

Short Communication

Is Parkinson's Disease a Very Rare Pathology in Centenarians? A Clinical Study in a Cohort of Subjects

Gabriella Marcon^{a,b,c,*}, Paolo Manganotti^{a,c} and Mauro Tettamanti^d

^a*Department of Medical Science, University of Trieste, Trieste, Italy*

^b*DAME, University of Udine, Udine, Italy*

^c*ASUITS (Azienda Sanitaria Universitaria Integrata di Trieste), Trieste, Italy*

^d*Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy*

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Abstract. The number of people reaching old age is growing dramatically and centenarians are among the fastest growing age groups. Since no epidemiological study on Parkinson's disease (PD) in this age class is present in the medical literature, we estimated PD prevalence in the Centenari a Trieste (CaT) study. Participating centenarians were examined by a neurologist, who also retrieved their remote and pharmacological anamnesis. Ninety centenarians received a neurological examination. No subject had PD clinical signs. Moreover, none had a previous diagnosis of PD or had taken or was taking anti-Parkinson treatment. This simple but consistent clinical observation permits some physio-pathological hypotheses.

Keywords: Alpha-synuclein, centenarians, Parkinson's disease, prevalence

INTRODUCTION

With the progressive increase in life expectancy, due to improvements in social and health measures in nutrition, education, sanitation, and medicine [1], many older populations have recorded impressive expansion, particularly centenarians that are among the fastest growing groups in developed and developing countries [2].

However, living longer does not necessarily mean staying healthy: aging is a complex time-dependent process in which individual genetic and epigenetic traits associated with environmental differences and

lifestyle heterogeneity have a great impact on the onset of the age-related disorders. Cardiovascular and cerebrovascular disorders, neurodegenerative diseases, diabetes mellitus, and cancer are among the most frequent pathological conditions of the elderly [3].

In the field of neurodegenerative diseases, after Alzheimer's disease (AD), Parkinson's disease (PD) is the most common disorder in developed societies. As a movement disorder, PD is clinically characterized by rigidity, resting tremor, bradykinesia, and postural imbalance. PD neuropathology shows a selective loss of dopaminergic neurons in the substantia nigra pars compacta and presence of Lewy body inclusions, that are alpha-synuclein intracellular aggregates, neuropathological hallmark of PD.

As in other age-related neurodegenerative disorders, brain aging is the main risk factor of PD, but different risk factors, such as use of postmenopausal

*Correspondence to: Gabriella Marcon, MD, PhD, Department of Medical Surgical and Health Sciences, University of Trieste, Strada di Fiume 447, 34100 Trieste, Italy. Tel.: +39 040 399 4007; E-mail: gmarcon@units.it.; Department of Area of Medicine and Surgery, University of Udine, Piazzale Kolbe 4, 33100 Udine. Tel.: +39 0432 494300; E-mail: gabriella.marcon@uniud.it.

48 hormones, exposure to pesticides or environmental
49 chemicals, brain microtrauma, focal cerebrovascular
50 damage, and genomic defects, may play a potentially
51 pathogenetic role in the onset of the disease [4]. On
52 the other hand, different habits and lifestyle have been
53 associated with a lower PD risk: smoking [5, 6], cof-
54 fee and caffeine [7, 8], and physical activity [9, 10]
55 have been described as protective factors.

56 PD is more prevalent in males than in females,
57 although some studies found no significant difference
58 in PD prevalence between men and women. Epidemi-
59 ological studies show that PD is uncommon before
60 50 years of age, with a progressive increase of preva-
61 lence at later ages [3]. Importantly data on prevalence
62 of PD in people over 100 years old are very rare.

63 In 2014, we started the population-based study
64 “CaT: Centenari a Trieste” with the purpose to enroll
65 all centenarians living in Trieste city and province, a
66 small coastal area in the North-East of Italy. This area
67 has wide genetic heterogeneity, different languages,
68 religions, and habits. According to the protocol, all
69 centenarians enrolled in the study underwent neu-
70 rological and neuropsychological examination [11].
71 Here we discuss the neurological findings in 93 cente-
72 narians from the CaT Study, focusing on PD clinical
73 signs, demographic data, and lifestyle. To our knowl-
74 edge, this is the first study on PD and subjects in the
75 11th decade of life.

76 METHODS

77 The CaT Study is a population-based study on the
78 centenarians living in Trieste, aimed at studying their
79 health status and health service use, with specific
80 focus on cognitive status. Centenarians are visited
81 at their place of residence after obtaining informed
82 consent. The aims of the CaT project, the protocol,
83 and the preliminary data have been published [11].
84 The study is currently ongoing.

85 To assess the presence of PD, we performed: 1)
86 medical history collection from interview with the
87 centenarian plus the caregiver or the family mem-
88 bers, recording all demographic data, family history,
89 habits and lifestyle, eating habits dating back, if possi-
90 ble, to 50 years ago, and past and present pathologies
91 and neuropsychiatric disorders, particularly agita-
92 tion, depression, and psychosis. We also reviewed
93 present and past therapeutic plans; 2) neurologi-
94 cal examination for PD diagnosis took into account
95 rigidity, bradykinesia, hypokinesia, resting tremor,
96 and postural imbalance. Atypical parkinsonism signs

97 were excluded during the neurological examina-
98 tion. Evaluation of non-motor disturbances included
99 neuropsychiatric and autonomic disorders; 3) neu-
100ropsychological evaluation for cognitive impairment
101 was performed using the Consortium to Establish a
102 Registry on Alzheimer’s Dementia (CERAD) battery
103 [12]. The diagnosis of dementia was made applying
104 the criteria of DSM-IV [13].

105 Trieste LHA Ethics Committee approved the first
106 wave of this study, while the Friuli-Venezia Giulia
107 Regional Ethics Committee approved the ongoing
108 wave.

109 RESULTS

110 Neurological evaluation was possible in 90 (97%)
111 of the 93 centenarians included in the project until
112 December 2018. Their general characteristics are pre-
113 sented in Table 1. The sex ratio (9 women for each
114 man) is in line with usual demographics at this age.
115 The high percentage of coffee consumers (particu-
116 larly compared to tea drinkers) is specific to the Italian
117 population. One in three centenarians still takes a
118 walk every day to keep fit, with a wide variety of mean
119 daily walking times (between 10 minutes and more
120 than an hour). None of the centenarians presented
121 orthostatic hypotension and drooling, while some of
122 them presented constipation or incontinence.

123 In subjects with a past history of depression, the
124 diagnosis was a reactive form resolved with antide-
125 pressants. Few centenarians showed slight depressive
126 mood disorder, especially those living in nursing
127 home. When asked about their professional his-
128 tory, we did not elicit any exposure to toxic agents.
129 Furthermore, we have no notice of specific environ-
130 mental toxic presence in the Province of Trieste and
131 neighborhoods. None of the centenarians presented a
132 clinical picture compatible with a classic form of PD
133 (prevalence 0%, 95% score confidence interval: 0% to
134 4.1%). Surprisingly, even the subjects with vascular
135 encephalopathy documented by CT scan, presented
136 pyramidal syndrome but not hypotonic-akinetic syn-
137 drome. Consistently with the diagnosis, no subject
138 took any anti-parkinsonian drug (ATC code N04).

139 In our study, 57% of the subjects met criteria
140 for diagnosis of dementia. Very few centenarians
141 performed cerebral CT scan. Subjects affected by
142 dementia presented clinical pictures compatible with
143 degenerative forms characterized by predominant
144 memory impairment, but not all of them presented
145 typical picture superimposable to AD. Other cases

Table 1
Characteristics of the 90 subjects studied

Demographics	Number (%)	Missing
Sex		0
males	9 (10%)	
females	81 (90%)	
Age, y: mean (SD)	102.4 (1.8)	0
Education, y: mean (SD)	6.8 (3.1)	5
Lifestyle (present/former)		
Smokers	18 (21%)	5
Alcohol consumption	42 (49%)	5
Coffee consumption	69 (80%)	4
Tea consumption	27 (33%)	7
Still walk every day	27 (31%)	7
Main profession		1
dealer, clerk, professional	23 (26%)	
farmer, manual worker	24 (27%)	
housewife	28 (31%)	
craftsman, other	14 (16%)	
Diagnoses		
Diabetes	9 (10%)	2
in therapy	3 (3%)	
Previous myocardial infarction	7 (9%)	16
Heart failure	19 (24%)	23
Atrial fibrillation	10 (15%)	25
Depression	10 (12%)	7
Dementia	51 (57%)	2
Previous stroke	9 (10%)	1
Parkinson's disease	0 (0%)	0

presented mixed form of degenerative and vascular dementia. Sporadic episodes of psychomotor agitation, mainly at nightfall or overnight, were observed in few centenarians affected by dementia.

DISCUSSION

In our study we studied PD prevalence in a cohort of Italian centenarians: the diagnosis of PD was made by medical history, neurological examination, and review of past medical records and treatment plans. To our knowledge, there are no systematic clinical data from studies focused on people over 100 years of age, of which only sporadic data have been published.

Despite the concomitant high prevalence of dementia in our centenarians, no one was affected by PD. The rarity of the presence of PD in centenarians is peculiar, considering that this neurodegenerative disorder is second for prevalence only to AD in subjects under 85 years and PD prevalence increases with age from 425 cases/100,000 at 65–74 years to 1903/100,000 at over age 80 [3]. Other studies reported a decline in prevalence of PD in the oldest population [14], but data differences probably could depend on methodological heterogeneity of the studies.

In recent studies on centenarians, PD prevalence was one out of 23 in one study [15] and one out of 40 in another [16], both roughly compatible with our estimate.

The strength of our study is the large number of ultra-centenarians (100–108 years) of different origins, habits, and lifestyle.

A limitation of our study is that postural instability, one of the classical symptoms of PD, was difficult to evaluate because some centenarians were not cooperating or were bedridden or affected by medical comorbidities. Furthermore we could not gather enough information on presence of neurodegenerative disorders in relatives of the centenarians.

In the centenarians affected by dementia, the clinical picture was predominantly characterized by loss of memory, similar but not always really superimposable to AD. In these cases, we could speculate that some centenarians suffer from LATE dementia [17]. Mixed forms of degenerative and vascular dementia were also observed. The criteria for the diagnosis of dementia have intrinsic difficulties when used in centenarians: indeed, a decline from previous levels of cognition is often regarded as “normal” in this population. Moreover, sensory limitations, such as deafness and blindness, can give false positive results to neuropsychological evaluation. In addition, acknowledged normative data are not available for this age group as already reported [18].

When clinical history was collected interviewing the family or caregivers of centenarians, we had a confirmation that in the past none of the subjects of the study presented symptoms or had a diagnosis of PD. In line with this, none of them took, at enrollment or before, any anti-Parkinson drugs.

Taking into account our results, some preliminary considerations can be made on the low prevalence of PD in centenarians.

The first one is the gender effect: the majority of the studies show that PD is more frequent in men than women and, since centenarians males are only 10% of the population, we can assume that male subjects with PD have already died before reaching 100 years. Following this line of thought, data on survival of subjects who had PD before 100 years of age would be important in shedding light on the real prevalence of PD in centenarians.

Second, recent neuropathological studies in centenarian and supercentenarian brains have reported the scarcity or absence of alpha-synuclein pathology, despite the high presence of amyloid- β , tau and TDP-43 pathology [19, 20]. We could specu-

late that alpha-synuclein aggregates when present in substantia nigra are not sufficient to cause a significant neuronal loss leading to PD signs. Other explanations may be attributed to the complex regulation by the metabolic pathways important in the aging process, such as REST or Sirtuins [21] or the genetic influence by genes associated to longevity. It has recently been reported that *FOXO3A*, whose gene variations correlate with longevity [22], controls autophagic and mitophagic flux in neurons, pointing to the gene as an important factor in substantia nigra neuron survival [23].

In conclusion, PD prevalence is very low in the centenarians and this could depend on the specific characteristics of our cohort, or on biological and genetic mechanisms intrinsic to the very elderly subjects.

This first study on PD prevalence in subjects 100 years old and over needs replication in larger datasets but is interesting in suggesting future fields of investigation on protective factors against PD.

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