Chapter 3
Tracking Neurodegeneration: Advancement in Experimental Study Models

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Abstract Neurodegeneration is the gradual deterioration and loss of conductive ability of neurons constituting the central and the peripheral nervous system, particularly involving the neurons in the brain and spinal cord. Neurodegenerative conditions are one of the leading causes of disability, affecting millions of people around the world. The risk of the onset of neurodegenerative diseases increases dramatically with age. Although age is considered a dominant factor in the mortality and prevalence rates of many neurodegenerative disorders, the number of cases has increased over the last 25 years. Most neurodegenerative diseases are challenging to diagnose early. On the other hand, reports have stated that early treatment can slow the progression of the disease. Thus, an early diagnosis of the disease would allow the clinician to predict further possible neural damage and subsequent disabilities. Neuro radio imaging tools are traditional methods for monitoring neurodegeneration in clinical settings. Lately, genetic and biochemical tools have also been successfully developed for early diagnosis. In addition, preclinical animal models and human organoids have also been successfully utilized in the neuro drug discovery program and early diagnosis of disease progression. Therefore, in the above-mentioned context, the authors have briefly discussed various strategies for monitoring neurodegeneration and the recent progress made in experimental models.

Keywords Neurodegeneration · Tracking of neurodegeneration · Neurodegenerative disorders · Radio imaging · Genetic test · Preclinical models · Human organoid models

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P. Elumalai, S. Lakshmi (eds.), *Functional Foods and Therapeutic Strategies for Neurodegenerative Disorders*, https://doi.org/10.1007/978-981-16-6703-9_3

Abbreviations

6-OHDA	6-Hydroxydopamine
Ach	Acetylcholine
AChT	Acetylcholine transporter
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APOE	Apolipoprotein E
Aβ	Amyloid beta
BBB	Blood–brain barrier
CAA	Cerebral amyloid angiopathy
CB2R	Cannabinoid receptor 2
CBF	Brain blood flow
CNS	Central nervous system
COX	Cyclooxygenase enzyme
DA	Dopamine
ET	Eye tracking
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GABA	Gamma-aminobutyric acid
HD	Huntington's disease
HIV	Human immunodeficiency virus
iPSCs	Pluripotent stem cells
LTP	Long-term potentiation
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NFTs	Neurofibrillary tangles
PD	Parkinson's disease
PET	Positron emission tomography
SN	Substantia nigra
SNc	Substantia nigra pars compacta
SNpc	Substantia nigra pars
SPECT	Single-photon emission computed tomography
TEQ	Therapeutic Engagement Questionnaire
TSPO	Translocator protein

3.1 Introduction

Neurodegeneration is the gradual deterioration with concomitant loss of neuronal ability to communicate across the central and peripheral nervous system. Neurodegeneration is synonymous with diseases such as amyotrophic lateral

sclerosis (ALS), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), and Parkinson's disease (PD). Neurodegenerative conditions are the most frequent cause of disability and affect millions of people worldwide (Checkoway et al. 2011). According to the US National Institute of Environment and Health Sciences, AD and PD are the most common neurodegenerative diseases globally. Furthermore, the risk of developing a neurodegenerative disease increases considerably with age. Although age is considered to be a predominant factor in mortality and prevalence rates for many neurodegenerative disorders, the number of cases has increased over the past 25 years (GBD 2015 2017). Therefore, the market size of therapies for neurodegenerative diseases is expected to grow by nearly USD 44.90 billion in 2026. This report provides a market analysis based on the findings of AD, PD, MS, HD, and others (Reportlinker 2021).

Neurodegenerative disorders typically cause cognitive or motor dysfunction or both. For example, AD is a common cause of dementia and impairs the individual's quality of life, mental judgment, financial implications, and memory functions. In addition, it is often associated with mood swings in patients (Relja 2004; Sugin et al. 2020). While ALS and PD are progressive degenerative diseases that damage the nerve cells (motor neurons) which control voluntary muscle movement, HD is predominantly an autosomal disease establishing itself by a triad of motor, cognitive, and psychiatric symptoms. Most neurodegenerative diseases are hereditary and progress over several years, ultimately leading to death (Relja 2004; Dugger and Dickson 2017). Unfortunately, it becomes increasingly difficult to treat as the disease progresses. Conditions such as ALS, AD, and PD might be difficult to diagnose early. On the other hand, reports have favored early treatment for slowing down the progress of the disease (Mancuso et al. 2011; Murman 2012; Czaplinski et al. 2006). Subsequently, it has also been believed that the neurodegenerative process is characterized by the loss of the myelin sheath, followed by cell death and behavioral changes; therefore, early diagnosis and treatment would facilitate the arrest of further damage of neurons.

Initially, scientists were not able to accurately correlate the physiopathological pathways with the rate of disease progression. As a result, it was difficult for clinicians to monitor the therapeutic responses and the severity of the disease. However, with recent advances in noninvasive brain imaging techniques, proteomics, and estimation of the biomarkers, a wide range of evidence is available. Now, the researcher can predict the progression of the disease and initiate proper counseling and medications. In the given context, the authors briefly address the monitoring strategies of neurodegeneration and recent advances in the experimental models.

3.1.1 Pathophysiology of Neurodegeneration

As discussed above, neurogenerative diseases have been explained by complex multifactorial pathogenetic mechanisms that vary depending on the clinical state. The exact pathogenicity of neurodegenerative diseases remains largely unknown.

However, the relevant neurochemistry and synaptic transmission levels have been extensively researched. It is important to note that protein abnormalities followed by neuroinflammation that define neurodegenerative diseases might occur prior to the onset of clinical signs (Relja 2004; Dugger and Dickson 2017). Consequently, a thorough knowledge of pathophysiology is necessary to understand the progression of the disease. The common pathophysiology associated with clinical conditions is discussed as follows.

The physiopathology of AD implies cortical atrophy, usually the most important in the medial temporal lobe, which is composed of several important structures related to cognitive function. The impacted brain regions suffer inflammation, granular degeneration, and Hirano bodies. Furthermore, two classical inclusions are considered pathognomonic of the disease: neurofibrillary tangles (NFTs) and amyloid plaques. NFTs are localized aggregates of tau proteins and neurofilaments found in neuronal cell bodies. The distribution and density of NFTs appear to be correlated with clinical conditions. Amyloid plaques are extra neuronal aggregates of Aβ-protein. The plaques, namely neuritic and diffuse, are two kinds that are responsible for the pathology of the disease. The neuritic plaque is an extracellular component of Aβ; the plaque also has a component of dystrophic neuritis that contains tau protein. On the other hand, the diffuse plaques consist mainly of Aβ protein. Interestingly, the histopathology of the brain section of autopsied elderly individuals who are clinically unaffected has also demonstrated the presence of diffuse, neuritic plaques, and NFTs (Pressman et al. 2014).

ALS affects both superior and lower motor neurons and is clinically associated with weakness, muscle atrophy, and spasticity fasciculations. There are instances of atrophy of the precentral gyrus. In addition, gray matter abnormalities, atrophy of the motor cortex, and white matter reduction are also observed in different segmental areas of the central nervous system, with a site predilection to the corticospinal tract and Betz cell degeneration in the motor cortex (Dickson and Weller 2011; Saberi et al. 2015). Other pathology features of ALS include vacuolization, large empty spaces close to neurons, and spongiosis. Recent studies point to the importance of the glial cells and their role in the pathophysiology of ALS (McGeer and McGeer 2002; Boillée et al. 2006a, b; Yamanaka et al. 2008).

HD is a rare, progressive, and degenerative genetic condition caused by a single defective gene on chromosome 4—one of 23 human chromosomes. It is especially identified by the neuronal loss of striatum and cortex (Vonsattel and DiFiglia 1998) but also affects many other nuclei, including the globus pallidus, thalamus, hypothalamus, subthalamic nucleus, substantia nigra, and cerebellum (Petersén et al. 2002, 2005; Kassubek et al. 2004). Additionally, diffusion tensor imaging confirmed white matter pathology in symptomatic patients before and prior to symptoms (Rosas et al. 2006). Recent evidence has suggested that the mutant Huntingtin gene RNA is toxic. On the DNA level, it causes a repeated expansion of somatic GAC in susceptible cells, influencing the progression of the disease (Tabrizi et al. 2020).

PD can be an inherited or a sporadic disease, but they all have neuronal loss in the substantia nigra pars (SNpc) compacta, which provides the dopaminergic

innervation to the striatum (Dickson 2018). The gradual loss of dopamine neurons is a characteristic of normal aging. However, the symptoms of PD are consistent with excessive loss (70–80%) of these neurons. If left untreated, PD progresses over a span of 5–10 years to a rigid and related condition, and patients are unable to fend for themselves. Subsequently, the cross-sections of the PD brainstem demonstrated the loss of the dark pigmentation zone in the SNpc and locus coeruleus. Pigmentation loss was observed to be directly correlated with the death of dopaminergic neurons (DA) containing neuromelanin in the SNpc and noradrenergic neurons of the locus coeruleus (Dickson 2012), which leads to malfunction in other nondopaminergic neurotransmitter systems (Kalia et al. 2013). Degeneration of these systems has been attributed to the various nonmotor symptoms of PD that are refractive to dopamine replacement therapies (Chaudhuri et al. 2006).

Moreover, the roles of neurotransmitters in the pathophysiology of neurogenerative diseases have also been investigated. In addition to clinical conditions, many neurodegenerative disorders have common phenomena in neurotransmitter levels in the central nervous system (Vorobyov and Bobkova 2017). Excitatory amino acids like glutamate are major excitatory neurotransmitters in the human nervous system. Glutamate hyperactivity caused by exogenous or endogenous factors is widely believed to be an etiological factor in chronic neurodegenerative disease (Lewerenz and Maher 2015). Exogenous or endogenous neurotoxic compounds could also activate glutamate receptors, resulting in neurodegeneration. The excitotoxicity of glutamate may also contribute to toxin-induced dopamine cell death, mainly due to the presence of glutamate receptors in substantia nigra (Relja 2004). Therefore, it could be concluded that the understanding of pathophysiology and relevant pathways is essential in the early diagnosis of the disease.

3.1.2 Classification of Neurodegenerative Diseases Based on the Clinical Manifestations

To the best of the authors' knowledge, the present attempt is the first of its kind in classifying the neurodegenerative diseases, based on the functional disability aspects, as follows:

- **Neurodegeneration with physical disability:** Movement disorders, including hyperkinetic, hypokinetic, cerebellar, or dysfunction of the superior and inferior motor neurons (e.g., HD, ALS or Lou Gehrig's disease, PD, MS, spinocerebellar ataxia, spinal muscular atrophy, and motor neuron diseases).
- **Neurodegeneration with mental disability:** Cognitive decline, dementia, and impairment of superior cerebral functions (e.g., AD and other dementias, PD and PD-related disorders, prion disease, and HD).

  Clinical manifestations of neurodegenerative diseases begin either as motor or cognitive dysfunction or early combinations of both.

3.2 Tracking Strategies for Neurogenerative Diseases

The tracking of neurodegeneration at a macroscopic level by identifying the clinical signs and up to the level of cellular pathology is one of the many recent advances achieved in the treatment and management of neurodegenerative diseases. The initial processes of neurodegeneration begin with neuroinflammation, which occurs in the brain and spinal cord regions (Przedborski et al. 2003; Dugger and Dickson 2017). Therefore, early diagnosis of the disease would allow the clinician to predict additional neural damage and subsequent disabilities. Neurodegenerative diseases have a group of pathophysiological events, and these differ with clinical conditions. Therefore, the authors classified the tracking strategies based on the disease progression (Fig. 3.1).

Disease progression could be monitored by imaging anatomical changes and/or quantifying pathophysiologically relevant biomarkers from various body fluids. Recent developments in imaging tools and proteomics analysis techniques would allow researchers to track the disease progression in clinical settings (Mathis et al. 2005; Shimizu et al. 2018). Neuroinflammation refers to the development of several neurodegenerative disorders (Guzman-Martinez et al. 2019), followed by demyelination and neuronal death (Fig. 3.1). Astrocytes and microglia are the dominant immune cells in the CNS (Carson et al. 2006). They are thought to play a critical role in the initial cascade of neuroinflammation by releasing many neurotoxins (Chen et al. 2016). Therefore, comparing the extent of neurochemicals in various body fluids and radio imaging would help understand the rate of progression with clinical correlation support.

3.2.1 Applications of Radio Imaging Tools in the Monitoring of Neurodegenerative Diseases

Recent studies have revealed that nuclear imaging approaches such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) have been helpful in monitoring the molecular consequences of neuroinflammation. Furthermore, the above-mentioned imaging tools have also been used in investigating changes in the integrity of the blood–brain barrier (BBB) and biomarkers for neuroinflammation, using specific radioligands.

3.2.2 Applying PET to Neurogenerative Disease Tracking

PET is the first nuclear imaging approach aimed at quantifying neuroinflammation in vivo (Jain et al. 2020; Kreisl et al. 2020; Meyer et al. 2020; Zimmer et al. 2014).

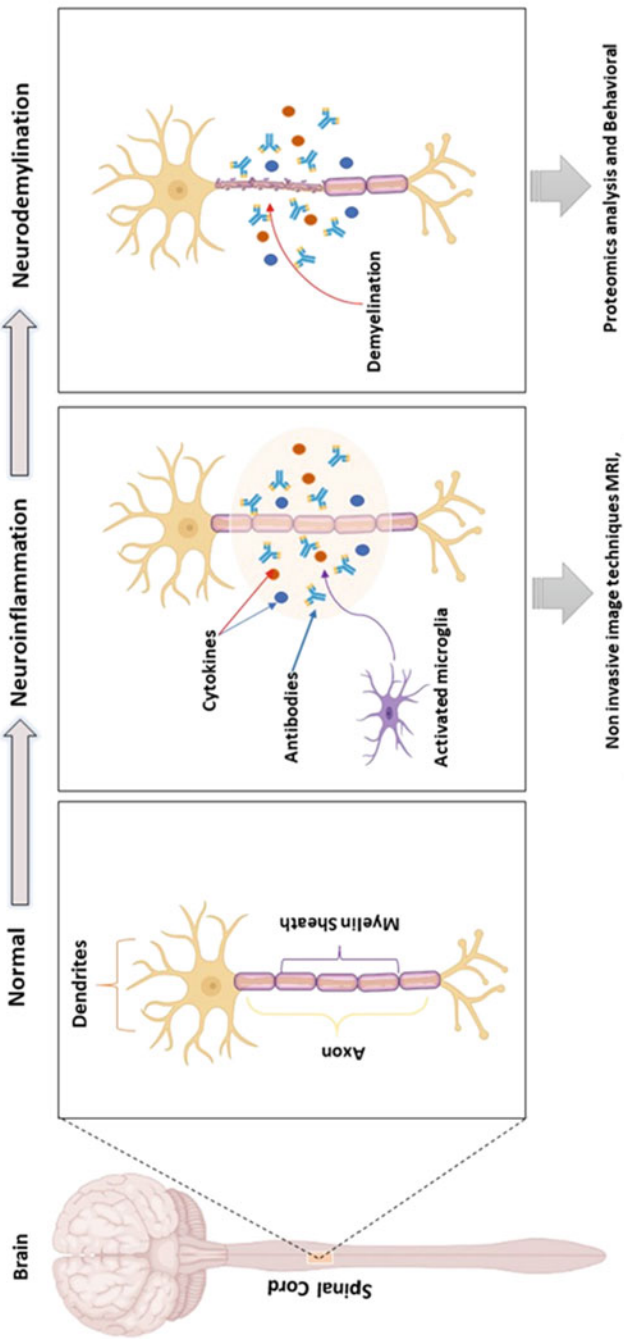

Fig. 3.1 Common neurodegenerative pathways and their applications in disease index tracking

Activation of microglia in the brain and spinal cord region would lead to infiltration of peripheral leukocytes into the CNS, followed by neuroinflammation (Carson et al. 2006; DiSabato et al. 2016). The microglia activation will trigger the release of inflammatory markers such as cytokines and chemokines and the generation of reactive oxidative species to sustain homeostasis (Harry and Kraft 2008; Wang et al. 2015; DiSabato et al. 2016). Increasingly, data from preclinical models and genomic association studies have highlighted the immune system's role in neurodegenerative diseases, which include AD, PD, and MS (Golde 2019). Since neuroinflammation is the primary cascade in neurodegeneration, an initial evaluation of inflammatory markers would enable to predict the neurodegeneration by clinicians and researchers at the early stage of disease progression. In addition, PET has discriminated a minor quantity of inflammatory markers in the brain and spinal cord areas (Carson et al. 2006; DiSabato et al. 2016). The above information would enable investigators to design clinical trials for neurodegenerative therapies. Recent studies have provided considerable evidence of the usefulness of PET studies in monitoring neuroinflammation; however, the clinical application is yet to be initiated. Therefore, additional studies are warranted to apply these strategies toward meaningful treatment.

The foremost advantages of PET in tracking neurodegeneration are that it could detect low concentrations of particular proteins or amino acids in the region of interest using specific radioligands (Kreisl et al. 2020). To detect specific proteins, the specific nontoxic radioligands needed are known as tracers (Fig. 3.2). Tracers are the radiolabeled chemical molecules with higher affinity toward the specific proteins; thus, the injected tracers will bind with the proteins, and the PET scanner would detect the radio signals. The ratio of radioligands between the region of interest and the nonspecific regions would be a surrogate marker of the extent of protein accumulation in the particular region. Changes in the radio signal ratio at baseline and/or after treatment would provide the opportunity to track the impact of the particular treatment on the condition and progression of the diseases (Fig. 3.2). Several PET radiotracers have been developed for candidate biomarkers of neuroinflammation, including 18 kD translocator protein (TSPO), cannabinoid receptor 2 (CB2R), and cyclooxygenase enzymes (Jain et al. 2020).

In clinical trials, TSPO is a presumed biomarker of neuroinflammation, and the elevation of PET ligands shows an increase in TSPO binding, which, in turn, positively correlates with the clinical conditions in AD, as well as during major depressive episodes of the disease (Ching et al. 2012; Dupont et al. 2017; Zhang et al. 2021). The PET ligand for cyclooxygenases enzyme systems such as COX-1 and COX-2, which are components of the cyclooxygenase (Narayanaswami et al. 2018), might be more beneficial in studying the conditions and also to understand whether the given treatment was effective or not.

Furthermore, the markers showed significant differences between the healthy volunteers and patients with neurodegenerative diseases such as AD, MS, HIV-associated cognitive impairment, frontotemporal dementia, chronic traumatic encephalopathy, HD, ALS, epilepsy, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies and stroke (Kepe et al. 2013;

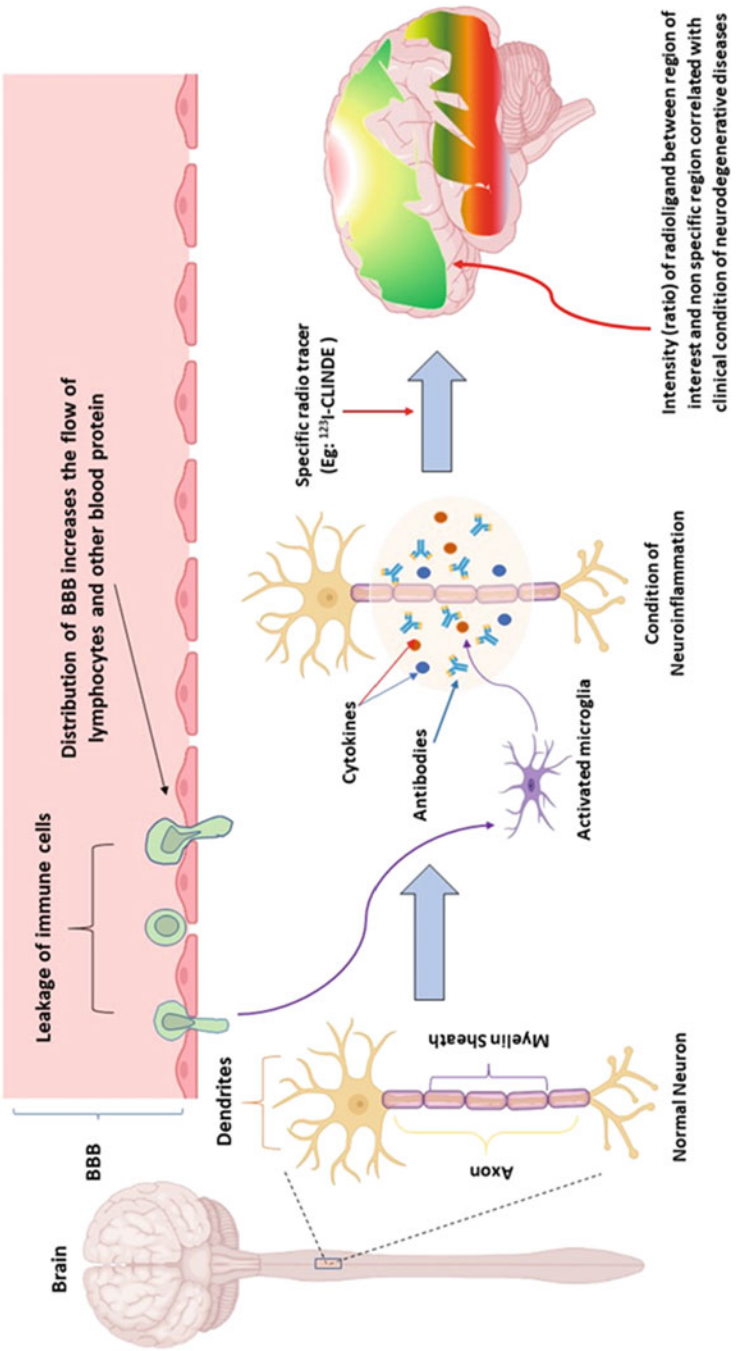

Fig. 3.2 Application of PET/SPET in tracking neurodegenerative disorders

Vera et al. 2017; Beyer et al. 2018; Tiepolt et al. 2019). In addition, the PET acquisition could create three-dimensional images that enable the detailed state of the brain region and spinal cord to be read. However, the main obstacle is the limitation of quantification with the most common neuroinflammatory markers, such as 18 kDa translocator protein (TSPO) due to higher nonspecific binding of the radioligands (Ching et al. 2012).

3.2.3 *Applying Single-Photon Emission Computed Tomography (SPECT) in Neurogenerative Disease Tracking*

The principle of SPECT and PET operation is always common (Fig. 3.2) with various devices. At the same time, PET and SPECT would be distinguished by the type of radiotracers used. PET tracers generally have a shorter half-life, whereas SPECT tracers have a longer half-life, allowing us to take more images (Rahmim and Zaidi 2008; Wahl et al. 2011). Thus, the PET scanner is crucial in the study related to BBB integrity, followed by the infiltration of inflammatory markers involved in the first line cascade of the neuroinflammation process (Breuer et al. 2017; Kreisl et al. 2020). Furthermore, early diagnosis of changes in the BBB integrity in the conditions of stroke and other diseases or injuries would help the physician plan proper treatment and arrest the progress of neuronal damages.

Lorberboym and his colleagues reported (99 m) Tc-diethylenetriamine penta acetic acid as a tracer for BBB integrity assessment during the acute stroke of the middle cerebral artery, occurring between 24 and 48 hrs. The data showed that measuring the degree of BBB disturbance at the initial stage of stroke and edema formation might be used to predict the delayed neurological and functional results (Lorberboym et al. 2003). In another clinical study, Elbert and the team used ^{123}I-CLINDE as a SPECT tracer to study the neuroinflammation in patients after mild traumatic brain injury. ^{123}I-CLINDE, a marker specific to TSPO, is an upregulated protein in the active immune cells. Interestingly, the results showed that neuroinflammation occurred after 1–2 weeks after the injury. Furthermore, it persisted up to 4 months as suspected in the pathogenesis of post-concussion symptoms in patients (Ebert et al. 2019). Thus, the above evidence strongly supported the hypothesis that early diagnosis of neuroinflammation via BBB integrity changes by neuroimaging techniques would be a potential treatment strategy to prevent late neuronal damage and subsequent disability.

In addition, unfortunately, there is no peripheral blood test for PD yet. Therefore, most of the time, PD gets diagnosed only in the advanced stages. Early detection of PD is essential in arresting further damage to the dopaminergic neurons. Nowadays, ^{123}I-ioflupane is widely used as a tracer for the diagnosis of early-stage PD. Many clinical studies have shown the logical relationship of changes in the ^{123}I-ioflupane binding report in left caudate, right caudate, left putamen, and right putamen with

clinical presentation (Pahuja et al. 2019). As discussed earlier in the present chapter, acetylcholine (ACh) is a key neurotransmitter involved in the pathophysiology of PD. Levels of ACh and its vesicular acetylcholine transporters (AChT) would be less in PD patients than in healthy volunteers (Bohnen and Albin 2011). Therefore, monitoring the density of AChT could be a potential diagnostic approach for the early detection of PD. The SPECT radiotracers like ^{123}I-iodobenzovesamicol bind specifically to AChT and reveal the density of acetylcholine containing vesicles. Therefore, changes in the AChT could be correlated with the clinical presentation for early detection of PD. Interestingly, the reduced density of AChT in parietal, occipital lobes and cerebral cortex in PD patients identified by the SPECT radiotracer was also correlated with dementia (Niethammer et al. 2012).

3.2.4 Applying Magnetic Resonance Imaging (MRI) to Neurogenerative Disease Tracking

MRI has taken on an essential and groundbreaking role in diagnostic imaging by enabling the acquisition of high-resolution images without harmful ionizing radiation. The major advantage of MRI is that it works through water molecules within the body and requires no specialized radiotracer. However, the specific proteins or inflammatory markers might not be detected through MRI. Instead, one can detect structural abnormalities such as alterations in brain volume, atrophy, diameter, area, etc. Melzer and his colleagues studied the structural abnormalities of twenty-three nondemented PD patients over the period of one year. The results showed atrophy in temporal and orbitofrontal cortices in the PD group compared with the control group. The significant changes in brain atrophy could be used to monitor dementias in PD patients (Melzer et al. 2015).

Furthermore, the substantia nigra (SN) region is primarily affected due to the after infarction, especially in conditions like stroke or serious injury. SN has dopaminergic neurons of the midbrain that play a vital role in motor and reward function. Therefore, the damage caused by immune cell infiltration due to infarction seriously affects motor function, which in turn leads to motor dysfunction. Linck and his colleagues studied the SN after ipsilateral infarct and the clinical outcomes in 181 participants in their study. After one year of follow-up, the study made a riveting conclusion that the patients with stroke had increased SN R2* in MRI. The elevated SN R2* was related to the increased iron content and clinical outcomes. Therefore, the study concluded that tracking of SN R2* by MRI could be a potential tool for tracking secondary neurodegeneration in stroke patients (Linck et al. 2019).

Astrocytes play a crucial role in cerebral blood flow (CBF). In the course of MS, CBF reduction is known as expected cerebral hypoperfusion. Therefore, changes in CBF would be a potential early marker for the neurodegenerative process. Van Schependom et al. described the comprehensive brain hypoperfusion in the cerebral cortex and cerebellum in MS patients utilizing the arterial spin labeling method

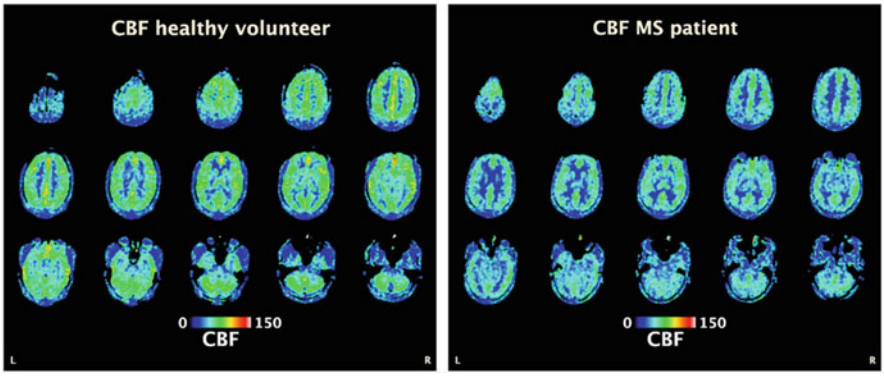

Fig. 3.3 Perfusion-weighted cerebral MRI (labeling of arterial spin) of a healthy volunteer (left) versus recurrent remission MS (right), with CBF map overlay with color code. Cerebral perfusion is generally reduced in multiple sclerosis, compared with healthy volunteers (image adopted in Van Schependom et al. 2019)

without using contrast administration (see Fig. 3.3 for an example from the authors' own records, unpublished data adopted from Van Schependom et al. 2019). The above findings supported the hypothesis that reduced CBF in the early stage of diagnosis would be a potential strategy for prevention from further deterioration.

3.3 Genetic Testing for Neurodegenerative Disease Tracking

Clinical genetic testing techniques on neurodegenerative disorders used for accurate diagnosis provide information on the risk of recurrence and assist family members involved in determining the personal risk and eligibility for counseling or clinical trials.

Genetic detection of neurodegenerative diseases through monogene analysis began in the 1980s when genes were identified for HD, AD, and other neurodegenerative diseases. Recent developments in genetic testing and multigenic panels, whole exome sequencing increases diagnostic efficiency, especially if the specific neurodegenerative state is unknown. At the beginning of the 1990s, genes responsible for AD were identified on chromosomes 21 (APP), 14 (PSEN1), and 1 (PSEN2) (Van Cauwenberghe et al. 2016). These genetic tests have been proposed in families with known or suspected mutations, while recent findings have confirmed the critical role of associations between Lewy's dementia and variants of the APOE, GBA, and SNCA genes (Sanghvi et al. 2020). In addition, another study confirmed that the mutation in a single multigene such as C9orf72, MAPT, and GRN causes 20–50% chances of frontotemporal dementia (FTD) (Olszewska et al. 2016). Unless a specific pathogenic variant of the family is known, genetic testing for FTD is

usually performed using multigene panels (Greaves and Rohrer 2019). Similarly, recent advancements in genome analysis could diagnose other neurodegenerative diseases as well. For example, genes, such as GBA and LRRK2, display the most common genetic variants associated with PD and serve as the basis for the emerging target-based therapies for PD, and it is currently being tested in clinical trials (Sardi et al. 2018).

Unfortunately, there is no diagnostic or radio imaging protocol for the early diagnosis of ALS. It is one of the primary neurodegenerative diseases of the motor neurons, ending in mortality within 3–5 years after the onset of symptoms. However, recent developments in the field of genetic diagnosis would provide the possibility of identifying family inheritance occurs in 5–20% using GWAS. A number of genes have been identified, including C9orf72, SOD1, FUS, and TARDBP, which are directly correlated with the onset of ALS (Peters et al. 2015). In addition, van Rheenen and co-workers recently identified MOBP and SCFD1 as new risk factors associated with ALS (van Rheenen et al. 2016).

HD is a progressive neurodegenerative condition, potentially fatal and incurable, and there is currently no diagnostic test for HD. In early 1983, the polymorphic marker was used to map a gene to a chromosome. The HD gene, now known as HTT, has been correlated with chromosome number 4. The HTT gene was identified and proved to be an extension of CAG trinucleotide replication, which opened the door to direct genetic testing for HD (MacDonald et al. 1993; Roberts et al. 2020).

Together, recent advances in whole-genome analysis and sequencing would make it possible to diagnose neurodegenerative diseases when clinical conditions are unknown. In addition, it also provides an occasion for early diagnosis and clinical advice for the management.

3.4 Advanced Study Models in Neurogenerative Disease Tracking

For the most part, conventional methods for monitoring neurodegenerative disorders include noninvasive imaging techniques and behavioral assessments. However, recent advances in proteomics and in vitro culture would make it possible to predict the rate of neurodegeneration from the patient's peripheral tissue samples. The following are some examples of recent preclinical and clinical models.

3.4.1 In Vitro Human Organoid Models for the Surveillance of Neurogenerative Disorders

Recent studies on iPSC-derived brain organoids using skin samples from AD patients showed that APOE4 exacerbated synapse loss and neurodegeneration

(Zhao et al. 2020). In the above study, human dermal biopsies of healthy volunteers and patients with the genotype APOE ε3/ε3 or ε4/ε4 were used. APOE genotype has been identified by Sanger sequencing using DNA samples from fibroblast lines. Cells were cultured, and induced pluripotent stem cells (iPSCs) were produced by electroporation of three epidermal vectors in fibroblast cells. The IPSC colonies were isolated and extended after 3–4 weeks of cultivation. The author then developed a 3D human brain organoid system to study the pathogenesis of AD. In the study findings, it was observed that APOE4 predominantly worsened the p-tau accumulation. At the same time, AD status has been linked to higher levels of Aβ and p-tau, apoptosis, synaptic loss, and increased formation of stress pellets. It is important to note that APOE4 potentially speeds up apoptosis and the formation of strain granules in the AD state in this 3D organoid model. Therefore, the human iPSC-organoids recapitulate that the APOE4-related model can be a tool for the early identification of degenerative pathways contributing to AD pathogenesis. However, detailed studies in this area are still warranted.

3.4.2 In Vivo Preclinical Models for Monitoring Neurogenerative Disorders Being Investigated

A wide range of animal models that can mimic the human context of the disease is being used to investigate the pathogenesis of the diseases and treatment strategies. The FDA relies on data produced from animal models to evaluate the effectiveness and safety of new drugs. Indeed, animal models have been the gold standard to study the pathophysiology of any disease. In the above context, the authors examined some recent animal models used for monitoring neurodegeneration, and the details have been discussed below.

3.4.2.1 Preclinical Models for AD

Conventional preclinical animals such as mice, rats, monkeys, dogs, and others do not naturally develop AD. However, the studies in animal models showed that several chemicals and physical injuries might develop memory deficits, neuroinflammation, and cerebral amyloid angiopathy (CAA). At the investigative stage, the manifestation of AD in the brain reveals the accumulation of extracellular amyloid plaques, intracellular neurofibrillary tangles, and neuronal loss. Several studies have identified a causal relationship between neocortical NFT and cognitive loss (Giannakopoulos et al. 2009; Nelson et al. 2012; Webster et al. 2014). Interestingly, the triple transgenic 3xTg mouse model displayed learning and memory deficits on the Barnes maze (Stover et al. 2015), and it expresses all disease characteristics of AD. Aβ deposition is progressive, with intracellular immunoreactivity detected in some areas of the brain from 3 to 4 months of age. These mice

develop progressive neuropathology associated with age, including plaques and tangles. The Aβ deposits become apparent in 6 months, and with progressing time, the deposition becomes discernible at the microscopic level. This is complemented by accelerating tau pathology, which becomes profound in 12 months' time. Synaptic dysfunction, including long-term potentiation (LTP) deficits, occurs prior to plaques and tangles (Oddo et al. 2003; Billings et al. 2005).

Interestingly, cognitive impairment occurs within 4 months. Initially, plaques and tangles deposition at the histological level begins to appear prior to the development of memory and learning deficits. Several transgenic mouse models have been developed and/or adapted to closely mimic a specific pathological characteristic of AD. The transgenic mouse model Tg-SwDI shows CAA and accumulation of diffuse and less prominent parenchymal vascular fibrillary plates Aβ, as early as 3 months (Davis et al. 2004). Tg-SwDI mice exhibit neurodegeneration of cholinergic neurons followed by impaired cognition. Furthermore, the APP E693Δ-Tg model expresses the Osaka (APPE693Δ) mutation, resulting in a unique phenotype of enhanced expression of Aβ oligomers and synaptic and cognitive impairment as early as 8 months of age, but no plaque or tau pathology formation (Tomiyama et al. 2010). The above-mentioned animal models are currently being involved in the AD drug discovery program to understand the efficacy of new chemical entities during the drug treatment.

3.4.2.2 Preclinical Models for Huntington's Disease

HD is a life-threatening neurodegenerative disorder and is a consequence arising out of mutation in the interesting transcription gene 15 (IT15), and it is challenging to develop an animal model for HD. Theoretically, in the HD state, nucleocytoplasmic transport is disrupted, and consequently, the drugs that cause restoration could be neuroprotective. Invertebrate models like *Caenorhabditis elegans* and *Drosophila melanogaster* are currently being used in drug discovery programs for high-throughput screening of various classes of novel therapeutics. The *C. elegans* model is known to express expanded polyglutamine repeats in its nervous system, which is comparable to HD in humans. However, none of the animal models show a potential clinical correlation.

3.4.2.3 Preclinical Models for Parkinson's Disease

Chemical-induced PD models show dopaminergic neuron degeneration in substantia nigra pars compacta (SNc) and a subsequent reduction in striatal dopamine content. MPTP-induced PD is a widely accepted animal model for research, which has led to the advancement of our PD knowledge and therapeutic approach (Benazzouz et al. 1993; Bezard et al. 2001; Dovero et al. 2016). Other familiar models for PD have been generated using 6-hydroxydopamine (6-OHDA) by intracerebral administration (stereotaxic approach) (Kin et al. 2019).

Genetic models are a relatively new approach to understand the disease at the molecular scale, and it involves manipulation of genes that are associated with PD. Transgenic animal models have been generated since the identification of human mutations in neurodegenerative conditions and disorders, which result in the abnormal production of PD-related proteins such as α-synuclein, parkin, PINK1, DJ-1, LRRK2, or UCHL1 (Duty and Jenner 2011; Klein and Westenberger 2012). Several types of α-sin transgenic mice have been established, and many behavioral deficits have been observed. These models, however, could not demonstrate profound nigrostriatal degenerations.

3.4.2.4 Preclinical Models for ALS

Due to the complexity of the pathogenicity of ALS, researchers are not able to produce a conventional animal model for ALS. Therefore, modern science focuses on the genetically modified animal model for ALS. The number of genetic animal models that are being added to ALS research is steadily increasing, and such rapid advancements empower the researchers to perform genetic incision of ALS, thereby adding greater clarity to the knowledge base of the disease pathology. Recently, zebrafish models have been used in ALS research to test the hypothesis (Babin et al. 2014). The degeneration of motor neurons in zebrafish after exposure to the industrial plasticizer Bisphenol A was studied (Morrice et al. 2018). Exposure to BPA induces motor neuron degeneration, activates microglia, and senses pathogenic stimuli at the axon terminal prior to cell death, thereby suggesting a retrograde mechanism of degeneration. BPA is an unlikely candidate toxin for ALS disease (Morrice et al. 2018). The most widely used mouse model of ALS is based on the expression of the human SOD1 protein containing the G93A mutation (Philips and Rothstein 2015; Lutz 2018). The mSOD1 model has successfully attempted to demonstrate the putative cellular dysfunction during disease pathogenesis, such as the noncell autonomous nature of ALS (Nagai et al. 2007; Philips and Rothstein 2015). The above model displays rapid worsening of motor neuron architecture leading to paralysis and ultimately resulting in mortality within the first 5 months. Recently, mouse models of TDP-43-Q331K have been developed, each with unique measures of face and construct validity (Lutz 2018). The disease progression in the TDP43-Q331K model is controlled by prion protein gene promoter and displays many ALS-like hallmarks such as progressive motor dysfunction, muscle atrophy, reduced NMJ integrity, and motor neuron degeneration at 10 months of age.

3.4.3 Recent Clinical Studies to Track Neurogenerative Disorders

Apart from the conventional radio imaging techniques, behavioral and biochemical evaluations also showed promising results in the early diagnosis of neurodegenerative diseases. A few of them are discussed below.

In recent days, eye-tracking (ET) studies have been commonly used in clinical configurations to monitor neurodegeneration. The main benefit of ET is its economic and rapid methodology to track changes in behavior. Previously, the Therapeutic Engagement Questionnaire (TEQ) was primarily used in psychological or developmental cognitive studies. However, there is increasing evidence for the application of ET in motion disorders and the measurement of cognitive processes in neurodegeneration. The major drawback is that data is not available for the application of ET studies at more advanced stages of the disease. On the other hand, theoretically, when patients' motor and verbal functions are significantly affected, it is difficult to assess the cognitive functions. Mostly, assessment is not possible. Therefore, ET is a promising tool to track the cognitive defects at the earliest stage of neurodegenerative conditions.

3.5 Ongoing Research Projects Related to the Monitoring of Neurogenerative Disorders

A few ongoing research projects focused on the monitoring of neurodegenerative disorders are as follows:

The project entitled NeuroTRACK (Grant agreement ID: 714388), funded by ERC (European Research Council), is expected to be completed in March 2022. The above project aims to apply the emerging network science tools to evaluate longitudinal, structural, and functional brain connectivity using 3 T magnetic resonance imaging data from patients with frontotemporal lobar degeneration—a devastating, relentlessly progressive, early-onset, neurodegenerative disorder. The project also aims to examine the sporadic and familial cases, including carriers of presymptomatic genetic mutations. The authors hope that the project team would develop tracking tools for diseases like AD and PD, which in turn would lead to early intervention and modification of disease progression (NeuroTRACK 2021).

In another clinical trial, the neurodegenerative tracking protocol for ALS diseases is being evaluated with human volunteers. The primary objective of the study is to assess frontotemporal dementia (FTD) and adult-onset neurodegenerative disorder (ClinicalTrials.gov Identifier: NCT03225144, https://clinicaltrials.gov/ct2/show/study/NCT03225144. Retrieved on July 2021).

Wolf–Hirschhorn syndrome (WHS) is a genetic disorder that affects sporadically anywhere in the body. It is characterized by facial appearance, growth and developmental retardation, intellectual impairment, muscle tone weakness, and seizures.

The clinical trial aims to study the pattern of early neurodegenerative changes in WHS. Preliminary evidence supports the feasibility of this approach and its potential to generate invaluable information about neurodevelopmental and neurodegenerative models within WFS (ClinicalTrials.gov Identifier: NCT02455414, https://clinicaltrials.gov/ct2/show/results/NCT02455414. Retrieved on July 2021).

3.6 Perspectives

Neurodegenerative diseases are those that are characterized by progressive loss of functional neurons terminating in dysfunctions and anatomical alterations associated with the deposition of proteins and neurochemical alterations. However, recent research reports revealed that the neurotransmission mechanisms might be more complex. Therefore, their characterizations might help the researchers to understand the pathogenesis of neurodegeneration in a better manner and design newer pharmacological strategies for the management of neurodegenerative disorders. In addition, the adaptation of genetic tests and calculation of risk scores of diseases with a high prevalence in a healthy population in order to effectively implement essential prevention strategies or to extend early care by initiating drugs administration to those patients devoid of symptoms but are likely to develop the disease due to genetic predilection could be followed.

Conflict of Interest The authors have no conflicting interests.

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