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## Neurological diseases: A perspective genetic approach & dietary intervention

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### Abstract

Neurological diseases account for a large and increasing health burden worldwide and most vexing afflictions known to mankind. This is since neurological problems are often terrible to patients and their families because the great majority of neurological and neurodegenerative conditions lack effective treatments. There is a plethora of neurological conditions such as Parkinson's, Huntington's, and Alzheimer's disease etc. To estimate the rising neurological burden due to genetic or non-genetic (Environmental) factors, DALYs (Disability-Adjusted Life Years) are an essential indicator for estimating the worldwide burden. A systematic and comprehensive data analysis of neurological diseases within the Indian population has warranted that in India prevalence and incidence of neurological diseases is doubled from 4.0% (95 percent UI 3.2-5.0) in 1990 to 8.2% (6.6%-10.2%) in 2019. Several variables contribute to the onset and progression of neurological diseases, including oxidative stress, inflammation, metal imbalances, microbiome, as well as genetic and nutritional factors. Therefore urgently needed to develop new and more effective genetic and therapeutic strategies to combat these devastating diseases. This review demonstrated the increasing global public health importance of neurodegenerative diseases with the help of a new era of omics, influence of dietary intervention, adequate dietary choices as part of a continuation of healthy lifestyle choices, genetic testing, interpretation of genetic testing results, and genetic counseling may help to reduce the risk and may help to decrease the burden of neurological problems.

**Keywords:** DALYs, environmental, genetic counseling, neurological diseases, neurogenetic

### 1. Introduction

In the 21<sup>st</sup> century, neurological diseases become a major public health concern <sup>[1]</sup>. Genetic testing may be the most precise method of determining the cause of neurological problems. However, studies established a true link between the neurological condition and genetic alterations. Most neurodegenerative diseases appear to be multifactorial in nature. The prevalence of neurodegenerative diseases is on the rise, but with the rapid advancement of information technology, novel molecular processes like genetic testing and the omics era marked a sea change in our understanding of multifactorial diseases and the pathomechanisms that underpin them <sup>[2, 3]</sup>. Central nervous system, consisting of the brain, is complex, mysterious, and equally fascinating with respect to its functioning and formation. The relevance of a central nervous system in the regular development of the human body cannot be overstated biologically, behaviourally and psychologically <sup>[3]</sup>. It involves the central and peripheral nervous system that includes brain, spinal cord, peripheral nerves, cranial nerves, autonomic nervous system, nerve roots, neuromuscular junction, and muscles <sup>[4, 5]</sup>. This is caused by the dysfunction of the brain, as well as the nerves that run throughout the body and the spinal cord can have catastrophic, even fatal, consequences for both mental and physical health and leads to neurological diseases <sup>[6]</sup>. There is currently substantial evidence that dietary nutrition can prevent and treat neurological symptoms in a variety of medical disorders. The impacts of nutrition on brain health are mediated by several critical processes, including the recently reported effects of dietary variables on alterations in epigenetic modifications, mitochondrial malfunction, and neuro inflammatory.

Nowadays, the vast range of complexities in the overlapping of observable symptoms of neurological and psychological diseases that require adequate dietary intervention by nutritional counselors & clinical care by genetic counselors or other healthcare professionals.

To decrease the range of these debilitating diseases, genetic counselors can help them out by giving the relevant genetic counseling.

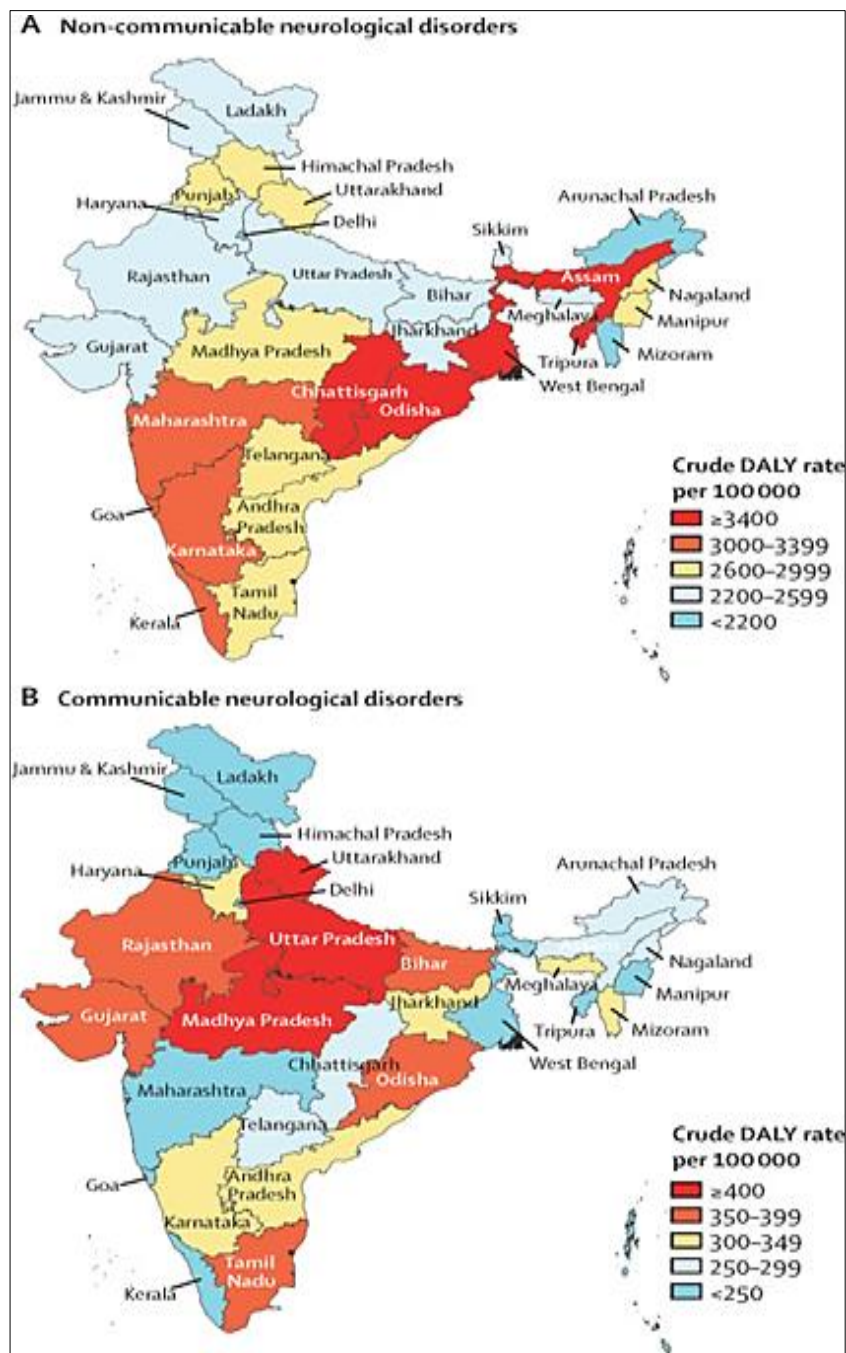
## 2. Genetic Perspective of Neurological Diseases

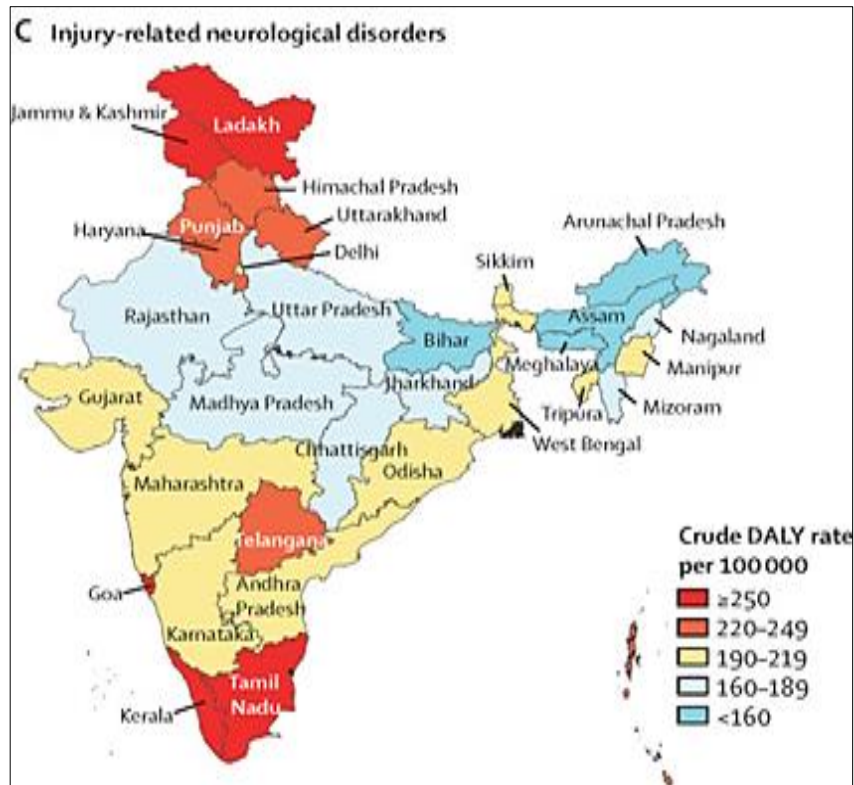
Neurological Diseases are the group of heterogeneous diseases of the nervous system which are caused by inherited genetic mutations, impaired functions of the brain, errors in gene regulation mechanisms, any chromosomal alterations including both structural and numerical during the development of the fetus, lifestyle and environmental factors that may cause neurological diseases [7, 8]. It can also be caused due to any abnormalities during the development of the fetus or any injury or any other conditions that might lead to the development of a neurological disease [9]. Another important factor is the interplay between the environmental and lifestyle patterns of the individuals that often lead to neurological diseases [10, 11].

## 2.1 Statistical analysis of neurological diseases in India and worldwide

“According to the Global Burden of Injuries, Diseases, and Risk Factors Study 2019, a study published in the Lancet medical journal, the prevalence and incidence of non-communicable neurological diseases to total DALYs in India doubled from 4.0% (95 percent UI 3.2-5.0) in 1990 to 8.2% (6.6%-10.2) in 2019 is shown in Figure. 1 [12]. During the same time period, however, the contribution of communicable neurological illnesses reduced from 4.1% (3.55-4.8%) to 1.1% (0.9-1.5%).

A. Non-communicable neurological diseases include stroke, epilepsy, headache, cerebral palsy, Alzheimer's disease and other dementias, Parkinson's disease, brain and CNS cancer, multiple sclerosis and motor neuron diseases. B. *Communicable* neurological diseases include; Meningitis, Encephalitis, Tetanus. C. *Injury-related* neurological disorders: Spinal cord injuries, Traumatic brain injuries.





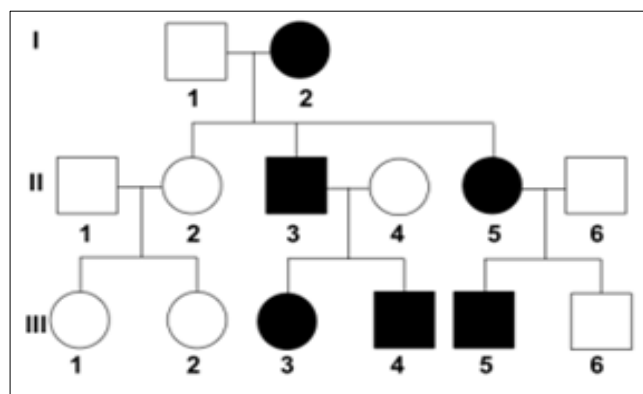
**Fig 1:** Rates of noncommunicable, communicable, and injury-related neurological illnesses in India's states, 2019 (DALY=disability-adjusted life-year).” (<https://pubmed.ncbi.nlm.nih.gov/34273302/>)

**2.2 Reasons for emphasis on Genetic Perspective**

The major genetic perspective of neurological diseases is *synaptogenesis* [13], commences prenatally but a significant portion of the process continues even after the birth. *Synaptogenesis* is the process of formation of synapses between the neurons [14]. When mutation takes place in the formation of neurons, it is found that it has been associated with neurodevelopmental abnormalities, and decreased function at multiple regions of the synapse is a common characteristic of neurodegenerative illnesses that are collectively known as synaptopathies.

Genetically, during family planning, the foremost prerequisite is the health of both parents. It is necessary for both parents to get them completely tested before they enter family planning. It is quite acceptable to go for family planning if both parents are healthy and if in any case,

either/both of the parents are unfit or the couple is not fecund as shown in Figure-2 then appropriate treatment for the same shall be brought into action to avoid the transmission of disease(s) in the coming generation. The figure demonstrates that all three generations are affected due to the inheritance of defective alleles or genes from either of the parents. So, it is necessary to go genetic testing suggested by a genetic counselor. The genetic counseling is done by reviewing the medical records, family histories, pedigree analysis, affected persons are interviewed (In case of infancy or early childhood parents are supposed to answer), physical examination, and more testing is obtained as needed to make a diagnosis (such as genetic testing and neuroimaging). Treatment plans and long-term follow-up are formed after the diagnosis.



**Fig 2:** Shows the three generation pedigree

**3. Comorbidities and Neurological Diseases**

Comorbidity can be defined as the situation wherein there is the presence of one or more medical conditions that are

reported to co-exist with the primary condition (often independent of the primary condition). These comorbidities may or may not be the outcomes of primary conditions and

even the chronology of occurrence might not overlap with that of the primary condition.

In the case of neurological diseases, the situation is relatively more convoluted than what has been reported in other diseases (or for that matter diseases). The reason for making such a statement is the diversified and closely interrelated range of functions that this brain of ours caters to. On a broader scale, the brain caters to three important functions- Behavioral, Cognitive and Movement. Hence comorbidities in such conditions might be either biological, hormonal, psychological and/or psychiatric [15, 16].

Biological and hormonal on the account of the brain housing; two most important glands of the human body are hypothalamus and pituitary Glands. Secretions of these glands not only influence the various important functions of

the human body both directly and indirectly regulates the production and/or release of hormones from other glands. This makes the situation not only convoluted but also hard to be understood and treated thereafter [17, 18].

Behavioral, Psychological and Psychiatric on the account of the brain catering to cognitive tasks. These types of comorbidities are relatively difficult to manage for they are to a great extent influenced by the social environment of the individual apart from the biochemical environment within the individual's body. Often it is more important to distinguish whether a particular comorbidity is psychological or psychiatric in nature because psychiatric comorbidities have a greater overlapping of biological dimensions compared to psychological comorbidities [19, 20].

**Table 1:** Major genes & comorbidities linked to Neurological Disease

S. No	Neurological Disease	Genes Associated	Comorbidities Associated	Recommended Diets
	Alzheimer's Disease	APP, BIN, CLU, APOE PSEN1 & PSEN2	Hypertension, Osteoarthritis, Depression, Osteoporosis, Cerebrovascular Diseases	LCHF Diet
	Parkinson's Disease	PARK7, PINK1, PRKN	Cerebrovascular Diseases, Hypertension, Diabetes, Chronic Pulmonary Disease, Paralysis	MIND Diet
	Dementia	APOE, PSEN1 & PSEN2	Hypertension, Coronary heart disease, Diabetes	Nordic Diet
	Epilepsy	SCN1A, GABRA1, GABRB3 & KCNT1	Depression, Anxiety, Dementia, Migraine, Heart disease	Ketogenic Diet
	Huntington's Disease	HTT	Rheumatoid arthritis, Spondylosis, Intervertebral disc degeneration, Allergies, Arterial hypertension, Acute myocardial infarction, Insomnia, Hypothyroidism, Hyperthyroidism	MIND Diet
	Amyotrophic Lateral Sclerosis	MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C21orf2, and CCFN	Dementia, Hypertension, Disorders of Thrombosis, Atrial Fibrillation	LCHF

#### 4. Management and Treatment of neurological diseases

Genetic counselors will recommend genetic testing by considering the risks, benefits, and limitations. Counselors will explain to patients the impact of the disease on them and their families, as well as their views on the etiology of the disease and the preferred outcome of their participation in the study, even if the counseling was individualized for the affected person. Counseling will be provided both before and after genetic testing to help patients understand and process the psychosocial implications of testing. In addition, the genetic counselor will play a role as a patient's support system [21].

Earlier there were only therapeutic practices of treatment however it was with advancement in medicine, the omics era, and allied sciences that this world witnessed the emergence of preventive measures (initially in the form of vaccines and now gene therapy) with the help of genetic testing advised by genetic counselors. With such great deal of sophistication, the strategies can be broadly classified under following heads based on the approach.

- Predictive Measures
- Preventive Measures
- Therapeutic Measures
- Post-treatment Measures

##### 4.1 Predictive measures

Predictive measures often tops the sequence of strategies and is the approach various genetic counselors use for accomplishing the tasks. In accordance with this strategy, a person is scanned for all the possible neurological diseases

that s/he might be prone to. This includes genetic, congenital, lifestyle triggered, age-related.

Genetic and congenital approaches are often conducted during the development stage of fetus using the amniotic fluid. Though it is often conducted during the process of family planning also to ensure the safety of the forthcoming baby. Such approaches are beneficial from the point of view that the concerned individual gets enough time to prepare himself or herself both mentally and physically to cope up with or to avoid the chances of any such disease/disorder being caused.

##### 4.2 Preventive measures

Preventive measures often follow the predictive approach because all those diseases (brought to knowledge under predictive measures) having relatively higher chances of occurrence are prioritized and the preventive measures are now followed for the same. The methodology under preventive measures includes- medications, changes in lifestyle, changes in food habits and others (as may be prescribed by competent professionals). The most common methodology includes Yoga as a preventive measure for a plethora of medical conditions, including neurological and psychological disorders & complete body tests to monitor the progress of adopted protocols. Asanas (postures), pranayama (breathing techniques), and dhyana are the three main elements of yoga (meditation). Yoga combines physical and mental activities to promote overall wellbeing by reducing stress, promoting healthy lifestyle choices, and enhancing mental/emotional health, sleep, and some neurological problems through a range of biological

mechanisms connected to either the aerobic components of yoga (the varying sequence of asanas) or the breathing and meditative components of yoga (pranayama and dhyana). Through a variety of mechanisms, including stimulation of the central nervous system's release of endorphins, monoamines, and brain-derived neurotrophic factor (BDNF) in the hippocampus, the aerobic elements of yoga improve mental health [22-24].

People might not be much aware about predictive measures but a great deal of awareness and heavy inclination towards the adoption of preventive measures has been observed in the population to ensure their health. Not only this, but people also tend to equip themselves with medical insurance to financially safeguard themselves about any unforeseen health expenditure. One of the most common reasons often cited for heavy inclination towards adoption of preventive measures is our hectic lifestyle and polluted environment and contaminated edibles.

### 4.3 Dietary interventions

Worldwide with medical advancement, understanding the etiology & pathology of many diseases has improved to a great extent, which has led to the development of more effective pathways of treatments. A view near the end of the twentieth century was that nutrition should be part of health & wellbeing. However, this generation also realizes that Medicines often present agonized side effects, during treatment or even curing many diseases, as well as extreme financial burdens. In a new era of awareness about health & longevity attracting more attention towards adequate & balanced nutrition and lifestyle. Many researchers have investigated the significant evidence of the relationship between the means of dietary nutrition for the prevention and elimination of neurological symptoms in various pathological conditions.

#### 4.3.1 Deficiency of vitamins & minerals in the progression of neurological disease

It is well acknowledged that vitamins & minerals are crucial to humans as they play vital role in the growth of the nervous system, variety of basic metabolic pathways and the maintenance of brain homeostasis. Food items like fruits and vegetables are frequently abundant in them. Dietary vitamins, particularly vitamins B6, B9, B12, and D, as well as minerals, including zinc, calcium, magnesium, and selenium, play a significant role in maintaining brain health in the central nervous system (CNS). There is a lot of data to suggest that deficiencies can cause a variety of neurological issues. On the contrary, adequate availability of vitamins and minerals is an important and necessary condition for the good functioning of the nervous system, as well as mental and emotional well-being in humans.

The B vitamins are crucial for the CNS and PNS to function normally. Vitamin B6 is vital for amino acid metabolism and involved in regulation of mental function & mood. It is necessary for the production of neurotransmitters like dopamine from L-DOPA, serotonin from 5-HTP, and gamma-aminobutyric acid (GABA) from glutamate. It is also necessary for the supply of energy to the nerve cells. Additionally, vitamin B6 contributes to the creation of "myelin sheaths," the fatty coverings for nerve fibres (axons). A water-soluble vitamin known as vitamin B12 is essential for the formation of blood cells, DNA synthesis, and the process of methylation, which is vital for rapid cell

division and growth, especially in the developing foetus and brain. Vitamin B12 plays an important role in the DNA synthesis of myelin-producing oligodendrocytes and the synthesis of myelin, synaptogenesis, myelination, and neurotransmitter synthesis. The efficiency of folic acid (vitamin B9), which is crucial for the metabolism of myelin proteins and neurotransmitters, depends on the amount of vitamin B12 present. Similar to omega-3 fatty acids, folic acid is believed to have a significant role in the early life development of the nervous system. Vitamin D is a fat-soluble vitamin that recognized role in the body to absorb and retain calcium and phosphorus, thus to maintain calcium-phosphorus homeostasis nerve conduction, skeletal development, bone growth, bone healing, immune system functioning, reduces cancer cell growth, controls infection, reduces inflammation, lowers the risk of type 2 diabetes and blood pressure regulation [25, 26]. Vitamin D is required for early brain development, reducing the apoptosis neural differentiation, neuro protection and anti-inflammatory effects in the brain. It is abundant in tuna, salmon, sardines, herring, mackerel, red meat, beef liver, dairy products, egg yolks, orange juice, mushrooms and almond beverages. Low level of Vitamin D is linked with cognitive impairment, neurodevelopmental disabilities, impaired psychomotor development, language impairment, impaired behavioural problems.

#### 4.3.2 Dietary Patterns in Neurological Disease

The human brain, which only makes up 2% of the body's total mass, uses 20% of the energy in the body overall. This high energy consumption is caused by the electrical impulses that neurons use to interact with one another. Significant epidemiological findings in recent years have indicated that eating particular nutrients or food categories in moderation has shown amazing clinical effects in treating neurological illnesses. Indeed, an adequate diet and the brain always intersect. In support of this different types of diet have been linked to neurological disease.

##### 4.3.2.1 Ketogenic Diet

The ketogenic diet (KD) involves drastically reducing carbohydrate intake and replacing it with fat. This reduction in carbs puts your body into a metabolic state called ketosis, in which fat is used as the primary energy source through the formation of ketone bodies (KBs) in place of glucose. One of the anti-seizure mechanisms of KD is to promote neuroinhibitory actions by increasing  $\gamma$ -aminobutyric acid (GABA) which is associated with modification of the tricarboxylic acid cycle leading to neuronal hyperpolarization [29]. "Adenosine triphosphate (ATP)-sensitive potassium channels are also activated by the KD, leading to membrane hyperpolarization that prevents neuronal excitability and directly inhibits vesicular glutamate transport, thereby decreasing the amount of glutamate present during synaptic transmission and providing positive feedback to GABAergic channels" [30, 31]. By efficiently regulating the balance between pro- and antioxidant processes, pro-excitatory, inhibitory neurotransmitters, pro-inflammation or disruption in brain energy metabolism, KD appears to be able to treat neurological disorders in patients. Therefore, KD has carved a niche as an adjuvant therapeutic option for some neurological diseases.

#### 4.3.2.2 MeDi Diet

The Mediterranean diet (MeDi diet), which is a medically prepared diet high in vegetables, fruits, and olive oil and low in meat and dairy products, is one of the most extensively studied diets [32]. Published evidence has shown that various components comprising MeDi diet such as  $\beta$ -carotene, phenolic components, vitamin C and vitamin E, act as neuroprotective against cognitive decline & brain health outcomes by its antioxidant and anti-inflammatory properties [33].

#### 4.3.2.3 Dietary Approaches to Stop Hypertension (DASH) Diet

Healthy eating habits are part of a nutritional approach, which is intended to treat or prevent high blood pressure (hypertension) [34]. The DASH diet includes foods rich in minerals and fiber, such as potassium, calcium, and magnesium. These nutrients help control blood pressure. The diet limits foods high in sodium, saturated fat, and added sugar. This diet was initially created to treat and prevent hypertension. These days, it has been demonstrated that following the DASH diet with a high level of adherence enhances cognitive function and guards against brain dysfunction [35].

#### 4.3.2.4 Mediterranean-DASH intervention for neurodegenerative delay (MIND) Diet

A combination of the MeDi diet and the DASH diet is used to create the MeDi-DASH Intervention for neurodegenerative Delay (MIND) diet [36]. This diet basically recommends a high intake of natural plant foods and a low amount of animal products and foods high in saturated fat and the use of extra virgin olive oil as the main source of fat.

The beneficial effect of MIND diet on cognition is abundant in antioxidants and anti-inflammatory agents from fruit, vegetables, and olive oil hence contributing to the defence against free radicals and oxidative stress which in turn can prevent DNA damage and cell death, hence prevent cognitive decline and dementia. The phenolic compounds presents in nuts & extra virgin olive oil can improve neurologic health by modulation of neuronal signaling.

#### 4.3.2.5 Nordic Diet

The Nordic diet is characterized with high amounts of fish, grains, fruits, vegetables, greens, rapeseed oil (also known as canola oil), fish, lean meats and low-fat dairy, and reducing sugar and salt intake. Canola oil is highly recommended in ND as it is rich in healthy monounsaturated fat and also contains a plant-based omega-3 fatty acid, alpha-linolenic acid, similar to the omega-3 fatty acids found in fish. This implies that this diet might be suggested for stroke prevention [37]. To make this premise clearer, more research is required. Furthermore, there is evidence that suggests that those with adequate cognitive function who adhere to the Nordic diet have higher global cognition scores [38].

#### 4.3.2.6 Gluten-free (GF) Diet

Any foods that contain gluten, abundant in wheat, rye, and barley, are prohibited from a gluten-free diet. It entails consuming solely fresh fruits, vegetables processed gluten-free foods (such gluten-free bread or pasta), meat and eggs. Gluten-related neurological disorders (GRND) represent a

range of neurological conditions that are triggered by gluten. Evidence that has been gathered throughout time suggests that those patients who are gluten sensitive (GS) also experience a variety of neurologic and mental issues [39].

#### 4.3.2.7 Low Carb Healthy Fat (LCHF) Diet

LCHF diet focuses on reducing carbohydrates and replacing them with healthy fats. In the LCHF diet the overall emphasis is on whole, unprocessed foods such as poultry meat, lean fish, nuts, eggs, and low-carb produce. It works by using ketones from the body's fat stores for energy, rather than glucose from carbohydrates and creating a metabolic state known as ketosis. LCHF diet is centered on weight loss in obese and overweight people and patients [40]. In addition this diet type is also beneficial for individuals who are facing the following conditions: type 2 diabetes, PCOS, alzheimer's disease & acne.

#### 4.3.2.8 Biome-Diet

We have coined the term Biome-Diet, which is based on the GUT-Microbiome test. Fecal metagenomics DNA was used to study the microbiome composition of the gut to identify the degree of gut dysbiosis and accumulation of disease specific microbe's fingerprint.

The Abundant and diverse microbial communities coexist in a human's gastrointestinal tract which is made up of bacteria, archaea, fungi, and viruses and are collectively referred as gut "microbiota". These microbial communities are crucial in the maturation and development of the immune system, metabolic homeostasis and protecting against pathogens. Normally, in a healthy individual the gut microbiota consists of a unique set of microbial populations, and this condition is known as "eubiosis." Conventionally, gut microorganisms were viewed as one of the blessings for humans as a result of these beneficial health effects but over the time period, a various factors like inadequate minerals & vitamins, sleep-wake cycle, improper diet, physical activities, pharmacological therapy, and many others, can disturb the diversity and abundance of the microbiota leading to a state of "dysbiosis". Dysbiosis of the gut microbiota is linked to extra intestinal diseases like metabolic and neurological problems in addition to intestinal issues. Recent studies have shown that neurodegenerative diseases progression and severity of symptoms have been catalogued due to modifications in the amount of gut flora to [41]. Consequently, an association between a range of gut microorganisms and the most prevalent forms of neurological disease (e.g., Alzheimer's disease, Parkinson's disease & amyotrophic lateral sclerosis), has been identified [42, 43, 44]. Additionally, a complex and bidirectional molecular interaction between the gut/microbiome and the CNS ensures the preservation of gut homeostasis and correct digestion. In addition, a number of mechanisms, including endocrine, neuronal, toll-like receptor, and metabolite-dependent pathways, have been proposed. Changes in the gastrointestinal tract's reciprocal communication with the central nervous system (CNS) are linked to the pathophysiology of gastrointestinal and neurological illnesses; thus, the microbiota/gut-brain axis is a new and widely accepted concept.

Therefore, the existence of a biological relationship between the microbiota, immune signalling, and CNS suggests that both neurological and immunological activity in the brain may be influenced directly by microbial metabolites or

indirectly by systemic signals obtained from the microbiota. So the role of GUT-Microbiome is very crucial & creating a new pathway of understanding & treatment of neurological diseases. In the new omics age, treatments that target the microbiome may help prevent or treat certain diseases; this hypothesis is now being tested by some researchers and businesses in human clinical trials.

#### 4.4 Therapeutic measures

Therapeutic measures are the measures that are taken once the patient has been diagnosed with a particular disease and the course of this approach is not only disease specific but also for complications arising due to the extreme diversification observed in the cases and the different conditions that the patients are subjected to. Such approaches are usually highly specialized and tailored in their nature. The biggest challenge is to better comprehend the disease's pathophysiology and to create neuroprotective therapies that can stop or prevent aberrant protein aggregation and neuronal degeneration in the brain.

#### 4.5 Post-treatment measures

Post-treatment measures are interestingly associated with the idea of plugging any loopholes that might cause either the recurrence or worsening or arising of any new conditions. Fact of the matter is a disease is not completely curable but to a practicable extent is manageable. Post-treatment Measures come into picture whenever any concerned neurological disease has been completely brought under control and no further leniency can be afforded. Hence such strategies come under the heading of Post-Treatment Measures.

#### 5. Conclusion

In today's time, it is important to have a healthy body and mind. On the contrary, the world has undergone radical and dynamic changes since the 2020 outbreak of COVID-19 pandemic. The changes are so humongous due to stress, depression and other factors which are becoming the major reason for neurological diseases in their coverage that stands bifurcated into pre-Covid and post-Covid worlds. It is important to not only keep them under manageable stretches but also take proactive measures to avoid the seriousness of the diseases. To keep neurological diseases strictly under manageable and practicable stretches, healthy routines & adequate diet supplements and genetic counselling has indispensable roles to perform at all levels of probable events.

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