

CLINICAL NEUROLOGY OF HUNTINGTON'S DISEASE: A PRACTICAL APPROACH

KLINIČNA NEVROLOGIJA HUNTINGTONOVE BOLEZNI: PRAKTIČNI PRISTOP

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1 INTRODUCTION

The core features of Huntington's disease (HD) clinically as well as genetically were outlined by George Huntington in 1872. In his paper, he summarized clinical features that are recognized as relevant and important even today: the hered-

ABSTRACT

Huntington's disease is a hereditary degenerative disorder outlined by progressive manifestation of movement disorder, cognitive decline, and psychiatric disorder. Since the identification of Huntington's disease mutation recognition of presymptomatic gene carriers as well as different clinical manifestations of the disease were enabled. Despite the identification of a pathologic gene's product, the mutant protein huntingtin, the therapy of Huntington's disease on clinical grounds remains symptomatic since no efficient disease modifying therapy prepared for clinical practice has been demonstrated so far.

KEY WORDS:

clinical approach, Huntington's disease, therapy

POVZETEK

Huntingtonova bolezen je dedno degenerativno obolenje, za katerega so značilni napredujoča ekstrapiramidna motnja gibanja, kognitivni upad in psihiatrični simptomi. Po identifikaciji genske mutacije za Huntingtonovo bolezen lahko kliniki opazujemo različne klinične manifestacije bolezni in spremembe že pri presimptomatskih nosilcih bolezenskega gena. Kljub temu, da so odkrili tudi patološki genski produkt, mutirani protein huntingtin, ostaja zdravljenje Huntingtonove bolezni simptomatsko, saj še nobena do sedaj uporabljena terapija ni uspešno spremenila kliničnega poteka bolezni.

KLJUČNE BESEDE:

Huntingtonova bolezen, klinični pristop, terapija

itary nature of the disease and usual onset in adulthood, the pronounced dyskinetic syndrome, the psychiatric disorder and cognitive decline, and above all the inexorably progressive course of the disease (1). In the past century, the identification of a HD gene on the 4th chromosome has enabled clinicians to recognize different manifestations of HD (2). Due to highly sensitive and specific genetic test, the diagnosis of HD is no longer based on characteristic clinical features which could only be confirmed neuropathologically. A definite diagnosis confirmed by a highly reliable laboratory test can nowadays be performed during the patient's lifetime. The pathologic gene product, the mutant huntingtin protein, was identified soon after the HD gene finding (3). Near the begin-

ning of the huntingtin protein, which has a molecular mass approximately 350 kDa, a glutamine tract is sited and expansion of the glutamine tract encoded by the expanded Cytosine-Adenine-Guanine (CAG) codon is considered to be the primary cause of Huntington disease symptoms (4). CAG repeat length codes for 8 to 35 glutamines in normal population and its expansion may explain most of the clinical variability in HD (5). Genetic factors were investigated that might play a role in the age of onset and presentation of the disease. CAG repeats have a strong effect on the disease onset, however, no independent relationship to the rate of progression has been found (6). Additional genetic factors that might play a role in the age of onset and disease presentation have not been identified unambiguously. A within-family variability, however, seems to be smaller than a between-family variability (7). The disease symptoms and signs change as the disease progresses and the age of onset and duration of the disease have an essential impact on that.

2 ONSET AND EARLY HD

HD may start at any age, since the age of onset described ranges from 2 years till the mid-80s (2). In Slovenia, this range is from 4 to 78 years (8). There is a broad consent among the clinicians that clinical diagnosis of HD can only be made with certainty in the presence of a specific motor disorder although cognitive problems accompanied or followed by mild motor abnormalities may as a rule appear before that (1). Affective disorders, behavioral disorders, and in some cases even delusions and hallucinations may precede the onset of motor symptoms of HD (9). Long-term longitudinal studies give us the best insight into development of early signs and symptoms. The study of Venezuelan kindred by Penney et al. demonstrated that patients pass through an onset period representing a transitional zone from the presymptomatic to early symptomatic phase. There is an insidious deterioration of intellectual functions, appearance of mild personality disorder, and minor motor abnormalities, e.g. restlessness and motor impersistence, abnormal eye movements, impaired rapid alternating hand movements, inappropriate movements during emotional stress, and mild dysarthria. A clear appearance of extrapyramidal signs (chorea, dystonia, hypokinesia, rigidity) already marks the disease progression, not the beginning. Minor abnormalities may precede the obvious extrapyramidal signs by at least 3 years (10).

3 MID-PHASE HD

This phase is dominated by motor abnormalities, such as progressive dyskinetic motor symptoms accompanied by progressive impairment of skilled movements. Chorea is the major motor sign which gave origin to the old name 'Huntington's chorea', but that might be avoided as 'part for the whole' name for the disease due to diversity of symptoms presented by the patients.

Choreatic movements are continuously present during the patient's alert time. They cannot be voluntarily suppressed and worsen during stressful situations, such as medical examination. Chorea is common in the facial area, usually pronounced in the perioral area and in the form of grimacing, forehead wrinkling, and lifting of eyebrows. The neck is also frequently involved causing forward and backward twisting and rotation of the head. Regarding the limbs, chorea usually involves upper extremities more severely presented as twisting, flexion, and extension movements, while legs may be crossed and uncrossed and the toes flexed and extended. Although chorea is most dramatically present in these patients, disturbances of voluntary movements are more highly correlated with functional disability (10). Dystonia, including shoulder rotation, fist clenching, foot inversion, and trunk posturing worsen during the course of the disease (11). In fact, these movement disorders easily merge into one another. Therefore, it is probably best to observe the patient for a period of time and assess whether a more prolonged period of involuntary movements represents chorea and/or dystonia (1). Bradykinesia and rigidity starts to intervene as patients approach the final stage of the illness, but impairment of voluntary motor function starts early in the disease course and clumsiness may increase with deterioration of functional capacity (12).

4 ADVANCED OR LATE HD

From the clinician's point of view, the advanced stage HD is characterized by hypokinesia, bradykinesia, rigidity, and loss of independence. Although remnants of chorea may still be visible, dystonia prevails. Severe dysarthria and im-

paired swallowing are common, therefore, feeding through nasogastric tube or percutaneous endoscopic gastrostomy (PEG) may be necessary. Patients spend most of their time in chair or bed and are transferred to a nursing home. By the rule, the patients use multiple psychotropic medication, e.g. benzodiazepines, neuroleptics, and antidepressant medication (1). Incontinence is common in men and women in the advanced stage of the disease reaching up to 43% when bedridden patients were excluded (13). Weight loss that may be prominent during the disease symptoms development could partly be overcome by improved attention to caloric intake (14).

5 JUVENILE AND LATE ONSET HD

In about 10% of HD patients, clinical disease has onset before the age of 20 and a small percent of them show first signs before the age of 10, the youngest patient known developed disease signs at the age of 2. According to inverse correlation between the age of onset and CAG repeat length number, juvenile patients have long repeats typically exceeding 50 CAGs with the longest repeat size described approximately 250 CAGs (2, 15). In Slovenia, the longest CAG repeat number observed in a recently diagnosed juvenile HD case was 106 and the disease started at about the age of 4 (Kobal J, unpublished data). Cognitive decline and therefore decline in school performance are typically followed by bradikinesia and rigidity, clumsiness, frequent falls, and dysarthria. Epileptic seizures are also by far more frequent compared to Huntington and general adult population (1). In 3 juvenile cases diagnosed in Slovenia so far aside to previously described, myoclonus was prominent in 2, in 1 case presenting 106 CAG repeats in the form of myoclonic epilepsy (Kobal J, unpublished data).

Late onset disease might be milder than classic adult onset HD. Chorea and gait disturbance and tendency to fall are common, while cognitive decline and psychiatric symptoms may be less pronounced. In a recent retrospective observational study, 34 patients were described aged 60 to 79 years at the disease onset. Their CAG repeat number was 38 to 44 and a significantly negative correlation was found between the age at onset and number of CAGs (16). In one of our cases diagnosed at the age of 78, we found 35 CAG repeats, the disease presented itself by behavioral

disturbance and bizarre gait, only about 1 to 2 years later some chorea and perioral dyskinesia were observed (8). Probably the fastest approach in doubtful cases is to perform genetic test for HD due to its high reliability and continue the rest of the diagnostic procedures afterwards.

6 THERAPEUTIC APPROACH TO HD

HD is a genetically inherited neurodegenerative disorder that affects children, adults, and elderly people and lasts over many years. Therefore, therapeutic approach, which so far is symptomatic, must be specifically customized for the individual patient. Pharmacological as well as supportive non-pharmacological interventions might be necessary. These include: coordinative and supporting activity from the neurologist in charge to make appropriate appointments, genetic counseling is necessary for patient and family about genetic risks and reproductive options, and predictive testing may be provided to presymptomatic individuals, e.g. family members. Cognitive testing as well as supportive psychological counseling to the patient and his family members may be necessary. Social services may provide financial, legal, occupational, and accommodation advices. When a patient is beginning to lose independence, social service may assist with disability, guardianship and alternative procedures, help identifying resources for long-term care either in home or institutional. Nursing support, occupational, physical, and speech/swallowing therapy may be necessary in mid-stage and advanced HD. Dietary counseling may be necessary about weight maintenance feeding strategies and eventually PEG placement. Volunteers from lay organization such as regional HD society may help by sharing their experience to patients and family members. Slovenian HD society was established in 1999 and works in collaboration to European HD society.

In onset and early HD patients, cognitive decline, affective, and behavioral disorders usually are those that require most attention from the attending neurologist and the rest of the HD team. Psychotic symptoms might also occur. Since no effective therapy has been found to counteract cognitive decline, pharmacological interventions are oriented towards coping affective and behavioral disorder. Antidepressant and anxiolytic drugs are used frequently,



but antipsychotic medication might also be necessary (17). There were also attempts to influence cellular mechanisms and modify the course of disease using antidepressive and dopamine-depleting drugs (18, 19), however, according to references as well as our experience with limited success.

During mid-stage HD, movement disorder is usually prevalent and a wide range arrhythmic dyskinesia can be seen in patients ranging from high-amplitude movements resembling ballistic, dystonic postures to choreatic and almost tic-like movements. The nature of involuntary movements however does not have any proven therapeutic relevance (20). Dopamine depleting drugs are the only approved for the treatment of movement disorder in HD (19, 21). Neuroleptics however also ameliorate chorea and calm the agitated and/or aggressive patient in mid-HD stage. A wide variety of antidepressants combined to antidopaminergic drugs are currently used for symptomatic treatment of movement disorder and mood disorders (22). Recently, however, the use of antidopaminergic drugs in HD has been disputed due to possibility of faster progress of functional disability in such patients, but further investigation is necessary (23). Therefore, dopamine depleting drugs, such as tetrabenazine and alternatives, might be the drugs of choice for HD patients with prevalent dyskinesic symptoms.

In advanced e.g. late HD patients, the main goal of management is to reduce pain and suffering, to provide good nursing care which may reduce medical complications (20). Chorea may be less pronounced, therefore, dopamine-depleting drugs may be reduced or abandoned, but dementia increases and may become severe. Drugs used to cope with psychiatric issues of HD, such as irritability, depression, anxiety, apathy, are found useful (24). According to our experience, rivastigmine also may ameliorate rigidity and improve behavior, but an effect on cognitive dysfunction has not been proven (25, 26). Combination of tetrabenazine and clonazepam may ameliorate impulsive involuntary movements and lorazepam in addition to clonazepam may provide sedation in case of aggressive behavior (27).

Juvenile and late onset HD represent special situations that may be treated symptomatically similar to THE adult onset HD. The prevalence of juvenile HD varies in different studies from 1 to 15% with a pooled proportion of about 5% in meta-analyses (28). Rigidity and dystonia are more

and chorea less common. In addition, epileptic seizures (in up to 25% of the patients) may represent a serious problem. One of our recent juvenile cases presented with a progressive myoclonic epilepsy and cognitive decline and epilepsy has been successfully treated by introduction of levetiracetam (Kobal J, unpublished data). In another one, rigidity was temporarily ameliorated by amantadine and dystonia improved after clonazepam (8). In late onset HD clinical course may however vary considerably from mild to moderate and severe course (16) and so does the therapeutic approach. One of our female patients has been diagnosed at the age of 78 presenting gait dystonia and mild chorea. She had 39 CAG repeats and her relatives remembered her due to 'funny' behavior for the last 3 or 4 years. Her movement disorder improved after clonazepam (8).

7 CONCLUSION

Despite of the progress on clinical and genetic grounds, the therapy of HD patients remains symptomatic and supportive. Inspired by that, clinicians should try to prescribe symptomatic therapy which may not speed up the progress of the disease, such as dopamine depleting drugs, anxiolytics, and antidepressants. Further therapeutic trials are ongoing and may give us some favorable results in the near future.

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Kakovostna in količinska sestava: Zdravilna učinkovina: rekombinanti koagulacijski faktor VIII (oktokog alfa). Ena viala vsebuje nominalno 250/500/1000/2000/3000 i.e. humanega koagulacijskega faktorja VIII. Pomožne snovi: Prašek: saharoza, histidin, glicin, natrijev klorid, kalcijevega klorida, polisorbitat 80. Vehikel: voda za injiciranje. **Terapevtske indikacije:** Zdravljenje in preprečevanje krvavitve pri bolnikih s hemofilijo A (pirorojeno pomanjkanje faktorja VIII). Zdravilo Kovaltry se lahko uporablja za vse starostne skupine. **Odmerjanje in način uporabe:** Zdravljenje mora potekati pod nadzorom zdravnika, ki ima izkušnje z zdravljenjem hemofilije. Odmerjanje zdravila in trajanje nadomestnega zdravljenja sta odvisna od stopnje pomanjkanja faktorja VIII, mesta in obsega krvavitve in od kliničnega stanja bolnika. Ena mednarodna enota (i.e.) aktivnosti faktorja VIII ustreza količini faktorja VIII v enem ml normalne humane plazme. **Kontraindikacije:** Znana preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Znane alergijske reakcije na beljakovine miši ali hrčkov. **Posebna opozorila in previdnostni ukrepi:** Tako kot pri vseh intravenskih zdravilih beljakovinskega izvora se lahko pojavijo preobčutljivostne reakcije alergijskega tipa. Nastanek nevtralizirajočih protiteles (inhibitorjev) proti faktorju VIII je znan zaplet pri zdravljenju bolnikov s hemofilijo A. Pri hemofilijah z dejavniki tveganja za srčnožilne bolezni ali s srčnožilnimi boleznimi, katerim se je strjevanje krvi normaliziralo z zdravljenjem s faktorjem VIII, obstaja enako tveganje za nastanek srčnožilnih bolezni, kot pri bolnikih, ki nimajo hemofilije. Če je potreben centralni venski kateter (CVK), je treba upoštevati možnost lokalnih okužb, bakteriemije in tromboze na mestu kateterizacije. **Nosečnost in dojenje:** Faktor VIII se sme med nosečnostjo in dojenjem uporabljati le, če je jasno indicirano. **Neželeni učinki:** *Pogosti:* limfadenopatija, palpitanje, sinusna tahikardija, bolečina v trebuhu, dispneja, pireksija, neprijeten občutek v prsnem košu, reakcije na mestu injiciranja (vključuje ekstremitacije na mestu injiciranja, hematom, bolečino na mestu infundiranja, pruritus, oteklino), glavobol, omotica, nespečnost, pruritus, izpuščaji (izpuščaji), eritematozni izpuščaji, srbeč izpuščaji, alergijski dermatitis. *Občasni:* preobčutljivost, disgeuzija, urtikarija, pordelost. **Način izdajanja zdravila:** Izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** Bayer AG, D-13342 Berlin, Germany **Za nadaljnje informacije o zdravilu Kovaltry, se lahko obrnete na:** Bayer d.o.o., Bravničarjeva 13, 1000 Ljubljana **Verzija:** EU/1 (02/2016)

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