

Brief Report

Essential Tremor Prevalence is Low in the Druze Population in Northern Israel

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Abstract

Background: Essential tremor (ET) and Parkinson’s disease (PD) are probably the most common movement disorders. As ethnic differences have been reported in ET, we designed the present study to evaluate the prevalence of ET and that of Parkinson’s disease (PD) in the Druze villages of northern Israel.

Methods: A two-phase, door-to-door survey was undertaken. Residents aged ≥ 51 years who agreed to participate and answered “yes” to tremor or PD-related screening questions and 3% of subjects who screened negative were evaluated. Diagnostic criteria for ET were similar to those used in Sicilian and Spanish studies. PD was diagnosed according to Gelb’s criteria.

Results: The target population consisted of 9,086, the study cohort of 3,980 residents. Tremor was observed in 36 subjects. In 27, the tremor fully met the criteria for ET. The prevalence of ET (age ≥ 65) was 1.49% (95% CI 0.91–2.07%). PD was diagnosed in 23 subjects. The prevalence of PD (age ≥ 65) was 1.13 (95% CI 0.62–1.64%). Leucine-rich repeat protein kinase 2 (G2019S mutation) was evaluated in subjects diagnosed with tremor PD and those screened for assessment of the validity of the questionnaire. None carried the mutation.

Discussion: The prevalence of ET in the Druze population is low and similar to the prevalence of PD.

Keywords: Essential tremor, Parkinson’s disease, epidemiology, Druze, leucine-rich repeat protein kinase 2

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Introduction

Essential tremor (ET) and Parkinson’s disease (PD) are probably the most common movement disorders.^{1–5} The range of prevalence estimates for ET in recent population-based studies among persons aged 40 years and older seems to be approximately 4%,^{6–13} substantially higher than all types of parkinsonism.¹⁰ The prevalence of both conditions increase with age.^{14–17} Above the age of 60 years, the reported prevalence of ET varies from 2.3% to 9.4% and that of PD from 0.7% to 1.5%.^{2,4,9,10,18–26}

Ethnic differences have been reported in ET. Louis et al.⁷ found that the prevalence of ET in white people was 1.7-fold higher than in African Americans, and 1.2-fold higher in Hispanics than in African Americans. However, in a study in the biracial population of Copiah County, Mississippi, prevalence ratios were not significantly higher for

white people than for African Americans.²⁷ A community-based survey performed in Singapore, comparing Singaporean Chinese, Malays, and Indians, showed that the prevalence of ET was marginally higher in Indians than in Chinese ($p = 0.08$).²⁸

Recently, a very low prevalence of ET (0.8%), and a PD prevalence of 1.4%, similar to that reported in Western countries, was reported in elderly people residing in Arabic villages of Wadi Ara in northern Israel.^{13,29} Another study from the Middle East documented an ET prevalence of 4.0% (95% CI 3.2–4.8%) among individuals aged 40 years and older and 6.3% among subjects older than 60 years in Mersin Province,⁹ and a prevalence of 3.1% (95% CI 2.42–3.91%) in a Turkish population over age 18, in Sile, Istanbul, Turkey.³⁰ One PD prevalence study has been conducted in Israel. In a study of the Kibbutz movement in Israel, Anca et al.³¹ reported a prevalence of

0.2% for the entire population, with an age-adjusted prevalence of 0.9% in the population over 69 years of age and 0.3% in the population over 40 years of age.

The aim of the present study was to determine the prevalence of ET and PD in the Druze population in Israel and evaluate whether the most frequent genetic cause of familial and sporadic PD, leucine-rich repeat protein kinase 2 (LRRK2), could be identified in this population. The contemporary Druze population constitutes a small minority in four countries in the Near East: Syria, Lebanon, Israel, and Jordan. The estimated population number is fewer than 1,000,000 in the Near East and fewer than 100,000 in the Druze Diaspora. The Israel Druze population is estimated at 150,000, distributed over three geographical subregions: the Carmel, the Galilee, and the Golan Heights. According to historical records, it has been postulated that the origin of Druze in each of these subregions is different. Although the Druze represent a percentage of the total population of the countries in which they reside, their concentration in mountain districts has produced a compact social structure, resulting in a nearly exclusive majority in some geographical regions, and a low frequency of admixture with other populations. Druze customs strongly favor marriage within the same village or the same geographical area. Unlike other monotheistic religions, the Druze tenets strictly close their religion to new adherents, thus forbidding admixture with other populations. This social structure has turned the Druze into transnational isolates, a population that remains genetically isolated largely through the social practice of endogamy and consanguinity.

Methods

The study comprised the Druze population aged ≥ 51 years residing in the Druze villages of the Galilee (Horfeish, Yanuch, Kisra-Smeah, Abu-Snan, Beit Jann, Yarka, Sajur, Ein El Asad, Peqim, Rame). According to the Israel Central Statistics Bureau, 9,086 subjects were 50 years or older on prevalence day (February 10 2008). The study was designed in two phases. In the first phase, one Druze interviewer (medical nurse by profession and trained by a senior clinical investigator specializing in movement disorders – JAP), approached village houses consecutively and personally interviewed residents aged ≥ 51 years. The interview included questions on demographics, medical and neurological disorders, family history, and medications. The questionnaire included a screening question for ET – “Have you ever had tremor of the head, hands, or legs that lasted longer than several days?” This question is an Arabic adaptation of the question used by the Italian Longitudinal Study on Aging Working Group and a Spanish study.^{32–34} In addition, subjects were asked questions related to PD (have you noticed slowness, change in voice and facial expression, handwriting, gait impairment, and cognitive decline). Residents who agreed to participate and answered “yes” to the tremor or PD-related questions, regardless of whether they were diagnosed with ET or PD in the past, were asked to draw an Archimedes spiral with both arms, and were evaluated in the second study phase, in their homes, by a senior neurologist (JAP), within 2 weeks. Medical and family history, medication, and response to medication were recorded.

The neurological evaluation included examination of speech, cranial nerves, strengths and tone, primary sensory modalities, reflexes, extensor toe signs, coordination, and gait, as well as the motor portion of the Unified Parkinson’s Disease Rating Scale.³⁵ During the neurological examination, participants were asked to perform three manual tasks to assess postural and kinetic tremors, including sustained bilateral arm extension and bilateral finger to nose maneuver (with a minimum of six repetitions with each arm), and draw an Archimedes spiral (second time) with both arms.³⁶ Examinations were performed in the presence of a Druze translator or a Druze physician. Diagnostic criteria for ET were similar to those used in Sicilian and Spanish studies.^{6,34}

Subjects were diagnosed as having ET if they reported tremor of the head, limbs, or voice without any other recognizable cause. The tremor had to be of gradual onset (i.e., slow and progressive) and had to have been present for at least 1 year or be accompanied by a family history of the same disorder. On the Archimedes spiral, tremor severity had to be moderate or greater (rating ≥ 2 according to the Washington Heights–Inwood ET rating scale.³⁶ Exclusion criteria consisted of sudden-onset tremor, cerebellar signs, evidence of parkinsonism, dystonia, peripheral neuropathy, hyperthyroidism, severe dementia, and psychiatric diseases. When tremor severity was considered less than 2 or when medication could not definitely be excluded, the tremor was classified as non-ET. Gelb’s criteria were used for PD diagnosis:³⁷ group A features, resting tremor, bradykinesia, rigidity, asymmetric onset; group B features, prominent postural instability, freezing, or hallucinations 3 or less years after onset, dementia preceding motor symptoms or in the first year, supranuclear gaze palsy, severe symptomatic dysautonomia unrelated to medication, documentation of a condition plausibly connected to the symptoms. Possible PD was diagnosed if two or more group A features were present, at least one being tremor or bradykinesia; had either no group B features, or in cases with symptom duration of 3 or less years none of the group B features present and with substantial sustained documented response to levodopa, dopamine agonist, or the patient did not have an adequate trial of levodopa or dopamine agonist. Probable PD was diagnosed when three or more group A features and none of the group B features were present (symptoms ≥ 3 years) and with substantial sustained documented response to levodopa or dopamine agonist. Since definite PD requires autopsy confirmation, we had no definite PD cases. Parkinsonism was diagnosed when two or more group A and three or more group B features were present.

To assess the performance of the screening questions, a random sample of 3% (120) of subjects who screened negative on the questions and on the Archimedes spiral drawing were approached and given a neurological evaluation including three manual tasks to assess postural and kinetic tremors. All rated 0 on the three items and did not manifest PD symptoms, indicating that the screening questions were likely to yield few false negatives.

Blood samples were taken from all patients who screened positive for ET, non-ET, PD, parkinsonism and from the random sample of those who screened negative (120 subjects). The study was approved by the

Institutional Ethics Committee. All participants signed a written consent form.

Results

The target population aged ≥ 51 years consisted of 9,086 residents, of whom 4,506 were aged 61 years and older and 1,681 were 65 years and older. Of the 3,988 subjects approached, eight were excluded: four refused to participate in the study (refusal rate 0.1%) and four patients were excluded (two due to recent ischemic stroke, one due to recent head trauma, one due to recent onset of chemotherapy). The cohort consisted of 3,980 subjects, 52% of whom were female. The proportion of study subjects in each age group was similar to that of the target population (Table 1).

Tremor was observed in 36 subjects. A postural, kinetic, oscillatory tremor that fully met ET criteria was observed in 27 subjects (mean age 75.5, SD \pm 7.8, mean years of education 2.7, SD \pm 3.2). In 9 subjects (mean age 72.2, SD \pm 9.1, mean years of education 3.5, SD \pm 2.1), diagnosis of tremor was questionable: (four patients had very mild hand tremor, tremor was considered to be possibly drug induced in five patients, i.e., three patients were treated with aminophyllin, two patients were on acetyl choline esterase inhibitors following diagnosis of mild dementia. None had head tremor). Prevalence of ET at age ≥ 51 was 0.68%. If all cases with tremor

(including questionable) were included (ET+), the prevalence of tremor would be 0.9% (Table 2). Prevalence stratification of tremor by age is depicted in Table 3. PD (probable and possible) was diagnosed in 23 subjects (mean age 74.7, SD \pm 10.0, mean years of education 5.0, SD \pm 4.2) and parkinsonism was diagnosed in nine subjects (mean age 78.1, SD \pm 12.9, mean years of education 2.7, SD \pm 5.1). PD and PD together with parkinsonism (PD+) prevalence stratification by age and gender is depicted in Table 4. Prevalence of tremor and parkinsonism increased with age (multivariate logistic regression significant statistics). In PD male gender was associated with an increased risk of developing disease (Hosmer–Lemeshow goodness-of-fit statistics: OR 2.9, 95% CI 1.1–7.5).

Questionnaires revealed that 80.8% of ET patients reported a positive family history of tremor in a first-degree relative.

LRRK2 (G2019S mutation) was evaluated in all subjects diagnosed with ET, non-ET, PD, and parkinsonism and in the 120 subjects screened for assessment of the validity of the questionnaire (mean age 66.4, SD 11.3, mean years of education 6.5, SD 4.5). None of these subjects was found to carry the mutation.

Discussion

A low prevalence of ET, similar to the prevalence of PD, was found in the Druze population of the Galilee. The PD prevalence in our

Table 1. Stratification by Age: Target Population vs. Study Population

Participation Rate	Study Population	Target Population	Age Group
44%	3980	9086	
42%	47.9%	1906	51–60
42%	26.6%	1059	61–70
52%	18.6%	739	71–80
51%	6.0%	238	81–90
42%	1.0%	38	90+

Please note: the first two columns of percentages are column percentages (i.e. they are not row percentages). Participation rate was obtained by dividing the study population by the target population and then multiplied by 100.

Table 2. Prevalence of Parkinson's Disease (PD), PD and Parkinsonism (PD+), Essential Tremor (ET) and Questionable Essential Tremor (ET+) in the Druze Population of the Galilee

Age ≥ 51 years					
	Number Screened	Number Diagnosed	Prevalence (%)	95% CI	
PD+	3980	32	0.80	0.53	1.08
PD	3980	23	0.58	0.21	0.95
ET+	3980	36	0.90	0.61	1.20
ET	3980	27	0.68	-0.19	1.55

Table 3. Stratification by Age. Parkinson's Disease (PD) and Parkinson's Disease and Parkinsonism (PD+), Essential Tremor (ET), and All Tremors (ET+)

Age Group (years)	Diagnosis	No. Screening	No. Patients	Prevalence (%)	95% CI	
51–60	PD +	1906	4	0.21	0.00	0.42
	PD	1906	3	0.16	–0.02	0.34
61–70	PD +	1059	6	0.57	0.11	1.02
	PD	1059	4	0.38	0.01	0.75
71–80	PD +	739	11	1.49	0.62	2.36
	PD	739	9	1.22	0.43	2.01
81+	PD +	276	11	3.99	1.68	6.29
	PD	276	7	2.54	0.68	4.39
51–60	ET+	1906	2	0.10	–0.04	0.25
	ET	1906	1	0.05	–0.05	0.16
61–70	ET+	1059	9	0.85	0.30	1.40
	ET	1059	6	0.57	0.11	1.02
71–80	ET+	739	16	2.17	1.12	3.21
	ET	739	12	1.62	0.71	2.54
81+	ET+	276	9	3.26	1.17	5.36
	ET	276	8	2.90	0.92	4.88

study is similar to those in Western communities and in the Jewish population in the Kibbutz movement in Israel.³¹ Our findings regarding the prevalence of ET are similar to recent findings regarding a low frequency of ET in Wadi Ara villages in Israel (almost identical CIs).^{15,29} These findings are quite unusual, since ET is regarded as the most common adult movement disorder, with other studies reporting significantly higher prevalences of 3.5%, 3.9%, and 4.8% in age groups older than 65.^{6,7,10} The similarity to the findings in Wadi Ara is intriguing, as Wadi Ara residents are Muslim Arabs, allegedly differing in ethnicity, and residing in a different geographical subregion. However, both populations reside in rural areas and consume a relatively similar Mediterranean diet regarded as protective to ET.³⁸

ET is often considered to be highly genetic. Estimates of the proportions of cases with a family history vary from 17% to 100%.^{39,40} Different ethnic groups may vary in terms of the importance of the genetic susceptibility, and an isolated population with high consanguinity may carry higher frequencies of disease-associated alleles. This issue has been raised with regard to a Finnish study on ET²² and may be the explanation to our finding regarding a high prevalence of ET in first-degree relatives of patients with ET (80.8%).

Another interesting finding of our study is the absence of the LRRK2 mutation in this population. The LRRK2 gene was recently found to have multiple mutations that are believed to be causative for

familial and sporadic PD. It encodes a putative protein kinase named dardarin. The mutational frequency of LRRK2 G2019S shows ethnic and geographical variability. It appears to be the most common PD-causing LRRK2 mutation in Caucasians, and is especially frequent in patients of Ashkenazi Jewish heritage (29.7% of familial PD and 13.7% for sporadic PD) and North African Arabs (37%),^{41,42} which suggests the influence of a founder effect on the mutation from populations of North African and Middle Eastern origin. The fact that no Druze patient or control was found to carry the LRRK2 G2019S mutation does not exclude the possibility of other variants in this gene conferring susceptibility to ET or PD.

This study has limitations. As consecutive houses were approached, those of working age, when not at home, were not screened. When family members were at home but the index subject was not, family members were interviewed. Nevertheless, these reports might be less than accurate, and few index cases might have been missed. Indeed, the proportion of screened subjects in young age groups is relatively lower than those screened in older ages (Table 1).

Offsetting these limitations is the design of our survey, which covered a homogenous ethnic population residing in a relatively narrow geographical area, with selection bias minimized by approaching consecutive households; an extremely low refusal rate is also a major advantage of the study.

Table 4. Age and Gender as Risk Factor for Essential Tremor and Parkinson's Disease (logistic regression model)

Variable	Coefficient	Sig.	Adjusted OR	95% CI	
				Lower	Upper
Essential Tremor					
Age	51–60		Ref		
	61–70	2.387	0.027	1.308	90.483
	71–80	3.449	0.001	4.086	242.556
	80+	4.033	<0.001	56.408	452.919
p trend<0.001					
Sex	M vs. F	0.258	0.51	1.294	2.785
	Constant	–7.684			
Parkinson's Disease					
Age	51–60		Ref		
	61–70	0.888	0.246	0.543	10.884
	71–80	2.061	0.002	2.118	29.101
	80+	2.767	<0.001	4.084	62.022
p trend<0.001					
Sex	M vs. F	1.083	0.023	1.158	7.527
	Constant	–7.114			

Abbreviations: M, male; F, female.

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