Review Article

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Lipidomics and cognitive dysfunction – A Narrative review

Lipidomik ve bilişsel işlev bozukluğu – Bir Anlatı İncelemesi

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Abstract

Background: More than half portion of the brain is formed by lipids. They play critical roles in maintaining the brain's structural and functional components. Any dysregulation in these brain lipids can lead to cognitive dysfunction which are associated with neurological disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, vascular dementia etc. Studies have linked lipids with cognitive impairment. But not much has been studied about the complex brain lipids which might play a pivotal role in cognitive impairment. This review aims to highlight the lipidomic profiles in patients with cognitive dysfunction.
Results: Forty-five articles were reviewed. These studies show alterations in complex lipids such as sphingolipids, phospholipids, glycolipids and sterols in brain in various neurological disorders such as vascular dementia, Parkinson's and Alzheimer's disease. However, the classes of fatty acids in these lipids involved are different across studies.
Conclusions: There is a need for targeted lipidomics analysis, specifically including sphingolipids in patients with neurodegenerative disorders so as to improve diagnostics as well as management of these disorders.

Keywords: cognitive dysfunction; glycerolipids; glycerophospholipids; lipidomics; sphingolipids

Öz

Amaç: Beynin yarısından fazlası lipitlerden oluşur. Beynin yapısal ve fonksiyonel bileşenlerinin korunmasında kritik roller oynarlar. Bu beyin lipitlerindeki herhangi bir düzensizlik, Alzheimer hastalığı, Parkinson hastalığı, şizofreni, vasküler demans vb. Gibi nörolojik bozukluklarla ilişkili bilişsel işlev bozukluğuna yol açabilir. Çalışmalar lipitleri bilişsel bozukluklarla ilişkilendirmiştir. Ancak, bilişsel bozulmada önemli bir rol oynayabilecek karmaşık beyin lipitleri hakkında çok fazla çalışma yapılmamıştır. Bu derleme, bilişsel işlev bozukluğu olan hastalarda lipidomik profilleri vurgulamayı amaçlamaktadır.
Bulgular: Kırk beş makale incelendi. Bu çalışmalar sfingolipidler, fosfolipidler, glikolipidler ve beyindeki steroller gibi kompleks lipidlerde vasküler demans, Parkinson ve Alzheimer hastalığı gibi çeşitli nörolojik bozukluklarda değişiklikler olduğunu göstermektedir. Bununla birlikte, bu lipitlerdeki yağ asitleri sınıfları çalışmalarda farklıdır.
Sonuçlar: Özellikle nörodejeneratif bozuklukları olan hastalarda sfingolipidleri de içeren, bu bozuklukların tanısını ve tedavisini iyileştirmek için hedefe yönelik lipidomik analizlere ihtiyaç vardır.

Anahtar Kelimeler: Bilişsel işlev bozukluğu; gliserolipidler; gliserofosfolipitlerdir; lipidomikler; sfingolipitler.

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Introduction

The human brain is a lipophilic organ which contains a vast range of lipids. Lipids play critical roles in maintaining the brain's structural and functional components as well as to maintain physiological functions of the neurons [1–2]. Moreover, they form lipid bilayers and contribute to cellular and protein function and develop a hydrophobic environment for the interaction of the membrane proteins. Any alterations in lipid content of the brain can hamper the normal functioning of the brain and can result in various neurodegenerative disorders such as vascular dementia, Parkinson's disease, Alzheimer's disease, etc [3]. To support this statement, many previous studies have shown the role of each lipoprotein such as total cholesterol, triglyceride, HDL, VLDL and LDL cholesterol in cognitive function. Measuring the complete spectrum of lipids (i. e. lipidomics) may help in finding some predictive markers of brain dysfunction which is now possible using nanoflow high performance lipid chromatography. The rapid development of this analytical technology has made the study of lipidomics in the brain an exciting nascent field to explore. This review aims to highlight the lipidomic profiles in patients with cognitive dysfunction.

Lipidomics, coined by Han and Gross in the year 2003 is a study which involves the broad characterization of pathways and network of thousands of classes of lipids in a cell in biological systems involving their association with gene regulation and proteins. The word lipidome is a subset of metabolome which implies the analysis of complete lipid profile parameters within the levels of organization. Lipidomics is an advanced and new technology which has come up in order to investigate the various pathways of various lipids that play essential roles in various biological processes and in diseased conditions. Lipidomics analysis is generally done by rapidly advanced technologies such as mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, fluorescence spectroscopy, dual polarization interferometry, and computational methods. Through this technology, the role of lipids in various metabolic disorders such as atherosclerosis, obesity, hypertension, stroke and diabetes are known. This swiftly developing technology has made vast progress in the field of proteomics and genomics which constitutes the family of systems biology. The investigators in the area of lipidomics examine the dynamic changes of lipids in the cell, their structures, functions, interaction and various other changes occurring in the system. In other words, lipidomics is a promising field which characterizes a complex mixture of lipids which are unknown in lipid metabolism [4].

Lipids and cognitive dysfunction

Serum lipids play a major role in cognitive dysfunction (CD). Studies have suggested that a decline in levels of HDL cholesterol increase the risk of mild cognitive impairment (MCI) and dementia [5–6]. An association was found between high HDL cholesterol levels with very good scores of cognitive function tests in many cross-sectional studies which had a population of age group over 75 years, [7] while another study showed contrary results as it suggested that HDL cholesterol measured during an advanced age had no association with increased risk of vascular dementia. Moreover, association was not found between HDL cholesterol with the risk of MCI, AD, and dementia [8]. A study in Western India showed reduced HDL cholesterol levels in demented and cognitive dysfunction patients when compared with elderly healthy controls. A study in Japan also showed a positive association with cognitive scores and levels of HDL cholesterol [9]. Another study, on the other hand, showed HDL cholesterol had a significant negative association with the risk of mild CD. Significant association was not observed between plasma HDL cholesterol and the risk of mild CD [10]. Among the women population, elevated levels of HDL and decline in Apo B levels which showed improved maintenance of cognitive function specifically visual ability and perceptual speed over the advancement of age depicting that this lipoprotein has a role in CD [11].

In both Finnish and Chinese population midlife total cholesterol (TC) levels were found to elevate the risk of vascular dementia which were significant predictors of cognitive impairment [12]. In a prospective longitudinal study done in Australia among an elderly population of age 75 years, hypercholesterolemia was strongly associated with the development of dementia and diminished cognitive function [13]. Independent of confounding factors rise in TC levels had significant association with elevated risk of MCI depicting the fractions of cholesterol might be involved in both AD and MCI.A study in Western India showed reduced total cholesterol levels in patients with MCI and dementia when compared with elderly healthy controls. A study in Japan also showed a positive association with cognitive scores and HDL cholesterol levels in the patients without Apo E4 allele [9]. Another study showed that in a group of participants age ranging from 46–71 years TC levels had significant association with more than 20 years drop in DSST scores suggesting that TC is responsible for CD.

At present, there are quite a few number of studies stating the direct association between cognition and

levels of triglycerides (TG). Some studies showed that TG levels were decreased in patients with cognitive dysfunction compared to that of the control group [10–11], while others found no association between TG and cognition [12]. Contrarily, some studies stated that an increase in levels of TG had an inverse relation with performance on various measures of cognitive function [13–14]. One study stated that high TG levels had significant association with the risk of MCI and dementia [5–6]. A large cohort study suggested that hypertriglyceridemia had an association with increased risk of dementia syndromes such as vascular dementia while no association was found with AD [15]. The studies done by Kim SH and Morren et al. showed an increase in TG levels, while study by Kim et al. suggested that triglyceride levels were found to be strongly correlated with the atrophy of brain which can be used to detect early stage of mild cognitive impairment with the implementation of Mini-Mental State Examination test [16]. These studies suggested the association of TG with CD.

A longitudinal study in Chinese population showed increased levels of LDL cholesterol associated with cognitive decline, MCI, and dementia [5–6, 13]. Moreover, the rise in LDL levels were associated with improvement in functional performance suggesting that LDL cholesterol is responsible for CD [17].

Apart from the general lipid profile, other lipoproteins were also found in a few studies showing significant roles in CD. Levels of Apo A1 and Apo B were found to be diminished in demented and MCI patients when compared with elderly healthy controls. A study in Japan showed significant positive association between the scores of cognitive tests and plasma Apo E level in both groups of patients having APO E4 allele and without E4 allele [9].

The different studies conducted across various parts of the globe suggested contrary results regarding the association of general lipid profile parameters with cognitive dysfunction and hence further studies are required in this field to confirm the biomarker leading to the CD.

Brain lipids and cognitive dysfunction

The classification of brain lipids was proposed by Fahy and co-workers and are divided into the following eight categories: glycerophospholipids, glycerolipids, sphingolipids, prenols, sterols, saccharides and polyketides. Most of the studies have examined the role of glycerophospholipids, glycerolipids, sphingolipids in CD but there are no studies on other brain lipids. The role of these brain lipids need to be explored in future studies.

Role of glycerophospholipids in cognitive dysfunction

Glycerophospholipids are amphipathic molecules which represent 20–50% of the dry weight of the adult brain. The most important glycerophospholipids are PE, PS, PC, PI, and PC. The most biologically important among these lipids is SM. Phospholipids play an active role in several intracellular signaling, neurological, and vital metabolic processes [18], such as development, necrosis, and cell death, transportation, replication of DNA, signaling of neurons, or secretion [19]. 50–60% of the total mass of the membranes of neurons along with proteins is represented by the glycerophospholipids, along with glycolipids and cholesterol. Increase in levels of PC (C40:6) and lyso PC (C18:2) respectively had significant association with high and low MMSE scores. Moreover, elevated concentrations of PC(C36:6), (C38:0), (C38:6), (C40:2) and PC (40:6) had a significant association with improved scores of incidental learning, which is a neuropsychological test assessing the performance of memory. On the other hand, rise in levels of PC (40:6) and (C38:0) were found to have an association with the better scores of attention tests and elevated concentrations of PC (C36:6) and (C3) were found to have an association with better scores in executive function tests [20]. In another study conducted in the USA, DHA was mostly related to cognitive function. High levels of DHA proportionally had better association with nonverbal reasoning, composite working memory score, and mental flexibility. The function of DHA seemed to have no effect on attention, concentration, and general memory whereas DHA was found to be proportional among the processing, verbal knowledge, and vocabulary tests. A study mentioned 10–20% of phospholipids were lost in individuals of age 89–92 when compared to that of old individuals of age 33–36 years. Moreover, the concentration of phospholipids in the brain remained unaltered during the advancement of age [21]. The reduction of phospholipids starts stealthily after 20 years of age and becomes more significant after 80 years showing no marked difference in the male and female lipid profile in the brains [22–23]. No significant alteration was found in the monounsaturated FA of PE, 18:1 in AD patients but a significant rise in comparison to the quantity of the saturated components 14:0, 16:0 and 18:0 were observed in a study conducted in Sweden. Another investigation by Oresic et al. identified that PC (16:0/16:0) is one of the clusters of

3 metabolites as predictive markers in developing AD in patients with mild cognitive dysfunction [24]. Plasmalogen is another example of a class of phospholipids which are considered as major constituents of membrane lipid rafts and play an important role in neurotransmitter vesicular fusion. Significant changes in the functions could alter postsynaptic signal transduction resulting in the negative alteration of the role of cholinergic pathways which is associated with cognition. Moreover, both alteration and decline in the release of acetylcholine was also observed [25]. Serum PPE levels along with contents of polyunsaturated fatty acid were found to be affecting highly in both MCI and Late-Onset Alzheimer's Disease patients. For example, levels of PPE 38:6 (16:0/22:6) declined in the MCI and Late-Onset Alzheimer's Disease (AD) cohorts with an MMSE score ranging from 19 to 24 while PPE 40:6 (18:0/22:6) declined in both MCI and Late-Onset AD cohorts [26–27]. In a study, PS was found to be elevated in the visual cortex of PD patients due to the change of certain species of molecules from PC to PS. A study in UK showed significant alteration in levels of PC in gray and white matter of patients with both neurological disorders such as schizophrenia and bipolar disorder while compared with the controls. The increase in PC was due to the influence of antipsychotic medications in the gray matter. Another study mentioned that a decrease in cortisol levels of PC in Lewy body disease suggested augmented diminished glycerophospholipids synthesis and degradation. Another study showed an increase in white matter phospholipids profiles indicating possible adaptive mechanism to chronic ischemia in subcortical ischemic vascular dementia. A study by Kim et al. showed 2-fold increase in PE levels in females with clinical dementia ranging from age group 65–80 years (Table 1) [16]. Wood et al. showed low circulating levels of PPE in both MCI and late onset Alzheimer's disease patients (Table 1) [26]. Another longitudinal cohort study showed decreased levels of PPE in young and old demented patients (Table 1). Contrary results were obtained from different studies across different parts of the globe through an untargeted lipidomics approach. Targeted phospholipidomics approach in CD could help in future management of the disease.

Role of glycerolipids in cognitive dysfunction

A study showed that two robust markers, i. e. DAG (34:2) and DAG (36:2) were elevated in both mild MCI and LOAD patients who had an MMSE score ranging from 10 to 18 and 19 to 24 respectively [28]. Increase in these levels of lipids which are highly regulated gains significant interest clinically taking into account the various uses of DAGs being antecedent of structural glycerophospholipids and lipids which are neutral in nature. These classes of lipids are considered as structural components of endoplasmic reticulum and nuclear membranes, serve as mediators for transduction of nuclear signal, and in biogenesis of Golgi transport carrier [29–30]. In MCI and LOAD patients alterations in any of the levels of functions which were DAG-dependent could lead to neuronal dysfunction and result in diminished cognitive function finally. Another study showed elevated DAG levels in the visual cortex of PD patients. The alteration of this lipid might be due to the primary dysfunction of the visual cortex of PD and these changes might have an impact on visual perceptions. One more study showed levels of DAG significantly increasing in the frontal cortex of the brain with PD and Lewy body disease. The findings suggested that alteration in the levels of DAG is a common nature of neurodegenerative disease which leads to proteinopathy and finally resulting into cognitive dysfunction. A study by Kim et al. showed 2-fold increase in the levels of DAG in females with clinical dementia ranging from age group 65–80 years (Table 1) [16]. Wood et al. showed high DAG levels in both MCI and late onset Alzheimer's disease patients (Table 1) [26]. In another study levels of MAG were found to be elevated in both young and old demented patients while DAG was only found to be increased in patients with MCI (Table 1). A study in Australia showed diglyceride levels (18:1,22:0) could be potentially used as one of the markers for the behavioral variant of fronto-temporal dementia. In a study done in USA, untargeted lipidomics was used to elucidate the roles of MAG and DAG in the frontal cortex of the brain and plasma of patients with MCI. DAG and MAG along with saturated, unsaturated, and polyunsaturated fatty acid contents were found to rise in plasma and frontal cortex of MCI patients. There are contrary results regarding the role of glycerolipids in cognitive dysfunction. Future studies should be conducted to identify a biomarker responsible for the development of CD.

Role of sphingolipids in cognitive dysfunction

Metabolism of sphingolipids is a dynamic process which helps in modulating the formation of various number of metabolites which are bioactive in nature and act as second messengers that play a vital role in cellular signaling. For the normal functioning of brains, the balance of

Table 1: Lipidomics and cognitive dysfunction.

Study	Design	Methods	Results	Comments
Kim et al. [16]	Out of 172 females with clinical dementia ranging from age group (65–80) years, 13 of them with average age of 71.5 years had normal cognition, 23 with an average age of 72.5 years had MCI and 14 of them with an average age of 72.6 years had AD.	– Mini-Mental Speed Examination as a cognitive tool. – Non targeted lipidomics was performed by (nUHPLC-ESI-MS/MS) for complete profiling of lipids	– To differentiate early stages of MCI – 14 lipids were highly abundant and significantly altered in AD. – 2 fold increase was used in the levels of LDL/VLDL including triacylglycerol (TAG), ceramide, PE, and diacylglycerol (DAG). – 3 species of lipids such as (TAG 50:1, DAG18:1_18:1, and PE 36:2) were found to be strongly correlated with the degree of atrophy of brain.	This study was done by using specific CSF biomarkers. They could have taken serum lipids from subjects in order to validate the mass screening with MMSE. More studies should be done in this area in future to detect the major species of lipid so that early stages of MCI are detected.
Abdullah et al. [46]	Longitudinal cohort – Blood was extracted from a mouse model with AD depicting human APOE isoforms and mutations of 5 AD patients. – 195 participants with normal cognitive function were recruited for the study. – Out of the normal 195 participants, 23 of them developed MCI/AD within 3 years.	– Hopkins Verbal Learning Test-Revised, Wechsler Adult Intelligence Scale-Revised (WAIS-R were used. – HPLC-MS was used for lipidomics analysis. – Dementia work up tests were included. Logical Memory I and II of the Wechsler Memory Scale-Revised (Wechsler), and Benton Visual Retention Test (Benton) were used.	– 31% of subjects had a normal cognitive function. Among them, 40% were found to have developed MCI and the other 50% developed AD. – APOE ε4-carriers which converted normal subjects to MCI/AD had elevated arachidonic acid/docosahexaenoic acid ratios in PL while comparing with patients with normal cognitive function with both ε4 and non-ε4 carriers. – On the other hand arachidonic acid and DHA containing PL species. with ε4-status and Aβ42/Aβ40 ratios showed accuracy level of 91% in detecting MCI and AD.	The limitations of the study were small size of the sample and shorter duration of follow up period. Further studies should be conducted in a larger population with long duration of follow up so that a potential lipid biomarker of MCI/AD is detected.
Kwang-Mook Jung et al. [47]	– Invitro Study – Postmortem samples of the brain were taken from 38 Alzheimer's disease (AD) patients and 17 control groups having age-matched subjects.	– Mini-Mental State Examination (MMSE) scores, Boston Naming test scores and Kendrick Digit Copy test scores were used as cognitive tools – Liquid chromatography/mass spectrometry was utilized to perform an endocannabinoid targeted lipidomics analysis of samples of brain which were sent for post mortem.	– Levels of endocannabinoid anandamide and its precursor 1-stearoyl, 2-docosahexaenoyl-sn-glycerophosphoethanolamine-N-arachidonoyl (NArPE) were found to be diminished in the midfrontal and temporal cortex tissue of AD patients when compared with controls. – The content of anandamide in midfrontal cortex and scores of Kendrick's Digit Copy test were positively correlated with each other in AD patients	In the present study, the molecular events involved by Aβ 42 affecting the change of anandamide were not taken into account. The pharmacological agents are FAAH inhibitors which help in strengthening anandamide signaling and plays a beneficial role in improving cognition in AD patients. Further studies should be done

Table 1: (continued)

Study	Design	Methods	Results	Comments
			– Similarly, anandamide content in the temporal cortex and Boston Naming test scores had a positive correlation with each other. – Moreover, anandamide content and levels of NArPE in the midfrontal cortex of the patients had inverse correlation with the neurotoxic amyloid peptide levels, amyloid -protein (A)42.	in this field so that the knowledge gap can be filled.
Iuliano et al. [48]	Cross-sectional study – 14 patients were diagnosed with amnesia along with single domain of MCI, 30 patients who had mild AD, and 30 subjects were without any complications.	– Mini-Mental State Examination and Mental Deterioration Battery tests were used as cognitive tools. – 30 molecular species were estimated in plasma by gas chromatography	Except for n3-PUFA there were differences in almost all the certain components of all classes of fatty acid. Patients without MCI and AD had elevated levels of arachidic (C20:0), erucic (C22:1, n-9), and vaccenic acid (C18:1, n-9) and diminished levels of cerotic (C26:0) and linoleic acid (C18:2, n-6) when compared with healthy controls. Particularly linoleic acid and mead acid levels were found to be progressively decreased and increased from healthy subjects to aMCI and to AD patients, and moreover, inverse correlation was found in AD and aMCI patients.	The results generated in this study on a comprehensive profile of fatty acid in Alzheimer's disease and MCI patients with amnesia suggest the need for studying the complex lipids rather than the simpler ones so that the compounds which were not recognized previously can be found playing a vital role in the pathophysiology of these neurological disorders.
Wood et al. [28]	– Longitudinal Cohort study – 51 controls, 77 patients with MCI and 100 late-onset AD patients were recruited for this study	– Assessment of cognitive function was done by the MMSE and the Babcock Story Recall Test (BSRT). – Plasma DAG and plasmalogen levels were analyzed in huge cohorts of MCI and LOAD subjects with the help of targeted lipidomics approach by high-resolution mass spectrometry.	Clear stratification of subjects suffering from both MCI and LOAD by lipidomics approach included 3 groups of patients including (1) Patients with lower circulating PPE levels (2) Patients with increased levels of DAG in plasma and (3) Patients with no changes in the lipid parameters.	Future studies are essential in this case which might enhance the process of investigation of these biomarkers of lipids in a greater patients population which on the other hand can longitudinally be assessed with respect to both of the cognitive and lipidomics parameters and finally pathology of the brain. The biochemical changes in lipidomics can further lead to the development of nascent molecular targets for cognitive abnormalities and future therapeutic trials should be designed for patients suffering from dementia.

Table 1: (continued)

Study	Design	Methods	Results	Comments
Wood et al. [49]	– Longitudinal Cohort Study – 20 young controls,8 old controls, 19 MCI, 17 young demented and 17 old demented patients were recruited for this study.	– Clinical Dementia Rating scale was used. – 650 levels of lipids were individually identified across 26 subclasses of lipids. – The lipid levels were analyzed by a MS technology with high resolution	The lipids which were found to rise in the gray matter of MCI and old demented cohorts were monoacylglycerols (MAG), diacylglycerols (DAG), and the very long-chain fatty acid (26:0). – In the gray matter of the young demented (YD) and old demented (OD) cohorts PPE levels were found to be diminished. – In MCI, YD and OD cohorts phosphatidylethanolamine was found to be decreased. – The decline in the levels of sulfatides were detected in the white matter of the YD patients whereas levels of DAG were increased in the MCI group. – Levels of MAG were found to be elevated in both the YD and OD patients.	The role of DAGs and MAGs should be studied further so that their role in pathogenesis and progression of AD can be known.

sphingolipids should be properly maintained and slight changes in the concentration of sphingolipid levels may lead to neurodegenerative disorders such as AD. The central nervous system contains a major proportion of sphingomyelins making it an important constituent of cell membranes. This class of lipid is a critical component of microdomains of membranes known as lipid rafts. These specialized membrane regions are important sites that play roles in signal transduction by regulating protein trafficking, sorting and scaffolding. Beta- and gamma-secretase processing the ATP has specifically been associated with these domains. Ceramides are biologically active sphingolipids that are both precursors to SM synthesis and can be developed by the hydrolysis of SM. A huge number of cellular events such as differentiation, proliferation, and apoptosis are regulated by a number of species of ceramide which act as secondary messengers. These events are regulated through temporal and spatial coding that can activate signaling cascades differentially. Studies involving clinical and laboratory findings thus can further state that disturbances in the balance of SM and ceramides may lead to the pathophysiology of AD, specifically leading to the development of amyloid-beta along with amyloid-plaques, and subsequent neuro degeneration [31–36]. The levels of sphingolipid were found to be changed significantly in the tissues of the brain in patients suffering from AD when compared to controls with normal cognitive function [32, 36]. In an epidemiological study, the ceramides and sphingomyelin levels were found to have a cross-sectional association with memory impairment [36–37]. They were found to have variation with the severity of AD in a well-defined clinic population having normal controls, amnestic MCI and early probable AD patients. In another study high levels of blood ceramide also predicted one-year decline in cognitive function and loss in hippocampal volume among amnestic MCI patients. However, plasma ceramides and SM have not been assessed as predictors of progression among AD patients. Previous studies of cognitively normal controls and amnestic MCI cases found that high ceramide levels were predictive of cognitive progression. The study by Kim et al. showed 2-fold increase in the ceramide levels in females with clinical dementia ranging from age group 65–80 years (Table 1) [16]. A study by Wood et al. stated that ceramide and SM levels were not altered in white matter, gray matter, and cerebrospinal fluid. In the white matter of the young demented patients sulfatides [24:1(OH), 16:0(OH), 24:0(OH)] were found to be diminished and quantization were not reliable in CSF [25]. A study showed sphingomyelin content was most significantly associated with the diagnosis of schizophrenia where cognitive tests such as continuous performance test, salience attribution test, and Wisconsin sorting tests were carried out. Pathologic relevance of fatty acyl chain of sphingolipid levels heterogeneity in the gray matter of demented patients and sulfatide bisphosphatidic levels were elevated in temporal cortex gray matter starting from control to subcortical ischemic vascular dementia to mixed dementia [38]. In another study conducted in China, higher levels of ceramide (14:0,24:1) were found in demented PD patients rather than in PD patients without any cognitive impairment. Verbal memory had a negative correlation with C14:0 and C24:1. Moreover, the elevated levels of ceramide were found to have a correlation with the decline in function of the memory and had association with larger odds of multi-neuronal psychiatric symptoms. The ceramide (22:0,20:0,18:0) levels had a significant association with hallucination, anxiety and disturbances associated with sleep respectively [39]. A marked increase of lipids in brain samples of AD patients suffering from MCI was found in another study. Apo E is responsible for the depletion of sulfatide levels at the MCI stage of AD patients. This lipoprotein also has an association with the transport of sulfatides and sulfatide homeostasis which is mediated in CNS through lipoprotein metabolic pathways. Alteration in Apo E mediated sulfatide trafficking can result in decline in levels of sulfatides in the brain. A study by Wood et al. showed decline in sulfatide levels in the gray matter of young demented patients (Table 1). A study in the UK also showed rise in ceramide levels in the white matter of the brain of both neuropsychiatric disorders as compared to controls [40]. In another study levels of sphingolipids and ceramides were found to be elevated in the visual cortex of PD patients which might be due to decreased sphingolipid catabolism [41]. The dairy products such as milk, butter, cheese, and curd are rich in sphingolipids and contain more than 20% SM. So, derangement of these classes of sphingolipids in the brain can lead to cognitive impairment. A targeted sphingolipidomics approach can help in better management of the disease and can help in changing the dietary intervention of an individual to prevent the future risk of CD.

Role of sterols in cognitive dysfunction

One study mentioned about the role of sterols in cognitive dysfunction. Lathosterol and 7-dehydrocholesterol levels were found to decline significantly in the anterior cingulate cortex of PD patients. However, there are not many studies to provide strong evidence showing the role of sterols in cognitive dysfunction.

Lipidomics analysis

Lipidomics is a technique which assesses the various classes of lipids globally using various types of approaches based on mass spectrometry. There are two approaches of lipidomics analysis, i. e. targeted and untargeted one. Both untargeted and targeted lipidomics is suitable to profile more than 300 lipids while the main difference between the targeted and untargeted lies as the later can analyze a wider variety of classes of lipids including all the three fatty acids in triacylglycerol. They are unbiased in nature and done in a semi-quantitative process by infusing directly or by LC-MS based approaches with certain aspects of the flow of work and including the normalization of data and identification of lipids. Moreover, untargeted lipidomics is time-consuming and the standards used are not standardized well. On the other hand, targeted lipidomics focuses on the quantification of quite a few numbers of predefined internal standards which are labeled isotopically. Lack of commercially available standards limits the number of targets. Due to quantitative, rapid and straight forward analysis and generation of data the targeted approaches are considered to have high-throughput. The targeted approach is also considered to have more limited coverage [4]. Previous studies have focused majorly on untargeted lipidomics analysis so studies on targeted lipidomics should be done in the future for better prognosis of the disease (Table 1).

Role of statins in cognitive decline

As dysregulation of lipids plays a major role in the CD it becomes important to review the use of statins for treating cognitive dysfunction. There were two epidemiological studies done earlier depicting a 60% lower magnitude rate of dementia in patients using statins [42–43]. A MedWatch database review showed 60 different reports of statin-induced loss of memory which took place within few months' post initiation of statins or increase in dosage with simvastatin, pravastatin, and atorvastatin [44]. The other confounding factors which include several medical comorbidities, neurological conditions and other therapies related to medicine had large variations. The measures of the objective were not reported and the nature of the loss of memory solely depended on the report of a patient. Many studies showed that participants who were in follow up with statins for many years were more prone to develop incident dementia while another study showed that use of pravastatin in elderly population marked a decline in the major vascular events. A Jupiter study done in the past also did not suggest about the impairment in memory or adverse effects of cognitive function due to statin therapy [45]. Long term studies had been done in the past which stated that use of satins leading to the prevention of dementia. The concerns regarding the neurocognitive effects of statin therapy should be reassured currently as there is no such evidence to violate the guidelines. A clear taxonomy, establishment of vivid protocols and focus on objective outcome measures should be used to investigate statins and cognition.

Conclusion

Several untargeted lipidomics studies had been performed in patients with neuro degenerative diseases such as Parkinson, Alzheimer's and dementia. These studies show alterations in complex lipids in brain. However, the classes of fatty acids in these lipids involved are different across studies. Hence, there is a need for targeted lipidomics analysis, specifically including sphingolipids in patients with neurodegenerative disorders so as to improve diagnostics as well as management of these disorders.

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