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Advanced Imaging and Biomarkers in Dopamine Dysfunction: Unravelling Neurodegenerative and Neurological Disorders

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ABSTRACT:
Neurological disorders such as epilepsy and Parkinson's disease can be better understood with the use of modern imaging and biomarkers in dopamine study. The neurotransmitter dopamine is associated with a wide range of movement problems; it also regulates cognition, emotion, and movement. The use of modern imaging techniques, such as MRI and PET scans, makes these issues more common. Brain structural and functional abnormalities connected to dopamine anomalies can be better understood with the use of these scans. In order to identify and define dopaminergic neurodegeneration, functional imaging biomarkers such as FPET scans and DAT scans are utilized. Dopamine neuron loss can be visualized with their help. Dopamine depletion also impacts the substantia nigra, which is why MRI and DTI are utilized to study structural abnormalities in this area. Early disease detection and treatment outcomes are improved with the use of imaging biomarkers in conjunction with genetic and metabolic data. Nevertheless, imaging data can be supplemented with inflammatory chemicals and oxidative stress indicators to provide a better explanation for dopamine anomalies. Personalized medicine and differential diagnosis can both benefit from the integration of these ground-breaking approaches with machine learning. Physiological and pathological systems, such as PD and epilepsy, can now have their dopamine functions predicted by neurobiology thanks to biomarkers and multimodal imaging. This chapter delves into the topic of advanced imaging techniques and biomarkers that can be used to diagnose dopamine dysfunctions. The primary goals include providing a foundational knowledge of imaging techniques, the biomarkers that are accountable for them, and another major advancement along with associated obstacles.
Keywords: Dopamine, Imaging biomarkers, neurotransmitter, MRI, DTI.

I. INTRODUCTION.

Neurodegenerative diseases result from a complex interplay of genetic, environmental, and aging factors. These conditions entail progressive dysfunction and gradual loss of specific neuronal subsets, leading to the accumulation of misfolded proteins, heightened oxidative stress, mitochondrial dysfunction, compromised bioenergetics, and neuroinflammatory processes [11].Neurodegenerative disorders have a profound impact on an individual's quality of life, marked by a gradual decline in cognitive and physical functions (12,13]. Parkinson's disease (PD) is the most common neurodegenerative movement disorder. The disease affects approximately 7 million people globally and has a very high socioeconomic impact. Clinically, PD is characterized by bradykinesia, akinesia, muscular rigidity, postural instability, and resting tremor, including also nonmotor symptoms such as cognitive and psychiatric impairment [14].Parkinson's disease was first described in 1817 by British physician James Parkinson in his essay "An Essay on Shaking Palsy"(36)Parkinson observed six patients with symptoms such as tremors, rigidity, and difficulty with movement. He recognized that these symptoms were related to a disease of the nervous system, which he called "paralysis agitans". Over the following decades, more and more cases of this disease were described, and the name "Parkinson's disease" became widely used. In the late 19th and early 20th centuries, researchers made important discoveries about the neuropathology of Parkinson's disease, including the loss of dopaminergic neurons in the substantia nigra region of the brain.

The incidence and prevalence of Parkinson's disease widely varies across different geographic regions and ethnic groups. Higher rates of Parkinson's disease have been reported in North America and Europe compared to Asia and Africa. The reasons for these geographic differences are not well understood, but environmental factors

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such as exposure to pesticides, herbicides, and other chemicals have been implicated(37-38).Neurodegenerative disorders are usually characterized by accumulation of abnormal protein aggregation that leads to inflammation as well as oxidative stress in the central nervous system (CNS). Parkinson's disease (PD) and Alzheimer's disease (AD) are the most common disorders of nervous system caused by environmental and genetic influences [44,45].Another important brain disorder related to CNS inflammation and characterized by learning and social disabilities with no definite pathogenesis is known as autism spectrum disorder (ASD). Multiple biochemical and molecular features could be observed for the neurodegeneration in the brain of ASD [46] including oxidative stress [47], activated astrocytes and microglia [48], neuronal loss [49], elevated levels of 8-oxo-guanosine [50], and development of proinflammatory cytokines [51].

Dopamine:

Dopamine is one of the neurotransmitters of great clinical importance for motor functions and motivational behaviors. Its dysfunction is involved in many psychiatric disorders, including drug addiction, Parkinson's diseases etc.The dopaminergic neurons are localized in the subsantia nigra pars compacta and in the ventral tegmental aera [3]. Dopamine seems to also be involved in drug addiction. For instance, it is known that cocaine inhibits the dopamine transporter[4].Dopamine receptors are present on various neuroimmune-related cells, including microglia and astrocytes.[5].Dopamine (DA) is an important member of catecholaminergic neurotransmitters that control movement, reward-seeking behavior, motivation, and cognition.[6] Dopamine is produced not only in the central and peripheral nervous system but also by chromaffin cells of the suprarenal gland, epithelial cells in the gut, and peripheral immune cells.[7] DA exerts widespread effects by acting on DA receptors (DRs), which are divided into two primary subfamilies: D1-like DRs that comprises DRD1 and DRD5, and D2-like DRs consisting of DRD2, DRD3, and DRD4.[8]

Neurotransmitter:

NTs consist of molecules that amplify, transmit, and convert signals in cells, being key players in brain functions, behavior, and cognition. More than 200 such chemical messengers have been identified since 1921, yet the exact number of NTs is unknown. This happens especially because new biomolecules that exhibit neuroactivity are continuing to be added to a growing list of NTs (1,2). There have been identified various types of NTs, with different functions produced in different regions of the brain [24]. From the point of view of their chemical nature, NTs are commonly divided into amino acids, amines, and other molecules. While depending on their activities, they can be of two types: positive and negative NTs or central and peripheral NTs [25]. The first classification is considered in the following subsections, as visually summarized in figure 1.

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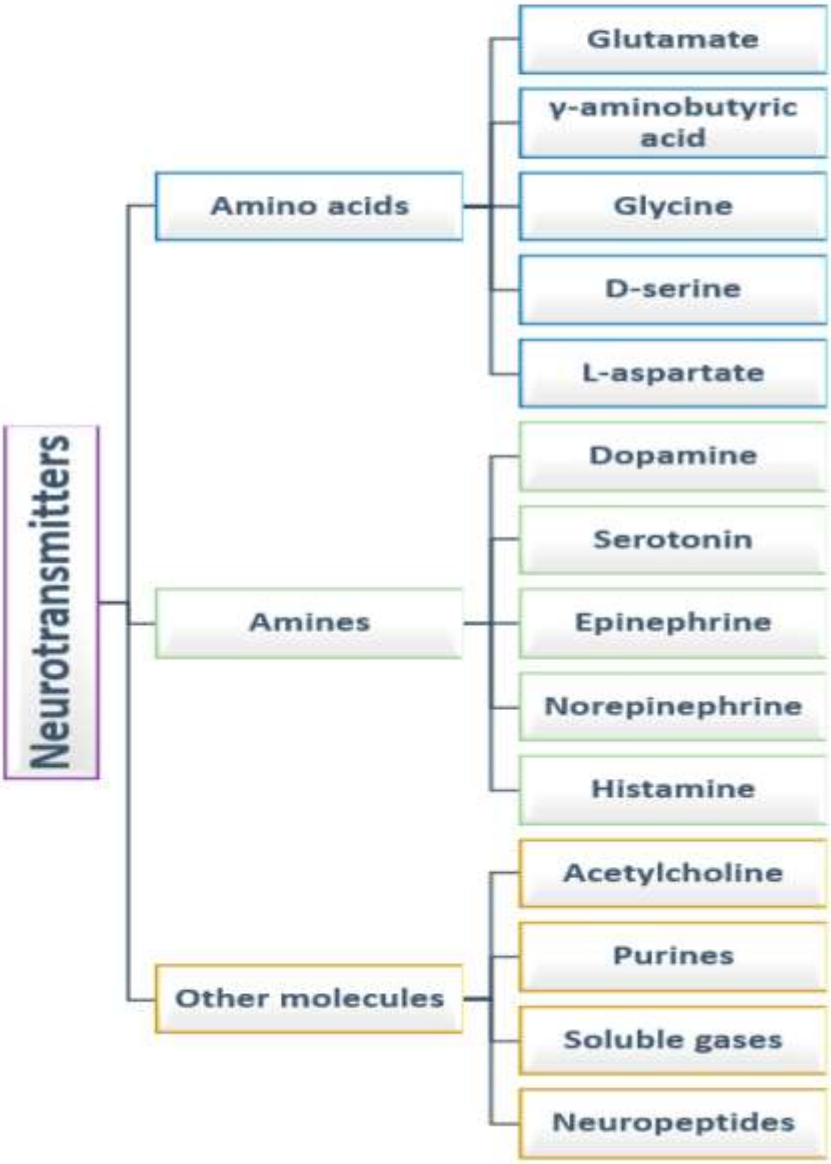

Figure.1

Imaging biomarkers: Biomarkers serve as measurable biological molecules or factors that can indicate normal or disease states. Extensive research over the past decades has aimed at developing reliable biomarkers for neurodegenerative diseases. These biomarkers can be employed independently or in conjunction with other factors to enhance the reliability and precision of diagnosis, prognosis, and treatment planning in CNS diseases [14,15,16].Numerous studies have demonstrated that miRNA dysregulation is associated with various diseases, suggesting their potential for diagnosis and treatment [17,18,19]. More recently, serum miRNAs and blood cell-derived miRNAs are being explored as non-invasive diagnostic biomarkers for PD, glioblastoma, and other diseases [20,21].Brain disorders' biomarker detection is mainly hampered by the blood–brain barrier (which maintains strict and different chemical climates between the brain and the periphery) and difficulty to probe the chemistry, i.e., neurotransmission, of an intact brain in vivo [26,27,28].

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Outlining imaging-based biomarkers in specific neurological disorders.(29)

Neurological disorders	Imaging-based biomarkers
1)Alzheimer's disease	Amyloid PET imaging, Tau PET imaging, FDG-PET hypometabolism
2) Parkinson's disease	DaTscan SPECT imaging, Dopamine transporter imaging, DTI(Diffusion tenser imaging)
3) Epilepsy	Hippocampal sclerosis on MRI, Cortical dysplasia on MRI, PET/SPCE imaging.

Molecular diagnostics can identify them using neuroimaging techniques such as PET, MRI, and nuclear magnetic resonance spectroscopy (NMRS) (39,40,41). The combination of biomarkers and NMRS has demonstrated promise in molecular diagnostics alongside other techniques such as diffusion tensor imaging (DTI), functional MRI, and PET. NMRS is a quantitative imaging method that allows researchers to use specific neuronal metabolites as biomarkers to study real-time metabolic dysfunction and permanent neuronal damage. Researchers investigated whether NMRS could serve as a molecular imaging biomarker for in vivo diagnosis of PD and monitoring treatment efficacy (42).

MRI.(Magnetic resonance imaging): Structural brain changes tend to be subtle in early PD and may not be apparent on conventional MRI. Voxel-based morphometry (VBM) studies have identified reduced gray matter (GM) volumes compared to controls in the frontal lobe.[9]MRI techniques that administer a pharmacological challenge to assess its effects on brainhemodynamics, and by doing so indirectly assess brain neurotransmitter function [22]Structural imaging is the imaging workhorse of neurode-generation, it is the most widely used and accessible, it is recommended in diagnostic guidelines and it forms part of most consensus criteria. Structural MRI (sMRI) has several advantages over computed tomog-raphy (CT). Its main uses are (a) excluding brain lesions,(b) determining patterns of atrophy and (c) assessing vascular burden. Research key aims include improving early diagnosis andtracking disesaseprogession.(23)In the case of brain volume measurements based on magnetic resonance imaging (MRI) scanning, this would be the demonstration that brain volume measurements are highly reproducible between scanners, operators and protocols for measurement [43].

DTI. Diffusion Tensor Imaging (DTI): It is a specialized form of magnetic resonance imaging (MRI) that focuses on the diffusion of water molecules in brain tissue, providing detailed information about the integrity of white matter tracts. White matter consists of bundles of axons that connect different regions of the brain, facilitating communication between them. In neurodegenerative diseases like Parkinson’s Disease, the integrity of these white matter tracts is often compromised, leading to disruptions in brain connectivity and function. (30)In Parkinson’s Disease, DTI has emerged as a valuable tool for studying changes in white matter integrity and their correlation with disease severity and progression. One of the key regions of interest in PD research is the substantia nigra, a brain structure that plays a critical role in movement control. (31)DTI is particularly useful in detecting microstructural changes in the brain that may not be visible on standard MRI scans. For instance, in multiple sclerosis (MS), DTI can identify the degradation of white matter tracts caused by demyelination, offering insights into disease progression.(32) In cases of traumatic brain injury (TBI), DTI helps reveal diffuse axonal injury, a condition where white matter fibers are damaged due to shear forces, even if the injury is not visible on conventional scans. (33) Furthermore, DTI has proven beneficial in studying neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) and Alzheimer's disease, where it can detect early signs of white matter degeneration that precede significant cognitive or motor impairments. (34) By providing a window into the brain's connectivity and structural integrity, DTI has become an essential tool for diagnosing and tracking brain diseases. (35)

II. CONCLUSIONS:

In summary, neurotransmitters are chemical moieties that can carry and amplify signals, ensuring information transmission throughout the nervous system. As they comprise a wide range of molecules (e.g., amino acids, amines, purines, soluble gases, neuropeptides) and are involved in numerous functions (e.g., emotions, thoughts, memories, movements, learning, sleep patterns, behavior, alertness, arousal, vasoconstriction, respiration), neurotransmitters are essential factors in maintaining brain health. Consequently, disturbed neurotransmitters' homeostasis and/or impaired neurotransmission results in severe diseases that significantly impact patients' lives and the global health system.To recapitulate, altered levels of neurotransmitters, such as glutamate, GABA, dopamine, serotonin, norepinephrine, histamine, and acetylcholine, were noticed to be involved in the pathophysiology of a long list of diseases, including autism spectrum disorders, schizophrenia, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, Alzheimer's disease, drug addiction, depression, and sleep disorders. Hence, monitoring and detecting NTs at early disease stages is mandatory to avoid complications of these associated disorders. Nonetheless, chemically diagnosing brain disorders represents a highly challenging task, and, despite recent advancements in designing nanotechnology-based NT sensors, there is still room for improvement of current detection methods. Moreover, further in-depth research is needed to investigate neurotransmitters' complex mechanisms of action and develop strategies for modulating their levels toward maintaining homeostasis.

A mounting body of evidence supports the application of biomarkers in diagnosing and treating CNS disorders. Nevertheless, additional research is imperative to comprehensively grasp the clinical efficacy of these markers and to pinpoint novel biomarkers. It is pivotal to underscore that the biomarker discovery process should unfold concurrently with clinical validation. Specifically, the validation of biomarkers ought to transpire in both retrospective and prospective manners, utilizing independent sample cohorts, ideally procured by multiple hospitals. Exploring and elucidating the regulatory mechanisms of miRNAs(microRNA), lncRNAs(long noncoding RNAs), and cimiRNAs(circulating micro RNAs) in neurodegenerative disorders is essential to enhance the applicability and accuracy of these molecules as biomarkers for clinical diagnoses. To augment the sensitivity and specificity of protein detection in biological samples, advancements in testing methods, such as mass spectrometry and immunoassays, are imperative. Additionally, there remains much to unravel about the dynamics of protein levels in the body, encompassing genetic and environmental factors, and how these levels evolve over time in both healthy individuals and those with neurological disorders. In conclusion, the integration of biomarkers into CNS research holds the potential to revolutionize the field by enhancing diagnostic precision, predicting disease progression and treatment response, ultimately culminating in the development of more effective therapies.

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