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Alzheimer's disease in Nigeria*

B.O. OSUNTOKUN, A.O. OGUNNIYI AND U.G. LEKWAUWA
Neurology Unit, Department of Medicine, University of Ibadan, Ibadan, Nigeria

Summary

The age-related dementias of the elderly (those aged 65 years or more) are of major public health importance in developed countries. Developing countries, most of which are undergoing epidemilogical transition and greying of population, currently contain more than half of the world's population of elderly, a proportion that would reach 75% by 2020. Apart from reports from China, there is little or no information on the dementias of the elderly in developing countries. Alzheimer's disease, which accounts for two-thirds of dementia of the elderly in Caucasian population, is under-documented and believed to be rare in black Africans. But black Americans who are of black African lineage commonly suffer from Alzheimer's disease. A recent autopsy survey of the brains of elderly Nigerians showed absence of senile plaques and neurofibrillary tangles, the pathognomonic histologic lesions of Alzheimer's disease and ageing found in 25% to 80% of normal undemented elderly Caucasians and Japanese. In a community-based door-to-door survey of a population of 9000, including 932 elderly Nigerians, no subject with dementia as defined by DSM-IIIR was found, although there was significant decline of cognition with age, female sex and less than 6 years of formal education. The distribution of cognitive scores is a highly skewed unimodal curve. We emphasize the potential value of cross-cultural epidemiological studies of ethnic groups in different environments and with different prevalence ratios of Alzheimer's disease, in identifying putative environmental factors for this disease.

Résumé

Les dementias qui sont relatif d'âge pour les gens d'un certain âge (qui sont de 65 ans et plus) sont important à la sonte publique majeux dans les pays devepper. Les pays developpant qui subir la transition epidemiologique et la grissant de la population ont couramment plus de la moitie des gens d'un certain age de la population du monde, une proportion qui va atteindre 75% par 2020.

Autre que le compte rendu de la Chine, il y'a un peu ou pas d'information sur les dementias des gens d'un certain âge dans les pays developant.

La maladie d'Alzheimer (AD), qui compte pour $^2/_3$ des dementias de les d'un certain âge dans la population causasian, est sous-documente et cru d'être rare dans l'Afrique noire. Un examen recent d'autopsie sur les cerveaux des Nigeriens qui ont un certain âge a montre l'absence de la peste ancien et les enchevetrements ou bien les fourres neuro- fibrillaire, la lesion pathogomonique histologique due AD et l'agent trouvé dans 25% à 80% des causasians et Japonais d'un certain âge qui ne sont pas dement. Une porte-à-porte examen d'une population de 9000, y compris 932 Nigeriens d'un certain âge, a été faire, et aucune sûjet ave dementia comme definir pas DSM-IIIR a été trouvé, quoi qu'il y avait une chute signiticatif de connaissance avec âge, la sexe feminin et moins de 6 ans d'education formale. La distribution pour les scores connaissances est la courbe en biais unimodale. Le role de geographie et race comme un agent supposer de risque pour AD sont revue en bref.

Nous appuyerons la valeur potential des études epidemiologique croix-culturel (cross cultural) de les groupes ethniques dans les environs different et avec les rapport ascendant different de AD, pour reconnaitre les facteurs autour supposer pour AD (dons les environs).

Introduction

The age-related dementias are of increasing public health importance, not only in the developed countries, but also in the developing countries, many of which are undergoing epidemiological transition and the longevity revolution or 'greying' of population. Currently, of the 400 million elderly (>65 years of age) people in the world, 52% live in the developing countries and the proportion will increase to 75% by 2020. Of the estimated world-wide increase of over

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one million elderly people per month, 80% occur in the developing countries [1]. Apart from reports on the Chinese in China [2,3], there is little or no information on the dementias of the elderly in the developing countries.

Rarity of Alzheimer's disease in developing countries in Sub-Saharan Africa

No authentic case of Alzheimer's disease has been reported in an indigenous black African. Most medical practitioners, neurologists and psychiatrists in Nigeria and other black African countries and other developing countries are consistent in their view that, in their practice, over several years, Alzheimer's disease is extremely rare or has not been seen [4]. In one community-based study to assess the magnitude of neurological disorders, reported in 1987 from Nigeria — a country which occupies 4% of the land mass of Africa, but, with an estimated population of 120 million, supports 25% of the population of black Africa — involving a door-to-door survey of nearly 19,000 subjects (4% whom were over 65 years of age) no patient with dementia was seen [5]. Of 2182 consecutive new patients seen in one year (1984) in Nigeria's best-known neuropsychiatric hospital at Aro, Abeokuta, 6% of whom were older than 65 years, no patient with Alzheimer's disease was seen [6]. From first-hand experience of neuropsychiatric practice of some 33 years dating back to 1957 in Nigeria's oldest and premier teaching hospital, and the National Centre of Excellence in Clinical Neurosciences, the University College Hospital (UCH), Ibadan, during which over 14 million patients had been seen, including 4% aged 65 years or more, the diagnosis of Alzheimer's disease had not been substantiated in any patient. Recently, between 1984 and 1989, 37 patients with dementia, including 28 males and nine females, were seen in UCH, Ibadan: none had Alzheimer's disease, whereas 18 suffered from undoubted multi- infarct dementia. Some authors from Nigeria have reported the occurrence of 'senile dementia' as a psychiatric diagnostic rubric among Nigerian patients, but criteria for diagnosis were not stated [7,8]. Among Ethiopian Africans 'senile dementia' was uncommon [9]. Yet the prevelence of Alzheimer's disease in black Americans in the U.S.A. who are predominantly of the lineage of West African negroes is as high as, or even higher than, in American Caucasians [10-12], although one recent report suggests that the frequency of Alzheimer's disease in white Americans is 2.6 times higher than in black Americans: the estimated relative risk for Alzheimer's disease was 3.86 times higher for Whites than Blacks, and in brains from non-demented elderly, the histologic hallmarks of Alzheimer's disease or Alzheimer's changes occurred in significantly higher frequency in white Americans than in black Americans [13]. In this study from Boston, U.S.A., Blacks, on the other hand, had significantly higher frequency of multi-infarct dementia and, except for Creutzfeldt-Jacob syndrome which was seen only in Whites, the frequencies of all other causes of dementia were similar for the two races. In Israel, the prevalence of Alzheimer's disease was significantly higher in Jews of Caucasian origin than in Jews of Asiatic or African origin [14].

Recent epidemiological studies of Alzheimer's disease in Nigerians

Autopsy survey for histologic hallmarks of ageing and of Alzheimer's disease in brains of undemented Nigerians

It has been suggested that an epidemiological approach which circumvents the problem of reliable and valid diagnosis of Alzheimer's disease is to work with the brains rather than with persons; for, although with increasing accuracy of up to 90%, or even sometimes up to 100% [15] in one series, of clinical and laboratory-aided diagnosis of Alzheimer's disease, errors can still be substantial [16-18]. In one study the Kappa coefficient for inter-rater reliability for the NINCDS-ADRDA clinical criteria for Alzheimer's disease was only 0.64, and 0.55 for the DSM-IIIR criteria [19].

In 1986 we commenced an autopsy survey of brains of consecutive undemented Nigerians above the age of 40 years who died at UCH, Ibadan (Table 1). Details of subjects and methodology have been described elsewhere [20]. Of 198 Nigerians aged 40 years or more, including 45 subjects aged 65 years or more, none showed the histological hallmarks — senile plaques, neurofibrillary tangles, amyloid vascular degeneration and granulovacuolar bodies — of Alzheimer's disease, and of a lesser degree reported in aging in 25% to 80% of normal undemented Causcasians and Japanese.

Community-based door-to-door survey for age-related dementia in Nigeria

We have modified the MMSE [21], one of the most useful instruments for community-based investigation of dementia, to carry out a door-to-door survey of dementia in elderly Nigerians in a stable population of about 9000 individuals, in an urban area. The study population consisted of all individuals aged 40

years and above who were residents in that community during the prevalence period which was October 1989, and included those who were temporarily away at farms or hospitals, or on transient travel. In the community studied, as elsewhere in Nigeria, there are no long-stay or residential nursing homes for the elderly. The modified MMSE was administered by trained medical (clinical) students who concurrently carried out a listing of houses and census demographic data on all members of each household. During training of the medical students in the use of the screening instrument, the inter-rater agreement in the responses obtained from subjects was 100%. For individual subjects with no recorded dates of birth, date of birth was estimated from table of 'historical' landmarks well- known to the population, a well-tested standing practice in Nigeria, for assessing ages of adults.

Table 1: Autopsy survey: age and sex distribution of the patients surveyed

Age range (years)	Males	Females	Total (%)
40-44	18	10	28 (14.1)
45-49	9	14	23 (11.6)
50-54	18	24	42 (21.2)
55-59	16	14	30 (15.1)
60-64	18	12	30 (15.1)
65-69	14	12	26 (13.1)
70-74	10	3	13 (6.6)
75-79	3	—	3 (1.6)
80+	1	2	3 (1.6)
Total	107	91	198 (100.00)

Subjects with cognitive impairment (irrespective of their educational status), and a one-in-five random sample of those whose scores were in the normal range were further evaluated for the presence of dementia. The criteria for the diagnosis of dementia were derived from DSM-IIIR[22]. Of the 932 who were found eligible, 930 were studied. One refuser had a febrile illness and the second refused for personal reasons. The two could not be located at subsequent visits but neither of them appeared to suffer from dementia based on interview with their relations. The age and sex distribution is shown in Table 1. One hundred and sixty-one subjects had at least 6 years of formal education; the illiteracy rate was about 83%. Ninety-one subjects (10%) had subjective memory inpairment.

Table 2: Population screened for dementia in door-to-door community-based study in Nigeria; age and sex distribution of the subjects

Ages in quantiles	Males	Females	Total (%)
40-44	57	109	266 (17.9)
45-49	47	96	143 (15.4)
50-54	58	89	147 (15.8)
55-59	35	48	83 (8.9)
60-64	46	36	82 (8.8)
65-69	49	38	87 (9.3)
70-74	29	57	86 (9.2)
75-79	20	37	57 (6.1)
80	17	46	63 (6.8)
Unspecified*	3	13	16 (1.8)
Total	361	569	930 (100.00)

*>40 years.

On cognitive assessment, the mean score of the educated subjects was 18.9 (s.d. = 2.5) and this was significanly different from the mean of 21.9 (s.d. = 3.4) of the illiterate subjects *($P < 0.01$)*. There was significant correlation of cognitive decline with increasing age (for females, $n = 569$, correlation coefficient 0.30, $P < 0.0001$; for males, $n = 361$, correlation coefficient 0.25, $P < 0.00001$), with female sex ($P < 0.001$) and with illiteracy (less than 6 years of education; $P < 0.0001$). Using a cut-off score, 21,534 subjects (58%) were adjudged to have normal cognition, and this group was made up to 141 educated subjects and 393 illiterate subjects. Overall, on clinical evaluation, cognitive impairment was present in 41 subjects (4.4%), but the abnormal mental status in seven of the subjects was attributable to depression from recent bereavement in four, social stress in two and economic constraints in one subject. None of the subjects had dementia as defined by DSM- IIIR. Based on the rating scale of Berg (1984) [22], none of the Nigerian subjects studied would be graded as having more than questionable dementia on the severity scale. The 34 subjects with age-dependent cognitive impairment exhibited mild 'benign forgetfulness' that did not interfere with everyday activities, were fully orientated, showed no impairment in solving problems, identifying similarities and differences, in use of money, involvement in community affairs, day-to-day living within the home and

self-care. The cognitive scores for the community showed a unimodal distribution for males and females and for both combined (Fig. 1). The distribution curve is similar to that described in a Caucasian community [24].

Comments

We were surprised by the finding in the autopsy survey of almost total absence in brains of Nigerians of Alzheimer's changes — senile plaques, neurofibrillary tangles and other histological hallmarks of Alzheimer's disease and 'ageing' of brain. The results in the autopsy study in Nigerians, if confirmed in the larger on-going study are unlikely to be due to basic biological fundamental difference. It is possible that the Nigerian subjects might not have had some as-yet-unknown exposure, or they might have had some protective factor against the neuronal changes characterized by the emergence of senile plaques, tangles and amyloid deposition in the brain, or they might constitute a biological survival elite. One possibility is that the methodology used by us was not sensitive enough to detect Alzheimer's changes. We did not use thioflavine S and immunocytochemistry with formic acid treatment on most of Nigerian brains, methods which are the most sensitive in detecting brain amyloid and amyloid plaques. However, our staining methods are not basically different from those used in studies of brains of normal undemented Caucasians, which showed tangles and/or plaques in 25% to 80% + of subjects aged 60 years or more.

Ours is the first study to determine the burden of age-related cognitive impairment in elderly Africans in the community. In agreement with the findings of others, our results showed a confounding effect of poor education [2,3,25-27]. The high frequency of 'impaired cognition' in the illiterate subjects, none of whom was subsequently found to have clinically significant dementing illness confirmed that an abnormal mental status during screening cannot be used to diagnose dementia. Although we found no case of dementia as defined by DSM-IIIR in the community-based study, one must be cautious in generalizing

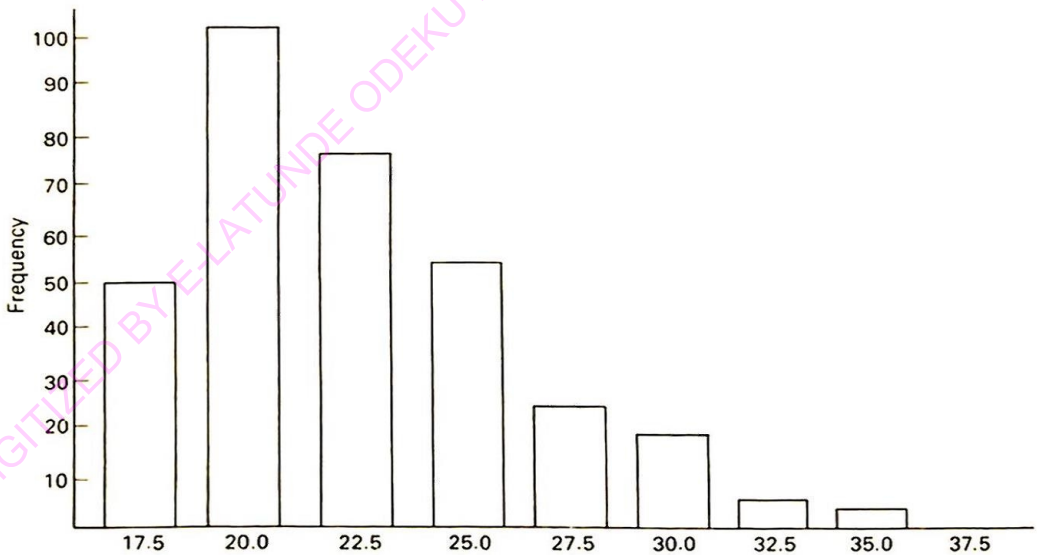

Fig.1: Distribution of cognitive scores in Nigerians (male and female > 65 years).

that Alzheimer's disease does not exist in Nigeria. Hospital-based studies in Nigeria have reported cases of dementia in association with various conditions [7,8,28-30]. In spite of our efforts to screen all residents in the community, including those transiently absent, it was still therefore possible that the moderate to severe cases were more likely to be found in hospitals, since they are the ones who would require constant supervision. The extended family system, which used to provide health care and social needs of the elderly in Nigerian communities, is being remorselessly eroded and dismantled and this may be one of the reasons why cases may not be encountered in community-based studies.

The prevalence of a disease is a function of incidence and duration of the disease and, if incident cases have short survival, no cases would be encountered during a prevalence survey. There was no epidemic of any rapidly fatal communicable diseases in the community when we undertook the study and hence we do not think reduced survival could account for the lack of cases. Although no study had looked at the survival pattern of demented cases in Nigeria, studies from other parts of the world have reported a reduced life expectancy of 0.58 at 5 years and 0.26 at 10 years after disease onset [30-32]. We do not have any reason to assume that the disease would be unusually fatal in Nigerians. Neither could we attribute the rarity of cases to young age structure of the population studied, because over 30% of the 930 individuals studied were above 65 years of age. Longitudinal study in such a community as the one we studied would be valuable to detect changing trends in prevalence of the age-related dementias and to delineate the early features. Studies also need to be carried out in other communities in Nigeria.

The Nigerian community we have studied is similar to others in age-related decline in cognition, and unimodal, although highly skewed, distribution of cognitive scores. The senile plaques and neurofibrillary tangles, pathognomonic changes associated with Alzheimer's disease and, to a lesser extent and degree, with normal aging in Caucasians and Japanese, if they are truly rare in the Nigerian Africans may reflect reactions to environmental insults presently uncommon in the Nigerian milieu.

Although one has to be cautious in interpreting available data, there seems to be some grounds for the hypothesis that Alzheimer's disease is the consequence of some exposure to environmental factors to which *Homo sapiens* is not adapted and which are not present in non-industrialized countries [34]. To test this hypothesis requires cross-cultural and trans-national, methodologically comparable epidemiological studies.

Conclusions

Compared with Caucasians, the prevalence of Parkinson's disease is low in black Africans [35,36] and, in two reports from U.S.A., also low in black Americans [13,37]. It is speculative that the low frequency of Parkinson's disease in black Africans is linked to the same mechanism or pathogenesis which accounts for the current low prevalence or rarity of Alzheimer's disease and Alzheimer's changes in black Africans. It has been suggested that Alzheimer's disease and Parkinson's disease are in a spectrum of disorders of the isodendritic core [38].

While the evidence accumulates that there is a genetic basis for at least a proportion of patients with Alzheimer's disease, it would seem likely that environmental factors play some role in the causation of Alzheimer's disease. The search for environmental factors nevertheless continues to be frustrating. Some have suggested that Alzheimer's disease might be a disease of Western culture [34]; however it has been found in almost every community so far investigated. Alzheimer's disease was thought to occur in low prevalence among the Chinese, until the recent studies of Zhang *et al.*, [3]. However, if populations could be found with significantly lower or significantly higher prevalence ratios of Alzheimer's disease, the search for environmental factors in the genesis of the disease could be greatly enhanced by comparing different aspects of their cultures and the relative exposures to disease pathogens or environmentally produced noxious agents. A proposed joint Ibadan-Indianapolis cross-cultural epidemiological study, as part of a WHO trans-national multi-site study is to explore this area of epidemiology by comparing prevalence, incidence and distribution of putative risk factors of Alzheimer's disease in Blacks residing in Indianapolis, IN, U.S.A. and Africans in Ibadan, Nigeria: the American Blacks are of West African stock or lineage. Such a study could enhance our understanding of the fundamental biology of aging and improve the effectiveness of health care for individuals with age-associated dementias. Longitudinal studies would be of value to detect trends in the changes in pattern of these disorders and help to forecast the impact on communities, especially in developing countries, where within the next decade the aging revolution will create enormous population of the elderly.

Finally, geographical epidemiological studies would complement the current intense research ef-

forts on molecular genetics of Alzheimer's disease [39]. Although the cause of Alzheimer's disease is unknown, it is speculative that Alzheimer's disease could be due to excess gene dosage of certain genes, with overproduction of corresponding proteins as the cause of the neuropathological changes in Alzheimer's disease. Such genes include the Alzheimer's disease gene, the beta amyloid precursor protein (APP) gene, the superoxide dismustase-1 gene on chromosome 21 and the alpha-1-antichymotrypsin gene on chromosome 14. Faulty regulatory mechanisms, including abnormal calcium metabolism, could also be involved. Alpha-1-antichymotrypsin, a protease inhibitor is a component of beta amyloid in Alzheimer's disease. Duplication of chromosome 21, as in Down's syndrome — possibly the Alzheimer's disease gene on chromosome 21 in familial Alzheimer's disease, free radicals (influenced by superoxide dismustase-1 gene) which increase with age, exposure to ischaemia, trauma, some drugs, organic solvents, interleukin-1, growth factors and phorbol esters are all known to increase expression of the amyloid protein precursor gene [40-43]. Other unidentified environmental factors currently present in developed industrialized countries, but rare in developing less industrialized countries, could be involved in increasing the expression of the APP gene. It is speculative, but, based on current evidence, possible that the pathogenesis of Alzheimer's disease involves age-related accumulation of some neurotoxin(s) brought about by biological process(es) initiated by some environmental exposure(s)/factors or genetic vulnerability or both, with overproduction of gene(s) products. Cross-national studies in different parts of the world, especially where prevalence ratios of Alzheimer's disease currently differ in the same racial groups, have great potential for delineating the putative risk factors.

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