Literature Review of Huntington's Disease Treatment

Introduction

The Huntington's disease (HD) is a severe autosomal dominant disease characterized by the accruing atrophy of basal ganglia and other departments of the CNS – central nervous system (Roos 1). The disease is caused by the expansion of the polyglutamine-coding tandem. The triple CAG repeats within the huntingtin (HTT) gene in a 4p16.3 chromosome; it is characterized by full penetrability of a mutant gene (Paulsen et al. 874). The lack of ethiopathogenetic treatment and the long-term progressing clinical course of HD are characterized by the expressed psychiatric manifestations (aggression, suicidality, etc). The existence of a risk group among relatives imposes a burden on the whole patient's family, which causes social importance of the disease. HD is under an undivided attention of the researchers due to the possibility of identifying latent stage of neurodegeneration at the asymptomatic mutant gene carriers being especially important in the preventive neuroprotection context (Chen, Ferrone, and Wetzel 18885; McColgan 3328). The given literature review will summarize, synthesize, and critique 20 peer-reviewed sources while discussing mainstreams and alternative approaches to the treatment of HD.

Recently, the unique international platforms created for the interaction between doctors, biologists, and pharmacologists with the families suffering from HD allow implementing basic researches with the participation of hundreds of patients and experts of various profiles (McColgan 3328). Such an experience results in the development of essentially new experimental approaches to the treatment of HD including various methods of the inactivation of a mutant gene or its derivatives. These new trends in the discussion of the approaches to HD became the main reason of the given literature review.

Nowadays, the analysis of the regularities of HD and the control of efficiency of the carried-out therapy demand the introduction of the quantitative methods of the disease

monitoring. At present, despite considerable attention to the problem of the HD biomarkers and a set of techniques offered for this purpose, the latest methods of neurovisualization remain the leading ones from the point of view of the objectivism of the neurodegenerative process (Vuono 1908). Position emission tomography (PET) and induced pluripotent stem cells (iPSCs) are among the most perspective techniques in HD treatment (Roussakis and Piccini 287; Liu et al. 11). The relevance of the articles, publications in scientific peer-reviewed journals as well as the variety of the approaches to the treatment of HD, starting from the pharmaceutical therapy up to the cell-based one, composed the main criteria for the given literature review.

Historical Background of Huntington's Disease

Huntington's disease is a chronic hereditary disease characterized by the progressing clinical course with degeneration. It is also characterized by the aggravated chorea, hyperkinesia, and dementia. Men are more exposed to the disease than women. The disease is not manifested in early childhood since the peak of its development falls onto the people aged between 35 and 50 years (Nance et al. 8).

Choreatic hyperkinesia is a sudden fast spasmodic non-derivative free movements arising randomly in different parts of a body. At an early stage of HD, hyperkinesia has a low amplitude and is observed in the distal departments of extremities, mimic muscles, and a tongue (Paulsen et al. 312). Later, hyperkinesia increases in amplitude and becomes generalized, thus making a patient lose the ability to suppress violent movements even for a short time. Hyperkinesia is amplified in the state of excitement, intensive mental activity, and changing body position. Patients have grimacing, unnatural gesticulation, and changes in speech (Paulsen 312). However, hyperkinesia usually disappears completely during sleep.

There are the descriptions of the HD clinical manifestations and the instructions on its hereditary character in the work of the Norwegian doctor Lund, who was a pioneer in

mentioning the chronic chorea in the first half of the 19th century (Novak and Tabrizi 34). The progressing hereditary chorea bears the name of George Huntington, who gave the complete description of the clinical manifestations and the course of the disease in 1872. Moreover, he provided the convincing proofs of its hereditary nature (Novak and Tabrizi 34). The HD doctrine was intensively developed later by neuropathologists, psychiatrists, neuromorphologists, and geneticists.

In the last decades, there were the attempts to influence the neurodegenerative pathogenesis, which composes the cornerstone of HD. It led to the development of the main directions of the pathogenetic therapy. The compensatory (replaceable) therapy is directed at overcoming the neurotransmitter deficiency in various mostly injured at HD neuron systems (Nance et al. 92).

Current Research Studies on HD's Biomarkers

Oculomotor apraxia, which consists of the increased latency and delay of the speed of the saccadic eye movements, is the earliest motive symptom of the Huntington's disease. In the course of the disease, the watching movements of eyeballs are roughly broken, and patients cannot fix a look on something. Moreover, such disorders as dystonia and parkinsonism are present at different levels of the disease manifestations (McColgan 3339). One of the main motive symptoms includes the impossibility to completely control the physical activity and to hold any pose owing to the rough violent movements. At the later stages of the disease, HD patients experience difficulties in performing movements demanding a steady coordination. The general rate of physical activity becomes more slowly and walking ability is considerably broken. Moreover, there are postural violations leading to falls as well as there are dysarthria and dysphagia (Roos 3).

Cognitive disorders appear at the early stages of HD and are almost universal manifestations of the disease, varying by its expressiveness (Cruickshank 6). The executive

functions and the ability to plan and estimate the actions suffer the most. There is a delay of the psychomotor processes, apathy, and decrease in attention among the majority of HD patients. Also, the functions of visual and spatial perception, recognition of the emotions expressed by other people, learning and memorizing of new information are also broken (Novak and Tabrizi 35; Roos 3).

The mental disorders at HD are characterized, first of all, by the depression and alarm. There is also irritability causing an aggressive behavior of the patients. The development of the obsessive and compulsive frustration can considerably worsen the life quality of family members and caregivers living together with such patients (Domaradzki 935). Psychoses can also be observed among patients with HD. Moreover, the committed suicides and suicidal attempts happen four times more often in the case of HD than in the general population (Dale 20).

The juvenile onset HD is a special form of the disease. It progresses much more severely and is characterized by a short life expectancy among the HD patients (Nance et al. 83). The akinetic-rigid type of juvenile HD is the most frequent one. It is characterized by the minimal manifestations of chorea but more distinct expressiveness of the Parkinson's and dystonic syndromes. The patients suffering from juvenile HD have bigger probability of the elliptic attacks than the patients with the first signs of the disease at adult age (Nance et al. 84; Roos 7).

The manifestations of HD can change in the pathological development process. The progression of this disease can be followed by gradual reduction of the chorea expressiveness and strengthening of other symptoms. Quite often, it is rather difficult to accurately define the beginning of the disease as the mental and cognitive disorders can precede the motive ones (Dale 21).

According to the results of a number of researches, the symptomatic HD is diagnosed in the following cases: a) CAG expansion repeats 36 and more times in the first HTT gene exon or the HD burdened family anamnesis; b) the motive disorders manifesting HD are present (Domaradzki 940; Chen, Ferrone, and Wetzel 18886). The motive manifestations of the disease expose the beginning of the HD. However, some multicenter observation researches devoted to the analysis of the natural clinical course of HD were conducted. In particular, the research 'Predict HD' covered about 800 asymptotic carriers of HD mutation and 200 healthy volunteers observed within ten years, and the 'Track HD' one included 240 carriers of HD mutation (half of which were asymptotic) and 120 healthy volunteers being examined for three years by means of various clinical and neurovisual techniques (Paulsen 876, 1197). Both specified researches showed that the cognitive and behavioral disorders among the HD mutation carriers sometimes preceded motive frustration, which could be classified in accordance with the present criteria as a motive debut of HD. It was found out that there is the selective atrophy of a number of the brain areas 12-15 years prior to the confirming the HD clinical diagnosis (Vuono 1908). These changes in the volume of a brain substance are supplemented with the changes in the physiology of movements. The latter can be estimated quantitatively by means of the sensitive Q-Motor system (Paulsen 878).

In this regard, the scientific community divided the asymptotic period of the HD mutation into actually pre-symptomatic and prodromal periods (Vuono 1909). The last one is characterized by the gradual emergence of the nonspecific changes in the motive, cognitive, and behavioral spheres which, however, do not fall under the formal criteria of the HD debut. Such an evolution of the understanding of an HD natural clinical course is sometimes compared to the evolution of the name of a disease – from the “Huntington's chorea” to the “Huntington’s disease”. The latter term is a new term emphasizing the complexity of the

pathological process, at which chorea is not the only manifestation of the disease (Paulsen 1197).

Main Findings of HD's Clinical Implications

Like schizophrenia, the Huntington's chorea can develop against the deviations difficult for diagnosing. HD usually develops due to the nervous defect (Dale 20). The middle age of people having the beginning of clinically expressed disease is lower than of the ones with other atrophic processes and equals 44-47 years. Among the atrophic diseases, HD possesses the greatest duration –12-15 years on average (Domaradzki 933).

Unlike other atrophic processes, HD has no uniform stereotype of development. Such mental disorders as personal changes, development of dementia, and psychotic frustration can arise after the emergence of the choreatic hyperkinesia, develop along with them, or precede them (Dale 21). The genealogical researches showed that these distinctions in the consecutive development of the disease symptomatology are most likely not determined genetically as various stereotypes of the disease development can be met in the same families (Ross 821).

The psychopathic deviations observed at the initial stages of the disease, sometimes long before the identification of the other clinical symptoms of the disease, are various. There are three main types of personal anomalies: 1) excitable (explosive, spiteful, and stenic); 2) hysterical (whimsical, inclined to the theatrical and display behavior, affective and labile); 3) closed (authentic and emotionally cold people) (Chen, Ferrone, and Wetzel 18887).

Unlike other forms of weak-mindedness, the HD dementia has a number of clinical features at the initially degenerate atrophic processes (Ossenkoppele 8). The disease progresses rather slowly. Besides, weak-mindedness becomes not always absolute. These features define relatively high quality of the development of the HD weak-mindedness. In the case of HD, dementia differs in the dissociation between long remaining ability to self-service at home and obvious intellectual insolvency in the situations demanding productive

mental work. The expressed unevenness of the intellectual working capacity is the characteristic feature of the choreatic dementia (Ossenkoppele 9).

According to the research of Cruickshank et al. (2015), there are the disorders of attention and inconstancy of the patients' beliefs. The easy loss of the direction and the purposes of cogitative activity compose the cornerstone of the disease. The mental process of the patients with HD is spasmodic owing to the continuous changes of directions. On the one hand, the Huntington's disease is characterized by the inverse relationship between the progression and the speed of the development of dementia. On the other hand, the disease is manifested by the frequency and clinical expressiveness of the psychotic frustration (Cruickshank 6).

Along with the described above clinically expressed disease forms, there are also patients with the rudimentary psychopathological and neurologic manifestations – so-called "abortive forms" (Martin et al. 245). They include:

- the early manifesting neurologic variants with the prevalence of the kinetically hypertensive syndrome;
- the forms with typical hyperkinesia, but with the minimum expressed psychotic changes without the development of the expressed dementia in particular;
- the forms with the prevalence of mental disorders in the form of dementia or psychopathic changes and with rudimentary hyperkinesia;
- the so-called "stationary forms" at which, despite more or less developed symptomatology, a disease lasts for decades without reaching a final stage (patients' deaths in a senior age are caused by the opportunistic diseases).

However, in most cases, there is a steady progression of the disease, which leads the patients to death in the condition of a total dementia and marasmus. In a terminal stage, the choreatic hyperkinesia usually decreases or stops at all.

Treatment of HD

There are active researches on the development of the HD treatment. The disease and disturbing excitement can be partially suppressed by the neuroleptics or reserpine (Martin et al. 244). The doses can be increased up to the manifestations of the side effects like sleepiness, parkinsonism, and hypertension. The purpose of the empirical therapy is to reduce the glutamatergic transfer and to support the energy production in mitochondria. The genetic testing and consultation are important because the symptoms of the disease are shown upon the termination of childbearing age. The people with the positive family anamnesis and those who are interested in testing are sent to the specialized centers taking into account all ethical and psychological consequences (Domaradzki 938).

There are also the attempts of the HD surgical treatment. The hyperkinesia often decreases or disappears after the stereotaxic operations. However, owing to the severe and progressing mental changes, this method can hardly find a broad application. The possibilities of labor therapy are limited because of the neurologic frustration. Patients with the lightly expressed mental disorders can be treated not only in psychiatric but also in neurologic hospitals. The genetic consultation takes place in the prevention of HD (Domaradzki 938). In the majority of cases, the HD patients' sufferings are disabled. The degree of disability is defined by the stage of the disease and expressiveness of the neurologic and mental disorders. At the progressing disease, the patients are legally incompetent. The expert difficulties arise at the inspection of the psychopathic people coming from the families with a hereditary Huntington’s chorea with the symptoms of a manifested disease. The treatment of HD always means not only the use of medicines but also a non-drug therapy. The latter includes the physiotherapy exercises and others rehabilitation actions, psychotherapeutic impact, work therapy, and logopedic sessions (Cruickshank et al. 7).

Symptomatic Treatment of HD

There is no effective treatment being able to stop the HD progressing. A great number of tests of different medicines showed little effect. The neuroleptics and other antagonists of dopamine receptors are widely used for the correction of mental disorders and involuntary movements of HD patients' bodies (Kegelmeyer 219). Respectively, neuroleptics are used for the easing of the excessive dopaminergic activity. However, these medications can cause the expressed cognitive and extrapyramidal side effects. Besides, their efficiency has not been proved yet. Neuroleptics often cause or aggravate dysphagia or other motive frustrations (Paulson 312; Martin 243). Such new generation neuroleptics as risperidone, clozapine, and olanzapine can be helpful for the HD treatment as they cause the extrapyramidal side effects to a lesser extent. Instead, these neuroleptics can weaken a paranoid syndrome or decrease irritability (Martin 243).

Tetrabenazine and reserpine also weaken the activity of the dopaminergic system and are capable of reducing the expressiveness of the involuntary movements at the HD early stage. However, these medications can cause depression (Liu et al. 2; Kegelmeyer 220). Owing to the fact that the Huntington’s disease often causes depression, this side effect significantly limits the application of reserpine and tetrabenazine (Liu et al. 2). In the late stage of the disease development, the cells bearing dopamine receptors perish; therefore, the efficiency of the antagonists of dopamine receptors is weakened or lost.

Neuroleptics, antidepressants, and anxiolytics are applied for the treatment of psychosis, depression, and irritability among the patients with HD; however, these medicines should be prescribed only for the period when the patient really has the symptoms (Paulson et al. 312). The preparations being useful at one stage of the disease can become inefficient or even have an adverse impact in the process of the disease development.

Neuroprotective Treatment of HD

Although the HD genetic defect is known, it is still not clear how it leads to the selective degeneration of neurons (Cruickshank 5). The preventive therapy is directed at the reduction of an oxidizing stress, and excitotoxic effect is potentially capable of slowing down or stopping the disease progression. In this regard, the hypothesis according to which HD is connected with the frustration of a power metabolism and death of cells owing to the excitotoxicity, draws a special attention. The disease itself can cause the death of cells due to the intranuclear aggregation of N-terminal fragments of huntingtin gene breaking the cellular and metabolic functions (Chen, Ferrone, and Wetzel 18888).

This process can strike some groups of neurons more than other ones, owing to their higher sensitivity to the excitotoxic damage. In this case, the preventive therapy by the antagonists of the exciting amino acids' receptors or the means preventing free radical damage will be capable of warning or postponing the beginning and the progression of the disease (Ahmed et al. 9753). The antioxidant means and antagonists of receptors can slow down the progression of the Huntington's disease (Ross 822; Martin 248).

Forecast and Perspectives of HD Treatment

Scientists constantly study molecular and biochemical mechanisms of the development of the HD pathological processes and try to influence its separate communications in experiments (Paulsen et al. 1199). The histone deacetylase ferment plays an important role in the mechanism of the interaction of the wrong gene and expands huntingtin protein onto the cells of the striatum body. The experiments on cellular culture and drosophila flies showed that the use of inhibitors of this enzyme slows down the degeneration of neurons. Scientists assume that the preparation on the basis of histone deacetylase inhibitor will help to prevent or slow down the development of HD (Ross 819).

The researchers seek for the methods of the change of the genetically modified cells capable to secrete various factors. The predict HD study showed that about 18 months after the transplantation of neurons into the patient's brain, an abnormal huntingtin was not found there (Paulsen et al. 878). However, it is not understandable what should be done with other affected brain areas. There were some clinical tests of riluzole applied at the treatment of the other neurodegenerative disease – a side amyotrophic sclerosis. At present, there is a temporary decrease of hyperkinesia at the HD treatment.

The progressing atrophic process composes the main cause of the HD. Therefore, the forecast is not favorable in general. There are no recorded cases of the HD treatment. The correct care for a patient and the observance of all doctor’s prescriptions are of great importance for the sufficient treatment of the disease. The statistical data shows that the life expectancy of patients composes 15-20 years after the first signs of HD (Paulsen et al. 878). Not the disease itself but the complications developing as a result of the impact of injuries, pneumonia, and cardiovascular pathologies are the reasons of a lethal outcome. Suicide is another common cause of the patients' deaths (Paulsen et al. 1198). However, in connection with a small progression, possibility of the relative temporary stabilization of the disease process, and the existence of abortive forms, the forecast should be considered individually. Thus, HD is not curable at the present stage of its development.

However, despite such a negative forecast of the treatment of the Huntington’s disease, the enormous perspective of the iPSCs technology will allow discovering the mechanism of the disease treatment at the cellular level.

> Therefore, using iPSCs lines for disease modeling may bridge the gaps between animal models and human neural cells and help elucidate the molecular basis of HD. Furthermore, iPSCs technology could be coupled with high-throughput screening that provides faster and more efficacious platform

in order to assess a number of former and novel drug candidates aimed at stopping or slowing the disease process (Liu et al. 11).

Conclusion

At present, the evidential base of the preparations for the correction of HD is introduced by the results of a small number of researches, which limit the opportunities for the compilation of the accurate recommendations of the HD treatment. Nevertheless, tetrabenazine is an officially approved pharmaceutical preparation used for the medicamentous correction of the choreatic hyperkinesia at HD. In the absence of the expressed mental manifestations of HD, first of all, depressions, suicide thoughts, irritability, aggressive behavior, and dysphagia, this preparation should be considered as the means of the first choice for the HD treatment. In other cases, it is expedient to consider the possibility of the application of neuroleptics in the form of monotherapy or in combination with the antiepileptic preparations or benzodiazepines.

The current literature review showed that the disorders in behavior as well as other symptoms of HD start a long time before a patient is diagnosed with HD. The most constant changes in the behavior and cognitive abilities of the patients are noticed in the last years before the official diagnosis is made. The review of 20 peer-reviewed sources showed that there is no existing method of HD treatment. However, the timely and correct care for the patient with HD and family members can hinder the disease development.