DISABILITY MILESTONES IN HUNTINGTON DISEASE

MILJOKAZI PROGRESIJE HUNTINGTONOVE BOLESTI

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Summary

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease which is characterized by the presence of involuntary choreatic movements, cognitive impoverishment and behavioral disorders.

The objectives of this research were: analysis of the clinical specifics of people with HD and definition of chronology in the occurrence of milestone disease progression.

56 patients with HD were interviewed by telephone about their age, family history, age at onset of the disease, first symptoms, current symptoms and their beginning. Also, the number of trinucleotide (CAG) repeats was determined by PCR method.

In group of 50 alive patients the average age was 54.5 years, age at the beginning of disease 46.7 years, disease duration 7.8 years and latency to diagnosis 2 years, approximately. Family history was positive for 22 patients. Most frequently first symptoms were involuntary movements as isolated symptom (24 patients). In a progression of the disease swallowing difficulty and choking were first problem in everyday life for patients and they occurred 4.5 years after the first symptoms. Talking difficulty, falls, dependence on the assistance of another person during bathing and eating and walking difficulty happened after 4.6, 5.2, 6.2, 7.5 and 7.5 years, respectively. The average number of trinucleotide repeats was 43.8, in range from 40 to 51 repeats.

HD in short term leads to significant disability with the emergence of problems with swallowing, speaking and walking, leading thus to complete depending on the physical assistance of another person.

Keywords: Huntington disease, progression, chorea, trinucleotide repeats

Sažetak

Huntingtonova bolest je autozomno dominantna neurodegenerativna bolest koja se karakteriše nevoljnim pokretima, kognitivnim osiromašenjem i poremećajem ponašanja.

Ciljevi istraživanja su analiza kliničke specifičnosti pacijenata sa Huntingtonovom bolesti i definisanje hronologije u razvoju miljkaza progresije bolesti.

Pedeset i šest pacijenata je intervjuisano telefonski i dobijeni su podaci o njihovoj starosti, porodičnoj anamnezi, starosti na početku bolesti, prvim simptomima i trenutnim simptomima kao i o trenutku njihovog nastanka. Takođe, broj trinukleotidnih CAG ponovaka je ispitan PCR metodom.

U našoj grupi ispitanika od 50 živih pacijenata prosečna starost je iznosila 54,5 godina, starost na početku bolesti 46,7 godina, trajanje bolesti 7,8 godina a latencija do postavljanja dijagnoze 2 godine. Porodična anamneza je bila pozitivna za 22 bolesnika. Najčešći prvi simptom bili su nevoljni pokreti kao izolovan simptom (24 bolesnika). U daljoj progresiji bolesti problem sa gutanjem i zagricjavanje su bili prvi problem koji je otežavao bolesnicima svakodnevni život i pojavio se u proseku za 4,5 godina posle prvog simptoma. Problemi sa gutanjem, padanje, zavisnost od drugih osoba prilikom kupanja i jela, otežano hodaње desili su se posle 4,6; 5,2; 6,2; 7,5 i 7,5 godina, redom. Broj trinukleotidnih ponovaka se kretao od 40 do 51, u proseku 43.8.

Huntingtonova bolest u kratkom vremenskom period dovodi do značajne onesposobljenosti sa nastankom problema pri gutanju, prićanju i hodaњу, dovodeći potom do potpune zavisnosti od fizičke pomoći druge osobe.

Ključne reči: Huntingtonova bolest, horea, pregoresija, trinukleotidni ponovci

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease which is characterized by the presence of involuntary choreatic movements, cognitive impoverishment and behavioral disorders (1).

The prevalence of HD is 3 -7 on 100 000 residents in Western Europe. It rarely appears in Japan, China, Finland and Africa, so the frequency of HD in Japan is from 0.1 to 0.38 per 100 000 inhabitants, while the prevalence in some populations of Western European origin exceeds 15 per 100 000 (2). Due to the isolation of the population frequency of HD on Lake Marakoibo in Venezuela is 700 per 100 000 (3).

Choreatic movements, by which it got its name, are typical for the disease but dystonia can also be recorded, later incoordination of movements with immobility, bradykinesia and rigidity in the final stages of the disease. These symptoms are associated with a damage of cognitive functions such as attention and memory, as well as psychiatric symptoms, including personality changes, depression, psychosis and dementia that often precede motor symptoms. Other symptoms, including weight loss, muscle atrophy, cardiac dysfunction, and testicular atrophy, as well as endocrine abnormalities that become evident with a progression of the disease (4).

The gene responsible for HD is located on 4p16.3 locus. In that gene multiple repetitions of the CAG triplet nu-

cleotides (cytosine, adenine, guanine) occur, encoding implantation of the amino acid glutamine in the protein called hantingtin (5). Forty and more repetitions are associated with the expression of the disease. If there are 36 to 39 repeats, penetrance of mutation is reduced, so some carriers will manifest the disease, and some will not (6).

The brain in the final stage of the disease is 400g lighter compared to the average weight of 1300-1400g (7,8). This atrophy is the result of an extensive atrophy in the caudate nucleus and in putamen, but it is also a result of a serious neuron loss in deeper layers of the cerebral cortex (9). The hippocampus and the thalamus are also affected, but cerebellum significantly less. White mass, including the corpus callosum is hypotrophic (10). The loss of cortical neurons leads to cognitive and behavioral problems (11).

In the treatment of HD tetrabenazine is used and it lowers vesicular depots of catecholamine, a drug that suppresses chorea and is associated with global clinical improvement (12). Neuroleptic drugs which block the postsynaptic dopamine receptors, fluphenazine (13), and haloperidol (14) can be effective in the suppression of chorea. It is considered that taking tricyclic antidepressants and serotonin reuptake inhibitors can improve the condition of HD patients (15).

AIM

The objectives of our research were:

1. Analysis of the clinical specifics of people with HD
2. Definition of chronology in the occurrence of milestone disease progression

MATERIALS AND METHODS

There were 56 patients who participated in the research all of whom were diagnosed with Huntington's disease through the neurological examination at the Neurology Clinic of the Clinical Center of Serbia. The diagnosis was based on clinical findings, positive family history, and confirmed with the analysis of trinucleotide repeats in IT 15 gene.

Patients were informed of the study over the telephone when they were asked if either them or the members of their family could answer the questions from an open questionnaire. The questionnaire collected data on the patient's age, family history related to HD, the age of the patient at the time of diagnosis and at the time of occurrence of the first symptoms. The patients were also questioned about the type of their first symptoms. Further, patients and their family members gave information about the current clinical picture and about the

problems associated with speaking, swallowing and chewing, walking, falling, mood, sleeping, appetite and weight changes. It is also tested whether the patient can independently feed, bath, go out of the house, do the housework and if he/she uses diapers, catheter or wheelchairs. Apart from all these symptoms, data were also given about when the symptoms first appeared, in relation to the occurrence of the first symptoms.

After data collection, answers from the patients or their family members were grouped and analyzed statistically.

In addition to the questionnaire, in the research we have also covered data on the number of trinucleotide CAG repeats by PCR method. Blood samples were taken from all patients to determine the number of CAG repeats in a known manner (16). Briefly, genomic DNA was isolated from peripheral blood samples using standard procedures which including proteinase K and phenol chloroform insulation. Polymerase chain reaction (PCR) was performed with the primers: HC-1 (5'-ATG GCC TTC AAG TCC CTC AAG GAG TCC TCC3') and HC-2 (5'-CAG CAG CTG CGG TGCBCGTG-3'). The amplification was performed in 25-ml reaction mixture which contained 1 X PCR buffer (Pharmacia), 200 mM each dNTPs, 1.5 mM Mg₂Cl, 100 ng of each primer, 5% glycerol (final concentration), 1 U of Taq polymerase (Pharmacia) and 200 ng of genomic DNA. Terms of the cycle were: 3 min. Initial denaturation at 97 ° C, followed with 35 cycles of 1 min at 95 ° C, 1 min at 60 ° C and 2 min at 72 ° C, and the final 10 min at 72 ° C. Samples were first analyzed on 2% agarose gel. For determination of the precise number of CAG repeats part of each reaction (7 mL) was mixed with 3 ml of buffer (0.25% bromophenol blue, 0.25% xylene cyanol in 100% formamide) and denatured with heat at 100 ° C for 10 min before adding to 6% polyakrilamid- urea denaturing gel. Samples were electrophoresis in 0.5 X TBE buffer. The product of amplification was detected by silver staining using the standard procedure. In our laboratory the genes which contain at least 40 repeats confirm the diagnosis of HD.

RESULTS

The research included 56 patients with the diagnosis of Huntington's chorea confirmed also by genetic testing. Of the contacted patients ten have died, and for the six of the dead families were not willing to give any information. There were 19 men and 37 women. At the time of the telephone interviews, patients were aged 54.45 ± 9.61 (25-74) years, and at the time when the first symptoms appeared they were 46.69 ± 10.37 (23-65) years. We did not get the data on family history from 10 patients, whose families have not been informed of any relatives with the same disease. For 11 patients family history was allegedly negative with frequent data of early deaths of one or both parents, for 7 it was insecure

Table 1. Clinical and demographic specifics of patients with Huntington's disease

Male/Female	19:37
Age*	54.45±9.61 (25-74)
Alive∞	50/56 (82,1)
Trinucleotide repeats number*	43.87 (40-51)
Age at onset*	46.69±10.37 (23-65)
Latency to diagnosis*	1.90±2.87 (0-12)
Disease duration*	7.81±5.18 (0-28)
First symptoms∞	
Involuntary movements	24/49 (42,9)
Involuntary movements, walking difficulty, instability, falls	5/49 (8.9)
Involuntary movements, aggressiveness, agitation, anxiety	4/49 (7.1)
Involuntary movements, depression	2/49 (3.6)
Other	14/49 (25)
Family history∞ ,	
No data	10/50 (20)
Negative	11/50 (22.5)
Uncertain	7/50 (14)
Positive	22/50 (44)

*average value with SD and range in a parenthesis; ∞ number of patients (percentage)

(there are relatives with similar symptoms who are not diagnosed and treated), and for 22 patients family history for HD was positive (in 9 cases mother was ill, and in 13 that was the case with the father).

The average age in the beginning of the disease for patients whose mother was ill was 42.55 ± 7.35 years, for those with diseased father 45.67 ± 6.62 years, and for patients with a negative family history of HD 50.1 ± 10.14 years. There is no statistically significant difference between the age at the begging of the disease for patients who have inherited disease from the mother and patients who inherited the disease from father. Also, although the disease occurred later in patients with a negative family history, compared to those with positive family history, this difference was not shown to be statistically significant. The number of trinucleotide repeats in our patients ranged from 40 to 51. Clinical demographic characteristics of the patients are shown in Table 1.

Involuntary movements were first, isolated symptoms for 24/49 patients, while the occurrence of walk disorder at the same time, with instability, falling and sticking was observed in 5 patients. In 4 patients aggressiveness, anxiety and nervousness were manifested along with the involuntary movements, and in 2 that was a case with depression. Other symptoms (absence, obliviousness, cognitive disorders, facial tics, swallowing disorders and /or speaking, dizziness, disturbance of sphincter control and psychiatric symptoms in the form of delusions) occurred in 14 patients alone or in combination.

In specified telephone interview patients' family members gave information that in the current clinical picture involuntary movements occurred in 45 patients. In five patients involuntary movements were not pres-

ent. Walk which is either difficult and requires help or is impossible was characteristic of 23/50 patients, while 20 patients were falling. Nearly 80% (39/50) of patients choked, and slightly higher percentage of them spoke with difficulty and incomprehensibly (42/50). In 34 patients mood change was recorded, of which 12 patients are depressive, reticent and recluse, 10 are anxious or aggressive, 7 have a changeable mood, and 2 are oblivious. The combination of anxiety, aggressiveness and obliviousness occurred in another 3 patients. Sleeping problems were found in 28 patients, most commonly in the form of early morning awakening and getting up frequently during the night (11 patients). Three patients reported that their sleep quality reduced because of the great anxiety during sleeping. Seven patients put themselves to sleep only with the help of sleeping pills, while 5 patients say that their need for sleep increased. Appetite is reduced in nine patients, and increased in four, while 29 patients lost weight. 23/50 patients depend on feeding and require help; 32/50 do not conduct their own hygiene; 35/50 do not leave the house, while ten go out periodically, often with the help in the walks. There are 38 patients who cannot perform, seven use diapers, one patient uses catheter and six wheelchairs (Figure 1).

Figure 1. Huntington disease symptoms representation

Table 2. Milestones in progression of Huntington disease

Milestone	Years after first symptom (average value±SD)
Swallowing difficulty	4.45±4.02
Talking difficulty	4.58±3.01
Falls	5.25± 4.02
Need for bathing assistance	6.22±4.05
Need for feeding assistance	7.47±4.27
Walking difficulty	7.53± 4.63
Catheter using	9±0
Diapers using	9.11±3.68
Wheelchair using	10±6.54

Listed symptoms and status patients reached out in a short period of time (Table 2). The earliest evolved interferences with swallowing, chewing and speech, and the latest complete immobility with the attachment to the wheelchair (Figure 2).

Figure 2. Milestones in progression of Huntington disease

DISCUSSION

Although it is known that Huntington's disease equally affects men and women, the sex ratio of the patients included in our study was almost 2: 1 in favor of women (37:19). These results can be explained by the fact that women are major participants in studies on subjects under the risk for HD, as well as being more likely to require predictive genetic analysis for HD (17,18,19). Also, it is known that women with Huntington's disease live longer, which could be another explanation for why there are more women in random sample (20).

The first symptoms in our patients were reported on average of 46.7 years of age, which is consistent with many other studies that indicate that the first symptoms occur in the 4th and 5th decade of life (21). Our youngest patient was 23 years old at the beginning of the disease, and the oldest was 65 years old, which fits the range of 8 to 83 years in other studies (22).

Of the total of 50 interviewed patients, 22 had a positive family history, of which 9 patients inherited disease from the mother and 13 from the father. It is known that sex of the parents does not affect the heriditet because HD is an autosomal dominant disease, and it is transmitted on 50% of the offspring (23). Significant difference was not shown between the age at diagnosis in our patients who have inherited the disease from their mother and

patients who have inherited the disease from their father, which is in accordance with the results of the study from Venezuela (24).

A quarter of our surveyed patients, more precisely 11 of them have a negative family history of HD. It is interesting that our results are consistent with research conducted in British Columbia, in which also a quarter of patients had a negative family history. In 7.8% of the total number of patients in the same research it is proved or probable de novo mutations due to the instability of CAG repeats (25).

The first symptom in our patients were involuntary movements (in 24 patients independently and in other 11 patients they were associated with other symptoms). These results were expected, due to the fact that other studies had shown that in the diagnostic stage chorea is the first and most evident sign of the disease (23). Changes in mood and behavior, including aggression, agitation, nervousness, depression, absence, obliviousness, cognitive disorders, as well as psychotic signs such as hallucinations and paranoia are reported in 15 of our patients as the symptoms with which the disease began. It is known that these symptoms often precede the motor signs of the disease, but are often ignored or attributed to other causes (5,26).

Latency of developing the first symptoms to diagnosis lasted for an average of about 2 years, although the longest latency was even 12 years long. This is common for patients with HD, especially if their involuntary movements are weakly expressed, the patient do not notice them or denies them, or they do not interfere with patients daily activities (on face, as in our patient).

With an average of 4.5 years after the appearance of first symptoms, patients have begun to swallow with difficulty, to chew and have spasms during meals, and shortly after that they started to speak difficult and incomprehensible. Our patients developed problems with speech much earlier than most patients in a similar research (27) where this symptom appeared between 6 and 10 years after the beginning of the disease. A year later, the patients would usually begin to fall, which would interfere with the independent walk and led to difficult and disabled walk for about 2 years, or 7.5 years after the beginning of the disease. Results of the research show that with the majority of patients problems with walking occurred in the period of 5-6 years from the beginning of the disease. Six to seven years since the beginning of the disease, patients are hampered in their daily activities such as eating and hygiene of the body and require help in performing them. Loss of the sphincter control our patients developed for an average of 9 years, which is a bit earlier than the majority of patients in the research mentioned above, in which urinary incontinence emerged after 10 years.

CONCLUSION

Huntington's chorea is a chronic progressive disease that in the short term it leads to significant disability with

the emergence of problems with swallowing, speaking and walking, leading then to complete depending on the physical assistance of another person.

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