

# Notification of Huntington's disease as primary cause of death in Brazil from 1984 to 2008

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**ABSTRACT.** The aim of this article was to conduct a retrospective observational study on reported deaths due to Huntington's disease (HD) in Brazil in the past 25 years (from 1984 to 2008). Data were obtained from the Brazilian Mortality Information System (SIM/ DATASUS), the official system of Brazilian Mortality Database. The data obtained included information regarding the gender of the deceased and the number of death notifications, which we stratified by demographic regions and states. HD mortality per 100,000 was calculated and plotted in a graph. Linear regression was calculated using ordinary least square technique. We observed that the mortality due to HD recorded by SIM/DATASUS from 1984 to 2008 had increased at much higher rates than the population in the same period. Also, some Brazilian regions still show very low rates of HD mortality compared to the national average of deaths due to HD. These findings suggest that

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HD mortality has been underestimated. Ignorance about the disease as well as the fact that death from HD can occur as a consequence of heart disease, pneumonia, or suicide can strongly contribute to the misguided notification of HD as the cause of death in the official reports.

Key words: Huntington's disease; Mortality; Brazil

# **INTRODUCTION**

Huntington's disease (HD) is a rare hereditary neurodegenerative disease characterized by choreic movements, psychiatric disorders, and premature dementia. Individuals with HD usually become symptomatic between 35 and 55 years of age, although the disease can occur at any age from 1 to 80 years old. The asymptomatic period turns from almost imperceptive to the pre-diagnostic stage, when the patient demonstrates a sudden change in their cognitive and motor skills (Walker, 2007).

The Huntington's disease gene *(HTT)* is located on the short arm of chromosome 4 (4p16.3). HD is one of several related disorders bearing excessive repetition of CAG trinucleotides. The *HTT* gene has repeated CAG sequences that vary in their length, but when the number of such repetitions reaches a certain level the protein encoded by this gene, huntingtin (htt), undergoes a structural change as a result of the increased number of glutamine residues, which causes neuronal death (Chan et al., 2002). This expansion of CAG repeats occurs on exon 1 and encodes a track of polyglutamines near the amino-terminal region of the htt protein (Margolis and Ross, 2003). When the number of CAG repeats is less than 27, the carrier does not present symptoms and the gene is considered normal. Individuals with intermediate alleles have 27-35 CAG repeats. Although there is risk of transmission of an expanded allele to the offspring, the bearer of an intermediate allele is phenotypically normal. Alleles with 36-39 CAG units have reduced penetrance and therefore can generate either a normal or HD phenotype. When the number of such sequences exceeds 39 CAG copies, the individual will be affected by HD due to full penetrance of the mutated allele (Walker, 2007).

HD in Brazil is still quite neglected. There are scarce data on the incidence or prevalence of this disease in the Brazilian population and little research has been published on the subject in the country, although two geographic clusters have already been identified in two regions of Brazil. One of these clusters is in Ervália, Minas Gerais State (89 cases in 100,000 inhabitants) (Agostinho et al., 2012, 2015) and the other in Feira Grande in Alagoas (100 cases in 100,000 inhabitants) (Alencar et al., 2010).

The aim of this study was to investigate the reported mortality from HD in the Brazilian Mortality Information System (SIM/DATASUS) for Brazil as a whole and in its demographic regions and states of the Federation for a period of 25 years (from 1984 to 2008). It also aimed to compare the Brazilian data with those of other countries, such as Sweden, Denmark, USA, and England.

### **MATERIAL AND METHODS**

A retrospective study was conducted using data for HD deaths (ICD 9-333.4 and ICD10 G10) from 1984 to 2008, totaling a 25-year period. Brazil is a country with 27 Federative Units (states) housing a total of 5570 municipalities. The collected data covered all municipalities of Brazil. For this, we used the SIM/DATASUS and the population data from

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IBGE (Brazilian Institute for Geography and Statistics). The data obtained were gender of the deceased and the number of death notifications, which were stratified by demographic regions and states. HD-notified mortality per 100,000 was calculated and plotted in a graph. Linear regression was calculated by the ordinary least square technique.

#### **RESULTS**

A total of 408 deaths from HD were reported for a period of 25 years: 191 men (47%) and 217 women (53%). This ratio is similar to the overall gender ratio in Brazil (48% men and 52% women).

Figure 1 shows the Brazilian population evolution from 1994 to 2008 according to IBGE. Figure 2 shows the growing number of HD death notifications per 100,000 inhabitants from 1984 to 2008. From the absolute data on notified HD mortality, we estimated the reported HD mortality per 100,000 inhabitants in a time series from 1984 to 2008 for each region (Table 1) and state (Tables 1, 2 and 3) of Brazil. The Federative Republic of Brazil consists of 27 units (26 states and a federal district - Brasília); however, only the federal units that had notified deaths from HD during the chosen period are listed in Tables 2 and 3. The apparent increase in number of HD deaths per 100,000 inhabitants (Figure 2) is greater than the increase in the Brazilian population number (Figure 1) in the same period.



Figure 1. Brazilian population from 1984 to 2008.



Figure 2. HD notified mortality per 100,000 (linear regression - ordinary least square technique).

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Table 1. Noti	ified mortality due to H	D per 100,000 inha	bitants in the regio	ns of Brazil from 19	984 to 2008.
Region	Southeast	South	Northeast	North	Midwest
1984	0.005	0	0	0	0
1985	0.002	0	0.005	0	0
1986	0.007	0	0	0	0
1987	0.007	0.010	0.002	0	0
1988	0.008	0.014	0	0	0
1989	0.007	0.009	0	0	0.011
1990	0.011	0.023	0.002	0	0
1991	0.008	0.018	0.002	0	0
1992	0.017	0.013	0.005	0.010	0
1993	0.014	0.018	0	0	0
1994	0.009	0.013	0	0	0
1995	0.012	0.004	0	0	0
1996	0.018	0.017	0.004	0	0.019
1997	0.015	0.017	0.002	0	0
1998	0.017	0.029	0.002	0	0
1999	0.013	0.008	0	0	0
2000	0.018	0.008	0	0	0
2001	0.012	0.012	0.002	0.008	0.008
2002	0.009	0.023	0	0	0
2003	0.021	0.019	0.004	0.007	0.008
2004	0.014	0.030	0	0	0.016
2005	0.017	0.030	0.004	0	0.023
2006	0.029	0.044	0.006	0	0.030
2007	0.029	0.033	0.002	0.007	0.037
2008	0.020	0.047	0.001	0	0.015

Table 2. Notified mortality due to HD per 100,000 inhabitants for each Brazilian state from 1984 to 1995.												
Brazilian state	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995
AL	0	0	0	0	0	0	0	0	0	0	0	0
AM	0	0	0	0	0	0	0	0	0	0	0	0
BA	0	0	0	0.009	0	0	0	0	0.017	0	0	0
CE	0	0	0	0	0	0	0	0	0	0	0	0
DF	0	0	0	0	0	0.063	0	0	0	0	0	0
ES	0	0	0	0	0	0	0	0.038	0	0	0	0
GO	0	0	0	0	0	0	0	0	0	0	0	0
MA	0	0.022	0	0	0	0	0	0	0	0	0	0
MT	0	0	0	0	0	0	0	0	0	0	0	0
MS	0	0	0	0	0	0	0	0	0	0	0	0
MG	0	0.007	0	0.007	0	0	0	0	0.006	0.006	0.012	0.006
PA	0	0	0	0	0	0	0	0	0	0	0	0
PR	0	0	0	0	0	0	0.024	0.036	0.012	0.035	0.012	0.011
PE	0	0.015	0	0	0	0	0	0	0	0	0	0
PI	0	0	0	0	0	0	0	0	0	0	0	0
RJ	0.008	0	0.016	0.016	0.024	0	0	0.023	0.039	0.008	0	0.008
RN	0	0	0	0	0	0	0,042	0	0	0	0	0
RS	0	0	0	0	0.023	0.011	0.033	0.011	0.022	0.011	0.011	0
SC	0	0	0	0.047	0.023	0.023	0	0	0	0	0.021	0
SP	0.007	0	0.007	0.003	0.007	0.013	0.023	0.003	0.016	0.021	0.012	0.018
SE	0	0	0	0	0	0	0	0	0	0	0	0
TO	0	0	0	0	0	0	0	0	0.106	0	0	0

# DISCUSSION

Our results showed that, considering absolute numbers, the Southeast Region in Brazil is the region with the highest number of notified deaths from HD (N = 245), responsible for 60% of all deaths from HD in the country in the period examined. The fact that the Southeast Region is the most populous region of Brazil (44% of the Brazilian population) led in part to the largest absolute number of deaths. However, when we looked at the relative numbers per

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Table 3 Notified mortality due to HD per 100 000 for each Brazilian state from 1996 to 2008

Brazilian state	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
AL	0	0	0	0	0	0.035	0	0	0	0	0	0	0
AM	0	0	0	0	0	0.034	0	0	0	0	0	0	0
BA	0	0	0	0	0	0	0	0	0	0.007	0.007	0	0.007
CE	0	0	0.014	0	0	0	0	0	0	0	0	0	0
DF	0.055	0	0	0	0	0	0	0	0.045	0.086	0.042	0.123	0
ES	0	0	0	0	0	0	0.031	0.031	0	0	0.029	0	0
GO	0.022	0	0	0	0	0	0	0	0	0	0.052	0.017	0
MA	0	0	0	0	0	0	0	0	0	0	0	0	0.016
MT	0	0	0	0	0	0	0	0	0	0	0	0.034	0.034
MS	0	0	0	0	0	0.047	0	0.046	0.045	0.044	0	0	0.043
MG	0	0	0.029	0.023	0.011	0	0	0.016	0.011	0.021	0.021	0.03	0.021
PA	0	0	0	0	0	0	0	0.015	0	0	0	0	0
PE	0.014	0	0	0	0	0	0	0	0	0.012	0.024	0	0.012
PI	0	0037	0	0	0	0	0	0.034	0	0	0	0	0
PR	0.022	0.033	0.032	0	0.021	0.01	0.031	0.02	0.04	0.029	0.048	0.01	0.066
RJ	0.03	0.022	0	0.007	0.014	0	0.007	0.007	0.007	0.02	0.019	0.025	0.006
RN	0,039	0	0	0	0	0	0	0	0	0	0	0	0,009
RS	0	0.01	0.01	0.02	0	0.01	0	0.01	0.028	0.046	0.046	0.054	0.054
SC	0.041	0	0.06	0	0	0.018	0.054	0.036	0.018	0	0.034	0.033	0.083
SP	0.023	0.02	0.02	0.011	0.024	0.024	0.013	0.028	0.02	0.015	0.037	0.031	0.026
SE	0	0	0	0	0	0	0	0.053	0	0	0	0.049	0.049
TO	0	0	0	0	0	0	0	0	0	0	0	0	0

100,000, the South Region has the highest mortality rate in the period. The South Region has a population with a strong European ascendancy (according to the 2008 household survey, white people account for 79.6% of the population in this region) (PNAD, 2008), a factor which strongly influenced the results. The State of Alagoas (Northeast Region) had one of the lowest HD mortality notification rates of all states; however, the state has an important cluster of disease in the city of Feira Grande. Feira Grande is described as the city with the highest prevalence of HD in Brazil (100 cases per 100,000 inhabitants). Nevertheless, until 2010 the diagnosis of HD was misguided and patients were treated as having Parkinson's disease. This lack of knowledge of HD might have contributed to under-notification of HD as a primary cause of death (Alencar et al., 2010).

HD is a devastating neurodegenerative disorder, with a prevalence of 5.7 per 100,000 people in North America, Europe, and Australia as well as 0.40 per 100,000 people in Asia. If we apply the prevalence of 5.7 cases for 100,000 inhabitants (Pringsheim et al., 2012) to the Brazilian population, we would expect 7410 people affected by HD in Brazil in 1984 (the Brazilian population was approximately 130,000,000). According to a study performed in Belgrade, Serbia with 112 patients with HD, the survival of these affected persons was only 4.5% after 20 years of the onset of the disease (Pekmezovic et al., 2007). Theoretically, it would be expected that the majority of these patients had died after 25 years from the onset of symptoms.

It is important to mention that we could not expect a value of prevalence as high as that found in Europe because our population is racially mixed with Afro-descendants and Indigenous peoples. For Brazil, we would expect a prevalence rate and the number of deaths from HD to be smaller than those numbers for Europeans and larger than those for Africans. It is important to mention that Brazil is a heterogeneous country concerning the ethnic origin of its population; therefore, regional differences within the country should always be considered. The African prevalence data are sparse and underestimated and some studies present prevalence ranging from 0.01-7 cases per 100,000 inhabitants, with an average of 1.9 cases per 100,000

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inhabitants (Bates et al., 2014) depending on the region and population group investigated. Similarly to what was previously reasoned considering the European HD prevalence and considering the African prevalence average of 1.9 cases per 100,000 inhabitants, we could expect 2470 HD-affected individuals for the Brazilian population of 130,000,000 inhabitants in 1984. It would be expected that most of these patients had died at the end of 25 years of onset of symptoms, but we just found 408 death notifications from 1984 to 2008.

Figure 2 shows the growing number of HD death notifications from 1984 to 2008. This increase is higher than the increase in the Brazilian population in the same period (Figure 1). The increase in the number of notifications of HD deaths reached 1300%, ranging from 3 in 1984 and 1985 to 42 in 2006. According to IBGE, the Brazilian population increased 44% in the same period of time. These findings point towards underestimation of HD deaths in the time series. This clearly indicates that HD deaths were not reported properly. We emphasize in this article that this increase in the number of deaths in the time series is unusual for genetic diseases, except in the case of sudden changes in population composition (e.g., migration flows). Two possible explanations for these results are better knowledge of the disease and changes in diagnostic patterns. Therefore, we suggest that many HD cases were not properly notified and were missed in the mortality records. Furthermore, the fact that HD causes death by secondary causes is another reason that may contribute to the low number of recorded HD deaths. The disease kills mainly due to aspiration pneumonia and cardiovascular diseases. Death notifications should include HD as one of the causes of death because, even if the patient actually died from pneumonia, the predisposition to this was caused by HD. Similar errors, but for other reasons, have occurred with acquired immune deficiency syndrome (AIDS). When human immunodeficiency virus was not known, many cases of death from AIDS were reported mistakenly since the disease was unable to cause death directly.

Suicide and gagging are other common causes of death in patients with HD that hamper the correct notification of cause of death. These causes, mainly suicide, are very difficult to correlate with the pathological condition of the patient but there is strong evidence that HD increases the chances that a patient will die by these causes (Walker, 2007). Kurtzke (1979) reported mortality rates for HD of 1.71 per million in Sweden, 1.76 per million in Denmark, and 1.55 per million in England. This author emphasizes the excellent health systems in those countries, which are responsible for the large number of correct death notifications.

Conneally (1984) reported that in different regions of the USA, the mortality rates ranged between 0.97 and 1.35 deaths per million inhabitants from 1968 to 1974. These values are four to six times the value calculated for Brazil in 2006 (the year with the highest rate of deaths - 0.22 deaths per million inhabitants). It is noteworthy that the USA provides a very interesting model for comparison with Brazil concerning the racial aspect. Both countries' populations are composed of a high degree of miscegenation between whites (Europeans), Asians, African blacks, and Indigenous native (Amerinds) people. Through mathematical simulation, death notifications of HD in Brazil totaled a number well below expectation in comparison with the USA and other countries (e.g., Sweden, Denmark, England, and Australia).

An increased focus of the Brazilian governmental health care authorities on the disease, providing a multidisciplinary treatment approach and free molecular testing for precise HD diagnosis, could increase the correct number of death notifications and could also favor differential diagnosis (Agostinho et al., 2013). The latter would lead to the exclusion of other diseases with a similar phenotype but better prognosis. Furthermore, the molecular diagnosis would favor precise genetic counseling to those who are affected and their families.

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In conclusion, our results have shown a small number of HD death notifications in Brazil. However, this number grew beyond the Brazilian population growth rate, which may reflect a more accurate notification of deaths from HD along the time series. States from the South Region showed the greater notification of HD per 100,000 inhabitants, followed by the Southeast, Midwest, Northeast, and North regions. This may be explained by: 1) the existence of a better health care system in the South Region compared to the rest of the country, leading to an increased diagnostic rate and notification of deaths from HD, and 2) the ethnic composition of the South Region, since more than 70% of its population is composed of whites from European origin, in contrast with the overall population of Brazil, which is composed of 47% whites.

## **Conflicts of interest**

The authors declare no conflict of interest.

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