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Neuropsychiatric Aspects of Huntington's Disease

Huntington Hastalığının Nöropsikiyatrik Yönü

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ABSTRACT

Huntington's Disease is a progressive neurodegenerative disorder inherited in an autosomal dominant fashion with distinct phenotypes as chorea and dystonia, incoordination, cognitive disorders, and behavioural problems. In addition to cognitive and motor symptoms, neuropsychiatric symptoms are among the core symptoms of the disease. Neuropsychiatric symptoms are quite common in Huntington's Disease and the prevalence of neuropsychiatric disorders in different stages of the disease is estimated to be 33-76%. Although the prevelance of neuropsychiatric symptoms varies among the stages of the disease, it is also known that the onset of these symptoms may be years before the onset of motor symptoms. Common neuropsychiatric symptoms and disorders in Huntington's Disease include depression, anxiety, suicide, irritability, apathy, obsessive-compulsive symptoms, perseverations, psychosis, sleep disorders, and sexual dysfunctions. Neuropsychiatric symptoms constitute one of the most important factors for the burden on families, and are considered to be the most important predictors of decrease in daily functionality and institutionalizations in care centers and hospitalizations. Considering both its frequency and outcomes, it is very important for patients, their relatives and caregivers to recognize and intervene in neuropsychiatric symptoms of Huntington's Disease. Although there are no studies with a high level of evidence on the treatment of neuropsychiatric symptoms of the disease, studies with lower levels of evidence, case reports and treatment guidelines based on expert opinions are found in the literature in recent years. Another issue to be considered in this area is the evaluation of individuals at genetic risk, genetic counseling and setting a safe protocol during these evaluations. In this article, neuropsychiatric disorders common in Huntington's Disease, the management of these disorders and the conditions to be considered in the evaluation of individuals at genetic risk are reviewed in the light of current literature.

Keywords: Huntington's Disease, neuropsychiatric disorder, treatment, genetic risk

ÖZ

Huntington Hastalığı; kore ve distoni, koordinasyon bozukluğu, bilişsel performansta bozulmalar ve davranışsal sorunlar gibi farklı fenotipler ile ortaya çıkabilen, genetik olarak otozomal dominant geçiş özelliğine sahip, ilerleyici tipte bir nörodejeneratif hastalıktır. Bilişsel ve motor belirtilerin yanı sıra nöropsikiyatrik belirtiler de hastalığın çekirdek belirtileri arasında yer almaktadır. Huntington Hastalığı'nda nöropsikiyatrik belirtiler oldukça sık görülmekte ve hastalığın farklı dönemlerinde psikiyatrik bozuklukların görülme prevelansı %33-76 olarak tahmin edilmektedir. Nöropsikiyatrik belirtilerin görülme sıklığı hastalığın evrelerine göre farklılık gösterse de başlangıcının motor belirtiler başlamadan yıllar önce olabileceği de bilinmektedir. Huntington Hastalığı'nda sık görülen nöropsikiyatrik belirti ve bozukluklar depresyon, anksiyete, intihar, irritabilite, apati, obsesif-kompulsif belirtiler, perseverasyonlar, psikoz, uyku bozuklukları ve cinsel işlev bozuklukları olarak sayılabilir. Nöropsikiyatrik belirtiler aileler üzerindeki yükün en önemli nedenlerinden birini oluşturmakta, günlük işlevsellikteki azalma ile bakım kurumlarına yerleştirilme ve hastaneye yatışların en önemli öngörücüsü olarak değerlendirilmektedir. Hem sıklığı hem de sonuçları göz önüne alındığında Huntington Hastalığı'ndaki nöropsikiyatrik belirtilerin tanınması ve bu belirtilere müdahale edilmesi hastalar, hasta yakınları ve bakımverenleri için oldukça önemlidir. Hastalıkta görülen nöropsikiyatrik belirtilerin tedavisi ile ilgili yüksek kanıt düzeyine sahip araştırmalar olmasa da daha düşük kanıt düzeyine sahip çalışmalar, vaka bildirimleri ve uzman görüşlerine dayalı tedavi kılavuzları son yıllarda yazında kendine yer bulmuştur. Bu alanda dikkat edilmesi gereken başka bir konu da risk altındaki bireylerin değerlendirilmesi, genetik danışmanlık ve bu değerlendirmeler sırasında güvenli bir protokolün oluşturulmasıdır. Bu yazıda Huntington Hastalığı'nda sık görülen nöropsikiyatrik bozukluklar, bu bozuklukların tedavisi ve risk altındaki bireyleri değerlendirmede dikkat edilmesi gereken durumlar güncel yazın ışığında derlenmiştir.

Anahtar sözcükler: Huntington Hastalığı, nöropsikiyatrik bozukluk, tedavi, genetik risk

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Introduction

Huntington's Disease (HD) is a progressive neurodegenerative disorder that has an autosomal dominant inheritance pattern. The disease may manifest in different phenotypes such as chorea and dystonia, incoordination, impairments in cognitive performance, and behavioral problems (Walker 2007). The gene associated with HD, namely the huntingtin gene (HTT), was identified about three decades ago. Since then, substantial progress has been made in understanding the pathogenesis and neurobiology of the disease. The underlying cause of HD has been reported as the expansion of CAG trinucleotide repeats, which are located on the short arm of the 4th chromosome and encode the polyglutamine among the structure of41 HTT protein (Ross and Tabrizi 2011). The presence of 36 or more repeats of this trinucleotide is considered pathological and results in the abnormal synthesis of polyglutamine. Polyglutamine is abundant in the brain tissue but its exact function has not been fully elucidated yet (Anderson 2005). Neuropathological changes in HD tend to be clearly selective as the disease begins with cellular loss and atrophy predominantly in the caudate and putamen (Craufurd and Snowden 2002). While neurodegeneration may not be prominent in the early stages of the disease, consistent evidence has shown significant neuronal dysfunction even in the asymptomatic period. In later stages, the disease is known to cause neurodegeneration, affecting the central nervous system widely (Walker 2007).

Most HD patients have an age of onset between 35 and 45 years with a mean disease duration of 16 years. For description purposes, the disease is divided into certain stages (premanifest/presymptomatic, mild symptoms, phenotransformation/phenoconversion, and manifest/symptomatic) based on the need for assistance in maintaining daily life activities that start to occur in parallel to the decrease in independent living skills, deteriorations in motor/cognitive functions, and the presence of psychiatric symptoms (Sinanović 2020). Although the prevalence of symptomatic cases is reported as approximately 10/100,000, HD is thought to be underreported owing to the social stigma associated with this condition and the inadequate availability of genetic testing in some units or countries (Rawlins 2010). While the definitive diagnosis of HD is established by genetic testing, neuroimaging may also guide the diagnostic process. Striatal volume loss and increased volume in the frontal horn of the lateral ventricles in structural neuroimaging tests are the findings that suggest HD; however, it should be noted that such findings may not be detectable in the early stages of the disease. On the other hand, functional neuroimaging techniques may reveal impaired brain functions such as dysfunction in the lateral prefrontal and cingulate regions even before the onset of symptoms (Stober et al. 1984, Wolf et al. 2008, Paulsen 2009).

Although the clinical diagnosis of HD is essentially based on the presence of motor symptoms, cognitive dysfunction and psychiatric symptoms appear to be the most significant causes of burden on families and considered to be the major predictor of the decrease in daily life functioning, hospitalizations and referral to long-term care centers (Ross et al. 2014, Ishihara et al. 2021). Moreover, neuropsychiatric symptoms and problems such as depression, apathy, and irritability may emerge years before the onset of motor symptoms (van Duijn et al. 2007). While the etiology of these signs and symptoms remains unclear, the progressive nature of the neurodegenerative process, especially the involvement of the basal ganglia-thalamo-cortical circuit, is thought to be the underlying cause of the neuropsychiatric symptoms frequently seen in subjects with HD (Martinez-Horta et al. 2016, van Duijn et al. 2007). Either before or after the onset of motor symptoms, almost all subjects with HD are expected to show changes in personality and behavior, which may also be described as hypofrontal or executive dysfunction syndrome. It should be highlighted that these signs and symptoms, which can be roughly defined as apathy, irritability, impulsivity, and obsessiveness, consequently have negative effects on marital life, social life, and financial well-being (Nance et al. 2011, Ishihara et al. 2021).

Currently, there is no cure or treatment option to reverse or halt the degenerative process in HD but this should not lead to an incorrect perception or misunderstanding that the neuropsychiatric symptoms and impairment in HD cannot be treated. In fact, clinical experience has shown that there are treatment options that may alleviate the neuropsychiatric symptoms and impairment associated with HD. These options have been included in relevant guidelines based mainly on expert opinions in the literature (Anderson et al. 2018).

The present article aims to review the studies on the epidemiology, phenomenology, and treatment of neuropsychiatric symptoms that may occur before and after the onset of motor symptoms in HD in order to provide a guide for clinicians in this field. For this purpose, this article discusses neuropsychiatric symptoms and disorders from general to common ones under relevant subtitles such as apathy, depression, irritability, impulsivity, anxiety, suicide, obsessions, psychosis etc.

Neuropsychiatric Disorders in Huntington Disorder

Historical data and body of knowledge on HD show that hereditary chorea cases were first described by John Eliotson in 1932. The first written text concerning HD was penned by Charles Waters in 1942. The symptoms and clinical course of the disease were fully described by George Huntington in 1872 and the disease was initially named Huntington's Chorea. However, the neuropsychiatric signs in addition to motor symptoms in HD were subsequently noted. After it has been reported that this condition creates "a predisposition to a kind of insanity that eventually leads to suicide", the disease has been referred to as HD in the literature starting from the 1980s (Bhattacharyya 2016).

Behavioral and psychiatric signs and symptoms of HD (also defined as prodromal symptoms) that often precede motor symptoms received attention early after the disease was first

described. The lifetime prevalence of psychiatric disorders in subjects with HD has been reported to range from 33% to 76% (van Duijn et al. 2007, Paoli et al. 2017, Sinanović 2020). In a cross-sectional observational study evaluating patients in symptomatic and presymptomatic periods (i.e. before the onset of motor symptoms), 98% of patients with HD were found to have at least one neuropsychiatric symptom (Paulsen et al. 2001). A recent study included 144 HD cases registered in a tertiary healthcare center. The study reported that 17 of the cases (11.8%) died during the cross-sectional evaluation and 3 of these 17 deaths were due to suicide. Furthermore, of the cases undergoing face to face evaluations (n=81), 91% had a psychiatric disorder with suicidal tendency noted in 21% (Ratna et al. 2020). Differences in prevalence rates may arise from methodological differences (some studies evaluate presymptomatic groups while others focus on symptomatic or mixed groups in terms of motor symptoms) and the use of different tools (interview-based assessments, rating scales, or self-reported scales) in studies that evaluate and detect psychiatric disorders (Paoli et al. 2017, Sinanović 2020). Although the transition from one psychiatric disorder to another is not uncommon in the clinical course, the following factors are considered confounding factors including the strict diagnostic criteria employed in psychiatric evaluation and diagnosis, accompanying physical symptoms, cognitive impairment, communication problems, and making the diagnosis based on information obtained from the patient's relatives and/or friends (Reedeker et al. 2012a).

The high incidence rates of neuropsychiatric disorders in HD may be attributed to the progressive neurodegenerative nature of this condition; however, in the retrospective observational study of Ishihara et al. (2021) evaluating 587 cases diagnosed with HD and Parkinson's Disease (PD) versus a matched control group without any neurodegenerative diseases, HD cases were found to be at a higher risk of several psychiatric symptoms and disorders compared to PD cases and the control cases. The average frequency of antidepressant use was 59.9% and the frequency of antipsychotic use was 39.5% in cases with HD, with figures increasing even further in those aged 50 years and above. In a study investigating at-risk subjects (n:254), who had a parent with a confirmed diagnosis of HD, the participants were divided into 4 groups. Group 1 consisted of subjects with a genetic risk for HD but these persons were not found to be carriers of mutant genes (<32 CAG repeats) in the genetic analysis (n:171). Group 2 consisted of preclinical cases with ≥38 CAG repeats but these persons had no motor symptoms (n:29). Group 3 consisted of those with ≥38 CAG repeats and motor symptoms potentially attributable to HD (n:20). Finally, Group 4 consisted of cases with ≥38 CAG repeats and motor symptoms definitely associated with HD (n: 34) (Marshall et al. 2007). This study is of importance because of the following factors including that all the at-risk subjects included in the study were raised in a similar environment with a parent with HD, the groups were comparable in terms of characteristics such as age, gender, and education levels, and that the investigators were blinded to genetic test results of the cases during the evaluations. Marshall et al. (2007) reported that neuropsychiatric symptoms and depression were significantly more common in the other three groups compared to Group 1. This study is valuable as it shows that the onset of psychiatric symptoms precedes the onset of motor symptoms and that these symptoms are more common in mutant gene carriers even if they are raised in the same environment under similar conditions. Furthermore, the study is important because it highlights the neurobiological background of neuropsychiatric symptoms in HD. The effects of neuropsychiatric symptoms on functionality were evaluated with semi-structured interview tools in a qualitative designed study on patients in the early stage of HD and their families. That study revealed that neuropsychiatric symptoms affected both physical and cognitive functions and social functionality, acted on activities of daily living unfavorably, and caused social withdrawal. On the other hand, interventions for neuropsychiatric symptoms were reported to improve functionality (Gibson et al. 2022).

Looking at the historical background of HD, one may see that the earlier descriptions of the condition were made on the basis of motor symptoms. Then, cognitive disorders have started to be discussed considerably. It occurred later in the process that psychiatric symptoms have been detected and included in the literature. In this context, neuropsychiatric problems should be considered the core symptoms of HD, as is the case with motor symptoms, rather than being addressed as psychiatric symptoms accompanying HD. Starting from the time of the diagnosis or if possible even earlier, from the evaluation of subjects with genetic risks, the most appropriate method is clearly to ensure teamwork across specialists from neurology, psychiatry, and genetics as well as psychologists and social workers to follow up patients.

A wide spectrum of motor symptoms is commonly observed and well-established in HD, with chorea being the most common motor sign in this spectrum. For treatment, tetrabenazine is recommended in the absence of concurrent depression or suicidal ideation, whereas second-generation antipsychotics are recommended with high-level evidence for the first-line treatment in the presence of accompanying behavioral problems and psychotic symptoms (Bachoud-Lévi et al. 2019). Despite the limited number of studies providing high-level evidence for the treatment of neuropsychiatric symptoms and disorders, there are studies with lower levels of evidence, case reports, and various guidelines based on expert opinions in the literature (Anderson et al. 2018, Loi et al. 2018, Bachoud-Lévi et al. 2019, Stahl and Feigin 2020). Recommendations for the treatment of neuropsychiatric disorders in HD will be discussed separately for each disorder or symptom in light of these guidelines and studies.

Mood Disorders

Depressive symptoms are reported to be one of the most common psychiatric issues encountered in individuals with HD (Morris 1991). While the prevalence of depression in HD has been reported in a wide range of 9-63% across different studies, most studies indicate that depression may be expected in approximately 50% of these patients at any stage of the disease (Paoli et al.

2017). In a study evaluating patients in the presymptomatic period, those in the stage immediately before the symptomatic period and those in the early-symptomatic period, Martinez-Horta et al. (2016) attempted to compare the estimated relative risks (odds ratio) of neuropsychiatric symptoms against a healthy control group. They reported depression in 65% of the cases in the early-symptomatic period. The same study reported that the prevalence of depression did not differ between different stages of HD although other studies reported that depression in HD may be associated with neurodegeneration (Slaughter et al. 2001) and early cellular loss in the medial caudate, which has connections with limbic structures (Gubert et al. 2020). Therefore, this result has been interpreted as that depression may not be associated with only progressive neuropathology. Growing up with a parent affected by a genetic disease negatively affects mental health in adulthood (van der Meer et al. 2014); furthermore, the uncertainty about symptoms expected to develop in the near future and witnessing the challenges in the treatment of relatives affected by the disease are of considerable importance in the development of depression (Vamos et al. 2007).

However, it would be inappropriate to interpret the depression in HD only as a reaction to a severe illness that is known to eventually develop in the future. It is known that mutant gene carriers suffer from depression more commonly than those, who are at risk but not mutant gene carriers. Therefore, it would be more appropriate to explain the high prevalence of depression in HD through a biological predisposition associated with both psychological and psychosocial factors (Goh et al. 2018). Depression is known to be one of the earliest symptoms of HD and is also considered among the core symptoms of this condition (Paoli et al. 2017, Paulsen et al. 2017). While reports indicate that depression in HD negatively affects cognitive skills, the prevalence tends to decrease in advanced stages of the disease, probably with reduced awareness of the condition in patients with severe cognitive impairment (Craufurd et al. 2001). Depressive symptoms are most commonly reported in the second stage of HD, with a prevalence gradually decreasing in advanced stages. The prevalence has been reported to be unrelated to the length of CAG repeats (van Duijn et al. 2014). Unlike depression seen in the general population, there is often not a significant difference between the genders in terms of the prevalence of depression in HD (Eddy et al. 2016). The age at the onset of depression is reported to be approximately 14 years earlier in those with HD than that in the general population (Paoli et al. 2017). It may prove to be challenging to diagnose depression due to some common symptom clusters that are found in HD, such as weight loss, decreased activity, and apathy (Eddy et al. 2016).

Depression should be invariably treated because it has unfavorable effects on the quality of life and functionality (Gibson et al. 2021, Ready et al. 2008) and it increases the risk of suicide (Kachian et al. 2019) in carriers of the mutant HD gene. Currently, there are no randomized controlled trials or meta-analyses about the treatment of depression in HD to provide a high level of evidence. Treatment recommendations are based on publications with a lower level of evidence such as case-control studies case series/reports and expert opinions. Psychotherapy may be an appropriate option in the presence of mild depression without concurrent cognitive impairment (Stahl et al. 2020). It has been reported that psychoeducation elaborated through cognitive behavioral therapy (CBT) techniques, has a positive effect on depression, anxiety, and coping skills in symptomatic and presymptomatic cases (n:41) (A'Campo et al. 2012). A case report of a symptomatic patient undergoing CBT reported that symptoms of moderate depression and anxiety decreased to the minimum level and the well-being was maintained during the follow-up of 6 months (Silver 2003). Recommended medical treatment includes selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitors (SNRI), and, in cases with sleep disturbances, mianserin or mirtazapine. In the presence of recurrent depression, mood stabilizing agents can be used in addition to antidepressants. In the event that depression is suspected to be a side effect of another drug, for example tetrabenazine, gradually reducing the dose of the culprit drug may be a good option. (Bachoud-Lévi et al. 2019). Electroconvulsive therapy should definitely be considered as an option in the presence of severe depression; which is resistant to medical treatment, associated with a high risk of suicide, or accompanied by psychotic symptoms (Adrissi et al. 2019, Stahl et al. 2020, Bachoud-Lévi et al. 2019).

Although depression is the most common psychiatric diagnosis in HD, it has been reported that mania characterized by elevated or irritable mood, impulsivity, agitation, decreased need for sleep, and grandiosity occurs much less commonly (Paoli et al. 2017). Of note, the prevalence of syndromes in the bipolar spectrum has been reported in the range of 5-10% in HD across studies using different diagnostic criteria. One should also bear in mind that the symptoms of personality changes such as disinhibition, irritability, and jocosity, which may suggest and can be misdiagnosed as a manic episode, may be common in HD even in presymptomatic patients (Goh et al. 2018). Treatment recommendations for manic episodes in HD are based on expert opinions referring to standard treatments. It is reported that mood stabilizers such as valproate and carbamazepine can be used in the treatment (Loi et al. 2018). Both lithium and valproate can be used in HD because of their neuroprotective and mood-regulating effects (not only for mania but also for other symptom clusters including disinhibition and irritability) (Scheuing et al. 2014). In a case series reported by Danivas et al. (2013), low-dose lithium (300mg/day) was initiated adjunctive to carbamazepine in cases with chorea and mood-related symptoms including irritability and aggression. The study reported stabilization of progressive chorea symptoms and alleviation of mood-related symptoms. In light of all these data, valproate, lithium, or carbamazepine can be considered for the treatment of comorbid HD and mania as options to be administered according to the standard usage principles.

Apathy

Apathy can be defined as a decrease in the level of consciousness and decreased motivation that is not related to cognitive impairment

and emotional stress. While it may be difficult to distinguish certain symptoms of apathy from those of depression, one should note that apathy is a different and separate condition from depression (Levy et al. 1998). Common features of depression and apathy include lack of interest, loss of enthusiasm, psychomotor retardation, a decline in energy, and amotivation. However, poor motivation not accompanied by sadness, dysphoria, and vegetative symptoms (e.g. insomnia, fatigue, lack of attention) should primarily suggest apathy (Goh et al. 2018). Apathy is one of the most common neuropsychiatric manifestations of HD (Camacho et al. 2018). Studies report prevalence rates in the ranges of 11-64% and 47-76% in the presymptomatic and symptomatic periods, respectively (Martinez-Horta et al. 2016, Paulsen et al. 2001). Apathy is considered an important predictor of conversion to the HD phenotype and disease progression and reported to be associated with global and executive cognitive performance (Goh et al. 2018). In a study conducted by Martinez Horta et al. (2016), the frequency of apathy was found to be 32% in mutant gene carriers long before the symptomatic stage and 62% in those in the early stage of HD. Reports have shown that the likelihood of apathy is 15-88 times higher in patients with presymptomatic HD compared to healthy controls. This risk increases as patients approach the symptomatic stage. Furthermore, the risk and the severity of apathy are higher in symptomatic HD patients compared to presymptomatic cases. Apathy is closely related to progressive neurodegeneration, which is a hallmark characteristic of the disease (Martinez Horta et al. 2016). It has been reported that mutant gene carriers with apathy symptoms are mostly males, have low general functionality, and use benzodiazepines and neuroleptics more compared to those without apathy; however, further studies are warranted to show whether such medications are the actual causes of apathy (Eddy et al. 2016, van Duijn et al. 2010).

Because apathy is a syndrome associated with reduced purposeful movements along with impaired cognitive skills and reduced emotions, it leads to a significant decrease in activities of daily living and a significant increase in caregiver burden independent of the loss of motor and cognitive skills (Camacho et al. 2018). Symptoms of apathy tend to worsen after they are detected. Such symptoms are most commonly seen at the last stage of the disease, where they are observed in the most severe forms (van Duijn et al. 2014, Paoli et al. 2017). The decline in cognitive and functional skills is more rapid in HD patients with apathy compared to those without (Paoli et al. 2017). Considering the magnitude of the effect of apathy on the quality of life of patients and their caregivers and considering the process leading to institutional care, the treatment of apathy as a core symptom of HD becomes even more important (Camacho et al. 2018).

Despite being a core symptom of HD and a cluster of symptoms with a substantial impact on functionality and caregiver burden, apathy remains an understudied field. It is known that motivational disorders including apathy may arise from damage to the circuits between the anterior cingulate-subcortical regions and impaired functional connectivity between the basal ganglia and the dorsolateral, orbitomedial, and dorsomedial portions of the prefrontal cortex (Boyle et al. 2003, Goh et al. 2018). However, apathy in HD cannot be effectively treated because of the poor insight into its specific etiology and pathophysiology. Although the following are not completely successful therapy methods, recommended interventions include personalized cognitive stimulation, selection of routine activities to be performed, and daily activity schedules (Bachoud-Lévi et al 2019). In the case series reported by A'Campo et al. (2012), six HD cases in the symptomatic stage were included and underwent remotivation therapy for apathy. Improvements in interest, awareness, attention, frustration tolerance, reading skills, and verbal communication were reported as results of this approach. Moreover, in the event that apathy is thought to be associated with drugs used for other symptoms (e.g. antipsychotics), dose reductions may be considered for relevant drugs. The presence of concomitant depression that may lead to apathy should be evaluated, and if present, treated adequately. In cases, where depression and apathy cannot be distinguished, antidepressant therapy can be attempted (Anderson et al. 2018). In the case series reported by Strassburger et al. (2008), treatment with bupropion at a dose of 300mg/day for 3 months resulted in improvement in apathy symptoms in one of seven patients. Although studies on methylphenidate, atomoxetine, modafinil, amantadine, and bromocriptine have not provided promising results (Eddy et al. 2016), antidepressants with activating characteristics or stimulants may be therapeutic options in apathetic cases without depression. However, caution should be exercised regarding potential side effects of such agents such as sleep disturbances or increased irritability (Anderson et al. 2018). Furthermore, it should be remembered that these recommendations are not based on randomized controlled studies but expert opinions.

Anxiety

Although anxiety symptoms are common in HD, the relationship between HD and anxiety is one of the less studied fields among the neuropsychiatric aspects of HD. The prevalence of anxiety in symptomatic HD cases is reported in a wide range of 34-61% depending on the disease stage of the sample and the use of different tools to measure/evaluate anxiety in relevant studies (van Duijn et al. 2007). Several studies report a prevalence of 0-17% in mutant gene carriers, who are in the asymptomatic period (Dale and van Duijn 2015). In a study comparing symptomatic and presymptomatic HD cases in terms of anxiety disorders, no difference was found in the frequency of panic disorder, agoraphobia, generalized anxiety disorder, and social phobia (van Duijn et al. 2008). In studies comparing mutant gene carriers at the presymptomatic stage and noncarriers (Duff et al. 2007, Marshall et al. 2007,), it has been reported that more symptoms of anxiety were found in mutant gene carriers, suggesting that some disease-specific factors may underlie the development of anxiety in HD.

Anxiety symptoms in HD have not been associated with age, gender, number of CAG repeats, motor functionality, cognitive skills, apathy, and disease duration/progression (Dale and van Duijn 2015). However, some studies have reported that anxiety

is associated with depression, agitation, and irritability (Paulsen et al. 2001, Nimmagadda et al. 2011). It is noteworthy that these studies have reported mixed results on the relationship between anxiety and suicide. While mixed depression/anxiety was not found out to be a predictor of suicide in the study on 1941 HD cases in the motor symptomatic period (Wetzel et al. 2011), a study conducted on 2106 HD mutant gene carriers reported anxiety as an independent predictor of suicidal ideation; however, the latter also reported that anxiety did not remain as a predictor after 4 years of follow-up (Hubers et al. 2013). In a study reporting that disease perception and coping skills are associated with anxiety, it was found out that a high perception of the disease identity and a low level of trust in treatment were associated with anxiety and that poor coping skills such as difficulty in accepting the disease and self-blame aggravated anxiety (Arran et al. 2014).

In treatment, psychiatric and general medical comorbidities that may be associated with anxiety should be evaluated, environmental factors should be addressed, and necessary interventions should be instituted (Anderson et al. 2018). CBT and CBT-oriented psychoeducation may be effective in reducing the severity of anxiety in cases at the early stages of the disease, where cognitive dysfunction is not evident (A'Campo et al. 2012). SSRIs and SNRIs can be used when there is a comorbidity of depression and anxiety. Benzodiazepines may be used for short periods of time when anxiety is very severe, warning of the risks of falling or worsening of symptoms (Bachoud-Lévi et al 2019). It should be remembered that SSRIs, which are often recommended as the first-line therapy, may initially aggravate anxiety. Therefore, benzodiazepines can be used during the first one or two weeks of therapy. Long-term benzodiazepine therapy should not be used in treating HD patients in outpatient settings unless all other treatment options fail (Anderson et al. 2018). In the event that there is no response to an SSRI, another SSRI or an SNRI may be used. If there are accompanying obsessive symptoms, clomipramine may be an option. Further options include mirtazapine and olanzapine. Mirtazapine can be used in cases with insomnia and olanzapine (Squitieri et al. 2001) can be used in patients with chorea symptoms and when other treatment options fail (Anderson et al. 2018).

The coexistence of HD and anxiety stands out as an open field for research. Currently, the extent of the contribution of each of the following factors including (epi)genetics, the biological nature of the disease, and familial and psychological factors to the development of anxiety is not known. It is clearly understood that there is a need for studies with high statistical power to investigate both pharmacological and psychotherapeutic approaches in treatment.

Suicide

The increased risk of suicide in HD had already been noted by George Huntington, whom the disease was named after and who defined "predisposition to insanity and suicide" as one of the characteristics of the disease (Huntington 1872). A study evaluated the rates of suicidal ideation, suicide attempts, and suicides in HD in the United States (USA) and in the global population (Kachian et al. 2019) and reported the rate of suicidal ideation in HD as 20-30%, the rate of suicide attempts as 7-10%, and the rate of suicides as 4.8-6.6%, with corresponding rates as 8-24.9%, 1.3-3.5%, and 1.5% in the USA population and 5.6-14.3%, 1.9-8.7%, and 1.4% in the global population, respectively (Nock et al. 2008). In a recent study on suicide in frontotemporal dementia (FTD) and HD, 267 subjects diagnosed with FTD or HD from 106 families were included, and completed suicide was reported in 7 out of 160 patients with a diagnosis of HD (6 out of 59 families). The rate of suicide was 4,375/100,000 in the HD subgroup and 934/100,000 in the FTD subgroup and the rate was reported as 10/100,000 in the Australian population (Sexton et al. 2020). The risk of death by suicide was estimated to be 400 times higher in the HD group compared to the general population. The mean age at the time of suicide was reported as 52.5 (35-73) years. In the same study, suicide was observed in 1 out of 15 families (in FTD and HD families) and suicidal ideations, suicide attempts or suicides were reported in 1 out of 5 families –in one or more of the genetically affected, unaffected, or presymptomatic family members. This rate was found to be higher, i.e. up to 30% in families with HD (Sexton et al. 2020). Although different rates have been obtained through the evaluation of patients in different stages of the disease by the use of different assessment tools across the studies, it is generally thought that the mean prevalence of suicidal ideation is 20% in HD (Honrath et al. 2018). The rate of suicide attempts is often reported as 7% (van Duijn et al. 2014, van Duijn et al. 2018). In a large-scale study conducted by Rodrigues et al. (2017) (n: 5,164), the rate of completed suicides was found to be 6.6%. Although different rates have been reported across several studies, it is clear that suicides, suicidal ideations, and suicide attempts are more common in patients with HD compared to the general population and even compared to those with other chronic neurodegenerative diseases (Ishihara et al. 2021). These findings should be kept in mind and patients should be inquired about the presence of such symptoms and events in the follow-up.

Another important question is in which HD cases suicide tends to be more common. Studies about the question of whether gender is a risk factor have reported conflicting results. In addition to studies reporting that male gender is a risk factor for suicide (Solberg et al. 2018) and female gender is a risk factor for suicidal ideations and suicidal behaviors (Fiedorowicz et al. 2011, Wesson et al. 2018), there are other studies reporting that gender is not a risk factor for suicide and related conditions (van Duijn et al. 2018). Depression and irritability are clinical characteristics found to be associated with suicidal ideation and behavior (van Duijn et al. 2018). Other risk factors may include anxiety, hopelessness, and aggression (Anderson et al. 2016), a previous history of a suicide attempt (Fiedorowicz et al. 2011, Anderson et al. 2016), and the use of antidepressants and benzodiazepines (Hubers et al. 2013). Alcohol/substance abuse has been associated with the severity of suicidal ideation (Wetzel et al. 2011). There is a lack of a relationship between the number of CAG repeats in the mutant gene and suicidal behavior (Hubers et al. 2013).

However, data is available showing that the stage of the disease and different aspects of suicidal behavior may be related. In a study, Paulsen et al. (2005) evaluated the risk of suicide according to HD stages by using the Huntington Study Group database (n:4171). Participants were assigned to HD stages from the early stage (Stage 1) to the final stage (Stage 5). It was found out that suicidal ideation was most commonly observed in patients in Stage 2 (21.6%), where independent living skills became impaired, and that the frequency of suicidal ideation decreased in later stages of the disease. A high rate of suicidal behavior was reported at later stages (Stage 4/5) (van Duijn et al. 2018). A study about the prodromal period, described as the period preceding the motor symptomatic period, showed that suicidal ideations were common in the period, when the motor diagnostic criteria were not met but mild motor symptoms were found suggesting probable HD (Paulsen et al. 2005). Taken together, certain clinical characteristics and some critical periods and stages have been associated with suicidal ideation and behavior in HD. Therefore, it is particularly important to question suicide in patients with these characteristics.

Data on the medical treatment of suicidal ideation and behavior in HD is insufficient, however, interventions that address the underlying risk factors such as depression, social isolation, and impulsivity may be considered as effective methods in preventing suicide (Bachoud-Lévi et al 2019). One should also keep in mind that tetrabenazine, which is used in the treatment of motor symptoms of HD, may increase the risk of depression and suicide (Bayram et al. 2015). Regarding the therapeutic approach toward suicidal thoughts and behavior, mainly case reports are available in the literature. Greenberg et al. (2020) reported a case, where the patient had severe suicidal ideation, did not respond to fluoxetine, and experienced clinical deterioration with tetrabenazine. That patient was reported to respond to a combination of paroxetine and lithium therapy. Deutetrabenazine, amantadine, or riluzole, which are safer for the treatment of chorea, may be preferred when depression or suicidal ideation is noted in a patient receiving tetrabenazine. In eligible cases, clinical symptoms may be improved by adding antidepressants to tetrabenazine regimens (Greenberg et al. 2020, Bayram et al. 2015). Since depression is the strongest predictor of suicide in HD (van Duijn et al. 2018), it would not be incorrect to conclude that recognizing and treating depression is the most important intervention to prevent suicide.

Irritability, Aggression, Impulsivity

Irritability refers to a mood that is subjectively unpleasant and leading to the development of negative emotions in interpersonal relationships. Irritability can be described as a tendency to develop certain emotions (e.g. rage), certain cognitions (e.g. hostile attribution bias), and certain actions (e.g. aggression). In summary, it is a trait that predisposes to develop anger (Craig et al. 2008). It is clinically manifested in sudden and unpredictable outbursts of anger. Neurobiological mechanisms (degeneration in the striatum and orbitofrontal-subcortical circuits) of HD are thought to be responsible for the etiology along with psychological causes such as cognitive overload resulting from progressive cognitive decline (Karagas et al. 2020). Irritability is mostly reported by families. Patients may not always be aware of their irritability even at stages when their cognitive skills are not considerably affected (Chatterjee et al. 2005). Furthermore, irritability, which may result in intense outbursts of anger and aggressive behavior, can negatively affect interpersonal relationships, weaken the patient's social support, and lead to adverse consequences such as divorce and even being taken into custody (Karagas et al. 2020). In an article, Chu et al. (2019) reported three female patients, who were carriers of the mutant gene for HD and who were taken into custody for different crimes in the period before the onset of motor symptoms. That article has highlighted the potential consequences of disease-related irritability before the occurrence of typical neurological, cognitive, or psychiatric symptoms.

Irritability is often described as the first sign of the disease before the motor symptomatic period (van Duijn et al. 2008). The prevalence of irritability is reported in the range of 35-73% in HD (Paoli et al. 2017). It has been established that irritability may not be the first symptom in every patient, that it may occur at any stage of the disease despite being more common in patients with motor neurological symptoms, and that the incidence and severity of irritability tend to increase with disease progression (Thompson et al. 2012). Irritability, impulsivity, and aggression are considered interrelated clinical manifestations. The prevalence of aggression in HD was reported in the range of 22-66% (Goh et al. 2018). The reported wide ranges of prevalence appear to be related to the use of different measurement tools and cut-off values, and the non-uniform characteristics of samples across several studies. In a follow-up study conducted on subjects at risk for being carriers of HD mutant genes, participants were followed up for an approximate study duration of 4 years. Genetic testing was performed, and researchers were blinded to the genetic test results. Findings of this study showed that irritability and hostility became significantly worse in mutant gene carriers during the follow-up and this increase was not associated with the number of CAG repeats (Kirkwood et al. 2002). In a study by Reedeker et al. (2012b), the number of CAG repeats was found to be associated with irritability. In the same study, being married/living with a partner and using benzodiazepines were also observed to be associated with irritability (Reedeker et al. 2012b). Van Duijn et al. (2014) reported that irritability/aggression is associated with male gender, young age, depression, psychosis, and history of attempted suicide. When the incidence and outcomes of irritability and aggression in HD are evaluated, it is undeniable that they affect the quality of life unfavorably both for patients and their families, act as an important stress factor, and increase the need for professional care (Reedeker et al. 2012b). Therefore, one may conclude that the recognition and treatment of such symptoms are considerably important.

Currently, there is no special treatment that is approved for the treatment of irritability in HD; however, there are some treatment algorithms recommended by clinicians working in this field. These recommendations are predominantly based on expert opinions (Groves et al. 2011). Environmental factors

that may cause irritability or frustration should be evaluated (such as factors that may cause excessive stimulation, e.g., pain, excessive noise, unmet needs, and medication side effects such as akathisia) before initiating pharmacological treatment. The recommendations to alleviate irritability primarily focus on behavioral methods. A quiet environment should be maintained and the patient should have a daily routine to be followed regularly. Caregivers should be trained via psychoeducation in strategies to switch the patient's attention from one stimulus to the other. Confrontations should be avoided as much as possible (Bachoud-Lévi et al 2019). Mostly, SSRIs are recommended as the first-line therapy for irritability (Groves et al. 2011, Bachoud-Lévi et al. 2019). There are no recommendations on which SSRI should be selected. It has been reported that the dose of the selected medicine should be increased up to the highest recommended dose. In the absence of an adequate response to SSRI therapy, mirtazapine or mianserin may be added to the treatment, especially in patients with insomnia (Bachoud-Lévi et al. 2019). Second-generation antipsychotics are often preferred as second-line agents but used as the treatment of first choice in the following cases, where the patient does not respond to SSRI therapy or where comorbid psychosis, marked aggression, prominent impulsivity, or hypersexuality was detected (Groves et al. 2011). Moreover, it is noted that antidopaminergic agents are effective in the treatment of chorea and irritability but augment the cognitive decline (Harris et al. 2020). Antiepileptic agents used as mood stabilizers are often preferred in the third line and recommended to be used alone or in combination therapy when there is no adequate response to antidepressants or antipsychotics (Bachoud-Lévi et al 2019). In general, benzodiazepines are not preferred to be used alone (due to risks of developing tolerance, dependence, and the risk of falls) and are often administered as short-term add-on therapy in the event of partial response to other treatments (Groves et al. 2011). Agitation is another symptom that may be observed in HD but it is quite different from irritability. Benzodiazepines and antipsychotics are recommended for the first-line treatment of acute agitation, while antipsychotics and mood stabilizer antiepileptics are primarily recommended in cases of chronic agitation and risk of harming oneself/others (Rossi and Oh 2020).

Obsessiveness/Perseveration

When evaluated independently of strict diagnostic criteria, the prevalence of obsessive and compulsive symptoms in HD is reported in the range of 20-50%, which is considerably higher than that in the general population (Goh et al. 2018). Perseverations are defined as the uncontrolled repetition or continuation of a response (such as motor behavior, a word, a piece of thought, activity, strategy, or emotion) regardless of the underlying cause or context. Unlike obsessive and compulsive symptoms, the individual is generally unaware of this behavior or lacks insight. Perseverations are often not annoying for the individual (Serpell et al. 2009). It is reported that perseveration and obsessive-compulsive symptoms arise from a similar neurobiological background in HD, in which cortico-striatal circuits are affected and that such symptoms may be evaluated in the same spectrum. Cognitive flexibility loss, which is known to begin long before the onset of motor symptoms and evaluated in the spectrum of personality changes, is reported to be the precursor of these two clinical phenomena (Paoli et al. 2017). Perseverative behavior is more common in HD, with reported rates of up to 75% (Oosterloo et al. 2019). Compared to the general population, obsessive and compulsive symptoms are more common not only in patients with motor symptoms but also in mutant gene carriers before the onset of motor symptoms (van Duijn et al. 2008). In a study by Beglinger et al. (2008), the proximity to the age of onset was estimated based on the number of CAG repeats in mutant gene carriers in the presymptomatic period. The findings showed an increased rate of obsessive and compulsive symptoms with increasing proximity to the onset of the disease (here, the onset of motor symptoms).

Aggression-related and contamination-related obsessions and control rituals were observed most commonly (Goh et al. 2018). The study conducted by van Duijn et al. (2014) reported that the prevalence of perseverative/obsessional thinking and compulsive behavior increased with disease progression. The prevalence was reported as 4.5% at the first stage and as high as 25% at the third stage of the disease. In the same study, patients with obsessive/compulsive symptoms and perseverative behavior were found to have longer disease duration, they more commonly had history of psychiatric disorders such as depression or psychosis, and they more commonly received treatment with psychiatric drugs compared to patients having no such symptoms (van Duijn et al. 2014). Taken together, obsessive/compulsive symptoms and perseverative behavior become more common and severe through the progression of the disease, with greater severity of impairment observed in executive functions of these patients in addition to a lower level of functionality (Oosterloo et al. 2019).

Taking into account the prevalence of obsessive/compulsive symptoms and the burden of this comorbidity in HD, the treatment becomes considerably important both for patients and caregivers. However, as is the case in any other neuropsychiatric disorder, there are no evidence-based guidelines for the treatment of these symptoms in HD, while case reports/series with lower levels of evidence and algorithms based on expert opinions are available. For the treatment of both obsessive and compulsive symptoms and perseverative behavior, especially in patients with predominant anxiety, SSRIs are recommended in the first line (clomipramine, a tricyclic antidepressant, is also included in this group quite often), whereas olanzapine and risperidone are recommended in perseveration-based thoughts accompanied by irritability (Eddy et al. 2016, Bachoud-Lévi et al. 2019). Cognitive behavioral therapy is another option for cases with relatively preserved cognitive skills (Bachoud-Lévi et al 2019).

Psychosis

Psychotic symptoms are less common in HD compared to other neuropsychiatric conditions, with a reported prevalence of 3-11% (van Duijn et al. 2008). The point prevalence rates of delusions

Table 1. Treatment of common neuropsychiatric disorders in Huntington's Disease

Symptom Area	Treatment	Recommendations	Warnings
Mood Disorders	CBT and psychoeducation SSRI SNRI NASSA MS ECT	CBT in mild/moderate depression and concurrent anxiety without cognitive impairment, Mianserin/mirtazapine in cases with concurrent sleep disturbance, Adding MS to treatment in the presence of recurrent depression, ECT in treatment-resistant cases and in the presence of suicide risk/psychotic symptoms, A standard approach (valproate, carbamazepine, lithium) is recommended in the presence of mania.	In tetrabenazine-induced depression, the dose of tetrabenazine can be reduced gradually or tetrabenazine can be discontinued based on the risk-benefit estimation.
Apathy	There is no drug recommendation that directly aims to treat the symptom.	Personalized cognitive stimulation, Setting routines, To structure daily life activities within a schedule, Activating ADs/stimulants are recommended.	If considered to be associated with antipsychotics, reducing the AP dose, Adding an AD is recommended in depression-induced apathy or when depression-apathy cannot be differentiated.
Anxiety	CBT SSRI (first choice) SNRI BZD TCA NASSA AP	CBT in anxiety without concurrent cognitive impairment, Short-term BZD in the presence of severe anxiety, warnings should be provided against the risk of falls, Clomipramine in the presence of concurrent obsessive symptoms, Mirtazapine in the presence of concurrent insomnia, Olanzapine is recommended if other options fail in cases with chorea symptoms.	In the event of failure with an SSRI, another SSRI may be used again as a second option or ano SNRI can be used as the second option. Long-term use of BZDs should be avoided due to the risk of side effects and falls.
Suicide	There is no drug recommendation that directly aims to treat the symptom.	Intervention for risk factors such as depression, social isolation, and impulsivity is recommended. It is highly important to recognize and treat depression because it is the most important one among these risk factors.	It should be taken into account that tetrabenazine may increase the risk of suicide.
Irritability Aggression Impulsivity	Behavioral methods SSRI (first choice) NASSA Second-generation AP (second choice) MS (third choice) BZD	For behavioral approach recommendations, see the text. Increasing the SSRI dose to high doses, if necessary, Mianserin/mirtazapine in the presence of insomnia, A second-generation AP is the first choice in cases with predominant psychosis, aggression, impulsivity, and hypersexuality, MSs alone or in combination with an AD/AP, BZDs or APs are recommended as the treatment of first choice in acute agitation; MSs or APs in chronic agitation.	Environmental factors that may cause irritability (such as pain, excessive noise, unmet needs, drug-induced akathisia) must be addressed
Obsessiveness Perseveration	SSRI TCA AP CBT	CBT in cases with relatively preserved cognitive skills, SSRI or clomipramine as first choice, Olanzapine or risperidone is recommended in the presence of irritability and mental perseveration.	
Psychosis	AP ECT	Second-generation APs are preferred in the first line. Clozapine is recommended as the first choice in resistant or akinetic HD cases. ECT should be considered as an option in patients without response to treatment.	Differential diagnosis should include medical conditions that may cause the acute onset of symptoms. It should be noted that perseverative thoughts can mimic psychosis.
Sleep Disturbance	Modafinil Melatonin Melatonin receptor agonists NASSA TCA Second generation AP BZD	Interventions for sleep hygiene, Modafinil in case of excessive sleepiness, Melatonin, agomelatine or ramelteon in case of insomnia, Or ADs with hypnotic effects such as mirtazapine/trazodone, Clomipramine in the presence of concurrent obsessive symptoms, Olanzapine or quetiapine when an AP is to be selected, BZDs are recommended when all other options fail.	It should be evaluated whether it is secondary to motor symptoms or to restless legs syndrome. BZDs should be the last choice due to the risk of falls.

Table 1 (Continued). Treatment of common neuropsychiatric disorders in Huntington's Disease			
Symptom Area	**Treatment**	**Recommendations**	**Warnings**
Sexual Dysfunction	AP Sexual therapy/ Psychoeducation	Haloperidol/olanzapine in the presence of hypersexual behavior General treatment principles and psychoeducation are recommended in the presence of hyposexual behavior.	

CBT: Cognitive Behavioral Therapy, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin Noradrenaline Reuptake Inhibitor, NASSA: Noradrenergic and Specific Serotoninergic Antidepressants, MS: Mood Stabilizer, ECT: Electroconvulsive Therapy, AP: Antipsychotic, AD: Antidepressant, BZD: Benzodiazepine, TCA: Tricyclic Antidepressant

and hallucinations in patients with HD have been reported to be 10-11.5% and 1.9-3%, respectively (Paulsen et al. 2001, Thompson et al. 2012). In a study conducted by Jaini et al. (2020), 7,966 patients, who were diagnosed with HD and who were in the motor symptomatic period were evaluated. It was found out that 12.95% of the patients had a history of psychotic symptoms, the mean age at the onset of psychosis was 48 years, motor symptoms of HD coincided with the age of this onset, and that history of psychosis was detected in 23.6% of first-degree relatives of the patients. The same study also reported that low education levels, unemployment, being single, depression, decrease in verbal fluency, and decrease in total functionality were all associated with psychosis. In a large-scale European cohort study conducted by van Duijn et al. (2014), psychosis was reported to occur most commonly at the third stage of the disease. Furthermore, it has been suggested that psychotic symptoms may decrease with disease progression and progressing cognitive decline (Goh et al. 2018). However, another study reported that psychotic symptoms may occur before the onset of motor symptoms (Kar et al. 2017). In a study comparing presymptomatic and symptomatic HD cases with controls, who were not mutant gene carriers but had parents diagnosed with HD, paranoid thought and psychoticism scores of mutant gene carriers -both at clinical and preclinical stages in terms of motor symptoms- were found to be significantly higher compared to controls (Marshall et al. 2007). Psychosis preceding motor symptoms is often interpreted as a predictor of the onset of motor symptoms (van Duijn et al. 2007). Until the first half of the twentieth century, patients with HD were often misdiagnosed as dementia praecox or schizophrenia. No distinctive features have been described for psychosis in HD to make a clinical differential diagnosis from non-organic psychosis. Persecution delusions are reported as the most common delusions. It is suggested that the reason for the low prevalence of psychosis in HD, even today, may be the use of antipsychotics widely for the treatment of concurrent movement disorders (Paoli et al. 2017, Goh et al. 2018).

In a 5-year follow-up study (n: 1082) conducted by Connors et al. (2020), patients who had HD with and without psychosis were compared. The study reported that 17.6% of the patients experienced psychotic symptoms during these 5 years, that the cognitive skills and functionality of the patients with psychosis were worse, and that the patients in this group experienced behavioral problems more. It has been reported that psychosis in HD may cluster in families and both motor symptoms and psychosis tend to emerge at a younger age as the number of CAG repeats increases (Tsuang et al. 2000). Chorea was found to be less common in HD patients with psychosis compared to those without psychosis. That difference persisted even when the groups were matched for antipsychotic and tetrabenazine use (Connors et al. 2020). Although these findings indicate a psychotic endophenotype with a distinct genetic background in HD, a genetic characteristic that distinguishes these patients has not been identified to date.

HD cases accompanied by psychosis often require inpatient treatment, especially in psychiatry clinics. The co-existent psychosis prevents these patients from receiving at-home care (Salman et al. 2018, Ataöv et al. 2020). Once psychotic symptoms are recognized, the primary approach should be to make a differential diagnosis to exclude medical conditions (infections; metabolic, toxic, drug-related causes; substance use, and delirium) that may cause an acute onset of such symptoms (Anderson et al. 2018). Because perseverative thoughts may sometimes mimic psychotic symptoms, they should be considered in the differential diagnosis. In the presence of perseverations, the intervention should include the use of serotoninergic antidepressants, as mentioned above. In the event that psychotic symptoms such as hallucinations and delusions are present, second-generation antipsychotics would be the agents to be recommended in the first line, with the power of evidence at the level of expert opinions (Bachoud-Lévi et al. 2019). It is not recommended to exceed the maximum dose of the medications used for this purpose or use a combination of antipsychotic agents (Anderson et al. 2018). Although clozapine is often recommended for the treatment of patients, who fail to respond to other antipsychotics (Anderson et al. 2018), this antipsychotic may be preferred as a first-line option in akinetic HD patients with advanced Parkinsonian symptoms (Bachoud-Lévi et al. 2019). One should keep in mind that patients, who start receiving clozapine, should undergo complete blood counts at regular intervals and that only patients, who can adhere to the follow-up process should be treated with clozapine. Electroconvulsive therapy may be an option in cases, where pharmacological treatment proves to be insufficient (Nakano et al. 2013).

Other Psychiatric Disorders

Sleep disorders are another group of psychiatric disorders in HD. Sleep disturbances appear to be highly common in patients with HD. Approximately 90% of HD patients report sleeping disorders and half of these patients report this condition as a significant problem (Goodman and Barker 2010). Sleep disturbances may

emerge long before the onset of motor symptoms (Goodman et al. 2011). It is reported that sleep disturbances tend to increase in parallel to the exacerbation of the clinical symptoms of the disease. No correlations have been found out between sleep disturbances and the number of CAG repeats (Herzog-Krzywoszanska and Krzywoszanski 2019). Sleep disturbances can be primary or a symptom of other psychiatric disorders (e.g. depression and anxiety disorders) that are commonly seen in HD. Therefore, the evaluation of potential psychiatric disorders in the differential diagnosis of an HD patient is critical when the patient presents with the complaint of a sleep disturbance (Baker et al. 2016). In addition, motor movement disorders may also cause sleep disturbances, especially in the advanced stages of the disease (Neutel et al. 2015). It has been reported that restless legs syndrome may be more common in this patient population and that restless legs syndrome may occur even years before the onset of motor symptoms of the disease, as is the case in other neuropsychiatric disorders (Savva et al. 2009). Thus, in the differential diagnosis of sleep disturbances, it should be evaluated whether sleep disturbances are secondary to motor symptoms or whether the patient has comorbid restless legs syndrome. It should also be taken into account that sleep-related complaints, such as insomnia or excessive daytime sleepiness, may be secondary to pain or may be medication side effects (Anderson et al. 2018).

One can argue that there are no comprehensive studies about the treatment for sleep-related symptoms in HD. Recommendations in this area are mostly based on studies providing a low level of evidence and on expert opinions. In the treatment, primarily, behavioral recommendations regarding sleep hygiene should be adopted for all kinds of sleep problems (Anderson et al. 2018). Sleep hygiene rules usually include scheduling regular times for going to sleep and waking up, avoiding short naps during the day, exercising regularly during the day if possible, and avoiding excessive caffeine, smoking or alcohol consumption (Herzog-Krzywoszanska and Krzywoszanski 2019). Modafinil may be an option in the case of excessive daytime sleepiness (Blackwell et al. 2008). Melatonin is suggested to be used for the treatment of insomnia because it facilitates sleep and normalizes the circadian rhythm. Again, melatonin receptor agonists (such as ramelteon and agomelatine) may be beneficial for the treatment of insomnia (Herzog-Krzywoszanska and Krzywoszanski 2019). Sedating antidepressants such as mirtazapine and trazodone are also agents that can be used in such cases. Olanzapine or quetiapine may be preferred as antipsychotics. Clomipramine may be an option for patients with concomitant obsessive-compulsive symptoms. Because of the associated risk of falls, the use of benzodiazepines is not recommended except when there are no other options (Anderson et al. 2018).

Sexual dysfunction is another psychiatric disorder that might be encountered in HD. Although sexual dysfunction is often in the form of decreased sexual desire and inhibition of orgasm, it has been reported that paraphilic behavior may also develop in some patients (Paoli et al. 2017). In a systematic review performed by Szymus et al. (2020), the most common sexual disorders included hypoactive sexual disorder (53-83%), hyperactive sexual disorder (6-30%), erectile (48-74%) and ejaculatory (30-60%) dysfunction, lubrication problems (53-83%) and problems with orgasm (35-78%). While neurobiological mechanisms associated with HD may be involved in the etiology of such disorders, one should also take into account the side effects of drugs used in the treatment and the effects of neuropsychiatric disorders (depression, anxiety, apathy, mania, etc.) commonly seen in HD. Some data show that paraphilias are more common in male HD cases, especially those with orgasm inhibition and increased sexual desire (Fedoroff et al. 1994). Hypersexual behavior is more commonly reported in male patients (Paoli et al. 2017, Szymus et al. 2020). In a study by Kolenc et al. (2017) investigating female mutant gene carriers in the presymptomatic period, sexual dysfunction was found to be more common in this group compared to healthy controls and increased sexual dysfunction was observed in parallel to the progression of HD. It has been reported that irritability, loss of mental flexibility, and obsessive-compulsive or perseverative behaviors are associated with hypersexual behavior (Craufurd et al. 2001).

There are no guidelines on the treatment of sexual dysfunction in this setting, not even those based on expert opinions. The available evidence is limited to case reports, especially about the treatment of hypersexual behavior that has the potential to cause forensic, social, familial or societal problems. It was reported that a 30-year-old female HD patient with hypersexual behavior (a significant increase in the sexual content of speech and increased sexual behavior) was given haloperidol for motor symptoms. Because hypersexual behavior was not resolved completely, olanzapine 20mg/day was added to the treatment. It was reported that a dramatic improvement occurred in the sexual behavior of the patient then (Jhanjee et al. 2011). Considering that, especially hypersexual disorders in HD can be evaluated as behavioral problems that develop on a background of disinhibition and impulsivity (Paoli et al. 2017, Craufurd et al. 2001), antipsychotic agents may be recommended primarily for the treatment. For the treatment of hypoactive sexual disorders, general therapeutic principles applied in sexual therapy and psychoeducation appear to be the most appropriate interventions.

Individuals at Genetic Risk

Children born to patients diagnosed with HD can be defined as "individuals at genetic risk". Although those at genetic risk are important enough to be the subject matter of a separate article, addressing this group briefly has been considered necessary for the purpose of the present article because the evaluation process of these individuals is critical.

Taking into account that the disease is autosomal dominant, having a parent diagnosed with HD indicates a risk of inheriting the mutant gene with a probability of approximately 50% (Walker 2007). Considering the progressive course of the disease and the fact that currently there is no definitive treatment, this risk is quite high and poses a significant concern. Today, mutant

gene carriers of HD can be detected easily by genetic testing. Even a short search on the internet shows that there are many institutions that perform genetic tests to detect HD. However, the literature in this field strongly emphasizes that a well-designed protocol is essential to provide professional genetic counseling and that the risk of suicide among counseled individuals should always be taken into consideration (Wahlin 2007). In a 20-year-long follow-up study by Mandich et al. (2017), the tendency to undergo predictive testing was found to be greater in men compared to women and in subjects older than 25 years of age compared to those aged 18-25 years. Furthermore, factors such as having a child, relationship status, and the gender of the parent with HD appeared to affect the decision to undergo genetic testing differently in men and women. It was found out that a well-designed and structured genetic counseling protocol would be a safe approach to prevent untoward events such as suicide.

Although early studies indicate higher rates, recent reports show that only 5% of individuals at risk of HD demand and request genetic testing (Laccone et al. 1999, Walker 2007). Karabulut et al. (2000) determined that at-risk subjects have a resistance toward predictive testing and avoid talking about the effect on their life plans. The literature indicates that the motivation to undergo testing is usually based on plans related to career and starting a family, while subjects, who choose not to undergo such testing, mostly base their decisions on the unavailability of effective treatment for the disease (Walker 2007). Genetic testing protocols highlight that children (<18 years of age) and those with suicidal ideation should not be tested. Furthermore, such protocols emphasize that comprehensive information should be provided about the interpretation of test results for close family members (e.g. monozygotic twins), that it should be explored whether the individual in question has adequate support, and that strict confidentiality conditions should be maintained prior to the genetic test (Tibben 2002). When all these factors and risks are considered together, it is reported that counseling for genetic testing should be a multidisciplinary team effort and a psychiatrist or psychologist should definitely be included in this team (Groves 2017). Genetic counseling should be provided in the form of a team effort, this team should definitely include a psychiatrist or psychologist together with specialists in genetics and neurology, adequate information should be given to the individual at risk (both from the genetic and clinical points of view), the consultant should be impartial and adopt a neutral approach that neither supports nor advises against undergoing the predictive testing, and depression, hopelessness, anxiety, suicidality, and availability of social support should be addressed in the evaluation process (Wahlin 2007).

Conclusion

Although HD is clinically diagnosed based on the presence of motor symptoms; neuropsychiatric symptoms have also been underlined since the first description of the disease. The literature to date has consistently shown that neuropsychiatric symptoms and disorders emerge years before the onset of motor symptoms. It is clear that neuropsychiatric symptoms in HD should be considered as core symptoms and disorders resulting from a neurobiological background associated with HD rather than being taken as comorbid conditions or reactions to the disease. Neuropathological events caused by genetic inheritance primarily lead to neuropsychiatric symptoms, followed by manifestations in motor symptoms. Depression, anxiety, suicide, obsessive-compulsive symptoms, perseverations, irritability, apathy, psychosis, mania, sleep disturbances, disinhibition, agitation, and impaired sexual function and behavior can be listed as psychiatric signs, symptoms, and disorders, which may commonly be encountered in HD. Compared to the effect of motor symptoms, there appears to be a greater effect of neuropsychiatric symptoms leading to unfavorable outcomes such as loss of functionality in social, occupational, familial and interpersonal areas, decreases in the quality of life, and increased need for referral to residential care institutions and hospitalizations. Therefore, recognition of these signs and symptoms is highly important not only for the patients but also for the family and caregivers. Studies, case reports, and protocols are available based on expert opinions. Despite the lower levels of evidence of such publications compared to guidelines based on strong evidence, promising outcomes can be achieved through the treatment of neuropsychiatric symptoms by using appropriate interventions. However, one should keep in mind that robust studies are warranted to provide a high level of evidence, especially in the field of treatment. In addition to mutant gene carriers, at-risk individuals, too, have special importance in this setting. These individuals should be evaluated for genetic testing by a team, which should definitely include a psychiatrist or psychologist.

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