Neurodegenerative Disorders: Today and Tomorrow

Somu Singh

Abstract

In today's growing world, neurodegenerative disorders are a major concern. While not immediately destructive as diseases like cancer, these disorders slowly affect patients and really cripple their quality of lives. This review will describe three prominent neurodegenerative disorders: Alzheimer's, Parkinson's and Huntington's Disease. The aspects described will include some background information, neuroanatomy of the disorders, current treatment methods & potential future treatments. A major focus will be given to the behavioral aspects of these disorders, so as to allow the future treatment methodologies to develop a holistic approach towards their cure. Throughout the review, it was deciphered that behavioral aspects, of the disorders described, were more or less similar, with the differences in symptoms mostly involving motor impairments of Parkinson's and Huntington's. This paper is intended to serve as a basic source of information for these diseases in the development of potential treatments for these neurodegenerative disorders.

Introduction

According to Qiu et al. with the percentage of the elderly population potentially increasing worldwide from 2000 to 2030 from 7% to 12%, neurodegenerative disorders are a growing concern (2009). This paper focuses on Alzheimer's, Parkinson's, and Huntington's disease, which are some of the most common neurodegenerative disorders primarily in the elderly. Alzheimer's disease is a progressive neurodegenerative disorder appearing first as mild cognitive impairment which progresses to dementia, and is characterized by loss of memory, behavioral changes and other cognitive impairments (Terracciano & Sutin, 2019). According to Terracciano and Sutin, “Alzheimer’s disease (AD) is the most common cause of dementia and the fastest-growing leading cause of death in the United States” (2019). Parkinson’s Disease is the second most common neurodegenerative disorder affecting the aging American population (Beitz, 2014), and is characterized by progressive loss of motor functions (Lotankar et al., 2017). Huntington’s disease (HD) is a genetic neurodegenerative disease which manifests in the form of “motor symptoms, progressive cognitive decline, and psychiatric disturbance” (Karagas et al., 2020).

Alzheimer’s Disease

Epidemiology and Etiology

Alzheimer's disease (AD) is perhaps the most commonly known neurodegenerative disorder, and accounts for about "75% of all dementia cases" (Qiu et al., 2009). Pohl & Lin believe that there might be more than 100 million Alzheimer's patients worldwide, by 2050 (2018). Hence, it is important that researchers make a concerted effort to untangle this disorder. Raji et al. mention that "AD causes atrophy in allocortex and limbic areas with the mesial temporal lobe (entorhinal cortex and hippocampus) being vulnerable to atrophy in AD such that hippocampal volume decreases at a rate of 4%– 6% per year in the disorder" (2009). As patients reach old age, neurons are lost in the neocortical, hippocampal and cerebellar regions of the brain and there is also "shrinkage of neurons, and suboptimal DNA repair, leading to compromised neuronal integrity and reduction in synaptic density" (Raji et al., 2009). The existing literature indicates that the formation of Aβ amyloid plaques is due to “rare genetic mutations in the gene encoding the amyloid precursor protein” (Masters & Beyreuther, 1998). Aβ amyloid is a protein that is expressed widely in the body but is primarily found in the brain and platelets whose functions are unknown. Some mice without it have been seen to be fairly normal with their synaptic functions subtly influenced, and the mutations described earlier result in early onset of AD (Masters & Beyreuther, 1998).

Another cause of AD are the mutations in the presenilin genes, a family whose discovery has been a significant research breakthrough, and together with the mutations in the amyloid precursor protein, can cause AD at an early age (<65) (Masters & Beyreuther, 1998). Along with the mutated genes that cause the disease, another thing that is also emerging as a significant factor for “sporadic Alzheimer’s disease”, with a contribution in around “80-90% of all cases” , are the genetic risk factors (Masters & Beyreuther, 1998). For example, the inheritance of the ApoE-ε4 allele, found on the 19th chromosome, can increase the risk of AD by up to eightfold (Masters & Beyreuther, 1998). Environmental factors also play a role in the onset of AD. For example "low education, head trauma, smoking, concomitant vascular disease, diabetes, and menopause" are also expected to play a role, though it hasn't been ascertained yet (Masters &

Beyreuther, 1998). Along with the usual focus on grey matter, it has also been shown that white matter is also negatively impacted by AD (Paola et al., 2009). The Corpus Callosum (CC) is subjected to callosal atrophy, which is the "anatomical correlate of Wallerian degeneration of commissural nerve fibers", and is affected in the disorder (Paola et al., 2009). After using many imaging techniques like ROI (region of interest), VBM (voxel based morphometry), DWI (diffusion-weighted imaging), or DTI (diffuse tensor imaging), patients with Alzheimer's were found to have "primarily a change in the anterior (genu and anterior body) and posterior (isthmus and splenium) regions of the CC" (Paola et al., 2009).

Behavioral Aspects

One of the major consequences of AD are non-cognitive behavioral changes (NCBCs), sometimes known as “behavioral and psychiatric symptoms of dementia” or “behavioral and psychological symptoms of dementia” which contribute to AD’s heterogeneity (Victoroff et al., 2018). These NCBCs include symptoms like depression, aggression, agitation, apathy, sleep disorders, etc. and have a major impact on factors such as life quality, increasing the stress of caregivers as well as accelerated mortality (Victoroff et al., 2018). Depression, a common symptom accompanying the disorder, "is thought to represent a risk factor for the cognitive decline from normal aging through mild cognitive impairment (MCI) to AD" (Victoroff et al., 2018). Apathy, which is a reduction in motivation and initiation of activities, subdivided into cognitive, behavioral, and emotional components" , and is the most frequent "non cognitive neuropsychiatric symptom", has been reported in up to 72% patients (Victoroff et al., 2018). Vascular risk factors appear to be closely associated with NCBCs implying that management of these factors might play a role in lowering NCBCs (Victoroff et al., 2018). In their review on the links between personality and AD, Terracciano & Sutin concluded that "conscientiousness and other personality traits may reduce risk of clinical dementia" (2019). They also mentioned that, though increased neuroticism and simultaneously decreased conscientiousness quite frequently accompany cognitive decline and the risk of dementia, conducting clinical research is difficult on these patients as most of them are less likely to volunteer themselves for the process (Terracciano & Sutin, 2019).

Current and Potential Future Treatments

There is no cure for AD and treatments mostly involve management of symptoms. Early detection is the key. Qiu et al. described three kinds of intervention strategies, primary, secondary and tertiary (2009). Primary intervention involves the "potential etiological" factors where the focus is on vascular pathways "including management of midlife high blood pressure and obesity, high blood glucose level, and diabetes", secondary strategies are based around early detection of Alzheimer's which could improve efficacy of therapeutics thereby "delaying the progression to clinical dementia" (Qiu et al., 2009). Tertiary interventions focus on improving quality of life and providing a caring environment (Qiu et al., 2009). With personality and Alzheimer's having a close association, Terracciano & Sutin believe that treatment should focus on changing dysfunctional personality traits, with these being thought to be potential factors in causing the disease and "linked to other risk factors and life outcomes" (2019). The most commonly known symptoms of the disorder involve changes in behavior. So, as concluded by Victoroff et al., the NCBCs could serve as potential biomarkers for diagnosis and therefore might help improve therapies associated with AD in the future (2018). With genes also playing a

substantial role in the cause of AD, perhaps the research could benefit from trying to find a cure at the genetic level.

Pohl and Lin, showed how plant extracts and natural products which have antioxidant properties can be used as potential treatments for neurodegenerative disorders like AD (2018). For example, "In C. elegans, Ginkgo biloba extract EGb761 alleviates Aβ-induced pathological behavior, inhibits Aβ oligomerization and deposits (not by reducing oxidative stress), and attenuates the basal as well as the induced levels of H2O2-related reactive oxygen species in AD models of neurodegeneration" (Pohl & Lin, 2018). With many developed countries having a continuously increasing older population and developing countries also staring at it in the coming years, it stands to reason that more and more research on Alzheimer's needs to be done and a potential cure is found.

Parkinson's Disease

Epidemiology and Etiology

Parkinson's Disease (PD), perhaps the second most widespread neurodegenerative disease, is a disease whose exact cause is unknown but it manifests itself due to "pathophysiologic loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the development of neuronal Lewy Bodies" (Beitz, 2014). It occurs generally, as in Alzheimer's, in older people, with a population-based study that was conducted on US Medicare beneficiaries finding its mean prevalence in older people(more than 65) to be 1.6, but can also affect younger people and can result in motor and non-motor impairments (Beitz, 2014). In his review, Lotankar et al. described how the degeneration of neurons "leads to dysfunction of the neuronal circuits that include motor cortical areas and the basal ganglia", ultimately resulting in movement impairments (2017). Jancovic categorized "the four cardinal features", under the acronym TRAP which translates to "TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability" (2007). Jankovic's team conducted a study on 297 patients that included 181 men and 116 women, that had been diagnosed with Parkinson's for at least three years, and by compiling data from 1731 visits in the duration of 6.36 years on average (range 3–17), the results were that the annual rate of decline in the "total UPDRS (The United Parkinson's Disease Rating Scale) scores was 1.34 points when assessed during ON and 1.58 points when assessed during OFF" (2007). In another study consisting of 145 patients who were followed-up for 1 year and 124 community based patients that were followed-up for 4 years, "the annual mean rate of deterioration in motor and disability scores ranged from 2.4% to 7.4%" (Jancovic, 2007). In Parkinson's, the brain changes at different levels with maximum change occurring due to continuous loss of dopaminergic neurons "in the substantia nigra pars compacta, one of the nuclei constituting the basal ganglia" (Lotankar et al., 2017). In his paper, Lotankar et al. mentioned that another characteristic of PD are the Lewy bodies inclusions, the "abnormal insoluble fibrillary aggregates that develop inside nerve cells in PD", that consist "mainly of α-synuclein (ASN)" (2017). Apart from these factors, "familial forms of PD can be traced to the mutations in the gene for ASN and single gene mutations, along with mutations of nuclear encoded proteins leading to the autosomal and recessive forms of PD" (2017). In addition, "genetic mutations that code proteins of the central nervous system play a role in neuronal death", in particular, "alpha-synuclein becomes abnormal and self-aggregates" (Beitz, 2014).

Behavioral Aspects

Though usually associated with motor dysfunctions, Parkinson's also shows a variety of neuropsychiatric symptoms. Jancovic described a study by the Sydney multicenter, where "84% of patients evaluated showed cognitive decline and that 48% met the diagnostic criteria for dementia after 15 years of follow-up" (2007). He also described other Neuropsychiatric impairments, in a study conducted on 537 patients, with 58% showing depression, 54% showing apathy, while 49% and 44% showed signs of anxiety and hallucinations, respectively (Jancovic, 2007). Apart from what Beitz describes as "classic" motor impairments such as "resting tremor (initially unilateral), bradykinesia (slow movements), rigidity, shuffling gait, and postural instability", other motor impairments associated with PD include, "masked facial expression (hypomimia), decreased eye blink rate, blurred vision, impaired upward gaze, dystonia, stooped posture, difficulty turning in bed, kyphosis, scoliosis, shuffling gait, 'freezing' (inability to move) and speech impairment, such as hypophonia (increasingly soft voice), or palilalia (repetition of word or phrase)" (2014). Beitz categorised the non-motor symptoms of Parkinson's Disease into 7 different categories, namely Autonomic Dysfunction- consists of sexual dysfunction, swallowing disorder, constipation, orthostatic hypotension, temperature control dysregulation rhinorrhea, etc., Sensory Disorders- include pain syndromes(aching), abnormal sensations & anosmia(Olfactory dysfunction), Integumentary- consist of Seborrhea, Malignant melonema, other skin cancers, flush, etc., Visual- include diplopia, blurred vision & impaired color discrimination, Miscellaneous- consist of fatigue & weight gain/loss, Neurobehavioural- include anxiety, depression, psychosis/hallucinations, cognitive dysfunction, dementia, apathy, bradyphrenia(slow thinking), and Sleep Problems- include daytime sleeplessness, sleep attacks, insomnia, REM sleep disorder & restless leg syndrome (2014). Non-motor symptoms, in particular, are a great concern as they diminish the quality of life, and appropriate management in PD is difficult because of the decreased efficacy of dopamine therapy when compared to the motor impairments (Beitz, 2014).

Current and Potential Future Treatments

Parkinson's Disease patients, like Alzheimer's, suffer the consequences of late detection and hence, early detection is the key to further treatment. According to Jancovic, Parkinson's doesn't have a particular test to determine its presence, its diagnosis is based on clinical criteria and "historically, pathological confirmation of the hallmark Lewy body on autopsy has been considered the criterion standard for diagnosis" (2007). PD doesn't have a cure. Levodopa, as mentioned by Jankovic & Aguilar, is perhaps the most common drug administered to PD patients, but its use has been questioned because some motor complications appear as a consequence of Levodopa therapy, hence they describe how "in order to delay or prevent levodopa-induced complications many parkinsonologists recommend using DA (dopamine agonists) as the initial or early form of dopaminergic therapy" (2008). A study showed that "deprenyl (selegiline) prevents MPTP-induced Parkinsonism", and this discovery has opened the doors in further research of using antioxidant therapy in neurodegenerative disorders like Parkinson's disease (Jankovic & Aguilar, 2008). As Lotankar et al. describe, by the time Parkinson's is confirmed, most of the dopaminergic neurons have already degraded, thus to facilitate early detection, identification of biomarkers, like biochemical biomarkers, inflammatory biomarkers, psychological biomarkers, etc., are key for an early diagnosis (2017). The use of imaging biomarkers, like molecular imaging, transcranial sonography, magnetic resonance imaging (MRI) and optical coherence tomography (OCT) is continuously increasing to assist in

clinical observations (Lotankar et al., 2017). Some clinical studies have shown that caffeine can also be used as a therapy in PD (Pohl & Lin, 2018). A study by Pohl & Lin mentioned how if further work on the role of asparagine endopeptidase (AEP) is done, "its inhibition could be of importance for other age-related neurological disorders" like Parkinson's disease (2018). Parkinson's disease, which many only associate with motor impairments, isn't actually one-dimensional, but the non-motor and neuropsychiatric aspects that accompany these motor dysfunctions, are what make it so dreadful. Hence, it becomes imperative that awareness about the complete aspects of Parkinson's increases. With so much advanced research being conducted in the field of genetics, even concepts like gene therapy could be of use in the quest for finding a cure for Parkinson's disease.

Huntington's Disease

Epidemiology and Etiology

Huntington's disease (HD) is a mostly genetic neurodegenerative disorder. According to McColgan & Tabrizi, among western populations, for every 100,000 people, Huntington's disease is present in 10.6-13.7 individuals (2017). In the words of Karagas et al., "Huntington’s disease (HD) is a completely penetrant autosomal dominant neurodegenerative disease caused by a trinucleotide repeat (CAG) expansion within the huntingtin gene (HTT) on chromosome", manifesting itself in the form of a "triad of motor symptoms", continuous impairment of cognitive function and "psychiatric disturbances" (2020). These impairments occur "due to neuronal dysfunction arising first within striatal medium spiny neurons and then spreading to other regions of the brain, including the cortex" (Karagas et al., 2020). In a paper describing the neuropathology of Huntington's disease, Reiner et al. mention that the region where major neuronal loss occurs is the "striatal part of the basal ganglia" and as the disorder reaches its advanced stages, the projection neurons are lost completely (2011). While describing the pathogenesis of the disorder, McColgan & Tabrizi describe how "at the cellular level mutant huntingtin results in neuronal dysfunction and death through a number of mechanisms" that include "disruption of proteostasis, transcription and mitochondrial function and direct toxicity of the mutant protein" (2017). Minkova et al. mention that in Huntington's, even before "functional deficits at the preclinical stage of disease (preHD)", "regional brain atrophy occurs" and continues as the first motor symptoms (mHD) appear (2018). But whether both the cerebral hemispheres are proportionately affected by neurodegeneration, across all stages of HD, is still up for debate (Minkova et al., 2018). In their paper, Minkova et al. describe a small scale study, with 9 preHD participants, which they claimed to be the "just one cross-sectional study" that has "has explicitly addressed brain asymmetry in HD, reporting bilateral GM loss in preHD followed by left lateralization at later disease stages" , but due to the small sample size, the results were inconclusive "in terms of disease stage-specific differences across the HD continuum" (2018). Reiner et al. point out that the neuronal losses in Huntington's are progressive and form the basis for the cognitive and motor Impairments, thus accounting for deaths about two decades after HD's onset in adults (2011).

Behavioral Aspects

Anderson et al. describe the behavioral changes associated with HD as a prominent part of the disorder and say that they lead to a great amount of difficulties for the patients and their relatives (2018). Agitation, which in the case of Huntington's, can be described as "observable,

situation-inappropriate behavior that is characterized by excessive motor or verbal activity and may manifest as a wide variety of behaviors including physical and verbal aggressive and non-aggressive behavior, general restlessness, pacing or screaming", and can manifest any time during the course of the disorder (Anderson et al., 2018). In their paper, Karagas et al. mention a number of studies to describe the prevalence of irritability in patients with Huntington's disease (2020). "Two early and relatively small (N< 100) studies assessing the neuropsychiatric profile of HD, using either the neuropsychiatric inventory (NPI) or the present state examination (PSE), found irritability rates of 65.4% and 64%, respectively", while another (N=134), found it to be prevalent among 44% patients and in their follow up study "in 2012 found that 49% of manifest HD patients were irritable at baseline while 83% were irritable during any assessment" (Karagas et al., 2020).

Another neuropsychiatric symptom in HD is apathy, which is "characterized by lack of motivation and diminished goal directed activities in three domains: behavior (lack of initiative or depending on prompts), cognitive (lack of interests or lack of concern), and emotion (constricted affect or lack of emotional responsiveness)", may arise before the appearance of motor impairments, and worsens as the disease progresses to higher clinical stages (Anderson, et al., 2018). The next symptom is anxiety. Anxiety in HD can be of various forms, be it social anxiety, panic or PTSD, (Post-traumatic stress disorder), etc. and it can be triggered by "external environmental factors including unfamiliar situations, changes in routine, physical discomfort, or performance anxiety due to cognitive and physical impairments" (Anderson et al., 2018). According to Anderson et al., in HD, anxiety occurs at each stage of the disease including the prodromal stage (before the motor diagnosis)", and as Huntington's progresses, it becomes difficult for the patient to communicate his/her distress, thereby causing restlessness (2018). The motor impairments in Huntington's disease are the ones which have mostly been used until now to diagnose HD and these dysfunctions usually arise in middle age, but as Karagas et al. mention, the neuropsychiatric symptoms such as irritability, apathy and depression are known to have an effect on the genes that carry Huntington's disease, thus, these symptoms can help in early diagnosis and perhaps, pave the way for development of novel methods to control the aforementioned neurodegenerative disorder (2020).

Current and Potential Future Treatments

Just like the previous two neurodegenerative disorders, HD does not have a cure yet. The methods that are used to control the disorder, usually include management of symptoms of the disease. In their paper, Anderson et al. describe three kinds of recommendations for managing some of the symptoms of HD, general, behavioral and pharmacologic recommendations. For example for Apathy, the general recommendations include differentiating it from the ill-functioning ability to execute cognitive or motor functions and managing medications that may have an effect on apathy (Anderson et al., 2018). In the case of anxiety, the behavioral recommendations involve the use of psychological behavioral therapy as the initial step in the treatment for patients who display anxiety at early stages of HD (Anderson et al., 2018). Similarly for psychosis, the pharmacological recommendations include the application of an antipsychotic drug as the primary treatment and using an alternative antipsychotic if the primary doesn't have much effect and keeping in check the recommended dose of the drug and clozapine is recommended "when psychotic symptoms have not adequately responded to other antipsychotics in those situations where interval blood testing is possible" (Anderson et al., 2018). An interesting case is the effectiveness of vasopressin in the management of

neuropsychiatric symptoms, reached upon due to the finding that "hypothalamic vasopressin-releasing neurons were reduced in early stages of the disease" but the exact association between vasopressin, HD-related neuropsychiatric symptoms and irritability is still vague (Karagas et al, 2020).

Anderson et al. concluded in their findings that "randomized controlled trials are needed to study the best treatment options for the various neuropsychiatric symptoms associated with HD" (2018). Karagas et al. mention that "no disease modifying therapies are approved to treat HD, although novel approaches targeting the genetic underpinnings of the disease hold promise" and as any curative therapy is currently not available and with the difficulties caused by the neuropsychiatric symptoms "improved symptomatic treatments are urgently needed" (2020). In a review by Mueller et al., that included six studies, they concluded that "exercise training seems to be a safe and feasible treatment approach in HD patients", with improvements in cardiovascular and mitochondrial function, the effects on motor functions and cognition aren't very clear, though a beneficial effect is seemingly caused, but they do mention that theirs was a small scale study and long term studies are desired (2019). As genes are an important factor in the cause of this disease, studies that involve concepts like genetic engineering can definitely be helpful. With no cure currently available, research that involves the genetic mechanisms and behavioral aspect, and possibly combine these, hold decent promise and should definitely be encouraged to bring this deadly disease under control.

Table 1: Similarities and Differences

	Similarities	**Alzheimer's**	**Parkinson's**	**Huntington's**
Characteristics	All are Neurodegenerative disorders	Formation of Aβ amyloid (Masters & Beyreuther, 1998)	Idiopathic (Beitz, 2014)	Mostly Genetic, autosomal dominant; trinucleotide repeat (CAG) expansion within the huntingtin gene (Karagas et al., 2020)
Neuroanatomy		Allocortex, limbic areas, entorhinal cortex, neocortex, hippocampus, and cerebellum are affected (Raji et al., 2009). Corpus Callosum(CC) is	Substantia nigra of the midbrain is affected (Beitz, 2014)	Striatal part of the basal ganglia (Reiner et al., 2011)

		affected (Paola et al., 2009)		
Behavioral Aspect	Most behavioral changes are similar such as agitation, apathy, depression, etc.	Mostly behavioral and psychiatric symptoms	Both motor and non-motor neuropsychiatric impairments. TRAP, acronym used for the four cardinal features of the disorder (Jankovic, 2007)	Both motor and non-motor behavioral impairments that worsen as the disease progresses. Irritability is a major behavioral symptom (Karagas et al., 2020)
Treatments	No definite cure; treatments usually involve management of symptoms	Focusing on vascular pathways, early detection & improving life quality (Qiu et al., 2009). NCBCs could be used as potential biomarkers (Victoroff et al., 2018)	Levodopa is the most common drug administered to PD patients (Jankovic & Aguilar, 2008). Biomarkers like biochemical ones could be used for early detection (Lotankar et al., 2017)	Combination of general, behavioral and pharmacologic therapies (Anderson et al., 2018). Vasopressin could potentially help in the management of neuropsychiatric symptoms (Karagas et al., 2020)

Conclusion

Each of the neurodegenerative disorders might be similar in the behavioral aspects, yet each of them has a vastly different origin. While Alzheimer's and Huntington's have proteinaceous and genetic causes, respectively, that are more or less known fairly well, Parkinson's is still idiopathic. In terms of behavioral changes, many things are common among them, such as anxiety, depression, apathy, agitation, etc. On one hand, Alzheimer's is usually associated with cognitive and NCBCs, Parkinson's & Huntington's on the other hand, are more famous for their motor dysfunctions, though the non-motor neuropsychiatric can hold as much

importance in diagnosis and treatment as they can potentially help in early diagnosis of these disorders. Unfortunately, there is no definite cure for these horrible diseases and treatments usually involve therapies to manage symptoms and improve life quality of patients and their caregivers. As genes can play a significant role in these disorders, future treatments can definitely be impacted by concepts like gene therapy and genetic engineering, etc. With many behavioral symptoms being similar in the three disorders described, it could be of use to researchers to develop a holistic and comparative approach to these disorders. In today's day and age, these horrible disorders that steal the very quality of people's daily routines, are a great concern, so treatments that incorporate all aspects, external & internal, behavioral & genetic, can be really effective.

References

1. Qiu, C. Kivipelto, M. Strauss, E.V. (2009). Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues in Clinical Neuroscience, 11(2), 111-128. doi: 10.31887/DCNS.2009.11.2/cqiu

2. Terracciano, A. Sutin, A.R. (2019). Personality and Alzheimer's disease: An integrative review. Personality disorders, 10(1), 4–12. doi: 10.1037/per0000268

3. Beitz, J.M. (2014). Parkinson's Disease: a review. Frontiers in Bioscience, S6, 65-74. doi: 10.2741/s415

4. Lotankar, S. Prabhavalkar, K.S, Bhatt, L.K. (2017). Biomarkers for Parkinson's Disease: Recent Advancement. Neuroscience Bulletin, 33(5), 585–597. doi: 10.1007/s12264-017-0183-5

5. Karagas, N.E., Rocha, N.P., Stimming, E.F. (2020). Irritability in Huntington's Disease. Journal of Huntington's Disease, 9, 107-113. doi: 10.3233/jhd-200397

6. Pohl, F. Lin, P.K.T. (2018). The Potential Use of Plant Natural Products and Plant Extracts with Antioxidant Properties for the Prevention/Treatment of Neurodegenerative Diseases: In Vitro, In Vivo and Clinical Trials. Molecules, 23, 3283. doi: 10.3390/molecules23123283

7. Raji, C.A. Lopez, O.L. Kuller, L.H. Carmichael, O.T. Becker, J.T. (2009). Age, Alzheimer disease, and brain structure. Neurology, 73(22), 1899-1905. doi: 10.1212/WNL.0b013e3181c3f293

8. Masters, C.L. Beyreuther, K. (1998). Science, medicine, and the future Alzheimer's disease. British Medical Journal, 316, 446–8. doi: 10.1136/bmj.316.7129.446

9. Paola, M.D. Spalletta, G. Caltagirone, C. (2010) In Vivo Structural Neuroanatomy of Corpus Callosum in Alzheimer's Disease and Mild Cognitive Impairment Using Different MRI Techniques: A Review. Journal of Alzheimer's Disease, 20, 67-95. doi: 10.3233/JAD-2010-1370

10. Victoroff, J. Lin, F.V. Cobourn, K.L. Shillcutt, S.D. Boon, V. Ducharme, S. (2018). Noncognitive Behavioral Changes Associated With Alzheimer's Disease: Implications of Neuroimaging Findings. *Journal of Neuropsychiatry and Clinical Neuroscience*, 30, 14–21. doi: 10.1176/appi.neuropsych.16080155
appi.neuropsych.16080155.ds001.pdf (psychiatryonline.org)

11. Jankovic, J. (2007). Parkinson's disease: clinical features and diagnosis. *Journal of Neuropsychiatry and Clinical Neuroscience*, 79, 368–376. doi: 10.1136/jnnp.2007.131045

12. Jancovic, J. Aguilar, L.G. (2008). Current approaches to the treatment of Parkinson's disease. *Neuropsychiatric Disease and Treatmen*t, 4(4) 743–757. doi: 10.2147/ndt.s2006

13. McColgan, P. Tabrizi, S.J. (2017). Huntington's disease: a clinical review. European Journal of Neurology. 25(1), 24-34. https://doi.org/10.1111/ene.13413

14. Reiner, A. Dragatsis, I. Dietrich, P. (2011). Genetics and Neuropathology of Huntington's Disease. International Review of Neurobiology, 98, 325-372. doi: 10.1016/B978-0-12-381328-2.00014-6

15.Minkova, L. Gregory, S. Scahill, R.I. Abdulkadir A. Kaller, C.P. Peter, J. Long, J.D. Stout, J.C. Reilmann, R. Roos, R.A. Durr, A. Leavitt, B.R. Tabrizi, S.J. Klöppel, S. TRACK-HD Investigators (2018). Cross-sectional and longitudinal voxel-based grey matter asymmetries in Huntington's disease. NeuroImage: Clinical, 17, 312-324. https://doi.org/10.1016/j.nicl.2017.10.023

16. Anderson, K.E. Duijn, E.V. Craufurd, D. Drazinic, C. Edmondson, M. Goodman, N. Kammen, D.V. Loy, C. Priller, J. Goodman, L.V. (2018). Clinical Management of Neuropsychiatric Symptoms of Huntington's Disease: Expert-Based Consensus Guidelines on Agitation, Anxiety, Apathy, Psychosis and Sleep Disorders. *Journal of Huntington's Disease*, 7, 355-366. doi: 10.3233/JHD-180293

17. Mueller, S.M. Petersen, J.A. Jung, H.H. (2019). Exercise in Huntington's Disease: Current State and Clinical Significance. *Tremor and Other Hyperkinetic Movements*, 9. doi: 10.7916/tm9j-f874