

# Brain Vascular Damage in Essential Tremor: Observational Study and Statistical Analysis in An Affected Population Compared with A Group with Parkinson's Disease and A Control Group

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**Received:** 26 January 2019; **Accepted:** 07 February 2019; **Published:** 01 March 2019

## Abstract

Previous studies of the Author pointed out that the incidence of vascular brain disease (cerebrovascular disease, CVD) in several expression modalities was statistically significant and relevant in Parkinson's Disease (PD); subsequently the Author investigated the incidence of CVD in an extrapyramidal disease frequently detected in clinical practice and involved in the differential diagnostics within movement disorders, that is Essential Tremor (ET). The statistical chi-square calculator test for association between two categorical variables was applied in a first step between a population of 60 patients (2 patients without information on CVD were not included in the statistics) with ET and a control population (patients suffering from various central nervous system diseases excluding PD and ET but including the so-called Vascular Parkinsonism –VP-) of 145 subjects (16 patients without information on CVD were not included in the statistics). The result was negative ( $p$ -value is 0.696914. This result is not significant at  $p < 0.01$ ). In a second step a statistical comparison was performed between the same group of 60 patients with ET and the group of 85 patients with PD (1 patients without information on CVD was not included in the statistics) obtaining a highly significant result (the  $p$ -value is 0.000003. This result is significant at  $p < 0.01$ ). The statistical analysis concerns the presence or not of morphologically imaging signs of CVD (TC and RM Scan) in the two groups. These results demonstrate that while there is a correlation in the incidence of CVD and PD according with previous observations (actual  $p$ -value is 0.000001. This result is significant at  $p < 0.01$ ), the same correlation does not occur with the ET. The incidence of CVD in the ET has a random feature comparable to the randomness of the general population. Therefore it is hypothesized that the CVD in the ET is a pure comorbidity without pathogenetic

value - even if apparently in contrast with what assumed in the classifications defining the atherosclerotic senile tremor as a variant of the same ET - according with hypothesized different neurotransmitter networks (dopaminergic vs supposed GABAergic).

We can also speculate that the different therapeutic approach may depend on the different pathogenesis of the two pathologies (ET and PD). Further investigations result of particular interest also considering the fact often observed in clinical practice that the ET can over time evolve into PD or that in some cases there is an overlapping between PD and ET mainly in the in the tremorigen symptom.

**Keywords:** Essential Tremor; Parkinson's Disease; Cerebrovascular Disease; dopaminergic treatment; Aging

## 1. Introduction

In medical practice the finding of signs of cerebral vascular damage ranging between minimal spotting defined leukoaraiosis to multiple microinfarct or even more evident infarct\ hemorrhagic lesions in a large number of cases both in elder and in younger patients is a common experience. These findings are detected during imaging investigations often performed with different medical purposes. Therefore a previous study was carried out with the aim to assess if there could be any statistic correlation between vascular brain signs of damage and PD [1]. A further step in the design of the present study included a comparison between the incidence of Vascular Brain Damage in PD and other types of degenerative extrapyramidal diseases starting more specifically from one of the most common in the neurological practice, i.e. Essential Tremor (ET). In the first instance, a statistical comparison was made between the incidence of cerebrovascular disease (CVD) in the population with ET and a selected control population matched in age distribution and clinical conditions.

Subsequently the comparison was made between the incidence of CVD in PD and in ET, in order to verify if there was a greater incidence of CVD in the group with PD compared to that with ET, moreover a cross comparison was performed between the PD group and ET group with respect the incidence of CVD. This observation may reinforce the hypothesis that CVD does not have a casual or marginal relevance, but could be a preliminary predisposing phase of PD clinical signs since a statistical significance has been demonstrated in favor of the latter.

## 2. Materials and Methods

We considered a population of 290 patients who accessed in the out-patients clinic of the movement disorders, aged 20-97, both sexes (during a period from June 2012 to end of June 2018). Among these patients were included 60 patients (plus 2 patients without information on CVD i.e. not included in the statistics) with a definite diagnosis of ET and 85 patients (plus 1 patient without information on CVD i.e. not included in the statistics) with a definite diagnosis of PD were included. The remaining patients affected by other movement disorders were recruited as a control group (145 subjects plus 16 patients without information on CVD i.e. not included in the statistics).

A first statistical comparison [1, 4] was made between the ET group and the control group with regard to the incidence of CVD. Afterwards the same statistical comparison was made between the PD group and the control group and at between the ET group and the PD group. Statistical analysis was performed using Chi-Square Calculator Test. This is a test for association between two categorical variables which require a random sample; observations must be independent of each other, and the cell count are 2 for each cell in a 2 x 2 contingency table. The null hypothesis asserts the independence of the variables under consideration so, for example, CVD and type of population (control group vs ET or PD). The statistical variable CVD was assessed by defining three types of lesions showed by neuroimaging: diffuse multiple micro-lesions corresponding to the leukoaraiosis description, multiple infarcts with different cerebral distribution often described as subcortical white matter junctional spots with hyperintensity signal in T2 without pathological potentiation with intravenous contrast medium; these areas were described by neuroradiologists as areas of tissue necrosis with a ischemic cerebrovascular basis (lacunar infarcts). Finally diffuse cerebral damage aftereffects of stroke by both infarct/cerebral hemorrhage.

### 3. Results

The first statistical comparison between the ET group and the control group with regard to the incidence of CVD is showed in Table 1. The chi-square is 0.1517 and the  $p$ -value 0.696914, i.e. not significant at  $p < 0.01$ . The second statistical comparison between the PD group and the control group with regard to the incidence of CVD is showed in Table 2. The chi-square is 26.1456 and the  $p$ -value is out of range lower, i.e. significant at  $p < 0.01$ . The chi-square statistic with Yates correction is 24.7251, the  $p$ -value is 0.000001, i.e. significant at  $p < 0.01$ . Finally the third statistical comparison between the ET group and the PD group with regard to the incidence of CVD is showed in Table 3. The chi-square is 22.0658 and the  $p$ -value is 0.000003, i.e. the result is significant at  $p < 0.01$ .

	<b>CVD Yes</b>	<b>CVD No</b>	<b>Marginal Row Totals</b>
<b>ET</b>	28 (29.27) [0.05]	32 (30.73) [0.05]	60
<b>Control Group</b>	72 (70.73) [0.02]	73 (74.27) [0.02]	145
<b>Marginal Column Totals</b>	100	105	205 (Grand Total)

The chi-square statistic is 0.1517. The  $p$ -value is 0.696914. This result is *not* significant at  $p < 0.01$

**Table 1:** The chi-square statistic,  $p$ -value and statement of significance appear beneath the table.

	<b>CVD Yes</b>	<b>CVD No</b>	<b>Marginal Row Totals</b>
<b>PD</b>	71 (52.85) [6.23]	14 (32.15) [10.25]	85
<b>Control Group</b>	72 (90.15) [3.65]	73 (54.85) [6.01]	145
<b>Marginal Column Totals</b>	143	87	230 (Grand Total)

The chi-square statistic with Yates correction is 24.7251. The  $p$ -value is 0.000001. Significant at  $p < 0.01$ .

**Table 2:** The chi-square statistic,  $p$ -value and statement of significance appear beneath the table.

	<b>CVD Yes</b>	<b>CVD No</b>	<b>Marginal Row Totals</b>
<b>ET</b>	28 (40.97) [4.1]	32 (19.03) [8.83]	60
<b>PD</b>	71 (58.03) [2.9]	14 (26.97) [6.23]	85
<b>Marginal Column Totals</b>	99	46	145 (Grand Total)

The chi-square statistic is 22.0658. The  $p$ -value is 0.000003. This result is significant at  $p < 0.01$ .

**Table 3:** The chi-square statistic,  $p$ -value and statement of significance appear beneath the table.

#### 4. Discussion

Hypotheses and clinical descriptions on the most common extrapyramidal diseases (PD, ET, Parkinsonism) have recently been proposed, which corroborate the idea of the need to review the classification and the framing of the various clinical forms that compose the galaxy of these diseases.

Few researches have stressed the importance of the incidence of aging related disorders such as ATS and cardiocerebrovascular disease as risk factors and not simple comorbidity even in extrapyramidal diseases; particularly increasing frequency and incidence of the latter are unanimously considered linked to the growing in age average and long- life expectancy in Western countries.

The present study aimed to focus attention on the statistically and clinically quantifiable signs of cerebrovascular damage in these pathologies in order to understand whether there is a cause-effect link in the pathogenesis of their frequency increase at the epidemiological level. In a previous paper [1], the presence of a correlation with statistical significance between the CVD and the PD was verified in a group of 54 patients cured in our clinic. Indeed this correlation was not found in the comparison between the newly studied group of 60 patients with ET and CVD compared to the control population. The statistical data were confirmed not only in the comparison of each group with the control population but also by carrying out a cross-test between the two groups; moreover a very high significance was found (the chi-square statistic is 17.9797. The  $p$ -value is 0.000022. This result is significant at  $p < 0.01$ ) in the difference in incidence of the CVD respectively in the group with ET and in the group with PD.

Notice that the control population was not necessarily fitting with the common criterion adopted with healthy adult subject recruited in most clinical studies, because elderly people are generally affected by multiple disease and hardly 'healthy'; on the other hand it was necessary to make an age homogeneous comparison; the concept of healthy subject in advanced age is certainly an abstraction not adherent to clinical practice, being the majority of older people affected by various often clinically silent diseases, especially those commonly known as aging diseases (among which the most widespread is ATS). In particular, it is noticeable that in the control population subjects suffering from pathologies definable as neurodegenerative or even affected by vascular brain disease and composing a group homogeneous as concerns mean and median age, with age distribution similar to the groups of pathologies examined (PD, ET, Vascular Parkinsonism - VP) were included. In fact, in the case in which there would be eventually found a statistical significance, this would have had a more relevant weight. The results obtained are

effectively consistent with this hypothesis. As already mentioned in a previous study [1-4], the difference in incidence of CVD between the group of patients with defined PD and the control population chosen according to the above criteria was statistically significant; it is noteworthy that in the control population a group of subjects affected by the so-called 'vascular parkinsonism', that is 100% with signs of cerebrovascular damage, was included : that should strongly increase the statistical probability of incidence of CVD in the control population compared to the more restricted population with PD, but this on the opposite did not lower enough the significance in the incidence of CVD in PD.

In the present study, the observation was extended by comparing the two groups of patients affected by the most frequently pathologies detected in the movement disorders outpatient clinic, i.e. PD and ET, compared with respect to the incidence of CVD. The results were very interesting as much indicative of a more selective presumed role of ischemic damage in PD, or at least in what can be defined Extrapyramidal Disease responsive to dopaminergic therapy, when compared to ET. In previous studies [5, 7] the different pathogenic role of ischemia in PD compared to ET is consistent with the hypotheses about the different networks involved in the two diseases. In ET heterogeneous genetic determinants prevailing in the forms transmitted with an autosomal dominant character have been discovered . On the other hand the definition of ET in the elderly has been questioned, often identifying it with the clinical entity called senile tremor too. In the pathogenesis of this tremor has been called into question a cerebellum-ponto-cortical circuit and, from the anatomical-pathological point of view, cerebellar structures such as the proximal bulge of the axon of Purkinje cells are also involved.

For this reason it would seem to be a different pathogenesis in ET compared to PD, although at least a part of the cerebello-thalamo-cortical circuit (intermediate ventral nucleus of the thalamus) could be in common between the pathways involved in the pathogenesis of both tremors. This would explain, for example, the presence of a non-resting component of PD tremor and a slight response observed in some patients with ET with dopaminergic stimulation.

So far for what has been said one can be led to think that there is not really a clear distinction between the so-called PD and the remaining forms of similar Parkinson's neurodegenerative diseases including the ET, but rather there are totally dopamine responsive clinical forms (at least in the initial and intermediate stages of their evolution) and scarcely or not at all responsive ones, according to a of semeiological-clinical gradualism. What is the role played by vascular damage in presynaptic localization, with relative preservation of post-synaptic dopaminergic receptors in the so-called idiopathic PD, is not clear. Of course our observational statistical study provides clinical evidence that there is a pathogenetic correlation at the level of the Basal Ganglia and/or elsewhere between vascular damage and loss of presynaptic nerve endings in the dopaminergic pathways. This would therefore lead to hypothesize that prevalent ischemic vascular damage precedes even by many years the onset of PD by opening new pathways in the prevention and risk prediction of the disease itself.

We talk about a possible preclinical phase similar to the Mild Cognitive (MCI) Impairment of Alzheimer's Disease with the difference that in the specific case of PD the vascular damage is predominantly and silent in most cases: this will in a certain percentage of cases lead to the onset of the first clinical symptoms, while MCI is a clinically relevant entity that will or may not have the outcome in Alzheimer's Disease. The study is still ongoing with the aim of expanding the statistical sample.

## 5. Acknowledgement

The author thanks the Nurse Coordinator Mariangela Puglielli, the Professional Nurse Barbara Middei for their support in the clinical management work, the Coordinator of Outpatient Clinic Dr Rita Bartolomei and the Director of the H 2 District Dr. Carla Paradisi, for their organizing work.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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**Citation:** Zarola F. Brain Vascular Damage in Essential Tremor: Observational Study and Statistical Analysis in An Affected Population Compared with A Group with Parkinson's Disease and A Control Group. *Journal of Psychiatry and Psychiatric Disorders* 3 (2019): 031-036.



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