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Epidemiology of Cognitive Aging in the Oldest Old

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ABSTRACT

The proportion of persons aged 85 and over, the so-called "oldest old", is increasing dramatically worldwide. While a quarter of this population is affected by dementia, little is known about the specific features of cognitive functioning in the oldest old. In the presence of clinical specificities such as numerous comorbidities, multi-medication and visual and/or auditory loss, which are very frequent in extreme old age, neuropsychological assessment can be particularly challenging. This article presents an overview of the epidemiology of cognitive functioning in the oldest old, and discusses the issues regarding neuropsychological assessment and dementia in this specific elderly population. (REV INVES CLIN. 2016;68:33-9)

Key words: Oldest old. Epidemiology. Dementia. Cognition. Neuropsychological assessment.

INTRODUCTION

While persons reaching 85 years were only an anecdotal phenomenon in the past, nowadays they represent 13% of the population aged 65 and over in the world. This age group is the fastest growing segment of the older population. Indeed, the number of people aged 100 and over has doubled each decade since 1950 in the more developed countries[1]. Since the 1980s, people over 85 have been qualified by the demographers as the "oldest old" population. The exceptional rise in this segment of the population is explained on the one hand by the general improvement of living conditions and medical care, contributing to increased life expectancy; and on the other hand, the baby boomers born in the 1930s who are currently reaching very advanced ages. Such phenomenon has important consequences. First of all, oldest old people usually represent a high economic burden for health insurance systems. In addition, with age being the strongest risk factor for dementia[2,3], the oldest old are the more likely group to develop dementia. Yet, despite the high prevalence of dementia beyond 80, four out of five persons with dementia do not access recommended diagnosis procedures[4]. Reaching advanced ages is accompanied by substantial changes in morbidity, cognition, physical condition, and autonomy. Therefore, distinguishing normal aging from pathological aging is in some cases particularly challenging. Moreover, because of their global health condition, it seems inappropriate to provide oldest old individuals with the same neuropsychological evaluation as that used in the younger old. Unfortunately, there is an obvious lack of tests and norms adapted

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to this population. In the present article, we present an overview of the epidemiology of cognitive functioning in the oldest old, and discuss the issues regarding neuropsychological assessment and dementia in this specific elderly population.

COGNITIVE FUNCTIONING

Little is known about the specificities of cognitive functioning in very advanced age. First of all, it is important to remember that cognitive functioning in the oldest old is the result of the long-term decline that progressively occurrs with advancing age in several cognitive functions, in particular episodic memory, executive functions, and cognitive speed[5]. As in the younger old, there seems to be a sex difference in cognitive performances as women have better performances in verbal memory and cognitive speed tasks than men, even after controlling educational level[6]. In addition to the long-term progressive age-related decline, van Exel, et al. report a "terminal decline" characterized by an acceleration of the decline preceding the death[7]. Indeed, this study showed that the proximity to death is associated with an accelerated decline of crystalized knowledge and verbal abilities in a non-demented oldest old population.

CHALLENGES IN THE NEUROPSYCHOLOGICAL ASSESSMENT

General characteristics of the oldest old

As we all know, age is a major risk factor of numerous health concerns affecting not only cognitive, but also physical and functional abilities. Indeed, the oldest old are often affected by multiple morbidities or at least two or more chronic diseases[8]. The more frequent pathologies in this population are: dementia[9,10], depression[11], frailty syndrome[12], osteoporosis, diabetes, osteoarthritis, chronic kidney disease, cancer, cardiovascular diseases including hypertension and strokes[13]. The prevalence of hearing impairment is estimated at 70-90% for people aged over 85[14] and the prevalence of visual impairment in the USA is more than 23% in persons aged 80 and over[15]. They usually have multimedication[13] and more than 44% of women and more than 35% of men aged 90 and more consume psychotropic drugs[16]. Multimorbidity weakens the global health condition of the oldest old and leads to functional disabilities, which are extremely common among the oldest old[17]. The incidence of functional disability increases with age from 8.3% for people aged 90-94 years to 25.7% for those aged 95 years and over[18]. Moreover, fatigability is a common feature in the oldest old, especially in the everyday mobility[19].

In this context, neuropsychological assessment is often a challenge for clinicians. How can we diagnose cognitive deficits in a person aged 95 exhibiting multimorbidity, consuming multiple medications including psychotropic drugs for several decades, and exhibiting significant visual and auditory loss? This is a question that many clinicians have to solve when it comes to assessing neuropsychological functions in their oldest old patients.

The need for normative scores

The numerous sources of variability of cognitive performances in this specific population lead to questioning the issue of normality in the fourth age. If a large number of articles provide normative scores for elderly population, those presenting norms for elders aged 85 and over are much scarcer. These studies are indexed table 1. Such studies are tremendously important for clinicians. Nonetheless, the characteristics of the samples from which they are derived have to be carefully considered. Indeed, the selection bias of the sample can affect the representativeness of the population and requires us to use norms with caution. For instance, the norms provided by the Georgia Centenarian Study are based on a sample including both demented and non-demented octogenarian and centenarian subjects[20]. In the 90+ Study, norms are based on a sample of middle-upper class and highly-educated oldest old participants[21]. The WISE Study provides norms only for women[22]. An interesting project lead by the National Institute of Aging of United States[23] provides an online z-score calculator estimating the percentile ranges for an individual according to sex, age, and/or education for several tests of the Uniform Data Set[24]. Finally, the PAQUID Study provides normative scores for seven widely used neuropsychological tests from a population-based sample of French oldest old[25]. Furthermore, for most of these tests, the specific cutoff scores with best sensitivity and specificity for dementia diagnosis remain to be

assessed. As an alternative, Kahle-Wrobleski, et al. have shown that the Mini-Mental State Examination has acceptable sensitivity and specificity in oldest old populations[26].

The need for adapted tools

It is not only important to have validated norms for commonly used tests. It should be also necessary to make special efforts to adapt neuropsychological tools to the clinical specificities of such populations. In particular, the multiple sensory impairments justify the development of new tools of assessment, combining verbal and visual modalities and providing the opportunity for clinicians to choose the appropriate test modality according to patients' sensory deficits. Moreover, due to increased fatigability, the duration of the tests to be developed or adapted has to be relatively short.

DEMENTIA IN THE OLDEST OLD

Prevalence and incidence

It is important to underline that aging does not necessarily mean developing neurodegenerative disorders. In most of the studies, the proportion of dementia-free cases and healthy individuals among centenarians is far from marginal[27-29]. However, prevalence rates of dementia in the oldest old are rather high. Inhomogeneous prevalence rates are reported in the studies according to sample selection procedures and methods used in the screening of dementia[30-37]. Nonetheless, the study by Ferri, et al.[38] based on the Delphi consensus method[38] reports estimates for prevalence of dementia in the American continent from 28.1 to 33.2% and around 25% in Europe for the age group of 85 and over.

Incidence rates of dementia in the oldest old are also controversial in the literature. For most studies, incidence of dementia increases exponentially with age in men and women[2,39-44]. In the 90+ Study, dementia incidence increases exponentially with age between 65 and 90 and doubles approximately every five years with an incidence of 41% in centenarians[2,45]. By contrast, in the Monzino 80-plus Study, the largest population-based study conducted in the oldest old, dementia increases linearly. These authors question the plausibility of an exponential increase in dementia, arguing that if the exponential model was verified, everyone should have dementia around the age 100[30]. Finally, in the Bronx Aging Study[40], the increase in incidence slows relatively from 65 to 85 years old.

Risk factors of dementia in the oldest old

Several studies have examined the risk factors for dementia in the oldest old. Besides the major risk factors existing whatever age, some specific factors seem to have slightly different effects in the very old age. Most of these factors are still controversial in the literature. The main factors identified are the following:

Conventional risk factors

As for the younger old, Poon, et al. have shown an effect of age, gender, race, and education on the risk of developing incidence in the Centenarian Study[27]. Among these factors, education level seems to have a strong impact[31], with a lower risk of dementia in highly educated individuals, suggesting that the benefit of cognitive reserve[46] seems to exist throughout the aging process including very old age. Depressive symptomatology[47], delirium[48] and multimorbidity[49] were also associated with incident dementia. Furthermore, the association between family history of dementia and the risk of developing Alzheimer's disease (AD) would be stronger in the younger old than in the oldest old[50].

Cardiovascular factors

– Diabetes: Diabetes is known to be associated with increased risk of dementia in the younger old. In the Vantaa 85+ Study, diabetes was associated with incident dementia[51]. Conversely, in the WISE cohort, diabetes was not associated with increased dementia in the oldest old. The authors explained the absence of association by the reduction of life expectancy of persons presenting both diabetes and cognitive impairment[31].

– High-density lipoprotein (HDL) cholesterol: As for the younger old, low HDL cholesterol was shown to be associated with cognitive impairment and dementia in the oldest old[52].

Table 1. Studies providing normative neuropsychological scores for oldest old populations

Studies	Neuropsychological tests
PAQUID Study[25]	Mini Mental State Examination (Folstein, et al., 1975); Benton Visual Retention Test (Benton, 1965); Digit Symbol Substitution Test (Wechsler, 1981); Verbal Fluency test: Isaacs's Set Test (Isaacs and Kennie, 1973); WAIS-III Digit Span Test (Wechsler, 1997); Wechsler Paired-Associates Test (Wechsler, 1945); Wechsler Similarities Test (Wechsler, 1981); Zazzo's Cancellation Task (Zazzo, 1974)
Uniform Data Set project[23]	Mini Mental State Examination (Folstein, et al., 1975); Boston Naming Test (BNT) (30 item-odd numbered) (Kaplan, et al., 1983); Digit Span Forward and Backward; Digit Symbol Coding subtest (Wechsler, 1987); Trail Making Test A and B (Delis, et al., 2001); Verbal Fluency Test: Semantic Fluency (animals and vegetables) (Morris, 1989); Wechsler Adult Intelligence Scale-Revised (WAIS-R); Wechsler Memory Scale-Revised (WMS-R) subtests Logical Memory IA and IIA (Wechsler, 2008).
Georgia Centenarian Study[20]	Mini Mental State Examination (Folstein, et al., 1975); Behavioral Dyscontrol Scale (Grigsby, et al., 1992; 1996); Fuld Object Memory Evaluation (Fuld, 1981); Severe Impairment Battery (Saxton, et al., 1990)
90+ Study[21]	Mini Mental State Examination (Folstein, et al., 1975); 3MS (Teng and Chui, 1987); Boston Naming Test (15-items) (Kaplan, et al., 1978); CERAD Constructions (Morris, et al., 1992); Clock Drawing Test (Freedman, et al., 1994; Rouleau, et al., 1992); Letter Verbal Fluency; Trail Making Test A and B (Delis, et al., 2001); Verbal Fluency test: Category (Animal); WAIS-III Digit Span Test (Wechsler, 1997)
Mount Sinai - Alzheimer's disease research center[72]	Mini Mental State Examination (Folstein, et al., 1975); Boston Naming Test (15-items) (Kaplan, et al., 1978); CERAD Constructions (Morris, et al., 1992); Trail Making Test A and B (Delis, et al., 2001); Verbal Fluency test: Category (Animal); Word list memory; Word list recall; Word list recognition
Cambridge city over-75 cohort[73]	Mini Mental State Examination (Folstein, et al., 1975)
Framingham heart study[74]	Wide Range Achievement Test-Third Edition (WRAT-III) (Wilkinson, 1993)

– Hypertension: In the Vantaa 85+ Study, both diabetes and incident strokes were associated with increased probability to develop dementia. On the contrary, a history of hypertension was associated with a low probability to develop dementia[51].

Genetic and inflammatory factors

– APOE: The Apolipoprotein E ε4 allele (APOE4) is a well-established risk factor for AD, whereas the APOE ε2 allele (APOE2) was reported as protective in the younger old. The role of APOE4 is debated in the oldest old. Some studies concluded that APOE4 was a risk factor of dementia in the oldest old as in the younger old[30,32], whereas others like the Vantaa 85+ Study reported that the incidence of dementia in carriers of APOE4 was not increased compared to non-carriers[53]. In the 90+ Study, the authors conclude that APOE4 no longer plays a role in dementia and mortality at very old ages[54]. Regarding APOE2, it was associated with preserved cognition in the 90+ Study[55]. Surprisingly, in the Monzino 80-plus Study, carriers of the APOE ε2/ε2 or the APOE ε2/ε3 presented a higher risk of dementia[56].

– Inflammatory markers: While in the 90+ Study inflammatory markers such as C-reactive protein (CRP) was associated with increased dementia prevalence and mortality[57], in the Leiden 85-plus Study, the association between cognitive decline and inflammatory markers was only moderate[58]. However, in both studies the associations tended to be stronger in APOE4 carriers.

Clinical specificities of dementia

Dementia occurring after 85 years is called "very late-onset dementia". Clinical manifestations as well as the diagnosis procedures of late-onset dementia are highly

controversial. However, we know that AD and mixed dementia are the most common types of dementia in the oldest old[31]. Compared to the younger old, the progression of cognitive decline associated with AD is slower in the cases of late-onset dementia[59]. On the contrary, the decline in functional capacity would be faster after 85 years[60].

Physiopathology of dementia in the oldest old

The study of the oldest old brains also provides rich lessons. Neuropathological markers of dementia, such as neuritic plaques and neurofibrillary tangles, in oldest old seem to have different clinical consequences[61-63]. Savva, et al.[64] autopsied 456 donated brains of five age groups (under 80, up to 94 years, and older). The association between AD neuropathological lesions and diagnosis of dementia before death was stronger in younger old than in the oldest old. More precisely, when comparing persons who died at 75 years to persons who died at 95 years, the presence of neuritic plaques and neurofibrillary tangles was less strongly associated with dementia at age 95. In the same vein, in a large cross-sectional study of 2,014 subjects aged 70 and over at death, Middleton, et al. have shown that even if the risk of clinical AD diagnosis was associated with neurofibrillary tangles for each age group (70-74; 75-84; 85 and above), the strength of the association was weaker among the oldest old[65]. Furthermore, there are no clear differences in the neuropathological damages evidenced in demented and cognitively normal oldest old individuals[66,67]. According to Haroutunian, et al., the lack of differences in the lesion density between demented and non-demented individuals could be due to a low density of lesions in the brains of oldest old individuals with dementia rather than an augmentation of lesions in the brains of non-demented oldest old[61]. In the Cambridge City over-75s Cohort, where a post-mortem study has been conducted, a particularly high prevalence of vascular lesions, including micro-infarcts and vascular dementia, was found in the brains of oldest old individuals. Alzheimer-type lesions and cerebrovascular pathology were very common. The greater burden of these lesions and pathologies, but also of Lewy bodies, and hippocampal atrophy, were associated with a higher risk of late-onset dementia, but were not sufficient to define clinical dementia[68]. In an ancillary study of the 90+ Study (i.e. 90+ autopsy study), 137 brain autopsies were performed. Interestingly, the results showed that the subjects with high and low AD neuropathology (neuritic plaques, diffuse plaques, and neurofibrillary tangles) presented a similar cognitive trajectory three years before death[69]. Finally, compared to the younger old, the oldest old seem to have less salient morphometric specificities of AD such as reduced hippocampal volume and cortical grey matter thickness[70]. Taken together, these findings suggest that the underlying physiopathology leading to clinical dementia would be slightly different in the oldest old and the younger old.

CONCLUSIONS

Being the fastest growing segment of the elderly population and exhibiting specific clinical issues, the oldest old individuals cannot be considered either as an anecdotal phenomenon or as a group presenting similar issues as the younger ones. Further researches are necessary in many fields. Defining dementia in the very old people calls for international debate in order to lead to consensual definition. Neuropsychological tools of assessment have to be set up along with validated norms. Better characterizing the impact of social representations is also necessary. The fourth age goes often with representations of "senility" and general reduction of activity so dementia is often perceived as normal. In this context, the oldest old are rarely oriented to specific consultations for memory disorders. Better understanding the neuropathology leading to dementia at very advanced age is also important since outstanding differences seem to exist in this specific group. Undoubtedly, in the next decades, the study of the oldest old, sometimes called the "exceptional survivors"[71], will offer many challenges in the understanding of aging.

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