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Neuropsychiatric and young-onset as clinical determinants for a delayed Huntington's disease diagnosis

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Abstract

Objective: *This study aims to identify the possible factors that delay the time-to-diagnosis of Huntington's disease (HD).* **Methods:** *A cross-sectional study in HD patients was carried out. Variables registered were CAG repeats, age of onset, primary symptom at onset, age of molecular diagnosis, and time-to-diagnosis, among others.* **Results:** *107 patients (50.5% female) with a mean age of 49 ± 12.8 years (y) were included in the study. Median CAG size was 45 (38-73). Mean age of onset, mean age of molecular diagnosis, and mean time-to-diagnosis were 39 ± 12.9, 45.1 ± 12.1, and 6.4 ± 6.4 years, respectively. In the comparative analysis, the neuropsychiatric- and the young-onset groups had a longer time-to-diagnosis than the motor- and typical-onset groups (p = 0.02 and p < 0.01, respectively). In the linear regression analysis, neuropsychiatric- and young-onset were independent risk factors.* **Conclusions:** *Delayed diagnosis showed relation to neuropsychiatric- and early-onset in HD.*

Keywords: *Huntington's disease. Molecular pathology. Delayed diagnosis. Age of onset.*

Inicio neuropsiquiátrico y juvenil como determinantes clínicos para el diagnóstico tardío de la enfermedad de Huntington

Resumen

Objetivo: *Este estudio tiene como objetivo identificar los posibles factores que retrasan el tiempo de diagnóstico de la enfermedad de Huntington (EH).* **Métodos:** *Se realizó un estudio transversal en pacientes con EH. Las variables registradas fueron repetidos de CAG, edad de inicio, síntoma primario de inicio, edad de diagnóstico molecular y tiempo hasta el diagnóstico, entre otras.* **Resultados:** *107 pacientes (50.5% mujeres) con una edad media de 49 ± 12.8 años fueron incluidos en el estudio. La mediana de repetidos de CAG fue 45 (38-73). La edad media de inicio, la edad media del diagnóstico molecular y el tiempo medio hasta el diagnóstico fueron 39 ± 12.9, 45.1 ± 12.1 y 6.4 ± 6.4 años, respectivamente. En el análisis comparativo, los grupos de inicio neuropsiquiátrico y juvenil tuvieron un tiempo de diagnóstico más prolongado que los grupos de inicio típico y motor (p = 0.02 y p < 0.01, respectivamente). En el análisis de regresión lineal, el inicio neuropsiquiátrico y juvenil fueron factores de riesgo independientes.* **Conclusiones:** *El diagnóstico tardío mostró relación con un inicio neuropsiquiátrico y la aparición temprana de la EH.*

Palabras clave: *Enfermedad de Huntington. Patología molecular. Retraso en el diagnóstico. Edad de aparición.*

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Introduction

Huntington's disease (HD) is a common monogenic disorder in adulthood[1]. The previous studies categorized the age of onset as young-onset (20-29 y), typical-onset (30-59 y), and late-onset (≥ 60 y)[2]. The primary symptom at onset can be variable, including motor, neuropsychiatric, or mixed[3]. While phenotypic differences at its debut have not been well-characterized, the primary motor symptom is chorea. Neuropsychiatric symptoms are common and impact their quality of life (QoL)[4]. The mean time from symptomatology onset to genetic diagnosis varies widely ranging between 2 and 10 years[5-7]. Factors associated with the time-to-diagnosis are scarce. Conventionally, the size of trinucleotides CAG expansion in the *HTT* gene is considered the main determinant of disease age of onset but recent studies have reported that other factor such as unknown/missing family history, marital status, living in larger urbanized contexts, and having a lower educational level is associated to a delayed onset[8]. Moreover, many of these factor can also be related with a delay in the diagnosis rather than with a delayed onset. A timely diagnosis is important to better treat the patients but also in the context of an autosomal dominant inheritance an early diagnosis might result in prompt genetic counseling. This study aims to identify the possible factors contributing to a delay in the diagnosis.

Methods

An observational, retrospective, cross-sectional, and analytical study was carried out. The study was approved by both the Institutional Review Board and the Local Ethics Committee. All participants gave their written informed consent.

Consecutive HD patients of all ages and severity grades attending the Movement Disorder Clinic at the National Institute of Neurology and Neurosurgery in Mexico City between 2003 and 2018 were recruited.

Clinical HD diagnosis was confirmed by DNA analysis. A positive genetic test was considered by ≥ 36 trinucleotides CAG expansion in the HTT by triple prime polymerase chain reaction[8]. Patients with chorea of other etiologies and those with a negative molecular diagnosis were excluded from the study. Information was acquired through physical and electronic records.

The demographic variables registered included gender and age. Positive family history was defined as a positive genetic test of one of their relatives, a report by the patient at the baseline evaluation, or both.

The clinical variables analyzed included age of onset, defined as the patient-reported age when the first symptoms appeared, and age of molecular diagnosis, defined as the age when genetic testing was performed. Other variables included years of education and socioeconomic status following the methodology of the Health Ministry (1, lower – 6, higher).[9]

According to family history, patients were classified into *de novo* cases, defined as no family history, and familiar cases, as positive family history. Age of onset categorization was young-onset (20-29 y), typical-onset (30-59 y), and late-onset (≥ 60 y).

The primary symptom at onset was classified depending on the predominant symptom that affected QoL within the 1st year of the presentation. These were motor, neuropsychiatric, or mixed. Mixed was selected when there was no predominant symptom, and both affected QoL equally.

The time-to-diagnosis was defined by the time between the age of perception of the primary HD symptom referred by the caregiver and patient at the first medical consultation (movement disorder and neuropsychiatric/behavioral/cognitive disturbance) until the age in which a positive molecular diagnosis for HD was reported[9].

For the statistical analysis, a Kolmogorov–Smirnov test was used to test normality. Description of sociodemographic data was done with proportions (percentages), measures of central tendency (modes, medians, and means), and dispersion ranges (standard deviations and interquartile ranges), according to their distribution. Bivariate analyses were conducted to identify the differences between motor, neuropsychiatric, and mixed groups. ANOVA test and Kruskal–Wallis test were used when comparing quantitative variables. The Chi-square test was used when comparing qualitative variables. Multivariate linear regression was performed to predict the relationship between the most clinically relevant variables that reach statistical significance and a longer time-to-diagnosis. Time-to-diagnosis was used as a dependent variable in the linear regression model. Violations of the normality assumption in the error distributions were assessed using normal probability plot or normal quantile plot of the residuals. Multicollinearity was assessed using variance inflation factors (VIF). Covariables with VIF > 5 were excluded from the analysis. Hosmer–Lemeshow test was used for goodness of fit. Variance explained by the model was assessed using the Nagelkerke square R or adjusted square R. $p < 0.05$ was considered for statistical significance. The statistical package SPSSv17.0 was used.

Results

One hundred and seven HD patients (50.5% female) with a mean age of 49 ± 12.8 years were included in the study. Familiar cases were more prevalent in 84 individuals (78.5%). The median CAG size was 45 (38-73). The mean age of onset was 39 ± 12.9 years and the mean age of molecular diagnosis was 45.1 ± 12.1 years. The mean years of education were 8.2 ± 6.8 and the mean socioeconomic status was 2 ± 0.4. The mean time-to-diagnosis was 6.4 ± 6.4 years. Patients with HD were categorized regarding the primary symptom at onset, 38 subjects in the motor group (35.5%), 33 subjects in the neuropsychiatric group (30.8%), and 36 subjects in the mixed group (33.6%). Table 1 shows the complete description of the participants.

In the comparative analysis, performed by family history, *de novo* cases tend to have an older-onset (mean 46.2 ± 11.6 yeras vs. 37.2 ± 12.7 years) and less time-to-diagnosis (4 years, IQR 4 vs. 5 years, IQR 5), in comparison to familiar cases, without reaching statistical significance (p = 0.07). In addition, the young-onset group had a longer time-to-diagnosis in comparison to the typical-onset group (10.7 ± 10 years vs. 5 ± 3.9 years, p < 0.01), and had more frequently neuropsychiatric symptoms at onset (51.9%). Motor symptoms were predominant in the typical- (39.4%) and late-onset (75%) groups. The neuropsychiatric group had longer time-to-diagnosis compared to the motor group (mean difference 4.2 years, 98.4% CI 0.01-8.44, p = 0.02) and a younger-onset (mean difference –10.05 years, 98.4% CI –18.5 - –1.6, p < 0.01). Table 2 compares the full clinical characteristics between primary symptoms at onset groups and Table 3 shows the comparison between HD groups according to the presence of family history.

For the univariate regression analysis, neuropsychiatric-onset and young-onset were found as risk factors to longer time-to-diagnosis (ß = 1.3, 95% CI 1.56-6.71, and ß = 5.828, 95% CI 3.19-8.47, respectively; p < 0.01). After being adjusted by gender and family history, neuropsychiatric-onset and young-onset persisted as independent risk factors (ß = 2.97, 95% CI 0.4-5.54, and ß = 4.97, 95% CI 2.2-7.75, respectively; p = 0.02). Given that age and CAG size correlate, these variables were excluded from the multivariate analysis and no collinearity between predictors was found. Other predictors included in the analysis did not show a statistical significance influence including years of education and socioeconomic status. Table 4 describes the step-wise regression models, adjusted by age and family history, using time-to-diagnosis as dependent variable, showing neuropsychiatric- and young-onset as independent risk factors. It should be pointed out that time-to-diagnosis was not normally distributed; the deviation from the reference line was due to outliers. The main goal of the regression analysis was to estimate its coefficients by minimizing the mean squared error and goodness-of-fit and residual analysis were carried out. Both probability plot and normal quantile plot (observed vs. predicted values, residuals vs. predicted values, and residuals versus individual independent variables) were considered within acceptable range so nonlinear transformation was not required.

Table 1. General clinical characteristics of HD patients. (n = 107)

Characteristics	
Female, n (%)	54 (50.5)
Age, mean (SD)	49 (± 12.8)
CAG, median (interval)	45 (38-73)
Familiar cases, n (%)	84 (78.5)
Novo cases, n (%)	23 (21.5)
Age at onset, mean (SD)	39 (± 12.9)
Age at molecular diagnosis, mean (SD)	45.1 (± 12.1)
Time to diagnosis, mean (SD)	6.4 (± 6.4)
Onset by symptoms groups, n (%)	
Motor	38 (35.5)
Neuropsychiatric	33 (30.8)
Mixed	36 (33.6)
Age at onset groups, n (%)	
Young	27 (25.2)
Typical	76 (71)
Late	4 (3.7)

HD: Huntington's disease, SD: standard deviation.

Discussion

HD symptoms result in a progressive condition that impacts activities of daily living, which translates into a poor QoL[10]. Due to the absence of an effective disease-modifying therapy, the current management of HD is centered on treating symptoms. However, since the introduction of genetic testing, persons with pre-symptomatic HD could be treated earlier, providing the opportunity for the future potential disease modification. On this matter, new clinical trials with early-onset candidates aim to halt or slow the progression, supporting the importance of an earlier diagnosis[11].

Table 2. Comparison between HD groups according to the primary symptom at onset

Characteristics	Motor (n = 38)	Neuropsychiatric (n = 33)	Mixed (n = 36)	p-value
Female, n (%)	22 (51.6)	25 (52.7)	17 (47.3)	0.9***
Age, mean (SD)	54 (± 8.8)	48.6 (± 12.6)	43.7 (± 14.9)	**< 0.01****
CAG, median (interval)	44.2 (39-62)	47 (38-61)	48 (40-73)	0.05*
Familiar cases, n (%)	26 (68.4)	30 (90.1)	28 (77.8)	0.07***
Age at onset, mean (SD)	44.7 (± 11.1)	34.7 (± 12.5)	37.3 (± 13.3)	**< 0.01****
Socioeconomic level, mean (SD)	1.9 (± 0.3)	1.9 (± 0.5)	2.1 (± 0.4)	0.34
Years of education, mean (SD)	4.5 (± 6.6)	7.7 (± 6.8)	8.9 (± 6.5)	0.57
Age at molecular diagnosis, mean (SD)	49.7 (± 11)	42.8 (± 10.7)	42.4 (± 13.4)	**0.01****
Time-to-diagnosis, median (IQR)	4 (3.25)	6 (5)	5 (3.75)	**0.03***
Age-at-onset groups, n (%) Young Typical Late	 5 (13.2) 30 (78.9) 3 (7.9)	 14 (42.4) 19 (57.6) 0 (0)	 8 (22.2) 27 (75) 1 (2.8)	*** 0.02 0.11 NA

HD: Huntington's disease, IQR: interquartile range, SD: standard deviation.
*Kruskal–Wallis test.
**ANOVA test.
***Chi-square test.

Table 3. Comparison between HD groups according to the presence of family history

Characteristics	Positive family history (n = 84)	Negative/Unknown family history (n = 23)	p-value
Female, n (%)	78 (92.8)	17 (73.9)	0.23
Age, mean (SD)	47 (± 11.7)	55.6 (± 14)	**< 0.01**
CAG, mean (SD)	46.5 (± 6.4)	47.8(± 5.4)	0.63
Age at onset, mean (SD)	41.7 (± 19.5)	49 (± 13.4)	0.06
Socioeconomic level, mean (SD)	1.9 (± 0.3)	1.9 (± 0.5)	0.34
Years of education, mean (SD)	9.8 (± 5.2)	8.4 (± 3.8)	0.1
Time-to-diagnosis, mean (SD)	5.1 (± 2.8)	6.7 (± 4.5)	0.07
Age-at-onset groups, n (%) Young Typical Late	 23 (27.4) 60 (71.5) 1 (0.1)	 4 (17.4) 16 (69.6) 3 (13)	 0.32 0.86 **0.01**

HD: Huntington's disease; SD: standard deviation.

The present study reports demographic and clinical data from Mexican individuals with molecular diagnosis of HD. Few studies of HD in the Mexican population have been conducted. For instance, Alonso et al. reported an age-at-onset of 37.4 ± 12.9 years from a series of 691 subjects[12]. In our study, a similar age-at-onset was found (39 ± 12.9 years). Unlike other series from a multicenter study[13], and Spanish[7] and Argentinian[14] studies, our study population had an earlier onset of disease (41 ± 13, 43.7 ± 15, and 45 ± 16 years, respectively). However, the earliest age of onset has been reported in the Venezuelan series from Maracaibo Lake, with an age of onset of 35.5 years[15].

Regarding CAG repeats, our series found a median of 45 (38-73), similar to the previously reported Mexican series (47.2 ± 5.39) and series from Canada, Spain,

Table 4. Step-wise regression models, adjusted by age and family history, using time-to-diagnosis as dependent variable, showing neuropsychiatric and young-onset as independent risk factors

Model	ß	Exp (ß)	95% CI		p-value
1. Gender	–1.04	–0.81	–3.53	1.45	0.41
Family history	1.62	0.10	–1.41	4.66	0.29
2. Gender	–1.17	–0.09	–3.58	1.23	0.34
Family history	0.69	0.04	–2.29	3.68	0.65
Neuropsychiatric-onset	4.02	0.29	1.38	6.67	**< 0.01**
3. Gender	–0.76	1.15	0.50	–3.05	1.52
Family history	–0.33	–0.02	–3.22	2.55	0.82
Neuropsychiatric-onset	2.97	0.21	0.40	5.54	**0.02**
Young-onset	4.97	0.33	2.19	7.75	**< 0.01**

and Argentina, 43.9 (39-64), 46.3 (38-70), and 45.1 (36-80), respectively[6,7,12,14]. Similarities between haplotype (hap) variants, where European ancestry populations more frequently presented the hap 1-3 variants[16], similar to Latin American populations[17], could explain this phenomenon. Therefore, the earlier presentation of disease in our population suggests the existence of modifier genes that may contribute to the CAG instability, in the addition of the CAG size[5,18-20].

The Canadian and Portuguese series report positive family history in 70.2% and 80.1%, respectively[6,21]. These data are similar to our series, in which family history was positive in 78.5% of the cases. Hence, this indicates no relationship between family history and time-to-diagnosis.

Ramos-Arroyo et al. previously justified the later diagnosis in their series to the difficulties in verifying the family history due to the absence of national registries of patients with HD[7], which could be one of the leading causes of delay[22]. The same situation could apply to our population. The importance of having this registry is mediated by how difficult anamnesis could be in some patients or caregivers, and fully trust their reported family history. Strategies for awareness of HD are necessary. Many patients in our population have a low educational level, while most of the time showing disinterested behavior, which could be due to apathy. These are factors that could be avoided by having a national database.

The mean time-to-diagnosis was 6.4 years. This time is not well-described in the literature. However, some series report it indirectly by describing the age of onset and the age of molecular diagnosis. In the present study, the time-to-diagnosis was longer than previously reported (2 years vs. 5.9 years)[1,6]. Notwithstanding, a longer time-to-diagnosis than ours was outlined by Ramos-Arroyo et al. (8.8 y) in the Spanish population[7]. Many factors could influence a longer time-to-diagnosis, as a public institution and a low-income population make it difficult to enter medical care, resulting in no access to molecular diagnosis[23] and a limitation that could translate into an increased time-to-diagnosis.

Another pertinent issue could be the absence of a trustworthy record of familiar history. Regarding the age of onset, the young-onset group had a longer time-to-diagnosis and was characterized as having a neuropsychiatric presentation. The lack of recognition of HD symptoms, often attributed to a different disease by patients and family members[24], results in a delayed time to seek medical attention.

A burden of neuropsychiatric symptoms is evident in HD. These prevalent symptoms can majorly impact the patient at the onset. As described, persons with HD have a considerable disturbance in identifying their symptoms, being the caregiver who notices the motor or neuropsychiatric disorders before the patient can be aware of it[25]. The general unawareness of the HD full spectrum, in terms of the neuropsychiatric symptoms and the possibility of a young-onset, could be responsible for the longer delay in the time-to-diagnosis. These factors could additionally be challenging for the first-contact physician, even for a neurologist or neuropsychiatrist to diagnose HD. Neuropsychiatric symptoms could present years before the onset of classic motor symptoms, apart from a young-onset of the disease. Thus, leading to an increased time-to-diagnosis.

This delay in the diagnosis could deprive patients of being included in clinical trials that focus their interventions on slowing the progression of the disease. Knowing the time-to-diagnosis and the factors that could delay it leads to developing possible strategies that could be applied to reduce this time. Moreover, this can lead to an earlier diagnosis and prompt treatment on behalf of improving patients' and caregivers' QoL.

Some limitations can be listed. Time-to-diagnose has been described by the literature, although it is not standardized. The fact that this time is rarely directly measured makes the comparison between series difficult. A memory bias in our patients was found based practically on subjects' testimony or on physician medical notes on the electronic or physical records. Emphasizing patients' insight could be needed by developing questionnaires to understand why many patients do not want to undergo the molecular test once the clinical

diagnosis has been established. This situation might be due to fear of its heritability and their descendants' likely involvement. Finally, several factors such as access to health services, years of education, and socioeconomic status may play a role in the time-to-diagnosis; unfortunately our study is subject to referral bias as most of the subjects shared similar features as shown by the lack of differences in terms of schooling and socioeconomic status. Further studies with a more diverse social background are needed to better address these factors.

The delay in the diagnosis of HD impacts the patient's QoL and their entire support group. The importance of an early diagnosis has been reported, affecting the impairment in professional and social life. Likewise, early treatment could improve the prognosis[25-27]. Hence these findings stand out the importance of knowing well the characteristics of our population with HD and promoting a national registry.

Conclusion

The mean time-to-diagnosis of HD was 6.4 years. A delayed diagnosis was related to a neuropsychiatric- and an early-onset of the disease. An improvement in the identification of the full spectrum of HD could reduce this time, translating into earlier treatment and a potential improvement in the QoL of the patients. Implementing a national bank or database could be a strategy for recognizing relatives at risk.

Conflicts of interest

None.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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