

Neuroimaging diagnosis in neurodegenerative diseases

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Abstract

Dementia affects about 8% of people age 65 years and older. Identification of dementia is particularly difficult in its early phases when family members and physicians often incorrectly attribute the patient's symptoms to normal aging. The most frequently occurring ailments that are connected with neurodegeneration are: Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis. A variety of powerful techniques that have allowed visualization of organ structure and function with exact detail have been introduced in the last twenty-five years. One such neuroimaging technique is positron emission tomography (PET), which measures in detail the functioning of distinct areas of the human brain and as a result plays a critical role in clinical and research applications. Radiotracer-based functional imaging provides a sensitive means of recognizing and characterizing the regional changes in brain metabolism and receptor binding associated with cognitive disorders.

The next functional imaging technique widely used in the diagnosis of cognitive disorders is single photon emission computed tomography (SPECT).

New radiotracers are being developed and promise to expand further the list of indications for PET. Prospects for developing new tracers for imaging other organ diseases also appear to be very promising.

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In this review, we present current opportunities of neuroimaging techniques in the diagnosis and differentiation of neurodegenerative disorders.

Key words: neurodegenerative disease, neuroimaging, central nervous system

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Introduction

Despite the fact that extensive progress in neuroimaging techniques of the brain has been made, there is no specific pattern of pathological changes in any type of dementia. This article is a brief review of the methods used in diagnosing the most frequent central nervous system diseases. We suppose that in the not-too-distant future it will be possible to assess not only the location, intensity, and aetiology of pathological dementive processes but also techniques that will detect the earliest changes in brain structure. Functional neuroimaging, that is positron emission tomography (PET) and single photon emission computed tomography (SPECT), are essential techniques for detecting regional changes in metabolic activity of the brain and blood flow that are closely associated with mild cognitive impairment and dementia.

Parkinson's disease

Parkinson's disease (PD) is a degenerative and progressive disorder of the central nervous system. It has an estimated occurrence of up to 329/100,000 [1]. It belongs to a group of movement disorders. It is characterized by motor (due to progressive degeneration of substantia nigra and other brain structures, which is connected with loss of dopamine-producing neurons) and non-motor symptoms [2]. The most characteristic motor symptoms are: tremor (resting), muscle rigidity, postural instability with problems with coordination, slowness of movements, bradykinesia (difficulty in initiating and stopping), and loss of physical movement (akinesia). The non-motor symptoms are specific for advanced stages of the disease and may include high-level cognitive dysfunction, psychiatric and emotional changes, depression, difficulty in swallowing and speaking, sensory symptoms, and constipation and/or urinary problems. The pathogenesis of Parkinson's disease has still not been explained. Researchers focus on genetic and

environmental factors contributing to this chronic and progressive ailment [3].

An accurate diagnosis of Parkinson's disease is crucial for the counselling and management of patients. Furthermore, proper diagnosis is also vital for conducting pharmacological and epidemiological studies. Frequently, recognition is based on clinical evaluation of symptoms over time and observations of the responses to applied therapies. Recently conducted research has shown that a high rate of misdiagnosis appeared when the diagnosis was founded only on clinical diagnostic criteria. Another method which allows the detection of Parkinson's disease is neuroimaging. Functional imaging techniques give a promising opportunity to find out the pathophysiology, progression, and complications of PD [5]. Various techniques have been used to visualize the extent of neuronal loss, and it can be measured *in vivo* using nuclear medicine tracers that bind selectively to dopamine neurons [2, 6–10].

Neuroimaging

Cranial computed tomography (cranial CT) and magnetic resonance imaging (MRI) brain scans are usually applied. Structural imaging with cranial CT may be applied in PD without complications, which means abnormal brain changes in mild-to-moderate phases of PD. MRI presents a fundamentally greater role in diagnosis of central nervous system degenerative illnesses. MRI is superior to CT for visualisation of many cerebral abnormalities, particularly in the search for periventricular white matter abnormalities, which are frequently related to dementia. MRI has been applied in differentiation of Parkinson's disease and atypical Parkinsonism [6, 11].

The application of imaging technologies such a positron emission tomography (PET) and single photon emission tomography (SPECT) radioligands is beneficial in detecting and characterising potential pathophysiological brain changes. It has been proven that these methods are of great importance in detecting early stages of cognitive impairment. Both of them contribute to the access of a topographic picture of brain function and detect impairment in cognitive domains [12].

Positron emission tomography (PET) presents the highest sensitivity. This method is able to detect femtomolar levels of positron-emitting radioisotopes at a spatial resolution of 3–5 mm and corrects for scatter. Positron emission tomography (PET) allows the examination *in vivo* of changes in regional cerebral blood flow glucose, oxygen, dopa metabolism, and brain receptor binding. Single photon emission tomography (SPECT) in comparison with positron emission tomography (PET) has lower sensitivity and is unable to correct for scatter. However, it is a more widely available method [11].

Imaging is divided into two groups: detecting changes in brain structure (structural imaging), and examining regional changes in brain metabolism and receptor binding associated with disorder. Functional neuroimaging of nigrostriatal dopaminergic pathways is an important method for the evaluation the dopaminergic terminals in the striatum. The function of dopamine terminals may be estimated *in vivo* in three pathways: the activity of terminal dopa decarboxylase (DDC), the availability of presynaptic dopamine transporters (DAT), and vesicle monoamine transporter density in dopamine ter-

minals (VMAT2). The radioligands are applied with both PET and SPECT [2, 11, 13, 14].

DOPA Decarboxylase (DDC)

DDC catalyses decarboxylation of L-DOPA to neurotransmitter dopamine.

The activity of DDC can be measured with 6- ^{18}F -L-dopa PET and it can be used as a means of measurement of neuronal loss. Scanning using this tracer is still considered to be the gold standard method for monitoring the course of PD. The *in vivo* action of ^{18}F -DOPA depends on the conversion to ^{18}F -dopamine by amino acid decarboxylase. Subsequently, ^{18}F -dopamine is taken up and trapped in synaptic vesicles. ^{18}F -DOPA is a marker of the accumulation and metabolism of levodopa. Uptake of this tracer relates to nigrostriatal cell loss and striatal concentrations of dopamine [7–11, 13–17].

Presynaptic dopamine active transporter (DAT)

DAT is an integral membrane protein that clears dopamine after its release in the synaptic cleft, thus terminating the signal of the neurotransmitter.

Radiotracers for measuring binding dopamine transporter are available for both PET and SPECT. Principally they are cocaine and tropane-based derivatives.

PET tracers include: ^{11}C -cocaine, ^{11}C -CFT (carbomethoxy-3beta-[4-fluorophenyl]tropane), ^{18}F -CFT, ^{11}C -RTI-32 (methyl [1R-2-exo-3-exo]-8-methyl-3-[4-methylphenyl]-8-azabicyclo[3.2.1]octane-2-carboxylate), ^{11}C -nomifensine, and ^{11}C -phenylethylamine. These radiotracers bind to dopamine and noradrenaline reuptake sites.

There SPECT tracers are: ^{123}I -beta-CIT (carbomethoxy-3-[4-iodophenyl]tropane), ^{123}I -FP-CIT (ioflupane), ^{123}I -altropane, and $^{99\text{m}}\text{Tc}$ -TRODAT-1. The first gives the highest striatal: cerebellar uptake ratio of these SPECT tracers, but it binds non-selectively to dopamine, noradrenaline, and serotonin transporters. The main disadvantage of ^{123}I -beta-CIT is the fact that scanning has to be deferred until the day after intravenous injection because it reaches equilibrium after 24 hours. Thus, SPECT tracers such as ^{123}I -FP-CIT and ^{123}I -altropane, despite their lower and time-dependent striatal: cerebellar uptake ratios, have become generally accepted and used. In comparison with ^{123}I -beta-CIT, these radiotracers enable a scan to be performed within 2–3 hours after injection [11, 18, 19]. $^{99\text{m}}\text{Tc}$ -TRODAT-1 gives a lower 2:1 striatal: cerebellar uptake ratio than the ^{123}I -based tracers and is less well extracted by the brain; however, it possesses the virtue that it is potentially available in kit form [11]. The first binds non-selectively to dopamine, noradrenaline, and serotonin transporters [18, 19].

Using the D_2 -dopamine receptor binding tracers ^{11}C -raclopride-PET and ^{123}I -iodobenzamide (IBZM)-SPECT for the assessment of D_2 receptor density gives good results to evaluate PD patients [2, 6–11, 13, 15, 20].

Vesicular monoamine transporter (VMAT2)

VMAT2 is an integral membrane protein transporting monoamines — particularly neurotransmitters like dopamine, histamine, serotonin, and noradrenalin—into synaptic vesicles. It can be examined with ^{11}C -dihydrotrabenazine-PET [11, 20].

In Parkinson's disease there is observed not only a loss of dopamine, but also a reduction in serotonin concentration was observed. Serotonin HT_{1A} receptor binding in the midbrain may be measured with ^{11}C -WAY100635-PET. This method permits the measurement of the functional integrity of serotonergic neurons [7, 9, 16].

Glial activation

Microglia are a type of glial cells that form the natural active immune defence in the central nervous system, but are also related to maintaining homeostasis. The highest concentrations of microglia in the brain are observed in the substantia nigra. Activated cells of microglia produce various inflammatory compounds, such as prostaglandins, cytokines, reactive forms of oxygen, and nitrogen. Induced by these factors, oxidative stress may lead to an increase in neurodegeneration in PD. The mitochondria of activated microglia express peripheral benzodiazepine (BDZ) sites, which may be selectively bound by isoquinoline ^{11}C -PK11195-PET — a new potential radiotracer for examining the inflammatory properties of neuroprotective agents in neurodegenerative disorders [2, 11]. The loss of substantia nigra neurons, characteristic of Parkinson's disease, is associated with microglial activation. ^{11}C -PK11195 enables the detection of increased signals in both the nigra and pallidum. The nigral ^{11}C -PK11195 uptake reflects local degeneration, whereas the pallidal signal may result from the excess glutamate release from subthalamic projections, which are a consequence of dopamine deficiency [11].

To quantify the effect of nigrostriatal neuron degeneration [^{18}F] fluorodeoxyglucose-PET (FDG/PET) can be used, a glucose analogue currently used for positron emission tomography imaging, or ethyl cysteine dimer-SPECT (ECD/SPECT) by measurement of regional rates of glucose utilization [14, 22, 23].

Alzheimer's disease

Alzheimer's disease is the most commonly occurring ailment among dementia in the elderly. It is a progressive neurodegenerative disorder, incurable at the current state of medical knowledge. It is characterized by a progressive pattern of cognitive and functional impairment, associated with the loss of neurons in certain parts of the brain. Symptoms of this dementia like memory loss, problems with abstract thinking, planning, flexibility, motor tasks, neuropsychiatric manifestations, or language are connected with the loss of neurons and synapses in the cerebral cortex and certain subcortical regions. In these parts of the brain characteristic pathological structures are observed: amyloid plaques (insoluble deposits of beta-amyloid protein called senile plaques), neurofibrillary tangles, and others, which may be the cause of neuronal death [24–27]. Alzheimer's disease is characterized by hierarchical progress that means that information about the stage of AD is correlated with density and spatial distribution of lesions. [28]

Neuroimaging

Advances in medical technology allow not only improved diagnostic accuracy, but also accelerated treatment discovery. New neuroimaging methods currently being used can measure specific

neurotransmitter systems, amyloid plaque, and tau tangle concentrations. Furthermore, neuronal integrity and connections between neurons might be evaluated by these techniques.

Structural neuroimaging with computerized tomography (CT) and volumetric magnetic resonance imaging (volumetric MRI) may reveal nondiagnostic cerebral atrophy observed in AD. Magnetic resonance imaging provides a sensitive method to study brain morphology, white matter, and vascular pathology. The improved resolution and higher soft tissue contrast offer greater potential for early diagnosis. Using MRI allows the measurement of the hippocampus and cortex-structures in the temporal lobe which are essential for normal memory function. MRI may also play a role in differentiating between Alzheimer's disease and other dementias [18, 19, 29–34].

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is a source of information about concentrations of tissue substrate or metabolite. This technique uses the neuronal marker N-acetylaspartate to diagnose AD and MCI (mild cognitive impairment) and to monitor the metabolite changes to differentiate between patients with MCI and those with AD.

Proton magnetic resonance spectroscopy studies of occipital grey matter (measurement of levels of N-acetylaspartate and myo-inositol) may also be helpful in diagnosis of AD.

PET/SPECT

Neuroimaging techniques in AD have been used for the measurement of regional cerebral blood flow or regional glucose and oxygen metabolism [35]. Neuropathology studies show that patients with AD typically have lesions of the hippocampus, temporal and parietal neocortex, and entorhinal cortex [33, 36, 37]. Functional brain imaging using SPECT to evaluate cerebral perfusion is a laboratory investigation that has been proposed as useful in the diagnosis of dementia [34, 38, 39]. PET and SPECT have the capacity to detect and quantify amyloid deposition *in vivo* when they are used in conjunction with trace amounts of radioligands [40].

Cerebral SPECT is based on brain uptake of lipid-soluble radionuclide- L,L-ethyl cysteinyl dimer or hexamethylpropylene amine oxime containing technetium 99m as a tracer (^{99m}Tc -ECD, ^{99m}Tc -HMPAO). These compounds are sensitive indicators of regional cerebral blood flow and may help in the differentiation and evaluation of the severity of dementia. ^{99m}Tc -HMPAO is taken up in the brain within 2–5 minutes of intravenous injection and distributes according to blood flow. It is widely known that brain blood flow is closely coupled with brain metabolism as determined by glucose and oxygen utilization. Thus, Tc-HMPAO SPECT scans are regarded as a good method of measurement of brain function. Another radiotracer which may be applied for the measurement of regional cerebral blood flow is ^{123}I -IMP-SPECT (N-isopropyl-p- ^{123}I iodoamphetamine) [25, 39, 41–44]. Clinical indications for SPECT are mainly patients with suspected dementia. The main disadvantage of SPECT is the fact that, unlike PET, imaging is not performed in real time. Furthermore, resolution is poor (10–15 mm), and what is more, similarly to CT, there is the need for exposure to radiation.

PET offers a more sensitive measure for detecting neuronal abnormalities prior to neuronal death. According to a multicenter

study, PET identified AD patients with a sensitivity and specificity of 94% and 73%, respectively. It has been used to determine the metabolic uptake of fluorine 18 [¹⁸F]-labelled 2 fluorodeoxyglucose (2-deoxy-2-[¹⁸F]-fluoro-D-glucose- FDG) and blood flow in patients with dementia [18, 25, 29, 31, 37, 45–47].

It is estimated that Calcium ions accumulate in the damaged nerve cell bodies and degenerating axons via a passive flow which is the result of a shortage of adenosine triphosphate (ATP) following ischaemia. ⁵⁷Co (SPECT) and ⁵⁵Co (PET), which are analogues of Ca²⁺, reflect Ca²⁺ influx in ischaemically or neurotoxically damaged cerebral tissue. So that these techniques may be used for estimating focal neurodegenerative changes, endangered brain tissue or dead neurons, reactive gliosis, and inflammatory lesions in various dementias including Alzheimer's disease [48].

Amyloid plaques and tau tangle binding compounds

Amyloid plaques are the most characteristic pathological change in the brain of AD, and their basic components are insoluble deposits of beta-amyloid protein, dystrophic neuritis, inflammatory factors, and cellular material inside and outside the neurons. Amyloid fragments are reliable AD biomarkers because they directly reflect pathophysiological processes in AD [49].

The tau tangles are pathological proteins, located mainly in neuronal axons, which are composed of paired helical filaments (PHF) derived from abnormally hyperphosphorylated microtubule-associated protein tau [24, 42, 50–52].

The degenerative process in AD probably starts 20–30 years before the clinical symptoms of the disease occur. There is a great need for biochemical diagnostic markers (biomarkers) that could assist in the diagnosis of AD in the early stages of the disease. They may also provide objective and reliable measurements of drug safety and disease-modifying treatment efficacy in clinical drug trials in AD.

Diagnostic markers for AD are divided into two groups: state markers and stage markers. State markers reflect the intensity of the disease process. The total amount of tau protein is an example of a state marker. The concentration of tau protein in the cerebrospinal fluid (CSF) probably indicates the intensity of the neuronal damage and degeneration. Stage markers give a measure of how far the degenerative process has proceeded. An example of a stage marker is atrophy of the hippocampus, which is measured by CT or MRI.

The CSF is in direct contact with the extracellular space of the brain, and hence biochemical changes in the brain affect the CSF. Because AD pathology is restricted to the brain, CSF is an obvious source of biomarkers for AD. Biochemical markers for AD should reflect the central pathogenetic processes (the neuronal degeneration, the deposition of amyloid-X peptide (AX) in plaques, and the hyperphosphorylation of tau with subsequent formation of tangles). Possible biomarkers for these pathogenetic processes are the concentrations in the CSF of total tau protein, and phosphorylated tau protein [53–56].

During the last few years there has been exponential growth in the development of radiolabelled peptides for diagnosis and therapy. Peptides can be labelled with a variety of radionuclides intended for specific applications, diagnostic or therapeutic, by using both conventional and novel chelating moieties [57].

The main component of amyloid plaques (insoluble forms of beta-amyloid) may also constitute a target for radiotracers. At present there are studies evaluating the practical application of the beta-amyloid binding compounds: [¹⁸F]-BAY94-9172, trans-4-(N-methyl-amino)-4'-{2-[2-(2-[¹⁸F]fluoro-ethoxy)-ethoxy]-ethoxy}-stilbene, ¹⁸F-labeled IMPY [6-iodo-2-(4'-N,N-dimethyl-amino) phenylimidazo [1,2- α]pyridine], 2-(2-[2-demethylaminothiazol-5-yl]ethenyl)-6-(2-[Fluoro]ethoxy)benzoxazole (BF-227), [¹¹C]labelled Pittsburgh compound B (2-[4'-(methylamino)phenyl]-6-hydrobenzothiazole, PIB), [¹²⁵I] IBOX (2-(40-dimethylaminophenyl)-6-iodobenzoxazole) and ¹⁸F-DDNP (2-(1-(6-[(2-[¹⁸F](fluoroethyl) (methyl)amino]-2-naphthyl)ethylidene)malononitrile) as radiopharmaceuticals for PET-imaging of β -amyloid plaques and tau tangles (¹⁸F-DDNP). [¹⁸F]-BAY94-9172, an amyloid- β ligand, has been used with PET to distinguish patients with AD from those with frontotemporal dementia and healthy controls. Extensive PET studies using [¹¹C]PIB, a derivative of thioflavin-T amyloid dye that binds to β -amyloid plaques but not tangles, show significantly greater cortical retention in patients with AD compared to controls. ¹⁸F-DDNP – PET scanning differentiates patients with AD from those with MCI and cognitively intact controls, and initial longitudinal studies show that ¹⁸F-DDNP binding values increase as cognitive symptoms progress [25, 27, 31, 34, 47, 52, 58–60].

Huntington's disease

Huntington's disease, also known as Huntington's chorea, is an autosomal, dominantly inherited, neurodegenerative disorder [61]. HD is characterized by a triad of motor, cognitive, and emotional abnormalities [62]. Its symptoms include dystonia (involuntary limb movement), incoordination, cognitive decline, and behavioral disturbances. It is typical for the first symptoms to appear in middle age, when patients usually have offspring and therefore have already (with different probabilities) passed the genetic malfunction onto the next generation.

The diagnosis of HD is not difficult in a patient with a known family history, typical choreiform movements and cognitive dysfunction. The diagnosis may be more difficult in patients with uncharacteristic presentations or a lack of family history [62, 63].

Computed tomography scans (CT) and magnetic resonance imaging (MRI) usually do not show any structural changes of the brain in the early course of the disease; however, atrophy of the caudate and frontal cortex can be seen with the help of CT and MRI in the later stages of HD [64, 65].

Functional imaging using techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have proven to be important tools when determining cerebral blood flow (both its decrease and increase) and local brain metabolism.

PET uses positron emitting radionuclides which have short half-lives such as ¹¹C (half-life — 20 min.), ¹⁵O (2 min.), and ¹⁷F (110 min.). Due to the fact that radionuclides used for this method emit pairs of positrons going in opposite directions, PET is more accurate than SPECT and can also be used as a quantitative method [61]. Routine magnetic resonance imaging (MRI) and computed tomography (CT) can detect different cerebral

changes as a direct result of Huntington's disease; however, they are unable to help diagnose the disorder in its early stages. PET can provide information allowing the diagnosis of Huntington's disease from as early as 9 to 11 years before the first symptoms appear [66, 67].

SPECT uses radionuclides, the half-lives of which are longer, i.e. ^{99}Tc (6 h) or ^{123}I (13 h). Due to this fact there is no need for the presence of a cyclotron; if such radiopharmaceuticals are available, SPECT is also a cheaper method than PET and is therefore more widely used.

Cerebral blood flow and glucose metabolism

Regional cerebral blood flow (rCBF) and brain glucose metabolism can be determined with the help of ^{18}F -deoxyglucose — FDG PET. Their levels reflect the activity of groups of neurons in certain areas of the brain. Patients with early HD have reduced striatal glucose metabolism — hypometabolism in caudate is responsible for bradykinesia and dementia, putamen hypometabolism connects with chorea and eye-movement abnormalities. Dystonia is caused by thalamic hypometabolism [61, 68, 69]. Additionally, a significant reduction of glucose metabolism in the striatum has been reported in relatives at risk of HD [67].

Dopamine receptors

One of the first structural changes in the brain due to the HD is the loss of medium spiny neurons from the striatum. These neurons express dopamine receptors, D1 and D2, on their surface. With the help of radiolabelled dopamine antagonists, like [^{11}C]Raclopride, it is possible to observe the binding potential (BP) of dopamine receptors and therefore assess the damage that the disease has already caused. Andrews et al. believe that this method surpasses local metabolism evaluation, providing a more direct measure of disease progression [61].

Opioid receptors

Opioid receptors are a group of G-protein coupled receptors with opioids as ligands. PET studies which involved the usage of [^{11}C]diprenorphine as a tracer showed severe loss of opioid receptor binding in structures such as caudate, putamen, globus pallidus, midbrain, cingulate, and medial temporal cortex. However, these studies also revealed increased opioid receptor binding in the thalamus and prefrontal areas in patients with early HD. This may prove HD to be not only a basal ganglia disorder. It is worth mentioning that the loss of opioid receptors in the striatum was not as severe as the loss of dopamine receptors at similar stages of the disease [61].

Benzodiazepine receptors

Benzodiazepines (BDZ) bind to certain sites on the GABA receptor complex, causing increased GABA affinity towards its receptors. Use of [^{11}C]flumazenil, a radiolabelled GABA_A antagonist, showed reduced benzodiazepine binding in caudate, and normal benzodiazepine binding in putamen in HD patients with decreased glucose metabolism in both these neurological structures. The PET signal regarding normal putamen binding is most likely to be a result of increased in globus pallidus and decreased BDZ binding in putamen [61].

Microglial activation

The presence and the BP of active microglia can be determined with the help of ^{11}C -(R)-PK11195 as a tracer. The accumulation of active microglia can be seen in the striatum, globus pallidus, and frontal cortex. It corresponds very well with the neuronal loss [70].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), known in the UK as motor neuron disease (MND), is, along with Alzheimer's disease and Parkinson's disease, one of the major neurodegenerative disorders, manifesting itself by a progressive deterioration of the corticospinal tract, brainstem, and anterior horn cells of the spinal cord [71, 72]. Motor neuron disease may manifest with pure upper motor neuron (UMN) degeneration as seen in primary lateral sclerosis (PLS), pure spinal lower motor neurons (LMNs) degeneration as seen in progressive muscular atrophy (PMA), pure bulbar LMN degeneration as seen in progressive bulbar palsy (PBP), or a combination of all the three as seen in the most frequently occurring form of ALS [73]. The symptoms are progressive muscle atrophy, fasciculation (muscle twitching), spasticity, and hyporeflexia. ALS is a disease with poor prognosis and there is no radical cure or treatment; the clinical syndrome usually evolves to death within 3–5 years [74, 75].

Magnetic resonance imaging

Structural magnetic resonance imaging (MRI) of ALS patients may show signal changes in the corticospinal tract, but these have been reported in the minority of ALS patients. Cortical atrophy emerges late in the disease and is hard to quantify. There have been CT studies reporting mild to moderate cortical atrophy in more than 60% of ALS individuals, but these have not been confirmed by other research centres. Functional magnetic resonance imaging (fMRI) is able to capture focal neuronal activation due to the increase in regional blood flow and increased regional oxygen extraction. However, the diagnostic value of fMRI — lack of sensitivity and specificity or no clear associations between MRI abnormalities in the corticospinal tract and disease stages — is, at present, questionable and should be addressed in future studies [73, 76].

Cerebral blood flow and glucose metabolism

SPECT imaging performed to evaluate brain perfusion with the help of $^{99\text{m}}\text{Tc}$ -ethyl cysteinyl dimer ($^{99\text{m}}\text{Tc}$ -ECD) shows a widespread decrease in regional central blood flow (rCBF) in the frontal as well as the parietal cortex and the cortex around the bilateral central sulcus [77, 78]. PET studies using ^{18}F -deoxy-D-glucose (FDG) have shown disturbed rCBF as well as disturbed glucose metabolism, especially in the sensorimotor cortex and the basal ganglia [76, 78].

Kalra et al., however, state that these techniques are unsuitable for patients due to their variability and sensitivity [78].

Glial activation

The ligand PK11195 (1-[2-chlorophenyl]-N-methyl-N-[1-methyl-propyl]-3-isoquinoline carboxamide) specifically binds to the peripheral benzodiazepine binding site or the PBBS. PBBS

are expressed on the mitochondria of the microglia. Their increased population is observed in different neurodegenerative disorders, including ALS. Radiolabelled PET ligand [^{11}C](R)-PK11195 is used to measure microglial activation. As a result of PET imaging a significant increase in ligand binding can be observed in the region of the motor cortex, pons, frontal lobe, and thalamus [79]. Unfortunately, this PET examination provides data of a more widespread microglial activation compared to imaging, with the help of PK11195, other neurodegenerative disorders.

Postsynaptic dopamine D_2 receptors

Another method used to help diagnose ALS would be the measurement of postsynaptic dopamine D_2 receptor binding abilities. SPECT studies using ^{123}I -benzamide (^{123}I -IBZM), a specifically binding substance with D_2 receptors, showed a significant decrease of postsynaptic striatal D_2 receptor binding when compared to results for control subjects [76, 80].

Benzodiazepine receptors

Similar to studies regarding Huntington's disease, several positron emission tomography (PET) studies have shown significantly decreased ^{11}C -flumazenil (a radiolabelled antagonist of benzodiazepine receptor) binding in the primary sensory, premotor, prefrontal, thalamic, and parietal regions [72, 81].

Amyotrophic lateral sclerosis (ALS) with cognitive impairment

Although the classical neuropathological description of ALS focuses on the degeneration of selective motor neuron pathways, therefore regarding ALS as a motor neuron disease, more than one-third of described cases involve cognitive impairment. Amyotrophic lateral sclerosis with cognitive impairment (ALSci) also includes slight frontal and temporal lobe dysfunctions, which are responsible for difficulties in speaking, word finding, abstract, thinking, etc.

Cerebral blood flow and glucose metabolism

The recognition of ALSci can be carried out with the help of both static and dynamic neuroimaging. The latter include techniques such as PET and SPECT. Both ^{123}I -N-isopropyl-p-io-damphetamine (^{123}I -IMP) and $^{99\text{m}}\text{Tc}$ -hexamethyl propylene amine oxime ($^{99\text{m}}\text{Tc}$ -D,L- HMPAO) proved to be sensitive markers when determining frontotemporal dysfunction in SPECT studies. Both radiopharmaceuticals will show reduced frontal and temporal cortex blood flow, whereas FDG-PET studies are used to observe decreased glucose metabolism in frontal and temporal lobes [82].

Multiple sclerosis

Multiple sclerosis (MS) is a chronic neurological disorder characterised by demyelination of neurons in the central nervous system, which results in the formation of scars better known as plaques or lesions [83]. Although the cause of MS is unknown, there is evidence suggesting an autoimmune mechanism which, some sources say, may be triggered by a viral infection. The condition is progressive yet very unpredictable and varies significantly

between cases. MS may take several forms, with new symptoms occurring during attacks (relapsing form) or accumulating over time (progressive form). The usual symptoms are depression, fatigue, anxiety, personality change, tremor, unilateral loss of vision, pain, bladder problems, constipation, impaired hearing, etc. Around 50% of cases involve cognitive impairment.

MS causes inflammation, demyelination, and as a result degeneration. The blood-brain barrier loses its integrity and allows lymphocytes to migrate to CNS. The lymphocytes recognise myelin as foreign body and so the inflammation process, targeted at the myelin sheath, begins. Lesions appearing in the course of MS are dynamic and they progress in time, as can be seen on MRI scans regarding different stages of the disease. Brain atrophy widely occurs and affects all brain structures, not only the white matter but the grey matter as well. However, brain atrophy may not be visible on MRI scans in the early stages of MS. This is simply due to the fact that all inflamed tissue tends to swell up; therefore, even though the patient has suffered neuronal loss there may not be any abnormalities on the MRI scans [84].

Cerebral blood flow and glucose metabolism

PET imaging using ^{18}F FDG as an agent shows decreased regional and global cerebral blood flow as well as decreased cerebral metabolic rate of glucose (CMRglc). Observed hypometabolism is widespread, affecting the cortical and deep central grey matter, supratentorial white matter, and infratentorial structures. However, the biggest decreases appear in the superior mesial frontal cortex, superior dorsolateral frontal cortex, mesial occipital cortex, lateral occipital cortex, deep inferior parietal white matter, and pons [85, 86]. PET imaging provides more important information regarding pathological processes than MRI.

Acute or chronic?

Differentiation between the acute and chronic phases of multiple sclerosis may prove problematic. However, performing SPECT with the help of $\text{Tc-}^{99\text{m}}$ -MIBI as a radiopharmaceutical shows multiple accumulation points in patients with the acute form whereas in patients with chronic MS no focal points are visible [87].

Glial activation

Very similar to the neuroimaging techniques assessing microglial activation in ALS, [^{11}C](R)-PK11195 is used to determine the binding potential of peripheral benzodiazepine binding sites (PBBS), and therefore the amount and location of microglia. Microglial activation corresponds to lesion locations and is especially high at the lesion's peripheral regions (active inflammatory process) [84, 85].

Spinal muscle atrophy

Spinal muscle atrophy (SMA) is a fatal, hereditary autosomal recessive disease which affects neuronal cells in the anterior horns of the spinal cord. It manifests clinically with symmetrical limb and trunk weakness affecting the proximal more than the distal trunk muscles and the lower more than the upper limbs [88, 89].

The diagnosis of SMA is primarily based on the clinical features and can also be supported by a positive family history.

SPECT imaging with the help of ^{123}I -N-isopropyl-p-iodoamphetamine (^{123}I -IMP) reveals areas of hypoperfusion such as the cerebral cortex, vermis, putamen, and frontal lobe [90]. This method, although not commonly used in SMA diagnosis, has proved sensitive in detecting CNS lesions.

Conclusions

To summarize, imaging using radiopharmaceuticals has been widely used for the investigation of dementing impairments during recent years. Molecular imaging offers a unique insight into the cholinergic, dopaminergic, and serotonergic systems that are inseparable elements of pathological processes that are observed in cognitive disorders. Moreover, these techniques allow the investigation of another structures related to dementing diseases: benzodiazepine receptors, opioid receptors, and glutamatergic receptors. The molecular imaging not only permits the observation of the pathophysiology and mechanisms of dementing disorders but also helps to evaluate the effects of treatment with drugs and may promote future drug developments. The continuing study of new techniques for imaging the central nervous system is expected to produce significant advances in our understanding of the changes in brain structure and function that are associated with neurodegenerative disorders.

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