REVIEW ARTICLE

Review: an Overview of Neurodegenerative Diseases: Huntington, Alzheimer, and Parkinson

Gambaran Penyakit Neurodegeneratif: Huntington, Alzheimer, dan Parkinson: Sebuah Tinjauan

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ABSTRACT

Neurodegenerative diseases occur due to dysfunction of the nervous system, which is accompanied by memory and movement disorders. Neurodegenerative diseases can be viewed from an etiological and pathological perspective (pathophysiologial and histopathological). The most common neurodegenerative diseases are Huntington's, Alzheimer's, and Parkinson's. This review article will review the etiology and pathology of Huntington's, Alzheimer's, and Parkinson's diseases. The method used in this writing uses journals and books from Google Scholar, PubMed, ResearchGate, and the Web. The keywords used are etiology, pathology, pathophysiology, histopathology, neurodegenerative disease, Huntington's, Alzheimer's, and Parkinson's. The author limited the last 10 years of literature used. Based on a literature review, it is known that the etiology of Huntington's disease is caused by mutations in the huntingtin gene on chromosome four. The pathology of Huntington's disease is caused by unstable expansion of trinucleotide-encoded polyglutamine (CAG) repeats. One of the histopathological features of Huntington's disease can be identified from increased iron levels in the striata of the brain. The etiology of Alzheimer's disease involves interactions between genetic factors, lifestyle, environment, and the aging process. The pathology of Alzheimer's disease occurs due to the presence of apolipoprotein and its relationship to 3 mutated genes. The histopathology of Alzheimer's disease is identified by the presence of neuronal cell death, which is characterized by the shrinking of the nuclei of brain neuronal cells and the cytoplasm has a more eosinophilic color. The etiology of Parkinson's disease is progressive nerve damage to certain areas of the brain. The pathophysiology of Parkinson's disease is thought to involve a reduction in striatal dopamine, which causes an increase in inhibitory output from the globus pallidus pars interna/substantia nigra pars reticulata (Gpi/SNr), resulting in movement suppression. Histopathologically, Parkinson's disease is characterized by degeneration of neurons and neurophagia. This review concludes that Huntington's, Alzheimer's, and Parkinson's diseases can be caused by aging and genetic factors. The pathology of the disease is due to mutations, increased levels of iron, apolipoprotein, neuronal cell death, increased inhibitory output, and neuronal degeneration. The symptoms caused can be motoric, cognitive, and psychiatric.

Keywords: Neurodegenerative diseases; Huntington’s; Alzheimer’s; Parkinson’s; Etiology; Pathology.
ABSTRAK

Kata Kunci: Penyakit neurodegeneratif; Huntington; Alzheimer; Parkinson; Etiologi; Patologi.

INTRODUCTION
Neurodegenerative disease is a disease that can occur due to dysfunction of the nervous system. This dysfunction causes general signs to appear in sufferers who experience neurodegenerative diseases, including sufferers experiencing memory and movement disorders. The incidence of neurodegenerative diseases is increasingly widespread. Various studies show that this disease ranks 8 out of 10 diseases that contribute to disability.1,2,3 In general, neurodegenerative diseases can be viewed in terms of etiology and pathology. Pathology can be viewed in terms of pathophysiology and histopathology. Etiology is a study that studies various factors that can cause the emergence of a disease, the mechanism by which the disease spreads, and the mechanism by which the disease can be prevented or treated. Pathophysiology is the study of disorders of mechanical, physical, and biochemical functions, whether caused by a disease, symptom, or abnormal condition that is not worthy of being called a disease. Pathophysiology can also be defined as a study that studies the biological and physical manifestations of disease, and its relation to underlying psychological disorders and disorders. Histopathology is a study that studies the condition and function of tissue about disease. Histopathology is very important in the diagnosis of disease. This is the basis for consideration in determining a diagnosis, through the results of observations of tissue that is suspected to be disturbed. Histopathological examination is carried
out by examining abnormal changes at the tissue level. The most common neurodegenerative diseases that occur in Indonesian society and other countries in general are Huntington's, Alzheimer's, and Parkinson's. Huntington's disease is an autosomal-linked neurodegenerative disorder that is dominant and can be inherited. Alzheimer's disease is a neurodegenerative disease that slowly destroys memory, and thinking skills, and ultimately loses the ability to remember and perform the simplest tasks. Parkinson's disease is a neurodegenerative disease the second most common after Alzheimer's, which involves the loss of dopaminergic neurons in the midbrain. Reviews regarding the etiology and pathology of these three types of disease have not been studied comprehensively. So, the novelty of this review article is that it will discuss the etiology and pathology of these three types of neurodegenerative diseases.

**METHODS**

The data sources used in this review come from Google Scholar, PubMed, ResearchGate, and the Web, to find articles and journals that are used as reference sources. The journals selected in this review are nationally accredited internationally reputable and indexed, and have a CiteScore ranging from 0.5-0.8. A selective selection of journals and appropriate keywords was carried out to reduce bias in this review. The keywords used are neurodegenerative disease, etiology, pathology, pathophysiology, histopathology, Huntington's, Alzheimer's, and Parkinson's. The author limited the last 10 years for the literature used. The data sources for this literature review consist of 28 journals, 1 website, and 1 electronic book. From the data source, 50 pieces of literature were obtained and 30 pieces of literature were used that met the criteria.

**RESULTS**

**Huntington Disease**

The etiology of Huntington's disease is due to a mutation process in the gene. Mutations are genetic changes either at the gene or chromosome level. The mutation is in the huntingtin gene or mutant gene (mHTT) on chromosome four. Huntington's disease is a fatal neurodegenerative disease that is progressive. Huntington's disease is an autosomal-linked neurodegenerative disorder that is dominant and can be inherited or genetic. This disease can be inherited directly from parents who have a history of Huntington's disease. Generally, defective genes can be passed on to children from both parents. In addition, aging is a risk factor for various diseases, one of which includes neurodegenerative diseases. Huntington's disease has the same signs of disease pathogenesis as signs of aging, namely the shortening of telomeres and epigenetic changes. Huntington's disease is a neurodegenerative disorder that is endemic to all populations of various races and ethnicities. Huntington's disease is considered a common neurodegenerative disorder in various countries such as Japan, China, and Finland. However, according to the European Huntington's Disease Network in 2022, in the last ten years, 15-20% of Huntington's disease occurred in populations in Australia, North America, and Western Europe. The prevalence of Huntington's disease has a ratio of 3 to 7 per 100,000 people, among the population in Western Europe.

The pathophysiology of Huntington's disease occurs due to a mutation in the huntingtin gene, the mutation is on chromosome four. The disorder is caused by the unstable expansion of trinucleotide-encoded polyglutamine (CAG) repeats. These repeats are translated into mutant
huntingtin protein (mHTT). Huntington’s disease begins with a mutation in the CAG-encoded glutamine repeat expansion. At the gene locus involved in Huntington’s Disease, there are usually 10-29 consecutive repeats of the CAG triplet encoding glutamine. In contrast, patients with Huntington’s disease have 36 to 121 CAG repeats (the plot and complete schematic representation are presented in Figure 1.). Symptoms of this disease most often occur between the ages of 35 and 50 years. The disease progresses relentlessly and becomes fatal after the onset of symptoms. Symptoms can include a variety of disorders, including; motoric, cognitive, and psychiatric. Motor disorders include involuntary choreiform movement disorders of proximal and distal muscles, and involuntary movement disorders in the form of progressive coordination disorders. Cognitive impairment in Huntington’s disease accumulates progressively. Patients with late-stage Huntington’s disease have deficits in memory and visuospatial abilities. The most common psychiatric disorders in patients with Huntington’s disease include depression, irritability, and abnormalities in emotional control.¹¹

**Figure 1. Huntingtin (HTT) structure and transformation.** 1. Expression of HTT produces an RNA transcript into mRNA encoding the total length of the Huntington protein; 2. The unnatural process of becoming an mRNA encoding only exon 1 gives rise to massive CAG repeats; 3. Translation produces a long Huntington protein; 4. The HTT exon 1 fragment consists of a mixed amino acid sequence HTTNT polyglutamine sequence encoded by CAG repeats and a proline domain (PRD) followed by irregular and disordered protein segments; 5. Irregular segment cleavage sites produce products including Huntington’s trigger HTT exon 1 fragments.¹⁰

The histopathology of Huntington’s disease can be seen from the signs and symptoms, namely progressive loss of neurons, especially striatal medial spiny neurons followed by atrophy. As the disease progresses, other areas of the brain including the white matter and cortex are also affected, ultimately resulting in global brain atrophy. Huntington’s disease is closely related to
increased iron levels in striate neurons. Research by Bulk et al. (2020) studied the histopathological characterization of ex vivo Magnetic Resonance Imaging (MRI) contrast changes in the brains of patients with Huntington's disease. The results showed that compared with control tissue, Huntington's disease striate neurons had a distinctive phenotype on MRI-T2. On ex vivo MRI, contrast changes are strongly biased by enlarged perivascular spaces. At this time, it is not yet known whether this is a fixation artifact and more specific further research needs to be carried out. Microscopically, iron is mostly found in reactive astrocytes. Clinically, these results are important for the interpretation and understanding of potential mechanisms underlying MRI-T2 results. However, the exact sequence of iron accumulation within astrocytes and microglia during disease progression and the implications of glial iron accumulation for disease progression requires further research.

Alzheimer Disease

The etiology of Alzheimer's disease is multifactorial, involving interactions between genetic, lifestyle, and environmental factors. Alzheimer's disease can also occur due to neurodegenerative processes in the brain that trigger dementia. Alzheimer's disease is a disease that is generally inherited from parents to their children. Some of the risk factors for Alzheimer's include; age, family history and genetics, Down syndrome, gender, head trauma, air pollution, excessive alcohol consumption, poor sleep patterns, lifestyle, heart health, lack of exercise, obesity, smoking, cholesterol, hypertension and type-2 diabetes which is uncontrolled. The genetic basis for the early onset of Alzheimer's disease follows an autosomal dominant inheritance pattern associated with gene mutations that alter the production, aggregation, or excretion of amyloid beta protein.

Epidemiological data estimates that Alzheimer's disease affects approximately 50 million patients worldwide. This number is projected to double every 5 years and will reach 152 million in 2050. The percentage of all patients suffering from dementia, 50-60% of whom suffer from Alzheimer's disease. The prevalence of Alzheimer's type dementia increases with age. In people aged 65 years, the prevalence of suffering from Alzheimer's is 0.6% in men and 0.8% in women. At the age of 90 years, the prevalence reaches 21%.

The pathophysiology of Alzheimer's disease is further linked to the process of increasing abnormal lipid levels (apolipoprotein). Familial type of early Alzheimer's disease is associated with 3 mutated genes, namely amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2). This mutation occurs due to excessive production and/or increased aggregation of beta-amyloid (Aβ). Dysregulation of the immune system plays a role in Alzheimer's disease. Central and peripheral immune responses are also involved in the pathogenesis of Alzheimer's. The two most important pathological features of Alzheimer's are the abnormal structure of amyloid beta (Aβ) and the microtubule-associated protein tau in the brain, which can cause cognitive impairment and neurological damage. Aβ is formed through the cleavage of amyloid precursor protein (APP) and can be cleaved into polypeptides by several proteolytic secretions. In Alzheimer's disease, neuropathological characteristics such as selective neuronal and synapse loss are found, as well as the presence of neuritic plaques containing Aβ peptides and neurofibrillary tangles (NFTs), which forms hyperphosphorylation of the tau protein. The neuritic plaque that occurs is an extracellular lesion composed of a central core of Aβ peptide aggregation surrounded by dystrophic neurites, activated microglial, and reactive astrocytes. While NFTs are bundles of filaments in the cytoplasm of nerve cells that surround nerve cells, Aβ deposition in the brain is one of the implications of the
pathogenesis of Alzheimer's disease. Accumulation of Aβ (especially Aβ42 peptide) in the brain, is the initiation of neuronal dysfunction, neurodegeneration, and dementia (complete flow and schematic representation are presented in Figure 2.).

Figure 2. Hypothetical schematic of the amyloid cascade with nomadic suppression causing Dementia. Aβ and tau oligomeric aggregates are neurotoxic leading to the formation of amyloid plaques and NFTs. Further research is needed regarding the role of Aβ which can trigger tau toxicity which leads to the formation of PHF and loss of neurons. However, there is still debate regarding the fact that tau pathology can occur independently of Aβ. A direct pathway to tau and aggregation via tau hyperphosphorylation is depicted. (Abbreviations: Aβ, amyloid-β; Aβ42, the 42-amino acid form of Aβ; APP, amyloid precursor protein; FAD, familial Alzheimer's disease; NFT, neutrophil tangles; PHF, paired helical filaments).

Alzheimer's disease can be diagnosed in various ways, one of which is through histopathological examination of the brain after death. Histopathological examination is the final way to determine the diagnosis of this disease. The study by Filon et al. (2016) in the brains of mice affected by Alzheimer's showed that neuronal degeneration occurred in the mouse cortex and hippocampus areas. Degeneration is a progressive decline in brain function. In addition, molecular studies show that the main component of amyloid plaques and the main component of damaged neurofibrils is tau protein. This abnormal protein causes toxic effects on nerve cells, impairing their function, and ultimately causing cell death. Research by Kristeningrum et al. (2016) related to the histopathological picture of rat brains resulting from trimethyltin injection as a model of Alzheimer's disease, which was injected with trimethyltin at doses of 6 and 8 mg/kg body weight showed increased brain neuron cell death in the cortex and hippocampus compared to the control group. Neuronal cell death was highest on day 14 in the hippocampus and day 21 in the cerebral cortex after trimethyltin injection. Neuronal cell death is characterized by brain neuron cells, with shrunken nuclei and more eosinophilic-colored cytoplasm.
Parkinson Disease

The etiology of Parkinson's disease is progressive nerve damage in certain areas of the brain, especially the substantia nigra, which disrupts the production of the hormone dopamine. The emergence of Parkinson's disease is influenced by age, genetic or hereditary factors, and the environment. Broadly speaking, the etiology of Parkinson's disease is the accumulation of alpha-synuclein in various parts of the brain, especially the substantia nigra, which causes degeneration and loss of dopamine in the basal ganglia which controls muscle tone and movement. Accumulation of alpha-synuclein protein can arise as a result of genetic predisposition, such as PARK-1 mutations, or be triggered by environmental agents. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's, involving the loss of dopaminergic neurons in the midbrain. Several studies indicate a link between infection and alpha-synuclein accumulation.20,21

Aging is considered a normative process that combines random predictable effects that lead to the accumulation of irreversible cell damage, weakening of cell repair, and compensatory mechanisms. The prevalence of Parkinson's disease is estimated at 329 people per 100,000 population, where the average incidence ranges from 16-19 per 100,000 people. The prevalence increases with age and varies across age ranges. The average rate of Parkinson's disease sufferers ranges from 1-2% at the age of 60 years or older, and more than 4% of patients suffer from Parkinson's disease at the age of 80 years or older.22

The pathophysiology of Parkinson's disease is thought to involve reduced production of the striate hormone dopamine. This is thought to cause an increase in the inhibitory results of the globus pallidus interna/substantia nigra pars reticulata (Gpi/SNr), resulting in movement suppression. In Parkinson's disease, depigmentation of the substantia nigra and locus coeruleus occurs with loss of dopamine neurons in the substantia nigra pars compacta due to the processes of apoptosis and autophagy. The process of loss of neurons also occurs in the basal nucleus of Meynert and the dorsal motor nucleus of the vagus nerve and Lewy bodies are also found in areas affected either directly or indirectly (the flow and schematic representation are presented in Figure 3.).23-26 The process of loss of dopamine neurons, is estimated that 60-80% occurs before the appearance of motor signs of Parkinson's disease. Several theories regarding neuron loss in Parkinson's sufferers include mitochondrial dysfunction, inflammation, protein handling abnormalities, oxidative stress, and changes in the gut microbiota. Symptoms of this disease vary depending on the motor phenotype and age of the patient. Visible motor symptoms include; tremors, spasms, and muscle stiffness. In addition, non-motor symptoms include; sleep disorders, cognitive disorders, and emotional disorders such as; depression, irritability, anxiety, fear, and unstable mood swings.27-29
Figure 3. Changes in the activity of motor cortex areas in Parkinson's disease. The motor area consists of the corticostriatal and primary, supplementary motor areas, cingulate motor cortex, and premotor cortex, which terminate in the dendrites of striatal medium neurons. There are 2 paths, namely 'direct' and 'indirect'. The 'direct' pathway is a monosynaptic connection between neurons expressing dopamine D1 receptors and GABAergic neurons in the globus pallidus internus and substantia nigra pars reticulata. The 'indirect' pathway originates from neurons expressing D2 receptors, which project to the globus pallidus externus, and reach the globus pallidus internus via the subthalamic nucleus as glutamatergic relays. Through these two pathways, striatal dopaminergic activity regulates GABAergic output from the basal ganglia (As shown in the schematic image above, Parkinsonism is associated with changes in these relays).

Studies using animal models of Parkinson's disease, one of which uses exposure to chlorpyrifos. Chlorpyrifos is a compound used as an active ingredient in pesticides. The organophosphate pesticide chlorpyrifos has been reported in various studies to increase the production of reactive oxygen species (ROS). This is consistent with the fact that Parkinson's disease can be caused by a decrease in the number of dopaminergic neurons after exposure to chlorpyrifos. Histopathological study of Parkinson's disease by Deveci and Karapehlivan in 2018, using a chlorpyrifos-induced Parkinsonian model in mice. The aspects studied are behavioral and histopathological. Histological observations were carried out, namely, cross-sectional sections of the substantia nigra brain tissue were examined to determine the success of induction in supporting the histopathological results of the biochemical parameters chlorpyrifos for Parkinson's disease. The results showed that there was degeneration in neurons and neurophagia in the chlorpyrifos group. Being one of the histopathological indicators of Parkinson's disease, the presence of Lewy bodies, which have a single or multiple granular structure, a brown appearance,
and intracytoplasmic localization in a small number of degenerative neurons. Histopathological results of the study have shown that chlorpyrifos is effective for experimentally inducing Parkinson's disease and Lewy bodies, determined in the substantia nigra area of the brain.

CONCLUSION

Based on the review above regarding the etiological and pathological (pathophysiological and histopathological) aspects of Huntington's, Alzheimer's, and Parkinson's neurodegenerative diseases. So, the following conclusions can be drawn: (1) Huntington's disease occurs due to abnormalities in the huntingtin gene on chromosome 4, the aging process, and genetic factors. Pathophysiologically caused by expansion of unstable trinucleotide-encoded polyglutamine (CAG) repeats translated into mutant huntingtin protein (mtHTT). Histopathologically the disease is characterized by progressive neuronal loss. Symptoms include motor, cognitive, and psychiatric; (2) Alzheimer's disease occurs due to genetic factors, lifestyle, environment, and neurodegenerative processes. The pathophysiology of Alzheimer's disease is abnormal lipid levels (apolipoprotein) and its relationship with 3 mutated genes, namely amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2). The histopathology that occurs is characterized by neuronal degeneration in the cortex area. Symptoms include memory loss; (3) Parkinson's disease occurs due to the influence of age, and genetic and environmental factors. The pathophysiology of Parkinson's disease is characterized by reduced striate dopamine. This causes an increase in the inhibitory results of the globus pallidus pars interna/substantia nigra pars reticulata (Gpi/SNr) which results in movement suppression. The histopathology that occurs is characterized by degeneration of neurons and neurophagia. Symptoms include motor and non-motor instability.

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AUTHOR CONTRIBUTIONS

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The authors declare that there are no conflicts of interest for this work.

REFERENCES


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