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Glycosphingolipids Associated Metabolic Disorders

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Abstract:

Lipids play diverse roles in sustaining life, including energy storage, hormonal balance, and cellular communication. Alterations in lipid metabolism can lead to various disorders, including diabetes, atherosclerosis, cancer, and neurodegenerative diseases. Among these disorders, lysosomal storage disorders (LSDs) related to glycosphingolipids metabolism present significant challenges. This review systematically analyzes the current literature on LSDs, focusing on classification, clinical presentations, diagnostic advancements, available treatments, and emerging therapeutic strategies. Glycosphingolipids biosynthesis, particularly its role in viral dissemination and melanin synthesis, underscores its significance in health and disease. Additionally, the review delves into specific LSDs, such as Fabry disease, Gaucher disease, Sandhoff disease, Tay-Sachs disease, and Krabbe disease, highlighting their pathophysiology, prevalence, and treatment options. Enzyme replacement therapy and hematopoietic stem cell transplantation are mainstays in LSD treatment, but gene therapy shows promise. Furthermore, the review explores the role of glycosphingolipids in non-communicable diseases like diabetes, cancer, atherosclerosis, lupus, Alzheimer's, Parkinson's disease, and influenza. Understanding glycosphingolipid metabolism offers insights into disease mechanisms and therapeutic targets, paving the way for improved treatments and ultimately enhancing patient outcomes.

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INTRODUCTION

Lipids have several life-sustaining functional, structural, and regulatory roles [1], including energy stockpile, hormone balance, nerve impulse transference, and fat-soluble nutrient transportation [2]. It modulates membrane protein activities (signalling receptor) in the form of glycosphingolipids [3,4], and also serves in cell growth, cell differentiation [1,4], proliferation, cell adhesion, and pathogen entry [1,5]. The dietary sources of glycosphingolipid include animal-based foods like meat and egg yolks which contain sphingomyelin and glucosylceramide. Milk and dairy products also have sphingomyelin, along with lactosylceramide. [6]. Glycosphingolipid biosynthesis is required for the viral dissemination of Influenza and severe acute respiratory syndrome coronavirus 2 [1]. It also support melanin synthesis by assisting the Tyrosinase enzyme in reaching melanocytes [7,18]. However, disruptions in lipid metabolism contribute to a range of disorders, including type II diabetes [8], atherosclerosis [9], lupus [10], asthma [11], cancer [12,13,14], inflammation [15], and neuropathies such as Alzheimer's and Parkinson's disease [1]. It may also cause glycosphingolipid storage diseases [16,17] such as Fabry disease, Gaucher disease, Sandhoff, Tay-Sachs disease, and Krabbe disease [18]. Among the accumulation of various substrates, few reported lysosomal storage disorders related to glycosphingolipids and some other diseases seem pertinent for further study. This review will examine the current research on glycosphingolipid metabolic disorders. It will cover different types of disorders, their symptoms, recent discoveries about their causes and diagnosis, available treatments, and their shortcomings. The review will also discuss new treatment ideas. The goal is to advance research and improve the lives of people with these disorders.

Glycosphingolipids synthesis occurs during the passage of substrates through the Golgi cisternae and depends on competing reactions catalyzed by Golgi-resident enzymes [3]. It starts in the cytosolic aspects of the Endoplasmic Reticulum with the formation of ceramide molecules through Ceramide Synthases. Synthesis of the oligosaccharide part of globotriaosylceramide (a subclass of glycosphingolipid) also occurs in the Golgi apparatus [3,4]. A lipid skeleton conjugates with an oligosaccharide to form globotriaosylceramide. Sphingosine and a fatty acid combine to form its lipidic part, including an amide bond that produces one ceramide molecule. If some modification is made on sphingosine, it makes analogs while isoforms are made if the same is done on fatty acid. These modifications are responsible for ceramide heterogeneity. The affinity of Shiga toxin, which is a toxin from bacteria, for globotriaosylceramide binding depends upon these changes. However, the lipidic fragment can modify the Shiga toxin remembrance according to its length and ratio of unsaturation, but the oligosaccharide part remains the main Shiga toxin recognition domain. The modification of lipidic fraction is considered as the biomarker for the disclosure of various analogs and isoforms in the plasma and urine of Fabry patients [4]. For instance – there are four crucial phases in the lysosome where globotriaosylceramide degradation takes place: 1) The terminal α-galactose residues in globotriaosylceramide are removed by α-Galactosidase A, which leaves Lactosylceramide; 2) The remaining terminal β-galactose residue in lactosylceramide is removed by GalCer-β-galactosidase, which leaves glucosylceramide; and 3) glucosylceramide -β-glucosidase eliminates the terminal glucose from the ceramide. Lastly, 4) acid ceramidase breaks down the fatty acid chain in the ceramide to produce sphingosine [3,4].

Lack of lysosomal enzyme activity due to gene mutations results in the buildup of substances like carbohydrates, lipids, proteins, and cellular waste in various organs, causing lysosomal storage disorders. These inherited metabolic diseases encompass over seventy different conditions [17,19,21]. Christian de Duve discovered Lysosome in 1955 and after ten years of that Hers developed the concept of lysosomal disease. However, in the 19th century many lysosomal storage disorders have been recognized and continued well into the 20th century, but not knowing about lysosomes, kept the fact hidden that various diseases share common features of lysosomal storage [22]. The global occurrence of lysosomal storage disorders is estimated to be approximately 1 in every 5,000 to 7,500 births [17].

1. ANDERSON-FABRY DISEASE

Fabry disease is a recessive monogenic [23] X-linked disorder and an inborn metabolic error [4,24-26]. Initially identified in 1898 by physicians William Anderson and Johannes Fabry, it manifests with red-purple skin spots termed 'angiokeratoma corporis diffusum' among other symptoms, initially thought to be a type of naevus or developmental defect [27]. However, the disease is a lipidosis [22] stemming from a mutation in the alpha-galactosidase A gene, causing

α-Galactosidase A enzyme deficiency and leading to progressive globotriaosylceramide accumulation in various cell types, including vascular cells, kidney epithelial cells, neuronal cells and cardiac cells [24], particularly in lysosomes. This accumulation triggers cell metabolic collapse, tissue hypertrophy, cell death [23], and multisystem dysfunction, often resulting in cardiac, renal, or cerebrovascular issues and death [25] and early diagnosis is crucial to avert these complications [26]. Initial symptoms in Fabry patients include acroparaesthesia, hypo- or anhidrosis, and heat intolerance due to peripheral neuropathy [29]. The disease, named after the two identifying physicians, is known as Fabry disease [27]. It's considered a rare disease [24,28], with a prevalence rate of 1:8,454 and 1:117,000 among males [23].

Enzyme replacement therapy is used to void the accumulated globotriaosylceramide in India [24], offered to lysosomal storage disorders patients through compassionate access programs by businesses such as Sanofi Genzyme and Takeda Human Genetic Technology [17,30].

2. GAUCHER DISEASE

The first and most common lysosomal storage disorder with an autosomal recessive trait [16,31], and a rare inborn error of metabolism [31] was first time described in 1882 by a French doctor Philippe Gaucher [32]. Mutations in both allelomorphs of the acid β-glucosidase gene, which aids in glucocerebrosidase encoding, are the cause of Gaucher disease. This mutation leads to the inadequacy of glucocerebrosidase in lysosomes which in turn causes [33] the build-up of glucosylceramides (glycosphingolipids) in the lysosomes of tissue macrophages [31] e.g.-lungs, liver, spleen, bones, and bone marrow, brain, and eyes [34]. The build-up of the substrates progresses to spleen and liver enlargement, thrombocytopenia, anemia, immune dysfunction, pulmonary disease, bone pain, osteoporosis, osteolytic lesions, avascular necrosis (osteonecrosis), and destruction of joints [16,33].

Type 1 (which is non-neuronopathic), Type 2 and Type 3 (which are neuronopathic) are considered three sub-class of Gaucher Disease [16]. 99% of Gaucher Disease patients have non-neuronopathic disease (type 1) however type 2 and 3 of the disease consist of the remaining fraction.

The global prevalence of Gaucher disease is about to reach 1:50,000 to 1:40,000 [32]. Despite the burden of fortnightly intravenous infusions, enzyme replacement therapy is highly effective in Gaucher Disease [35].

3. SANDHOFF DISEASE AND TAY SACHS

Sandhoff disease and Tay Sachs are types of sphingolipidoses where the scarcity of the enzyme [36] (β-N-acetylhexosaminidase) leads to the pile-up of substrate GM2 ganglioside in tissues [37], Tay Sachs was first diagnosed by Warren Tay, in April 1881 [38] and in 1887 Bernard Sachs, unaware about the Tay's report wrote about the clinical manifestation and pathologic features, which is later known as infantile Tay Sachs.

Like other lysosomal storage disorders (except Fabry [36]), Sandhoff and Tay Sachs have the autosomal recessive inheritance [36,37] where gene (HEXA and HEXB) encodes β-N-acetylhexosaminidase [36]. The A isoenzyme of hex (HexA, a heterodimer of α and β subunits) is only catabolized GM2 ganglioside and the B isoenzyme (HexB, a homodimer of β subunits) degrades the other uncharged substrate, mutations in the Hex β-subunits affects both HexA and HexB, induces Sandhoff disease [37,39], however mutations in α-subunits leads to the deficiency in HexA activity causing Tay Sachs.

Failure to the degradation of GM2 ganglioside results in abnormal accumulation of the substrate predominantly in the nervous system. Sandhoff disease and Tay Sachs [38] are categorized based on symptom onset into infantile, juvenile, and adult forms [37]. Infantile patients with Sandhoff disease encounter issues such as muscle weakness, developmental delay regression, and seizures, typically with a life expectancy of around four years [37]. Juvenile Sandhoff disease typically presents between 2 and 10 years of age with symptoms like dysarthria, ataxia, mental decline, and seizures. In adult Sandhoff disease, symptoms include movement disorders, pyramidal and extrapyramidal signs of lower motor neuron disease, and eye muscle control issues [40]. Tay-Sachs tends to impact the central nervous system, leading to symptoms like dementia, increased startle response, sensory impairments, and progressive loss of mental capacity. Both diseases may also present with retinal spots [37], paralysis, and difficulty in various functions like swallowing and vision.

The global prevalence of Sandhoff disease and Tay Sachs is approximately 1 in 1,000,000 and 1 in 320,000 live births, respectively [39]. Although standard

care for sphingolipidoses is enzyme replacement therapy, Gene therapy has an advantage over enzyme replacement therapy [41] for the treatment of Sandhoff and Tay Sachs disease, as gene therapy administration does not require as frequent as enzyme replacement therapy. Sphingolipidoses affect the central and peripheral nervous system which is a limiting factor for enzyme replacement therapy [36].

4. KRABBE DISEASE

Krabbe Disease is a lysosomal storage disorders [17,30] with an autosomal recessive inheritance causing neurodegenerative disorder [42,43] and an inborn error of metabolism with progressive demyelination of peripheral and central nervous systems [36,39,18]. It is also known as globoid cell leukodystrophy [44].

Krabbe disease is caused due to the pathogenic mutation [45] in the acid hydrolase galactosylceramidase [18] or galactocerebrosidase gene that encodes the enzyme galactosylceramidase. Decreased activity of enzymes, leads to the toxic accumulation of substrate (galactosylceramides) and galactosphingosine (psychosine) in the nervous system (oligodendrocytes and neurilemma cell) resulting in loss of the myelin covering of the Cerebrospinal and Peripheral nervous system causes impaired functions [36,42,45].

There are three phenotypes of Krabbe disease: Infantile (birth to about 3 years [43,44]), Later onset/ Juvenile (3 to 16 years [44]), and Adult onset Krabbe Disease (>16 years [44]). Infantile Krabbe Disease typically exhibits symptoms such as spasticity, feeding challenges, irritability, staring episodes, peripheral neuropathy, developmental delays, and regression of milestones before the child reaches one year of age. Neurological decline leads to fatality around 24 months (approximately 2 years) on average [39,45]. The blood-brain and blood-nerve barriers can be broken down by the establishment of a pro-inflammatory milieu in the peripheral nervous system, central nervous system, and peripheral organs. This disruption results in the demise of essential neural cells like neurons, oligodendrocytes, and Schwann cells, contributing to severe neurological side effects in Krabbe disease, including developmental delays, seizures, loss of motor function, and cognitive deficits. These findings further our comprehension of the disease's mechanisms and help pinpoint crucial targets for the development of effective therapies for Krabbe disease [39].

The global prevalence of Krabbe Disease is 1:100,000 [36,18,44,45]. It was first described 100 years ago as a “familial infantile form of diffuse brain sclerosis” by Dr Knud H. Krabbe. Still, after so many years we don’t have any suitable cure for this disease [18]. The current standard of care just slows down the progression [45].

At present, Hematopoietic Stem Cell Transplantation stands as the most promising treatment for Krabbe disease [17,39,42-45]. Hematopoietic Stem Cell Transplantation is advised to be performed before the emergence of significant signs or symptoms. Treatment outcomes are predominantly influenced by the extent of KD involvement during hematopoietic Stem Cell Transplantation, as determined through a comprehensive neurological evaluation. Therefore, hematopoietic Stem Cell Transplantation can still be effective if performed somewhat later. Existing case series indicate that hematopoietic Stem Cell Transplantation can prolong the lives of individuals with infantile Krabbe disease, but the impact on neurological and other outcomes varies. Notably, there is a lack of studies assessing the effects of hematopoietic Stem Cell Transplantation on quality of life and family functioning, which is common for rare disorders. Hematopoietic Stem Cell Transplantation carries a risk of morbidity and mortality within the first 100 days post-transplant. Consequently, some families of infants with Krabbe disease opt not to pursue hematopoietic Stem Cell Transplantation for their children [42].

5. TYPE II DIABETES

Diabetes is a major global health concern, characterized as both a worldwide pandemic and a significant threat to human well-being and the global economy. Edwin Gale (Gale E, personal communication, University of Bristol) has even coined the term "diabetes apocalypse" to describe it [46]. As per the International Diabetes Federation, an estimated 537 million individuals (aged 20–79) are presently coping with diabetes globally, representing over one in 10 adults. Projections suggest this figure could increase to 643 million by 2030 and further to 783 million by 2045 [47].

This chronic endocrine system disorder [48] has two primary types based on its etiology. Genetic or autoimmune deterioration of insulin-producing islet beta cells leads to Type 1 diabetes mellitus, representing 5-10% of all diabetes cases. On the other hand, about 90% of diabetes cases, known as type II diabetes, are

primarily marked by insulin resistance [48,49]. Type II diabetes commonly exhibits symptoms such as heightened polydipsia, polyphagia, fatigue, polyuria, and delayed wound healing. Significant complications associated with type II diabetes encompass kidney failure, retinopathy, cerebrovascular disease, heart disease, neuropathy, and limb amputation [50].

Glucosylceramide and ceramide are lipid molecules that are involved in insulin resistance, but glucosylceramide acts as an independent antagonist, while ceramide disrupts insulin signaling by inhibiting Akt/Protein Kinase B activation in cell models. Enhancing acid ceramidase expression in cells reverses ceramide accumulation induced by free fatty acids, improving insulin signaling. At the same time, the administration of short-chain ceramide analogs to cultured 3T3-adipocytes demonstrated an obstruction in insulin signaling and its efficacy. Moreover, an excessive presence of gangliosides within caveolae/Detergent Resistant Membranes appears to impede insulin signaling by displacing the insulin receptor from these domains [8]. Elevated quantities of both these lipids could play a part in fostering insulin resistance, a pivotal element in the progression of type II diabetes and associated metabolic conditions [48]. So, it can be concluded that diabetes II is not just a lifestyle disorder, other causative factors should also be explored.

6. CANCER

Cancer is characterized by a group of illnesses combined with aberrant cell development and spread that is uncontrollable and, in the worst-case scenario, results in death. The eleven cancer types categorized according to the organs affected are as follows: colorectal, liver, stomach, cervical, bladder, lung, esophageal, non-Hodgkin lymphoma, cancers of the lip and oral cavity, nasopharyngeal cancer, and Kaposi sarcoma [51]. The cancer types classified according to the tissue affected are lymphomas, carcinomas, adenomas, leukemias, and sarcomas [51]. Studies show that among various genetic and environmental factors, metabolic disorder of glycosphingolipids also causes cancer [12,13,48,52]. glycosphingolipids in vertebrate animal tissues are typically categorized into three primary groups: the ganglio-, lacto- and neolacto-, and Globo-series. These distinctive glycosphingolipids signatures in embryonic stem and cancer cells have been harnessed in glycan-targeted anti-cancer immunotherapy. The exploration of their mechanisms involved using anti-GD2 monoclonal antibodies and Globo H as specific examples. Abnormal podocalyxin expression has served as an indicator for various types of human cancers [52]. Sphingolipids induce brain insulin resistance, leading to the advancement of impaired brain glucose processing, resulting in reduced insulin availability for glucose metabolism. This decline in glucose processing often hampers synaptic, metabolic, and immune functions in the brain. Consequently, brain insulin resistance could heighten the likelihood of neuron inflammation and degeneration. The decline in the brain cells' capacity to metabolize glucose contributes to the appearance of symptoms evident in several conditions, such as diabetes and cancer. By encouraging the synthesis of pro-inflammatory eicosanoid (such as arachidonic acid), a potent signaling molecule, ceramide-1-phosphate also played a role in chronic inflammation. In the same manner that it causes atherosclerosis, ceramide-1-phosphate influences cancer cells [48].

7. ATHEROSCLEROSIS

Atherosclerosis, often termed "the disease of the century" [53], has been on the rise globally, resulting in over 50% of deaths among people with circulatory conditions. According to epidemiological studies until 2020, cardiovascular disease impacted approximately 422.7 million individuals and was responsible for over 17 million deaths globally in 2015, accounting for 31% of all global fatalities [54]. Over 75% of cardiovascular disease -related deaths globally occur in low- and middle-income countries due to limited access to healthcare, resulting in delayed detection of atherosclerosis and increased premature mortality. Early evidence of atherosclerosis origins was observed in autopsies performed on American soldiers in Korea, revealing changes in arterial walls characterized by lipid aggregation, complex carbohydrates, fibrous tissue, calcium deposits, and structural alterations. Atherosclerosis is a chronic, evolving, immune-inflammatory, and fibrous disease involving alterations in medium and large artery walls due to lipid aggregation, carbohydrates, fibrous tissues, and arterial wall changes. Cholesterol, triglycerides, phospholipids, and free fatty acids are key lipid components in the blood [53,54].

A. Windaus, in 1910 when studying atherosclerotic lesions in humans discovered the fact that as Cholesterol serves as a precursor to a steroid hormone, inherited cholesterol synthesis disorders can result in a wide range of health issues, while elevated cholesterol levels in those with hypercholesterolemia

are a key factor in atherosclerosis [55]. One other reason is ceramide-1-phosphate, which is a metabolite of ceramide, causes chronic inflammation in diseases like - cancer, atherosclerosis, asthma and thrombosis. Ceramide-1-phosphate, in the periphery, hinders the growth of adipocytes, leading to hypertrophy. In response to inflammatory signals, adipose tissue produces ceramide-1-phosphate. Once ceramide-1-phosphate reaches a critical level, it hampers adipocyte proliferation, resulting in increased size and insulin resistance [48] which causes elevated blood glucose which is associated with oxidative stress and inflammation, which can damage the lining of blood vessels (endothelium), a key step in atherosclerosis. Sphingomyelinase activity, which converts sphingomyelin into ceramide, is an inherent characteristic of low-density lipoprotein. This activity may increase during low-density lipoprotein aggregation. In advanced atherosclerotic lesions, the ceramide concentration is higher than in normal arterial tissue. Furthermore, the concentration of sphingomyelin associated with plasma-low-density lipoprotein is positively correlated with the severity of coronary artery disease [56].

8. LUPUS

Systemic lupus erythematosus is an autoimmune disease arising from the immune system's inability to tolerate multiple self-antigens [57]. Typically affecting individuals between 15 and 45 years old, it shows a significantly 9 times higher prevalence in women. Symptoms encompass skin rashes, photophobia, mouth canker, fever, and arthritis. The disease involves alternating phases of recovery and symptom exacerbation, potentially causing irreversible involvement of almost all organs and tissues. This can significantly impact the patient's mental and physical health and disrupt their quality of life [58]. Lupus is characterized by the production of autoantibodies and inflammatory cell infiltration into specific organs like the kidneys and brain. T cells play a pivotal role in lupus's development, contributing to tissue damage by regulating B cell responses and targeting tissues. Dysfunctional signaling events affect gene transcription and cytokine production in T cells, leading to atypical behavior in lupus [57]. Research indicates that individuals with lupus exhibit altered lipid raft-associated glycosphingolipids [59] in CD4+ T cells, with increased levels of specific glycosphingolipids — lactosylceramide, globotriaosylceramide, and monosialotetrahexosylganglioside [10]. Microdomains in the plasma membrane that are in the liquid-ordered phase due to their lipid composition—which is rich in cholesterol, glycosphingolipids, and sphingomyelin—are referred to as lipid rafts [59]. This elevation in glycosphingolipids correlated with heightened liver X receptor β expression, affecting cellular lipid metabolism and immune responses. Glycosphingolipid expression rose when liver X receptor agonists were used to activate CD4+ T cells from healthy donors; this effect was countered by an liver X receptor antagonist [10].

Sphingolipids act as a biomarker of lupus. Sphingolipids are present in plasma, urine, cerebrospinal fluid, synovial fluid, and, more recently, kidney biopsies. Sphingolipids are present in bloodstreams as lipoprotein particles (very-low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein) that are in circulation. The most researched sphingolipid in the bloodstream, sphingosine-1-phosphate, is mostly found in red blood cells and platelets. It is primarily carried by high-density lipoprotein particles and can also bind to albumin [60].

Targeting glycosphingolipid biosynthesis may help restore T cell function in lupus. Deficits in lipid metabolism may play a role in the development of lupus. Inhibiting glycosphingolipid biosynthesis with an approved inhibitor normalized glycosphingolipids metabolism corrected CD4+ T cell signaling, and decreased the production of anti-dsDNA antibodies by B cells in lupus [10].

9. ALZHEIMER'S & PARKINSION’S DISEASE

Since the late 19th century, research has extensively explored the structure, metabolism, and significance of sphingolipids following the isolation of the first sphingolipid from the brain. Sphingolipids contribute to brain insulin resistance, impacting the development of neuronal degenerative diseases like Alzheimer's [48,61] and Parkinson's.

Measuring characteristic motor symptoms of Parkinson's disease, studies show connections between brain insulin resistance, alterations in α-synuclein, and dopamine loss in brain areas. This resistance affects mesencephalon cortex circuits engaged in important dopamine pathways governing energy-related activities. The central nervous system, rich in sphingolipids, engages in diverse signaling functions, influencing neuron development, the release of exosomes from neurons, and nerve impulse conduction [48].

After Alzheimer's disease, Parkinson's disease is the most prevalent neurodegenerative movement disorder [50], shares similarities with Alzheimer's Disease and commonly overlaps with Alzheimer's and is marked by a steady tremor, reduced voluntary motion, increased stiffness, inactivity, and instability in the posture [62] involves a progressive loss of nigrostriatal dopaminergic neurons (DANs).

Ceramide plays a role in promoting Parkinson by regulating mitochondrial autophagy, as shown in research pertaining to 1,2,3,6-tetrahydropyridine 1-methyl-4-phenyl in humans, causing selective DAN injury and parkinsonism. Dysfunctional mitochondria and Parkinson were linked through 1-methyl-4-phenyl, which down-regulated sphingolipid synthesis in mice, indicating a potential link between sphingolipid metabolism destruction and significant neuronal damage [63].

Furthermore, Alzheimer's and Parkinson's diseases are connected with type II diabetes-related neurodegeneration. Classic motor symptoms of Parkinson's disease are reflected in the way brain insulin resistance impacts mesencephalon cortex circuits implicated in important dopamine pathways governing energy-related activities. These circuits have been shown to be associated with changes in α-synuclein and dopamine depletion in brain areas [48].

The idea that Alzheimer is a "type 3 diabetes" or a "brain insulin-resistant state" is strengthened by the fact that Alzheimer, the most prevalent kind of dementia, is associated with type II diabetes [61]. The molecular signaling route of insulin affects neuronal and glial metabolism, synaptic neural communication, and modulate neuroinflammatory processes in the neural network. There are some similar pathways between Alzheimer and type II diabetes, such as inflammation, oxidative stress, dyslipidemia, altered brain insulin signaling, and decreased mitochondrial and synaptic function [48,50,64].

The accumulation of phosphorylated proteins such as Tau and amyloid beta (Ab) in the form of tangled neurofibrillary cells is the hallmark pathology of Alzheimer's disease. Ceramide contributes to Ab formation, disrupting membrane potential, reducing oxidative phosphorylation, and triggering the release of proteins that encourage apoptosis. ceramide -rich organelles create a condition called oxidative stress that damages neurons and glia, resulting in the buildup of proteins or peptides that are harmful (especially for neurons). When hippocampus neurons are exposed to Ab, their cell membranes experience oxidative stress, cholesterol, and ceramide buildup.

By preventing lipid overload, treatment with alpha-tocopherol or sphingomyelin production inhibitors guards against Ab-induced cell death. These results imply that ceramide and cholesterol metabolism are disrupted by Ab-induced membrane-related oxidative stress, which results in neurological damages [48].

10. INFLUENZA

Influenza viruses, categorized into four types (A, B, C, and D) based on antigenic differences in nucleoprotein and matrix protein, pose a significant threat to public health.

In particular, influenza A virus, with the broadest host range, is a crucial zoonotic pathogen affecting animals like poultry and pigs, as well as humans, often leading to severe infections and fatalities.

Influenza A virus, an enveloped virus, heavily relies on host cell metabolic systems, especially lipid metabolism, for its life cycle [65]. While there's substantial research on human immunodeficiency virus type 1 (HIV-1), studies on other viruses like influenza A virus, measles virus, hepatitis C virus (HCV), dengue virus, Ebola virus, and severe acute respiratory syndrome coronavirus type 2 are still in early stages [66].

Gangliosides, complex sialic acid-containing glycosphingolipids, play diverse roles in immune defense but can also serve as receptors for microbes, including influenza viruses and cholera toxin. Optimal concentrations of glucosylceramide are crucial for influenza A virus infection, with both excessive and insufficient levels inhibiting replication [65]. Influenza A virus lacks its metabolic system and relies on the host cell's lipid metabolism, leading to a competitive relationship between the virus and the host in terms of metabolism [65]. Several viruses, such as influenza, Ebola, and vesicular stomatitis virus, are sensitive to glucosylceramide-related enzymes, influencing their entry and internalization into host cells. Ceramide-enriched membrane domains, responding to specific enzymatic activities, serve as platforms for the endocytic uptake of pathogens, creating an environment that enhances viral infections [66].

CONCLUSION

The essential roles of lipids in physiological processes such as energy storage, hormone regulation, nerve

transmission, and cell growth. Disruptions in lipid metabolism can lead to serious health issues like type II diabetes, atherosclerosis, lupus, asthma, cancer, neuropathies, and neurodegenerative diseases. Glycosphingolipids are crucial for viral spread and serve as biomarkers for diseases. Deficiency of α-galactosidase enzyme leads to lysosomal storage disorders, such as Anderson-Fabry and Gaucher diseases etc. Understanding glycosphingolipid metabolism offers insights into disease mechanisms and therapeutic targets, paving the way for improved treatments and ultimately enhancing patient outcomes.

AUTHORS' CONTRIBUTION

Prerna Jyoti – Research, writing original draft, editing, and proofreading, Devindra S – conceptualization, supervision

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We the undersigned declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

[1] Budani M, Auray-Blais C, Lingwood C. ATP-binding cassette transporters mediate differential biosynthesis of glycosphingolipid species. J Lipid Res 2021; 62. https://doi.org/10.1016/j.jlr.2021.100128

[2] Natesan V, Kim SJ. Lipid metabolism, disorders and therapeutic drugs-review. Biomol Ther 2021; 29(6): 596. https://doi.org/10.4062/biomolther.2021.122

[3] Rizzo R, Russo D, Kurokawa K, *et al*. Golgi maturation-dependent glycoenzyme recycling controls glycosphingolipid biosynthesis and cell growth via GOLPH3. EMBO J 2021; 40(8): e107238. https://doi.org/10.15252/embj.2020107238

[4] Celi AB, Goldstein J, Rosato-Siri MV, *et al*. Role of globotriaosylceramide in physiology and pathology. Front Mol Biosci 2022; 9: 813637. https://doi.org/10.3389/fmolb.2022.813637

[5] Lingwood CA, Branch DR. The role of glycosphingolipids in HIV/AIDS. Discov Med 2011; 11(59): 303-13.

[6] Yamashita S, Kinoshita M, Miyazawa T. Dietary sphingolipids contribute to health via intestinal maintenance. International Journal of Molecular Sciences 2021; 22: 13: 7052.

[7] Lingwood CA. Glycosphingolipid functions. Cold Spring Harb Perspect Biol 2011; 3(7): a004788. https://doi.org/10.1101/cshperspect.a004788

[8] Langeveld M, Aerts JM. Glycosphingolipids and insulin resistance. Prog Lipid Res 2009; 48(3-4): 196-205. https://doi.org/10.1016/j.plipres.2009.03.002

[9] Chatterjee S, Bedja D, Mishra S, *et al*. Inhibition of glycosphingolipid synthesis ameliorates atherosclerosis and arterial stiffness in apolipoprotein E−/− mice and rabbits fed a high-fat and-cholesterol diet. Circulation 2014; 129(23): 2403-13. https://doi.org/10.1161/CIRCULATIONAHA.113.007559

[10] McDonald G, Deepak S, Miguel L, *et al*. Normalizing glycosphingolipids restores function in CD4+ T cells from lupus patients. J Clin Invest 2014; 124(2): 712-24. https://doi.org/10.1172/JCI69571

[11] Karman J, Tedstone JL, Gumlaw NK, *et al*. Reducing glycosphingolipid biosynthesis in airway cells partially ameliorates disease manifestations in a mouse model of asthma. Int Immunol 2010; 22(7): 593-603. https://doi.org/10.1093/intimm/dxq044

[12] Prinetti A, Prioni S, Loberto N, *et al*. Aberrant Glycosphingolipid Expression and Membrane Organization in Tumor Cells: Consequences on Tumor-Host Interactions. In: The Molecular Immunology of Complex Carbohydrates-3. Springer 2011; pp. 643-67. https://doi.org/10.1007/978-1-4419-7877-6_34

[13] Uddin MB, Roy KR, Hosain SB, *et al*. An N6-methyladenosine at the transited codon 273 of p53 pre-mRNA promotes the expression of R273H mutant protein and drug resistance of cancer cells. Biochem Pharmacol 2019; 160: 134-45. https://doi.org/10.1016/j.bcp.2018.12.014

[14] Liu YY. Glucosylceramide synthase, a factor in modulating drug resistance, is overexpressed in metastatic breast carcinoma. Int J Oncol [Internet] 2011 May 23 [cited 2024 Jan 27]. https://doi.org/10.3892/ijo.2011.1052

[15] Bedja D, Yan W, Lad V, *et al*. Inhibition of glycosphingolipid synthesis reverses skin inflammation and hair loss in ApoE−/− mice fed western diet. Sci Rep 2018; 8(1): 11463. https://doi.org/10.1038/s41598-018-28663-9

[16] Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. The Lancet 2008; 372(9645): 1263-71. https://doi.org/10.1016/S0140-6736(08)61522-6

[17] Sheth J, Nair A, Jee B. Lysosomal storage disorders: from biology to the clinic with reference to India. Lancet Reg Health-Southeast Asia 2023; 9. https://doi.org/10.1016/j.lansea.2022.100108

[18] Bradbury AM, Bongarzone ER, Sands MS. Krabbe disease: New hope for an old disease. Neurosci Lett 2021; 752: 135841. https://doi.org/10.1016/j.neulet.2021.135841

[19] Sprong H, Degroote S, Claessens T, *et al*. Glycosphingolipids are required for sorting melanosomal proteins in the Golgi complex. J Cell Biol 2001; 155(3): 369-80. https://doi.org/10.1083/jcb.200106104

[20] Nagueh SF. Anderson-Fabry disease and other lysosomal storage disorders. Circulation.2014; 130(13): 108190. https://doi.org/10.1161/CIRCULATIONAHA.114.009789

[21] Platt FM, d'Azzo A, Davidson BL, *et al*. Lysosomal storage diseases. Nat Rev Dis Primer 2018; 4(1): 27. https://doi.org/10.1038/s41572-018-0025-4

[22] Ballabio A, Gieselmann V. Lysosomal disorders: from storage to cellular damage. Biochim Biophys Acta BBA-Mol Cell Res 2009; 1793(4): 684-96. https://doi.org/10.1016/j.bbamcr.2008.12.001

[23] Tuttolomondo A, Baglio I, Riolo R, *et al*. Molecular Pathogenesis of Central and Peripheral Nervous System Complications in Anderson-Fabry Disease. Int J Mol Sci [Internet] 2023 [cited 2024 Jan 27]; 25(1): 61. Available from: https://www.mdpi.com/1422-0067/25/1/61

[24] Do HS, Park SW, Im I, *et al*. Enhanced thrombospondin-1 causes dysfunction of vascular endothelial cells derived from Fabry disease-induced pluripotent stem cells. EBioMedicine 2020; 52. https://doi.org/10.1016/j.ebiom.2020.102633

[25] Bichet DG, Aerts JM, Auray-Blais C, *et al*. Assessment of plasma lyso-Gb3 for clinical monitoring of treatment response in migalastat-treated patients with Fabry disease. Genet Med 2021; 23(1): 192-201. https://doi.org/10.1038/s41436-020-00968-z

[26] Umer M, Kalra DK. Treatment of Fabry Disease: Established and Emerging Therapies. Pharmaceuticals 2023; 16(2): 320. https://doi.org/10.3390/ph16020320

[27] Mehta A, Beck M, Linhart A, *et al*. History of lysosomal storage diseases: an overview. Fabry Dis Perspect 5 Years FOS 2006.

[28] Nampoothiri S, Yesodharan D, Bhattacherjee A, *et al*. Fabry disease in India: A multicenter study of the clinical and mutation spectrum in 54 patients. JIMD Rep 2020; 56(1): 82-94. https://doi.org/10.1002/jmd2.12156

[29] Bodamer OA, Ratschmann R, Paschke E, *et al*. Recurrent acroparaesthesia during febrile infections. The Lancet 2004; 363(9422): 1698. https://doi.org/10.1016/S0140-6736(04)16254-5

[30] Tóth GD, Koplányi G, *et al*. Nanoformulation of Therapeutic Enzymes: A Short Review. Periodica Polytechnica Chemical Engineering 2023. https://doi.org/10.3311/PPch.22826

[31] Xu R, Mistry P, Mckenna G, Emre S, Fiel MI, Schiano T, *et al*. Hepatocellular carcinoma in type 1 Gaucher disease: a case report with review of the literature. In: Seminars in liver disease. Copyright© 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New 2005; pp. 226-9. https://doi.org/10.1055/s-2005-871201

[32] Xiaojie B, Yanxia Z, Lirong S, *et al*. Research progress on the pathogenesis, diagnosis and treatment of bone damage in Gaucher disease [J]. Advances in Clinical Medicine 2023, 13(4): 5680-5685. https://doi.org/10.12677/ACM.2023.134802

[33] Belmatoug N, Di Rocco M, Fraga C, *et al*. Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe. Eur J Intern Med 2017; 37: 25-32. https://doi.org/10.1016/j.ejim.2016.07.011

[34] Prisila E, Majdawati A. Gaucher's Disease: A Case Report. Ahmad Dahlan Med J 2023; 4(1): 30-41.

[35] Hughes DA, Pastores GM. Eliglustat for Gaucher's disease: trippingly on the tongue. The Lancet 2015; 385(9985): 2328-30. https://doi.org/10.1016/S0140-6736(15)60206-9

[36] Shaimardanova AA, Solovyeva VV, Issa SS, *et al*. Gene Therapy of Sphingolipid Metabolic Disorders. Int J Mol Sci 2023; 24(4): 3627. https://doi.org/10.3390/ijms24043627

[37] McNulty MA, Prevatt PB, Nussbaum ER, *et al*. Abnormal epiphyseal development in a feline model of Sandhoff disease. J Orthop Res 2020; 38(12): 2580-91. https://doi.org/10.1002/jor.24803

[38] Fernandes Filho JA, Shapiro BE. Tay-sachs disease. Arch Neurol 2004; 61(9): 1466-8. https://doi.org/10.1001/archneur.61.9.1466

[39] Pandey MK. Exploring Pro-Inflammatory Immunological Mediators: Unraveling the Mechanisms of Neuroinflammation in Lysosomal Storage Diseases. Biomedicines 2023; 11(4): 1067. https://doi.org/10.3390/biomedicines11041067

[40] Tavasoli AR, Parvaneh N, Ashrafi MR, *et al*. Clinical presentation and outcome in infantile Sandhoff disease: a case series of 25 patients from Iranian neurometabolic bioregistry with five novel mutations. Orphanet J Rare Dis 2018; 13(1): 1-8. https://doi.org/10.1186/s13023-018-0876-5

[41] Shaimardanova AA, Chulpanova DS, Solovyeva VV, *et al*. Increasing β-hexosaminidase A activity using genetically modified mesenchymal stem cells. Neural Regen Res 2024; 19(1): 212-9. https://doi.org/10.4103/1673-5374.375328

[42] Rafi MA, Luzi P, Wenger DA. Conditions for combining gene therapy with bone marrow transplantation in murine Krabbe disease. BioImpacts BI 2020; 10(2): 105. https://doi.org/10.34172/bi.2020.13

[43] Yoon IC, Bascou NA, Poe MD, *et al*. Long-term neurodevelopmental outcomes of hematopoietic stem cell transplantation for late-infantile Krabbe disease. Blood J Am Soc Hematol 2021; 137(13): 1719-30. https://doi.org/10.1182/blood.2020005477

[44] Jain M, De Jesus O. Krabbe disease 2020.

[45] Lahr A, Williams L, Henderson N, *et al*. Overview of Newborn Screening of Lysosomal Storage Diseases for Pediatric Care Providers. OBM Genet 2023; 7(3): 1-12. https://doi.org/10.21926/obm.genet.2303194

[46] Zimmet PZ, Magliano DJ, Herman WH, *et al*. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol 2014; 2(1): 56-64. https://doi.org/10.1016/S2213-8587(13)70112-8

[47] Marrano N, Biondi G, Borrelli A, *et al*. Type 2 diabetes and Alzheimer's disease: the emerging role of cellular lipotoxicity. Biomolecules 2023; 13(1): 183. https://doi.org/10.3390/biom13010183

[48] Mei M, Liu M, Mei Y,*et al*. Sphingolipid metabolism in brain insulin resistance and neurological diseases. Front Endocrinol 2023; 14. https://doi.org/10.3389/fendo.2023.1243132

[49] Tatti P, Singh P. Insulin Resistance: An Unresolved Riddle. J Clin Med 2023; 12(19): 6394. https://doi.org/10.3390/jcm12196394

[50] Chornenkyy Y, Wang WX, Wei A, *et al*. Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline. Brain Pathol 2019; 29(1): 3-17. https://doi.org/10.1111/bpa.12655

[51] Mathur G, Nain S, Sharma PK. Cancer: an overview. Acad J Cancer Res 2015; 8(1). https://doi.org/10.5829/idosi.ajcr.2015.8.1.9336

[52] Ho MY, Yu AL, Yu J. Glycosphingolipid dynamics in human embryonic stem cell and cancer: their characterization and biomedical implications. Glycoconj J 2017; 34: 765-77. https://doi.org/10.1007/s10719-016-9715-x

[53] Burlutskaya AV, Tril VE, Polischuk LV, *et al*. Dyslipidemia in pediatrician's practice. Rev Cardiovasc Med 2021; 22(3): 817-34. https://doi.org/10.31083/j.rcm2203088

[54] Luca AC, David SG, David AG, *et al*. Atherosclerosis from Newborn to Adult—Epidemiology, Pathological Aspects, and Risk Factors. Life 2023; 13(10): 2056. https://doi.org/10.3390/life13102056

[55] De Geest B, Mishra M. New Perspectives on Cholesterol and Lipoprotein Metabolism. Vol. 24, International Journal of Molecular Sciences. MDPI 2023. https://doi.org/10.3390/ijms241411298

[56] Katsel P, Li C, Haroutunian V. Gene expression alterations in the sphingolipid metabolism pathways during progression of dementia and Alzheimer's disease: a shift toward ceramide accumulation at the earliest recognizable stages of Alzheimer's disease? Neurochem Res 2007; 32: 845-56. https://doi.org/10.1007/s11064-007-9297-x

[57] Moulton VR, Tsokos GC. Abnormalities of T cell signaling in systemic lupus erythematosus. Arthritis Res Ther 2011; 13: 1-10. https://doi.org/10.1186/ar3251

[58] Aghili M, Poorbahman Z, Babaee E. Comparing the effectiveness of acceptance and commitment-based therapy and compassion-focused therapy on basic psychological needs, maladaptive magnification, and stress coping strategies in patients with lupus. Psychol Achiev 2023. https://doi.org/10.22055/psy.2023.44152.3069

[59] Jury EC, Flores-Borja F, Kabouridis PS. Lipid rafts in T cell signalling and disease. In: Seminars in cell & developmental biology. Elsevier 2007; pp. 608-15. https://doi.org/10.1016/j.semcdb.2007.08.002

[60] Harden OC, Hammad SM. Sphingolipids and diagnosis, prognosis, and organ damage in systemic lupus erythematosus. Frontiers in Immunology 2020; 11: 586737. https://doi.org/10.3389/fimmu.2020.586737

[61] Duarte AI, Candeias E, Correia SC, *et al*. Crosstalk between diabetes and brain: glucagon-like peptide-1 mimetics as a promising therapy against neurodegeneration. Biochim Biophys Acta BBA-Mol Basis Dis 2013; 1832(4): 527-41. https://doi.org/10.1016/j.bbadis.2013.01.008

[62] Tong M, Dong M, de la Monte SM. Brain insulin-like growth factor and neurotrophin resistance in Parkinson's disease and dementia with Lewy bodies: potential role of manganese neurotoxicity. J Alzheimers Dis 2009; 16(3): 585-99. https://doi.org/10.3233/JAD-2009-0995

[63] Huang Q, Chen C, Chen W, *et al*. Cell type-and region-specific translatomes in an MPTP mouse model of Parkinson's disease. Neurobiol Dis 2023; 180: 106105. https://doi.org/10.1016/j.nbd.2023.106105

[64] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, *et al*. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 2018; 14(3): 168-81. https://doi.org/10.1038/nrneurol.2017.185

[65] Zhou Y, Pu J, Wu Y. The role of lipid metabolism in influenza A virus infection. Pathogens [Internet] 2021 [cited 2023 Dec 10]; 10(3): 303. https://doi.org/10.3390/pathogens10030303

[66] Avota E, Bodem J, Chithelen J, *et al*. The manifold roles of sphingolipids in viral infections. Front Physiol 2021; 12: 715527. https://doi.org/10.3389/fphys.2021.715527