Micrographia and its related deficits in Parkinson's Disease- A cross sectional study

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Micrographia and Related Deficits in Parkinson's Disease: A cross sectional study

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Running Title: Micrographia and Parkinson's disease

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Article Summary:

Article Focus: In this study prevalence of micrographia in Parkinson's Disease(PD) is ascertained and the relationship of micrographia with bradykinesia and hypophonia is determined using standardized and quantitative assessment tools.

Key Messages:

Micrographia is present in nearly 50-60% PD cohort

Disease severity and impaired cognition are imporatant correlates.

It has significant relationship with bradykinesia and hypophonia

Strengths and Limitations:

Large sample size, systematic assessment methods

This study is a cross-sectional, single visit study, does not determine the effects of dopaminergic medications or shed light on the therapeutic measures.

Abstract

Background: Since 1972, there has not been a large study that has evaluated the clinical characteristics of micrographia in Parkinson's Disease (PD). Surprisingly little has been published on the prevalence and clinical profile of this phenomenon with available cohorts being case reports or alternatively retrospective signature analysis. Micrographia has been proposed to correlate with other motor issues such as bradykinesia and hypophonia.

Methods: PD subjects were prospectively enrolled from a large Movement Disorders clinic, their demographics, Hoehn & Yahr stage (H&Y), Unified Parkinson's Disease Rating Scale (UPDRS) and Mini Mental Status examination (MMSE) scores were recorded. History of micrographia was specifically ascertained, and handwriting performance quantitatively documented. Bradykinesia was determined by history and quantified by standardized tests including a finger tap, Purdue pegboard and a timed walk test, similarly hypophonia by history and the volume of speech quantified using a

decibel meter. Age-matched controls were recruited for validation of handwriting test and decibel meter recordings.

Results: Sixty-eight subjects with PD were enrolled (68 men; mean age 72.3 years), micrographia was identified in 63.2% of the cohort when verbal history used, and in 50% when handwriting test was used for ascertainment. Micrographia on history correlated significantly with disease severity (H&Y), motor impairment (UPDRS), cognitive impairment (history and MMSE) and bradykinesia and hypophonia determined both by history and quantitative testing. Micrographia correlated with age (p=0.02), MMSE testing (p=0.04), hypophonia by history (p=0.01) and bradykinesia (p = 0.04). Further, a correlation was observed with bradykinesia and hypophonia determined both by history and by quantitative testing.

Conclusion: The study revealed that micrographia was present in nearly half of the PD cohort and that the disease severity and impaired cognition were important clinical correlates. There was also an important relationship between micrographia and bradykinesia and micrographia and hypophonia , suggesting a potential overlap in pathophysiology.

Introduction:

Micrographia is a clinical feature commonly associated with Parkinson's disease (PD). The literature, however reveals a paucity of data on the prevalence and on the clinical characteristics of this potentially disabling disease manifestation. In one study, an overall prevalence of 30% was observed (at any time during their disease course, with 5% reporting micrographia as a prodromal symptom [1]. In questionnaire based cross-sectional studies, the prevalence has ranged from as low as 9% [2] to as high as 75% [3]. Additionally, micrographia has been found to have a high positive likelihood ratio [4,5] of being associated with an accurate diagnosis of PD. The phenomenon of micrographia is not restricted to PD (Huntington's disease [6], amyotrophic lateral sclerosis [7] and

lupus [8]), and these studies have not addressed an adequate number of patient to draw conclusions on the specificity of the symptom.

Micrographia has been defined as an impairment of a fine motor skill manifesting mainly as a progressive reduction in amplitude during a writing task. Micrographia can manifest in two dimensions. Handwriting may decrease in amplitude across a single line, or manifest as each line becoming progressively more affected with continued writing [9-11].

In PD, micrographia has been observed to accompany both bradykinesia, and hypophonia [9,2,13], and there has been a noted overlap in the pathophysiology of micrographia and hypophonia [12]. In this current study we sought to study PD patients utilizing systematic clinical assessments in order to accomplish the following three aims: 1 - To identify the prevalence of micrographia in a large well-characterized PD cohort, 2 - To document the clinical profile of micrographia, and 3 - To determine if a correlation exists between micrographia, bradykinesia or hypophonia.

Methods

Subjects with PD were diagnosed using United Kingdom Parkinson's Disease Society criteria [14] and were enrolled from a movement disorders clinic located in a Veterans Adminstration medical center. The study was approved by the local Institutional Review Board and all patients gave written informed consent to participate.

This was single visit study. Subjects were studied in the "ON" medication condition which was defined as being on their regular PD medications, and subjectively reporting their typical "on" response while being examined. Demographics (age, handedness, language preference), disease duration, L Dopa dose, disease severity measured by modified Hoehn & Yahr staging and Unified Parkinson's Disease Rating Scale (UPDRS) and Mini Mental Status examination (MMSE) scoring were documented (Table 1). Subjects unable to provide informed consent (MMSE <18) were excluded. Micrographia was determined by history and by a bedside clinical handwriting test designed by us for assessment of micrographia; this test was validated among age-matched controls. Neurological control patients were enrolled from general neurology clinics, including

headache, seizures, low back pain and other non-basal ganglia neurological conditions. We specifically sought a non-basal ganglia control group that had a neurological disease in an effort to create a reasonable comparator group. A specific question structured to address decrease in size of letters noted by patients during the handwriting task was used to identify subjective micrographia. Presence of micrographia was rejected if subjects reported a change in handwriting attributable to interference by tremor. Subsequently the bedside handwriting test was administered to both PD and to the neurological controls. In this test, subjects were asked to write the letters 'p' and 'd' using lower case in print style, and using a standard diameter ball point pen on a lined paper. They were instructed to do this 20 times in 2 separate rows (Fig 1). These 20 trials for each letter were written in blocks, and there were 4 such blocks consisting of 5 trials each. Time was not a constraining factor, but subjects were allowed to lift the pen only at the end of each block. A visual model was presented at the beginning of the test, and no practice session for writing was allowed. Auditory cues by the examiner were allowed. For analysis, trials from the first and last block of the letter 'd' were used, and areas of the 2 blocks were calculated (height x width). For each block, height was calculated as the maximum vertical stroke achieved, and the width was calculated as the total distance traveled by the pen horizontally. Areas were determined for the last and first block and ratio of these areas was calculated; micrographia was defined as an area drop ≥30%; a drop of >50% represented severe micrographia (Fig 1). This method of testing was validated amongst the neurological controls.

Subjective hypophonia was determined by historical information from a detailed interview, but also from objective documentation of loudness utilizing a decibel meter. Subjects were asked specifically if they experienced a clear reduction in the volume of their speech. Difficulty in speaking such as stuttering or slurring of words was rejected for the diagnosis of hypophonia. Syllable 'A' was spoken 10 times in a natural voice at 3 second intervals in a quiet room. The loudness was recorded at a set distance of 50 cm from the device. A loudness decline of >10 dB between the first and tenth trials was defined as an objective hypophonia (the method was also validated in controls).

Bradykinesia was detected clinically and quantified by a finger tap task, performance on Purdue Peg board, and a standardized timed motor walk [13,15]. In the finger tapping task, the subject was required to tap repetitively on a hard surface using the index finger of the right and left hand, done for each side, for 30 seconds; the number of taps performed in this duration was recorded. The pegboard task involved placement of as many pegs as possible over a 30 second period, and was performed with the right and left hands separately, and with both hands simultaneously. For the walking test, subjects walked a distance of 7 m back and forth as fast as possible; and the time required for walking including that for turn was recorded. This test was same as done for CAPSIT [15].

Statistical Analysis:

All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Data were described with plotting of mean/median for all variables, including age, disease duration, disease severity on H&Y staging and on total as well as motor subsection of UPDRS scale, L-DOPA dose, micrographia determined by history and handwriting test analysis, hypophonia by history and by decibel meter recordings, scores on MMSE testing, scores on finger tap task, Purdue Pegboard and timed walking test. Chi-square test was used for comparison of PD and control cohorts with regards to handwriting test and decibel meter readings. Spearman's correlation with respective approximated 95% confidence intervals based on Fisher's z-transformation was performed to compare all of the above variables with micrographia (Figure 2). Cohen's Kappa statistic was used to assess the agreement levels between micrographia and dichotomous variables, such as handwriting scores (≤ 0.7 or >0.7; a 30% decline) and hypophonia scores (<10 or ≥ 10 dB). All results were based on two-sided test with p-values < 0.05 considered statistically significant.

Results:

Sixty-eight PD subjects were enrolled (all were men, mean age = 72.3 years; mean disease duration = 7.8 years). Seven subjects had disease duration of <3 years, and six had disease durations >15 years. (see Table)

Table: Clinical characteristics of PD subjects

	Mean (Std Dev)
Age in yrs	72.3 (±9.5)
PD Duration in yrs	7.8 (±5.5)
H&Y Stage	2 (±0.8)
UPDRS Total (on score)	49.3 (±18.8)
UPDRS I	3.1 (±2.1)
UPDRS III	29.1 (±9.5)
L-DOPA Equivalent in mg	766.6 (±500.5)
MMSE	24.8 (±2.65)
Purdue Pegboard score	
Right hand	7.7 (±2.9)
Left hand	6.8 (±3)
Bilateral assessment	8.5 (±4.1)
Finger Tap score	
Right hand	61.7 (±27.2)
Left hand	60 (±30.3)
Walk time in sec	16.5 (±7.1)

H&Y(Hoehn & Yahr stage); UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, mini mental status examination.

All but two subjects were right handed; one of these two was ambidexterous. In language preference, all except two spoke only one language (English). With regards to disease severity, patients had a mean (median) H&Y stage of 2 (2), UPDRS total score of 49.3 (51.0), and UPDRS on-medication motor score of 29.1 (30). Since the presence of dyskinesia and tremors can potentially interfere with handwriting assessment of patients, these issues were recorded. Subjects were studied on- medications and in this cohort tremors were not noted at the time of assessment. Five subjects reported dyskinesia on history, and two had mild dyskinesia at the time of assessment. In this cohort, fifteen subjects had a unilateral disease (defined by Hoehn and Yahr Staging scale) with six having a score of 1, and nine having a score of 1.5. Eight of these nine subjects demonstrated micrographia, with the affected side being the dominant right side in all patients.

Micrographia was present in 63.2% of the PD cohort when subjects were asked by verbal history, and in 50% when assessed on the bedside handwriting test. Controls were all age-matched and were all men. All were right handed and like PD subjects, were not polyglots. On chi square testing, the control handwriting scores (dichotomized ≤ 0.7 or > 0.7; p= 0.0001) and the decibel meter scores differed significantly from PD (p = 0.0001). Sensitivity for the handwriting test was = 0.74 (95% CI: 0.59 – 0.86) and specificity = 0.88 (95% CI: 0.68 – 0.97). Cohen's kappa established moderate agreement between micrographia assessment on history and handwriting tests (0.5, 95% CI = 0.38-0.77); hypophonia assessment on history and objective assessment (0.85, 95% CI = 0.72–0.98). Micrographia determined by the handwriting test (thirty five subjects) was further divided into subgroups with mild and severe impairment based on criteria defined by us and as described in methods (area decrease >30% is micrographia and area decrease >50% defined as severe micrographia). Twenty three subjects had mild micrographia, 10 had severe micrographia and 2 could not write at all.

Micrographia identified on historical evaluation correlated significantly with overall disease severity and motor impairment (H & Y, UPDRS total and UPDRS III). There was a correlation with cognitive impairment determined on verbal history and on MMSE testing (p = 0.02 and p = 0.002 respectively; Figure 2). Further, a correlation was seen between this group and bradykinesia determined both by history and quantitative testing, similarly with hypophonia determined both by history and decibel meter testing (Figure 2 shows the p values).

Subjects found to have micrographia based on handwriting analysis showed correlation with age (p=0.02), MMSE testing (p=0.04), hypophonia by history (p=0.01) and bradykinesia determined by Purdue testing for the right hand (p = 0.04) and for both hands (p = 0.04).

Micrographia determined to be severe on the handwriting analysis revealed a significant correlation with disease severity: H & Y staging, the UPDRS total score, and UPDRS III

motor score. It also correlated with cognitive impairment that included verbal history, MMSE testing and UPDRS I (p for all of the above variables < 0.01 except UPDRS total p< 0.003). In this subgroup micrographia correlated with bradykinesia and hypophonia only when determined by verbal history (p = 0.0001).

Discussion

This study offers data on a large cohort of PD and control patients. Micrographia was detected in 63.2% of the PD cohort when subjects were asked by verbal history, and in 50% when assessed on the bedside handwriting test and the occurence of micrographia was influenced by disease severity and by cognition. Previous studies and estimates have been hampered by methodological issues including small sample sizes and lack of objective measures. Further micrographia assessment in this study showed strong correlation with hypophonia and bradykinesia, suggesting a possible overlap in the pathophysiology.

This was a single visit study where micrographia was identified by history and was established by a quantitative bedside handwriting test. PD patients with handwriting problems may switch their writing style from cursive to print in order to maintain legibility. For simplicity, we therefore utilized only a print style of writing for the assessment; a hierarchy of tasks including writing in cursive style, words, phrases, sentences and paragraphs was not provided to the subjects. Subjects were asked to write letters in a specific and standardized way. The area of writing covered by the specified task was determined, calculated by multiplication of height and distance. It has been observed that handwriting seems to decline along subsequent lines as the writing continues in a paragraph. In this study we therefore chose to compare the handwriting sample of the second line instead of the first. In a previous study [16], micrographia was determined based on the decline of height proportional to an increase in the length of writing. We found a similar decline in height of letters, in addition, we found the letters to be overall smaller and more crowded as the handwriting task continued which is an observation often reported by clinicians. There was a substantial increase in micrographia when the last and the first blocks in second line were compared.

It has been suggested that L-DOPA may partially improve micrographia, but this notion remains to be verified. L-DOPA seems to improve writing speed more than the size [17] and affects the amplitude of the pre-movement EEG potential (Bereitschaft potential) which is abnormal in PD. [18] Dopaminergic medication also increases striatal-frontal connectivity between the caudate nucleus and prefrontal cortex during motor timing.[19] These results suggest L-DOPA effects on handwriting occur possibly at the level of motor programming. In this study, subjects were studied on medications, and no correlation was found for micrographia and L-DOPA equivalent dose. A study on and off medications is definitely required to provide further insight.

In literature, micrographia has been reported to be more frequent in native than secondary languages, owing to impaired execution of more utilized tasks.[20] In our population, most subjects spoke only one language (English). We had only two veterans who were fluent in more than one language (they knew English and Vietnamese); therefore in this study we suspect the true effects of language on micrographia could not be discerned as the sample size of multilingual subjects was small.

There was also a possible confound of handedness on the clinical manifestation of micrographia, which has been proposed to be more frequent in those with left hemispheric lesions. [21] In our sample all subjects except two were right-handed (one of them was ambidexterous). Due to this homogeneity, the effects of handedness could not be determined. Although handwriting assessment was performed using only the dominant hand; presence of micrographia showed positive correlation with bradykinesia scores determined for both sides (Purdue pegboard and finger tap scores). It would therefore be interesting to determine if handwriting performance was affected bilaterally which was something not focused on in this study.

Presence of micrographia did not reveal any statistical correlation with the overall disease duration though there was a correlation with disease severity determined on H&Y staging [22] and UPDRS motor assessments. It is also important to note that most subjects were

unable to recall the exact onset of timing for handwriting impairment. Thus, a longitudinal follow-up of these patients will be required to determine the effects of disease progression.

The effects of external cues on the task of handwriting in PD are not clear from literature. One study demonstrated micrographia to get better in the presence of both visual as well as auditory cues [23]; in contradistinction Ondo et al [16] found handwriting to get larger when the subjects performed the handwriting task with eyes closed. We decided to keep the task simple and allowed both visual and auditory cues to be provided during the bedside handwriting test. The handwriting test was conducted on lined paper and a visual model was presented at the beginning of the task. Auditory announcements for task commencement and task conclusion were made; although unlike the previous study [23] no specific reminder to keep handwriting big was provided.

In this study, micrographia whether determined on historical evaluation or on the bedside handwriting test demonstrated a correlation with cognitive impairment.
It has been observed that there is a significant influence of mental load on micrographia [24], and increased processing demands within the writing task contribute to reduction in writing size. [25]In this study, though the mental load was kept at a minimum during the handwriting test, a hierarchy of tasks was not tested we found those with reports of cognitive impairment on history and also with lower scores on MMSE testing showed a correlation with micrographia. This study had a limitation, in that a detailed cognitive battery was not used and therefore, the effects of individual domains could not be clearly elucidated.

In this cohort micrographia revealed a significant correlation with both bradykinesia and hypophonia. Inappropriate scaling of the dynamic muscle force to the movement parameters has been proposed to be one of the underlying mechanisms for bradykinesia. [26] Handwriting issues have been found to be more apparent when a sustained ramp force is required over the duration of a writing stroke. [27] Micrographia similar to

bradykinesia, could potentially be due to a hypometric output driven by motor-premotor cortex with defects in programming or execution of handwriting instructions. Similarly hypophonia in PD may result from a hypometric output sent by motor-premotor cortex that results in inappropriate scaling of laryngeal muscles during speech. PET studies have found abnormal patterns of activation in motor-premotor cortex that may be influenced by Lee Silverman Voice therapy, with activation pattern shifting to basal ganglia and insula. [28] Based on the weight of the evidence once may hypothesize that micrographia is actually an abnormal activation of motor-premotor cortex which affects motor programming and execution and that this may explain the link to bradykinesia and hypophonia.

Future studies of PD related micrographia should be directed towards functional imaging and electrophysiological assessment of the cerebral cortex and its basal ganglia connections, and the on/off effects of dopaminergic medications. This study is the largest of its kind in the area of micrographia and it will help practitioners to understand that the issue is present in about half of all PD patients and that disease severity, cognitive impairment, bradykinesia and hypophonia all seem to be correlated, suggesting an overlap in the pathophysiology.

Legends:

Figure 1 A: Handwriting sample of subject 1 with PD. The letters 'p' and 'd' have been written using lower case in print style, on a lined paper, 20 times in 2 separate rows (Fig 1). These 20 trials for each letter are written in blocks, there are 4 such blocks consisting of 5 trials each. H2 and H1 represents maximum vertical stroke in last and first block respectively and W2 and W1 represents respective total distance traveled horizontally for the two blocks; these measurements are for the letters in the second row. Areas for the last (H2*W2) and the first (H1*W1) block was calculated and an area drop of ≥30% (0.7) designated as micrographia; a drop of >50% as severe micrographia.

*H2*W2/H1*W1 <0.7 consistent with micrographia*

*H2*W2/H1*W1 <0.5 consistent with severe micrographia*

Figure 1 B: Handwriting sample of subject 2 with PD. Second row letters are more crowded than the first, crowding particularly notable in the last few trials.

Figure 2: Forest plot used for demonstration of micrographia determined by history and its correlation with demographics, bradykinesia and hypophonia measures. $p < 0.05$ indicated by (*) and $P \leq 0.01$ by (**).

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Contributorship Statement:
Aparna Wagle-Shukla was involved in conception, organization and execution of research project, execution and critique of statistical analysis, writing of first draft, review and critique of manuscript; Song Ounprasueth was involved in design, execution, review and critique of statistical analysis, review and critique of manuscript; Michael Okun in review and critique of manuscript; Vickie Gray in execution of research project; John Schwankhaus in execution of research project; W. Steven Metzer in organization and execution of research project, review and critique of statistical analysis, review and critique of manuscript.

Conflict of Interest:
Aparna Wagle Shukla: employment - *University of Florida;*
Song Ounprasueth: employment - *University of Arkansas for Medical Sciences;*
Michael Okun- employment - *University of Florida*
Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, and the UF Foundation. Dr. Okun has in the past >24 months received nosupport from industry including travel. Dr. Okun has received royalties for publications with Demos, Manson, and Cambridge (movement disorders books). Dr. Okun has participated in CME activities on movement disorders sponsored by the USF CME office, PeerView, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria.
Vickie Gray: employment - *Central Arkansas Veterans Health Care System;*
John Schwankhaus: employment- *Central Arkansas Veterans Health Care System;*
W. Steven Metzer: employment - *Central Arkansas Veterans Health Care System*

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

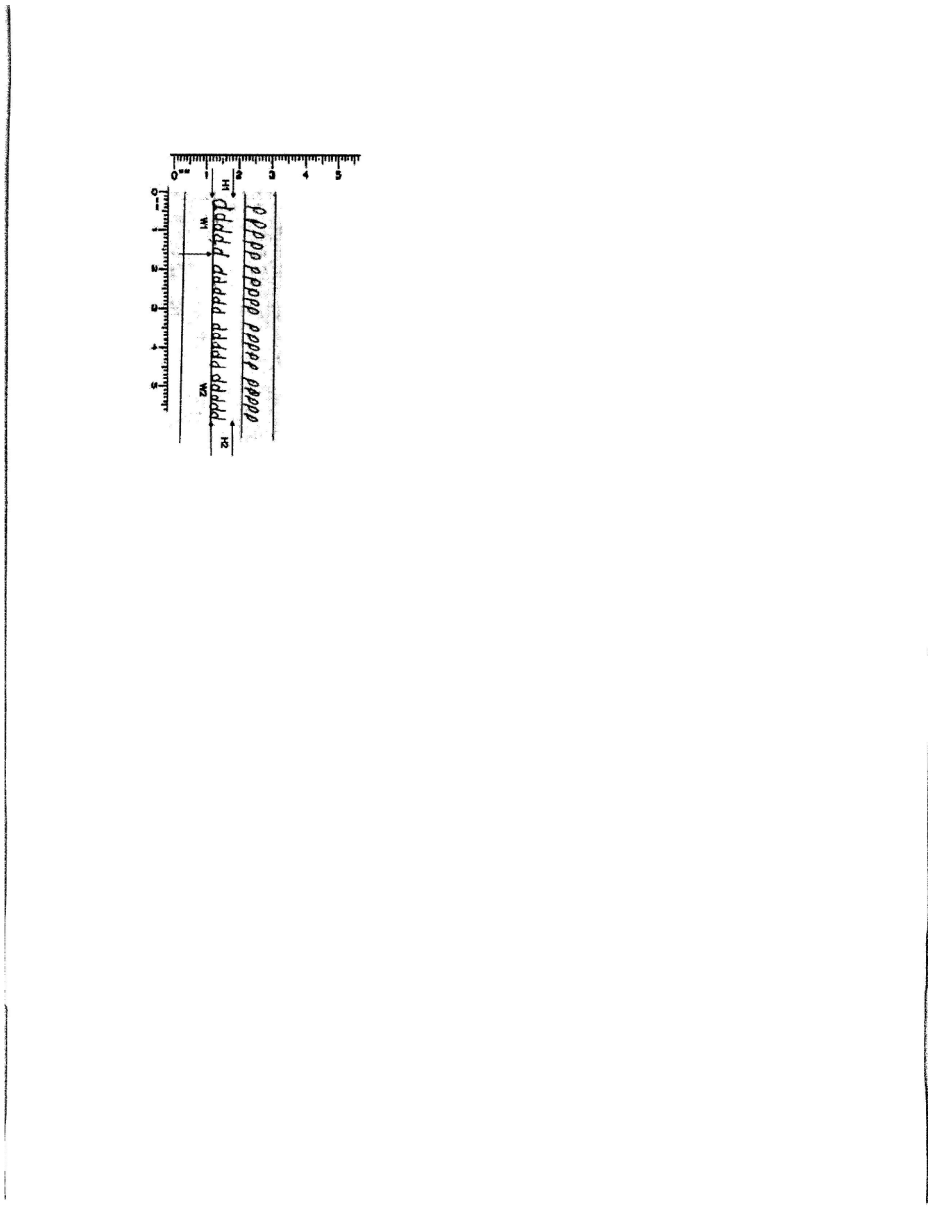
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



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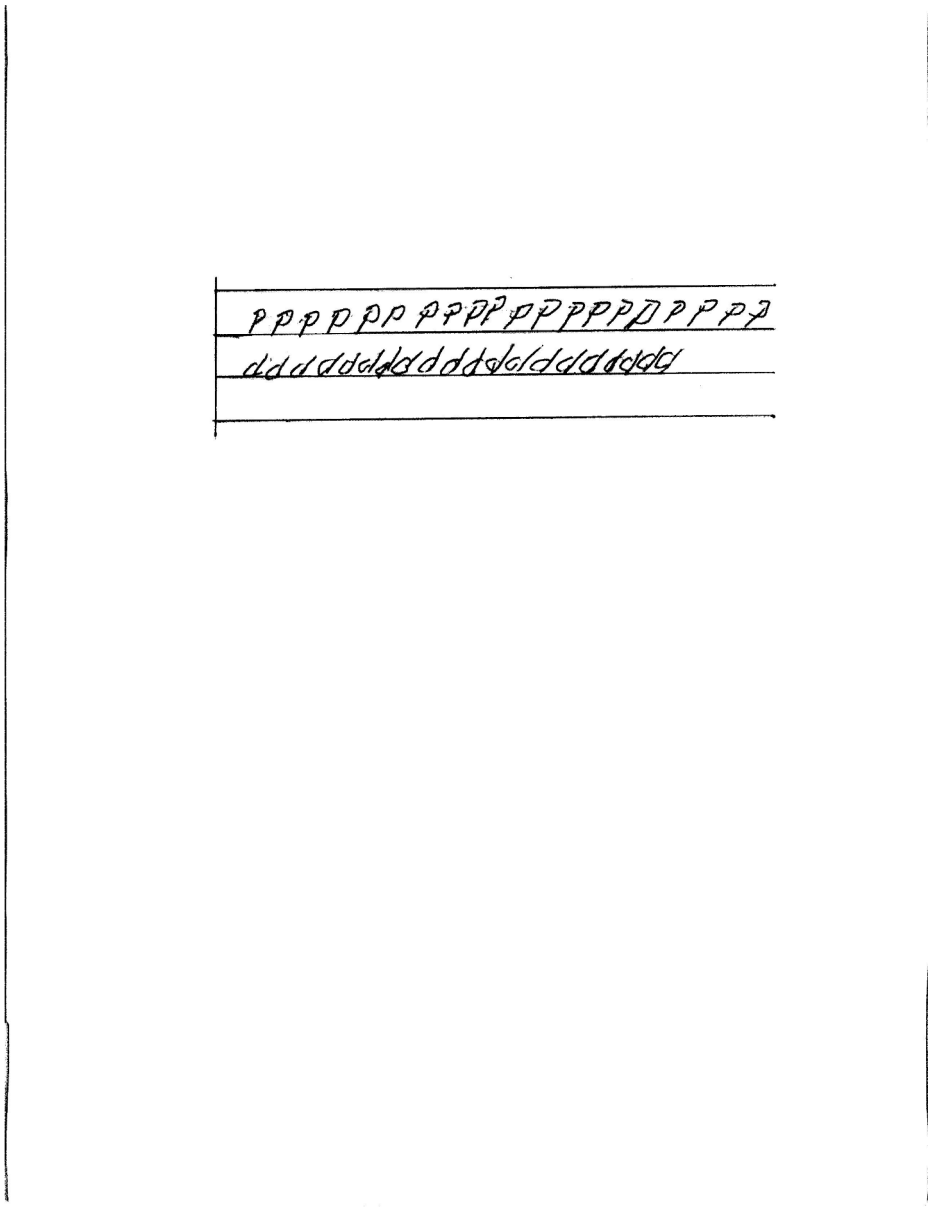

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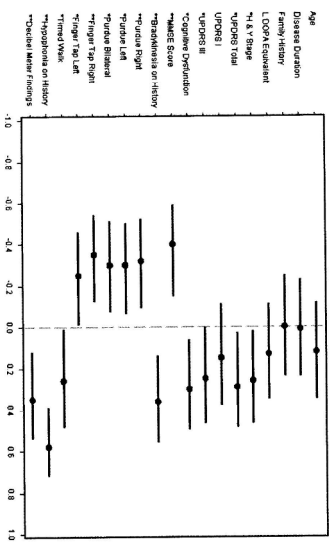

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Micrographia and its related deficits in Parkinson's Disease- A cross sectional study

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Micrographia and Related Deficits in Parkinson's Disease: A cross sectional study

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Running Title: Micrographia and Parkinson's disease

Keywords: Parkinson's disease, micrographia, bradykinesia, hypophonia

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Article Summary:

Article Focus: In this study prevalence of micrographia in Parkinson's Disease (PD) is ascertained and the relationship of micrographia with bradykinesia and hypophonia is determined using standardized and quantitative assessment tools.

Key Messages:

Micrographia is present in nearly 50-60% PD cohort

Disease severity and impaired cognition are important correlates.

It has significant relationship with bradykinesia and hypophonia

Strengths and Limitations:

Large sample size, systematic assessment methods

This study is a cross-sectional, single visit study, does not determine the effects of dopaminergic medications or shed light on the therapeutic measures. The study finds significant correlation of cognition with micrographia based on MMSE testing but does not use detailed cognitive assessment battery.

Abstract

Objectives: To determine the prevalence and clinical features associated with micrographia in Parkinson's Disease (PD).
Setting: This study was conducted at a Movement Disorders clinic located in a Veteran Administration Hospital.
Participants: PD subjects were included only if they satisfied UK Parkinson's Disease Society criteria for diagnosis. Subjects with h/o severe tremors, dystonia, dyskinesia, strokes, peripheral neuropathy and dementia were excluded.
Design: This was a case-control study where PD subjects were prospectively enrolled, their demographics, Hoehn & Yahr stage (H&Y), Unified Parkinson's Disease Rating Scale (UPDRS) and Mini Mental Status examination (MMSE) scores were recorded. All subjects were specifically asked for micrographia on history and the handwritings were quantitatively documented. Bradykinesia was determined by history and quantified by a finger tap, Purdue pegboard and a timed walk test. Similarly hypophonia was determined by history and the volume of speech quantified using a decibel meter. Controls were enrolled for validation of handwriting test scores and decibel meter recordings.
Primary outcome measures: Prevalence of micrographia in the PD cohort and the clinical factors that correlate with micrographia.

Results: 68 subjects with PD were enrolled (68 men; mean age 72.3 years). Micrographia was identified in 63.2% of the cohort on verbal history and in 50% of the cohort when the handwriting test was used for ascertainment. Micrographia ascertained on history correlated significantly with disease severity (H&Y), motor impairment (UPDRS), cognitive impairment (MMSE) and bradykinesia and hypophonia determined both by history and quantitative testing. Micrographia on handwriting test correlated with age (p=0.02), MMSE testing (p=0.04), hypophonia by history (p=0.01) and bradykinesia by quantitative testing(p = 0.04).
Conclusion: Micrographia was found in nearly half of the PD cohort. Disease severity and impaired cognition were important clinical correlates. Micrographia had a significant relationship with bradykinesia and hypophonia, suggesting a possible overlap in their pathophysiology.

Introduction:

Micrographia is a clinical feature commonly associated with Parkinson's disease (PD). The literature, however reveals a paucity of data on the prevalence and on the clinical characteristics of this potentially disabling disease manifestation. In one study, an overall prevalence of 30% was observed (at any time during their disease course, with 5% reporting micrographia as a prodromal symptom [1]. In questionnaire based cross-sectional studies, the prevalence has ranged from as low as 9% [2] to as high as 75% [3]. Additionally, micrographia has been found to have a high positive likelihood ratio [4,5] of being associated with an accurate diagnosis of PD. The phenomenon of micrographia is not restricted to PD but has been reported in Huntington's disease [6], amyotrophic lateral sclerosis [7] and lupus [8] conditions, however these studies lack adequate number of patients to draw any conclusion on the specificity of the symptom.

Micrographia has been defined as an impairment of a fine motor skill manifesting mainly as a progressive reduction in amplitude during a writing task. Micrographia can manifest in two dimensions. Handwriting may decrease in amplitude as one writes across a single line, or manifest as each line gets added with continued writing in a paragraph [9-11].

In PD, micrographia has been observed to accompany both bradykinesia, and hypophonia [9,2,12], and it has been suggested that there is an overlap in the pathophysiology of micrographia and hypophonia [13]. In this current study we sought to study PD patients

utilizing systematic clinical assessments in order to accomplish the following three aims: 1 - To identify the prevalence of micrographia in a large well-characterized PD cohort, 2 - To document the clinical profile of micrographia, and 3 - To determine if a correlation exists between micrographia, bradykinesia or hypophonia.

Methods

The study was a single visit study approved by the local Institutional Review Board and all subjects gave written informed consent to participate. Subjects with PD were enrolled from a movement disorders clinic located in a Veterans Adminstration medical center. PD subjects using United Kingdom Parkinson's Disease Society criteria [14] were included. All PD patients who presented to the clinic for their regular follow-up visit were approached on a consecutive basis over a period of two years and those who consented to participate were enrolled.

Subjects with neurological conditions like stroke and peripheral neuropathy that could potentially impair the handwriting assessment were excluded. Subjects with possibility of atypical parkinsonism, stroke, neuropathy in hands, h/o of significant tremors, dystonia and levodopa induced dyskinesias and those unable to provide informed consent (MMSE <18) were all excluded. Age and sex matched control subjects were enrolled from general neurology clinics, including headache, seizures, low back pain and other non-basal ganglia neurological conditions. We specifically sought a non-basal ganglia control group that had a neurological disease in an effort to create a reasonable comparator group. Demographics of PD subjects (age, handedness, language preference), disease duration, L Dopa dose and disease specific assessments such as modified Hoehn & Yahr staging and Unified Parkinson's Disease Rating Scale (UPDRS) were used. All Subjects were asked if they had experienced any change in their mental faculties during the course of PD and Mini Mental Status examination (MMSE) scoring was used during the physical exam. (Table 1). Subjects were studied in the "ON" medication condition which was defined as being on their regular PD medications, and subjectively reporting their typical "on" response while being examined. Presence of "micrographia" was ascertained on history. Subjects were asked if they had specifically noted a decrease in size of letters in their handwriting during the writing task. Handwriting was then documented by a bedside clinical handwriting test in both PD and control groups. The handwriting test was

designed by us specially for assessment of micrographia and was validated amongst the control group. In this test, subjects were asked to write the letters 'p' and 'd' using lower case in print style, and using a standard diameter ball point pen on a lined paper. They were instructed to do this 20 times in 2 separate rows (Fig 1). These 20 trials for each letter were written in blocks, and there were 4 such blocks consisting of 5 trials each. Time was not a constraining factor, but subjects were allowed to lift the pen only at the end of each block. A visual model was presented at the beginning of the test, and no practice session for writing was allowed. Auditory cues by the examiner were allowed. For analysis, trials from the first and last block of the letter 'd' were used, and areas of the 2 blocks were calculated (height x width). For each block, height was calculated as the maximum vertical stroke achieved, and the width was calculated as the total distance traveled by the pen horizontally. Areas were determined for the last and first block and ratio of these areas was calculated; micrographia was defined as an area drop ≥30%; a drop of >50% represented severe micrographia (Fig 1). The investigators (AWS and WSM) performed this assessment, were not blinded to the two groups and the method of testing was validated amongst the neurological controls.

Hypophonia was determined by history based on specific questioning during interview where subjects were asked if they experienced a clear reduction in the volume of their speech. Difficulty in speaking such as stuttering or slurring of words was rejected for the diagnosis of hypophonia. The volume of speech or loudness was documented objectively with a decibel meter. Syllable 'A' was spoken as naturally as possible 10 times at 3 second intervals in a quiet room. The loudness of speech was recorded with the decibel meter being placed at a set distance of 50 cm from the mouth. A loudness decline of ≥10 dB between the first and tenth trials was defined as an objective hypophonia (the method also validated in controls).

Bradykinesia was ascertained on history by specifically asking for problems with slowness in movement and UPDRS II questions. Quantitative assessment of bradykinesia was achieved with the help of a finger tap task, Purdue Peg board testing and a standardized timed motor walk [13,15]. In the finger tapping task, the subject was

required to tap repetitively on a hard surface using the index finger of the right and left hand, done for each side, for 30 seconds; the number of taps performed in this duration was recorded. The pegboard task involved placement of as many pegs as possible over a 30 second period, and was performed with the right and left hands separately, and with both hands simultaneously. For the walking test, subjects walked a distance of 7 m back and forth as fast as they could; and the time required for walking including turns was recorded.[15].

Statistical Analysis:

All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Data were described with plotting of mean/median for all variables, including age, disease duration, disease severity on H&Y staging and on total as well as motor subsection of UPDRS scale, L-DOPA dose, micrographia determined by history and handwriting test analysis, hypophonia by history and by decibel meter recordings, scores on MMSE testing, scores on finger tap task, Purdue Pegboard and timed walking test. Chi-square test was used for comparison of PD and control cohorts with regards to handwriting test and decibel meter readings. Spearman's correlation with respective approximated 95% confidence intervals based on Fisher's z-transformation was performed to compare all of the above variables with micrographia (Figure 2). Cohen's Kappa statistic was used to assess the agreement levels between micrographia and dichotomous variables, such as handwriting scores (≤ 0.7 or >0.7; a 30% decline) and hypophonia scores (<10 or ≥ 10 dB). All results were based on two-sided test with p-values < 0.05 considered statistically significant.

Results:

Demographics (see Table)

68 PD subjects were enrolled (all were men, mean age = 72.3 years; mean disease duration = 7.8 years). 20 additional subjects were approached however they did not consent for participation.

Seven subjects had disease duration of < three years, and six had disease durations >15 years. All but two subjects were right handed; one of these two was ambidexterous. In

language preference, all except two spoke only one language and that was English. Their levodopa equivalents, UPDRS, MMSE assessments are shown in the table. There were no subjects noted to have tremors and dystonia at the time of assessment most likely due to the fact that subjects were studied on- medications. However mild dyskinesia was observed in two subjects at the time of assessment. In addition, general neurological exam did not reveal presence of neuropathy or stroke like deficits.

Controls were all age-matched and were all men. All were right handed and like PD subjects, were not polyglots.

Table: Clinical characteristics of PD subjects

	Mean (Std Dev)
Age in yrs	72.3 (±9.5)
PD Duration in yrs	7.8 (±5.5)
H&Y Stage	2 (±0.8)
UPDRS Total (on score)	49.3 (±18.8)
UPDRS I	3.1 (±2.1)
UPDRS III	29.1 (±9.5)
L-DOPA Equivalent in mg	766.6 (±500.5)
MMSE	24.8 (±2.65)
Purdue Pegboard score	
Right hand	7.7 (±2.9)
Left hand	6.8 (±3)
Bilateral assessment	8.5 (±4.1)
Finger Tap score	
Right hand	61.7 (±27.2)
Left hand	60 (±30.3)
Walk time in sec	16.5 (±7.1)

H&Y(Hoehn & Yahr stage); UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, mini mental status examination.

Prevalence of Micrographia

Micrographia was present in 63.2% of the PD cohort (43 subjects) when subjects were asked on history if their handwriting had specifically become small. Nearly 50% of the PD cohort (35 subjects) demonstrated micrographia when the bedside handwriting test was performed. There was no control subject who reported micrographia on history. On chi square testing, the control handwriting scores (dichotomized ≤ 0.7 or > 0.7; p= 0.0001) differed significantly from PD (p = 0.0001). The sensitivity for the handwriting

test was determined to be = 0.74 (95% CI: 0.59 – 0.86) and specificity = 0.88 (95% CI: 0.68 – 0.97). Cohen's kappa established moderate agreement between micrographia assessment on history and handwriting tests (0.5, 95% CI = 0.38-0.77); 15 PD subjects had a unilateral disease (defined by Hoehn and Yahr Staging scale) with six having a score of 1, and nine having a score of 1.5. Eight of these nine subjects demonstrated micrographia, with the affected side being the dominant right in all patients.

Assessment of hypophonia and Bradykinesia

38 PD subjects (out of 68) reported presence of hypophonia when specifically asked on history. 36 subjects showed a decline of ≥10 dB when decibel meter scores were used for determination. Cohen's kappa revealed significant correlation between hypophonia assessment on history and objective assessment (0.85, 95% CI = 0.72–0.98). On chi square testing, there was significant difference between decibel meter scores in PD cohort and controls (p = 0.0001). There were 54 subjects who reported bradykinesia when specifically asked on history. Their quantitative assessment results are shown in the table.

Factors affecting micrographia

In the PD cohort, 43 subjects were found to have micrographia based on history. This group showed significant correlation with overall disease severity and motor impairment (H & Y, UPDRS total and UPDRS III) and cognitive impairment determined both by history and the MMSE testing (p = 0.02 and p = 0.002 respectively; Figure 2). It correlated with bradykinesia (determined both by history and quantitative testing) and hypophonia (determined both by history and decibel meter testing). Figure 2 shows the p values.

Micrographia when identified based on handwriting analysis (35 subjects), showed significant correlation with age (p=0.02), MMSE testing (p=0.04), hypophonia by history (p=0.01) and bradykinesia determined by Purdue testing for the right hand (p = 0.04) and for both hands (p = 0.04).

This group with micrographia on handwriting test was further divided into subgroups with mild and severe impairment based on criteria described in methods (area decrease >30% is micrographia and area decrease >50% defined as severe micrographia). 23

subjects had mild micrographia, 12 had severe micrographia and two of these 12 had extreme difficulty in completion of the handwriting test. The subgroup with severe micrographia revealed a significant correlation with H & Y staging, the UPDRS total score (p=0.003), and the UPDRS III motor score (p= 0.01), bradykinesia (p = 0.0001) and hypophonia (p = 0.0001) determined by history. Severe micrographia also correlated with cognitive impairment assessed by history, MMSE testing and UPDRS I (p= 0.01).

Discussion

This study offers data on a large cohort of PD and control patients. Micrographia was identified in 63.2% of the PD cohort when subjects were specifically questioned for micrographia on history and detected in nearly 50% of the cohort when bedside handwriting test was used for quantitative assessment. Disease severity and cognition were identified as important factors affecting micrographia and further there was a strong correlation of micrographia with hypophonia and bradykinesia, suggesting a possible overlap in the pathophysiology.

Previous studies and estimates have been hampered by methodological issues including small sample sizes and lack of objective measures. This was a single visit study where micrographia was identified by history and was established by a quantitative bedside handwriting test. PD patients with handwriting problems may switch their writing style from cursive to print in order to maintain legibility. For simplicity, we therefore utilized only a print style of writing for the assessment; a hierarchy of tasks including writing in cursive style, words, phrases, sentences and paragraphs was not provided to the subjects. Subjects were asked to write letters in a specific and standardized way. The area of writing covered by the specified task was determined, calculated by multiplication of height and distance. It has been observed that handwriting seems to decline along subsequent lines as the writing continues in a paragraph. In this study we therefore chose to compare the handwriting sample of the second line instead of the first. In a previous study [16], micrographia was determined based on the decline of height proportional to an increase in the length of writing. We found a similar decline in height of letters, in

addition, we found the letters to be overall smaller and more crowded as the handwriting task continued which is an observation often reported by clinicians. There was a substantial increase in micrographia when the last and the first blocks in second line were compared.

We found 12 PD subjects with severe micrographia and two out of these twelve could barely complete the handwriting test. The handwriting capacity for these two subjects was noted to be significantly diminished and almost illegible even at the time of signing the consent form and on the item of writing a sentence for the MMSE test. These two subjects were assessed at the time when their dopaminergic medications had begun to wear off. Besides a possibility of underlying apraxia for writing cannot be ruled out but we did not specifically test for limb-kinetic or ideomotor apraxia.

Handwriting assessment can be potentially marred by the presence of dystonia, tremors, dyskinesias, history of stroke and peripheral neuropathy affecting the hand. These factors were specifically excluded for the PD subjects though we did not exclude limb apraxia, hand injuries, arthritis of neck and hand joints. These factors should be considered too and excluded for future studies.

The subjects who participated in the study were all men and veterans. They were enrolled from a tertiary care center and their handwritings were determined by unblinded raters. These factors may have introduced a selection and assessment bias in the methods.

It has been suggested that L-DOPA may partially improve micrographia, but this notion remains to be verified. L-DOPA seems to improve writing speed more than the size [17] and affects the amplitude of the pre-movement EEG potential (Bereitschaft potential) which is abnormal in PD. [18] Dopaminergic medication also increases striatal-frontal connectivity between the caudate nucleus and prefrontal cortex during motor timing.[19] These results suggest L-DOPA effects on handwriting occur possibly at the level of motor programming. In this study, subjects were studied on medications, and no correlation was found for micrographia and L-DOPA equivalent dose. A study on and off medications is definitely required to provide further insight.

In literature, micrographia has been reported to be more frequent in native than secondary languages, owing to impaired execution of more utilized tasks.[20] In our population, most subjects spoke only one language (English). We had only two veterans who were fluent in more than one language (they knew English and Vietnamese); therefore in this study we suspect the true effects of language on micrographia could not be discerned as the sample size of multilingual subjects was small.

There was also a possible confound of handedness on the clinical manifestation of micrographia, which has been proposed to be more frequent in those with left hemispheric lesions. [21] In our sample all subjects except two were right-handed (one of them was ambidexterous). Due to the homogeneity in the cohort, the effects of handedness could not be determined. Although handwriting assessment was performed using only the dominant hand; presence of micrographia showed positive correlation with bradykinesia scores determined for both sides (Purdue pegboard and finger tap scores). It would therefore be interesting to determine if handwriting performance was affected bilaterally which was something not focused on in this study.

Presence of micrographia did not reveal any statistical correlation with the overall disease duration though there was a correlation with disease severity determined on H&Y staging [22] and UPDRS motor assessments. It is also important to note that most subjects were unable to recall the exact onset of timing for handwriting impairment. Thus, a longitudinal follow-up of these patients will be required to determine the effects of disease progression.

The effects of external cues on the task of handwriting in PD are not clear from literature. One study demonstrated micrographia to get better in the presence of both visual as well as auditory cues [23]; in contradistinction Ondo et al [16] found handwriting to get larger when the subjects performed the handwriting task with eyes closed. We decided to keep the task simple and allowed both visual and auditory cues to be provided during the bedside handwriting test. The handwriting test was conducted on lined paper and a visual model was presented at the beginning of the task. Auditory announcements for task

commencement and task conclusion were made; although unlike the previous study [23] no specific reminder to keep handwriting big was provided.

It has been observed that there is a significant influence of mental load on micrographia [24], and increased processing demands within the writing task contribute to reduction in writing size. [25]In this study, although the mental load was kept at a minimum during the handwriting test and a hierarchy of tasks was not tested we found those with reports of cognitive impairment on history and also with lower scores on MMSE testing showed a correlation with micrographia. We found the MMSE scores in this cohort were lower than what one could expect for the H&Y scores recorded. This was very intriguing and we think there could be multiple factors contributing. The study was performed in an older population, we did not record the educational backgrounds of participants, their medication records were not reviewed and a detailed cognitive assessment was not performed. Unfortunately, MMSE testing in PD serves only as a screening tool and does not capture all aspects of cognitive functioning.

In this cohort, micrographia revealed a significant correlation with both bradykinesia and hypophonia. Inappropriate scaling of the dynamic muscle force to the movement parameters has been proposed to be one of the underlying mechanisms for bradykinesia. [26] and handwriting issues have been found to be more apparent when a sustained ramp force is required over the duration of a writing stroke. [27] Similarly inappropriate scaling of laryngeal muscles during speech that results from a hypometric output sent by motor-premotor cortex is the underlying basis of hypophonia in PD. PET studies have found abnormal patterns of activation in motor-premotor cortex that may be influenced by Lee Silverman Voice therapy, with activation pattern shifting to basal ganglia and insula. [28] Based on the weight of the evidence one could hypothesize that micrographia similar to bradykinesia and hypophonia, is probably due to a hypometric output driven by motor-premotor cortex with defects in execution of handwriting instructions (inappropriate scaling) and that this may explain the link to bradykinesia and hypophonia.

Future studies of PD related micrographia should be directed towards functional imaging and electrophysiological assessment of the cerebral cortex and its basal ganglia connections, and the on/off effects of dopaminergic medications. This study is the largest of its kind in the area of micrographia and it will help practitioners to understand that the issue is present in about half of all PD patients and that disease severity, cognitive impairment, bradykinesia and hypophonia all seem to be correlated, suggesting an overlap in the pathophysiology.

Legends:

Figure 1 A: Handwriting sample of subject 1 with PD. The letters 'p' and 'd' have been written using lower case in print style, on a lined paper, 20 times in 2 separate rows (Fig 1). These 20 trials for each letter are written in blocks, there are 4 such blocks consisting of 5 trials each. H2 and H1 represents maximum vertical stroke in last and first block respectively and W2 and W1 represents respective total distance traveled horizontally for the two blocks; these measurements are for the letters in the second row. Areas for the last (H2*W2) and the first (H1*W1) block was calculated and an area drop of ≥30% (0.7) designated as micrographia; a drop of >50% as severe micrographia.
*H2*W2/H1*W1 <0.7 consistent with micrographia*
*H2*W2/H1*W1 <0.5 consistent with severe micrographia*

Figure 1 B: Handwriting sample of subject 2 with PD. Second row letters are more crowded than the first, crowding particularly notable in the last few trials.

Figure 2: Forest plot used for demonstration of micrographia determined by history and its correlation with demographics, bradykinesia and hypophonia measures. $p < 0.05$ indicated by (*) and $P \leq 0.01$ by (**).

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Contributorship Statement:
Aparna Wagle-Shukla was involved in conception and design, acquisition of data, interpretation of data, drafting the article and final approval of the version;

Song Ounprasueth was involved in interpretation of data, drafting the article and final approval of the version;
Michael Okun was involved in revising the article critically for important intellectual content, final approval of the version to be published
Vickie Gray was involved in revising the article critically for important intellectual content, final approval of the version to be published
John Schwankhaus was involved in revising the article critically for important intellectual content, final approval of the version to be published
W. Steven Metzer was involved in conception and design, acquisition of data, drafting the article and final approval of the version;

Conflict of Interest:

Aparna Wagle Shukla: employment - *University of Florida;*
Song Ounprasueth: employment - *University of Arkansas for Medical Sciences;*
Michael Okun- employment - *University of Florida*
Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, and the UF Foundation. Dr. Okun has in the past >24 months received nosupport from industry including travel. Dr. Okun has received royalties for publications with Demos, Manson, and Cambridge (movement disorders books). Dr. Okun has participated in CME activities on movement disorders sponsored by the USF CME office, PeerView, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria.
Vickie Gray: employment - *Central Arkansas Veterans Health Care System;*
John Schwankhaus: employment- *Central Arkansas Veterans Health Care System;*
W. Steven Metzer: employment - *Central Arkansas Veterans Health Care System*

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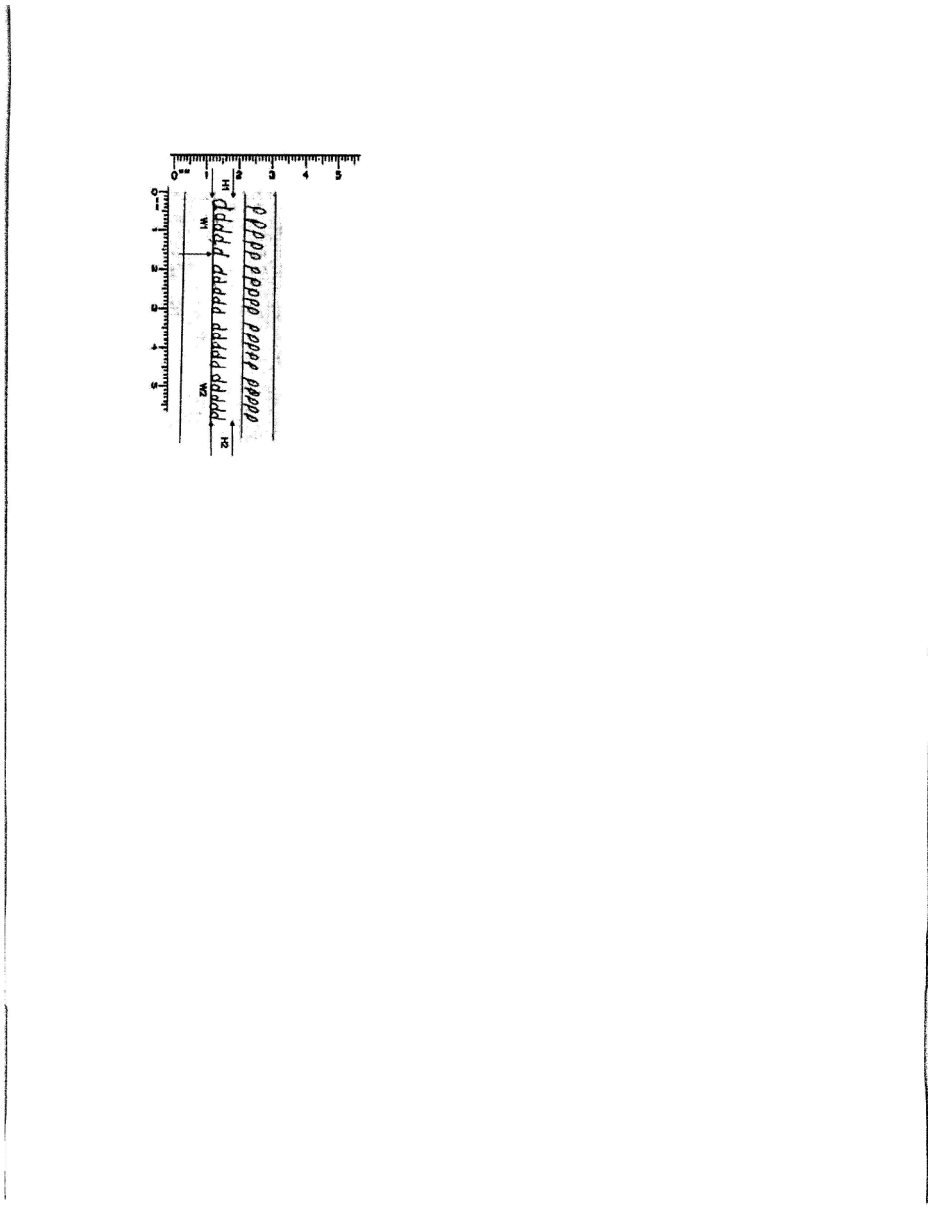

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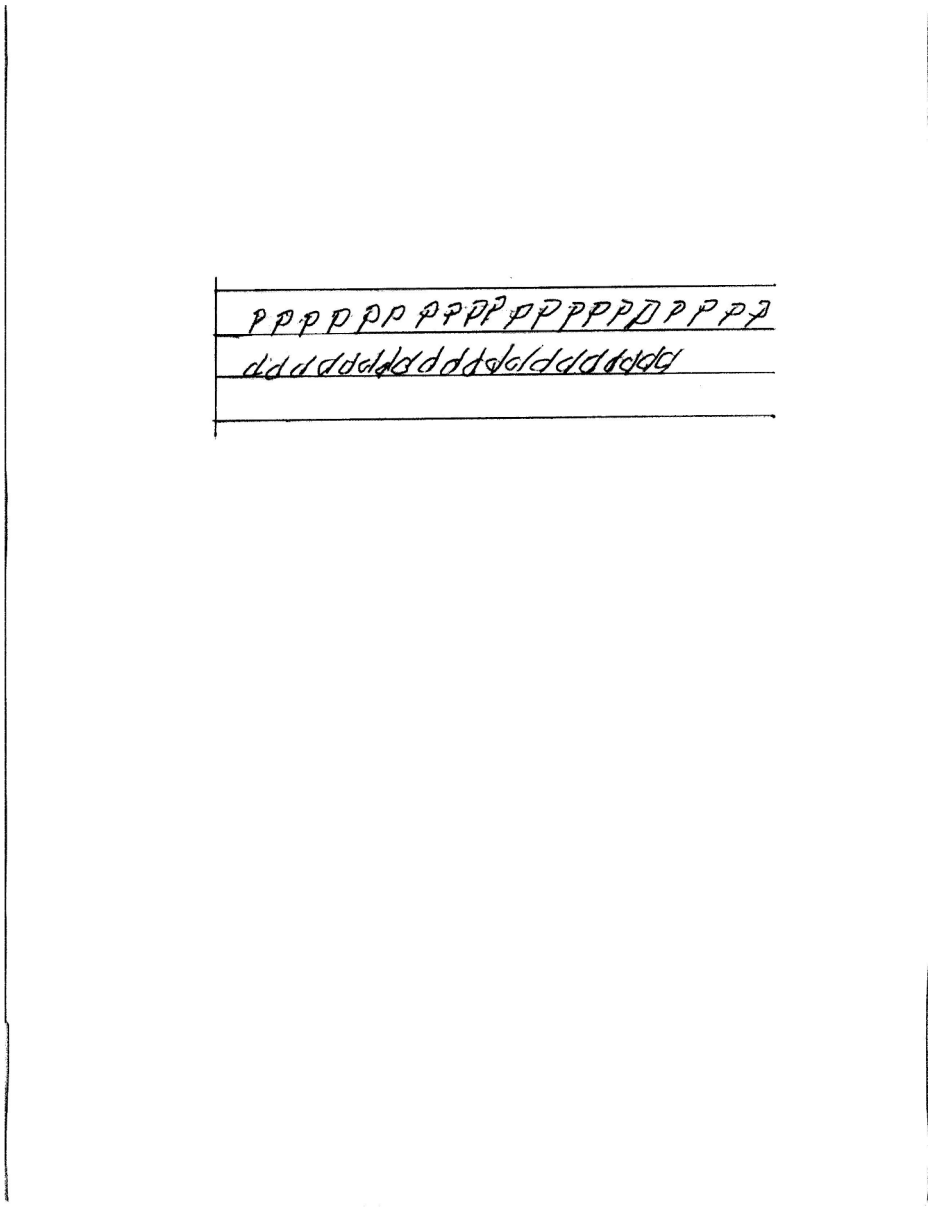

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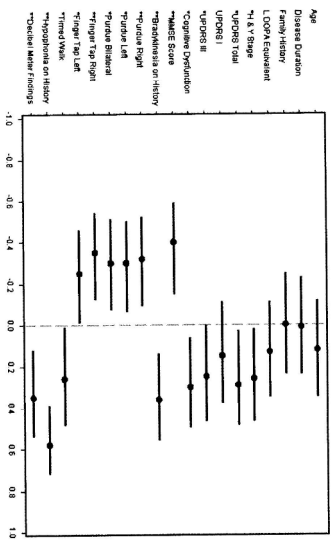

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.