated by researchers and well known by clinicians managing patients with this movement disorders. Moreover, neuropsychiatric syndromes are often associated and encountered in literature [14-27]. The cognitive functions mainly affected are the executive, memory and visual-spatial ability, but other cognitive domains can be also impaired, even as a secondary consequence of the primary executive disorder. Indeed, from a clinical point of view, in many cases it can be difficult to make a clear-cut distinction between cognitive and psychiatric disorders, such as anhedonia, depression or psychosis with personality changes, as the symptoms are closely intertwined. Researchers claim that the relationship between cognitive

functions impairment and eventual incidence of dopamine therapy on the actual cognitive deficit, as well as its evolution in the course of the disease is not yet completely clarified. However, the description of the complex of symptoms definable as Dementia in PD or PDD, despite some degree of overlapping, shows different characteristics compared to dementias of neuro-degenerative type, as Alzheimer's disease, frontal-temporal dementia, or the secondary types, like vascular dementia. There are also mixed variants of Alzheimer's disease and vascular dementia that are often unrecognized, as well as small vessel disease's dementias, which are currently still being studied and classified. Each of these dementia types shows symptomatic and neuroimaging features, and different biomarkers are increasingly proposed for routine diagnostic purposes [28-30]. The peculiar characteristics of PD patients' cognitive default involve frontal functions, resulting in dysexecutive syndrome, increased reaction times and information processing slowing. It has been confirmed that nearly half of patients with PD develop cognitive decline during the disease; of these, approximately the majority develop dementia at the latest after 15-20 years of the disease history, with careful treatment along time [6,7]. Currently, PD is known to be an incurable neurodegenerative disease, but it is important both to stem the neurocognitive decline, and the motor impairment of patients for as long as possible. In this regard, particular relevance has been attributed to the subjective variability of Cognitive Reserve (CR) and Motor reserve (Mres) [31-34]. In fact, it is also evident that these parameters, which have been more recently focused, cause a large range of inter-individual variability and can make the exact diagnostic definition heterogeneous and in some cases ambiguous for some time in the clinical history. This complexity is worthy of accurate consideration for clinical investigations, but on the other hand constitute a knot and a limit to the statistical data processing of patients' populations, which require the availability of absolute numerical values, and do not take into account the continuity of variables typical of the reality of individual clinical evolution; that is why it was necessary to adopt a relative simplification of the parameters chosen for the study of the groups under investigation. Clinical details regarding comorbidities and changes in drug doses over time cannot be retrieved from the computer routine database. These data in any case fell outside the scope of this investigation, which was exploratory and providing an initial approach to the topic. Furthermore, due to the peculiarity of our routine computerized data recording system over time (settled to data overwriting during the subsequent updates of clinical follow-up), in this study data collection does not take into account the time of onset of the dementias' symptoms or the prevalence of some cognitive domains decline with respect to others, nor the evolution time compared to other symptoms, both motor or non-motor. In fact, patients could have been admitted randomly at a given point in their clinical history, maybe already affected by full-blown dementia, or have developed it during the time they were visiting the clinic at a later date. However, this does not constitute a hindrance to the study, as it has a statistical value classified as prevalence and not as incidence. The use of a sharply defined criterion to classify patients with dementia, with a specific cut-off value of MMSE, allowed to ignore those who may have had at that point initial, subtle signs attributable to Mild Cognitive Impairment (MCI of PD or VP), which were intended out of the full-blown pathology taken into account. In any case, the selected patients were chosen by excluding other types of extrapyramidal diseases than PD (identified during the prior phase of the study also by checking the patients'paper medical records): therefore, known cases of LBD, as well as all atypical parkinsonisms, like Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), Cortico-Basal Degeneration (CBD), Primary Orthostatic Hypotension and other Aps were preliminarily excluded.

The aim of this retrospective study was to obtain a statistical feedback on the prevalence\influence of vascular damage in PDD, like previous studies by this and other authors have demonstrated a statistically significant co-morbidity of cerebral vascular damage in patients suffering from PD, while reversely many patients diagnosed with vascular parkinsonism have been described as responding to dopaminergic therapy [10-14]. These statistical observations, consistent with studies on motor parkinsonian symptoms induced in animal models, concerned the diagnostic category 'PD" without considering non-motor aspects. The VP population proved to be more suitable for the comparison than the 'neutral' control population adopted in the previous investigations about the statistical incidence of CVD in patients affected by PD, which was intended to represent a standard population homogeneous by age, regardless of whether or not affected by other pathologies (that is, a comparison between the population with PD and a generic age-range homogeneous group of individuals of the geographical area under study) [12,13]. Adding to that, the choice of the group of patients with VP as a comparison appeared more applicable since these patients, were both affected by symptomatic characteristics that overlap with PD in the motor domain, and by a dementia with high probability of vascular nature, therefore they can assume a role of a sort of "tare" with respect to clinical features not only determined by the vascular damage (motor parkinsonian impairment). The adoption of the MMSE cut-off criterion for statistical investigation appeared the most suitable paradigm to perform statistical calculations, despite it requires, as already noted, the unavoidable simplification of the complex clinical set of cognitive disease; this is a methodology applied in clinical routine and MMSE, despite its limitations, remains the standard for large-scale retrospective studies 35), albeit on patients with different cognitive diseases: in fact, it allows to explore briefly the main cognitive domains, including visual-spatial ability and executive skills. On the other hand, the final score of MMSE do

not discriminate which cognitive domain is predominantly affected in the single cases or in groups of subjects: however, this lack of distinction, which in clinical practice represents a diagnostic limitation in the use of the test, in our study can be considered non-influential or surmountable. Other tasks for assessing cognitive deficits, such as the Montreal Test for Cognitive Assessment (MOCA), did not turn out to be suitable for this investigation, because they had not been used extensively in the routine investigation in the Clinic, which requires relatively rapid testing on large patients' numbers and in a short time. Moreover, the assessment of MOCA had been tested to PD MCI and was therefore considered irrelevant in the purposes of this study; note that many patients had been already evaluated and diagnosed with full-blown dementia elsewhere prior to come to our center. Considering the possible influence of aging, larger populations should be enrolled in further studies, in order to extend the analysis within subgroups with smaller and homogeneous age ranges, as already analyzed in studies on incidence of CVD in PD populations [12,35].

Another issue is represented by the numerical homogeneity of the samples chosen for statistics: in fact, it would be recommended to compare numerically homogeneous groups. However, it is noteworthy that similar disparities are found in many analogous studies [36-38]. In this as well as in other studies, such a limit is also given by the restrictive criteria adopted by this Author [12,13] to consider the diagnosis of VP as certain, due to the fact that it is known by scientists that VP is often ambiguous and difficult to be ascertained. Indeed, in many subjects, it can be difficult to distinguish VP from the idiopathic Parkinson's disease phenotype with early onset of postural instability and gait disturbance. It is worth remembering that, with an alternative hypothesis, patients can be considered as affected by both neurodegenerative and cerebrovascular disease, and therefore, the two etiologies can coexist, whether or not there is a causal correlation. In fact, although the extrapyramidal syndrome defined as "vascular parkinsonism" is a widely investigated nosological category, only recently some Authors have highlighted several aspects that make it even more difficult with respect to the past, to clearly distinguish PD from VP, both from a symptomatic point of view and from that of the efficacy of dopaminergic therapy [39-41]. Therefore, this has called into question the previous certainties for expressing this diagnosis, with possible repercussions on the evaluation of the actual frequency of the disease, which also presents a wide variability of symptoms and is therefore a heterogeneous syndromic constellation. In fact, at least in the case history of our clinic, this diagnosis has been found to be less frequent than expected, according to the accepted diagnostic criteria. For all these reasons, we also adopted Yates' correction in the statistical analysis, to mitigate the quantitative mismatch of the samples examined, although both samples can be considered numerically large enough. It is also noteworthy that the absolute distinction between PD and VP has recently also been questioned by studies that have highlighted on the one hand the efficacy of dopaminergic therapy in patients with VP ascertained (for example with sudden onset of the motor symptoms, like bradykinesia and resting tremor, after a stroke), and on the other hand the significant incidence of CVD in populations of patients with ascertained PD [12,13,39]. The results obtained from the general comparison between the two pools of patients showed a significant difference in the incidence of dementia (chi-square statistic is 5.3493, p-value is .020731, significant at $p < .05$; with Yates correction the test is still significant with p= .037085), which is consistent with what can be expected, being the probability of developing dementia with brain vascular damage generally known higher (Table 1) [42-45]. The comparison of PD patients with and without dementia with respect to prevalence of CVD was performed to verify whether there is a significant difference between the two subgroups to be ascribed to vascular disease, or dementia alternatively being an independent clinical variable (Table 2). The non-significance of the comparison is favorable for an independence of PD dementia from CVD in the whole population, therefore, according to this result, the mechanisms underlying the development of dementia in PD can be statistically deduced to be peculiar to the disease; this is consistent with the polymorphism and variability of dementia in PD, which besides seems to be less extensive and frequent with respect to brain vascular disease (regardless of whether one considers CVD in general or Parkinsonism of vascular origin), as also descripted by many clinical studies in the literature [46-48]. More restrictively, the third analysis considered the subgroup of PD patients with CVD in comorbidity compared with VP patients as concerns incidence of dementia. Interestingly, the result still shows a significance albeit low with the raw analysis, but this disappears with the restrictive criteria application of the Yates correction factor (chi-square statistic =4.0923, p-value =.04308, <.05; chi-square with Yates correction =3.215, p-value = .072964, not significant at $p < .05$, Table 3). This data could confirm on the one hand that dementia in PD is a process mainly independent from CVD (at least it is not directly related to it in etiological terms) and probably driven by multiple chemical mediators and neuronal networks degeneration, on the other hand that cerebrovascular damage is a coexisting worsening element with respect to the incidence of dementia, resulting in a threshold of statistical significance that could be exceeded with an increasing number of observations; as already explained, the discrepancy observed in this part of the analysis can be considered an effect of the numerical disparity of the samples. Moreover, this fact is sustained also by the almost equal frequency of Dementia in the examined PD patients' group with CVD as in VP patients' group. The results of the cited previous studies questioned the clear cut distinction between idiopathic, non-genetic Parkinson's syndrome and

"vascular parkinsonism": they made more plausible the hypothesis of a gradation of the two pathological categories, in which hypoxic/oxidative damage prevails to varying degrees, with the involvement of differentiated brain networks, along with other pathogenic noxae, such as synucleinopathy, and other neurodegenerative factors, at least in the motor domain. Note that L-dopa, used for the long-term treatment of PD, has been hypothesized as a possible indirect vascular risk factor, because it can induce an increase in blood homocysteine levels. In many investigations an influence of vascular damage on the dopaminergic receptor system was supported by experimental animal studies [49-52]. In particular, chronic hypoxic damage or acute stroke damage which does not directly disrupt the substrate of synaptic transmission, could explain the efficacy of dopaminergic therapy in VP. Anyhow, as already mentioned, a similar hypothesis does not appear likely to be sufficient to explain the clinical features of the complex frame described for PDD, since it involves multiple networks and diversified receptor systems, including limbic system, cortico-nuclear and brain-stem circuitries, the cholinergic system with the basal nucleus of Meynert, which are also, and more extensively involved in Atypical Parkinsonisms [7,53,54]. For example, apathy is attributed to a disorder of the fronto-caudate pathway, while anhedonia is attributed to the meso-cortical and meso-limbic pathways; as well as the more specifically affective disorders, which could be considered an integral part of PDD, dementia in Parkinson's disease is linked to changes in the connectivity and functioning of several neuronal cognitive pathways, particularly those involving dopamine, norepinephrine, acetylcholine, and serotonin, which receptor system is not yet unequivocally subject to clinical or experimental evidence of indirect susceptibility to hypoxic-oxidative damage [53-57].

Conclusion

A further study is in progress for dementia in the PD group with little or no vascular damage, to be published. However, in our opinion, the results of this study, on the one hand confirm that PDD is a syndromic complex that requires multidisciplinary clinical and instrumental investigations to understand its biochemical and neurobiological causes, on the other hand support the need to pay additional attention to the contribution of CVD among the causes of dementia in PD, considering them for prevention and treatment purposes, according to what stressed by the studies on the incidence of CVD in PD.

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