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PROPOSED PLAN TO DELAY THE ONSET OF SYMPTOMS OF INHERITED GENETIC DISEASES USING NATURAL PRODUCTS

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ABSTRACT

In genetic diseases, mutated genes markedly elevate existing oxidative stress and chronic inflammation, which contribute to the rapid development of disease symptoms. At present, there is no established plan to delay the onset of symptoms of genetic diseases. We propose a novel plan to delay the onset of symptoms of four genetic diseases: familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, and sickle cell anemia. This plan includes simultaneously reducing oxidative stress and chronic inflammation with an appropriate micronutrient mixture and abolishing the harmful effects of intestinal dysbiosis through supplementation with probiotics and prebiotics. Except in Huntington's disease, daily use of collagen peptides may reduce the rate of progression and improve some symptoms of the other three genetic diseases. Daily supplementation with omega-3 fatty acids may replace oxidized, dysfunctional omega-3 fatty acids, slow the rate of progression of these diseases, and improve some of the symptoms of each genetic disease.

KEYWORDS: Delayed progression; genetic diseases; micronutrients; probiotics; collagen peptides; omega-3 fatty acids.

1. INTRODUCTION

Before discussing the factors that lead to the rapid development of symptoms of inherited genetic diseases, it is essential to describe the factors that gradually initiate and promote the development of the corresponding acquired diseases. It has been suggested that increased oxidative stress, chronic inflammation, intestinal dysbiosis (an increase in the number of harmful bacteria and a decline in the number of beneficial bacteria), loss of collagen, and dysfunctional omega-3 fatty acids are primary causes of acquired diseases. The rate of progression of acquired diseases depends on diet, lifestyle, and environmental toxins.

Mutated genes inherited from parents often trigger increased oxidative stress and inflammation, which may further aggravate intestinal dysbiosis, loss of collagen, and dysfunctional omega-3 fatty acids. Together, these factors may be primarily responsible for increasing the rate of disease progression and causing symptoms to appear at an early age. In fact, studies of individuals with inherited genetic diseases have demonstrated elevated blood levels of biochemical markers of oxidative stress and inflammation at an early age; these processes play a central role in the early onset of disease symptoms.[1,2] At present, there are no effective plans to delay disease onset in these patients.

This review will show that, in selected inherited genetic diseases, individuals have greater oxidative stress and chronic inflammation at an early age than individuals with the corresponding acquired diseases. These conditions allow the disease to progress rapidly, causing symptoms to appear at a much earlier age. This review will also show that intestinal dysbiosis, loss of collagen, and dysfunctional omega-3 fatty acids participate in the progression of inherited genetic diseases and may increase the rate of disease progression. This review proposes that the use of natural products, such as a micronutrient mixture, probiotics with prebiotics, collagen peptides, and omega-3 fatty acids, may markedly delay disease onset in selected genetic

diseases, including familial Alzheimer's disease (FAD), familial Parkinson's disease (FPD), Huntington's disease (HD), and sickle cell anemia.

Familial Alzheimer's Disease (FAD)

Increased oxidative stress and neuroinflammation in familial Alzheimer's disease (FAD): Alzheimer's disease (AD) is a serious, progressive, and irreversible neurodegenerative disorder characterized by the gradual loss of cognitive function due to the degeneration and death of cortical neurons in the brain. In the United States, more than 90% of cases are acquired during a person's lifetime, while 5–10% of AD cases are considered familial. Individuals carrying mutations in the AD genes encoding amyloid precursor protein (APP), presenilin-1 (PSEN1), or presenilin-2 (PSEN2) experience accelerated, early-onset AD-related neurodegenerative changes caused by a vicious cycle of high beta-amyloid production, increased oxidative stress, and chronic inflammation. These mutations induce mitochondrial dysfunction, causing reduced energy production and heightened microglial activation that enhances neuroinflammation. These cellular changes cause substantial brain damage and rapid cognitive decline.[3–7] Increased oxidative stress increases the activity of the enzyme gamma-secretase, which rapidly cleaves amyloid precursor protein (APP) into beta-amyloids.[8,9] Beta-amyloids cause the neurodegeneration and death of cholinergic neurons by producing free radicals.[10,11] Increased oxidative stress also causes hyperphosphorylation of tau protein.[12] Oxidative stress activates glial cells, which produce neuroinflammation in the brain. Both increased oxidative stress and neuroinflammation accelerate the progression of FAD symptoms.

Intestinal dysbiosis in familial Alzheimer's disease (FAD): Intestinal dysbiosis refers to an increase in the number of harmful bacteria and a decline in the number of beneficial bacteria. Harmful bacteria produce many toxic chemicals, including pro-inflammatory cytokines. Mutations associated with familial Alzheimer's disease (FAD) promote intestinal dysbiosis, which causes systemic inflammation and breakdown of the gut–blood barrier, leading to accelerated beta-amyloid aggregation and cognitive decline at an early age. Enhanced intestinal dysbiosis causes a hyperresponsive immune system, leading to the activation of microglial cells, which increases the rate of progression of FAD symptoms.[13–16]

Collagen in familial Alzheimer's disease (FAD): Specific brain collagens, such as collagen VI and collagen XVIII, are upregulated in FAD. These locally secreted collagens often bind to beta-amyloid, forming dense amyloid plaques. The upregulation of collagen IV causes stiffness of blood vessels in the brain, which leads to cognitive dysfunction.[17] Mice lacking the collagen VI gene show increased spontaneous neuronal apoptosis and greater sensitivity to oxidative stress.[18] This suggests that familial AD may involve a loss of collagen VI that contributes to the rapid progression of AD symptoms. Therefore, supplementation with collagen VI may protect against beta-amyloid toxicity.[19]

Dysfunctional omega-3 fatty acids in familial Alzheimer's disease (FAD): Dysfunctional omega-3 fatty acids are not inherited as such, but in the presence of high oxidative stress, they are easily oxidized and become dysfunctional. In addition, supplemented omega-3 fatty acids, especially docosahexaenoic acid (DHA), function normally outside the brain in FAD; however, within the brain, the genetically driven accumulation of amyloid-beta (Aβ) plaques creates a toxic microenvironment that disrupts the mechanisms required to deliver omega-3 fatty acids to brain cells.[20–22]

Abnormal behavior in familial Alzheimer's disease (FAD): Familial Alzheimer's disease (FAD) is an early-onset inherited genetic disease that causes serious neuropsychiatric and behavioral abnormalities. These noncognitive symptoms include severe apathy, depression, anxiety, agitation, and psychosis. These symptoms may appear before the decline in cognitive function and become worse as the disease progresses.[23–26]

Familial Parkinson's Disease (FPD)

Increased oxidative stress and neuroinflammation in familial Parkinson's disease (FPD): Parkinson's disease (PD) is a chronic, progressive neurological disease associated with the loss of dopaminergic neurons in the substantia nigra pars compacta of the brain. PD is also a complex genetic disease caused by a combination of aging, environmental factors, and genetic factors.[27] Most PD cases are acquired. Only about 10% of patients carry a familial mutation in a PD gene.[28] Of the six genes unequivocally linked to heritable monogenic PD, mutations in SNCA (alpha-synuclein) and LRRK2 (leucine-rich repeat kinase 2) are responsible for autosomal-dominant forms of PD. Mutations in the Parkin gene, PINK1 (PTEN-induced kinase 1), DJ-1 (also called the PARK7 gene), and ATP13A2 (also called PARK9) are responsible for PD with an autosomal-recessive mode of inheritance.[29,30] These PD mutations markedly enhance oxidative stress through multiple pathways, including mitochondrial damage.[31–33] Oxidative stress activates glial cells, which produce neuroinflammation in the brain. Both increased oxidative stress and neuroinflammation accelerate the progression of disease symptoms.

Intestinal dysbiosis in familial Parkinson's disease (FPD): Intestinal dysbiosis refers to an increase in the number of harmful bacteria and a decline in the number of beneficial bacteria. Harmful bacteria produce many toxic chemicals, including pro-inflammatory cytokines. Intestinal dysbiosis disrupts the intestinal barrier and is strongly implicated in triggering alpha-synuclein misfolding, which may spread to the brain through the vagus nerve along the gut–brain axis, causing the early

appearance of PD symptoms. Several studies show that both oral and intestinal dysbiosis play an important role in the initiation and progression of PD symptoms.[34–38]

Loss of collagen in familial Parkinson's disease: Mutations in PD markedly enhance oxidative stress through multiple pathways, including mitochondrial damage.[31–33] Oxidative stress activates glial cells, which produce neuroinflammation in the brain. Both increased oxidative stress and neuroinflammation accelerate the progression of disease symptoms. Increased oxidative stress enhances the activity of collagenase, which degrades collagen.[39]

Genes associated with familial Parkinson's disease (FPD) enhance oxidative stress by triggering the production of additional reactive oxygen species (ROS), which directly activate matrix metalloproteinases (MMPs), including collagenases such as MMP-1 and MMP-9, leading to a gradual loss of collagen. Enhanced oxidative stress activates glial cells, which release mediators of neuroinflammation. Together, these processes contribute to the degeneration of dopaminergic neurons in the substantia nigra. Mutations in familial PD genes such as DJ-1, PINK1, and Parkin cause mitochondrial dysfunction, which drastically increases cellular oxidative stress. Mutated alpha-synuclein rapidly aggregates, causing enhanced oxidative stress and neuroinflammation.[40–43] These mechanisms demonstrate the interconnected relationship among genetics, oxidative stress, and collagenase activity in PD. Increased collagenase activity may degrade collagen in the brain, causing decreased collagen levels in certain regions and increased cognitive dysfunction.

Omega-3 fatty acids in familial Parkinson's disease: Because increased oxidative stress and neuroinflammation play a central role in the progression of familial PD, omega-3 supplementation may reduce neuroinflammation and oxidative stress and thereby slow the progression of familial PD. Omega-3 supplementation may also improve impaired mitochondrial function in familial PD. Some clinical trials and systematic reviews indicate that adjunctive omega-3 therapy may attenuate general PD symptoms and reduce depressive symptoms.[44–46]

Huntington's Disease (HD)

Huntington's disease is a hereditary, progressive neurological disorder caused by a mutation in the HD gene on chromosome 4. Unaffected individuals typically have fewer than 27 CAG (cytosine, adenine, and guanine) repeats. However, individuals with HD generally have 36 or more repeats. The larger the CAG expansion, the more severe the symptoms and the earlier the onset of the diseas. [47,48]

The inheritance pattern is autosomal dominant, meaning that only one copy of the mutated gene, inherited from either biological parent, is required for a person to develop HD. If a parent carries the mutated gene, each child has a 50% chance of inheriting it. Children who do not inherit the gene will neither develop nor pass on the disease. Sporadic cases of HD can occur spontaneously without a family history in approximately 1–3% of the population. It is estimated that the incidence of HD in the United States is approximately 1,550 cases per year.

Huntington's disease (HD) is a progressive, fatal, autosomal-dominant, hereditary, and currently incurable neurodegenerative disease of the brain in which the striatum and cortex, which are primarily involved in regulating movement, intellect, and emotions, are gradually destroyed. The disease is characterized by jerking, uncontrollable movements of the limbs, trunk, and face (chorea); progressive loss of cognitive function; and the development of psychiatric problems. Muscle rigidity progresses rapidly, leading to akinesia (loss of control of voluntary muscle movements).[49]

Increased oxidative stress and neuroinflammation in HD: Expansion of the CAG trinucleotide repeat in the HD gene drives Huntington's disease by producing a toxic mutant huntingtin protein. This mutation causes severe mitochondrial dysfunction, leading to the excessive release of reactive oxygen species (ROS), as well as early immune-cell activation, which produces neuroinflammation. Together, these processes cause neurodegeneration. As the CAG repeat expands, the level of oxidative stress increases.[50–53]

Increased neuroinflammation enhances the rate of neurodegeneration. The mutant HD gene disrupts defensive signaling pathways, such as the Nrf2 pathway, thereby preventing the formation of new antioxidant enzymes.[54,55]

Approximately 5% of patients who develop symptoms of Huntington's disease before 21 years of age are classified as having juvenile Huntington's disease. The expanded CAG repeat in the huntingtin gene causes early disease onset. Age at onset is inversely correlated with CAG repeat length. Patients with juvenile Huntington's disease show more severe pathology in the involved brain structures than patients whose disease begins in adulthood.[56 57]

Intestinal Dysbiosis in Huntington's Disease (HD)

Intestinal dysbiosis is strongly associated with gastrointestinal distress, unintended weight loss, and worsening motor and cognitive symptoms. It also impairs the integrity of the intestinal barrier, which can allow harmful bacteria to enter the blood. It increases the production of pro-inflammatory cytokines and oxidative stress and also enhances the rate of cognitive decline.[58–61]

Collagen in Huntington's Disease (HD)

Collagen plays no significant role in the progression of HD.

Omega-3 Fatty Acids in Huntington's Disease (HD)
Omega-3 fatty acids may support the management of HD by reducing neuroinflammation, stabilizing mitochondrial function, and mitigating severe weight loss. They may also help reduce the rate of cognitive decline and improve psychiatric symptoms such as depression and irritability.[62–64]

Familial Sickle Cell Anemia
Sickle cell anemia is an inherited genetic blood disorder in which red blood cells become rigid, sticky, and crescent-shaped. This prevents normal blood flow, causing severe pain, anemia, and a higher risk of infection. This genetic disease is inherited in an autosomal-recessive pattern. Both parents must pass on a copy of the mutated gene for their child to have the disease. If a child receives the gene from only one parent, the child has sickle cell trait. Such individuals are generally healthy carriers but can pass the gene to their own children.[65]

Prevalence: In the United States, sickle cell anemia occurs in approximately 1 in every 365 Black or African American births, compared with 1 in 16,300 Hispanic American births and an even lower rate among White births.[66]

Increased Oxidative Stress and Chronic Inflammation in Sickle Cell Anemia
Oxidative stress and chronic inflammation form a vicious, self-amplifying cycle in sickle cell anemia. Repeated red blood cell sickling causes hemolysis (premature destruction of red blood cells), releasing free hemoglobin into the bloodstream. This release generates extensive reactive oxygen species (ROS), which cause systemic chronic inflammation, vaso-occlusive crises, and progressive tissue damage.[67–69]

Intestinal dysbiosis in sickle cell anemia: Intestinal dysbiosis is present in individuals with sickle cell anemia. Chronic hypoxia, recurrent abdominal ischemia, opioid use, and prophylactic antibiotics aggravate dysbiosis, thereby enhancing inflammation. Intestinal dysbiosis impairs intestinal barrier integrity, leading to a "leaky gut." It also increases the risk of infection and worsens vaso-occlusive pain crises.[70–73]

Collagen in Sickle Cell Anemia
Chronic leg ulcers are a common and debilitating complication of sickle cell anemia. Because these ulcers are highly resistant to standard medical therapy, the topical application of collagen peptides has been useful in promoting healing. Collagen peptides can also be used as biomarkers in the blood for bone complications and bone disease in sickle cell anemia.[74–78]

Omega-3 Fatty Acids in Sickle Cell Anemia
Red blood cells in sickle cell anemia are stiff and depleted of omega-3 fatty acids. Supplementation with omega-3 fatty acids, particularly EPA and DHA, can help rebalance red blood cell membranes and reduce chronic inflammation in sickle cell anemia. Clinical studies show that omega-3 supplementation can decrease the frequency of painful vaso-occlusive crises, lower rates of severe anemia, and reduce the need for blood transfusions. Multiple studies and clinical trials have demonstrated the benefits of omega-3 supplementation as adjunctive therapy in both adults and children. Daily use of omega-3 fatty acids can reduce pain episodes from 7.8 per year to 3.8 per year. Supplementation with omega-3 fatty acids causes significant reductions in the rate of severe anemia and the overall need for blood transfusions. Omega-3 supplementation also reduces inflammation and oxidative stress associated with sickle cell anemia.[79,80]

Proposed Plan to Delay the Onset of Symptoms of Familial Alzheimer's Disease, Familial Parkinson's Disease, Huntington's Disease, and Sickle Cell Anemia
Reducing oxidative stress and chronic inflammation: Mutated genes aggravate existing oxidative stress and chronic inflammation in familial genetic diseases. Therefore, reducing oxidative stress and chronic inflammation may help delay the symptoms of familial Alzheimer's disease (familial AD), familial Parkinson's disease (familial PD), Huntington's disease (HD), and sickle cell anemia (SCA). To reduce oxidative stress and chronic inflammation simultaneously, it is essential to elevate the levels of both antioxidant enzymes and antioxidant compounds. Elevating antioxidant enzymes requires the activation of Nrf2, a nuclear transcription factor. Normally, reactive oxygen species (ROS) activate Nrf2, but during prolonged oxidative stress, Nrf2 becomes resistant to ROS and can be reactivated by certain antioxidants (6). A novel micronutrient mixture contains multiple antioxidants, some of which can activate ROS-resistant Nrf2 (6). Daily supplementation with this micronutrient mixture may simultaneously reduce oxidative stress and chronic inflammation in all four genetic diseases discussed.

Abolishing the impact of intestinal dysbiosis: Because intestinal dysbiosis contributes to the rapid progression of symptoms in all four genetic diseases discussed, supplementation with probiotics and prebiotics may slow the progression of these diseases.

Loss of collagen: Collagen has no significant role in the progression of Huntington's disease, but it plays a significant role in familial AD, familial PD, and sickle cell anemia. Loss of collagen may increase the rate of progression of these diseases. Therefore, supplementation with collagen peptides and collagenase inhibitors may reduce disease progression and improve some symptoms.

Dysfunctional omega-3 fatty acids: Because oxidative stress and chronic inflammation are present in all four diseases discussed here, and because omega-3 fatty acids

are easily oxidized, they can become dysfunctional and impair brain function. Therefore, supplementation with omega-3 fatty acids may slow the progression of these diseases and improve some symptoms of each disease.

CONCLUSIONS

Mutated genes associated with genetic diseases often trigger increased oxidative stress and inflammation, which further aggravate intestinal dysbiosis, loss of collagen, and dysfunctional omega-3 fatty acids. Together, these factors may be primarily responsible for increasing the rate of disease progression and causing symptoms to appear at an early age. At present, there are no effective plans to delay disease onset in patients with inherited genetic diseases. Because increased oxidative stress, chronic inflammation, intestinal dysbiosis, loss of collagen, and dysfunctional omega-3 fatty acids participate in the rapid progression of disease, reducing these factors may delay the onset of symptoms. Supplementation with a micronutrient mixture may reduce oxidative stress and chronic inflammation; probiotics with prebiotics may reverse the harmful effects of intestinal dysbiosis; collagen peptides may be beneficial in all of the selected diseases except Huntington's disease (HD); and omega-3 fatty acids may replace oxidized, dysfunctional omega-3 fatty acids. Together, these approaches may delay the onset of symptoms in all four selected genetic diseases: familial Alzheimer's disease, familial Parkinson's disease, HD, and sickle cell anemia.

Conflict of interest: The author is the Chief Scientific Officer of Engage Global, a Utah-based company that sells nutritional products to consumers.

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