ASSESSMENT OF METABOLITES: A NEW ERA IN NEUROLOGY.

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ABSTRACT:

Neurological disorders are one of the most common causes of disability all around the world. Alzheimer's and Parkinson's disease, depression, anxiety, and amyotrophic lateral sclerosis afflict millions of people aged 60 and up around the world. Despite the fact neurotransmitters have been identified as a bio target for neurological illnesses, current therapeutic measures only provide symptomatic relief and do not stop problems from progressing. Since the worldwide incidence rate is steadily rising, there is a need for alternative therapies that can specifically address the disease's source. Targeting neurotransmitter metabolites as a biomarker for early diagnostic measures is one of the newly established techniques that can target specific biomarkers. Unfortunately, no techniques or preventive measures have been discovered to yet that can control the progression of illness. This review focuses on the most common disorders that have increased the global burden, as well as how neurotransmitter metabolites can be used as a biomarker for a prevention measure.

Keywords: Neurological Disorders, Biomarkers, Metabolites, Alzheimer’s Disease, Parkinson’s Disease, Dopamine, Serotonin, Epinephrine, Norepinephrine, Depression.

Abbreviation's

ALS  Amyotrophic lateral sclerosis
GBD Global Burden of Diseases
AD  Alzheimer's disease
CSF Cerebrospinal fluid
Ab42 Amyloid- b- 42 peptide
FDG18F- fluorodeoxyglucose
MRI Magnetic resonance imaging
NIA- AANational Institute on Aging- Alzheimer’s Association
PET Positron emission tomography
T181 Threonine 181
MTLMesial temporal lobe
SN Substantia nigra
NMS Non-motor symptoms

UPDRS Unified Parkinson’s Disease Rating Scale

TCS Transcranial B-mode sonography

DWI Diffusion-weighted imaging

SPECT Single-photon emission computed tomography

SWI Susceptibility-weighted imaging

NINDS National Institute of Neurological Disorders and Strokes

NIH National Institutes of Health

PDBP Parkinson’s Disease Biomarkers Programme

PPMIP Parkinson’s Progression Markers Initiative

5-HT 5-Hydroxy tryptophan

5-HIAA Hydroxy indole acetic acid

NE Norepinephrine

DA Dopamine

ACTH Adrenocorticotropic hormone

MAO Monoamine oxidase

COMT Catechol-o-methyl transferase

DOPAL3, 4-dihydroxy phenylacetaldehyde

DOPEGAL3, 4-di hydroxyphenyl glycolaldehyde

DHPG3, 4-dihydroxyphenyl glycol

HVA Homovanillic acid

VMA Vanillylmandelic acid

AADC Amino acid decarboxylase

TH Tyrosine hydroxylase

DOPA Dihydroxyphenylalanine

PEA Phenylethylamine

ALDH Aldehyde dehydrogenase

ALR Aldehyde reductase

I. INTRODUCTION

Neurodegenerative diseases are progressive neurological disorders that could be characterized by the degeneration of specific nerve cells. The most common cause of dementia is due to Alzheimer’s which disturbs the
memory functional part of the patients and the cognitive function is affected too. Again, Parkinson's disease considered a progressive movement disorder manifests symptoms like tremors, slower movements, and increased muscle tone. Amyotrophic lateral sclerosis (ALS) is the most common cause of neurological disease death in adults and the most occurring degenerative motor neuron disorder in that particular age group. Now, out of all of the neurodegenerative diseases take Alzheimer's or Parkinson's or even the other neuro disorders like dementia and bipolar disorders, all are detected when the manifested symptoms are way too conspicuous. The patient visits the doctors or the neuro centres in an acute stage of a precarious state when they need clinical treatment as an emergency. An exception is only seen when the symptoms are clear in the childhood or teenager state. The challenge thus is to detect the signals displayed by the body either internal or external as early as possible to treat the patient at the earliest.

Neurodegenerative diseases are associated with cellular dysfunction caused by the signalling of protein misfolding. In the later stages of the symptoms, several neuropathologies are diagnosed. These occur in response to molecular dysfunctions. Late detection offers a treatment that is too late and is only able to slow the process of cell death. Here, it is evident that the most important aspect is to identify the early biomarkers that would be capable of predicting the disease progression at a point where cell dysfunction hasn't yet reached the mark of the process being irreversible. So, the identification of the biomarkers is of paramount interest to target the disease pathway at an early stage.

Recent days have been seeing through the latest studies and researches aided by the latest techniques in the pharmacological and clinical experiments to identify the exact time of onset of the diseases. To obtain a functional and pathophysiological state of the organism and to enhance disease diagnostic approach along with biomarker discovery. It has been found that there are numerous metabolites deposited in human biofluid specimens like blood, urine, and cerebrospinal fluid. In recent days this is included in a new discipline called metabolomics. The discipline of study enables to get meaningful data of the patients corresponding to their ages.

Biomarkers or biological markers are considered as the biological measures for a biological state. It is evaluated as an indicator of normal biological processes, pathogenic processes, and even therapeutic intervention (1). It is the potential of a biomarker that the occurrence of a particular disease depends and that it contributes to its progression. Although it is established that the identification of the biomarkers plays a pivotal role to know about the neurological disease progression but the treatment parameters are still at a nascent stage (2). The preventive measure to control the disease progression is not discovered yet. As the statistics go that millions of people globally are neurological patients, Alzheimer's and Parkinson's being the leaders. It is the need of time to have a detailed study and research on the biomarkers and the metabolites to detect neurodegenerative diseases (3). This could lead the pathway to a novel process of diagnosis that could have pinned the early onset of the disease. The focus is to reduce the burden of the disease from patients above 60 years of age who could opt for healthy aging ahead.

2. The burden of Neurodegenerative Diseases

Neurological diseases and disorders are considered to be the leading cause of disability globally. Alarming their contribution to the greater picture of health conditions is ever increasing. Neurodegenerative diseases affect millions of people across the world. It wouldn't be wrong to predict that the neurological disorder scenario is expected to observe a surge as the population is getting older. As medical science and technology advance the mortality rate decreases which mounts the population of the older generation to live longer and this very fact makes neurodegenerative diseases more prevalent. The evident analysis results according to Global Burden of Diseases (GBD), injuries and risk factors study in 2016 had an estimation of the prevalence, incidence rate, and death rate due to neurodegenerative diseases and hence classified it into this category (4).

2.1 Alzheimer's Disease

Alzheimer's disease (AD) could be identified as a progressive brain disorder that destroys memory slowly. It is irreversible which also destroys the thinking skill and gradually makes it difficult to carry out the simplest tasks. Among the aging adult population, Alzheimer’s disease is the main cause of dementia. The disease is named after Dr. Alois Alzheimer who had identified the brain tissue changes due to the disease in a woman (5). The preliminary diagnosis of AD follows an array of clinical tests that includes a neurological examination, brain imaging, or mental status tests. The procedures are challenging enough if the patients have either mild or show early stages of AD. These were the criteria that were in the need of biomarker identification evolved that displayed indications of the disease as well as provided with the diagnostic features of early onset of AD.
Validated biomarkers could be identified for early detection and diagnosis of the onset of AD. Owing to the current scenario now an early diagnostic approach needs to control the progression of AD by using the cerebrospinal fluid as the biological fluid with advanced molecular imaging and neuropsychological testing to detect AD as early as possible (7).

Presently, cerebrospinal fluid (CSF) is analyzed with identified biomarkers such as amyloid-beta protein, tau protein, phosphor-tau expression levels (8). CSF is considered an important source of biomarkers as it is in direct contact with the Spink cord and the brain. The CSF provides a representation of various biochemical and metabolic profiles of the brain as a whole (9). Newly, developed imaging technique are possibly used to identify low-level of amyloid-b-42 peptide (Ab42), high CSF concentrations of tau or phosphor-tau and brain atrophy identified by using magnetic resonance imaging (MRI) also brain hypometabolism or hypoperfusion on 18F-fluorodeoxyglucose (FDG) – PET is the emerging biomarkers that are involved in the progression of AD. This could be a great potential in the clinical utility (10). The National Institute on Aging- Alzheimer’s Association (NIA- AA) evolving new ideas primarily focusing on the pathogenesis of AD where prognostic fluid and biomarkers imaging technique to establish a correlation between AD pathogenesis along with stages of preclinical AD and its progression in clinically diseased patients (11,12). The techniques incorporated likely CSF Ab42, amyloid positron emission tomography (PET), CSF total tau, threonine 181 (T181) phosphor-tau, mesialtemporal lobe (MTL) atrophy on 18F- fluorodeoxyglucose (FDG)- PET (13) as shown in table no.1 can be used in clinical utility. Present-day researches find that elevated amyloid PET signal and less CSF Of Ab42 are the most important leading biomarkers that show a crucial role in neurodegeneration and synaptic dysfunction before the occurrence of cognitive impairment due to AD (14).

2.2 Parkinson’s Disease

Parkinson’s disease (PD) is the second most devastating neurodegenerative disease that affects around 1% of the total adult population globally those above 60 years of age. That comprises around 1% of the total adult population of the age group above 60 years (15, 16). Parkinson’s disease affects movement which is a nervous system disorder. The symptoms occur due to low dopamine levels in the brain. The symptoms of Parkinson's disease develop with a slight tremor in one hand and stiffness is felt in the body.

PD is a progressive neurodegenerative disease and the symptoms are that leads to the deterioration of the motor and non-motor functions that occurs due to declined dopaminergic neurons showing features like bradykinesia, tremor, rigidity, or postural disbalance (17). The use of imaging techniques in recent times has been of greater importance to diagnose PD and the genetically associated biomarkers as well where a similar pattern of PD pathogenesis could be recognized. The diagnosis of PD depends mostly on clinical motor identification that appears only when half of the substantia nigra (SN) dopamine neurons are lost. This is why PD is diagnosed when disease progression is well ahead and in the advanced stage (18).

As the disease advances the biochemical biomarkers could be targeted as the diagnostic tools to approach those which facilitate drug development and pharmacodynamic biomarkers during clinical trials. Owing to this there is a need to aggravate contemporary biomarkers available for PD that can be discovered and validated proven upon clinically diseased patients showing the transition from the pre-motor to motor symptoms. There are some non-motor symptoms (NMS) that contribute to disease progression influences changes in sleep patterns, olfactory dysfunction, bowel disturbances, mood disorders. They are not essentially seen in PD but if detected they might contribute to disturbances in motor functions. Hence there is a need for the identification of biomarkers that would help to predict the disease progressions which lead to motor dysfunctions.

According to the Unified Parkinson’s Disease Rating Scale (UPDRS). The UPDRS system has been accepted as an effective tool for the evaluation of interventions and as a clinical tool to check up on patients. This instrument is used to track the severity of the disease among the population (19). Commonly used in clinical trials, the slightest alteration in scale rating help in evaluating the effect of a drug on the motor dysfunction symptoms and the severity of the disease. Other biomarkers aid in evaluating the effect of drug and disease progression.

1. Genetic biomarkers: genetic studies help towards clinical diagnosis and identify the patient at risk. Genetic reasons for parkinsonism may be dormant in individuals might be for years or longer periods before the manifestation of the symptoms.

2. Biochemical markers: In search for the biomarkers body fluids provide for a relatively non-invasive test of protein levels and other molecules for the disease in particular.
3. Neuroimaging markers for PD- Several imaging techniques nowadays have been developed which are capable to detect abnormalities in the brain successfully in the case of PD patients. Some of these are positron emission tomography (PET), transcranial B- mode sonography (TCS), diffusion-weighted imaging (DWI), single-photon emission computed tomography (SPECT), and susceptibility-weighted imaging (SWI).

A program on biomarker was held at the National Institute of Neurological Disorders and Strokes (NINDS) in National Institutes of Health (NIH) that focussed on developing the biomarkers that would contribute to designing the clinical trials even better. This would attribute to a better treatment approach. The program hence was named Parkinson’s Disease Biomarkers Programme (PDBP) (20).

The PDBP investors developed biomarkers either through individuals or collaborative projects selected by the NIH research group. About 1400 participants had participated in PDBP. Also, Michael J. Fox Foundation established the Parkinson’s Progression Markers Initiative (PPMI) that dealt with the collection of biofluids and clinical trial data that could be used and linked for biomarker research with an approach that biomarker assays could be used in a clinical trial.

2.3 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) could be categorized as a motor neuron disease that is progressive as well as degenerative that destroys the nerve cells, in particular, that control voluntary muscle movement. It is also known as Lou Gehrig’s disease. The motor neurons from the brain to the muscles control the movement in the arms, legs, mouth, throat, and chest. They run through the brainstem or the spinal cord. In the case of patients suffering from ALS, these cells die off leading to wasting of the muscle tissue. The mental faculty or the sensory functions of a person are not affected by ALS.

Since the last few years, there has been considerable development of biomarker studies and their validation in ALS. Researchers have now focussed on biomarkers for the prevention and treatment of this disease that has been of great benefit due to the latest advanced techniques and collaborative research efforts to study the biomarkers. There are established and reputed organizations in the USA and Europe that facilitate research and clinical efforts that include Northeast ALS Consortium (NEALS), Project Mine, European Network for the Cure of ALS (ENCLS), Sampling and Biomarker Optimization and Harmonization in ALS, and other motor neuron diseases (SOPHIA) and Clinical Research in ALS and related disorders for Therapeutic Development (CREATE) (21).

Individual or panels of RNA or protein biomarkers have been used too to stratify patient populations. The important aspect of patient stratification is to enrich for a particular cause of disease or that enrich patient populations for those that may respond to particular drug treatment. The ALS Association is now collaborating with FDA to acquire guidance on clinical trials of ALS with the use of some supportive biomarkers for drug discovery.

2.4 Depression

Depression is a common mental disorder affected worldwide that poses a silent threat to the worldwide population. Depressive disorders are often going into oblivion because there is either less or no outward manifestation at the initial stage.

Depression is now a common mental disorder found worldwide with a risk high in women than men. The currently available treatment and pathogenesis of depression have gained interest for performing preclinical and clinical trials but the neurobiological basis is still not defined (22). The Depression hypothesis was first established forty years back (23) postulating that the occurrence of depression is a result of decreased 5-HT or NE levels along with dysfunction of serotonin, noradrenaline, dopamine receptors in the brain. These neurotransmitters regulate the motor symptoms like mood, sleep, anhedonia, appetite, concentration and motivation, suicidal behaviour, cognitive and autonomic functions (24) that are disturbed in depression. Numerous attempts have been performed for reproducible neurochemical alterations in the brain of the depressed patient, showing negative results. In depression serotonin converted into 5-HIAA in CSF thus can be used as a target for treating depressed subjects. Several reported studies found a reduction of 5-HIAA levels in CSF (25) but failed to distinguish between depressed patients and healthy (normal control) (26). Some recent studies showed elevated brain serotonin levels in depressed patients as compared to normal control specifically in those...
where it carries short forms of the gene for the serotonin transporter (27). Though it is still unclear that an increase in brain serotonin level is due to an increase in neuronal activity, vesicular leakage increased intraneuronal metabolism or reduction in brain serotonin availability for transport. Thus, platelet serotonin (5-HT) levels, 5-HTT, and 5-HT 2A receptors were identified in depression. The estimations were done based on the results found in depressive patients where decreased levels of platelet 5-HT (28), altered 5-HT2A receptors, and amount serotonin uptake sites (29). The currently available treatment aids only by affecting the 5-HT, DA, NE levels including receptors and enzymes involved in synthesis and degradation (30). After 2 weeks of antidepressant treatment, clinical improvement is observed. It is thought that delayed therapeutic efficacy is affected due to less sensitivity of serotonergic and noradrenergic receptors.

2.5 Alcoholism

Alcohol use is substance abuse that is of largely growing public health concern. Alcoholism does rank as one of the leading threats to the health of society worldwide. World Health Organisation (WHO) estimated in 2010 that 38.3% of the population across the world is reported to consume alcohol on regular basis. 3.3 million death is observed every year as a result of harmful use of alcohol. Indian doctors and health agencies have reported alcoholism as one of the prominent reasons that are responsible for neuropsychiatric disorders.

As the studies suggest regarding the hazards of alcoholism, that there are alteration levels of serotonin in cases of alcohol abuse and dependence (31). Histological studies suggest that reduced serotonin transporter binding in the hippocampus (32), striatum (33) reduced density of 5-HT1A receptors (34) in alcoholic patients than in normal patients. In vivo studies revealed a reduction in serotonin receptor activity in the brain of alcoholics which was analysed by the Single Photon Emission Computed Tomography (SPECT) method. (35) The concentrations of 5-HIAA I CSF are in line due to the serotonergic disturbances in the patients consuming alcohol. It shows a lower level of 5-H1AA in the CSF in brains of early onset of the alcoholic brain,(36)in abstinence (37), and then in the alcoholic impulsive offenders (38). In the case of alcoholism, the serotonin is altered to great extent due to the decreased plasma tryptophan and serotonin precursor (31) The blood transporter activity in alcoholic patients displayed inconsistent results by lowering (39),increasing (40), and when unaltered (41) serotonin uptakes in platelets of the alcoholic patients as compared to the normal person. Thus, based on the analysis it is proven that there is a decrease in serotonin transporter activity in induced alcoholism in both males and females but independent in serotonin neuropsychiatric disorders (42). The serotonergic drug includes fenfluramine, 6-chloro-2-1- piperazinyl pyrazine, and adrenocorticotrophic hormone (ACTH) response to m-chlorophenyl piperazine on administration where prolactin or cortisol showed less response against prolactin or cortisol due to altered serotonin receptor function in alcoholism (43).

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Table 1: Newly established techniques and their targeting biomarker.

II. BIOGENIC AMINES METABOLITES AS BIOMARKERS.

Catecholamines

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Catecholamines are neurotransmitters of the monoamine category. They are organic compounds that possess catechol and a side-chain amine. Catechol is the organic compound having benzene with two hydroxyl side groups next to each other. Catecholamines in the body are derived from the amino acid tyrosine. They are involved in the functions both as neurotransmitters and hormones that carry out a spectrum of physiological processes vital to maintaining homeostasis. This is carried out through the autonomic nervous system. Dopamine, norepinephrine, and epinephrine are active molecules called catecholamines. These monoamines mediate the sympathetic nervous system and different neurological pathways as well. Certain unbound forms of catecholamines lead to a myriad of psychiatric and clinical disorders. The mechanism of degradation which leads to the formation of metabolites could be used to study biomarkers.

Dopamine is classified as a catecholamine chemically. The majority of its production occurs in the brain where the dopaminergic pathways it follows have vast implications on cortical neurophysiology. Also, undergoes synthesis (some parts) in the adrenal medulla with an affinity for adrenergic receptors. Neuroendocrine chromaffin cells are the ones responsible for the biosynthesis of the catecholamines which are located throughout the brain and the adrenal glands. Functionally, the most significant area of catecholamine production is the adrenal medulla where the density of the chromaffin cells is found the highest. The by-products of the degradation of catecholamines are excreted by the kidneys.

Catecholamines synthesis within the adrenal medulla is controlled by serum concentration of the amino acid tyrosine. Tyrosine after hydroxylation through hydroxylase forms DOPA that undergoes decarboxylation which is dopamine. Dopamine might be secreted into the bloodstream or goes through further hydroxylation to form norepinephrine. Norepinephrine now could be secreted into the bloodstream or again get undergo changes by methyltransferase to epinephrine and then get into the bloodstream. Catecholamines get degraded to their metabolites by monoamine oxidase (MAO) which is located in the outer mitochondrial membrane of the cell and also by catechol-o- methyltransferase (COMT) sometimes too that is found within the cytosol of the cell. Catecholamines are synthesized in a four-step process. The first step observes the dopamine to be converted into 3, 4- dihydroxy phenylacetaldehyde (DOPAL), and norepinephrine and epinephrine get converted to 3, 4- di hydroxyphenyl glycolaldehyde (DOPEGAL) undergo deamination in presence of MAO forming aldehyde products.

The second step involves the conversion of DOPAL into 3, 4- dihydroxy phenyl glycol (DHPG) by the influence of aldehyde dehydrogenase, and aldehyde reductase converts DOPEGAL into 3, 4- dihydroxyl phenyl glycol (DHPG). The sympathetic neurons and chromaffin cells also called aldose reductase those which converts DOPEGAL to DHPG metabolites. This step is significant as methylation occurs. DOPAC is converted into homovanillic acid (HVA), one of the major metabolites while norepinephrine and epinephrine DHPG gets converted into vanillylmandelic acid (VMA) like the end product of NE and epinephrine.

As earlier mentioned, catecholamines are involved in various life processes in the body so a minute increase or decrease in its level indicates the occurrence of a disease. In the case of Parkinson’s disease, dopamine levels are decreased. The reason might be that dopamine is highly degradable in the extracellular space and the available treatment offered inhibits this degradation process. Just the inverse to PD, dopamine is in excess in the case of the schizophrenic condition. The drugs primarily target D2 receptors thereby increasing intracellular degradation of DA. Pheochromocytoma is an adrenal medullary tumour that occurs due to excess catecholamine degraded into its metabolites HVA and VMA. Hence, could be used as prominent biomarkers to detect pheochromocytoma and the tumours caused due to catecholamines.

3.2 Dopamine (DA)

Dopamine is a neurotransmitter that belongs to the class of catecholamines. Dopamine could be defined as a neurotransmitter that is synthesized in the body and used by the nervous system to send messages within the system between the nerve cells. It is also called a chemical messenger alternatively. It is made in the brain following a two-step process. In the first step, amino acid tyrosine to a substance named DOPA, and then it is
Monoamine oxidases are those enzymes that are responsible for catalyzing the oxidation of monoamines using oxygen to take off the amine group. They are mostly found in the outer membrane of mitochondria in most cell types of the body. The MAOs are included in the protein family of flavin-containing amine oxidoreductases. Mary Bergheim was the first to discover this class of enzyme in the liver and it was termed tyramine oxidase. MAOs have their importance in breaking down the monoamines ingested in food and also act to inactivate monoamine neurotransmitters. This particular activity enables them to be involved in several psychiatric and neurological diseases as well when some of them could be treated with monoamine oxidase inhibitors which block the monoamine oxidases. While it catalyzes the oxidative deamination of some dietary amines, monoamine neurotransmitters like dopamine, norepinephrine, epinephrine, and serotonin and hormones it also catalysestryptamines and beta-phenylethylamine (PEA), tyramine, and octopamine too. The degradation of monoamines is required for proper signal transmission that mainly regulates mood, emotion, control motor, blood pressure, heart rate, coagulation system, and peristaltic movement and is the most abundant neurotransmitters present in peripheral tissues of the brain and considered as one of the largest systems in the brain. The serotonergic system consists of 9 groups of cell bodies distributed in brain stem raphe nuclei and the nerve terminals are found throughout CNS. The raphe projections are widely distributed and collated with an axon system. Serotonin is a tryptamine that is essential amino acid where the main precursor being the L-tryptophan is provided by food. L-tryptophan and the 5-hydroxytryptophan are transported through BBB but serotonin (5-HT) unable to pass through endothelial cells due to chemical structure but some evidence suggests that it can be transported across endothelial cells using a transporter. The biosynthesis occurs in 2 steps, first in CSF and then in urine. The degradation of serotonin into metabolites is mainly done by enzymatic mitochondrial MAO, firstly degradation of serotonin into 5-hydroxy indole acetaldehyde, second degradation by aldehyde dehydrogenase into 5-hydroxy indole acetic acid (5-HIAA) major metabolite of 5-HT. The Peripheral serotonin is synthesized by enterochromaffin cells of the GIT, regulated by TPH1. Then released via blood and stored in blood platelets. The other peripheral glial cells also contain serotonin (i.e. macrophages and mast cells). Peripheral available serotonin is metabolized or degraded in the liver by the MAOA enzyme into 5-HIAA as metabolite and then filtrate and excreted by the kidney. The increase in urine excretion containing 5-HIAA is found in carcinoid syndrome which is due to increased production of serotonin by carcinoid cells. In humans, a direct linkage between neurotransmitters in the brain and their excretion in the urine is not yet clearly defined. Recent study reports suggest that neurotransmitters excreted via urine can be used as biomarkers for central nervous system activity. The difference in brain serotonin levels and those excreted by urine showed the difference in levels when experimented with rats. Serotonin also regulates vascular resistance, BP, haemostasis, and platelet function. The 5-HT and 5-HT2A promote platelet activation and aggregation.

Monoamine Oxidase

Monoamine oxidases are those enzymes that are responsible for catalyzing the oxidation of monoamines using oxygen to take off the amine group. They are mostly found in the outer membrane of mitochondria in most cell types of the body. The MAOs are included in the protein family of flavin-containing amine oxidoreductases. Mary Bergheim was the first to discover this class of enzyme in the liver and it was termed tyramine oxidase. MAOs have their importance in breaking down the monoamines ingested in food and also act to inactivate monoamine neurotransmitters. This particular activity enables them to be involved in several psychiatric and neurological diseases as well when some of them could be treated with monoamine oxidase inhibitors which block the monoamine oxidases. While it catalyses the oxidative deamination of some dietary amines, monoamine neurotransmitters like dopamine, norepinephrine, epinephrine, and serotonin and hormones it also catalysestryptamines and beta-phenylethylamine (PEA), tyramine, and octopamine too. The degradation of monoamines is required for proper signal transmission that mainly regulates mood, emotion, control motor.
perceptual and cognitive functions. The chemical reaction taking place in the degradation process is catalysed by MAO where aldehyde dehydrogenase (ALDH) converts aldehyde intermediate into acid which is converted into alcohol or glycol by aldehyde reductase (ALR). The by-products formed produce hydrogen peroxide ions and ammonia which contributes to the formation of reactive oxygen leading to mitochondrial damage and neuronal apoptosis (54). MAO enzyme is of 2 types again- MAO- A and MAO- B. Both of which function differently but their enzymatic reaction overlaps to a certain extent. MAO-A has a greater affinity for serotonin and norepinephrine whereas MAO-B has an affinity for PEA. It is these isoenzymes of MAO which carry out the metabolism of monoamines (dopamine, tryptamine, tyramine) while MAO- B only plays a substantial role. It has been established 20 years ago that the MAO enzyme isoenzymes are unequally distributed. (55). The deduced amino acid has shown that MAO and B in the primary sequence share 70%. They contain a pentapeptide sequence (Ser- Gly- Gly- Cys- Tyr) that binds to cofactor FAD by thioester covalent linkage to the cysteine (55). Both proteins are located in the outer membrane of mitochondria at the C- terminal domain (63). In the last few years, studies have explored the genetic and transcriptional regulation of MAO-A and MAO-B genes and their promoters (56-57). Some reports explore that MAO isoforms are activated and repressed by different transcriptional factors that may change the localization of isoenzymes (58). In humans, these are mostly expressed in peripheral tissues and organs, MAO-A in fibroblast and placental tissues, and MAO-B in platelet and lymphocytes (59,60). Immunohistochemical and autoradiographic studies suggested that MAO-A is located in catecholaminergic neurons and MAO-B is located in serotonin, histamine-containing neurons, and astrocytes (61-62). Several laboratory experiments have explored that 5-HT levels are enhanced by MAO-A and not MAO-B but it is not clear yet.

III. CONCLUSION:

Neurodegenerative disorders are one of the most prevalent disorders worldwide. The currently available treatments are not effective enough to identify the progression of the disease. The worst part is that there is no therapy yet to identify the early onset of disease that could have led to prevent the progression of the particular disease. One of the approaches could be to track the neurotransmitters that played a crucial role in signal transmission in the brain thereby controlling various functions and the second approach could be metabolites that are formed after degradation of metabolites after enzymatic reaction thus could be used as a biomarker for identification of disease progression. This review is to study the approach to track and find the biomarker responsible for the disease progression with an attempt to prevent the progress of the particular disease with successful therapy.

Conflict of interest:
The authors declare no conflict of interest.

Authors declaration:
The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Author’s contribution:
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Vaishali Undale: critical reviewing of manuscript, conceptual understanding.

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