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REVIEW ARTICLE

Muscle MRI in motor neuron diseases: a systematic review

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Abstract

Objective: To summarize applications of muscle magnetic resonance imaging (MRI) in cross-sectional assessment and longitudinal monitoring of motor neuron diseases and evaluate associations with clinical assessment techniques.
Methods: PubMed and Scopus were searched for research published up to May 2021 relating to muscle MRI in motor neuron diseases, according to predefined inclusion and exclusion criteria. Studies were systematically appraised for bias and data were extracted for discussion.
Results: Twenty-eight papers met inclusion criteria. The studies assessed muscle T1- and T2-weighted signal, diffusion, muscle volume, and fat infiltration, employing quantitative, qualitative, and semi-quantitative approaches. Various regions of interest were considered; changes in thigh and calf muscles were most frequently reported. Preliminary evidence of concordance between clinical and radiological findings and utility as an objective longitudinal biomarker is emerging.
Conclusion: Muscle MRI appears a promising objective, versatile, and practical biomarker to assess motor neuron diseases.

Keywords: *MRI, ALS, MND, SMA, MUSCLE*

Introduction

Magnetic resonance imaging (MRI) is an established biomarker for many neuromuscular disorders (1–4). However, the role of muscle MRI in motor neuron disease (MND) research and clinical practice remains unclear, and no literature reviews have focused on this topic to date. MND is clinically heterogenous in terms of anatomy, relative upper and lower motor neuron burden, genetics, pathophysiology, and prognosis. Therefore, objective biomarkers of disease progression are necessary to facilitate clinical trials.

Current biomarkers for MND each have limitations. Biometric markers such as forced vital capacity (5) rely on patient technique and effort, and interpretation may be challenging in patients with bulbar or cognitive dysfunction. Functional rating scales (6) are subject to assessor interpretation and may be influenced by symptomatic treatment. Cerebrospinal fluid and serum biomarkers such as neurofilament (7,8) and TDP-43 (9) probe pathophysiology, but utility in longitudinal assessment remains uncertain (10). Neuroradiological techniques accurately exclude ALS "mimics", but have limited sensitivity at an individual level and correlations with clinical measures are variable (10). Neurophysiological techniques such as motor unit number index (MUNIX) (11) and electrical impedance myography (12) are emerging, but a limited number of muscles can be assessed. Muscle MRI represents an objective, noninvasive and effort-independent tool, and multiple metrics such as muscle volume, fat fraction (FF), and T1/T2 signal characteristics are available to assess pathology.

This review summarises muscle MRI applications in MND (particularly the most common form, amyotrophic lateral sclerosis (ALS)), and other diseases of the motor neuron, namely spinal muscular atrophy (SMA) and spinal and bulbar muscular atrophy (SBMA).

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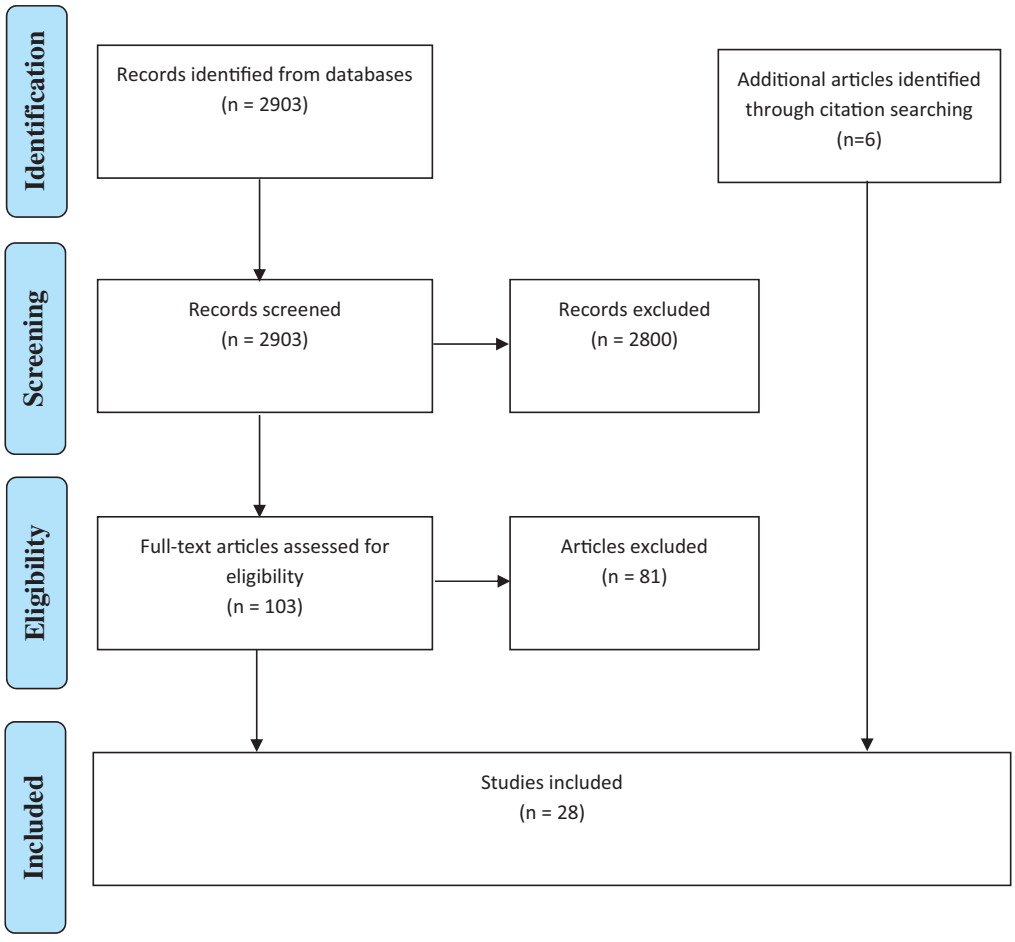

Figure 1. PRISMA flow diagram of the study appraisal process.

Materials and methods

The PubMed and Scopus databases were searched for literature published up to May 2021 with no filters applied. The search strategy was as follows:

- Title: ALS OR MND OR amyotrophic lateral sclerosis OR motor neuron disease OR motor neuron disease OR Lou Gehrig's disease OR spinal muscular atrophy OR spinal bulbar muscular atrophy OR spinal and bulbar muscular atrophy OR SMA OR SBMA OR Kennedy's disease
- AND (title/abstract/keywords): MRI OR magnetic resonance imaging
- AND (title/abstract/keywords): Muscle OR muscular

To ensure no omissions, the search of PubMed was then repeated with the "muscle OR muscular" term replaced with "NOT brain" and "NOT spinal cord".

Grey-research databases and search engines were also searched for relevant material. Clinical trials in progress in the registry "ClinicalTrials.gov" were assessed.

Results were screened by one reviewer (AK). Inclusion criteria were primary research papers reporting applications of muscle MRI in MND/ALS, SMA or SBMA in humans. Animal studies, case reports, non-motor neuron diseases research, non-MRI imaging studies, and non-English language studies were excluded. Google Scholar and reference lists were used to perform forward and backward citation searching on all included studies.

Summary data from identified manuscripts were manually extracted into tables, including disease studied, participant numbers, and clinical, MRI, and neurophysiological data measurement techniques. Results in three categories of interest were reported: differences in muscle MRI findings between patients and controls, correlations between muscle MRI and clinical/neurophysiological assessment techniques, and longitudinal changes in muscle MRI measures.

Studies were appraised for bias using both the National Institute of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies (13), and the Newcastle-Ottawa Scale (NOS) for cohort (14) and cross-sectional (15) studies. The threshold for adequacy of follow-up of cohorts in the NOS was set at 20%. To satisfy case ascertainment criteria, MND diagnoses required application of either El-Escorial (16) or

Table 1. Studies included in a literature review.

Paper	Outline	Participants	Clinical Measurements	MRI Measurements
MND				
Cha and Patten (18)	Investigates tongue morphological and microarchitectural changes in ALS	16 ALS 20 other-disease	Dynamometry (grip strength)	Volume (quantitative) Internal structure (qualitative)
Bryan et al. (19)	Characterises leg muscle abnormalities and correlations with standard neurological clinical tests in ALS patients measured at 0 and 4 months	11 ALS 8 HCs	CMAP, MVIC and NCS.	Volume and T1/T2 relaxation time (quantitative)
Jenkins et al. (24)	Measures muscle volume changes in ALS patients and controls over 12 months	6 ALS 14 HCs	MVIC, dynamometry, MUNE	Volume (quantitative)
Staff et al. (25)	Assesses MRI abnormalities of peripheral nerves and muscle in ALS and MMN	60 ALS 8 MMN	Muscle strength testing scored with neuropathy impairment score	Visual abnormality score (qualitative)
Gerevini et al. (26)	Assesses MRI of the brachial plexus and limb girdle muscles in ALS	23 ALS 12 HCs	MRC, UMN burden score, ALSFRSr	Signal intensity alterations, edema, Stramare score, and Mercuri score (all qualitative)
Jenkins et al. (27)	Assesses clinical, electrophysiological, and whole-body muscle MRI measurements of progression in MND at 0 and 4 months	26 ALS, 3 PMA 22 HCs	ALSFRSr, MRC, Handheld dynamometry, Maximal CMAP, MUNIX	Relative T2 signal (semi-quantitative)
Lee et al. (23)	Assesses differences in tongue microarchitecture between ALS patients and controls.	2 ALS 5 HC	ALSFRSr	Mean diffusivity and fractional anisotropy (quantitative)
Diamanti et al. (28)	Images of hand, paraspinal and lower limb muscles in newly diagnosed ALS patients are compared against clinical findings and controls	10 ALS 9 HC	ALSFRSr and UMN burden score MUAPs MRC	Mercuri scale (qualitative)
Kronlage et al. (21)	Magnetic resonance neurography used to assess fascicular lesions and muscle denervation signs for differentiation between ALS and MMN.	22 ALS 8 MMN 15 HCs	–	Visual muscle denervation score (qualitative)
Diamanti et al. (30)	Evaluates the role of paraspinal muscle MRI as a diagnostic biomarker in ALS	14 ALS 11 HCs 10 inflammatory myopathy 19 lumbar radiculopathy	ALSFRSr	Mercuri scale (qualitative)
Jenkins et al. (31)	Measures longitudinal changes in clinical, electrophysiological and MRI data measured at 0, 4 and 12 months in MND patients	26 ALS, 3 PMA 22 HCs	ALSFRSr, MRC, Handheld dynamometry, CMAP, MUNIX, MUSIX	Relative T2 signal (semiquantitative) Apparent diffusion coefficient (quantitative)
Hensiek et al. (22)	Assesses tongue muscle volume and T1 intensity in a cohort of ALS and PLS patients	175 ALS 10 PLS 104 HCs	ALSFRSr Ventilation status Gastrostomy status	Volume and mean T1 signal intensity (quantitative)
SMA				
Liu et al. (41)	Describes muscle MRI findings of the lower extremity in SMA	17 SMA	–	Visual grading of fat infiltration and atrophy (qualitative)

(*Continued*)

Table 1. (*Continued*).

Paper	Outline	Participants	Clinical Measurements	MRI Measurements
Mercuri et al. (36)	Thigh muscle MRI is performed on SMA patients with a rare phenotype	11 SMA	EMG, muscle biopsy, ECG, FVC, muscle power, functional ability	Mercuri scale (qualitative)
Sproule, Punyanitya, et al. (32)	Compares muscle volume and signal against dual-energy X-ray absorptiometry and clinical measurements in SMA	14 SMA	Dual-energy X-ray absorptiometry, HFMSE, Handheld dynamometry, CMAP, MUNE	Volume (quantitative) Binarised into normal or abnormal signal (qualitative)
Sproule, Montgomery, et al. (33)	Investigates 6-month changes in thigh muscle volume in SMA	11 SMA	HFMSE	Volume (quantitative) Binarised into normal or abnormal signal (qualitative)
Durmus et al. (37)	Describes the pattern of muscle involvement in SMA type IIIb	25 SMA	MRC	Fischer scale (qualitative)
Bonati et al. (35)	four muscle MRI scans were performed over 1 year to assess changes in quantitative MRI measurements	18 SMA 19 HC	Motor function measure score 6MWT	Fat fraction, cross-sectional area, water-T2 signal (all quantitative)
Kollmer et al. (38)	Describes MR neurography of lesions in SMA, compares findings against clinical measurements	31 SMA 31 HCs	ALSFRSr, CMAP, Sensory nerve action potentials and NCS, HFMSE, Revised Upper Limb Module, 6MWTD.	Modified Goutallier classification (qualitative)
Brogna et al., (40)	Describes pattern of muscle involvement in patients with types 2 and 3 SMA	55 SMA	HFMSE	Mercuri scale (qualitative)
Barp et al. (39)	Two year follow up involving muscle MRI of two SMA patients after taking nusinersen	2 SMA	Revised upper limb module and HFMSE	Mercuri scale (qualitative) Tractography and fractional anisotropy (quantitative)
Otto et al. (42)	Describes muscle involvement patterns in the lower limbs of types II and III SMA patients using quantitative MRI	31 SMA 20 HC	HFMSE MRC	Fat fraction, water-T2 signal, mean diffusivity, fractional anisotropy (all quantitative)
Otto et al. (43)	Measures longitudinal changes in quantitative MRI results from the lower limbs of types II and III SMA patients	10 SMA	HFMSE MRC dynamometry	Fat fraction, water-T2 signal, mean diffusivity, fractional anisotropy (all quantitative)
Savini et al. (44)	Muscle fat fraction and T2 signal assessed every 4 months for 21 months in a cohort of SMA IIIa patients on nusinersen	3 SMA 11 HC	Neurological examination, HFMSE, RULM, 6MWT	Fat fraction, water-T2 signal (quantitative)
Souza et al. (34)	Assesses clinical and radiological features of a cohort of SMA IV patients	20 SMA 15 HC 15 other-SMA phenotype controls	HFMSE, ALSFRSr, RULM, SMAFRS, fatigue severity score, 6MWT, time up and go test, MRC, NCS, EMG, MUNIX	Mercuri scale (qualitative)
SBMA				
Hamano et al. (20)	Investigates the pattern of muscle involvement in SBMA	3 SBMA 2 ALS 1 HC	–	Visual assessment of signal intensity and muscle atrophy (qualitative)
Klickovic et al. (29)	Qualitative MRI and clinical measurements compared between ALS and SBMA cohorts	21 SBMA 21 ALS 16 HCs	ALSFRSr SBMAFRS Adult myopathy assessment tool	Mercuri scale (qualitative) Morrow scale (qualitative) Fat fraction & cross-sectional area (quantitative)

(*Continued*)

Table 1. (*Continued*).

Paper	Outline	Participants	Clinical Measurements	MRI Measurements
Dahlqvist et al. (45)	Observational cross-sectional study. MRI used to describe muscle degeneration in SBMA and findings are correlated with clinical measures	40 SBMA 25 HCs	Dynamometry. 6MWTD. SBMAFRS and bulbar rating scale. Swallowing function. BMI. Total body fat with dual-energy X-ray absorptiometry. ECG. FVC. blood biochemistry and sex hormones.	Mercuri scale (qualitative) Fat fraction & cross-sectional area (quantitative)

6MWTD: 6 minute walk test distance; ALSFRSr: ALS functional rating scale revised; BMI: body mass index; CMAP: compound muscle action potential; DTI: diffusion tensor imaging; DWI: diffusion weighted imaging; ECG: electrocardiogram; EMG: electromyography; FVC: forced vital capacity; HC: healthy control; HFMSE: Hammersmith functional motor scale expanded; MMN: multifocal motor neuropathy; MRC: medical research council (muscle strength scale); MUNE: motor unit number estimation; MUNIX: motor unit number index; MUSIX: motor unit size index; MVIC: maximum voluntary isometric contraction; NCS: nerve conduction studies; PLS: primary lateral sclerosis; PMA: primary muscular atrophy; SBMA: spinal bulbar muscular atrophy; SBMAFRS: SBMA functional rating scale; SMAFRS: SMA functional rating scale; TA: tibialis anterior.

Awaji-Shima (17) criteria, and SMA/SBMA diagnoses required genetic confirmation, except in papers published before availability. Criteria relating to multiple assessments of exposure, exposures varying in amount, and non-respondents were not applicable to these observational studies and were omitted.

The terms "qualitative", "quantitative" and "semi-quantitative" MRI assessment techniques were defined as follows: Qualitative methodologies require subjective judgment and produce non-continuous data, for example, graded analog scales (such as the Mercuri scale). Quantitative techniques are objective methodologies producing continuous data, directly reflecting tissue characteristics, for example, T2 relaxometry, diffusion, volumetrics, or fat fraction. Semi-quantitative techniques are objective methodologies producing continuous data that indirectly reflect inherent tissue characteristics, necessitating expression relative to a reference region.

Results

After removal of duplicates, the initial search strategy returned 2903 results (PubMed = 2166, Scopus = 737), of which 2800 were excluded based on screening. Eighty-one further papers were excluded for failure to meet inclusion criteria, and a total of 22 papers were included (see Figure 1). Additionally, six further eligible papers identified through citation searching were included, for a final total of 28 papers. Four relevant ongoing clinical trials were identified but not included in this review as none had published preliminary results (NCT04691011, NCT04262570, NCT04690998, NCT02044029).

Among these 28 articles, there were 14 MND/ALS (18–31), 13 SMA (32–44) and three SBMA (20,29,45) patient groups. There were eight multiple-region (21,24–26,28,29,37,45), 13 lower-limb (19,20,32–36,38,40–44), one paraspinal (30), three bulbar (18,22,23) and three whole-body (27,31,39) studies. These papers are summarized in Tables 1 and 2.

Assessment of bias

The risk of bias tools revealed a generally robust study design. Frequent issues identified were omission of a control group (32,33,36,37,39–41,43), lack of blinding (18–20,23,31,34–36,39–43,45) and inadequate ascertainment of disease status (23,25,40). Only four studies justified the sample size (22,27,31,38). More than 20% cohort attrition was reported in 5/9 longitudinal studies, typical in MND research. Five studies explicitly reported adjustments made for confounding factors (27,32,33,35,42) and none adjusted for disease duration, potentially significant in the context of degenerative diseases. Studies generally performed well on participant recruitment (e.g. selecting representative population samples), evidence of reliable measurement, and outcome reporting. No issues relating to conflicts of interest or funding sources were identified. Overall risk of bias was determined to be low/medium; results are reported in Tables 3–5.

MND

The first application of muscle MRI in MND was in 1989 when tongue morphological changes were investigated in 16 ALS patients and 20 disease controls (18). Abnormalities of size, shape, position, structure, and signal intensity were seen in ALS patients, who had significantly smaller tongues (9.99 mg vs. 13.3 mg, $p < .001$) and

Table 2. MRI acquisition sequences.

Paper	Sequence	Field strength (T)	Slice thickness (mm)	Matrix size	Repetition time (msec)	Echo time (msec)	Plane	Field of view (mm)	Scan time (min:sec)
MND									
Cha and Patten (18)	T1 SE	0.5/1	5–6	256 × 256	50–600	15–35	Sag	–	–
Bryan et al. (19)	T1 & T2 3D vol grad echo	–	1.6	205 × 256	2000	20–160	Cor/ax	450	–
Jenkins et al. (24)	3D T1 FFE	3.0	1	–	25	3.5	Ax/sag	–	–
	T2 TSE	3.0	6	–	2600	100	Cor	–	–
	3D T1 FFE	3.0	1.6	–	11	4.8	Sag	–	–
Gerevini et al. (26)	PD FSE	1.5	3	292 × 224	3500	30		307 × 307	40:00
	T2 FSE	1.5	3	456 × 360	6038	100	Cor	307 × 307	
	3D T2 FSE	1.5	3	252×250×360	2250	230	Sag/cor	250×250×180	
	STIR	1.5	3	376 × 300	4086	60	Cor	307 × 307	
	T1 FSE	1.5	3	384 × 308	543	18	cor	307 × 307	
	3D T1 FFE	1.5	3	356 × 543 × 94	24	4.6	Ax	349 × 349 × 160	
Jenkins et al. (27)	T2 FSE	3	5	–	1107	80	Cor	–	–
Lee et al. (23)	T2 TSE	3	1.2	256 × 256 × 200	3380	107	Sag	–	–
	DWI SSSE EPI	–	4.6	128x128x72	2300	55	Sag	–	–
Diamanti et al. (28)	T1	1.5	10	–	500	15	Ax/sag	–	–
	T1	1.5	10	–	500	8	Ax	–	–
	T1	1.5	3	–	300	10	Ax/cor	–	–
Kronlage et al. (21)	2D T2 TSE	3.0	3.5	512 × 333	8150	54	Ax	160 × 160	–
	3D T2 SPACE	3.0	1	320 × 320	3000	206	Cor/Ax	305 × 305	–
Diamanti et al. (30)	T1 TSE	3.0	10	512 × 512	803	11	Ax	230	–
	T1 TSE	3.0	5	512 × 512	714	12	Cor	400	–
Jenkins et al. (31)	T2 FSE	3.0	5	–	1107	80	Cor	–	20:00
	DWI	3.0	5	–	9412	66	Ax	–	40:00
Hensiek et al. (22)	3D T1 MPRAGE	3.0	1	256x256x192	2500	4.82	Sag	–	
SMA									
Liu et al. (41)	T1 SE	0.5	–	–	600	20	Ax/Cor	–	15:00
Mercuri et al. (36)	T1 SE	1.0	5	256 × 256	500	20	Ax	250-500	–
Sproule et al. (32,33)	T1 FSE	1.5	5	–	–	–	–	–	30:00
Durmus et al. (37)	T1 TSE	1.5	5	384 × 384	561	14	Ax	440 × 400	2:22
	T2 TSE	1.5	3	272z224	4135	120	Ax	340 × 340	
	T1 TSE	1.5	5.5	320 × 320	480	12	Ax	230 × 230	2:06
	T2 TSE	1.5	4	384 × 384	5700	128	Ax	170 × 170	2:13
Bonati et al. (35)	T2 SE	3.0	3	384 × 384	1800	9.1 – 127.4	–	400 × 400	
	3D VIBE	3.0	3	384 × 384	20	2.46, 3.96	–	400 × 400	
	6-echo 3D VIBE	3.0	3	384 × 384	20	1.53 – 8.33	–	400 × 400	
Kollmer et al. (38)	3D T2 IR SPACE	3.0	1	320x320x104	3000	205	Ax	305 × 305	12:17
	2D TSE	3.0	3.5	512 × 512	5860	14-86	Ax	170 × 170	33:40
Brogna et al., 2020	T1 FSE	–	5	–	550	8	Ax	–	20

(*Continued*)

Table 2. (*Continued*).

Paper	Sequence	Field strength (T)	Slice thickness (mm)	Matrix size	Repetition time (msec)	Echo time (msec)	Plane	Field of view (mm)	Scan time (min:sec)
Barp et al. (39)	T1	1.5	10	–	530	9.9	Ax	–	–
	STIR	1.5	10	–	4000	94	Ax	–	–
	MSE	1.5	4	124 × 123	2860	10-100	Ax	160 × 160	–
	DTI	1.5	4	–	7500	71	Ax	250 × 72.5	–
Otto et al. (42),	4-point Dixon	3.0	6	320 × 320	210	2.6/3.4/4.1/4.9	–	480 × 480	1:20
	T2 MSE	3.0	6	–	4598	17 × 7.6	–	–	3:05
	DWI SE EPI	3.0	6	160 × 92	5000	57	–	480 × 276	3.30
Savini et al. (44)	3D 6-point GRE	3.0	5	432 × 396 × 52	35	1.7–9.2	–	–	15
	T2 TSE	3.0	10	–	4100	10.9	–	–	
Souza et al. (34)	T1 SE	1.5	7	360–464 × 512	335	19	Ax	–	–
	STIR	1.5	7	480–576 × 512	3650	52	Ax	–	–
SBMA									
Hamano et al. (20)	T1	1.0–1.5	–	–	333–516	14–10.7	–	–	–
Klickovic et al. (29)	3-point Dixon, T1, STIR	3.0	–	–	–	–	–	–	35:00
Dahlqvist et al. (45)	T1	3.0	6	–	450	21	–	170	–
	T1	3.0	6	–	650	19	–	400–450	–
	2-point Dixon	3.0	3.5	–	3.675/5.59	2.45	–	400–450	–
	T1	3.0	3	–	656	39	–	200	–
	2-point Dixon	3.0	2	–	3.675/5.64	2.45	–	245	–

Cells marked '-'indicate data not provided by the author. Ax: axial; Cor: coronal; DTI: diffusion tensor imaging; GRE: gradient echo; IR: inversion recovery; SE: spin echo; SSSE: single-shot spin-echo; EPI: echo-planar imaging; MPRAGE: magnetization prepared rapid gradient echo; MSE: multi-echo spin-echo; Sag: sagittal; SPACE: sampling perfection with application-optimised contrasts using different flip angle evolution; STIR: short-tau inversion recovery; VIBE: volumetric interpolated breath-hold examination.

Table 3. Assessment of bias using the NHLBI quality assessment tool.

	Cha and Patten (18)	Bryan et al. (19)	Jenkins et al. (24)	Staff et al. (25)	Gerevini et al. (26)	Jenkins et al. (27)	Lee et al. (23)
Research objective clearly stated?	✓	✓	✓	✓	✓	✓	✓
Study population clearly defined?	×	✓	✓	✓	✓	✓	×
Subjects recruited from similar populations with uniform entry criteria?	×	✓	✓	✓	✓	✓	×
Sample size justification, power description, or variance and effect estimates provided?	×	×	×	×	×	✓	×
Were the exposures of interest measured prior to the outcomes being measured?	✓	✓	✓	✓	✓	✓	✓
Sufficient timeframe allowed for association between exposure and outcome?	×	×	✓	×	×	×	×
Were the exposure measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	×	✓	✓	×
Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	×	✓	✓	✓	✓	✓	✓
Were the outcome assessors blinded to the exposure status of participants?	×	×	✓	✓	✓	✓	×
Was loss to follow-up after baseline 20% or less?	–	×	×	–	–	×	–
Were key potential confounding variables measured and adjusted?	×	×	×	×	×	✓	×
NOS score	1/8	3/9	5/9	2/8	6/8	7/9	0/8

	Diamanti et al. (28)	Kronlage et al. (21)	Diamanti et al. (30)	Jenkins et al. (31)	Hensiek et al. (22)	Liu et al. (41)	Mercuri et al. (36)
Research objective clearly stated?	✓	✓	✓	✓	✓	✓	✓
Study population clearly defined?	✓	✓	✓	✓	✓	×	✓
Subjects recruited from similar populations with uniform entry criteria?	✓	✓	✓	✓	✓	×	×
Sample size justification, power description, or variance and effect estimates provided?	×	×	×	✓	✓	×	×
Were the exposures of interest measured prior to the outcomes being measured?	✓	✓	✓	✓	✓	✓	✓
Sufficient timeframe allowed for the association between exposure and outcome?	×	×	×	✓	×	×	×
Were the exposure measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	✓	✓	✓	✓
Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	✓	✓	×	✓
Were the outcome assessors blinded to the exposure status of participants?	✓	✓	✓	×	✓	×	×
Was the loss to follow-up after baseline 20% or less?	–	–	–	×	–	–	–
Were key potential confounding variables measured and adjusted?	×	×	×	×	×	×	×
NOS score	6/8	7/8	6/8	5/9	8/8	2/8	2/8

	Sproule, Punyanitya, et al. (32)	Sproule, Montgomery, et al. (33)	Durmus et al. (37)	Bonati et al. (35)	Kollmer et al. (38)	Brogna et al. (40)	Barp et al. (39)
Research objective clearly stated?	✓	✓	✓	✓	✓	✓	✓
Study population clearly defined?	×	×	✓	✓	✓	✓	✓

(*Continued*)

Table 3. (*Continued*).

	Sproule, Punyanitya, et al. (32)	Sproule, Montgomery, et al. (33)	Durmus et al. (37)	Bonati et al. (35)	Kollmer et al. (38)	Brogna et al. (40)	Barp et al. (39)
Subjects recruited from similar populations with uniform entry criteria?	×	×	×	✓	✓	✓	×
Sample size justification, power description, or variance and effect estimates provided?	×	×	×	×	✓	×	×
Were the exposures of interest measured prior to the outcomes being measured?	✓	✓	✓	✓	✓	✓	✓
Sufficient timeframe allowed for the association between exposure and outcome?	×	×	×	×	×	×	✓
Were the exposure measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	✓	✓	×	✓
Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	✓	✓	✓	✓
Were the outcome assessors blinded to the exposure status of participants?	✓	✓	✓	×	✓	×	×
Was the loss to follow-up after baseline 20% or less?	–	✓	–	✓	–	–	✓
Were key potential confounding variables measured and adjusted?	✓	✓	×	✓	×	×	×
NOS score	4/8	4/9	5/8	7/9	8/8	2/8	4/9

	Otto et al. (42)	Otto et al. (43)	Savini et al. (44)	Souza et al. (34)	Hamano et al. (20)	Klickovic et al. (29)	Dahlqvist et al. (45)
Research objective clearly stated?	✓	✓	✓	✓	×	✓	✓
Study population clearly defined?	✓	✓	×	✓	×	✓	✓
Subjects recruited from similar populations with uniform entry criteria?	✓	✓	×	✓	×	✓	×
Sample size justification, power description, or variance and effect estimates provided?	×	×	×	×	×	×	×
Were the exposures of interest measured prior to the outcomes being measured?	✓	✓	✓	✓	✓	✓	✓
Sufficient timeframe allowed for the association between exposure and outcome?	×	✓	✓	×	×	×	×
Were the exposure measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	✓	✓	✓	✓
Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	✓	✓	✓	✓	×	✓	✓
Were the outcome assessors blinded to the exposure status of participants?	×	×	✓	×	×	✓	×
Was the loss to follow-up after baseline 20% or less?	–	×	✓	–	–	–	–
Were key potential confounding variables measured and adjusted?	✓	×	×	×	×	×	×
NOS score	6/8	3/9	7/9	6/8	2/8	7/8	6/8

Table 4. Assessment of bias in cohort studies using the NOS.

	Bryan et al. (19)	Jenkins et al. (24)	Jenkins et al. (27)	Jenkins et al. (31)	Sproule, Montgomery, et al. (33)	Bonati et al. (35)	Barp et al. (39)	Savini et al. (44)	Otto et al. (43)
Representativeness of the exposed cohort	*	*	*	*		*			
Selection of the non-exposed cohort			*	*					
Ascertainment of exposure	*	*	*	*	*	*	*	*	*
Demonstration that outcome not present at the start of the study	*	*	*	*	*	*	*	*	*
Comparability of cohorts on the basis of design or analysis			**			**		**	
Assessment of outcome		*	*		*			*	
Was follow-up long enough		*		*		*	*	*	*
Adequacy of follow-up of cohorts					*	*	*	*	
Total score	3/9	5/9	7/9	5/9	4/9	7/9	4/9	7/9	3/9

Table 5. assessment of bias in cross-sectional studies using the NOS.

	Cha and Patten (18)	Staff et al. (25)	Gerevini et al. (26)	Lee et al. (23)	Diamanti et al. (28)	Kronlage et al. (21)	Diamanti et al. (30)	Hensiek et al. (22)	Liu et al. (41)	Mercuri et al. (36)
Representativeness of the sample		*	*		*	*	*	*		*
Sample size justification								*		
Ascertainment of exposure	*		**		**	**	**	**	**	*
Comparability of cohorts on the basis of design or analysis			*		*	**	*	**		
Assessment of outcome		*	*		*	*	*	*		
Statistical test			*		*	*	*	*		
Total score	1/8	2/8	6/8	0/8	6/8	7/8	6/8	8/8	2/8	2/8

	Sproule, Punyanitya, et al. (32)	Durmus et al. (37)	Kollmer et al. (38)	Otto et al. (42)	Brogna et al. (40)	Souza et al. (34)	Hamano et al. (20)	Klickovic et al. (29)	Dahlqvist et al. (45)
Representativeness of the sample		*	*	*	*	*		*	*
Sample size justification			*						
Ascertainment of exposure	**	**	**	**		**	**	**	**
Comparability of cohorts on the basis of design or analysis			**	**		**		**	**
Assessment of outcome	*	*	*					*	
Statistical test	*	*	*	*	*	*		*	*
Total score	4/8	5/8	8/8	6/8	2/8	6/8	2/8	7/8	6/8

weaker grip strength (21.8 lb vs. 47.6 lb, $p < .001$) than disease controls.

Nine years later, the first longitudinal muscle MRI study in MND/ALS investigated 11 ALS patients and eight healthy controls, with follow-up at four months (19). Lower-limb muscle volume and quantitative T1 and T2 relaxation time (T1r/T2r) measurements were compared with compound muscle action potential (CMAP), and maximal voluntary isometric contraction (MVIC). Only mean T2r was significantly different between cohorts at baseline (41.4msec vs. 33.4msec, $p = .009$), with no longitudinal radiological changes evident. At baseline, MVIC correlated with T2r ($r = -0.926$, $p = .001$) and tibialis anterior (TA) volume ($r = 0.777$, $p = .005$) but not with T1r.

CMAP and T2r also correlated at baseline (r=–0.903, p = .001) and longitudinally (r=–0.63, p = .037). This study provided a solid foundation for quantitative muscle MRI as a potential biomarker in MND/ALS.

In 2013, a longitudinal pilot study demonstrated the stability of muscle volume in 11 healthy control subjects (<5% variability over 12 months) and found trends toward volume decrements in the thenar eminence (–26.84%, p = .056) and TA (–8.29%, p = .077) in four ALS patients (24). The interpretation was however limited by the small sample size and clinical heterogeneity.

Subsequently, nerve and muscle abnormalities were reported in a 2015 cross-sectional cohort of 60 ALS and 8 multifocal motor neuropathy (MMN) patients who underwent MRI of the brachial or lumbosacral plexus (25). MRI abnormalities were more frequent in ALS patients (57% vs. 33%) but did not correlate with muscle strength. Two years later, multiple MRI parameters were assessed in the limb-girdle muscles of 23 ALS and 12 healthy subjects (26). Alterations in T2-weighted and short-tau inversion recovery (STIR) signal intensities were seen in subscapularis and supra/infraspinatus, with fat infiltration and atrophy evident on T1 in all patients, but not controls.

The first whole-body muscle MRI application in MND was reported in 2018, with further longitudinal follow-up in 2020 (27,31). Whole-body semi-quantitative T2-weighted scans were acquired in 29 MND patients (26 ALS, three progressive muscular atrophy (PMA)), and 22 age/gender-matched healthy controls. At baseline, MND patients demonstrated 18% higher whole-body relative T2 signal vs. controls (p < .01), with per-muscle differences ranging from 0.6% in right trapezius to 71.4% in left TA. Relative T2 changes over 4 months were significant only in bilateral TA (p < .017) and not in the tongue, biceps brachii or paraspinal, with no changes found in controls (27). At 12 months, relative T2 signal increased significantly in several lower-limb muscles (bilateral quadriceps, hamstrings, TA, and gastrocnemius/soleus, and right psoas) and also in right first dorsal interosseous (1DIO). Whole-body diffusion-weighted MRI demonstrated no changes. The researchers reported numerous associations between relative T2 signal and Medical Research Council (MRC) muscle strength scores, dynamometry, MUNIX and CMAP (27). In 2018, another small study investigating diffusion-weighted MRI of the tongue in two ALS and five healthy control subjects found decreased fractional anisotropy (FA), increased mean diffusivity (MD), and fewer connecting muscle fibers in patients compared to controls (23).

In 2019, qualitative muscle MRI findings were assessed in 22 ALS, 8 MMN and 15 healthy participants. ALS patients demonstrated significantly more muscle edema and atrophy than the other cohorts (21). Another 2019 study assessed 68 muscles in ten ALS patients and nine healthy controls (28). Overall, muscle atrophy and fatty infiltration were more common in ALS patients, the latter differing significantly from controls in iliopsoas (p = .046), and anterior, (p = .020) and posterior calf (p = .047) muscles, but not in thoracic paraspinal, gluteus maximus, thigh, or hand muscles. Atrophy and fatty infiltration in dominant hand muscles correlated inversely with the ALS functional rating scale revised (ALSFRSr) hand function scores (r=–0.72, p = .01), and associations between these MRI measurements and electromyography (in 1DIO, paraspinal and TA) and MRC scores (in 1DIO and TA) were evident. The authors concluded that electromyography appeared more sensitive for quantification of muscle damage, with radiological techniques preferred to study deeper, inaccessible muscles. A 2020 paper by the same group found that ALS patients and disease controls could be differentiated using MRI of paraspinal muscles, and differences in longissimus dorsi distinguished between bulbar and spinal-onset ALS patients (30).

Finally, in 2020, tongue volume and mean T1 intensity were assessed in large cohorts of 185 MND patients and 104 healthy controls (22). Tongue T1 intensity was lower in bulbar-onset than limb-onset patients (p < .001) and correlated with ALSFRSr bulbar sub-scores (r=–0.2, p = .02), and larger or more ellipsoidal tongues at baseline predicted a slower decline in ALSFRSr. There were however no significant differences in MRI measures between patients and controls.

SMA

The first published study of muscle MRI in SMA, in 1992, described patterns of lower-limb muscle involvement in 17 biopsy-proven SMA patients (3 severe-type, 9 intermediate-type, 5 mild-type) (41). Phenotypes demonstrated distinct radiological signatures, but all exhibited increased subcutaneous fat and preservation of adductor longus. Another small SMA study, from 2004, qualitatively assessed thigh muscle MRI in 8 patients with a rare, genetically unclassified SMA phenotype (36). Subjects were selected on clinical grounds, such as talipes at birth, predominant lower-limb involvement, and signs of neurogenic muscle damage. An increased fat: muscle ratio, diffuse atrophy, and selective sparing of adductor longus and semitendinosus were seen.

In 2011, a comprehensive quantitative protocol measuring thigh muscle volume, percentage muscle, normal signal volume, and normal signal percentage was applied to 14 genetically-confirmed SMA patients (1 SMA I, 6 SMA II and 7 SMA

III). Researchers found multiple correlations between MRI and clinical-electrophysiological measures including CMAP, motor unit number estimation (MUNE), dynamometry and functional scales (32). In the same year, this group also published the first longitudinal SMA study, assessing 11 genetically-confirmed patients (4 SMA II and 7 SMA III) (33). Muscle volume remained relatively stable over six months and corroborated previous clinico-radiological associations. Limitations included a lack of control groups and significant heterogeneity between SMA subgroups.

In 2017, fatty infiltration was graded qualitatively in 25 genetically-confirmed SMA IIIb patients (37). Selective involvement of iliopsoas, triceps brachii and quadriceps was evident radiologically, with comparable findings on MRC scores. In the same year, investigators assessed longitudinal changes in quantitative T2 signal, FF and cross-sectional area (CSA) in thigh muscles of 18 genetically-confirmed SMA III patients and 19 healthy controls (35). Significant between-group differences were found in all MRI measures, but there were no longitudinal changes. However, most MRI measures demonstrated excellent reliability (intra-class correlation coefficient >0.9) and correlated well with clinical assessments and age.

In 2019, fat infiltration of lower-limb muscles was assessed in 31 genetically-confirmed SMA patients (10 SMA II, 11 SMA IIIa, 10 SMA IIIb) and 31 healthy controls using T2-weighted MRI, as part of a neurography study (38). SMA subtype dictated infiltration severity, which was particularly marked in types II and IIIa, with no associations found between CMAP and T2-weighted muscle MRI data.

In 2020, muscle involvement patterns in 36 pediatric and 19 adult cases of SMA (18 SMA II, 12 SMA IIIa, 25 SMA IIIb) were investigated using T1-weighted MRI (40). Selective involvement of the glutei and anterior and posterior thigh, and preservation of the medial thigh was again seen, and there were inverse correlations between the Hammersmith functional motor scale expanded (HFMSE) and fatty infiltration ($r = 0.69$, $p < .01$) and total atrophy ($r = 0.59$, $p = .01$) scores.

Two studies assessing SMA patients taking nusinersen were published in 2020/21. The first investigated whole-body qualitative T1-weighted MRI and lower-limb quantitative diffusion tensor imaging (DTI) changes in two siblings with molecularly-confirmed SMA IIIb (39). No T1 signal changes were observed but DTI demonstrated increased number, length, and organization of muscle fiber tracts at follow-up. The second study assessed thigh FF and quantitative water-T2 signal in three female genetically-confirmed SMA IIIa patients and 11 healthy controls (44). Mean FF in patients increased by 6.7% and the average water-T2 signal decreased by 4.7%. Despite small sample sizes, these studies provided proof-of-concept for muscle MRI applications in therapeutic trials. In 2021, fatty infiltration and atrophy were qualitatively assessed in 20 genetically-confirmed SMA IV patients (34). Relative preservation of tibialis posterior, fibular and extensor digitorum longus, and sparing of the medial thigh compartment was seen. Atrophy and fatty infiltration scores correlated with clinical measures including walking speed, ALSFRSr, HFMSE, and disease duration.

In 2020/2021, FF, T2 relaxometry, and DTI were assessed in leg muscles of 31 genetically-confirmed SMA patients (15 SMA II, 7 SMA IIIa, 9 SMA IIIb) and 20 healthy controls (42), with ten patients completing one-year follow-up (43). At baseline, patients exhibited higher FF (+40%, $p < .001$), lower MD (1.13 vs. 1.47, $p < .001$), higher FA (0.41 vs. 0.24, $p < .001$) and mean *T2r* differences ($p < .001$) when compared to controls. Functional scale and MRC scores correlated with FF, MD, and FA but not *T2r*. At follow-up, there were no significant changes in clinical measurements, but mean thigh FF increased by 1.3%, with a small change in *T2r*, becoming significant after exclusion of adductor longus and biceps femoris (–0.4ms, $p = .02$). Limitations of this study included increased fat fractions potentially influencing T2 relaxation results, and no follow-up of controls.

SBMA

The first SBMA muscle MRI study, in 2004, involved one healthy control, three genetically-confirmed SBMA and two ALS patients (20). SBMA patients exhibited involvement of vastus lateralis and the posterior thigh and preservation of gracilis and sartorius. Quantitative fat infiltration and functional remaining muscle area (FRMA) were assessed by another group in lower-limb and bulbar muscles of 21 ALS, 21 genetically-confirmed SBMA and 16 healthy control subjects (29). SBMA and ALS functional rating scores correlated with FF and FRMA, and significant differences were found between patient cohorts and controls for FF.

In 2019, muscle FF was assessed in 40 genetically-confirmed SBMA patients and 25 healthy controls (45). Researchers found increased muscle fat in patients' paraspinal (12%), thigh (22%), calf (22%), upper arm (12%), and forearm (11%) muscles (all $p < .05$). Quantitative FF correlated with peak torque ($r > 0.68$, $p < .0001$), functional rating score ($r = 0.86$, $p < .0001$), walking speed ($r = 0.79$, $p < .0001$) and forced vital capacity ($r = 0.66$, $p < .0001$).

Discussion

Studies in motor neuron diseases have applied quantitative (18,19,22–24,29,31–33,35,39,42–45), qualitative (18,20,21,25,26,28–30,32–34,36–41,45), and semi-quantitative (27,31) techniques, often in combination, and imaging protocols vary between studies. Most qualitative studies used the five-point Mercuri scale, which grades change from an early moth-eaten appearance to muscle replacement by connective tissue and fat (46). Other applied scales include the modified Goutallier (47), Fischer (48) and Stramare (49) classifications. Quantitative measurements included FF, FRMA, diffusion, volumetrics and relaxometry. A consensus on optimal muscle MRI methodology is yet to emerge.

Whole-body MRI maximizes anatomical coverage but, to date, has necessitated qualitative (39) or semi-quantitative (27,31) methodologies, which have limitations (50). Results from these studies and others assessing isolated regions-of-interest suggest that leg muscle changes appear more easily detectable, likely for technical reasons rather than disease effects. Future research determining the most sensitive and specific protocols to detect muscle damage would enable more standardized approaches, which would facilitate meta-analyses. Preliminary evidence suggests that MRI techniques assessing T2 tissue metrics, FF and FRMA appear particularly sensitive to change in motor neuron diseases. Volumetric studies detect atrophy but there may be clinico-radiological lag. Diffusion-based sequences have not yet demonstrated clear utility, but more research is needed. While qualitative methodologies have informed muscle involvement patterns, objective and quantitative approaches appear more suited candidate biomarkers for future clinical trials.

Associations between clinico-electrophysiological measures and muscle MRI across numerous studies suggest that clinically relevant pathophysiological loss of motor units is reflected. However, clinico-radiological associations were not the primary outcome of any study, and further research is needed.

Identification of selective muscle damage patterns in SMA/SBMA has facilitated diagnosis, with high levels of concordance between studies. However, in ALS, there appears greater clinical heterogeneity, and variance in outcome measurements limits comparisons between studies.

In conclusion, muscle MRI appears a promising tool to study muscle pathophysiology in motor neuron diseases, but further research is required to define its place in clinical and research practice. Changes in patients compared to healthy controls are evident at the group level, but there is individual variability and relatively few studies of disease controls. Group-level clinical and electrophysiological associations suggest that radiological changes in muscle reflect clinically relevant loss of motor units, and longitudinal studies suggest that muscle MRI may represent an objective measure of disease changes. However, the clinical importance of individual-level changes in longitudinal studies remains to be determined, as detected changes have sometimes been subclinical. Some muscles appear more sensitive for the detection of radiological change than others, which has implications for clinical trial applications. Future studies are necessary to investigate the role of fully quantitative, anatomically comprehensive muscle MRI protocols in longitudinal assessment, within achievable timeframes.

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