The Libyan International Medical University

Faculty of Basic Medical Science

Progression of symptoms in Huntington Disease (HD)

Mariam Mohammed Elabbar

2251

Supervised by : Dr,Amal Elnaily

Assisted by: Dr, Nawar Montasser

Report Submitted to fulfill the requirements for ScientificResearch Activity

Date of Submission: 12 /3 / 2019

Abstract

Background : disease previously described as genetically programmed cell death in human CNS is known now days as Huntington's disease (HD) previously as (Huntington chorea) ,basically this report explains the progression of symptoms in the early and middle stages of Huntington disease , Material and methods : in this paper the progression is clarified through a survey of question answered by first degree relatives to the participants , the survey mentioned below holds 19 symptoms of (HD), the goal of this report is to describe or portray the progression of symptoms in the early and middle stages of Huntington disease (HD), Result : the symptoms were classified into 6 groups which are (initial , early ,early-middle, middle , middle-late and late) varying in the time of onset from 1 year to 2-5 years then 6-10 and finally up to 10 years , Discussion : patients who suffered of HD for more than 10 years adequately lower the sample size; therefore, the answers for the category of after more than 10 years were excluded in the analysis, . after the analysis of the answers of the affected questioner (AQ) the larger slope estimates indicate an early onset, while the symptoms with smaller slope indicate symptoms that happen later in disease progression. Conclusion: in conclusion the early and middle symptoms of Huntington are unclear unlike the middle-late and late stages , also describing the initial symptoms helps better the development of the therapeutic agents .

Introduction :

A disease previously described as genetically programmed cell death in human CNS is known now days as Huntington's disease (HD) previously as (Huntington chorea) , whoever to understand the progression of symptoms, the pathogenesis of HD must be clarified .[3],Therefore HD is an inherited neurodegenerative disorder, as a result from an abnormal polyglutamine (CAG) repeat expansion inside the coding region of the Huntington protein (IT15) this gene on chromosome 4 (4p63) encodes the protein Huntington [5] , This mutation leads to protein aggregation and neurotoxicity. despite its widespread expression in the brain and body, mutated Huntington causes selective degeneration of striatal projection neurons [1] . The major pathological features of HD are a primary loss of cells in the caudate nucleus and putamen (striatum) but other regions of the basal ganglia, hypothalamus, and brain stem are also involved. Not only

is there neuronal loss but there is also a decrease in the level of a number of neurotransmitters and associated enzymes, together with abnormalities in some receptor sites. [2] , HD can serve as a model for other trinucleotide repeat disorders, protein aggregation disorders, as well as dementia, psychiatric, and movement disorders.[6] , the clinical symptoms consist of motor, cognitive and psychiatric disturbances. Other less common, often debilitating features of HD include unintended weight loss, sleep- and circadian rhythm disturbances and autonomic nervous system dysfunction. The mean age at onset is between 30 and 50 years, with. The mean duration of the disease is 17-20 years[3] At early stages , the patient is employed, but at a lower level of capacity and can manage his or her daily affairs. in more progressed stages, he or she is unemployed and can no longer manage household responsibilities but activities of daily living may be only marginally impaired. next , the patient is no longer independent in activities of daily living but is capable of being supported by the family.

In the final stage, the patient can no longer function independently and requires complete support in all activities of daily living. The progression of the disease leads to more dependency in daily life and finally death. [3]

The most common cause of death in HD is cardiovascular disease and pneumonia following general debility from incessant choreic movements. Choking secondary to aspiration of food and suicide are also relatively common causes of death[2],[3]

Materials and Methods:

This survey was done by The National Huntington Disease Research Roster for Patients and Families, Indianapolis, Ind. In the paper my report is based on, the survey of patients with symptomatic HD answered by a first-degree relatives has been done . the survey had 1238 participants with at least a 6-year history of symptomatic HD , However, many of these people were diagnosed as having HD in recent years and thus have not been through the majority of the symptoms that they sought to clarify . Consequently, to describe the typical HD prodrome, the sample in the original study included only those individuals (1) who had disease onset at least 6 years before questionnaire end ; (2) who had the typical adult-onset choreic form of Huntington's; and (3) whose AQ was answered completely by a first-degree relative or spouse of a

first-degree relative to ensure that the respondent was sufficiently familiar with the patient's symptoms to accurately delineate disease progression. As the clinical presentation for juvenile- and adult-onset HD is quite distinct, those individuals whose disease onset with HD symptoms occurred at younger than 20 years or whose diagnosis of rigid or juvenile-onset HD were excluded before analysis.

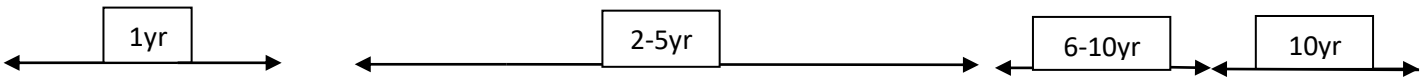
Owing to the known cognitive decline with manifested HD, particularly among individuals who are at least 6 years beyond their reported age at onset, participants who completed their own questionnaires (n = 90) were excluded before analysis. A total of 1238 individuals were included in the final analysis of the AQ data. These data include 600 individuals whose disease onset occurred more than 10 years before completion of the AQ[(4)]

Results :

The symptoms are categorized into 6 onset periods (intial , early ,early-middle, middle , middle-late and late). is composed of Involuntary movements are put in a group alone as the earliest reported symptom. The 2nd group which is made up entirely of mental and emotional symptoms, including sadness, depression, and difficult to get along with. The 3rd group includes clumsiness, sexual problems, lack of motivation, and suspiciousness-paranoia. As the disease develops, a variety of motor, emotional-behavioral, and cognitive symptoms have been experienced, including unsteadiness, trouble holding onto things, trouble walking, sleeping patterns changes , delusions and hallucinations, intellectual decline, and memory loss. when the late-stages of HD are closer, affected people begin to experience speech difficulty and weight loss. In the late stage, patients lose bowel and bladder control. . The results of this study aid in clarifying HD progression from early involuntary movements and emotional changes to motor symptoms and difficulty with activities of daily living , the result of this study is to assist in clarifying HD progression from

early involuntary movements and emotional changes to more overt motor symptoms and difficulty in activity of daily living [(4)]

Initial	Early	Early-middle	Middle	Middle - late	Late
Involuntary movement	Sadness	Clumsy	Sleeping trouble	Wight loss	Bowel control
	Depression	Lack of motivation	Unsteadiness and delusions	Speech difficulty	Bladder control
	Difficulty to get along	Sexual trouble	Holding and walking trouble		
		Paranoia	Intellectual decline & memory loss		



Discussion:

Now that the symptoms and their onset are already categorized seen in the table above this brings us to the case study of the original paper , where families of participant patients had completed a series of surveys, including the Affected Individual Questionnaire (AQ), that consists of 19 physical, emotional, and cognitive signs regularly occurs during HD progression , , the results are based on the response of the groups according to when the symptoms happened during the course of the disease: (1) within 1 year, (2) within 2 to five years, and (3) within 6 to 10 years. in the study the modified Bonferroni multiple comparisons test was used to categorize the symptoms into 6 onset periods labeled *initial*, early, early-middle, middle, middle-late, and late to identify the progression of the 19 physical and mental signs of this

disease , the proportional odds model, a regression model for ordinal data, was useful to analyze the AQ data of the participants . For each of the individual were given 19 signs, the 3 first responses were (1) within 1 year, (2) within 2 to 5 years, and (3) within 6 to 10 years.

basically the purpose of these analyses was to set out the progression of symptoms in the early and middle stages of Huntington's , as the progression of the symptoms in these stages is still uncertain, while the disease development in the late stages of Huntington's is well characterized. Also, demanding the participants to have reflected or manifested HD for more than 10 years adequately lower the sample size; therefore, the answers for the category of after more than 10 years weren't included in the analysis.

for each symptom, the model used the numbers of answers in each of the 3 periods to calculate a cumulative probability of the symptom that have had happened , a logarithmic function of these cumulative probabilities has been used to calculate slope estimates for each participant's symptom, which will then be compared directly with each other, allowing the ordering of the symptoms. Larger slope estimates imply an early onset, while the symptoms with smaller slope estimates happen later in disease progression. [(4)]

Conclusion :

In conclusion this disease progression of symptoms is tricky because it's not clear at the begging but as it keeps progressing the more aggressive and apparent symptoms will be much easier to understand and note their progression , hence a table organizing the symptoms and their time of onset was include it also mentioned the 19 symptoms, on the other hand describing the disease progression is very important to improve the understanding of the pathogenesis of HD and also to evaluate the therapeutic agents that are designed to slow the progression of HD symptoms [(4)]

References

1-. Charvin, D., Vanhoutte, P., Pages, C., Borrelli, E., & Caboche, J. (2005). Unraveling a role for dopamine in Huntingtons disease: The dual role of reactive oxygen species and D2 receptor stimulation. *Proceedings of the National Academy of Sciences*, *102*(34), 12218–12223. doi: 10.1073/pnas.0502698102

2- Conneally, P. (1984). Huntington disease: Genetics and epidemiology. American journal of human genetics. 36. 506-26

3- Roos, R. A. (2010). Huntingtons disease: a clinical review. *Orphanet Journal of Rare Diseases*, *5*(1). doi: 10.1186/1750-1172-5-40

4- Kirkwood, S. C., Su, J. L., Conneally, P. M., & Foroud, T. (2001). Progression of Symptoms in the Early and Middle Stages of Huntington Disease. *Archives of Neurology*, *58*(2), 273. doi: 10.1001/archneur.58.2.273

5- Vonsattel, J. P. G., & Difiglia, M. (1998). Huntington Disease. *Journal of Neuropathology and Experimental Neurology*, *57*(5), 369–384. doi: 10.1097/00005072-199805000-00001

6- Cuturic, M. (2020). Huntington's Disease. *Mind and Brain*, 81–108. doi: 10.1007/978-3-030-38606-1_8

.