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Review Article

Roles of multimodality imaging in rare neuromuscular and neurodegenerative diseases

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ABSTRACT

Physicians face challenges in diagnosing and managing of neuromuscular and neurodegenerative diseases, such as amyotrophic lateral sclerosis and Huntington's disease, as they are rare, clinically variable, and often misdiagnosed by traditional diagnostic methods. To overcome these challenges, multimodality imaging, combining techniques like magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and ultrasound, has emerged to provide complementary structural, functional, and molecular data. This review discusses the roles of multimodality imaging in diagnosing, monitoring, and managing these rare diseases. Structural changes and neural connectivity are identified by MRI, and metabolic and molecular abnormalities are detected by PET. Real time evaluation of nerve and muscle abnormalities is provided by ultrasound, whereas CT aids in evaluation of respiratory function and skeletal structures. These methods are combined to improve diagnostic accuracy and to provide further understanding of disease mechanisms. Emerging multimodal imaging techniques, such as ultra-high-field MRI and hybrid PET-MRI systems, are being developed to provide greater resolution and efficiency. Multimodality imaging is a critical tool in improving the care of patients with rare neuromuscular and neurodegenerative disorders. However, its widespread use is hindered by high costs, limited access, and the need for standardized protocols and validation. Future directions include the development of imaging biomarkers, integration with other diagnostic methods, and the use of artificial intelligence to analyze complex imaging data.

Keywords: Multimodal imaging, Neuromuscular diseases, Neurodegenerative diseases, Diagnosis

INTRODUCTION

Neuromuscular and neurodegenerative diseases are a diverse group of uncommon disorders that cause progressive degeneration of motor neurons, peripheral nerves, or muscle tissue. Examples include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), Charcot-Marie-Tooth disease (CMT), and Huntington's disease (HD). Diagnosis and treatment of these conditions are challenging due to their low incidence, clinical variability, and complex pathophysiology.[1] Traditional diagnostic methods, such as clinical evaluation, electrophysiology, and histopathology, face limitations in accuracy and tracking progression.[2] Multimodality imaging, however, offers detailed information about structural, functional, and molecular changes in affected tissues, addressing many of these difficulties.[3]

Multimodality imaging combines techniques like magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and ultrasound to address the limits of individual methods. MRI provides detailed images of nervous system structures, while PET identifies metabolic and molecular changes that indicate early pathology.[4] Advanced MRI techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI), assess microstructural integrity and neural connectivity, respectively.[5] Ultrasound is widely used to evaluate muscle morphology and nerve abnormalities in real-time.[6] Using these methods together enhances understanding of diseases, improves early diagnosis, and informs therapy development.[7]

Multimodality imaging in rare neuromuscular and neurodegenerative diseases is still in its infancy, with further research focusing on tailoring the imaging protocol and developing novel biomarkers and validating these findings across a variety of patient populations.[8] In this review, the combined role of multimodality imaging in the diagnosis and management of these diseases is discussed and the aspects, where imaging could be used to transform clinical practice and improve patient outcome, are highlighted. This review summarizes the current evidence, outlines future directions, and highlights the need for concomitant use of advanced imaging techniques as part of the routine care of patients with rare neuromuscular and neurodegenerative diseases.

REVIEW

This narrative review is based on a comprehensive literature search conducted on 31 December 2024 in the Medline and Cochrane databases. Utilizing medical subject headings (MeSH) and relevant keywords, the search aimed to identify pertinent studies on multimodal imaging in patients with rare neuromuscular and neurodegenerative diseases. To ensure thoroughness, a manual search was also performed through Google Scholar, examining the reference lists of identified papers to find additional relevant studies. We focused on articles discussing the roles of multimodal imaging in diagnosis and treatment of rare neuromuscular and neurodegenerative disorders. No restrictions were applied regarding publication date, language, or type of publication, allowing for a broad exploration of existing literature.

DISCUSSION

Multimodality imaging plays a variety of roles in rare neuromuscular and neurodegenerative diseases, including diagnosis, disease monitoring, and treatment assessment. Every imaging modality has special benefits, and when combined, they offer a more thorough insight of disease pathophysiology than when used separately.[9] In this section, we discuss the contributions of several imaging modalities to the management of these conditions, backed by data from recent research, along with new approaches and challenges in this field.

Magnetic resonance imaging

The ability to provide detailed anatomical and functional information makes magnetic resonance imaging (MRI) a cornerstone of imaging in neuromuscular and neurodegenerative diseases. Structural MRI is widely used to assess brain and spinal cord abnormalities in conditions such as ALS and HD.[10,11] In ALS, MRI can detect corticospinal tract degeneration and hyperintensities in the motor cortex, which both correlate with disease severity.[12]

A study by Christidi et al, demonstrated that voxel-based morphometry (VBM) analysis of MRI data revealed significant gray matter atrophy in the motor and extramotor regions of ALS patients, suggesting the global neurodegenerative nature of the disease.[13] Advanced MRI techniques, such as DTI, can evaluate white matter integrity by estimating water diffusion in neural tracts. Muller et al, reported that axonal loss and demyelination in the corticospinal tracts of ALS patients were reflected by DTI measurements, such as reduced fractional anisotropy (FA) and increased mean diffusivity (MD).[14]

In HD, MRI detects progressive atrophy in the caudate nucleus and putamen, which occurs before symptoms appear and serves as a marker of disease progression. A longitudinal study by Tabrizi et al, in the TRACK-HD cohort showed that striatal atrophy rates measured by MRI predicted clinical decline in premanifest and early-stage HD patients.[15]

Functional MRI (fMRI) measures brain activity by tracking blood oxygenation changes. In ALS, it has identified altered connectivity in motor and extra motor networks, indicating neuronal dysfunction beyond the motor system. Mohammadi et al, found reduced connectivity in the default mode network of ALS patients, which correlated with cognitive impairment.[16] In HD,

resting-state fMRI has revealed disruptions in networks associated with cognitive and motor decline. Wolf et al, reported that changes in frontostriatal network connectivity correlated with disease progression.[17]

Magnetic resonance spectroscopy (MRS) measures metabolic changes in the brain, including reduced N-acetylaspartate (NAA) levels, which reflect neuronal loss in ALS. Foerster et al, reported that lower NAA/creatine ratios in the motor cortex, detected by MRS, correlated with disease severity and progression in ALS patients.[18]

Positron emission tomography

Positron emission tomography (PET) imaging provides distinctive molecular and metabolic information complementing structural imaging. In ALS, PET with radiotracers such as (18F) FDG and (11C) PK11195, has demonstrated glucose hypometabolism in the motor cortex and neuroinflammation in the brain and spinal cord. According to Corcia et al, (11C) PK11195 PET imaging detected microglial activation in the motor cortex and corticospinal tracts of ALS patients, which correlated with disease severity.[19] In HD, PET imaging with dopamine receptor ligands has demonstrated striatal dopaminergic dysfunction, which precedes structural atrophy and clinical symptoms.

In a study conducted by Pavese et al, (11C) raclopride PET imaging revealed early dopaminergic dysfunction indicated by decreased dopamine D2 receptor binding in the striatum of premanifest HD gene carriers.[20] PET is also being investigated for the evaluation of proteinopathies, including tau and TDP-43 deposition, associated with the pathogenesis of several neurodegenerative diseases. A review by Villemagne et al, demonstrated that (18F) AV-1451 PET imaging can be a potential biomarker for disease diagnosis and monitoring as it detected tau pathology in the brains of patients with Alzheimer's disease and other tauopathies.[21]

Computed tomography

CT is less frequently used in neuromuscular and neurodegenerative diseases as it has a lower soft tissue contrast than MRI. However, it can be useful in certain situations, such as evaluating bone anomalies in CMT or ALS respiratory function.[22,23] Diaphragmatic atrophy can be identified by CT chest imaging, which can also help guide non-invasive ventilation options. According to a study by Sanli et al, diaphragmatic thinning was detected by CT imaging in ALS patients, and this finding correlated with respiratory impairment.[24]

Furthermore, CT myelography is still a useful diagnostic technique for spinal cord compression in patients for whom MRI is not appropriate. In patients with obstetric brachial plexopathy, spinal cord compression was reliably detected by CT myelography, according to research by Steens and colleagues.[25] By integrating anatomical and metabolic data, the combination of CT with other modalities, including PET (PET-CT), improves its diagnostic potential.[26] A review conducted by Xie et al, demonstrated that PET-CT imaging enhanced the localization of metabolic anomalies in patients with neurodegenerative disorders.[27]

Ultrasound

Muscle and nerve ultrasound is a common, non-invasive, real-time imaging modality for neuromuscular diseases. In CMT, ultrasound aid in differential diagnosis by detection of peripheral nerve hypertrophy and fascicular abnormalities. Shahrizaila et al, demonstrated that increased nerve cross-sectional area (CSA) was detected by ultrasound in patients with CMT and was associated with disease severity.[28]

Muscle ultrasound is useful for assessing muscle echogenicity and thickness, which correlate with disease severity in patients with SMA and Duchenne muscular dystrophy.[29] In research by Pelosi et al, muscle ultrasound detected increased echogenicity and reduced muscle thickness in adult patients with SMA, providing a non-invasive method to monitor disease progression.[30] Ultrasound is also being explored for guiding muscle biopsies and monitoring treatment response. A study by Raithatha et al, demonstrated that ultrasound-guided muscle biopsies improved diagnostic yield in patients with neuromuscular diseases.[31]

Integration of multimodality imaging

Combining different imaging modalities provides a more comprehensive view of disease pathophysiology and improves diagnostic accuracy. Integrating MRI with PET can simultaneously evaluate structural and metabolic alterations in ALS, connecting neurodegeneration and neuroinflammation. According to Van Weehaeghe et al, ALS can be accurately differentiated from mimics using a combination of brain and spine MRI and FDG PET scans.[32]

Similarly, integrating ultrasound and MRI enhances the evaluation of nerve and muscle abnormalities in CMT. Decard and colleagues, declared that these methods together provided complementary data for diagnosing CMT and differentiating it from other neuropathies.[33] Multimodality imaging also facilitates biomarker development.[34] Menke et al, demonstrated that a composite score combining DTI metrics and clinical data predicted ALS progression.[35]

Emerging techniques and future directions

Emerging multimodality imaging approaches, including ultra-high-field MRI and hybrid PET-MRI systems, are being investigated for their roles in management of rare neuromuscular and neurodegenerative diseases. By offering greater spatial resolution and sensitivity, ultra-

high field MRI can detect very subtle structural and functional brain and spinal cord changes which may be missed with MRI at standard field strength.[36] Ultra-high field MRI can detect iron deposition in the brain of Alzheimer's disease patient, representing a potential biomarker for disease progression, as reported by Acosta-Cabronero et al Simultaneous acquisition of metabolic and anatomical data on hybrid PET–MRI systems allows for shortening of scan time and improving co-registration accuracy.[37,38]

Active research is also ongoing to develop novel imaging biomarkers. For example, quantitative susceptibility mapping (QSM) has been employed to quantify iron deposition in the brain implicated in the pathogenesis of neurodegenerative diseases including ALS and HD.[39] Acosta-Cabronero et al, showed that levels of iron in the basal ganglia were increased in HD patients, and that this correlated with disease severity.[37]

Dynamic contrast enhanced MRI (DCE-MRI) can also assess blood brain barrier integrity, disrupted in some neurodegenerative conditions. Montal et al, have shown that DCE-MRI can help understand the pathophysiology of Alzheimer's disease via detection of leakage from the blood-brain barrier in the hippocampi of patients with that disease.[40]

Despite being promising, there are challenges to the widespread adoption of multimodality imaging in rare neuromuscular and neurodegenerative diseases. They include high cost, limited availability, the need to establish standardized protocols, and the lack of large-scale studies to validate imaging biomarkers. Filippi et al, recently described the need of standardized MRI protocols in multiple sclerosis research to achieve reproducibility and comparability of results.[41] Interpretation of imaging data can also be complex, demanding special expertise and further advanced analytical tools. Furthermore, rare diseases are heterogeneous meaning that the development of universal imaging protocols and biomarkers is challenging.

Further research should involve optimization of imaging protocols; development of efficient techniques with low cost; and creation of tools for combined imaging data with other biomarkers including genetic and fluid biomarkers. Jack et al, pointed out that there is a need for combining imaging biomarkers with fluid biomarkers in the diagnosis and monitoring of Alzheimer's disease.[42]

Validation of imaging biomarkers and production of standardized guidelines necessarily requires collaborative effort in and through multicenter studies and data-sharing initiatives. Artificial intelligence and machine learning are promising tools for analyzing complex imaging data and finding the patterns that the human eye might miss. Litjens et al, showed that deep learning algorithms have led to a significant improvement in the accuracy of medical image analysis for a broad range of clinical applications.[43]

CONCLUSION

In rare neuromuscular and neurodegenerative diseases, multimodality imaging has shown to be a key tool by integrating structural, functional and molecular information that surpasses what is available by single modality techniques. The use of advanced MRI, PET, CT and ultrasound techniques have improved diagnostic accuracy and disease monitoring, but implementation is hindered by cost barriers and lack of protocol standardization. Multicentre research, cost effective protocols and integration of artificial intelligence is required for future advancement. Emerging multimodal imaging technologies should be validated via large scale studies before establishing their role in routine clinical care to drive transformation of patient management and outcomes based on other biomarkers.

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