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The Rising Importance of Proton Magnetic Resonance Spectroscopy in the Diagnosis of Selected Neurodegenerative Diseases of the Brain

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Abstract:

Introduction: Neurodegenerative diseases pose a significant diagnostic challenge due to the increasing elderly population and the rising prevalence of these conditions.

State of Knowledge: Differential diagnosis among these diseases is particularly challenging; thus, numerous clinical trials have been conducted to identify markers that could facilitate accurate disease diagnosis. Among various diagnostic approaches, imaging techniques play a crucial role, especially magnetic resonance imaging (MRI), which includes advanced modalities such as proton magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS offers a non-invasive assessment of neurometabolite profiles, providing critical information that aids in precise diagnosis.

Conclusions: With ongoing clinical trials, the importance of ^{1}H-MRS in diagnosing neurodegenerative diseases continues to grow. This paper reviews the results of recent and relevant clinical trials examining changes in ^{1}H-MRS in the most prevalent neurodegenerative diseases.

Key words: proton magnetic resonance spectroscopy, ^{1}H-MRS, metabolites, neurodegenerative diseases,

1. Introduction

Owing to the persistent phenomenon of societal aging, a progressive increase in the demographic of individuals exceeding 60 years of age has been noted. As of 2005, Poland recorded a population of 5.9 million in this age bracket, with projections indicating an escalation to 9 million by the year 2030 [1]. Concomitant with the rise in the elderly populace is the paramount importance of diagnosing neurodegenerative and dementia-related pathologies, which predominantly afflict this age group [2]. In the realm of neurodegenerative disease diagnostics, considerable emphasis is placed on imaging techniques, such as computed tomography and magnetic resonance imaging. Histopathological examinations also hold critical significance in certain cases for establishing a definitive and reliable diagnosis [3].

Proton magnetic resonance spectroscopy (^{1}H-MRS) is increasingly gaining importance in the diagnostics of neurodegenerative diseases of the central nervous system. ^{1}H-MRS provides information about how the concentration and spatial distribution of metabolites in the analyzed tissue changes. It is a non-invasive method, thereby eliminating the risk of life-threatening and health-compromising complications that can occur during the collection of a biopsy for histopathological examination [3, 4].

2. Classification of Neurodegenerative Diseases

Neurodegenerative diseases are a group of incurable diseases that result in the weakening of the body, gradual degeneration, and/or death of nerve cells in the central nervous system. The development of these diseases is characterized by problems with movement (ataxia) or reduced mental capacity (dementia). The process leading to the symptoms of a neurodegenerative disease begins much earlier and is asymptomatic for a long period (sometimes lasting many years). The initial symptoms manifest when a considerable number of neurons are damaged or a specific region of the central nervous system is affected. The susceptibility of brain structures to pathological factors varies depending on the developing disease syndrome. Currently, neurodegenerative diseases, including the most prevalent forms of Alzheimer's and Parkinson's diseases, represent one of the most significant health challenges facing humanity. The observed increase in the incidence of such diseases appears to be largely attributed to the general aging of the human population. It is estimated that approximately 36 million people worldwide suffer from Alzheimer's disease and other types of dementia, and approximately 7.3 million people in Europe (EC data from 2013). In Poland,

the number of these patients is approximately 350,000. Specialists emphasize that these numbers, among other things, may increase threefold by 2050 due to the aging of the population [5, 6]. The classification of neurodegenerative diseases can be distinguished by comparing their main clinical features and dividing them into disorders related to motor function or related to memory and leading to dementia [7]:

- Related to memory and causing dementia:

- Alzheimer's disease (AD)

- Dementia with Lewy bodies (DLB)

- Frontotemporal dementia (FTD)

- Posterior cortical atrophy (PCA)

- Corticobasal degeneration (CBD)

- Related to motor function:

- Huntington's disease (HD) and other choreas

- Parkinson’s disease (PD)

- Amyotrophic lateral sclerosis (ALS)

- Ataxia–telangiectasia (AT), Friedreich's ataxia (FRDA), Spinocerebellar ataxia (SCA)

Pathophysiological mechanisms in neurodegenerative disorders differ between selected diseases, but many of them are characterized by abnormalities in protein deposition and folding, leading to the formation of aggregates. These pathologies can be divided according to the type of protein involved in the disease process. Among the most common proteins involved in the neurodegenerative process are beta-amyloid, prion protein, tau, alpha-synuclein, and the 43 kDa TAR-DNA binding protein [8].

2.1. Alzheimer’s Disease

Alzheimer's Disease (AD) is a primary neurodegenerative disorder. It is the most prevalent cause of dementia in the elderly, as reported by numerous sources [9,10]. With the

aging of societies globally, the incidence of AD diagnoses is expected to rise steadily. The World Alzheimer Report of 2016 indicated that approximately 46.8 million individuals were afflicted by AD worldwide. Projections suggest that the incidence rate of AD will double every 20 years, leading to an estimated AD population of 74.7 million in 2030 and 131.5 million by 2050 [11].

The condition results in a spectrum of cognitive and behavioral impairments, including disturbances in memory, orientation, concentration, and mood. Additionally, affected individuals may experience sleep disturbances, delusions, hallucinations, wandering behavior, and even an inability to recognize one's own reflection [1]. The precise etiology of the disease remains to be fully elucidated.

AD is characterized as an amyloidosis, a condition marked by the aberrant accumulation of amyloid protein within the brain tissue. Dysfunctional metabolism of the amyloid precursor protein by secretase enzymes results in the formation of insoluble β-amyloid forms. These forms initially deposit intracellularly as plaques and subsequently accumulate extracellularly. Extracellular deposits of β-amyloid (Aβ) are particularly noted in regions of the brain associated with memory and cognitive function. Moreover, Aβ aggregates can also gather in the walls of small cerebral vessels within the cortical layer [1]. The existence of insoluble β-amyloid interferes with the metabolism of tau protein, which binds to microtubules. This interference leads to tau protein hyperphosphorylation, augmenting protein aggregation, diminishing its microtubular affinity, and thus impacting neuronal plasticity [12]. Structural and functional aberrations of tau compromise axonal transport. The deposition of hyperphosphorylated tau results in neurofibrillary tangles, consequent neuronal weakening, and ultimately cell death. The neurodegenerative process reduces neurotransmitter levels, including acetylcholine. It is important to note that Aβ and tau protein accumulations are not the sole mechanisms implicated in AD pathology [13].

2.2. Parkinson’s Disease

Parkinson's Disease (PD) ranks as the second most prevalent neurodegenerative disorder, afflicting approximately 2-3% of individuals aged 65 years and older. In Europe, morbidity and incidence rates for PD are estimated to be around 108-257 per 100,000 and 11-19 per 100,000 per annum, respectively [14].

The etiopathogenesis of the disease remains incompletely elucidated. Recent research indicates the participation of pathways and molecular mechanisms in PD progression,

including α-synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, and axonal transport [15]. The neuropathological hallmarks of PD are intracellular aggregates of α-synuclein and the degeneration of neurons in the substantia nigra. Neurons afflicted with PD exhibit Lewy bodies, which are inclusions composed of misfolded α-synuclein protein. The accumulation of these protein deposits within nerve cells precipitates neuronal damage and ultimately cell death. The neurodegenerative process affecting the grey matter leads to a reduction in dopamine levels within the striatum [1], manifesting clinically as motor symptoms including bradykinesia, resting tremor, muscular rigidity, and impaired postural reflexes—symptoms characteristic of Parkinsonian syndrome. PD is also linked to a plethora of non-motor symptoms; the most prevalent include excessive salivation, dysphagia, gastrointestinal issues such as constipation or delayed gastric emptying, and additionally, orthostatic hypotension, sexual dysfunction, and weight loss [16].

2.3. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is an age-related neurodegenerative disease belonging to the synucleinopathy group. DLB is also a common neurodegenerative dementia in people over 65 years of age [17]. The disease has been observed to affect men more often than women. It is caused by the formation of eosinophilic inclusions in the cytoplasm of nerve cells, called Lewy bodies (LBs), which are composed mainly of incorrectly folded α-synuclein. Other proteins that make up the Lewy body include ubiquitin, neurofilament proteins, and alpha-B crystallin. Tau proteins may also be present. LBs accumulate in the central and peripheral nervous systems, leading to the death of neurons and the subsequent manifestation of clinical diseases. LBs typically occur in the neocortex and limbic system. The genetic basis of the disease has not yet been fully investigated. To date, several genetic mutations have been identified that are associated with dementia with LBs. The disease may occur when mutations are present in the SNCA gene, which encodes alpha-synuclein, and the SNCB gene, which encodes beta-synuclein. Mutations in the genes encoding glucocerebrosidase A, LRRK2, apolipoprotein E (APOE), and microtubule-associated protein tau have also been associated with the disease [18]. The clinical picture of this disease is characterized by a triad of symptoms, namely cognitive impairment, neuropsychiatric symptoms, and extrapyramidal signs. The initial symptoms of DLB frequently manifest as visual hallucinations, episodes of disorientation during the day and sleep disturbances [19]. Due to its clinical similarity to other forms of dementia, such as AD and dementia in the

course of Parkinson's disease, dementia with Lewy bodies (DLB) poses a diagnostic challenge and is sometimes misdiagnosed. To avoid misdiagnosis, it is essential to monitor for the appearance of symptoms of Parkinson's syndrome and dementia. If the two conditions occur together within the first year of the disease, DLB is diagnosed. If dementia occurs later than one year after the onset of Parkinson's symptoms, Parkinson's disease dementia is diagnosed. Ultimately, DLB can only be diagnosed after the patient's death, either through a brain autopsy or, in rare cases of familial disease, through genetic testing [20].

2.4. Frontotemporal Dementia

Frontotemporal dementia (FTD) is a general clinical term that encompasses a heterogeneous group of neurodegenerative diseases. These diseases are characterized by progressive deficits in behavior, executive function, or language skills. FTD is the third most common form of dementia in all age groups, after AD and DLB. It is the most prevalent form of early-onset dementia [21], developing most frequently in individuals aged 45 to 65. It accounts for approximately 15 to 20% of dementias that begin before the age of 65. Due to its clinical manifestations, frontotemporal dementia is divided into two main groups. The group with dominant behavioral disorders is designated the behavioral or "frontal" variant, while the group with dominant language disorders is designated the linguistic or "temporal" variant, which includes primary progressive aphasia (PPA) and semantic dementia (SD). The molecular basis of FDTs allows for their classification into two groups: tauopathies, in which the deposited protein is tau, and TDP-43 proteinopathies, in which the aggregates consist of TDP-43 protein [22]. It is well established that protein mutations influence the occurrence of the disease. In the case of familial occurrence of FDT, mutations in genes for microtubule-associated protein tau (MAPT), progranulin (GRN), or the expansion of hexanucleotide repeats in the C9ORF72 gene have been identified as influencing the development of the disease [23]. Frontotemporal lobe degeneration is characterised by neuronal loss, gliosis, and microvacuolar changes in the frontal lobes, anterior temporal lobes, anterior cingulate cortex, and insular cortex.

2.5. Huntington's disease (HD)

Huntington's disease (HD), previously designated as Huntington's chorea, is a progressive neurodegenerative disease that typically results in death within 15 to 20 years of

diagnosis [24]. It is a genetic disorder that is inherited in an autosomal dominant manner in approximately 10% of cases, with a de novo mutation being the cause in approximately 90% of cases. The disease typically manifests in the 4th decade of life, importantly HD in patients under the age of 20 is diagnosed as juvenile HD.

HD is the most prevalent monogenic neurological disorder in developed countries [25]. The disease is caused by an excess of CAG trinucleotide repeats in the IT15 gene, which encodes huntingtin, located on the short arm of chromosome 4 at the 4p16.3 locus. The mutation results in the production of a mutant huntingtin protein with a large number of polyglutamine residues (polyQ). The disease becomes fully manifest when the number of CAG repeats is greater than 39. When the number of repeats is 36-39, gene penetrance is incomplete, indicating that not all carriers will develop HD. Mutated huntingtin causes neuronal dysfunction, leading to their death, through a number of mechanisms. The mutated protein forms aggregates that affect numerous cellular processes, including protein homeostasis, transcription and translation, axonal transport, as well as mitochondrial and synaptic functions [25, 26]. Aggregates of mutant huntingtin have a selective effect on medium spiny neurons (MSNs) located in the striatum, leading to damage in their area. Damage is also caused by glutamate-induced excitotoxicity and loss of brain-derived neurotrophic factor (BDNF).

A typical symptom of HD is chorea, which gradually spreads to all muscles, significantly impairing psychomotor functions. Patients also experience dystonia, lack of coordination, cognitive decline, dementia, and behavioral changes [27]. Genetic tests and neuroimaging results demonstrate that the neurodegeneration process in individuals affected by HD may begin many years before the signs and symptoms of the disease manifest [28].

2.6. Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a chronic, inflammatory-demyelinating disease of the central nervous system with an unfavorable course, which also leads to neurodegenerative changes. MS is the most common non-traumatic neurological disease that leads to disability among young adults [29]. The average age of onset is between 20 and 40 years of age. Women are more likely to suffer from the disease; in the European population, the ratio of cases among women to men is approximately 2:1. The familial form accounts for approximately 10-15% of cases [30]. The cause leading to the development of MS itself is not fully understood, but the role of the immunological background and environmental factors is mentioned. Factors that

play a role in the development of MS include: Epstein-Barr virus (EBV) infection, human herpesvirus type 6 (HHV-6) infection, stress, childhood obesity, smoking, and low concentration of vitamin D in blood serum, and UVB rays [31, 32] have been identified as potential risk factors for the development of MS. However, the pathogenesis of this disease is multifactorial and not yet fully understood. These factors include damage to the blood-brain barrier (BBB), which allows T lymphocytes and macrophages to migrate to the CNS and cause the formation of inflammatory-demyelinating foci around the vessels. By activating microglia, pro-inflammatory cytokines are released, which cause oligodendrocyte damage and demyelination. Additionally, axonal destruction and astroglial hypertrophy occur [30, 33]. The dominant mechanism ultimately leading to demyelination and neurodegeneration is a cascade of oxidative damage, mitochondrial damage, and "virtual hypoxia" [34]. In the early stages of the disease, axons are preserved, but as the disease progresses, they become irreversibly damaged. The clinical symptoms of MS include visual and sensory disorders, as well as weakening of the muscle strength of the limbs, difficulty walking, and impaired bladder and intestinal function. Non-specific symptoms such as fatigue, spasticity, depression, euphoria, and sexual dysfunction may occur in 80% of patients [35]. Patients often seek specialist help after experiencing paresthesia, numbness, vision, or speech disorders [30].

3. Proton magnetic resonance spectroscopy

3.1 Basics of ^{1}H-MRS

Proton magnetic resonance spectroscopy (^{1}H-MRS) stands out as a minimally invasive modality capable of yielding extensive information regarding the biochemical composition of specific tissues. It is becoming progressively more important in the diagnosis of neurodegenerative diseases [36, 37].

The ^{1}H-MRS technique employs the phenomenon of chemical shift to distinguish diverse metabolites within the central nervous system based on the surrounding atomic environment of the evaluated hydrogen atom. Multiple resonance lines can be identified in the ^{1}H-MRS spectrum, with their intensity being directly proportional to the number of equivalent hydrogen nuclei present in the analyzed sample [38, 39]. The proton magnetic resonance spectroscopy spectrum may be perturbed by signals emanating from hydrogen atoms in water molecules, the predominant constituent of living organisms. To mitigate water signal interference, the CHESS sequence is frequently employed. This technique employs three

selective radiofrequency pulses followed by gradient pulses, resulting in the dephasing of spins in all spatial directions [39, 40].

An MRS examination usually commences with an initial scan of the entire patient's brain to assist in selecting the suitable location for biochemical analysis. In single-voxel spectroscopy (SVS), the region of the patient's brain that displays a tumor or shows potential metabolic disruption due to disease is identified for study. An important aspect of the process is determining the voxel size, which serves as the focal area in MRS studies. The appropriate dimensions and precise spatial localization are established through a combination of radiofrequency pulses and gradient fields. Within the array of single-voxel spectroscopy techniques, the dual-echo spin-echo sequence PRESS and the stimulated echo sequence STEAM have garnered notable recognition [39, 41, 42]. To generate spectra showcasing particular metabolites, various echo times (TE) are employed [41]. An alternative method is the multi-voxel technique, which entails segmenting a larger cerebral region into smaller voxels and concurrently obtaining MRS spectra from each of these subdivisions. This approach is instrumental in ascertaining the spatial distribution of metabolites being examined, a crucial aspect in the oncological diagnostics of the central nervous system [38, 41].

3.2. Selected metabolites assessed in proton magnetic resonance spectroscopy, their significance and abbreviations used in ^{1}H-MRS

3.2.1. N-acetylaspartate

N-acetylaspartate (NAA) is synthesized within the mitochondria of neuronal cells before being transported to the cytoplasm. It is a component of myelin sheaths and is involved in the synthesis of neuronal proteins. Additionally, this metabolite is present in immature oligodendrocytes and astrocytic progenitor cells. While the exact role of NAA remains elusive, it is consistently utilized as a biomarker for neuronal viability and density [37, 44].

3.2.2. Creatine

Creatine (Cr) acts as a biomarker for energy metabolism in central nervous system (CNS) cells. Clinically, Cr is regarded as a stable metabolite; therefore, it is frequently used in calculating ratios with other metabolites, such as Cho:Cr and NAA:Cr [43]. In cases of CNS tumors, the peak intensity for Cr may be diminished due to the tumor's elevated energy

metabolism [44]. Additionally, it is important to acknowledge that Cr is not exclusive to the CNS, and systemic conditions (notably renal diseases) may alter its concentrations [37].

3.2.3. Choline

Choline (Cho) serves as a metabolic marker of cellular membrane density. Its water-soluble precursors, Cho and phosphocholine, are detectable via proton magnetic resonance spectroscopy [37]. In central nervous system tumors, there is typically an observed increase in the peak intensity corresponding to Cho, attributed to heightened cellularity [38].

3.2.4. Lipids

The detection of lipid (Lip) peaks in proton magnetic resonance spectroscopy can suggest the presence of adipose or connective tissue within the selected voxel, particularly when the voxel is situated near structures typically containing these tissues [39].

3.2.5. Myo-inositol

Myo-inositol (mI) is exclusively found in astrocytes, thus serving as an astrocytic marker [39].

3.2.6. Lactic acid

In normal conditions, the concentration of lactic acid (Lac) within the CNS is typically low and generally not a focal point. However, elevated Lac levels may suggest ischemia or hypoxia in neural tissues or occur in metabolic disorders [39].

Moreover, it is important to highlight that metabolite concentrations may vary with the patient's age. Notably, in children under two years, there is a reversal in the ratios of NAA:Cr and Cho:Cr. With increasing age, NAA concentrations rise, whereas Cho concentrations decline [37, 43].

4. Application of proton magnetic resonance spectroscopy in the diagnosis of selected neurodegenerative diseases.

4.1. Alzheimer's disease

The early diagnosis of AD is crucial. Consequently, numerous scientific studies are currently underway to examine the potential of MRS in the diagnosis of AD. Methods of early diagnosis of the disease, differentiation from other dementias, and imaging of early changes in AD in relation to the brain of a healthy person are being developed. The majority of scientific works focus on the frontal, parietal, and temporal lobes, as well as the hippocampus, and the imaging changes occurring in these structures. These include a decrease in the concentration of the NAA metabolite, the NAA/Cr ratio, and NAA/Cho in [44]. In addition, a notable feature of the MRS image of AD is a reduction in NAA/Cr in correlation with changes in the concentration of the Cho/Cr and mI/Cr metabolite [45, 46].

In a scientific paper that examined the cingulate gyrus and occipital cortex, it was observed that in the early stage of the disease, there is an increased mI/Cr ratio [47]. Subsequently, there is an increase in Cho/Cr and a decrease in NAA/ ratios. An essential factor in making a diagnosis is determining the mI/Cr ratio. If the ratio is greater than 0.70 and the NAA/Cr ratio remains normal, the diagnosis of AD should be considered. Conversely, if a decrease in the NAA/Cr ratio occurs but mI/Cr is normal or low, other types of dementia should be considered [46].

The analysis of the NAA/Cr, Cho/Cr, and NAA/ml ratios in subsequent stages of dementia enabled the determination of their order of occurrence in the brain tissue of an individual with AD. Furthermore, the monitoring of these ratios, particularly NAA/ml in the posterior cingulate cortex, presents potential opportunities for the prediction of whether a patient with mild cognitive impairment may progress to AD [48, 49].

4.2. Parkinson’s disease

The diagnosis of PD is primarily based on the patient's clinical picture. Imaging tests, such as computed tomography or magnetic resonance imaging, only allow us to exclude other causes of the observed neurological deviations [1]. Proton magnetic resonance spectroscopy is becoming increasingly important in the clinical diagnosis of neurodegenerative diseases, including PD. The usefulness of proton MRS in the diagnosis of PD is still being investigated [50]. In proton MRS performed in patients diagnosed with PD, a decrease in the NAA/Cr ratio

in the substantia nigra is observed compared to the control group of patients without diagnosed PD. A correlation between the reduced NAA/Cr ratio in the given location and the severity of the disease has been demonstrated [51]. Decreased levels of NAA and the NAA/Cr ratio were also observed in other locations of the central nervous system. These changes were observed in the lenticular nucleus, temporoparietal cortex, posterior cingulate cortex, and premotor cortex when compared to the control group. However, no correlation was found between the NAA/Cr ratio and the severity or duration of PD in the aforementioned locations [52]. In patients with PD and dominant tremor, reduced values of the NAA/Cr and Cho/Cr index in the thalamus were observed compared to patients with resting essential tremor [53]. One study suggested the usefulness of proton magnetic resonance spectroscopy in monitoring the effectiveness of pharmacological treatment of PD [54]. This study demonstrated a reduction in the concentration of metabolites such as NAA, Cr, and mI in patients who were not taking medications. The administration of levodopa resulted in the restoration of normal Cr and NAA concentrations in patients, thereby suggesting a therapeutic response to the drug [55].

4.3. Dementia with Lewy bodies

This heterogeneous group of diseases presents a challenge for researchers, as the results of studies on changes in individual metabolites are ambiguous. However, monitoring the values of these metabolites is useful in the differentiation of neurodegenerative diseases. In the study by Zhang et al.[56], patients suffering from DLB were found to have higher levels of NAA/Cr in the posterior cingulate gyrus compared to patients suffering from AD. In the study by Kantarcz et al. [57], results indicated that patients diagnosed with DLB had normal NAA/Cr levels, while patients with AD and vascular dementias had lower NAA/Cr levels in the posterior cingulate cortex. However, NAA/Cr levels in the white matter were lower than in the control group. In the study by Graff-Radford et al. [58], patients suffering from DLB and DLB with AD were compared. The study revealed that patients with DLB exhibited lower NAA/Cr levels in the occipital region, yet higher levels than patients with AD in the frontal and posterior cingulate regions. Additionally, DLB and AD patients exhibited elevated Cho/Cr and mI/Cr levels in the posterior cingulate gyrus. Due to the overlap of DLB abnormalities in the occipital lobe, as well as the abnormalities characteristic of AD, it is possible to distinguish dementia caused by DLB, AD, or the overlap of DLB and AD. The results of this study provide a basis for more accurate diagnosis and diagnosis of dementia,

which will facilitate the selection of appropriate therapy and improvement of the patient's quality of life.

4.4. Frontotemporal dementia

Research on FTD is limited. In 1997, Ernst et al. [59] demonstrated that patients diagnosed with frontotemporal dementia exhibited lower NAA values (decrease by 28%), as well as glutamate + glutamine (decrease by 16%), and mI values deviated from the norm (increase by 19%). Additionally, the presence of a lactate peak was observed. A reduction in the concentration of the first two metabolites would indicate damage and loss of nerve cells, while an increase in mI would be associated with an increased number of glial cells [59]. In the study by Kizu et al. [60], the results of six individuals with FTD were compared with those of six individuals with AD and five healthy individuals. A statistically significant decrease in the NAA/Cr ratio was observed in the posterior cingulate cortex (PCC) in patients with FTD and AD. Other studies, such as that by Kantarcz et al. [61] and Mihara et al. [62], also confirmed a decrease in the NAA/Cr ratio and an increase in the mI/Cr ratio in the PCC area. In a more recent study by B. Murley et al. [63], 60 patients with FTD and 38 from the control group participated, levels of nine metabolites were examined in different brain regions. The study results demonstrated that individuals with FTD disorders exhibited reduced concentrations of N-acetyl-aspartate and N-acetyl-aspartate-glutamate (NAA + NAAG) in the prefrontal cortex. Another conclusion of the study was the demonstration that differences in the concentrations of these metabolites correlate with the severity of cognitive and behavioral disorders. The studies did not show any changes in metabolites in the parietal lobe of patients with FTD, and they did not clearly demonstrate changes in the temporal lobe, motor cortex, or anterior cingulate cortex. Changes in the frontal and temporal lobes may suggest that metabolic changes occur in the areas of the brain affected by the disease. Subsequent studies have demonstrated that patients with behavioral variant FTD and progressive supranuclear palsy (PSP) exhibit lower levels of NAAG and NAA compared to controls. Additionally, glutamate deficiency has been observed in PSP in the right superior temporal gyrus. NAA concentrations are also low in the right visual cortex in PSP [63].

4.5. Huntington's disease

The pathophysiological mechanisms underlying Huntington's disease are still not fully elucidated, and the search for potential biomarkers continues. Proton magnetic resonance spectroscopy is becoming increasingly valued for its diagnostic potential in this disorder [64]. In individuals with diagnosed Huntington's disease, notable reductions in gray matter volume and concomitant increases in cerebrospinal fluid volume have been documented within the visual cortex and striatum. Adjustments for these volumetric alterations in the central nervous system were necessary to mitigate their influence on the quantification of metabolites in proton MRS analyses [65]. In a clinical study, a reduction in concentrations of metabolites such as NAA, Cr, Cho, Glu (glutamate), and Glx (glutamate+glutamine) was observed in the caudate nucleus, correlating directly with the nucleus's volumetric decrease. Research results suggest that individuals with Huntington's disease may experience not only volumetric loss of the caudate nucleus but also qualitative alterations. A diminution in NAA levels indicates neuronal integrity compromise, while reduced Cr levels point to compromised cellular energetics [66]. Further, evidence from subsequent clinical research indicates a continued diminishment of NAA and Cr concentrations as Huntington's disease progresses. Additionally, a correlation has been established between the decreased levels of NAA or Cr and both the deterioration of patient health and the exacerbation of disease symptoms [67].

4.6. Multiple Sclerosis

At present, proton magnetic resonance spectroscopy is not the preferred modality for diagnosing multiple sclerosis. Nevertheless, the method remains an area of active research interest, with the potential that new techniques may augment the utility of proton MRS in the diagnosis of multiple sclerosis [68].

In a clinical investigation, metabolite concentrations were compared between healthy subjects and those diagnosed with multiple sclerosis. The findings revealed a substantial reduction in the NAA/Cr ratio in the white matter of patients with multiple sclerosis compared to the control group [69]. This decline in the NAA to Cr ratio among MS patients is attributed to metabolic alterations not confined to focal lesions but present across the white matter [70]. Additionally, an elevated Cho/NAA ratio was noted in MS patients relative to controls, indicating that Cho, a participant in inflammatory and demyelination processes, is more prevalent [69, 71]. Notably, the variations in these markers among multiple sclerosis patients were dependent on the specific brain regions assessed. In the frontal white matter, the

NAA/Cr ratio was found to be 11% lower than in the control group, 23% lower in the parietal white matter, and 12% lower in the parieto-occipital white matter [69]. The frontal lobe is chiefly associated with cognitive functions. The pronounced decrease in the NAA/Cr ratio within the frontal lobe's white matter could be indicative of an intensified inflammatory and demyelination process in that specific region [69]. Such a reduction may account for the cognitive impairments and memory disorders observed in patients with confirmed MS [72].

5. Conclusion

The data presented in this paper demonstrate increasing role of the proton magnetic resonance spectroscopy (^{1}H-MRS) in the diagnostics of neurodegenerative diseases. ^{1}H-MRS facilitates non-invasive monitoring of metabolite concentration alterations within specific regions of interest in the central nervous system. The results of proton magnetic resonance spectroscopy, along with other neuroimaging studies, combined with laboratory tests, patient history, and physical examination – once standardized – may form the basis for the diagnosis of neurodegenerative diseases in the future. Furthermore, ^{1}H-MRS has potential utility as an instrument for monitoring the clinical response to administered therapies.

Authors contribution

Conceptualization: , Katarzyna Szmyt, Maciej Superson; Methodology: Sylwia Samojedny; Validation: Katarzyna Szymańska, Kamil Walczak; Formal analysis: Katarzyna Szmyt, Maciej Superson; Investigation: Julia Krasnoborska, Wiktoria Mika, Klaudia Wilk-Trytko, Maciej Superson, Julia Zarębska; Resources: Sylwia Samojedny; Katarzyna Szmyt; Writing - Original Draft Preparation: Maciej Superson, Katarzyna Szmyt, Klaudia Wilk-Trytko, Julia Zarębska; Writing - Review & Editing: Kamil Walczak, Wiktoria Mika, Julia Krasnoborska, Katarzyna Szymańska.

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Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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