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Alzheimer's Disease in Latin America and Caribe

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ABSTRACT

Alzheimer's disease is the most common dementia in elder people, where Apolipoprotein E ε4 genotype is the most clearly documented and studied risk factor. Today, over 46 million people live with dementia worldwide and 46% of it lives in Latin America making it a global health and social care challenge. In this review, we aimed to gather all the studies done in Alzheimer's disease and ApoE in Latin America in order to acknowledge the level of research, allele frequency along the continent and ethnic groups, level of awareness, status and cost of this disorder represents. The search yielded around 50 publications performed in differents parts of Central and South America and Caribe. However, in several countries no data were found, meaning whether the search was no so inclusive or research in that field is still missing. ApoE Odds ratios varied along the continent, finding the highest in Brazil and Cuba. In most of the populations and ethnic groups ApoE allele frecuencies followed the same pattern ε3>ε4>ε2 and the variation of these are thought to be result of admixture, genetic drift and natural selection. Latin America is and will face dementia

epidemic in coming years and we lack of medical, social and economic infrastructure. We should start now prioritizing the development and implementation of intervetions in demented subjects to ensure that the health and social care needs of them to be anticipated and met.

Keywords: Alzheimer's disease; Allelic frequencies; Apolipoprotein E; Genotype; Genetic polymorphisms; Incidence; Prevalence

Abbreviations: AD: Alzheimer' disease, ApoE: Apolipoprotein E, LMICs: low and middle-income countries, HIC: high-income countries, LA: Latin America, SNPs: single nucleotide polimorphisms, WAR: WorldAlzheirmer Report, OR: Odds Ratio, CI: Confidence Intervals

INTRODUCTION

This disorder is the one of the main contributor of incapability, dependence and mortality in older people [1,2]. It was thought to be a merely problem of developing countries however; recent projections had shown that by 2030the prevalence of AD would increase in 63% in low and middle-income countries (LMICs), product of improvings in economy and education. It also had enhanced health status of the population, having a direct impact in longer lifespan. In high-income countries (HIC), population older than 60 years by 1970 was 291millions. In 2000, it was about 600 millions (2 fold), while in LMICs the increased in older populations went from 137 to 354 in the same period of time (2.6 fold) [2]. The estimated population in Latin America (LA) is 572 millions. So, assuming the prevalence of AD and related disorders is 6%, there are already about 2 million sufferers. This is almost the same proportion as the one expected for the USA, and Canada combined [3]. Making it a global health and social care challenge, which until now has not been treated as a priority in developing countries and much less in LMICs [4].

As life expectancy increases, late onset diseases trend intensifies due to low levels of education, high rates of brain injury, smoking, poor diet, infrequent participation in mentally or socially stimulating activities, sedentary lifestyle, high rates of cardiovascular risk factors such as high blood pressure, diabetes and other diseases [3,5]. These facts are getting commoner in middle-income countries; besides, fertility rates are declining, meaning older people are going to constitute the biggest proportion of the total population. By 2050, the percentages of older people in LMICs are going to match those of first world countries [4]. Although, the number of AD cases in LA is increasing, there is still a lack of investor support from the governments. According to Prince et al 2015, the best-represented regions in AD studies are North America and LA, as is shown in (Figure 1). However, almost half of the studies were done in North America, and the rest of them are dispersed in 8 countries (Cuba, Dominican Republic, Jamaica, Peru, Venezuela, Mexico, Chile and Brazil) from the 20 ones and only 4 new population-based studies of the prevalence of dementia among people aged 60 years and over have been made since 2009.

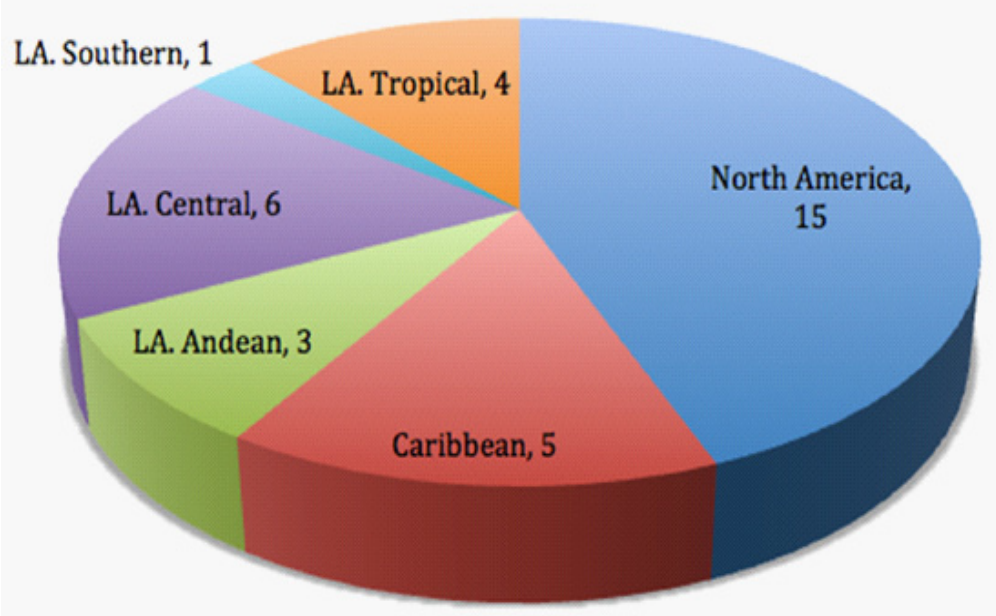

Figure 1: Number of eligible dementia prevalence studies [4].

Specifically, the prevalence in LA and Caribe is high from 6 - 6.5 in 100 adults of and over 60 years old (Table 1). Specifically, by the year 2020, Cuba will have the oldest population in Latin America, with adults aged 60 years accounting for 21.6% of total population [7]. It has also evidenced large family groups in certain regions of Dominican Republic, Colombia and Venezuela highly afflicted with dementia [3]. It is expected that from 2001 to 2040 the number will increase in a 77% in Argentina and Chile and a 134% to 146% in the rest of LA. Being the highest expected global percentage, which means a lower survival rate comparing to high-income countries [1].

Table 1: Estimated number of people with dementia (2015), cost of dementia in 2010 and 2015 (billion US$ and percent of Latin America and the Caribe) by Global Burden of Disease world region classification.

Geographic area	People with dementia ≥ 60 years 2015 (millions)	Year for cost estimates (basis for prevalence estimates)				
		2010[a]		2015[b]		2010-2015
		US$ (billions)	Per cent	US$ (billions)	Per cent	Percent change
Latin America	684382	4.9	0,825	10.65	1.3	95.01%
Caribe	66001	3.0	0.5%	3.5%	0.4%	18.2%

Source: [a] World Alzheimer report 2009[6]. [b] World Alzheimer report 2015 [4].

As almost all the studies have been performed in Caucasians populations. Latino genetics is different and the risk factors identified until now could not represent such risk for us, and others which might not be proposed as it for Caucasians could be the leading cause in Latin America.

There are several causes of Alzheimer's disease, which are classified according its genetics and age of onset (Table 2). All of these forms are indistinguishable from a clinical point of view. As most of the cases of AD are late onset (75%), there is little doubt that other, most likely that multiple polymorphisms play an important role in the patho-physiology of Alzheimer's disease. Until now, Genome wide associations studies and other population base researchers have identified 2973 new single nucleotide polymorphisms (SNPs) in 695 genes that act like susceptibility modifiers [1,8-10].However, in 1993 ApoEε4/ε4 was identified as the most important genetic risk factor in the development of AD. It is located on chromosome 19 and had shown to add 30% of lifetime risk. Since its discovery several studies all over the globe have been performed, acknowledging that the frequency and the risk of it changes in each population given the presence of gene by environment, and/or gene-by-gene interactions [1,8].

In this review we attempt to join all the studies perform in ApoE in LA due to their clinical significance and to know the distribution of ApoE alleles in populations from diverse ethnic groups in order to have a better idea of its real risk and frequency in LA and Caribe and the amount of studies, which at the same time will give us an idea of the level of importance of AD, research effort and the cost that this disorder represents.

Table 2: Causes and genes of Alzheimer's disease.

CAUSE	GENES	% CASES
All familial		~25%
- Early-onset familial < 65	APP (29) PSEN1 (166) PSEN2 (10)	< 2% 10%-15% 20% -70%
- Late-onset familial > 65 years old	ApoE	Rare 15% -25%
Chromosomal (Down syndrome)	APP	< 1%
Late-onset	Unknown Includes genetic/environment interactions	~75%

Modified from: Pagon RA, Adam MP, Ardinger HH, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2015 [8].

MATERIALS AND METHODS

The search was performed in Pubmed, Scopus and Latin index databases. Most of the studies are from 1997 until 2015. We also used some studies as reference as the World Alzheimer Report 2015 (WAR) and the 10/66 Dementia Research group and data from the World Bank, Alz forum, and Pan American Health Organization. The search terms strategy used in English and Spanish was: ApoE, Alzheimer's disease, the country or capital, environmental factors, diet, Latin America. We included some studies that were not taking into account in WAR due to their strict exclusion criteria, since as the main objective of this review is to gather all the work done in this area (ApoE in LA) so small or big in order to understand and acknowledge, the level of interest, support and investigation in AD in LA. Papers were excluded when the abstract clearly demonstrated that the publication entailed all Latinos or Hispanics without making any difference of the country, like most of the studies done in the USA. Also, studies where ApoE was evaluated as increase factor (interaction) with other genes related to AD. All eligible studies were systematically classified by country and year.

RESULTS AND DISCUSSION

Risk Factors

A common hypothesis is that sporadic AD is a multi factorial disease where the interaction between aging, genetic predisposition, and exposure to one or more environmental agents are directly involved in its pathogenesis [8].

ApoE in Latin America and Caribe

Some but no all studies suggest that the influence of the ApoEε4 allele may be less robust in Latin compared with Anglo individuals [11]. The search of ApoE as risk factor yielded 20 publications from Argentina, Brazil, Caribe, Chile, Colombia, Cuba, Ecuador, Mexico and Venezuela and one study performed in the USA where they took into account Mexican vs. Caucasian, all of this is resumed in Table 3. Odds ratio (OR) varied between countries and within them. In one hand, the highest odds ratios were found in in Vitoria-Brazil where the population is made up of 80% of Caucasians and 20%Afro-Brazilian 13,94 (95% CI: 3,14-64.50) and in Cuba 13.3 (95% CI: 1.6-105.5). The lowest OR belonged to other study done in Brazil too, although the population group was different 2.43(95% CI: 0.93-6.36).On the other hand, from all this studies only in Villalpando-Berumen et al., 2008 (Mexico Mestizos urban population) and Lavados et al., 2005 (Chile) did not find any association with ApoE and AD, although the presence of this allele seems to modify its clinical expression [29].

Table 3: List of studies performed in Latin American taking an ApoE as risk factor.

Study	Population	Source	AD Cases		Normal Controls		Result	OR, 95% CI
			# Subjects	Onset Age (range)	# Subjects	Age (Range)		
Morelli et al 1996 [12].	Argentina	CC	45	ma 69.6	45	ma 71.89	P	3.33 (1.2-9.0)
Almeida &Shimokomaki 1997[13].	Brazil - Sao Paulo		55	Mean age 64,71	56	45-89	P	2.63 (1.09-6.31)
De Andrade et al 2000 [14].	Brazil - Porto Alegre Caucasians (Portuguese manly but also Italians, Spaniards and Germans) and Afro Brazilians	CC	23	-	100 100	31±11.5 35±15.2	-	Caucasians prevalence was 4 times higher in the AD group P<0.001 but e4 was even higher in Afro-Brazilians
Souza 2003 [15]	Brazil	-	68	-	58	>65	P	2.43(0.93-6.36)
Bahia et al 2008 [16].	Brazil	-	120		120	75 ± 2.9	P	4.01(1.97-8.17)
De Almada et al 2012 [17].	Brazil, from Vitoria Caucasians 80% and Afro-Brazilian 20% [16]	-	82	-	182	78 ± 8.3	P	13,94 (3,14-64.50)
Romas et al 2002 [18].	Caribbean Hispanics	C	306	-	218	-	P	P = 0.001
Olarte et al 2006 [19].	Caribbean Hispanics	PB	111 FAD 163 SAD	-	406	-	-	ApoEmay accelerate the onset of dementia.
Quiroga et al 1999 [20].	Chile	CS	95	Mean age 78.2	187	-	P	2.9 (1.75-5.1)
Lavado et al 2005 [21].	Chile		17	-	18	67.5 ± 5.9	N	-
Jacquier et al 2001 [22].	Colombia: late onset, early onset	CC	83	69.1 ± 10.3 67.6 ± 10.4	44	65.8 ± 7.1	P	5,1(1.9-13.6)
Parra-Bonilla et al 2003 [23]	Colombia	-	79	68 ± 3.8	67	71.5 ± 12.4	P	-
Arboleda et al 2001 [24].	Colombia: Caucasian-Mestizos	-	61	67.6 ± 9.1 (43-86)	61	54 - 88	P	FAD 9.3(2.3-37) SAD 8.2 (2.1 - 31.2)
Sevush et al 2000 [25].	Cuban American	-	80	-	21	-	P	4.3 (1.27-14.79)
Teruel et al 2011 [26].	Cuba: - White - Black - Mixed race	CS	235	-	349	-	P	PR 2.83 (2.18-3.68) PR 2.38 (1.43-3.95) PR 0.87 (0,25-2.98)
Manrique-Suárez et al 2014 [27].	Cuba	-	46	72.5 ± 3.8	28	73.7±4.2	P	13.3 (1.6-105.5)
Paz y Miño et al 2010 [28]	Ecuador	CC	39	-	39	-	P	2.58(0.2-76.8)
Villalpando-Berumen et al 2008 [29].	Mexican Mestizos	CS	49	-	141	65-96	N	1.01 (0.45-2.23)
Campos et al 2013 [30].	Mexican Hispanic/ White Non Hispanic	-	28 28	- -	28 28	- -	P P	2.04 (0.59-7.1) 3.77 (1.23-11.57)
Molero et al 2001 [31].	Venezuela: Maracaibo	LS	121	-	1665	66.5±8.4	P	10.02 (1.16-86.28)
De Mendonça et al 2014 [32].	Venezuela: Caracas	CL	79	-	100	71±10	P	2.8(1.7-4.6)

CL: clinical based, LS: longitudinal study, PB: population based, C: Cohorte, CS: cross sectional, CC: case control, PR: prevalence ratio, FAD: Familiar AD, SAD: Sporadic AD, ma: mean age, P= Positive association, N=No association.

The study done by Campos et al 2013 was the one performed in the USA between Mexican Hispanic and White Non Hispanic. They found that APOEε4 had a stronger association with AD in White non-Hispanics (OR=3.77; CI 1.23, 11.57; p=0.02) than in Hispanics (OR=2.04; 95% CI: 0.59 - 7.1). Thus, ApoEε4 allele was a determinant of AD risk in whites, however, the increased frequency of AD in African Americans and Hispanics suggested that genetic differences between races (European admixture present in African American), environmental differences or likely a combination of factors may contribute to the increased risk in these groups [33]. Given that previous studies showed that African ancestry protects against Alzheimer's disease-related neuropathology (neuritic plaques), with an adjusted OR of 0.43. Unknown genetic variants or environmental factors associated with African ancestry could be reducing the accumulation of β-amyloid or increasing its clearance [34].

Results does not have a clear cut off, heterogeneous ethnic sample have a great impact in allele frequency. A factor that is prevalent in LA as was evidenced before, plus data regarding the genetics of AD in our countries remain scarce, underscored the importance of our findings. For example, in Brazil the distribution of APOE alleles between the two ethnic groups was significantly heterogeneous (P = 0.013). Although, the relative frequency of the ε4 allele (22.5%) was higher in Afro-Brazilians than in Brazilian Caucasians (11.5%) [12,35].

We failed finding studies of AD and ApoE as risk factor performed in countries like Bolivia, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay and Uruguay. Perhaps, they have not done research in this area, or the search was not that inclusive.

Overall, these data supported the association between APOE ε4 and the different forms of AD. However, to clarify the present results it is important to analyze the contribution of different ApoE alleles not only in the Caucasian-Mestizo population, but also in Amerindians and Afro-Americans, in order to be able to estimate the population attributable risk for disorders where ApoE has a role in susceptibility [24,36].This could be seen in (Table 4), we had gathered most of the studies done in Latin America and in some of their Native-Indians.

For instance in Bolivia, the one publication we were able to retrieve was focused in APOE/C1/C4/C2 gene cluster which presents high relevance in lipid metabolism. They studied 25 polymorphisms and 15 SNPs in Aymaras and Quechuas as well as in one European sample as external reference. The findings showed low diversity in both Bolivians and Europeans. The lower gene diversity observed in the Andean populations compared to Europeans for several markers could be related to the particular demographic history of Native Americans, where drift and founder effects might have had an important impact, which is consistent with a more recent origin and/or a bottleneck during the first settlement of the Americas and particularly of South America [37].

In most of the cases, it could be appreciated a pattern in the distribution of alleles that followed the tendency observed in other population and countries (ε3>ε4>ε2). In other words, ε3 is the

most frequently found and the allele ε2 is very scarce and even absent in most of the Native-Americans [47].Although, the percentage of each polymorphism in LA countries varied; this suggests a common evolutionary history as other researchers have proposed [53].The frequency of ε4 is similar to populations of Asia and India and lower when comparing to Africa and Oceania. It has been noticed that ε4 is considerably higher in Afro-Americans. The ε2 and ε3 alleles are increasingly represented in different human populations where the access of food becomes easier and constantly available [26, 57].

In Cayapas, the frequency of ε4 was higher than ε3 where besides of a drift effect, it can be attributed to an effect of selection. Because this allele enhances the absorption of cholesterol by the intestine, it could confer an advantage to carriers in an unfavorable environment (i.e., diet poor in cholesterol) [49].

As is seen in (Table 4), Colombia accounted with the highest number of population studies. In both researches performed in Quindio-Colombia the results showed that the frequency of ε2 (0.084 and 0.05) is higher than ε4 (0.016 and 0.031) [43, 45]. This could be attributed to the ancestral component, which in Quindio is mainly Caucasian, natural selection and/or to small sample size [47].

Table 4: ApoE allelic frequencies by country and population.

Country	Population	Results		
		ε2	ε3	ε4
Bolivia [37]	Aymaras Quechuas	- 0.013 - Absent	- 0.936 - 0.947	- 0.051 - 0.053
Brazil [38]	Eldery Brazilian	- 0.066	- 0.79	- 0.14
Chile [39]	Chilean	- 0.07	- 0.73	- 0.19
Colombia [40]	Risaldara	- 0.072	- 0.86	- 0.089
Colombia [41]	Bogotá	- 0.05	- 0.87	- 0.08
Colombia [42]	Centro Oriente	- 0.04	- 0.86	- 0.08
Colombia [43]	Quindío	- 0.05	- 0.916	- 0.031
Colombia [44]	Colombia: Casos Controles	- 0.041 - 0.07	- 0.85 - 0.84	- 0.11 - 0.09
Colombia [45]	Quindío	- 0.084	- 0.899	- 0.016
Colombia [46]	Antioquia: Paisa population	- 0.075 ± 0.005	- 0.814 ± 0.009	- 0.111 ± 0.007
Colombia [47]	Medellín	- 0.039	- 0.92	- 0.042
Colombia [48]	Barranquilla	- 0.18	- 0.85	- 0.13
Ecuador [49]	Cayapas	- Absent	- N/A	- 0.280
Mexico [50]	Purapecha	- 0.025	- 0.797	- 0.177
Mexico [51]	- Mexican - Mazatecan	- Absent - Absent	- 0.91 - 0.9	- 0.084 - 0.1
Mexico [52]	Guadalajara Nayarit Durango Huichol	- 0.078 - 0.016 - Absent - Absent	- The most common allele	- 0.084 - 0.115 - 0.117 - 0.28
Peru [53]	Lima La Libertad Ayacucho Junín Loreto	- 0.031 - 0.021 - 0.014 - Absent - Absent	- 0.933 - 0.896 - 0.932 - 0.952 - 0.9	- 0.036 - 0.083 - 0.054 - 0.048 - 0.1
South American Indian [54]	Nine Tribes	- Absent	- 0.816	0.184
South American Indian [35]	- Surui - Gavião - Zoró - WaiWai - Xavante - Mataco - Apalai-Wayana - Wayampi -Arara - Kayapo - Yanomami - Yanomami - Yanimami - Makiritare - Macushi - Wapishana - Baniwa	- Absent - Absent - Absent - 0.02 - Absent - 0.04 - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent	- 0.83 - 0.67 - 0.70 - 0.51 - 0.98 - 0.94 - 0.82 - 0.58 - 0.93 - 0.90 - 0.96 - 0.84 - 0.90 - 0.89 - 0.83 - 0.64 - 0.75	- 0.17 - 0.33 - 0.30 - 0.47 - 0.02 - 0.02 - 0.18 - 0.42 - 0.07 - 0.10 - 0.04 - 0.16 - 0.10 - 0.11 - 0.17 - 0.36 - 0.25

Native Americans [55]	- Mbyá-Guarani -Kaingang - Toba Formosa - Toba Chaco - Wichí Chaco - Pilagá - Wichí Formosa - Aché, Paraguay - KaiowáÑandeva-Guarani - Wichi Salta - Xavante - Suruí - Zoró - Gavitão - Kayapo - Arara - Wayana-Apalai - Wayampi - WaiWai - Baniwa - Coreguaje - Embera - Nukak - Tule - Wapishana - Waunana - Macushi - Guahibo - Makiritare - Yuco - Butaregua - Ijka - Kogui - Maya- Pima/Maricopa/Papago	- 0.05 - 0.03 - Absent - Absent - Absent - Absent - 0.03 - 0.02 - 0.01 - 0.04 - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - 0.02 - Absent - Absent - Absent - Absent - 0.03 - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - Absent - 0.01	- 0.78 - 0.84 0.83 0.88 - 0.95 - 0.84 - 0.93 - 0.98 - 0.83 - 0.94 - 0.98 - 0.83 - 0.70 - 0.67 - 0.90 - 0.93 - 0.82 - 0.58 - 0.51 - 0.75 - 0.59 - 0.86 - 0.63 - 0.91 - 0.64 - 0.91 - 0.83 - 0.81 - 0.89 - 1 - 0.90 - 0.81 - 0.90 - 0.91 - 0.86	- 0.17 - 0.13 - 0.17 - 0.12 - 0.5 - 0.16 - 0.4 - Absent - 0.16 - 0.2 - 0.2 - 0.17 - 0.30 - 0.33 - 0.10 - 0.7 - 0.18 - 0.42 - 0.47 - 0.25 - 0.41 - 0.14 - 0.37 - 0.6 - 0.36 - 0.9 - 0.17 - 0.19 - 0.11 - Absent - 0.1 - 0.19 - 0.1 - 0.9 - 0.13
Venezuela [56]	Bari (Amerindians) Yucpa (Amerindians) Curiepe (Negroid) Colonia Tovar (Caucasoid) Caracas (Mestizo)	- Absent - Absent - 0.162 - - 0.189	The most common allele in all populations.	

The distribution of the ApoE allele in the western population of Mexico was similar to those described in Mexican American migrants living in the United States but was different from those populations living in Mexico City. This study showed the heterogeneity of the Mexican population, where the frequency of the APOE ε2 allele is higher in Guadalajara than in other urban areas of Mexico and is similar to frequencies described in the Caucasian population. On the contrary, the Huichols revealed the highest frequency of the APOE ε4 allele in Mexico and in the Americas. This information could be useful for the study of dyslipidemias associated with chronic diseases and as markers of ethnic variation in the Americas [52].

A study of dementia in Chile found a prevalence of 5.98 percent for elders 65 years and older, with the majority of these cases meeting criteria for AD (60%) [20]. Dementia rates in Brazil appear to be equivalent to those found in Europe and among white Americans, and rates are highest among illiterates [58]. Rates of dementia and cognitive impairment in other South American countries appear to be comparable to Europe and the United States [2].

The results contribute to a better understanding of the geographic and ethnic variability of ApoE in the world and its distribution in LA. It also provided useful information for genetic association studies with various diseases and environmental factors. ε4 allele has one of the lowest frequencies reported in other regions of the world, which may have implications for the risk of diseases as AD. The ethnic differences observed mean that as each population group has its own genetic structure; future health decisions should be based on that [53].

There are countries such Costa Rica and Honduras (Langue city) where they are just starting to research AD prevalence and risk factors as diabetes, obesity, arterial hypertension, depression, alcohol consumption, smoking, level of education and frequencies of ApoE in older population [58,59]. In Honduras the prevalence of dementia was 8.2%, which is higher than the one reported worldwide, but as these data are from only one location we should be cautious. The results revealed a sad truth as a low social economic status since in the 73.5% of the cases, family incomes are below the minimum wage, there are high levels of illiteracy (42.9%), and incomplete schooling (66.3%). Besides, older people presented little physical activity (18.8%), obesity (24%) and overweight (39%) [60].

Environmental Risk Factors

A risk factor could be any potential interaction that we could have with any stimulus in our daily life since the moment we were conceived until we grow old. The effects of these elements can be additive, interact independently or in a dependent way. The influence of all these factors determines the beginning of the onset of certain diseases [61]. For instance, poor social-economic conditions in most of cases lead to fetal malnutrition that entails low birth weight plus the lack of breastfeeding will be translated in higher susceptibility of some chronic diseases in mid-life, which might end up in dementia. Another disadvantages of scarce income families are privation of education, health services and therefore lower cognitive performance [1]. The level of education produces a selection bias since as higher it gets then better life style, profession, health, superior scores in cognitive tests and higher IQ are achieved. Also, it increases the cognitive reserve, which gives certain kind of neuroprotection [62]. The cognitive reserve hypothesis holds that these enriched lifestyles may result in more efficient cognitive networks, thus providing a cognitive reserve that delays the onset of the clinical manifestations of dementia [63].

The main risk factor for AD is age, it is been noticed that in Latin America and in the Caribbean the prevalence of dementia increased exponentially as we get older, doubling with every 5.9 years and 7,2 correspondingly. Also, it was found an independent effect of gender; this disease seems to be less prevalent in a 14% to 32% in men than in women [4].

Diet

A study performed in Latin America (Cuba, Dominican Republic Venezuela, Mexico and Peru), China and India (n=14960) where they tried to determine if there is an association between fish and meat consumption with dementia in low and middle-income countries. They found that the

dietary intakes and the prevalence of dementia varied between sites, as was expected, and that there is a dose-dependent inverse association between fish consumption and dementia (PR: 0.81; 95% CI: 0.72-0.91) except for India [64]. Several studies also indicate that diet can have a protective effect against AD. Intake of omega-3 fatty acids from fish, vitamins E, B6, B12, and foliate, and a moderate intake of red wine, is all associated with a reduced risk of developing sporadic AD. Conversely, high calorie intake increases vascular diseases, strokes and AD risk as well [63].

Inbreeding and Consanguinity

It is well known that inbreeding and consanguinity modify diseases risk due to excess of homozygosity of recessive alleles. A study performed in Caribbean Hispanics from Dominican Republic calculated the inbreeding coefficient in 3392 subjects (1,451 late-onset Alzheimer disease patients and 1,941 age-matched healthy controls) of Caribbean Hispanic ancestry using 177,997 nearly independent SNPs from genome-wide array. The average inbreeding coefficient was F = 0.018 (±0.048), suggesting a mating equivalent to that of second cousins. Adjusting for admixture from three parent populations, F = 0.0034 (±0.019) or close to third-cousin mating. Inbreeding coefficient was a significant predictor of Alzheimer disease when age, sex, and APOE genotype were used as adjusting covariates (P = 0.03). Meaning that this population's inbreeding coefficient is significantly higher than of the general Caucasians population in North America. One advantage of these findings is that as the frequency of recessive variants is higher, the identification of rare variants increases as well [65].

Smoking

A cross sectional survey conducted on 15022 individuals aged 65 assessed dementia diagnosis and detailed information on past and current tobacco consumption. Never smokers belonged to Peru and Dominican Republic (83% and 52%, respectively). Most of those who ever used tobacco in China and India were still smoking at the age of 65 and above (80% and 84%, respectively). It was found a positive association between history of tobacco smoke exposure (pack years up to age 50) and Alzheimer's disease (pooled Prevalence Ratio = 1.007; 95% CI, 1.003-1.011) [66].

After in life, factors as diet, smoking, alcohol consumption, drugs abuse, lack of exercise, diabetes, vascular diseases, hypercholesterolemia and so on predispose people to AD and other dementias [1]. All these elements excluding age could be avoided. Epidemiological researches suggested that at least the 50% of dementia types could be prevented [67, 68].

Blood Pressure

The association between dementia and lower blood pressure was heterogeneous across geographically diverse samples, strongest where prevalent hypertension was highest (in Cuba), and relatively small compared with that found in Western settings. Both the mechanisms and the extent to which different levels of lifetime hypertensive disease explain this heterogeneity remain uncertain. However, because rapid increments in both dementia and hypertension are predicted in low- and middle-income countries, closer monitoring is warranted [69].

There are several studies performed in the Hispanic population living in the USA, however the results found could not be apply to the reality of each country since first Latino people are geographic and genetically diverse group linked by a common cultural and linguistic heritage and second, in multifactorial diseases as AD, the environment plays an effect in the incidence and prevalence. For example, most of immigrants are a specific group of people that meet certain conditions, as lack of work place in their birth place due to lack of proper education and opportunities which is translating in low incomes, poor diet, stress, depression and so on. Some of these conditions could improve once they migrate, but others could remain or intensify as loneliness, depression, anxiety, socioeconomic and family stress, isolation, etc. and even acquire new bad habits as smoking. In a study of Latino population living in the USA found that they develop AD 4.7 years earlier than Anglo patients and the onset is 6.8 years earlier as well. Although, is not known if there are any differences in the rate of symptom progression or total duration of AD [11].

As is going to be addressed several of the studies performed in the United States of America analyzed Hispanic populations when referring people who speaks Spanish however the admixture of each country is quite different. In some places indigenous population was almost extinct and in others very prevalent, the number of Africans varies too. In the former British Caribbean, average European admixtures levels may be even lower, just 7% in Jamaica [26]. The increased risk of AD associated with one APOE e4 allele or two APOE ε4 alleles is also found in African-Americans and Caribbean Hispanics [18].

Cost

It was estimated that there are 46.8 million people worldwide living with dementia and by 2030 the global cost would cross the threshold of US$ 1 trillion. AD represents a cost of US$ 612 billion worldwide [4]. The 11% of it corresponds to LA and the Caribe where 44% of people with dementia live (Table 1) [1]. Meaning that each patient represents an extremely high value beyond of neither the social systems could cover nor families. The health system is not prepared; there are no specialized geriatrics or appropriately trained staffs. Those specialized private places cost a lot and are very scarce. General practitioners do not recognize AD cases or they consider these symptoms as part of the normal process of aging, so they do not perform exhaustive clinical exams and much less referral them to a specialist center. To make it worse, people often go to the GP when the cognitive development is already impaired. So most of sufferers do not have a diagnosis and the adequate treatment either [2,70]. Alzheimer's Associations in each country are responsible for the spread of these diseases in the massive public sector and in some countries as Mexico, the knowledge has improved greatly [2].

From these estimates, the human cost contributes highest proportion since family and careers who apart of suffering psychological physical and financial consequences they also have to deal with high levels of anxiety and depression [1]. In LAMICs informal care is predominantly

(unpaid care provided by family). Changes in population demographic could lead to that in the coming decades the availability of familial member; those who provide such care could be reduced enormously [71]. This is very disturbing and though the cost now and in the future is astronomical AD is not considered as important as other chronic non-communicable diseases as cancer or cardiovascular disorders. It is not a priority in healthcare systems or for government either, because the impact of mortality rate is not that high [1].

Based on previous data, could be expected that at least in high-income countries the cost could diminish if the number of cases decreases or the onset of AD begins later in life. This had been very little achieved through the raise of the level of education, exercise, decreasing high fat intake diets, and better health programs which are more aware in preventing diabetes, cardiovascular diseases and even smoking that are the main risk factors [4].

All the information collected in this review showed that major efforts in dementia and AD have been done in countries as Mexico, Brazil, Colombia, Peru, Dominican Republic and Cuba while in others there is a lack of data of neurodegenerative diseases prevalence. Latin American countries also count with international attempt known as 10/66 Dementia Research Group's. The name refers to the 66% of people with dementia that live in developing countries and the less than one tenth of population-based research is carried out in those settings. Their aim is to redress this imbalance, through the creation of an evidence base to empower advocacy, which will raise awareness about dementia, and ensure that the health and social care needs of older people are anticipated and met. The studies are executed in ten LAMICs (India, China, Nigeria, Cuba, Dominican Republic, Brazil, Venezuela, Mexico, Peru and Argentina), with a sample size of between 1000 and 3000 (generally 2000) in people aged 65 and over. A follow up of 2.5 to 3.5 years is conducted in 7 countries (China, Cuba, Dominican Republic, Venezuela, Mexico, Peru and Argentina) to assess risk factors for incident dementia, stroke and all cause and cause-specific mortality [72].

Given that LA encompasses an amalgam of cultures populations, socioeconomic disparities, languages and ethnic origins, AD is not geographically homogenous and it is hard to generalize among countries [3].This report was intended to be a detailed account of the reality of AD in Latin America we think we have gathered as much information as possible. The lack of data and the absence of publications in some countries we believe that at least it reflects the importance of the "epidemic of this century" which will affect HICs as LMICs, but the difference is, that in this case, LA has deficits of medical, social and economic infrastructure and lack of awareness of the problem we face [2].With limited resources, we must prioritize the development and implementation of interventions to increase the well-being of demented subjects and their caregivers. As well as prevention strategies which should be targeted at individuals at high risk such as promoting cerebrovascular disease prevention through lifestyle modifications without expensive health care infrastructure [3].

CONCLUSION

The racial, ethnic, cultural, and socioeconomic diversity found within LA provides an excellent opportunity to evaluate biological and environmental risk factors for cognitive impairment and Alzheimer's among elders; however, more work must be carried out in this area to equal the epidemiological information available in other regions.

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