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Screening of Idiopathic Parkinson Disease in First Degree Relatives in A sample of Egyptian Patients

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Abstract

Aim of the study: Screening of idiopathic Parkinson's disease in first degree relatives in a sample of Egyptian patients by smell test and hyperechogenicity of substantia nigra and hypotrophy of vagus nerve.

Methods: This is a cross-sectional observational study was done on forty-one Egyptian patients of idiopathic Parkinson disease and sixty of their first degree relatives collected from outpatient movement disorder clinic in Al Zahraa University Hospital and Kasr ELainy hospital from period February 2020 to November 2020. Demographic, clinical data, smell test, and transcranial sonography, and vagus nerve ultrasound of patients and their relatives were correlated to each other.

Results: As regards 41 Parkinson patients: 25 (61.0%) have vagus nerve hypotrophy, 27 (65.9%) have substantia nigra hyperechogenicity, and 24 (58.5%) have hyposmia.

As regard 60 relatives: 36 (60.0%) have vagus nerve hypotrophy , 26 (43.3%)have substantia nigra hyperechogenecity ,and 24 (40.0%) have hyposmia .

There was no statistically significant difference (P > 0.05) found between patients and their relatives regarding vagus nerve caliber, and smell test while there was a statistically significant(P <0.05) difference between them regarding total substantia nigra hyperechogenicity.

Conclusion: We found substantia nigra hyperechogenicity, vagus nerve hypotrophy, and hyposmia in first-degree relatives as well as that is seen in Parkinson patients.

Keywords: *Substantianigra hyperechogenicity, vagus nerve hypotrophy, Hyposmia, Relatives of idiopathic Parkinson, Non-Motor Symptoms Questionnaire.*

INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer disease .It is considered a sporadic disease with 15% of patients have family history and 5-10% have a monogenic form of the disease with Mendelian inheritance. **(Deng *et al., 2018*).**

The diagnosis of PD is based on clinical symptoms because no validated diagnostic biomarker of PD is available. However, multiple family aggregation studies supported that the relatives of PD,

especially the siblings of patients, had a higher risk of PD than the relatives of non-PD patients ***(Heinzel, et al., 2019).***

The first-degree relatives (FDR) of PD patients had a higher risk of PD and also had more NMS ***(Liu et al., 2019).***

In Parkinson's disease (PD) approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before patients fulfill the clinical criteria of PD **(*Jellinger, 2019).***

Transcranial sonography (TCS) is a noninvasive diagnostic imaging technique that allows scanning of brain parenchyma. Over 90% of Patients with idiopathic PD exhibit hyperechogenecity of substantia nigra and also in about 9% of healthy adults. There also appears to be a genetic susceptibility for SN+ in relatives of PD patients ***(Toomsoo, 2019).***

Olfactory dysfunction and autonomic dysfunction can precede the motor features of PD by many years suggesting that hyposmia may be a biomarker for premotor PD with sensitivity (77 %) and specificity (85 %) ***(Postuma & Berg, 2016).***

Many other studies also showed that olfactory dysfunction in asymptomatic first-degree relatives of PD is associated with elevated risk to develop clinical PD. ***(Fullard et al., 2017).***

High-resolution ultrasound (HR-US) is the method of choice for imaging mid-cervical vagus nerve caliber ***(Walter et al., 2018).***

AIM OF WORK

Screening of idiopathic Parkinson Disease in first degree relatives in a sample of Egyptian patients by transcranial sonography of substantia nigra, ultrasound of vagus nerve and hyposmia.

SUBJECTS AND METHODS

Type, place and period of the study
cross-sectional study was done at neurology department at Al Zahraa university hospital, Al-Azhar University . It was carried out during the period from February2020 to November 2020.

Study population
First group included 41patients of PD who meet the UK PD Brain Bank criteria for diagnosis.
Second group included sixty first-degree relatives siblings, brothers, or sisters of mentioned patients.

Exclusion criteria
History of vascular disorders e.g diabetes or hypertension, Alzheimer disease**,** Other extrapyramidal disorders including secondary Parkinsonian syndromes e.g multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration , diffuse Lewy body disease .Possible causes of hyposmia e.g (Head injury, infections, such as the flu, polyps in the nose, or sinuses) . Cognitive function affection.

Ethical consideration
The study protocol was approved by ethical review committee of Faculty of Medicine for Girls, Cairo, Al-Azhar University, Egypt. Participants of the study was voluntary; an informed written consent was taken from each participant before enrolment into the study. Data were unnamed and coded to guarantee privacy of the participants.

METHODS
Evaluation of Group A patients according to the Unified Parkinson disease rating scale UPDRS and Hoehn and Yahr stage.

Identification of non-motor symptoms of Parkinson disease in Group B participants using NMSQ.

Clinical assessment of olfaction for Parkinson patients and their relatives through Odor detection threshold smell test (BUTANOL THRESHOLD TEST): We used aqueous dilutions of 1-butanol (n butyl alcohol) as the odorant. The highest concentration (4%) in deionized water is called dilution step 0, and then the solution is diluted by successive factors of 3 up to step 14. With the patient`s eyes closed the test solutions were presented in polyethylene bottles. Testing began with a low concentration of butanol dilution, e.g. bottle number 14 which is the least concentration, and a blank (Deionized water only). The patient had to decide which was smelled the strongest. If the answer was wrong, the concentration was increased (**Risberg-Berlin, 2009).**

NeuroSonological investigations including:
Transcranial sonography of substantia nigra:
SN was visualized in the mesencephalic brainstem plane with a high-end (important for a sufficient B-mode resolution) ultrasound machine (Samsung HS60) equipped with PA1-5A phased array transducer in temporal bone windows. Through the midbrain, the butterfly-shaped hypoechogenic midbrain was delineated from the highly echogenic basal cisterns. The area of ipsilateral hyperechogenicity is encircled manually and thereby measured planimetrically. PD patients and their relatives were classified according to the ultrasound pattern of the SN into a group of subjects with a signal extension at the SN of more than 0.25 cm2 (hyperechogenic SN) and a group of subjects with SN signal extension equal to or below 0.25 cm2 Figure (1).

Ultrasonography of vagus nerve:
Cases were examined with HRUS using an ultrasound system (Samsung HS60) LA3-14 AD linear array transducer. The VN was located laterally to the common carotid artery and dorsally to the internal jugular vein within the carotid sheath (Fig. 2). The VN was visualized bilaterally at the level of the proximal carotid sinus where the distal common carotid artery just starts to bulge. at the level of the proximal carotid sinus where the distal common carotid artery just starts to bulge.

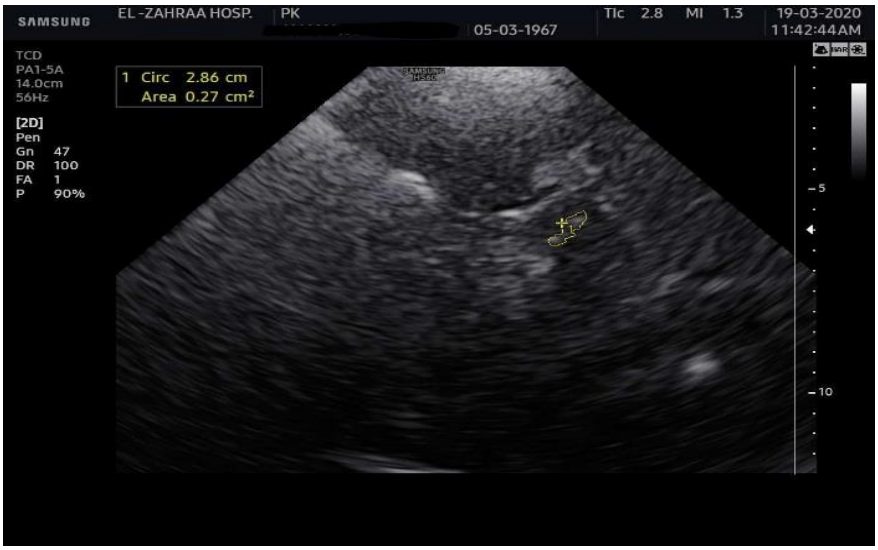

Fig 1 : Transcranial sonography of the midbrain through a temporal bone window in Son of Parkinson patient . We identified the butterfly-shaped midbrain , and manually encircled the interior hyperechogenic area of substantia nigra .It is 0.27cm2 (hyperechogenic SN).

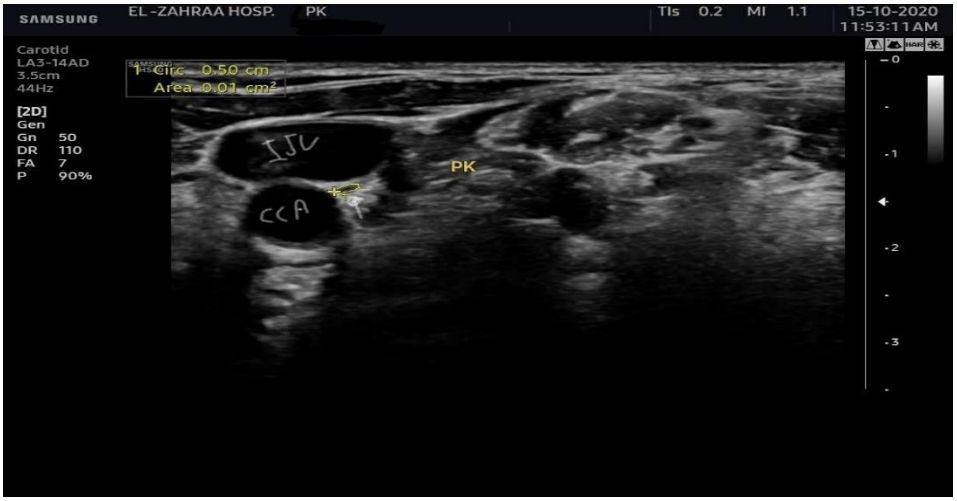

Fig 2: High-resolution ultrasonography (HR-US) of vagus nerve in the carotid sheath between the common carotid artery and the jugular vein in Son of Parkinson patient showing (CSA 0.01 cm2) hypotrophy .

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and

ranges. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using *Chi-square test* and/or *Fisher exact test* when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using *Independent t-test* .The comparison between two independent groups with quantitative data and non-parametric distribution was done by using *Mann-Whitney test* .The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as:P-value > 0.05: Non significant (NS) .P-value < 0.05: Significant (S) .P-value < 0.01: Highly significant (HS).

RESULTS:

Figure (3): Non Motor Symptoms Questionnaire in relative group
Table (1): Demographic data of the studied patients.
Table (2): Demographic data of the studied patient's relatives.
Table (3): Neurosonological investigations and smell test in patients and their relatives **.**
Table (4): Relation of vagus nerve caliber results of patients group with demographic, characteristics, severity and smell test results**.**
Table (5): Relation of substantia nigra hyperechogenicity results of patients group with demographic, characteristics, severity and smell test results.
Table (6): Relation of vagus nerve caliber result of relatives group with Non Motor Symptoms Questionnaire (NMSQ).
Table (7): Relation of substantia nigra hyperechogenicity results of relatives group with demographic data, relation to patient, and smell test.
Table (8): Relation of substantia nigra hyperechogenicity results of relatives group with NMSQ.
Table (9): Relation of smell test of relatives with their demographic, characteristics and sonological examination .
Table (10): Relation of smell test of relatives with their (NMSQ).

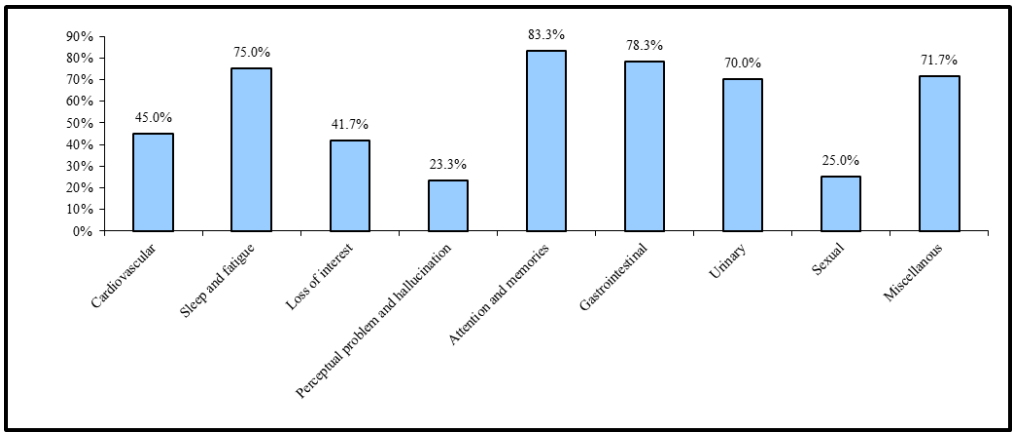

Figure (3): (NMSQ) in relative group

Table (2): Demographic data of the studied patients

Patients		**No. = 41**
Age of Patients	Mean±SD	67.46 ± 9.68

	Range	51 – 85
Sex	Male Female	25 (61.0%) 16 (39.0%)
Onset	Median(IQR) Range	6 (3 - 8) 1 – 15
Type	Rigidity Tremors Mixed	7 (17.1%) 13 (31.7%) 21 (51.2%)
F.H	Negative Positive	29 (70.7%) 12 (29.3%)
Mentation, Behavior and Mood (max. 16)	Median(IQR) Range	8 (5 - 9) 3 – 12
Activities of Daily Living (max,52)	Mean±SD Range	22.68 ± 8.15 10 – 38
Motor Examination (max.108)	Mean±SD Range	54.34 ± 15.52 28 – 80
TOTAL SCORE (176)	Mean±SD Range	84.63 ± 24.45 44 – 127
Sleep Disturbance	No Yes	10 (24.4%) 31 (75.6%)
Heohn and Yahr	Unilateral involvement Bilateral involvement Mild to moderate involvement Severe disability	4 (9.8%) 7 (17.1%) 20 (48.8%) 10 (24.4%)

Table (2): Demographic data of the studied patient's relatives

Relative		**No. = 60**
Age of relative	Mean±SD Range	44.88 ± 11.94 30 – 70
Sex	Male Female	45 (75.0%) 15 (25.0%)
Relation	Brother/Sister Son/Daughter	39 (65.0%) 21 (35.0%)

Table (3): Neurosonological investigations and smell test in patients and their relatives

		Patients **No. = 41**	**Relative** **No. = 60**	**Test value**	**P-value**
Vagus n					
Right	Normal Hypotrophy	18 (43.9%) 23 (56.1%)	26 (43.3%) 34 (56.7%)	0.003	0.956
Left	Normal	20 (48.8%)	32 (53.3%)	0.321	0.571

	Hypotrophy	21 (51.2%)	28 (46.7%)		
Total	Normal Hypotrophy	16 (39.0%) 25 (61.0%)	24 (40.0%) 36 (60.0%)	0.010	0.920
SN					
Right	Normal Hyperechogenic	22 (53.7%) 19 (46.3%)	42 (70.0%) 18 (30.0%)	2.802	0.094
Left	Normal Hyperechogenic	26 (63.4%) 15 (36.6%)	41 (68.3%) 19 (31.7%)	0.264	0.607
Total	Normal Hyperechogenic	14 (34.1%) 27 (65.9%)	34 (56.7%) 26 (43.3%)	4.953	0.026*
Smell test	Normal Hyposmia	17 (41.5%) 24 (58.5%)	36 (60.0%) 24 (40.0%)	3.356	0.067

P > 0.05: Non significant (NS); P < 0.05: Significant* (S); p < 0.01: Highly significant (HS) *: Chi-square test**

Table (4): Relation of vagus nerve caliber result of patients group with demographic, characteristics, severity and smell test results

Patient		**Vagus total**		**Test value**	**P-value**
		Normal	**Hypotrophy**		
		No. =	**No. =**		
Age	Mean ± SD Range	69.25 ± 11.47 51 –85	66.32 ± 8.40 52 –81	0.944	0.351
Sex	Male Female	11 (68.8%) 5 (31.3%)	14 (56.0%) 11 (44.0%)	0.667	0.414
Onset	Median (IQR) Range	7 (4 - 10) 1 –15	5 (3 - 7) 1 –15	-0.635	0.525
Type	Rigidity Tremors Mixed	3 (18.8%) 2 (12.5%) 11 (68.8%)	4 (16.0%) 11 (44.0%) 10 (40.0%)	4.671	0.097
F.H	Negative Positive	13 (81.3%) 3 (18.8%)	16 (64.0%) 9 (36.0%)	1.402	0.236
Mentation, Behavior and	Median (IQR) Range	8.5 (5.5 – 9.5) 3 –12	8 (5 - 9) 4 –12	-2.077	0.038*

Mood (max. 16)					
Activities of Daily Living (max,52)	Mean ± SD Range	26.13 ± 8.44 13 –38	20.48 ± 7.29 10 –36	2.274	0.029*
Motor Examination (max.108)	Mean ± SD Range	60.06 ± 14.51 30 –80	50.68 ± 15.31 28 –80	1.953	0.058
TOTAL SCORE (176)	Mean ± SD Range	94.13 ± 23.92 47 –127	78.56 ± 23.25 44 –123	2.068	0.045*
Sleep Disturbance	No Yes	4 (25.0%) 12 (75.0%)	6 (24.0%) 19 (76.0%)	0.005	0.942
Heohn and Yahr	Unilateral involvement only Bilateral involvement Mild to moderate involvement Severe disability	1 (6.3%) 2 (12.5%) 9 (56.3%) 4 (25.0%)	3 (12.0%) 5 (20.0%) 11 (44.0%) 6 (24.0%)	0.956	0.812
Smell test	Normal Hyposomia	6 (37.5%) 10 (62.5%)	11 (44.0%) 14 (56.0%)	0.170	0.680

P > 0.05: Non significant (NS); P < 0.05: Significant (S)*; p < 0.01: Highly significant (HS)*
***: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test**

Table (5): Relation of substantia nigra hyperechogenicity result of patients group with demographic, characteristics, severity and smell test results

Patient		**SN total**		**Test value**	**P-value**
		Normal	**Hyperechogenic**		
		No. =	**No. =**		
Age	Mean ± SD Range	69.93 ± 10.46 52 –84	66.19 ± 9.19 51 –85	1.180	0.245
Sex	Male Female	9 (64.3%) 5 (35.7%)	16 (59.3%) 11 (40.7%)	0.098	0.754
Onset	Median (IQR) Range	6.5 (4 - 8) 1 –15	6 (3 - 10) 1 –15	-0.222	0.824
Type	No Type I Type II	0 (0.0%) 5 (35.7%) 9 (64.3%)	7 (25.9%) 8 (29.6%) 12 (44.4%)	4.446	0.108
F.H	Negative Positive	11 (78.6%) 3 (21.4%)	18 (66.7%) 9 (33.3%)	0.631	0.427
Mentation,	Median (IQR)	8 (6 - 9)	8 (5 - 10)	-1.420	0.156

Behavior and Mood (max. 16)	Range	4 –10	3 –12		
Activities of Daily Living (max,52)	Mean ± SD Range	24.86 ± 8.07 10 –38	21.56 ± 8.11 11 –36	1.239	0.223
Motor Examination (max.108)	Mean ± SD Range	58.29 ± 14.37 30 –80	52.30 ± 15.96 28 –80	1.177	0.246
TOTAL SCORE (176)	Mean ± SD Range	90.71 ± 22.04 44 –123	81.48 ± 25.44 44 –127	1.151	0.257
Sleep Disturbance	No Yes	8 (57.1%) 6 (42.9%)	2 (7.4%) 25 (92.6%)	12.366*	0.000**
Heohn and Yahr	Unilateral involvement only Bilateral involvement Mild to moderate involvement Severe disability	1 (7.1%) 0 (0.0%) 11 (78.6%) 2 (14.3%)	3 (11.1%) 7 (25.9%) 9 (33.3%) 8 (29.6%)	8.536*	0.036*
Smell test	Normal Hyposomia	7 (50.0%) 7 (50.0%)	10 (37.0%) 17 (63.0%)	0.638	0.424

P > 0.05: Non significant (NS); P < 0.05: Significant (S)*; p < 0.01: Highly significant (HS)**
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

Table (6): Relation of vagus nerve caliber result of relatives group with (NMSQ).

	Vagus total (Relative)				**Test value***	**P-value**
	Normal		**Hypotrophy**			
	No.	**%**	**No.**	**%**		
Cardiovascular	11	45.8%	16	44.4%	0.011	0.916
Light headedness	10	41.7%	13	36.1%	0.188	0.665
Falling	5	20.8%	4	11.1%	1.068	0.302
leg swelling	2	8.3%	1	2.8%	0.936	0.333
Sleep and fatigue	15	62.5%	30	83.3%	3.333	0.068
Diffic. Getting sleep	13	54.2%	22	61.1%	0.286	0.593
Vivid dreams	4	16.7%	11	30.6%	1.481	0.224
Talking or moving in sleep	5	20.8%	12	33.3%	1.108	0.293
Restless leg	6	25.0%	5	13.9%	1.187	0.276
Mode and cognition	19	79.2%	29	80.6%	0.017	0.895
Loss of interest	12	50.0%	13	36.1%	1.143	0.285
feeling sad	7	29.2%	16	44.4%	1.422	0.233
Anxious,Panic	6	25.0%	9	25.0%	0.000	1.000
diffic.working	10	41.7%	15	41.7%	0.000	1.000
Perceptual problem and hallucination	5	20.8%	9	25.0%	0.140	0.709

Seeing or hearing things	1	4.2%	2	5.6%	0.058	0.809
Double vision	1	4.2%	5	13.9%	1.512	0.219
False believes	4	16.7%	3	8.3%	0.970	0.325
Attention and memories	22	91.7%	28	77.8%	2.000	0.157
remembring problem	16	66.7%	19	52.8%	1.143	0.285
Difficult conc.	17	70.8%	20	55.6%	1.422	0.233
Gastrointestinal	21	87.5%	26	72.2%	1.980	0.159
Dripling saliva	2	8.3%	6	16.7%	0.865	0.352
difficulty Swallowing	7	29.2%	6	16.7%	1.326	0.250
Vomiting or nusea	6	25.0%	6	16.7%	0.625	0.429
Constipation	15	62.5%	23	63.9%	0.012	0.913
Urinary	19	79.2%	23	63.9%	1.601	0.206
Incontinence	1	4.2%	2	5.6%	0.058	0.809
Incomplete.bowel.emptying	9	37.5%	7	19.4%	2.401	0.121
Urgency	10	41.7%	11	30.6%	0.781	0.377
Regular night urination	13	54.2%	19	52.8%	0.011	0.916
Sexual	7	29.2%	8	22.2%	0.370	0.543
Less or more sex interst	4	16.7%	6	16.7%	0.000	1.000
Difficult have sex	4	16.7%	4	11.1%	0.385	0.535
Miscellanous	15	62.5%	28	77.8%	1.655	0.198
change in Taste, Smell	12	50.0%	16	44.4%	0.179	0.673
Unexplained pain	6	25.0%	10	27.8%	0.057	0.812
Unexplained weight change	2	8.3%	2	5.6%	0.179	0.673
Execcive sweeting	4	16.7%	8	22.2%	0.278	0.598

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (7): Relation of substantia nigra hyperechogenicity result of relatives group with demographic data, relation to patient, and smell test

Relative		**SN total**		**Test value**	**P-value**
		Normal	**Hyperechogenic**		
		No. =	**No. =**		
Age	Mean ± SD Range	41.82 ± 10.69 30 –70	48.88 ± 12.49 30 –70	-2.357	0.022*
Sex	Male Female	28 (82.4%) 6 (17.6%)	17 (65.4%) 9 (34.6%)	2.262	0.133
Relation	Brother/Sister Son/Daughter	27 (79.4%) 7 (20.6%)	12 (46.2%) 14 (53.8%)	7.163	0.007**
Smell test	Normal Hyposomia	26 (76.5%) 8 (23.5%)	10 (38.5%) 16 (61.5%)	8.869	0.003**

P > 0.05: Non significant (NS); P < 0.05: Significant *(S); p < 0.01: Highly significant** (HS)
*: Chi-square test; •: Independent t-test

Table (9): Relation of smell test of relatives with their demographic, characteristics and sonological examination

		Smell test (Relative)		Test value	P-value
		Normal	Hyposmia		
		No. = 36	No. = 24		
Relative data					
Sex	Male Female	27 (75.0%) 9 (25.0%)	18 (75.0%) 6 (25.0%)	0.000	1.000
Age	Mean ± SD Range	41.58 ± 10.96 30 – 65	49.83 ± 11.83 31 – 70	-2.767	0.008**
Relation	Brother/Sister Son/Dauther	27 (75.0%) 9 (25.0%)	12 (50.0%) 12 (50.0%)	3.956	0.047*
Vagus ,Rt	Normal Hypotrophy	15 (41.7%) 21 (58.3%)	11 (45.8%) 13 (54.2%)	0.102	0.750
Vagus ,Lt	Normal Hypotrophy	20 (55.6%) 16 (44.4%)	12 (50.0%) 12 (50.0%)	0.179	0.673
Total	Normal Hypotrophy	15 (41.7%) 21 (58.3%)	9 (37.5%) 15 (62.5%)	0.104	0.747
SN,Rt	Normal Hyperechogenic	30 (83.3%) 6 (16.7%)	12 (50.0%) 12 (50.0%)	7.619	0.006**
SN, Lt	Normal Hyperechogenic	27 (75.0%) 9 (25.0%)	14 (58.3%) 10 (41.7%)	1.849	0.174
Total	Normal Hyperechogenic	26 (72.2%) 10 (27.8%)	8 (33.3%) 16 (66.7%)	8.869	0.003**

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S)*; P-value< 0.01: highly significant (HS)**
*:Chi-square test; •: Independent t-test

Table (8): Relation of substantia nigra hyperechogenicity result of relatives group with (NMSQ).

	SN total (Relative)				Test value*	P-value
	Normal		Hyposmia			
	No.	%	No.	%		
Cardiovascular	15	44.1%	12	46.2%	0.025	0.875
Light headedness	13	38.2%	10	38.5%	0.000	0.986
Falling	5	14.7%	4	15.4%	0.005	0.942
leg swelling	3	8.8%	0	0.0%	2.415	0.120
Sleep and fatigue	25	73.5%	20	76.9%	0.090	0.764
Diffic. Getting sleep	20	58.8%	15	57.7%	0.008	0.930
Vivid dreams	7	20.6%	8	30.8%	0.814	0.367
Talking or moving in sleep	10	29.4%	7	26.9%	0.045	0.832
Restless leg	5	14.7%	6	23.1%	0.690	0.406
Mode and cognition	29	85.3%	19	73.1%	1.374	0.241
Loss of interest	13	38.2%	12	46.2%	0.380	0.538
feeling sad	16	47.1%	7	26.9%	2.527	0.112
Anxious,Panic	9	26.5%	6	23.1%	0.090	0.764
diffic.working	15	44.1%	10	38.5%	0.194	0.660
Perceptual problem and	9	26.5%	5	19.2%	0.432	0.511

hallucination						
Seeing or hearing things	3	8.8%	0	0.0%	2.415	0.120
Double vision	4	11.8%	2	7.7%	0.271	0.602
False believes	3	8.8%	4	15.4%	0.615	0.433
Attention and memories	29	85.3%	21	80.8%	0.217	0.641
remembring problem	19	55.9%	16	61.5%	0.194	0.660
Difficult conc.	23	67.6%	14	53.8%	1.187	0.276
Gastrointestinal	24	70.6%	23	88.5%	2.773	0.096
Dripling saliva	3	8.8%	5	19.2%	1.381	0.240
difficulty Swallowing	3	8.8%	10	38.5%	7.625**	0.006
Vomiting or nusea	7	20.6%	5	19.2%	0.017	0.896
Constipation	19	55.9%	19	73.1%	1.876	0.171
Urinary	23	67.6%	19	73.1%	0.207	0.649
Incontinence	2	5.9%	1	3.8%	0.129	0.720
Incomplete.bowel.emptying	9	26.5%	7	26.9%	0.002	0.969
Urgency	13	38.2%	8	30.8%	0.361	0.548
Regular night urination	14	41.2%	18	69.2%	4.659	0.031
Sexual	6	17.6%	9	34.6%	2.262	0.133
Less or more sex interst	4	11.8%	6	23.1%	1.357	0.244
Difficult have sex	4	11.8%	4	15.4%	0.167	0.683
Miscellanous	21	61.8%	22	84.6%	3.789	0.052
change in Taste, Smell	11	32.4%	17	65.4%	6.459*	0.011
Unexplained pain	8	23.5%	8	30.8%	0.395	0.530
Unexplained weight change	2	5.9%	2	7.7%	0.078	0.781
Execcive sweeting	4	11.8%	8	30.8%	3.326	0.068

P > 0.05: Non significant (NS); P < 0.05: Significant *(S); p < 0.01: Highly significant** (HS)
*: Chi-square test; •: Independent t-test

Table (10): Relation of smell test of relatives with their (NMSQ).

	Smell test (Relative)				**Test value***	**P-value**
	Normal		**Hyposmia**			
	No.	**%**	**No.**	**%**		
Cardiovascular	16	44.4%	11	45.8%	0.011	0.916
Light headedness	14	38.9%	9	37.5%	0.012	0.914
Falling	5	13.9%	4	16.7%	0.087	0.768
leg swelling	2	5.6%	1	4.2%	0.058	0.809
Sleep and fatigue	25	69.4%	20	83.3%	1.481	0.224
Diffic. Getting sleep	20	55.6%	15	62.5%	0.286	0.593
Vivid dreams	6	16.7%	9	37.5%	3.333	0.068
Talking or moving in sleep	13	36.1%	4	16.7%	2.681	0.102
Restless leg	6	16.7%	5	20.8%	0.167	0.683
Mode and cognition	29	80.6%	19	79.2%	0.017	0.895
Loss of interest	13	36.1%	12	50.0%	1.143	0.285
feeling sad	14	38.9%	9	37.5%	0.012	0.914
Anxious,Panic	9	25.0%	6	25.0%	0.000	1.000
diffic.working	15	41.7%	10	41.7%	0.000	1.000

Perceptual problem and hallucination	11	30.6%	3	12.5%	2.624	0.105
Seeing or hearing things	2	5.6%	1	4.2%	0.058	0.809
Double vision	5	13.9%	1	4.2%	1.512	0.219
False believes	5	13.9%	2	8.3%	0.431	0.511
Attention and memories	29	80.6%	21	87.5%	0.500	0.480
remembring problem	20	55.6%	15	62.5%	0.286	0.593
Difficult conc.	22	61.1%	15	62.5%	0.012	0.914
Gastrointestinal	25	69.4%	22	91.7%	4.190	0.041
Dripling saliva	3	8.3%	5	20.8%	1.947	0.163
difficulty Swallowing	4	11.1%	9	37.5%	5.908	0.015*
Vomiting or nusea	7	19.4%	5	20.8%	0.017	0.895
Constipation	18	50.0%	20	83.3%	6.890	0.009**
Urinary	24	66.7%	18	75.0%	0.476	0.490
Incontinence	2	5.6%	1	4.2%	0.058	0.809
Incomplete.bowel.emptying	9	25.0%	7	29.2%	0.128	0.721
Urgency	13	36.1%	8	33.3%	0.049	0.825
Regular night urination	17	47.2%	15	62.5%	1.350	0.245
Sexual	6	16.7%	9	37.5%	3.333	0.068
Less or more sex interst	4	11.1%	6	25.0%	2.000	0.157
Difficult have sex	3	8.3%	5	20.8%	1.947	0.163
Miscellanous	20	55.6%	23	95.8%	11.505	0.001
change in Taste, Smell	8	22.2%	20	83.3%	21.607	0.000**
Unexplained pain	9	25.0%	7	29.2%	0.128	0.721
Unexplained weight change	2	5.6%	2	8.3%	0.179	0.673
Execcive sweeting	7	19.4%	5	20.8%	0.017	0.895

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: Chi-square test

DISCUSSION:

The aim of our study was for the screening of Parkinson in first degree relatives of idiopathic Parkinson disease in a sample of Egyptian patients clinically by hyposmia and neurosonologicaly by transcranial sonography of substantia nigra and ultrasound of vagus nerve for early detection, management, and better prognosis.

Analysis of our findings revealed that patients with idiopathic Parkinson fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for the diagnosis of idiopathic PD with The duration of disease ranged from 1 to 15 years (median 6 (3-8)years), Their age ranged from 51 to 85 years with mean ±SD of 67.46 ± 9.68. They were 25 males (61.0%) and 16 females (39.0%), with Hoehn and Yahr (HY) stages I–IV, and 60 relatives with ages ranged from 30 to 70 years with mean ±SD of 44.88 ± 11.94, 45 (75.0%) were male and 15 (25.0%) were females.

In our study, we assessed the Substantia Nigra hyperechogenicity SN+ in patients and their first degree relatives; and revealed that 27 (65.9%) patients of 41 have SN+, and 26 (43.3%) of their

first degree relatives has SN+. So The data of this study demonstrate that this echo feature of SN hyperechogenicity seen in the majority of PD patients is also common in first-degree relatives of patients with idiopathic PD. Interestingly, no increased prevalence of hyperechogenicity could be found in first degree relatives of patients who do not exhibit SN+. These findings indicate that differences in the sonographic phenotype of PD patients appear to be transmitted to the offspring.

Our findings is congruent to the study of **Ruprecht-Dörfler et al. (2003)** that conducted on 14 patients with Idiopathic PD with the duration of PD ranged from 2 to 19 years (median 4.75 years), and A total of 58 first-degree relatives with median age 45.9 [30; 63] years) were included in that study., Twenty-six (44.8 %) of the relatives exhibited hyperechogenic signals. Hyperechogenic signals at the SN were more often identified in relatives of the 13 PD patients with SN+.

In the present study, we demonstrated that there was no statistically significant relationship found between substantia nigra hyperechogenicity result of patients group and demographic characteristics, type of parkinsonism, family history, and UPDRS part (I, II, III).

These findings are supported by the study of **Behnk et al. (2012),** that conducted on 50 parkinsonian patients, transcranial ultrasound, and clinical examination was performed twice with a mean time interval of 6.4 years. SN1 did not change in size significantly between the first and second examination, whereas clinical parkinsonian symptoms—as determined by the motor part of the UPDRS—significantly worsened ($P < 0.001$). The size of SN1 did not correlate with the UPDRS part III at the time of the first or second ultrasound examination. Progression of motor symptoms between the first and second investigation did not correlate with the size of SN1 at baseline. Furthermore, even in the subgroup of patients with an interval of 8 years between examinations, there was no significant change in SN1 size.
So, substantia nigra hyperechogenicity represents a largely stable biomarker in idiopathic PD and does not reflect disease progression. The size of substantia nigra hyperechogenicity does not predict the further course of the disease.

Against our findings, the study of **Berg et al. (2005)** and **Weise et al. (2009)**, found significant positive correlations between SN size and clinical scores in their specific patient samples, indicating a direct relation of echo feature and neurodegeneration, whereas others, including ourselves, have not found any correlation.

Possible explanations would be that there are indeed idiopathic PD subtypes, within the whole spectrum, and our findings seem not to be the rule. We require more advancing knowledge regarding genetic contribution in the development of "sporadic" IPD and presumable pathogenetic differences among IPD subtypes, we may eventually understand differences in SN hyperechogenecity characteristics in clinically "typical" idiopathic PD patients.

Olfactory impairment is one of the most common and best characterized non-motor features in PD with a prevalence of 50%–90%. The olfactory bulb (along with the lower brainstem) are thought to be induction sites for alpha-synuclein pathology, which later spreads through the

rostral brainstem to the cerebral cortex. In this review, we discussed the role of olfaction as a biomarker in PD for "pre-motor" diagnosis (***Fullard et al., 2017).***

We aimed to determine whether unexplained (idiopathic) olfactory dysfunction can be used as a biomarker for early detection of Parkinson's disease.

In the present study, 24 (58.5%) of 41 Parkinson patients exhibit hyposmia, and 24 (40.0%) of sixty first-degree relatives exhibit hyposmia.

Supporting our results, A study by **Ponsen et al. (2004)** on 361 asymptomatic relatives of PD patients selected 40 relatives with the lowest olfactory performance. Within 2 years of follow up, 10% of these first-degree relatives of PD patients with significant olfactory loss developed clinical PD. Hyposmia showed no statistically significant relationship with the type of relation to the patient nor age.

Also, this is in accord with the results of a large longitudinal study by **Ross et al. (2008)**; they assessed olfactory function in 2267 elderly men in the Honolulu Heart Program and found an association between smell loss and future development of PD. They concluded that impaired olfaction can predate PD by at least 4 years and may be a useful screening tool to detect those at high risk for the development of PD in later life.

Nonmotor symptoms (NMS) are an important prodromal feature of Parkinson's disease .Rates of NMS in enriched at-risk populations, such as first-degree PD relatives, have not been delineated. We assessed NMS in, first-degree PD relatives. 60 first-degree PD relatives, using the (NMSQ). We found that 83.3% had an abnormality in Attention and memories, 78.3% had an abnormality in the gastrointestinal system, 63.3% of them had Constipation, 75% had an abnormality in Sleep and fatigue, 70% had an abnormality in the urinary system, 53.3% of them had Regular night urination, 45% had an abnormality in cardiovascular systems, 41% had difficult working, 23.3% had Perceptual problem and hallucination.

Our results are supported by the study of **Liu et al. (2019)** in which the first degree relatives showed a higher incidence of moderate to severe depression (OR = 4.08; 95% CI: 1.12–14.92;), anxiety (OR = 4.22; 95% CI: 1.87–9.52;), and excessive daytime sleepiness (OR = 3.40; 95% CI: 1.00–11.48;) . They also found that RBD (OR = 11.65; 95% CI: 3.82–35.54;), constipation (OR = 4.94; 95% CI: 1.85–13.21;), sleep disorders (OR = 4.51; 95% CI: 1.73–11.78;), cognitive impairment (OR = 3.55; 95% CI: 1.62–7.77;).

Also **Arabia et al. (2007)** supported our study, they analyzed the medical records of 1000 FDR of PD probands and found an increased risk of anxiety disorders and depressive disorders in FDR of PD probands compared with the controls.

Against our results, the study of **Baig et al. (2015)** that conducted on 1,154 participants (769 PD, 98 at-risk including first degree relatives, and 287 controls). The relative group was comprised of 60 siblings, 23 children, and 12 with at least one of each. They found that NMS was very common in the PD group. In order of frequency, the most common NMS experienced in PD were hyposmia, pain, sleep disturbance, urinary symptoms, and fatigue, each affecting

over half of the subjects. The PD group experienced more NMS than the control group in each symptom assessed. They also experienced more NMS than the at-risk group in each symptom, except for impulsive-compulsive behavior (ICB) and orthostatic hypotension. The at-risk and control groups were similar across each domain tested. The biggest differences comparing the PD group to the control group were anxiety and hyposmia (OR, >4.0). The at-risk group of PD relatives did not show any significant increases across the range of NMS studied, compared to controls.

These contradictory results can be attributed to the biggest percentage in our studied relatives were either brothers or sisters 39 (65.0%) while sons or daughters were the biggest percentages in **Baig et al. (2015)** about (61.0%) and so older age may be associated with the preclinical time of Parkinson disease.

The vagus nerve has been suggested to represent one major route of disease progression in Parkinson's disease (PD) with an active retrograde transport of α-synuclein originating in the enteric nervous system ascending the vagus nerve and eventually reaching the dorsal motor nucleus of the vagus in the lower brainstem ***(Braak et al ., 2016).***

Our study confirms these hypotheses, revealing the high prevalence of constipation in PD patients. Also Khedr et al., 2013 reported the presence of constipation in 51.8% of PD patients in their study carried out in Upper Egypt. And this could be attributed to vagus nerve hypotrophy.
In the study on our hands, we found that 25 (61.0%) of patients had vagus nerve hypotrophy (less than 0.02 cm2, the cutoff value we had gotten for our ultrasound system) and 36 (60.0%) of their first degree relatives had vagus nerve hypotrophy.

Pelz et al. (2018) study supported our results as regard vagus nerve hypotrophy in Parkinson's disease patients, they measured both VNs cross-sectional area (VN-CSA) of 35 patients with PD and 35 age- and sex-matched healthy controls at the level of the thyroid gland using HRUS. And they found that the VN-CSA was significantly smaller in PD patients than in controls.

But unfortunately, I had not found a study about vagus nerve hypotrophy in first degree relatives of idiopathic Parkinson yet.

We also found that there was no statistically significant relationship found between vagus nerve caliber result and demographic and characteristics of the studied cases except mentation, behavior and mood score, activities of daily living score and the total score showed a statistically significant increase in normal cases than hypotrophy cases.

These results are supported by **Pelz et al. (2018)**, they found that there was no correlation between the right or left VN-CSA and age, the Hoehn & Yahr stage, disease duration, the motor part of the Unified Parkinson's Disease Rating Scale score, the Montreal Cognitive Assessment score, or the Non-motor Symptoms Questionnaire, and Scale for Parkinson's disease score including its gastrointestinal domain.

And also supported by the study of **Walter et al. (2018)** which reported that in PD patients, vagus nerve CSA did not correlate with disease duration, nor with cumulative levodopa dose (each, $p > 0.2$).

LIMITATIONS OF THE STUDY

The small sample size is a limitation to the current study. Studies with a greater sample size would confirm our findings regarding the availability of using hyposmia, substantia nigra hyperechogenicity, and vagus verve hypotrophy as a biomarker for early detection of Parkinson disease. Also, there is a need to use a case-control study instead of an observational cross sectional study to confirm results.

CONCLUSION

We found substantia nigra hyperechogenicity, vagus nerve hypotrophy, and hyposmia in first-degree relatives, as well as that, is seen in Parkinson patients, so may be used as a biomarker for early detection of Parkinson disease. Follow up these relatives is mandatory.

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