Neuroprotection In Neurodegeneration by Omega-3-Fatty Acid

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***Abstract*—neurodegenerative diseases, characterized by progressive neuronal loss, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation, include Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), prion diseases, frontotemporal dementia (FTD), Lewy body diseases (LBD), and argyrophilic grain disease (AGD). The main omega-3-polyunsaturated fatty acids (PUFAs) are Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).**

They have potent antioxidant, anti-inflammatory, and neuroprotective effects. By reducing pro-inflammatory cytokines and increasing specialized pro-resolving mediators like resolvins and protectins, these essential fatty acids enhance the fluidity and integrity of neuronal membranes, regulate neurotransmission, and control inflammatory pathways. Amyloid accumulation, tau hyperphosphorylation, and synuclein aggregation are all critical aspects of AD and PD pathology that are decreased by EPA and DHA. Furthermore, by promoting mitochondrial function, neurogenesis, and the expression of brain-derived neurotrophic factor (BDNF), omega-3s aid in neuronal survival and cognitive resilience. According to clinical and experimental research, a sufficient intake of omega-3s may lower the likelihood of neurodegeneration, cognitive impairment, and mood disorders.

***Index Terms*—Neuron, Omega-3-Fatty Acid, Neuroprotection, Neuroinflammation, Oxidative stress, neurodegenerative diseases.**

I. INTRODUCTION

Numerous pathophysiological issues, including as neuronal cell loss and malfunction, increased oxidative stress, and neuro-inflammatory disorders, lead to neurodegenerative illnesses of the central nervous system. [1-2]

II. NEURONS

Since neurons are essential to brain function, they are crucial for effective communication in the human brain. Despite coming from the brain, neurons are found throughout the body. The production of neurons in childhood is attributed to neural stem cells, however in adulthood, the number of neurons is decreased.
Neurodegeneration is the gradual loss of neurons that alters the structure and function of neurons, resulting in a number of brain illnesses. [3-8]

Types of Omega-3 Fatty Acids

1) ALA (α-linolenic acid): Plant-based (flaxseed, chia, walnuts)
2) EPA (eicosapentaenoic acid): Marine-based (fatty fish, fish oil)
3) DHA (docosahexaenoic acid): Marine-based, crucial for brain and retina. [9]

Structure of omega-3-fatty acid-

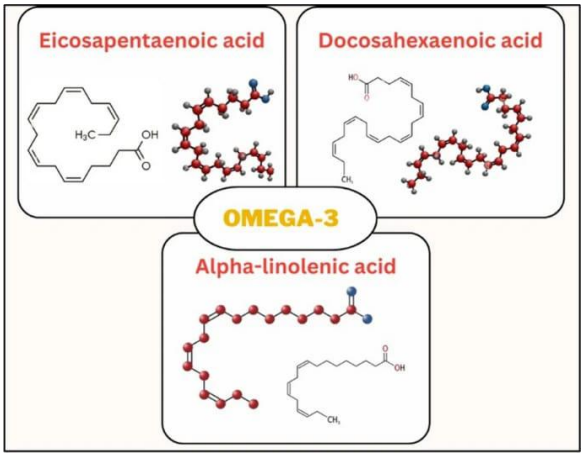

Fig-1 Structure of Omega Fatty Acids [10]

General Structure

Long-chain polyunsaturated fatty acids (PUFAs) are known as omega fatty acids. The general formula =

$CH–(CH_2)$ _m–COOH = $CH_3–(CH_2)$ _n–CH CH_3 is the omega (ω) end's methyl group. COOH is an alpha-end carboxyl group. The type is determined by the first double bond from the methyl (ω) end: ω-3 (n-3): the first double bond from the methyl end at the third carbon (ALA, EPA, DHA, etc.) The initial double bond is located at the sixth carbon in ω-6 (n-6), such as in linoleic acid and arachidonic acid and ω-9 (n-9): oleic acid, for example, has the first double bond at the ninth carbon. [11]

Structural Features

Several double bonds, typically in cis-form, are known as polyunsaturation, impacts the fluidity of the membrane. Because of their hydrophilic head (carboxyl group) and hydrophobic tail (methyl end), they are amphiphilic in nature. DHA and EPA are highly versatile and necessary for the fluidity of neuronal membranes and for signal transmission due to their abundance of double bonds. The initial methylene-broken double bond in omega- 3 on the third carbon atom from the methyl end of the fatty acid chain is what gives these fatty acids their name- ALA, DPA, SDA, EPA, DHA, and other polyunsaturated fatty acids. Alpha linoleic acid undergoes chain elongation and desaturation to produce omega-3 polyunsaturated fatty acids, which are then transformed into EPA or DPA. Alpha-linoleic acid is an essential un-saturated fatty acid with eighteen carbons. [12-13]

III. PHARMACOKINETICS OF OMEGA-3-FATTY ACID

Absorption-

The digestion of omega-3 fatty acids starts in the stomach when gastric lipases break down triglycerols into diacylglycerol and fatty acids. Bile salts and pancreatic lipase subsequently break down the fat globules that have formed in the small intestine. Different fatty acid transport proteins carry fatty acids into enterocytes, where they bond with apolipoproteins to create chylomicrons, which are then again transformed into triacylglycerol in the endoplasmic reticulum. These chylomicrons eventually find their way into the bloodstream and reach the targated tissue. [14-15]

In the small intestine, omega-3 fatty acids are absorbed alongside dietary lipids because they are lipophilic. Through fatty acid transport proteins or passive diffusion, they enter enterocytes as micelles with bile salts. Taking it with meals that contain fat increases its bioavailability. Formulation is important because triglycerides and re-esterified triglycerides are more readily absorbed than ethyl ester forms. [16]

Distribution-

The bioavailability of omega-3 fatty acids is influenced by their presence in triacylglycerol, free fatty acids, phospholipids, and ethyl esters. The estimated volume of distribution for EPA is 80L. The amount of omega-3 fatty acid distribution in the body is also influenced by age and gender. [17-18] Transported to the bloodstream via lymph and chylomicrons. distributed throughout the brain, retina, liver, heart, and adipose tissue. Long term incorporation into cell membrane phospholipids and short-term incorporation into plasma triglycerides. Whereas EPA circulates in plasma and regulates inflammation, DHA is abundant in the brain and retina. [19]

Metabolism –

Omega-3 fatty acids undergo oxidation and processing in the liver, which results in the production of VLDL, which carries fatty acids in plasma to different bodily tissues. [20] Alpha linolenic acid (ALA) undergoes beta-oxidation, elongation, and desaturation to produce long-chain polyunsaturated fatty acids like docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA). After fat is emulsified by bile released into the small intestine, ALA is absorbed as triglycerides and carried by plasma. Triglycerides, phospholipids, and oxidation are then esterified to produce saturated longer chain products. Fatty acids are hydrolyzed by pancreatic carboxylic acid and ester lipase to produce free fatty acids, which are initially absorbed in the small intestine and subsequently bound to fatty acid binding proteins that are integrated into chylomicrons and released into the lymphatic system. [21] Interaction of polyunsaturated fatty acids with plasma proteins and their distribution in different cellular membrane mainly affects PUFA's concentration in human body. [22] Also the difference in rate of incorporation of PUFA's into membrane phospholipids is important for studying PUFA's complex interplay. [23] Study on animal model, omega-3 -fatty acid regulates inflammatory process

[24] by altering cellular composition and receptors like NR1C3 (intracellular) and GPR-120 (cell surface) which maintains gene expression pattern and inflammatory cell signaling. [25-26]

[Differing absorption rates into various blood component and tissues, genetic variations in desaturase gene and unique fatty acid makeup of brain are the several factors that influences the metabolism of omega-3- fatty acid. Omega-3s undergo beta-oxidation in the liver for energy.]

ALA is converted to EPA (~5–10%) and then to DHA (~2–5%). EPA and DHA are precursors for anti-inflammatory lipid mediators (resolvins, protectins, maresins). [27]

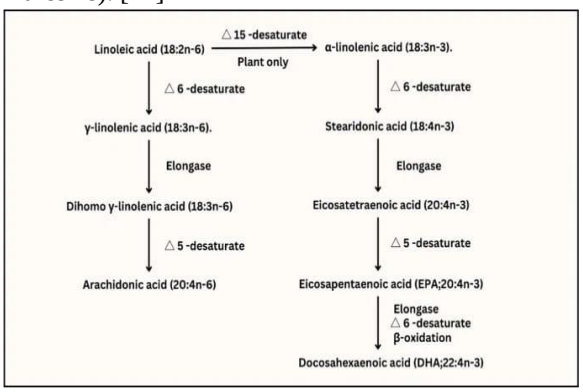

Fig - 2 Metabolic pathway of omega-3-fatty acids [28]

Elimination-

The mechanism of omega-3 fatty acid removal is unknown. ALA, DHA, and EPA have biological half-lives of one hour, twenty hours, and forty-nine to sixty-seven hours, respectively, according to compartmental studies [29] The main mechanism of action of omega-3 fatty acids is oxidation. Bile and urine contain trace amounts of metabolites.

Plasma half-life: EPA approximately 37 hours, DHA approximately 46 hours; this depends on dietary intake and tissue assimilation. [30]

Sources of omega-3-fatty acid-

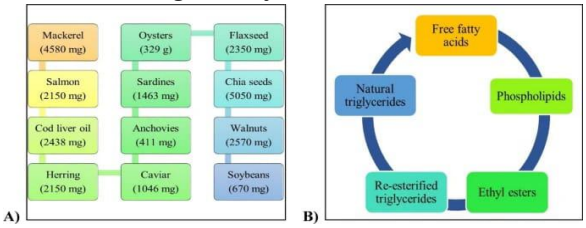

Fig-3 Sources of omega-3-fatty acid [31-32]

1) Marine source

1. Fatty Fish

(Rich in EPA & DHA) Tuna, trout, anchovies, herring, sardines, salmon, and mackerel are a few examples. These are the main sources of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). [33]

2. Fish Oils

Cod liver oil, krill oil, and other purified fish oils are concentrated sources of EPA and DHA. Widely used as dietary supplements. [34]

3. Shellfish

Among the shellfish that contain omega-3 fatty acids are oysters, mussels, clams, squid, and crab. Together with other nutrients, give modest quantities of EPA and DHA. [35]

4. Algae (Microalgae and Seaweed)

Because of their high DHA content, microalgae oils offer a plant-based marine omega-3 source that is appropriate for vegans and vegetarians. EPA and DHA levels in seaweed vary by species. [36]

It is well recognized that marine species are the main source of omega-3 fatty acids, particularly EPA and DHA. Omega-3 fatty acids are present in both freshwater and marine fish. [37]

River mullet fillets has 1.87% polyunsaturated fatty acid (PUFA), whereas freshwater fish such as barbel fillets contain 18.51% monounsaturated fatty acids (MUFA), Rayan fillets have 1.1% omega-6, and river mullet fillets have 1.87% omega-3. Russian Sturgeon has 46.8% total PUFA, 11.3% EPA, and 0.7% DHA, while salmon has 12.4% total PUFA, 0.8% EPA, and 1.6 DHA. [38]

2) Animal source-

Fatty Fish –

(Rich in EPA & DHA) Salmon, mackerel, sardines, herring, anchovies, trout, tuna. These fish are the most concentrated sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). [39]

Fish Oil Supplements-Cod liver oil, krill oil, and other purified fish oils contain high levels of EPA and DHA. [40]

Shellfish-Oysters, mussels, and squid provide small but significant amounts of EPA and DHA. [41]

Mackerel -have 4580 mg of EPA and DHA (combined) in 3.502 (100g) serving omega 3- content is present.
Salmon-have 2.150 mg of EPA and DHA (combined in 3.5oz (100gm) serving omega-3 content is present.
Cod Liver oil -consists 2438 mg of EPA & DHA (combined) per tablespoon.
Oyesters- have Omega-3 content 329 mg per serving. [42]

Eggs from Omega-3 Enriched Hens-
Eggs enriched with DHA (from hens fed flaxseed or fish oil) contain higher levels of omega-3 fatty acids. [43]

Dairy Products-
(Fortified or from Grass-Fed Animals)
Milk, cheese, and yogurt from grass-fed cows have higher omega-3 content, particularly ALA, and minor amounts of EPA/DHA. [44]

3) Plant Source-
Flaxseed-
The plant-based omega-3 fatty acid α-linolenic acid (ALA) is abundant in flaxseeds (linseed). Flaxseed oil, powdered seeds, or whole seeds can all be eaten. [45] About 73% of its total lipids are PUPA, and its oil is rich in fatty acids such as ALA (40–60%), linoleic acid (12–17%), oleic acid (13–19%), palmitic acid (5–8%), and stearic acid (2–4.5%). [46]

Soyabean-
Soybeans consists more than 8% ALA. [47] Soya Products like tofu, and soy milk contain moderate amounts of ALA. Useful for vegetarians and vegans as a source of plant omega-3. [48]

Perilla Oil-
Used in East Asian cuisines. very high in ALA (~50–60% of total fat). [49]

Chiaseeds-
lt's oil contains major constituents are PUFA particularly ALA (68%), LA (19%). [50] High in ALA; also contain fiber and antioxidants. Suitable for adding to smoothies, cereals, or baking. [51]

Walnuts-
Rich in ALA; also contain polyphenols that contribute to anti-inflammatory effects.
[52] carry short chain omega-6 and omega-3 - polyunsaturated fatty acids like linoleic acid, ALA. It is marine sources of omega-3 fatty Acids. [53]

Hemp Seeds-
Contains ALA along with a favorable omega-6: omega-3 ratio (~3:1). Can be consumed as seeds, oil or protein powder. [54]

Canola Oil-
A commonly used cooking oil with a good content of ALA. Suitable for salad dressings and low-heat cooking. [55]

Factors Causing Neurodegeneration-
1. Genetic Factors: Neurodegenerative illnesses can result from mutations in genes that encode proteins essential to neuronal survival and function. Examples include APP, Parkinson's disease (LRRK2), Huntington's disease (HTT), Alzheimer's disease (PSEN1/2), and SNCA. [56]

2. Oxidative Stress: When reactive oxygen species (ROS) are produced in excess, they harm neurons' lipids, proteins, and DNA. The brain's high oxygen use and lipid-rich composition make it extremely vulnerable. [57]

3. Mitochondrial Dysfunction: Neuronal death results from reduced energy production seen in ALS, Alzheimer's, and Parkinson's diseases. [58]

4. Protein Misfolding and Aggregation: Neuronal toxicity results from the accumulation of misfolded proteins like tau, α-synuclein, huntington, or β-amyloid. [59]

5. Neuroinflammation: When microglia and astrocytes are activated, inflammatory cytokines and chemokines are released, which exacerbates neuronal damage. [60]

6. Excitotoxicity: When glutamate receptors are overactivated, calcium excess results, which triggers neuronal death. [61]

7. Environmental and Lifestyle Factors-Exposure to toxins (pesticides, heavy metals), chronic stress, poor diet, and aging contribute to neuronal degeneration. [62]

Oxidative stress in neurodegenerative diseases

Oxidative stress alters the body's biochemical and biomolecular components, which results in neurodegenerative illnesses like multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and ALS, among others. [63-64]

However, a small quantity of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are necessary for brain signalling because they facilitate cell-to-cell and memory transfer. [65-66] A higher concentration of these ROS and RNS, on the other hand, damages cell components like DNA, proteins, and lipids, [67] causing stress and ultimately nerve cell death. An increase in reactive oxygen species and reactive nitrogen species can lead to oxidative stress, which is the result of inadequate antioxidant activity. Oxidative stress can readily harm the human brain due to its high oxygen consumption, high levels of metals and fatty acids, and low glutathione levels. [68] In Alzheimer's disease, ROS damages the brain, causing alterations in the affected person's RNA, DNA, and lipids.[69] Markers of Parkinson's disease that point to high levels of physical and chemical stress in the body include protein carbonyls,3-nitro tyrosine, 8- hydroxy-2-deoxyguanosine, and 4-hydroxy-2-nonenal.[70]

Inflammation in neurodegenerative diseases-

Neuroinflammation refers to innate and adaptive reactions to a variety of stimuli, including infections, stress, trauma, and ischemia. [71] Conditions such as localized tissue injury, peripheral immune cell migration, increased cytokine release, and microglial cell activation are all part of this neuroinflammation. [72] Monocytes, neutrophils, lymphocytes, astrocytes, and microglia are immune cells that release inflammatory mediators such cytokines, histamines, and reactive oxygen species (ROS) to cause the previously mentioned diseases. [73] neurodegenerative diseases and other neurological disorders are caused by chronic inflammation. [74] neurodegenerative disease development, which includes neural tissue degradation and mortality, is linked to neuroinflammation, which mostly affects the brain and spinal cord.[75]

Mechanism of Neurodegeneration

[Oligomers of different structure is formed from amyloid - beta (AB) monomer's that clumps together. Then these oligomers aggregate closely to form AB - fibres that again form AB- plaques due to their misarrangement. There is rise of inflammatory responses due to plaque formation that result in Tau-aggregates production which ultimately results in conversion of healthy neurons into unhealthy or diseased neurons. Number of diseased neurons leads to development of another Inflammatory response result in more neuron loss subsequently leads to loss in brain functioning and decline in cognitive function.]

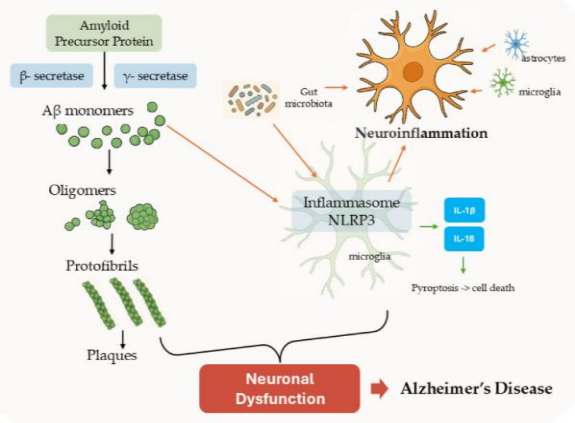

Fig- 4 Mechanism of Neurodegeneration [76]

Omega-3-fatty acid in Neuroinflammation-

When arachidonic acid is metabolized, it produces a variety of oxygenated derivatives. [77] Phospholipase A2 hydrolyzes membrane phospholipids into polyunsaturated fatty acids (PUFAs), which are then metabolized by the enzymes COXs, LOXs, and cytochrome P450

[78] to produce eicosanoids such as prostaglandins (PGS), thromboxanes (TXs), leukotrienes (LTS), lipoxins (Lxs), etc. [79] As precursors of lipoxins, protectins, and resolvins, PGs and Tx are produced from the Cox pathway, whereas LTs and Lxs are produced from the LOX pathway. [80-81] Intracellular systemic inflammation is triggered by eicosanoids and their associated metabolites (Tx, PGS, LTs, and resolvins). [82] The anti-inflammatory effects of 0-3-Fatty Acid are mediated by particular RvD1 and PD1 and neuroprotectins via the COX and LOX pathway.

RvD1 are derived from EPA and shows ant-inflammatory action by resolving inflammation by function:

Inhibiting neutrophil in Filtration

(i) Promotes macrophages to phagocytosis apoptotic cell

(ii) Terminating inflammatory responses [83-84]

PDI Shows anti-inflammatory, neuroprotective and anti-apoptic (anti-cell death) action which are derived from DHA. [85]

1) Minimize oxidative stress
2) Safeguard cell from harm/damage
3) Decreases apoptosis mainly in nerve cells.

Neuroprotectins- derived from DHA. Mainly shows neuroprotective action known as neuroprotective hormin D1 (NPDI). [86] Its action is to inhibit -amyloid toxicity. [87]

By competitively inhibiting the Arachidonic Acid pathway, omega-3 fatty acids reduce the synthesis of pro-inflammatory mediators, inhibit Arachidonic Acid, and stop it from binding to the Cox-2 and LOX enzymes through EPA. [88] At the same time, anti-inflammatory mediators are generated through RvD1 and PD1.

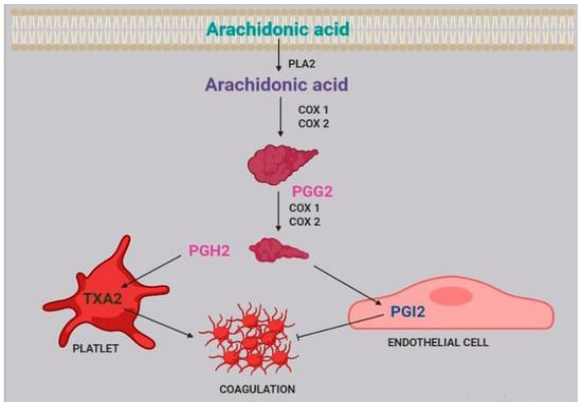

Fig-5 Inflammatory pathway of Arachidonic acid [89]

Mechanism of Omega-3 Fatty Acid:

1. Incorporation into Neuronal Membranes

DHA and EPA are incorporated into phospholipid bilayers of neurons and glial cells. This modifies membrane fluidity and receptor function. Also improves synaptic plasticity and neuronal signaling. [90]

2. Anti-Inflammatory properties

Specialized pro-resolving mediators (SPMs), such as resolvins, protectins, and maresins, are precursors of omega-3 fatty acids. These compounds have anti-inflammatory properties because they inhibit microglial activation, lower pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6), and encourage inflammation resolution. [91]

3. Decreasing oxidative Stress

EPA and DHA enhance antioxidant defences and reduce ROS production. Protect neurons from oxidative damage which is major contributor to neurodegeneration. [92]

4. Modulation of Neurotransmission and Synaptic Plasticity

Omega-3s regulate dopamine, serotonin, and glutamate neurotransmission. DHA enhances BDNF expression and supports neuronal survival, neurogenesis, and synaptic plasticity. [93]

5. Preventing Protein Aggregation

Tau hyperphosphorylation and amyloid-β build up are key components of Alzheimer's disease pathogenesis, and they are decreased by DHA and EPA. Neuronal apoptosis and neurodegeneration are prevented by omega-3-fatty acids. [94]

The importance of omega-3-fatty acids and their function in the therapy of ailments such as is being studied in ongoing research:

- Cancer
- The wellbeing of the mother and the babys health during pregnancy
- Heart and blood vessel conditions
- Rheumatoid arthritis
- Diabetes mellitus type II
- Brain and visual growth
- Gum disease
- Dementia and Alzheimer disease
- Depression [95]
- Prebiotics helpful conditions [96]
- Intervertebral disc deterioration [97]
- ADHD (attention deficit hypersensitivity disorder) [98]
- Maternal depression [99]
- Heart failure [100]
- Night sweats from menopause [101]
- Asthma [102,103]
- Epilepsy [104]
- Hypertriglyceridemia [105]
- Diabetic retinopathy [106]
- Chemotherapy adjunct [107]
- Premenstrual syndrome [108]
- Fatty liver disease that isn't caused by alcohol [109]

Neurodegeneration

1) Alzheimer diseases [110]
2) Multiple sclerosis [111]
3) Parkinson's diseases [112]
4) Huntington diseases [113]
5) Amyotrophic lateral Sclerosis [114]
6) Prions diseases [115]
7) Frontotemporal dementia [116]
8) Lewy body diseases [117]
9) Argyrophilic grain diseases [118]

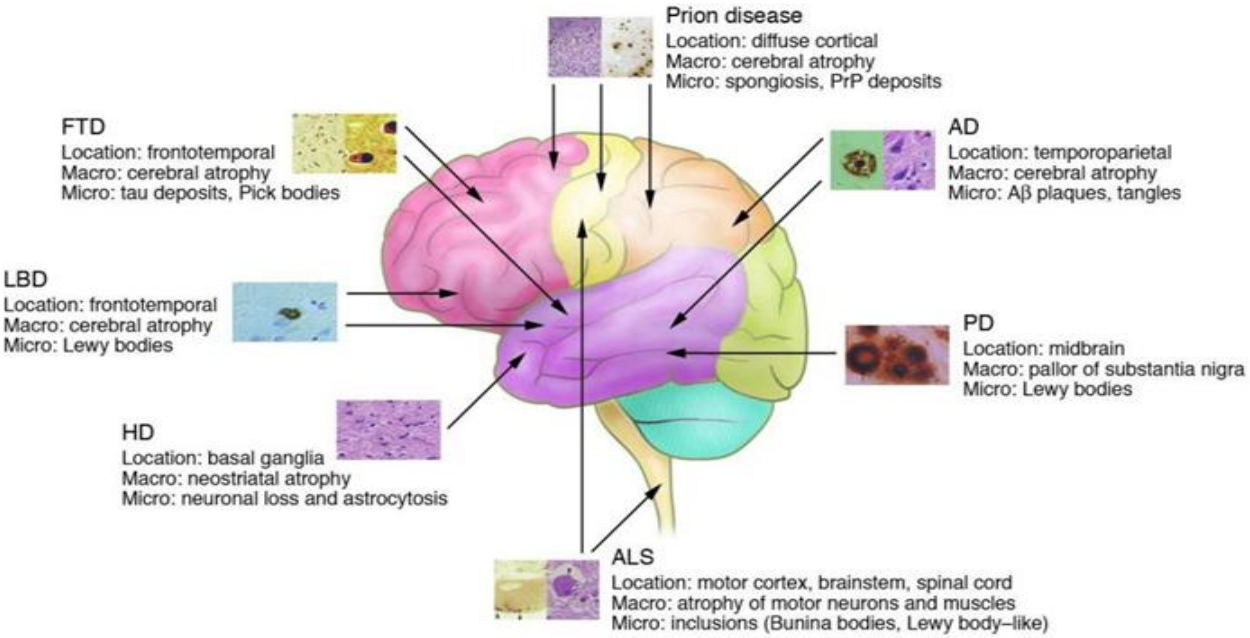

Fig- 6 Neurodegenerative disorders [119]

The condition primarily affects mental and physical health, which in turn affects an individual's ability to survive. [120]

The majority of cases occurs in older people. In addition to its many health advantages, omega-3 fatty acids lower the risk of neurological diseases. [121] Omega-3 fatty acids have anti-inflammatory qualities and control the integrity of cell membranes. [122,123] Omega-3 fatty acids must be received from diet because the human body is unable to manufacture them. [124,125] Fish and other seafood are important sources of omega-3 fatty acids. [126,127]

Omega-3-Fatty acid is consisting of biomolecules such as-polyunsaturated fatty acids (PUFAs), they are-

1) alpha-linolenic acid (ALA)
2) docosahexaenoic acid (DHA)
3) eicosapentaenoic acid (EPA),

which is very important component of human brain cells membranes.[128]

Omega-3 fatty acids have been found to have neuroprotective effects in animal studies. [129] Long chain PUFA (polyunsaturated fatty acids) omega-6 and omega-3 are found in the central nervous system; their presence in the membrane of neurons enhances cellular function. PUFA helps with neurological, cardiac, and optical visual impairment function. [130] Omega-3 fatty acids reduce inflammation, preserve neurotransmitter function, and promote neuroplasticity. [131] The activity of membrane bound enzymes, the functions of ion channels, and the signal transmission pathway that regulates neurotransmitter release are all affected by changing the fluidity of the brain mambrane. Dietary supplements with omega-3-fatty acids promotes cognitive function by stimulating neuronal growth factor activity. [132]

The desaturase delta-15 enzyme catalyzes the elongation and desaturation of alpha linoleic acid (ALA), an important omega-3 fatty acid, to produce DHA and EPA. Each of these fatty acids is essential to the human body's normal operation. [133] Numerous scientific studies have provided data for the potential effectiveness of PUFA supplements in treating neurodegenerative disorders [134,135] such as Parkinson's and Alzheimer's.[136]

The absence of the conversion enzyme desaturase

prevents the human body from synthesizing ALA and LA, although it may generate monosaturated fatty acids. [137] DHA, EPA, and ARA contribute to inflammation by producing thromboxane, leukotrines, prostaglandins, and eicosanoids. [138] Important PUFAs found in the brain and ratinal cells, DHA and AA control both mental and visual processes. Pathological conditions such as neurological, mental, cardiovascular, dermatological, and rhumatological problems are prevented by it. [139]

Neurodegenerative Disorders:

1)Alzheimer's Disorder:

AD is a neurological disease that worsens over time and is typified by behavioral abnormalities, memory loss, and cognitive decline. [140] Amyloid-β (Aβ) plaque buildup, neurofibrillary tangles (tau hyperphosphorylation), oxidative stress, neuroinflammation, and synaptic dysfunction are all part of the pathophysiology of AD. [141]

The absence of large long-chain omega-3-fatty acids causes physiological changes in the brain as people age. Since the brain contains 30–35% omega-3-fatty acids, this process leads to neurodegenerative conditions like Alzheimer's disease.[142] The brain's phospholipid membrane contains this lengthy chain of omega-3 fatty acids, primarily at the location of synapses.[143]

(Patients with Alzheimer's disease must take long-chain omega-3-fatty acid DHA supplements because their brains have decreased levels of this fatty acid.)

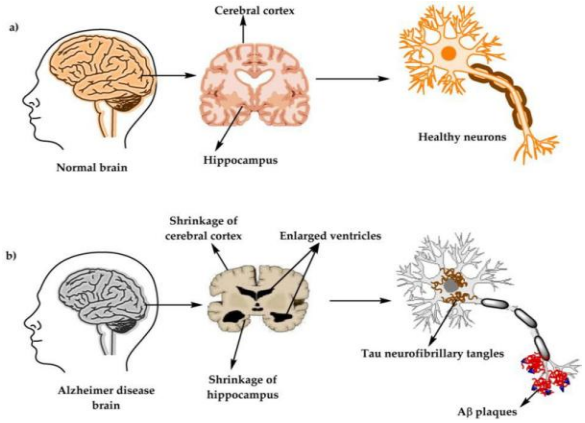

Fig- 7 Alzheimer's Diseases mechanism [144]

Disorder which constitutes 60-80% dementia. [145] Risk of cognitive decline can be reduced by consuming fish oil and polyunsaturated fatty acids. [146] Aging is major risk factor for development of Alzheimer's disease. [147] But 0mega- 3- fatty acids reduces morbidity and thereby lowers risk of cognitive decline or dementia there by Alzheimer's disease. [148]

Symptoms-

Early (Mild)-Memory loss, confusion, difficulty with familiar tasks, personality change Moderate-Behavioral changes, loss of recognition, wandering, language impairment Severe-Loss of mobility, inability to communicate, total dependency. [149-151]

Role of Omega-3 Fatty Acids in Alzheimer Disorder-

1. Decrease in amyloid-β accumulation: DHA and EPA improve clearance and minimize Aβ deposition, which lessens neurotoxicity. [152]

2. Anti-inflammatory and antioxidant effects: Omega-3 fatty acids fight oxidative stress in neurons and block microglial activation, which lowers levels of pro-inflammatory cytokines (TNF-α, IL-1β). [153]

3. Protection of synapses and neurons: DHA encourages neurogenesis and maintains the flexibility of neuronal membranes. Thus, it preserves synaptic plasticity and guards against tau hyperphosphorylation. [154]

Studies on omega-3 supplementation in AD mice models have demonstrated decreased neuroinflammation, decreased Aβ plaques, and enhanced cognitive performance. [155]

Human research: Epidemiological research indicates that a lower risk of AD is linked to a higher dietary intake of DHA and EPA. Early intervention yields greater advantages, although clinical trials in mild cognitive impairment (MCI) or early AD indicate only limited cognitive gain. [156]

2)Parkinson's Disorder:

Parkinson's disease (PD) is a progressive neurodegenerative illness that causes motor symptoms (such as tremor, bradykinesia, and stiffness) as well as non-motor symptoms (such as depression and cognitive decline) due to the death of dopaminergic neurons in the substantia nigra. [157] Parkinson disease pathogenesis includes oxidative stress, neuroinflammation, mitochondrial dysfunction, α-synuclein aggregation (Lewy bodies), and compromised proteostasis. [158]

Symptoms- Bradykinesis, restingtremor muscular rigidity, dystonia Others-memory difficulties, mood disturbances, day time drowsiness, dystonia, pain, excessive sweating, fatique, frequent nightmares, post meal fullness.[159]

Treatment-

By observational Study:

Consuming total fat, such as MUFAS and PUFAs, considerably lowers the risk of Parkinson's disease, according to the Rotter Dam Study. [160] The Nurses Health study (1984-2000) and the Health Professionals follow-up study (1986-2002) assess the strong correlation between nutritional lifestyle and the risk of Parkinson's disease. It has been shown that a prudent diet, which includes a high intake of fruits, vegetables, and fish, considerably reduces the risk of Parkinson's disease, whereas a western diet does not. [161]

Using a case-control study, the link between dietary consumption of specific fatty acids and the risk of Parkinson's disease in Japan, within six years after the onset of PD, was investigated that, omega-3-polyunsaturated fatty acids do not increase risk of PD while consumption of ARA and cholesterol could increase their risk. [162]

Thus, by prospective observational study, there is close association between omega-3- polyunsaturated fatty acids with lower risk of PD.

Randomized, Double blind placebo controlled Clinical trial published papers gives indication that omega-3-polyunsaturated fatty acid supplement is especially used for depression in parkinson's diseases along with demonstration that 1g/day of DHA is effective dose.[163]

Role of Omega-3 Fatty Acids in PD

1. Neuroprotection: DHA and EPA improve fluidity by integrating into neuronal membranes. Additionally, they shield dopaminergic neurons from apoptosis and oxidative damage. [164]

2. Anti-inflammatory effects: Omega-3 fatty acids inhibit pro-inflammatory cytokines (TNF-α, IL-1β) and decrease microglial activation, both of which accelerate the progression of Parkinson's disease. [165]

3. Dopaminergic support: DHA may alleviate motor and cognitive symptoms by increasing dopamine release and enhancing receptor function. [166]

Studies on omega-3 supplementation in PD animal models (MPTP or 6-OHDA caused) have demonstrated that it improves motor function in animals by lowering inflammation, oxidative stress, and dopaminergic neuron death. [167]

Human studies: According to a small number of clinical research, omega-3 fatty acids may help PD patients with their quality of life and depressed symptoms. Reducing inflammation and oxidative stress as an adjuvant treatment is supported by some data. [168]

3) Multiple Sclerosis -

Multiple sclerosis is a chronic autoimmune demyelinating disorder of the central nervous system (CNS), characterized by inflammation, axonal damage, and neurodegeneration. [169] Main causes of multiple sclerosis involves autoreactive T cells (Th1/Th17), B cell activation, microglial inflammation, and loss of oligodendrocytes leading to demyelination and impaired neurotransmission. [170]

Role of omega-3-fatty acid in multiple sclerosis

Anti-inflammatory effect:

DHA and EPA inhibit production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and promote anti-inflammatory mediators (IL-10, resolvins, protectins). [171]

Neuroprotection:

Omega-3s integrate into neuronal and oligodendrocyte membranes and enhancing membrane fluidity. They protect myelin integrity, and reduces oxidative stress.[172]

Immune modulation:

By changing T-cell response from pro-inflammatory Th1/Th17 to regulatory T cells, omega-3-fatty acids acids in lowering the autoimmune attack on myelin.[173]

4) Amyotrophic lateral Sclerosis-

The progressive neurodegenerative illness known as Amyotrophic lateral sclerosis results in muscle atrophy, paralysis and death due to loss of motor neuron in the brain and spinal cord.

[174] Oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, neuroinflammation, and protein aggregation which mainly cause Amyotrophic lateral sclerosis. [175]

Symptoms-
dyspenia, diffculty in speaking and swallowing, loss of arm and hand function, loss of ambulation, spasticity in arms, legs, bulbar regions, aspiration pneumonia mortality and respiratory insufficiency [176]

Role of Omega-3 Fatty Acids in ALS
Anti-inflammatory action:
TNF-α and IL-1β, two pro-inflammatory cytokines that are significantly linked to the course of ALS, are inhibited and microglial activation is reduced by DHA and EPA. [177]

Neuroprotection:
DHA improves fluidity, lowers excitotoxicity, and incorporates into neuronal membranes. They guard against motor neuron apoptosis. [178]

Support for mitochondria:
Omega-3 fatty acids lessen oxidative damage and enhance mitochondrial activity. In the pathophysiology of ALS, they aid in maintaining neuronal energy metabolism. [179] Higher omega-3 intake may be linked to a lower chance of developing ALS, according to epidemiological research. According to a large cohort research, people who consumed more omega-3 fatty acids in their diet were around 34% less likely to develop ALS. [180]

5)Huntington's Disorder
Autosomal dominant neurodegenerative disorder caused by CAG trinucleotide repeat expansion in the HTT gene that leading to mutant huntington protein (mHTT) aggregation is a Huntington disorder. [181] Huntington`s diseases are mainly characterized by neuronal loss in the striatum and cortex, oxidative stress, mitochondrial dysfunction, and impaired synaptic transmission. [182]

Symptoms-
Depression, apathy, irritability, Impulsiveness, sati suicidal behaviours, functional impairement, global dementia, bradykinesia, spasticity, dysarthria, dysphagia, incontinence. [183,184]

Role of Omega-3 Fatty Acids in HD
Neuroprotective effects:
Docosahexaenoic acid (DHA), a key omega-3 PUFA which integrates into neuronal membranes, improves fluidity, and supports synaptic signaling. [185]

Reduction of neuroinflammation:
Omega-3s reduce pro-inflammatory cytokines (TNF-α, IL-1β) and microglial activation which are the processes elevated in HD brains. [186]

Mitochondrial function:
DHA and EPA improve mitochondrial biogenesis and reduce oxidative stress. Both processes are impaired in HD pathology. [187]

Treatment of Huntington's Disease with Omega-3 Fatty Acids
Rationale: Omega-3 fatty acids (EPA, DHA) may promote mitochondrial function and neuronal survival due to their anti-inflammatory, antioxidant, and membrane-stabilizing properties. The testing of omega-3s, primarily ethyl-EPA, as a potential treatment for HD was made possible by these methods. [188] Clinical Proof Pilot Trials: Puri et al., Neurology 2002: Small RCTs of ethyl-EPA (2 g/day) demonstrated motor score improvements and slower regional brain atrophy on MRI in some patients.
Trial TREND-HD (2008): Design: Randomized, double-blind, large, multicenter, placebo- controlled study. 316 HD patients make up the sample.

Treatment: 2 g/day ethyl-EPA for 6 months.
Results: No significant benefit on Unified Huntington's Disease Rating Scale (UHDRS) motor score, function, cognition, or global outcomes compared with placebo.
Extension: 12-month open-label extension also failed to show consistent benefit. Conclusion: Ethyl-EPA did not slow disease progression at 6 months.

Systematic Review & Meta-analysis
Morsy et al., Acta Neuropsychiatrica 2019: Pooled analysis of ethyl-EPA trials. At 6 months: No benefit vs placebo.
At 12 months: Modest improvement in motor scores in small subsets. Overall: Evidence inconclusive, not strong enough for recommendation. [189]
Safety- Generally well tolerated (GI upset, fishy

aftertaste). High doses may increase bleeding risk in patients on anticoagulants/antiplatelets. No major safety issues reported in HD trials. [190]
Clinical Takeaway-Not an established treatment. Early small trials suggested benefit, but the largest RCT (TREND-HD) showed no effect.
Meta-analyses indicate possible longer-term modest motor improvements, but evidence is weak and inconsistent. Omega-3 fatty acids may be considered as adjunctive nutritional support (especially if diet is deficient), but should not replace standard symptomatic therapy or clinical trial participation. [191]

6) Prions diseases-
Prions diseases is an autosomal neurodegenerative disorder i.e., degeneration of PrP^C protein encoded by PRNP gene. In prions disorder there is autosomal dominant mutution occurs in PRNP gene. [192] In an ageing brain, there are variable amount of misfolded proteins / peptides developes that leads to prions diseases. [193] Misfolded prion protein (PrP^Sc) serves as a template in pathogenesis, causing normal PrP^C to misfold. Neurotoxicity, synaptic malfunction, gliosis, and neuronal death are the results of accumulation. [194]

Symptoms:
1. Rapidly progressive dementia
2. Ataxia, myoclonus
3. Visual disturbances, insomnia, psychiatric symptoms
4. Death usually within months to a few years depending on subtype. [195]

Types of Prion Diseases-
1. Human:
Creutzfeldt–Jakob disease (CJD, sporadic, familial, iatrogenic, variant), Gerstmann–Sträussler–Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI), Kuru.

2. Animal:
Scrapie (sheep), Bovine spongiform encephalopathy (BSE, "mad cow disease"), Chronic wasting disease (CWD in deer/elk). [196]

Role of omega-3-fatty acid in prions diseases-
EPA or DHA increases the activity of phospholipase A2, an enzyme that influences the synthesis of PrP. [197] DHA or EPA alters endocytosis and intracellular trafficking of PrP^c, both of which are essential for PrP^sc production. [198]

7) Frontotemporal Dementia -
Frontotemporal dementia is neurodegenerative disease occurs due to multiple pathological features, particularly prescence of intracellular protein inclusion of protein TDP-43 which is imp RNA binding protein whose accumulation in cytoplasm of neurons causes neurodegeneration. [199]

Causes of motor neuron death in FTD are
1) integrated stress response
2) oxidative stress [200]
3) dysregulation in protein synthesis [201]
4) neuroinflammation. [202,203]

Role of e Omega-3-fatty acid-
Eating fish has been shown to reduce the risk of dementia or cognitive decline in nine epidemiologicam studies. These studies are listed below: In 1997, Kalmin et al. [204] and Kalmijn et al. [205], Kalmin et al. (2004), [206] Morris et al. (2003) [207] Huang et al. (2005), [208] Morris et al. (2005), [209] and Nurk et al. (2007) [210] Van Gelder et al., [211] and Barberger Gateau et al., [212] in 2007.

8) Lewy body diseases-
Lewy body illnesses are 15% more common in people over 60 and 40% more common in people over 85, according to community-based population studies. [213] Lewy body illnesses are premotor Parkinson's diseases characterized by a reduction in dopamine levels in the striatal densities and dopaminergic nigral neurons. [214]

Role of omega-3-fatty acid in LBD-
1. Anti-inflammatory Effects
Omega-3 polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), reduce neuroinflammation by: Inhibiting NF-κB activation and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Increasing anti-inflammatory mediators such as resolvins and protectins. This reduces microglial activation, which contributes to neuronal protection in LBD. [215]

2. Protection Against α-Synuclein Toxicity
DHA can modulate α-synuclein aggregation and help maintain protein homeostasis. Omega- 3s may stabilize neuronal membranes, reducing α-synuclein misfolding and Lewy body formation. [216]

3. Neuroprotective and Antioxidant Action
Minimizes oxidative stress, a major contributor to the death of dopaminergic neurons in LBD [217]
The brain's primary structural lipid, DHA, enhances synaptic plasticity and membrane fluidity. Through improved neurotransmission, LBD patients may have improved cognitive and memory abilities. [218]

9) Argyrophilic grain diseases-
Neurodegenerative disorder involves development of small, grain like inclusions near to neuronal dendrites and axons, which contains 4-repeat tau filaments commonly occurs in brain of older persons mostly.

Symptoms-
Mild cognitive impairment, Behavioural & psychiatric symptoms in older people. [219]

Dementia and Depression
Depression and dementia have a close relationship. Studies on epidemiology suggest that late-onset depression itself could be a precursor to dementia. [220] In the early phases of neurodegenerative disorders, depression symptoms may appear. [221] Accordingly, depression symptoms may be a precursor to conditions that eventually lead to dementia, but they are not a risk factor for dementia [222]

Role of omega-3-Fatty acid:
PUFAs lessen the incidence of dementia, lowers the chances of neurological a psychiatric symptom, and improves mood stability due to their anti-inflammatory effects. [223]
The 2017 study by Cutuli et al. demonstrates that omega-3 PUFAs are beneficial for neuroplasticity and cognitive impairment. Omega-3 polyunsaturated fatty acids were found to improve synaptic functioning and have a neuroprotective effect on cognitive impairment.[224]

Grosso et al. (2016) conducted a meta-analysis of findings from observational studies investigating the relationship between fish, omega food intake, and depression. The study covers 31 studies in total, involving 255,076 participants and more than 20,000 episodes of depression. According to data from 21 datasets, there is correlation between a decreased incidence of depression and consumption of fish that are rich in omega-3-fatty acids, or omega-3-PUFA. [225]

Omega-3-fatty acid in diet
According to certain findings, taking supplements of omega-3 fatty acids can help people with neurodegenerative diseases including Parkinson's disease and MC-I, which enhance cognitive performance. [226-229] Evidence of the positive and advantageous benefits of omega- 3 fatty acid supplementation in disorders involving omega-3 fatty acid deficiency has been provided by meta-analysis studies. [230] According to a comprehensive review, taking supplements of omega-3 fatty acids can help those with moderate Alzheimer's disease. [231] A 0.1% g/d increase in dietary DHA reduces the risk of dementia and Alzheimer illnesses, per a systematic review of 21 studies that assessed risk for MCI, PD, AD, and cognitive decline. [232]

1. Essential Nutrients
Essential polyunsaturated fatty acids, omega-3 fatty acids must be received from diet because the human body is unable to produce them effectively. DHA (docosahexaenoic acid), EPA (eicosapentaenoic acid), and ALA (α-linolenic acid) are the three primary dietary types. [233]

Dietary Sources
Omega-3-fatty acids are frequently found in foods including flaxseeds, chia seeds, walnuts, soybean oil, and canola oil.
Primary source of EPA and DHA are fatty fish (salmon, mackerel, sardines, and tuna), fish oil, krill oil, and algae-based supplements for vegetarians and vegans. [234]

2. Recommended Intake
Adults should consume 250–500 mg of EPA + DHA per day, according to WHO/FAO recommendations. Approximately 1.1 g per day for women and 1.6 g per day for males are advised for ALA. [235]

Health benifits:

Cardiovascular health: Lowers triglycerides, reduces blood pressure, and decreases risk of heart disease.

Neuroprotection: DHA supports brain development and may slow cognitive decline.

Anti-inflammatory action: EPA and DHA regulate inflammatory mediators (resolvins and protectins).

Eye health: DHA is crucial for photoreceptor membrane function. [236]

Stem cell in neurodegenerative diseases

Stem cells can differentiate into a variety of specialized cells and are capable of self-renewal. [237] Neurodegenerative illnesses can now be treated using stem cell therapy. [238] It includes modifying acetylcholine esterase inhibition and neurotransmission activity. [239] When it comes to neurodegeneration, stem cells exhibit neuroprotective effect by

A. self-renewal and differentiation
B. Angiogenesis to Release cytokine
C. Homing activity
D. Paracrine effect, immunomodulation
E. Anti-inflammatory action,
F. Anti-apoptic and
G. chematactic signaling. [240]

Contraindications

1. Omega-3-fatty acids reduces platelet activity hence caution and monitoring is recommeded in patients taking antiplatelet and anticoagulant medications, [241]
2. Also contraindicated for patients with hypersensitivity,
3. Omega-3 fatty acids are not allergic but FDA Labels states to use with caution in patients with allergic to seafood. [242]

Toxicity

In general, EPA and DHA are safe. According to certain research, pregnant women should eat foods high in DHA. [243] Because DHA and EPA supplements can be highly concentrated, it is not advised for nursing moms to consume them as they only need 200–300 mg of DHA per day. [244] Pregnant and nursing women who rely on fish as their main source of omega-3 should limit their consumption to two to four meals or switch to fish with lower levels of methyl mercury, such as salmon or trout. Methyl mercury is a dangerous organometal found in fish. [245-247]

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