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Review Article

Neuroferritinopathy comprehensive review

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ABSTRACT

Neuroferritinopathy is a rare, autosomal dominant neurodegenerative disorder characterized by the accumulation of iron in the brain due to mutations in the ferritin light chain gene (FTL). This article explores the incidence, prevalence, pathogenesis, types, and treatment options for neuroferritinopathy, drawing on current scientific literature to provide a comprehensive overview. Neuroferritinopathy clinically presents in mid-adulthood, most frequently between the third and the fifth decade of life. Onset: Symptoms are often gradual, though patients may develop dystonia, chorea, parkinsonism, and cognitive dysfunction.

1. Introduction

Neuroferritinopathy (NF) is a rare autosomal dominantly inherited neurodegenerative disease that is brought about by FTL gene mutations with resultant aberrant iron accumulation in the brain. This excessive deposition of iron occurs in parts of the brain that control motor activity, specifically the basal ganglia, and results in a host of movement disorders. Neuroferritinopathy falls under a class of diseases called Neurodegeneration with Brain Iron Accumulation (NBIA). First reported in 2001, it has only been identified as a separate disease in the NBIA spectrum in the current year, along with other disorders caused by abnormalities in iron handling, including PKAN and Aceruloplasminemia.

Neuroferritinopathy clinically presents in mid-adulthood, most frequently between the third and the fifth decade of life. Onset: Symptoms are often gradual, though patients may develop dystonia, chorea, parkinsonism, and cognitive dysfunction. These symptoms become gradually more severe and result in a highly impaired motor function and, in some cases, a severe disability. Motor disturbances are clearly manifested, but in addition to them, the severity of cognitive and psychiatric disorders such as depression or behavioral changes is also characteristic of the disease. Neuroferritinopathy has, however, benefited from increased studies in the recent past as research in genetic testing, neuroimaging, and treatment escalates. MRI is useful in showing iron accumulation in the brain through a visible differential diagnosis of the disease's progress. The current treatment for this condition still entails non-curative but only suppressive approaches; current specific treatments target movement disorder and try to balance iron levels.[1] Due to further study, more ways targeted at investigating and managing the irregularities of iron in neuroferritinopathy have the potential to be developed in the future.

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2. Discussion

2.1. Pathophysiology

Iron is an essential component for various enzymatic processes in the human body, playing a vital role in oxygen transport, neurotransmitter synthesis, and neuron metabolism.[2] Despite its critical functions, iron is present in the brain in small amounts, less than 1% of the body's total iron, which is approximately 30 to 40 mg. The basal ganglia exhibits relatively elevated levels of iron owing to its implication in motor control and other major functions.[3] Neuroferritinopathy represents a mutational disruption of the FTL1 gene encoding ferritin light chain-a significant player in maintaining iron homeostasis. These genetic changes disturb the normal iron balance, resulting in an overload of iron in the brain. This excessive deposition, within motor control areas especially, disrupts normal neuronal activity and forms the basis for neurodegenerative processes associated with neuroferritinopathy.

The impact on iron management within the brain due to the mutation in the FTL1 gene is tremendous. Ferritin's role is to sequester and safely store iron, but in neuroferritinopathy, the structure of ferritin is altered, diminishing its capacity to bind and regulate iron levels correctly. This dysfunctional ferritin allows iron to react freely, increasing the amount of reactive oxygen species (ROS) produced, which are highly cytotoxic.[4] The resulting oxidative stress leads to neuronal cells being typically rich in iron, especially in the basal ganglia. Cellular injury described here forms the basis for symptoms such as movement disorders in neuroferritinopathy. Indeed, evidence has shown that unregulated iron accumulation in neuronal cells causes damage to cellular structures with interference in normal cellular processes, leading to the progression and exacerbation of neurological symptoms over time.[5]

The brain does not distribute iron homogeneously but concentrates high amounts in specific nuclei within the so-called basal ganglia, such as the caudate, putamen, and globus pallidus; these are areas responsible for maintaining motor function. Neuroferritinopathy presents with abnormalities in movement due to iron-induced oxidative damage in these key brain areas. In contrast, other parts of the brain, such as the cortex, brainstem, and cerebellar, exhibit lower iron levels and later involvement during the disease. The focal accumulation of iron in the basal ganglia amplifies cellular stress in these regions, potentially leading to motor dysfunctions such as dystonia, parkinsonism, and chorea. The selective vulnerability of the basal ganglia in neuroferritinopathy strongly underlines the pivotal role that iron dysregulation exerts in the pathogenesis of this disorder and fits well within the symptomatic profile observed in this patient subgroup.

11'In addition to iron overload, recent neuroferritinopathy research has focused on trying to understand the cellular pathways that exacerbate iron toxicity. The mutation in the FTL1 gene changes how ferritin cycles iron-greatly impairing its normal storage and release functions, allowing unregulated iron release. This free iron participates in increased ROS production and resultant cellular stress and apoptosis in neurons. Ongoing research is focused on the specific molecular pathways changed by this oxidative stress but also seeks to identify interventions that might minimize cellular injury and slow disease progression.[6] By targeting the iron-handling mechanisms that go awry due to the FTL1 mutation, scientists are developing therapies that may mitigate iron's toxic effects, possibly opening new avenues for treatment. Although such therapies are still experimental, they hold significant promise to alter the course of neuroferritinopathy by attacking the root cause: defective iron metabolism.

2.2. Genetics of neuroferritinopathy

Neuroferritinopathy is a genetic disease mainly attributed to mutations in the FTL1 gene of chromosome 19q13.3. This mutation is classified as an autosomal dominant inheritance, so only one copy of the new gene in everyone is needed to develop this disorder. FTL1 is the gene for the ferritin light chain, which is an essential subunit of the iron storage and regulation protein, the ferritin. Ferritin consists of light and heavy subunits and is the main intracellular storage form of iron, which binds to the metal and remains soluble. It also acts as an iron reservoir for the regulation of iron in the cells to suppress the generation of many forms of ROS, which may cause cellular damage. However, in the case of neuroferritinopathy, certain changes in FTL1 lead to the formation of flawed ferritin proteins, which are unable to regulate iron as the molecules should. Consequently, iron levels become unhealthy in specific parts of the brain that are related to physical movements and abnormal iron deposits.

The molecular basis of the mutation at the FTL1 gene that results in neuroferritinopathy has been investigated comprehensively. This invariably leads to a change of glutamic acid at position 62 to Lysine (E62K); however, other mutations resulting from altered amino acid sequences have also been reported in affected families. This amino acid substitution on the ferritin light chain cycling compromises the efficiency at which this protein cycles iron and results in iron buildup in the brain.[7] Iron at the end accumulates in the body, the overload of which provokes the destruction of neurons, especially in the basal ganglia, which are responsible for motor coordination. This leads to the motor phenotype associated with neuroferritinopathy, such as dystonia, chorea, and parkinsonism. However, the diagnosis of neuroferritinopathy is confirmed through genetic tests

since different research has pinpointed that it involves a mutation in the FTL1 gene that causes the disorders. Consulting a genetic counselor is advised because the condition is autosomal dominant; therefore, there is a 50% chance that each child of an affected individual will inherit the mutation. Proper intervention is important in controlling the symptoms and even reducing the progression of the illness, though no cure has been developed for it.

With the progression of gene therapy practice, a lot of emphasis is placed on treating the clinically expressed bad gene FTL1 to control iron deposits in the brain. Science regarding mending technologies like the CRISPR-Cas9 method is still active. However, both methods stay in the experimental stage.[8] However, they offer great potential for carrying out a radical cure of neuroferritinopathy because of direct intervention with the defective gene. Besides gene therapy, other medical treatments currently undergoing research include drugs that target iron homeostasis or molecules that can bind to iron in the body to get rid of the excess iron. Therefore, neuroferritinopathy is a phenotypically heterogeneous genetic disease with profound consequences for patients and their families. Knowledge of the genetic basis of this condition, especially the defects in the FTL1 gene, has aided in the appreciation of the proffered causes of neuroferritinopathy. While research continues, these newer therapies targeting specific genes may hold the promise for prevention or cure for this crippling disease leading to a better prognosis for the affected individuals.

2.3. Clinical presentation

Neuroferritinopathy is typically by a gradual onset, starting symptoms within adulthood. Symptoms usually occur within the age of 40 to 60 years. Due to genetic or environmental modifications, there has been great variation in the age of onset; thus, some cases occur before or after this period of life. These early symptoms are primarily in the form of movement disorders, as neuroferritinopathy results from the toxic action of iron on the basal ganglia, the part of the brain that controls voluntary movements. The early manifestations include dystonia, a disorder characterized by abnormal postures and twisting movements resulting from muscle contractions, and chorea, a neurological disorder with spontaneous, unpredictable body movements.[9] Many of the patients also exhibit tremors, which are defined as rhythmic shaking and can also be seen early during the disease. These early motor manifestations are usually subtle but tend to progress and interfere with daily functions, portending the course of the illness.

During neuroferritinopathy, there is progressive worsening of these movement-related symptoms, which further depletes the ability of the individual to carry out daily activities independently. Bradykinesia, or slowness in initiating and executing movements, and rigidity, or muscle stiffness common in neuroferritinopathy, share many similarities with Parkinson's disease. These symptoms complicate basic tasks, such as walking, dressing, and eating. With a predisposition toward progressive motor strikes, gait and balance are affected, patients usually have gait disorders that make them trip and injure themselves. Over time, mobility is decreased due to the physical limitations inherent in the condition, reducing one's capacity for daily tasks to a minimal level; the person requires supportive care to help them through the day. Eventually, as these motor deficiencies progress, patients find it increasingly difficult to carry out basic activities, leading to substantial dependency.

Cognitive impairments and psychiatric symptoms are developed aside from neuroferritinopathy with motor dysfunction and further worsen the effects of the disease on the quality of life. The cognitive dysfunction may be mild at its outset, where patients have memory lapses, attention deficits, or executive function impairments regarding such areas as planning and decision-making. Cognitive problems may evolve with time to dementia-a condition characterized by significant decline in core cognitive capacities including reason, problem-solving, and memory. In addition to cognitive decline, speech disturbances are common, dysarthria being a common feature. Dysarthria is a motor speech disorder characterized by neurological injury to the speech muscle control apparatus, producing slow and slurred communication. In this constellation of symptoms, the poor communication and social interaction become well-defined burdens to the psychological and emotional risks that individuals with neuroferritinopathy face.

These psychiatric symptoms make neuroferritinopathy a very challengingly manageable disease. The most frequent psychiatric disturbances in patients are various mood disorders, especially depression and anxiety, which accompany many neurodegenerative diseases in their chronic course. Such psychiatric manifestations can enhance the emotional and social burden of a patient who struggles to cope with both physical and cognitive decline, often resulting in social isolation and dependence upon family or caregivers. Other behavioral changes may also include irritability and apathy that can arise with the progression of the disease and, further complicate the management of the disease load and burden on caregivers. Consequently, the relationship among neurological, cognitive, and psychiatric symptoms necessitates a multidisciplinary strategy to treatment: given the broad range of discomfort for patients and their families.

Neuroferritinopathy is associated with severe losses in personal autonomy, including assistance with almost everything, as the disease progresses. By this time, such patients may need full-time assistance in basic self-care activities such as eating, dressing, and mobility.

Assistive equipment includes walkers, wheelchairs, and communication aids that provide critical support to functional independence and safety.[10] Moreover, physical or speech therapy offers important interventions to help retain residual competencies of motility and communication. Despite these interventions, the relentless disease progression is associated with a profound loss of both motor and cognitive abilities, leading to increased dependency and a reduction in the quality of life. Generally, prognosis is poor, with neuroferritinopathy requiring an increasingly high level of care and assistance. This therefore calls for new therapeutics that would more effectively manage symptoms of the disease process and may, thus, modify its course.

Neuroferritinopathy presents a complex special consideration in its assessment on the lives of those patients due to the comprehensiveness of the care. Initial symptoms of the disorder typically involve motor activities without more insidious onsets of complex cognitive and psychiatric changes. The psychological and physical burdens, immense in proportion, could accrue to both patients and caregivers many times, entailing social and emotional support and medical assistance as the disease progresses. Neuroferritinopathy treatment is symptom-oriented and directed toward maintaining the quality of life due to the progressive nature of the disease, with debilitating features. Research studies on gene therapy and neuroprotective strategies are still ongoing, looking for novel treatments that may target the very core of the disease; hence, offering the prospect for more effective interventions that may furnish a brighter prognosis for future generations diagnosed with neuroferritinopathy.

2.4. Diagnosis of neuroferritinopathy

Neuroferritinopathy diagnosis depends on clinical evaluation, genetic analysis, and advanced neuroimaging. It is at this stage that the clinician would usually rely on a patient's history and physical findings in guiding initial assessments, with emphasis on movement disorders, cognitive symptoms, and speech abnormalities that are hallmarks of the condition. However, based on only clinical features, neuroferritinopathy may share similarities with other neurodegenerative disease entities; hence, imaging studies are necessary in confirming the presence of brain iron accumulation, which is basically characteristic of the disease. Magnetic Resonance Imaging (MRI) is the cornerstone of diagnosis in the detection of iron deposits in the brain tissue, especially in the basal ganglia, where a high degree of accumulation takes place.[11] In this disease, increased iron deposition typically involves the globus pallidus and putamen, portions involved with motor regulation; therefore, it relates to the main presenting symptoms that involve movement. Structural information will be greatly obtained with MRI studies, although emerging imaging modalities continue to enhance diagnostic accuracy.

Susceptibility Weighted Imaging (SWI), an advanced MRI technique, has proven particularly useful in neuroferritinopathy, visualizing iron deposition better than standard MRI. This technique, using magnetic susceptibility differences, is very effective in outlining the details of the images and is thus very sensitive to detecting subtle iron accumulation in neurodegenerative disorders.[12] This approach gives a more accurate estimation of the distribution of iron in the affected brain region, which is highly critical for neuroferritinopathy differentiation from other movement disorders that may not exhibit the same profile of iron deposit. SWI measures the quantity of iron deposited in the basal ganglia, thus allowing diagnosis and informing about the disease's course. The increased sensitivity of SWI contributes to the more accurate and personalized diagnosis of neuroferritinopathy, especially in cases where MRI findings are not evident or one wants to do early detection.

Genetic testing, specifically molecular testing remains confirmatory for the mutation in the FTL1 gene for neuroferritinopathy. The gene FTL1 encodes ferritin light chain responsible for maintaining iron stores and homeostasis in the brain. A dysfunction in iron regulation due to this mutation leads to characteristic symptoms associated with deposition of iron as seen in neuroferritinopathy. This molecular test detects the mutations within FTL1 that provide a definitive diagnosis when imaging and clinical signs have pointed toward neuroferritinopathy. Once the FTL1 mutation is identified in a patient, other family members can be provided with genetic testing to identify asymptomatic carriers. Genetic counseling is recommended for families with the disease since this is caused by an autosomal dominant gene and is therefore carried by each child born from a subject with 50% chances of hosting the mutational change.

The significance of dynamic assessment of family history cannot be overestimated, given the rarity of neuroferritinopathy. The knowledge of the clinical pattern of the disease in the family will reveal asymptomatic carriers and persons with early, barely detectable manifestations of the disease. Regular testing should be offered to all members of families with the known FTL1 mutation so that neuroferritinopathy may be diagnosed and treated early before the symptoms seriously affect the quality of their lives. This will be beneficial not only in the follow-up and support of asymptomatic carriers but also in the understanding of the disease course and participation in clinical trials for emerging therapies. Neuroferritinopathy being a progressive condition, the earlier the diagnosis with intervention, the better it will result in the management of symptoms, provision of supportive care, and maintenance

of quality of life if possible.

2.5. Management and treatment

Currently, there is no cure for neuroferritinopathy, so treatment primarily focuses on managing symptoms and enhancing patients' quality of life. Supportive care includes pharmacological treatments aimed at controlling motor symptoms such as dystonia, chorea, and rigidity. For example, dopamine replacement therapies, commonly used for Parkinson's disease, are employed to help alleviate dystonia, offering some relief but not halting disease progression.[13] These medications work by compensating for the neurotransmitter imbalances caused by neurodegeneration in the basal ganglia, although their effects in neuroferritinopathy are modest. Anticholinergic drugs are also used to manage muscle spasms, while botulinum toxin injections are sometimes applied to reduce muscle stiffness and involuntary movements, helping patients manage daily discomfort.

In addition to medication, managing neuroferritinopathy often involves iron-chelating agents designed to reduce iron levels in the brain. Drugs like deferiprone and deferoxamine are examples of chelators that bind to excess iron, allowing it to be removed from the brain and body, thereby potentially reducing iron's neurotoxic effects. These drugs have shown some potential in reducing the brain iron content, but their efficacy in altering disease progression remains limited, and hence further research is being done to improve these therapies. Chelation therapy is practiced with caution, given possible side effects like reduction of systemic iron levels, which might affect overall health, and thus careful monitoring is necessary.[14] Clinical studies are currently in progress to test the long-term effects of iron chelators on neuroferritinopathy patients and seek new active agents that may target more specifically brain iron deposits with fewer adverse events.

Most specifically, promising new treatments are explored in gene therapy. Research in gene therapy targets the correction or mitigation of the mutation in the FTL1 gene responsible for neuroferritinopathy and hence could offer a cure for this debilitating condition in the future. Though still in their experimental stages, these therapies pursue the modification of the gene responsible for dysfunctional iron metabolism with potential decrement in iron accumulation and associated neurodegeneration, offering hope beyond symptomatic relief.[15] Further research is ongoing in neuroprotective agents and antioxidant therapies, considering the need to counteract the oxidative stress caused by excess iron in brain cells. Such treatments may offer protection of neurons from oxidative damage, with the added benefit of slowing disease progression and improving quality of life.

2.6. Prognosis of neuroferritinopathy

Neuroferritinopathy is an inflammatory neurological disorder that has a generally poor prognosis, as it is currently incurable and the disease is relentlessly progressive. The rate of disease progression is slow, with a concomitant decline in both motor and cognitive functions, which leaves the patients completely dependent on their caregivers. The movement disorder becomes progressively more severe, with dystonia predominating but with additional features of chorea and bradykinesia. Cognitive and psychiatric manifestations also worsen, leading to profound disability.[16] As the disease progresses, patients lose their basic motor functions, which makes speaking, walking, and even swallowing increasingly difficult. Cognitive impairment often follows, characterized by amnesia, executive impairment, and, in the final stages, dementia, which further destroys independence and quality of life. Such an unrelenting trajectory often renders patients dependent upon full-time caregiving to support them through basic self-care activities-a testimony to the formidable neuroferritinopathy challenges and a reminder of how family dynamics and quality of life can be so dramatically affected.

However, the relentless nature of the disease still allows many supportive treatments to alleviate symptoms in and improve the quality of life of neuroferritinopathy patients. Such drugs as muscle relaxants and anticholinergic ones could reduce movement disorders; thus, making common life activities partially easier and less distressing. Speech and physical therapy also play an important role: speech therapy-things that can be undertaken, which aim at maintaining functions of communication, and physical therapy-attempts to preserve mobility and muscle function as far as possible, enabling patients to stay active.[17] These would address psychiatric symptoms common in neurodegenerative conditions, including depression and anxiety, which improve the quality of life. Psychological support, along with directed pharmacological intervention, can be helpful in managing the emotional stressors associated with neuroferritinopathy and thereby help the patients and their families cope better with the challenges posed by the disease and adapt to new caregiving roles.

Assistive devices and environmental modifications serve to enhance safety and independence among individuals with neuroferritinopathy. Walking aids, hand-held communication devices, and home modifications are some of the devices and modifications that support daily activities, enabling patients to be as independent as possible while minimizing injury risks associated with mobility problems.[18] Vehicles adapted for accessibility can enable mobility outside the home, reducing social isolation and generally improving quality of life by keeping patients connected to their communities. With the advancement of the disease, such aids become important to help the

patient safely live through various physical limitations and preserve a semblance of independence. Neuroferritinopathy will eventually lead to marked decline both physically and cognitively, but by employing assistive technologies judiciously, affected individuals can have meaningful interactions and continue with a sense of autonomy. These adaptations also benefit caregivers by affording them greater ease in assisting the patients and therefore serve to enhance the caregiving experience and reduce the burden of care.

Neuroferritinopathy progresses variably, with some experiencing a more rapid decline than others may, further indicating the variability within neuroferritinopathy itself. This variability further raises the need for active research regarding new therapies aimed at slowing down its progression and improving symptom management in offering hope for more tailored treatment options. Gene therapy, iron chelation, and neuroprotective agents remain active fields of study for further options that may target the underlying mechanisms of the disease.[19] A potential slowing in the progression of neuroferritinopathy could offer major relief to patients and their families, who must endure the difficult trajectory of this debilitating disease. Though these experimental treatments themselves are in the promising stages of development, such a pursuit of innovative therapies reflects commitment by the medical community toward the enhancement of outcomes for neuroferritinopathy patients and offering a better quality of life, fostering hope for those impacted by this challenging condition.

2.7. Future directions in neuroferritinopathy research

Future research in neuroferritinopathy will be directed to understand the molecular mechanisms leading to neuronal iron accumulation and seeking ways to prevent this pathological process, with the hope of fundamentally altering the course of the disease. Central to the progression of the disease is the accumulation of iron within neurons, leading to oxidative stress and cellular damage that manifests as neurodegenerative symptoms in patients. By studying how this iron imbalance occurs at the molecular level, strategies to prevent or reverse such harmful accumulations can be developed. In this regard, one of the most important areas of interest is gene therapy, promising to impact neuroferritinopathy at its very root by targeting the FTL1 gene mutation responsible for faulty iron regulation. Gene therapy may correct or replace the malfunctioning gene and consequently reestablish normal iron metabolism in the brain, preventing further damage to neurons. This could be a revolutionary approach that might alter the practice from symptomatic management to actual cure for neuroferritinopathy and bring hope to the patients and their families, and might also change treatment paradigms for neurodegenerative diseases.

Another promising frontier in the study and management of neuroferritinopathy is provided by advances in the realm of neuroimaging. Advanced MRI techniques have only just begun to give unprecedentedly detailed views of iron deposition in the brain, particularly in areas of highest involvement commonly seen in neuroferritinopathy. Techniques such as functional MRI (fMRI) and Susceptibility Weighted Imaging (SWI) detection of simple changes in iron levels; hence, the efficiency of the disease's progression and treatment regarding new treatments can be processed. Besides, these types of advanced imaging techniques allow the researcher to infer the correlation of iron deposition with neurological dysfunction by highlighting how iron affects health and function in the brain. Clearly, such an improvement in imaging capability will increase not only diagnostic precision but will also serve as an important tool for monitoring treatment efficacy and guiding therapeutic adjustments over time. Imaging, in the future of neuroferritinopathy study, will play an imperative role both in early diagnosis and in therapeutic monitoring of the disease, as it can visualize and measure disease markers with a high degree of precision, thus further advancing patient care.

Biomarkers represent another critical development in the early detection and management of neuroferritinopathy. Other than gene therapy or imaging, biomarkers provide molecular or biochemical indicators that reflect the state of iron metabolism in the brain, often before clinical symptoms surface. These biological markers could serve as predictors of iron imbalance, which would allow the clinician to identify those at risk before they show neurological signs, thus enabling proactive treatment. Validated biomarkers may allow the implementation of early intervention strategies that delay disease progression before irreversible brain damage has occurred.[20] If biomarkers were stable and could be measured in a consistent manner over time, there would be many more opportunities for healthcare providers to institute much earlier therapeutic measures that might alter the trajectory of the disease and improve quality of life. Biomarkers could then guide personalized treatment in selecting appropriate interventions for a patient's specific disease characteristics, thus improving overall prognosis and quality of life in individuals with neuroferritinopathy.

Alongside these advancements, neuroferritinopathy research also needs a multidisciplinary approach whereby neuroscientists, geneticists, and clinicians come together for the development of innovative therapeutic approaches and to address the complex aspects of the disease at large. The relationship between genetic mutation and iron metabolism concerning neuronal health requires treatment that shall incorporate all the aspects of the disease. Such topics for further research may include

gene therapy, biomarkers, and advanced imaging into a comprehensive approach, addressing both the root cause while facilitating ongoing monitoring of the disease process and personalized intervention. By integrating these new technologies and approaches, a proactive framework for the management of neuroferritinopathy should be enabled by both researchers and clinicians, moving toward preventive but curative treatments. As these fields continue to evolve, they provide a base upon which a future with hopefully much-improved outcomes and quality of life is envisioned for neuroferritinopathy patients, thereby redefining the prognosis for this debilitating disease.

3. Conclusion

Neuroferritinopathy is a very rare, incapacitating neurodegenerative disease caused, in most instances, by mutations in the FTL1 gene that disrupt normal iron regulation in the brain. The resultant genetic alteration leads to the accumulation of iron, especially in the basal ganglia, which in turn causes progressive movement disorders, cognitive decline, and other severe neurological symptoms. While much has been understood about the pathophysiology and genetic underpinnings of neuroferritinopathy, effective treatments remain very limited. Current treatment methods are mainly palliative, aiming at symptomatic management and enhancement of the quality of living without arresting the progression of the disease. The realization of curative treatments is difficult because of the complexity of iron metabolism in the brain, besides difficulties in directly addressing the FTL1 mutation. This basically leaves patients and families with the grim reality that progressive disability makes new options for therapy overwhelmingly needed for these patients.

Some of the possible avenues include gene therapy and iron chelation, promising ways of improved treatments. Gene therapy would seek to correct the genetic mutation responsible for neuroferritinopathy, thus hopefully normalizing iron metabolism and perhaps arresting or even reversing the disease process. Iron chelation therapy, although in its limited scope yet, may also employ treatments directed toward reducing iron accumulation in the brain and thus diminishing oxidative stress and neuronal damage. These techniques are experimental and may take some years before they can be applied.

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None.

5. Conflict of Interest

None.

References

1. Pardo-Moreno T, García-Morales V, Suleiman-Martos S, Rivas-Domínguez A, Mohamed-Mohamed H, Ramos-Rodríguez JJ, et al. Current Treatments and New, Tentative Therapies for Parkinson's Disease. *Pharmaceutics*. 2023;15(3):770. doi:10.3390/pharmaceutics15030770.
2. Ems T, Huecker MR, Lucia K. Biochemistry, Iron Absorption. Treasure Island (FL): StatPearls Publishing; 2023.
3. Ghaderi S, Amir S, Mohammadi S, Fatehi F. Iron quantification in basal ganglia using quantitative susceptibility mapping in a patient with ALS: a case report and literature review. *Front Neurosci*. 2023;17:1229082. doi:10.3389/fnins.2023.1229082.
4. Nakamura T, Naguro I, Ichijo H. Iron homeostasis and iron-regulated ROS in cell death, senescence and human diseases. *Biochim Biophys Acta Gen Subj*. 2019;1863(9):1398–409.
5. D'Mello SR, Kindy MC. Overdosing on iron: Elevated iron and degenerative brain disorders. *Exp Biol Med (Maywood)*. 2020;245(16):1444–73.
6. García-Sánchez A, Miranda-Díaz AG, Cardona-Muñoz EG. The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- and Antioxidant Properties in Chronic Diseases. *Oxid Med Cell Longev*. 2020;p. 2082145. doi:10.1155/2020/2082145.
7. Everett J, Brooks J, Lermyte F, Connor PO, Sadler PJ, Dobson J, et al. Iron stored in ferritin is chemically reduced in the presence of aggregating Aβ(1-42). *Sci Rep*. 2020;10(1):10332. doi:10.1038/s41598-020-67117-z.
8. Rasul MF, Hussen BM, Salihi A, Ismael BS, Jalal PJ, Zanichelli A, et al. Strategies to overcome the main challenges of the use of CRISPR/Cas9 as a replacement for cancer therapy. *Mol Cancer*. 2022;21(1):64. doi:10.1186/s12943-021-01487-4.
9. Chinnery PF. Neuroferritinopathy. Seattle (WA): University of Washington, Seattle; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1141/.
10. Muthu P, Tan Y, Latha S, Dhanalakshmi S, Lai KW, Wu X, et al. Discernment on assistive technology for the care and support requirements of older adults and differently-abled individuals. *Front Public Health*. 2009;10:1030656. doi:10.3389/fpubh.2022.1030656.
11. Lehéricy S, Roze E, Goizet C, Mochel F. MRI of neurodegeneration with brain iron accumulation. *Curr Opin Neurol*. 2020;33(4):462–73.
12. Guan X, Lancione M, Ayton S, Dusek P, Langkammer C, Zhang M, et al. Neuroimaging of Parkinson's disease by quantitative susceptibility mapping. *Neuroimage*. 2024;289:120547. doi:10.1016/j.neuroimage.2024.120547.
13. National Institute of Neurological Disorders and Stroke. Parkinson's Disease: Challenges, Progress, and Promise | National Institute of Neurological Disorders and Stroke [Internet]; 2023. Available from: https://www.ninds.nih.gov/current-research/focus-disorders/parkinsons-disease-research/parkinsons-disease-challenges-progress-and-promise.
14. Porter J, Kattamis A, Cappellini MD. Iron chelation [Internet]. In: 2021 Guidelines: For the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 4th edition. Nicosia (Cyprus): Thalassaemia International Federation; 2023.
15. Ndayisaba A, Kaindlstorfer C, Wenning GK. Iron in Neurodegeneration - Cause or Consequence? *Front Neurosci*. 2019;13:180. doi:10.3389/fnins.2019.00180.
16. Morozova A, Zorkina Y, Abramova O, Pavlova O, Pavlov K, Soloveva K, et al. Neurobiological Highlights of Cognitive Impairment in Psychiatric Disorders. *Int J Mol Sci*. 2022;23(3):1217. doi:10.3390/ijms23031217.
17. Schwab SM, Dugan S, Riley MA. Reciprocal Influence of Mobility and Speech-Language: Advancing Physical Therapy and Speech Therapy Cotreatment and Collaboration for Adults with Neurologic Conditions. *Phys Ther*. 2021;101(11):pzab196. doi:10.1093/ptj/pzab196.
18. Morris L, Cramp M, Turton A. User perspectives on the future of mobility assistive devices: Understanding users' assistive device experiences and needs. *J Rehabil Assist Technol Eng*. 2022;p. 20556683221114790. doi:10.1177/20556683221114790.

19. Marupudi N, Xiong MP. Genetic Targets and Applications of Iron Chelators for Neurodegeneration with Brain Iron Accumulation. *ACS Bio Med Chem Au*. 2024;4(3):119–30.
20. Ausó E, Gómez-Vicente V, Esquiva G. Biomarkers for Alzheimer's Disease Early Diagnosis. *J Pers Med*. 2020;10(3):114. doi:10.3390/jpm10030114.

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