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RESEARCH ARTICLE

Muscle hypertrophy following acquired neurogenic injury: systematic review and analysis of existing literature

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Abstract

Objectives: Neurogenic muscle hypertrophy (NMH) is a rare condition characterized by focal muscle hypertrophy caused by chronic partial nervous injury. Given its infrequency, underlying mechanisms remain poorly understood. Inspired by two clinical cases, we conducted a systematic review to gain insights into the different aspects of NMH. **Methods**: We systematically searched online databases up until May 30, 2023, for reports of muscle hypertrophy attributed to acquired neurogenic factors. We conducted an exploratory analysis to identify commonly associated features. We also report two representative clinical cases. **Results**: Our search identified 63 reports, describing 93 NMH cases, to which we added our two cases. NMH predominantly affects patients with compressive radiculopathy (68.4%), negligible muscular weakness (93.3%), and a chronic increase in muscle bulk. A striking finding in most neurophysiological studies (60.0%) is profuse spontaneous discharges, often hindering the analysis of voluntary traces. Some patients exhibited features consistent with more significant muscle damage, including higher creatine phosphokinase levels, muscle pain, and inflammatory muscle infiltration. These patients are sometimes referred to in literature as "focal myositis." Treatment encompassed corticosteroid, Botulinum Toxin A, decompressive surgery, antiepileptic medications, and nerve blocks, demonstrating varying degrees of efficacy. Botulinum Toxin A yielded the most favorable response in terms of reducing spontaneous discharges. **Interpretation**: This systematic review aims to provide a clear description and categorization of this uncommon presentation of an often-overlooked neurological disorder. Though questions remain about the underlying mechanism, evidence suggests that aberrant fiber overstimulation along with increased workload that promotes focal damage may result in muscle hypertrophy. This may serve as a guide for therapeutic interventions.

Introduction

Muscle atrophy following chronic denervation is a common and cornerstone manifestation of many neurogenic diseases.[1] However, in rare cases and under a poorly understood set of circumstances, partial chronic denervation can be associated with muscle hypertrophy, resulting in a unique and paradoxical condition. This phenomenon, generally referred to as neurogenic muscle hypertrophy (NMH), has been described in a discrete number of single reports and short case series over the last century. Despite its rarity, NMH has been observed in diverse settings, including compressive radiculopathies, immune neuropathies, and postpolio syndromes.

The mechanisms underlying NMH are largely unknown and are thought to involve both neural and non-neural factors, such as changes in motor unit recruiting, muscle fiber remodeling, and metabolic adaptations.[2] Moreover, its clinical implications remain uncertain, due to the limited and often nonconclusive follow-up of most of the reported cases. In a subgroup of patients, discernible inflammatory infiltrates were observed in muscle biopsies; however, pathogenetic and clinical criteria for categorizing this particular subgroup remain ambiguous. In the last years, we encountered two cases of patients with NMH following chronic radiculopathy (reported hereafter) and found the scattered nature of the existing literature to constitute a major obstacle in gaining a comprehensive understanding of this condition.

We conducted a systematic review of the literature with three distinct aims: (1) to collect and describe the clinical, instrumental, and histological features of NMH cases, (2) to explore, through existing evidence, the putative biological mechanisms for this uncommon phenomenon, (3) to compile information of therapeutic strategies and their respective effectiveness.

In light of the composition of the existing literature, comprising a consistent number of discretely characterized case reports and small series, our study incorporates an exploratory analysis of the clinical, instrumental, and histological characteristics reported in these patients. Our goal is to offer a comprehensive overview of the state-of-the-art literature in NMH, encompassing its diagnostic features, clinical implications, putative physio-pathological mechanisms, and therapeutic options.

Methods

We performed a systematic review of the literature according to the guidelines recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[3]

Search strategy

A systematic search of peer-reviewed articles was performed in PubMed, Scopus, Embase, and Web of Science, for studies published up to May 30, 2023, that investigated the presence of muscle hypertrophy sustained by a neurogenic cause. Detailed search strategy is provided in Appendix A. Reference lists of the included studies were also sieved. Rayyan software was used by two authors (CMMS and BS) to identify, through title and abstract, articles eligible for a full-text revision. Duplicate records were eliminated with an automated tool (Auto Resolve) with a confidence score greater than or equal to 95%. Possible remaining duplicates were then evaluated visually by two authors (CMMS and BS).

Study selection

Full texts were independently reviewed by two authors (CMMS e LB) to check for inclusion/exclusion criteria. Studies were included if they were original full-text articles in the English language, reporting cases of human subjects showcasing muscle hypertrophy that was attributed by the authors to be generated and sustained by an acquired neurogenic affection. Congress abstracts and neuroimaging reports were excluded. We also excluded clinical reports that presented a poor characterization of the patient or provided questionable proof of an acquired neurogenic pathogenesis. The review flow diagram of systematic search and study selection is summarized in Figure 1.

Quality assessment

The quality assessment of each included report was performed through the eight-item tool for evaluating the methodological quality of case reports and case series proposed by Murad et al.[4] This assessment was independently performed by two authors (CMMS and LB) as summarized in Appendix B.

Variable selection and definition

A database was created to collect available variables of all reviewed cases. Data collection included demographics, clinical history, clinical presentation, creatine phosphokinase (CPK) serum levels, neurophysiological and MRI information, histological characteristics of muscle biopsies, treatment trials, and treatment responses. Methods for data retrieval, categorization, and definitions are summarized in Table S1.

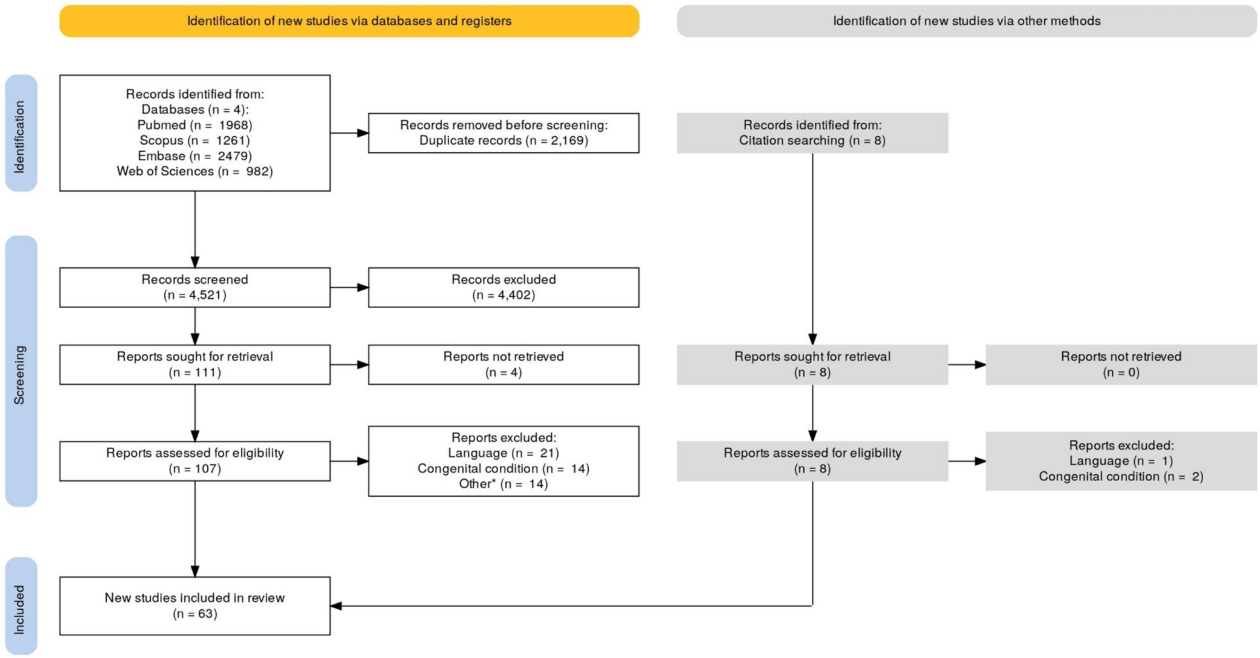

Figure 1. Flowchart of systematic search and study selection. "*Language*" includes articles in French (n = 8), Spanish (n = 8), Italian (n = 2), Dutch (n = 2), Japanese (n = 1), and Portuguese (n = 1). "*Congenital condition*" includes Charcot Marie Tooth (n = 7), Spinal Muscular Atrophy (n = 4), occult spinal dysraphism (n = 2), neuromyotonia (n = 1), and unknown (n = 1). "*Others*" includes two categories: not full article (congress abstracts or teaching neuroimages, n = 12) and poorly characterized patients (n = 2).

Statistical analysis

Extracted data were summarized using descriptive statistics. To explore the consistency between the type of spontaneous discharges described by the original authors, we reevaluated the trace images or trace descriptions (whenever present), using an established nomenclature for reference.[5]

Furthermore, we performed analysis on summarized data to investigate potential associations between clinical/paraclinical data and the presence of spontaneous discharges or biopsy evidence of inflammation. Spearman's rank-order correlation was used to measure the strength and direction of the relationship between continuous or ordinal variables. Chi-square statistics or Fisher's exact test were used for categorical variables, whenever appropriate. A Mann–Whitney U test or Kruskal–Wallis H test was used to explore potential differences in continuous or ordinal dependent variables.

All statistical analyses in the study were performed using the SPSS statistical package (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp).

Results

Report of two patients encountered in our clinical practice

Patient 1

A 50-year-old male presented at the Neuromuscular Diseases Unit of Sant'Andrea Hospital in Rome complaining of a painful swelling of the left calf and nocturnal cramps in the left leg. His medical history included a neurosurgical intervention for L4-L5 spinal disc herniation at the age of 45. Over subsequent years, he consistently exhibited elevated CPK levels ranging from 500 to 900 U/L. Neurological examination revealed left leg posterior compartment hypertrophy (Fig. 2A) with normal strength in both legs and normal heel and toe walking, but slight impairment in left single-leg jump, without sensory deficits. Notably, the left Achilles jerk reflex was absent. Electromyography (EMG) studies unveiled signs of bilateral asymmetric chronic neurogenic involvement in muscles innervated by L4-L5 and S1 roots, with a predominance in the left lower limb muscles. Both complex repetitive discharges (CRDs) and neuromyotonic discharges were

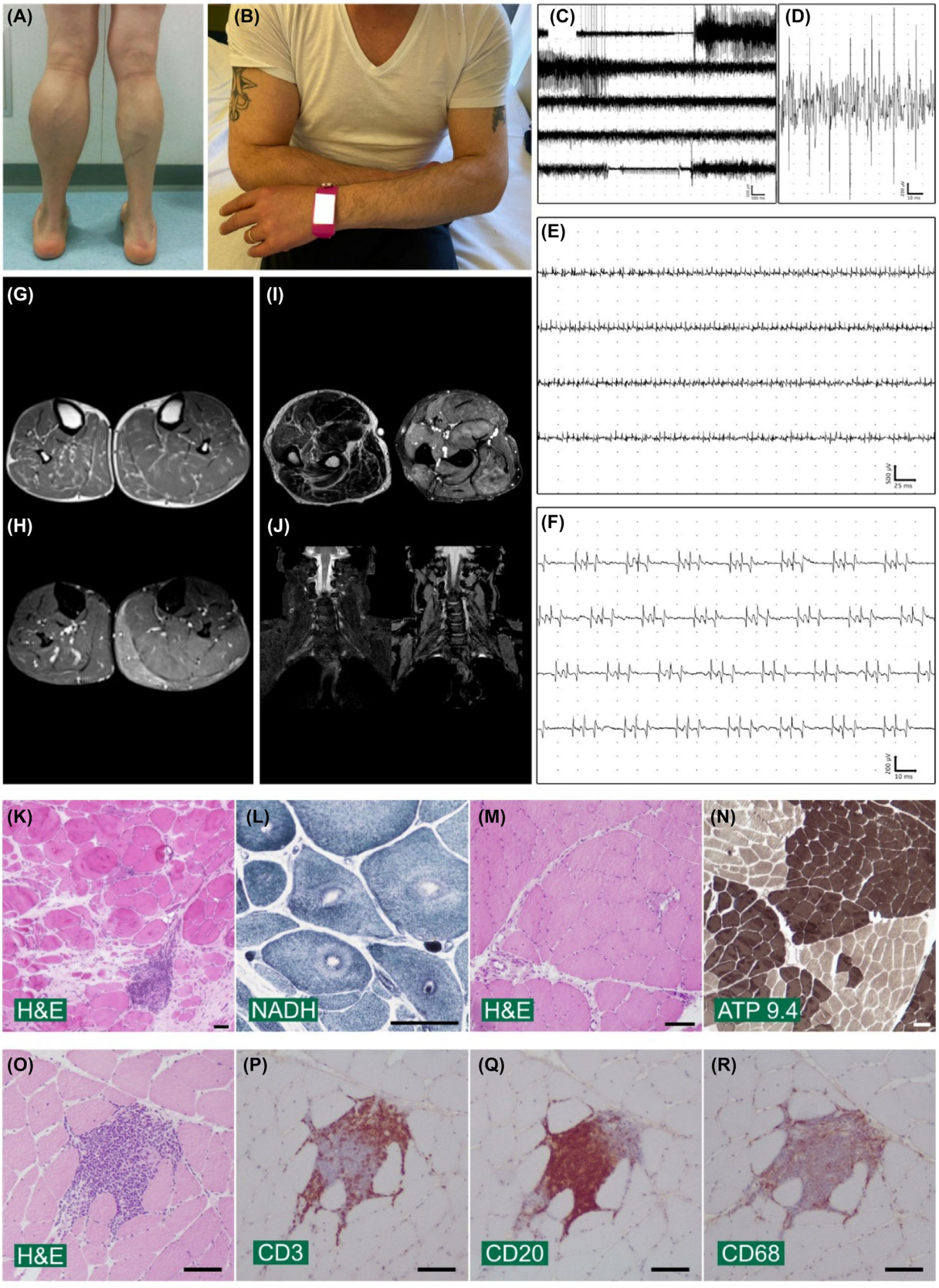

Figure 2. Clinical, neurophysiological, imaging, and pathological features of our patients. (A, B) Clinical appearance of left calf (Patient #1) and right arm (Patient #2) hypertrophy. (C–F) Spontaneous EMG activity recorded from right biceps brachii muscle of Patient #2. (G, H) MRI imaging of the calf muscles (Patient #1), T2-weighted and T1 contrast enhancement, respectively. (I) MRI of the right forearm muscles from Patient #2 (right: T2-weighted; left: T1 contrast enhanced). (J) MRI examination of the cervical roots from Patient #2 (T2-weighted and T1 contrast enhanced, respectively). (K, L) Hematoxylin and eosin (H&E) and Nicotinamide Adenine Dinucleotide (NADH) staining of the left lateral gastrocnemius biopsy from Patient #1. (M, N) H&E and Adenosine triphosphatase (ATPase) staining at pH 9.4 of the right biceps brachii biopsy from Patient #2. (O) H&E staining of a endomysial inflammatory infiltrate in Patient #2. (P–R) Immunohistochemistry staining characterizing the infiltrate for CD3, CD20, and CD68, respectively.

abundant in the left medial gastrocnemius muscle. Spine MRI showed diffuse lumbosacral degenerative discopathies with asymmetric protrusion of the L5-S1 disc toward the left. Lower limb muscle MRI revealed global hypertrophy of the left leg muscles, accompanied by edema and very mild fatty infiltration of the left medial gastrocnemius (Fig. 2G,H). A muscle biopsy of the left medial gastrocnemius corroborated marked neurogenic damage with inflammatory features (Fig. 2K,L). Findings included a pronounced increase in interfiber space, the presence of angulated atrophic and giant hypertrophic fibers, splitting phenomena, and whorled fiber appearance. Nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase (NADH-TR) staining disclosed the presence of target fibers, along with numerous vacuolated muscle fibers. Immunohistochemical analysis revealed isolated small inflammatory infiltration, predominantly comprising CD68+ macrophages and some CD3+ T-lymphocytes, with some non-necrotic fibers displaying sarcolemmal major histocompatibility complex type 1 (MHC-I) overexpression and membrane attack complex (MAC) complement deposits.

Patient 2

A 49-year-old man was admitted to the Neurology department of San Raffaele Hospital in Milan, experiencing a subacute onset of weakness in his right hand, leading to complete paralysis of the hand muscles in 48 h. The patient had a history of C5-C6 radiculopathy, diagnosed 7 years earlier, which had been managed with physiotherapy. Initial examinations revealed significant weakness in intrinsic hand muscles (Medical Research Council, MRC grade 0/5), as well as in the wrist and finger flexors and extensors (MRC 1/5). Additionally, an increase in muscle bulk and consistency was observed in the forearm, upper arm, and shoulder on the right side (Fig. 2B), accompanied by a slight reduction in strength (MRC 4/5). Deep tendon reflexes in the affected arm were diminished, while sensory deficits were absent. The patient recalled an increase in the size of his right arm about a year prior but did not seek medical advice due to the absence of symptoms. Laboratory tests showed a slight increase in CPK (426 U/L, reference range: 20–195) and aldolase (10.6 U/L, reference range: <7.5) levels. Nerve conduction studies demonstrated the absence of compound muscle action potentials in the right median, ulnar, and radial nerves, with normal sensory action potentials in all nerves. Needle EMG showed complete acute denervation of the right C8 and D1 nerve root territory. Muscles served by the C5 to C7 nerve roots showed profuse spontaneous activity (high-frequency CRDs, neuromyotonic activity, and myokymia) that intensified with needle movement and voluntary muscle activation, to the point that it hindered the analysis of the voluntary trace (Fig. 2C–F). Analysis of motor unit potential showed chronic neurogenic involvement with a radicular pattern in muscles presenting this abnormal activity. A cervical spine MRI highlighted extensive disc disease and foraminal stenosis, particularly affecting the right side, leading to compression of nerve roots from C5 to D1 (Fig. 2J). Ultrasound revealed hyperechogenicity (Grade IV according to the Heckmatt Qualitative Muscle Scoring System) of the right biceps, deltoid, wrist, and finger flexor muscles. MRI of the right arm showed patchy T2 hyperintensity and contrast enhancement with a marbled pattern in muscles innervated by C7–D1 roots (Fig. 2I). Confirmation of a neurogenic process was obtained through a biopsy of the right biceps brachii (Fig. 2M–R), revealing a slight increase in interfiber space, scattered atrophic muscle fibers, small, angulated fibers, nuclear centralization, nuclear clumps, and voluminous type groupings. An isolated, large endomysial inflammatory infiltrate, primarily composed of polyclonal B lymphocytes (CD20+), with a minority of T lymphocytes (CD3+) and macrophages (CD68+), was also observed. The diagnosis was compressive cervical radiculopathy, causing chronic partial denervation of C5 to C7 nerve roots and complete subacute-on-chronic denervation of C8 to D1 levels. Despite recommendations for surgical consultation, the patient opted against surgery. Treatment began with dexamethasone 16 mg daily and subsequent tapering, and pregabalin 100 mg twice daily. After 6 months, some improvement was noted in the right biceps size, along with a mild decrease in abnormal electromyographic activity in all muscle groups. The patient's muscle strength remained unchanged after 1 year, although he reported some subjective improvement in manual dexterity.

Search results and characteristics of the included studies

Our literature search resulted in 4521 records. Eight additional records were identified by searching through reference lists of screened articles. Based on titles and abstracts, 109 articles were further assessed through a full-text review, of which 63 met our inclusion criteria, resulting eligible for the analysis, as summarized in the flow chart of publication selection in Figure 1. This search provided 93 NMH patients with sufficient clinical characterization to be reported in English literature.[6–68] The two additional cases encountered in our clinical practice were added to the list, for a total of 95 analyzed patients.

Description of the population

The main clinical and instrumental characteristics of these patients are summarized in Table 1, while the full list with individual patient data, classified per first author and year of publication, is available on request.

Clinical features

Patients predominantly consisted of males, accounting for 75% of the cohort, with a median age of 45 years. A history of isolated muscle hypertrophy was the most common complaint, with the calf muscle being affected in 72% of cases. Muscle weakness, while present, was generally of mild severity, with only 7% of patients exhibiting severe debilitating weakness. Additionally, a subset of patients reported muscle pain (31%) and fasciculations (37%), though these symptoms were less frequent. The most prevalent etiological factor underlying this phenomenon was identified by the authors as an S1 radiculopathy, with compressive radiculopathies comprising the primary category of potential causes overall (68.4%). For the rest, in 10% of patients it was sustained by mononeuropathy, another 10% by inflammatory mononeuritis multiplex, 3% by an inflammatory or postradiation plexopathy, 1% by an inflammatory polyneuropathy, and 4% by the sequelae of poliomyelitis. Serum CPK levels were moderately elevated (median 362.0 [IQR 150.0–531.0]), consistent with the involvement of single muscles or small muscle groups.

Neurophysiological features

A sufficient description of performed neurophysiological studies was present in 85 patients. In these studies, a feature observed with an unusual frequency was the abundant presence of spontaneous discharges (60.0% of

Table 1. Baseline clinical, laboratory, instrumental, and histological characteristics of the 95 NMH patients.

Females, *n* (%)	24 (25.3)	CPK, median (IQR)	362.0 (150.0–531.0)
Age, median (IQR)	45.0 (37.0–53.0)	EMG spontaneous activity, *n* (%)	Total = 85
		Discharges	51 (60.0)
		Active denervation	41 (48.2)
Pathogenesis, *n* (%)		EMG remodeling, *n* (%)	Total = 81
Compressive radiculopathy	65 (68.4)	Neurogenic	70 (87.6)
Inflammatory	10 (10.5)	Myopathic	5 (6.2)
Other/unknown	20 (21.1)	Normal	5 (6.2)
Limb, *n* (%)		MRI, *n* (%)	Total = 50
Upper	17 (17.9)	Edema	24 (48.9)
Lower	78 (82.1)	Fatty infiltration	19 (38.0)
		Muscle biopsy, *n* (%)	Total = 68
Site of injury, *n* (%)		Endomysial fibrosis	39 (57.4)
Motor neuron	4 (4.2)	Inflammation	24 (35.3)
Nerve root	68 (72.3)	Fiber hypertrophy	54 (80.9)
Plexus	3 (3.2)	Type grouping	45 (67.2)
Nerve	19 (20.3)	Internal nuclei	37 (54.4)
		Fiber splitting	36 (53.3)
Disease duration, median (IQR)	24.0 (18.0–60.0)		
Muscle pain, *n* (%)	29 (30.5)		
Weakness, *n* (%)			
None	36 (40.0)		
Mild	48 (53.3)		
Severe	6 (6.7)		
Fasciculations, *n* (%)	33 (34.7)		

Continuous or discrete variables are reported as medians and IQR in brackets, while multinomial or dichotomous variables are presented as absolute numbers and percentages, in brackets.

studies), often so pronounced that they hindered the analysis of voluntary traces. Among the authors, a relative majority ($n = 20$) categorized these discharges as CRDs, while a part of them used alternative terminologies, including myokymic ($n = 8$), neuromyotonic ($n = 1$), or pseudomyotonic ($n = 10$) discharges. This heterogeneity in nomenclature reflects the underlying different assumptions that the origin of these discharges may involve ephaptic transmission between muscle fibers or have a neural generator instead. Furthermore, certain authors recognized the coexistence of CRDs alongside neuromyotonic or myokymic discharges ($n = 4$), whereas others simply referred to them as spontaneous discharges ($n = 8$) without providing additional characterization. Visual representations of these discharges were included in 12 reports (23.5%), while textual descriptions of this abnormal activity were presented in 26 reports (50.9%). Our unblinded visual assessment of the trace images or trace description (whenever present), in comparison with the authors' definitions of spontaneous discharges, presented a good level of agreement (using established nomenclature as reference).[5] Active denervation on the other hand was evident in approximately half of the patients (48.2%), although its visual assessment was often impeded by the concurrent presence of spontaneous discharges. In cases where analysis of the EMG trace was feasible, neuropathic voluntary patterns with coherent neuropathic distribution were observed in most patients (86%).

MRI and muscle biopsy features

Considering the atypical presentation, the majority of patients underwent magnetic resonance imaging (MRI, $n = 50$, 52.6%) and/or muscle biopsy ($n = 68$, 71.5%). MRI revealed muscle edema in nearly half of the examined muscles (48.9%) and varying degrees of fatty infiltration in 38% of muscles, typically of mild to moderate extent.

Muscle biopsies predominantly indicated hypertrophic fibers in 80% of patients, with unequivocal neurogenic sigs (type grouping) present in 67.2% of biopsies. Fiber splitting and internal nuclei were either mentioned in the histopathological description or evident upon review of presented biopsy images, in more than half of the biopsied population (53.3% and 54.4%, respectively). Inflammation at muscle biopsy was identified in a subset of patients, constituting a relative minority (35.5%) of the cohort. Among the 24 patients reported to have signs of inflammation on muscle biopsy, histopathological images were also accessible for review in 16 cases. In these biopsies, inflammatory infiltrates were primarily or exclusively located in proximity to necrotic and atrophied muscle fibers, often accompanied by myophagocytosis. Conversely, in four patients, infiltrates were described to be observed near histologically normal muscle fibers, but the invasion of healthy myofibers by inflammatory cells was never reported.

Treatments and outcomes

Treatment strategies aimed to either address the primary source of injury through decompressive spinal surgery ($n = 10$), reduce symptoms related to muscular hyperexcitability (such as cramps and fasciculations) using antiepileptic medications ($n = 7$), nerve blocks ($n = 3$), and Botulinum Toxin A ($n = 13$), or mitigate inflammatory symptoms (such as inflammatory pain and muscle tenderness) using oral corticosteroids ($n = 11$). A summary of treatment data is provided in Table 2. None of these interventions demonstrated unequivocal superiority over the others. It is noteworthy that Botulinum Toxin A treatment and nerve blocks appeared to yield the most favorable response in terms of reducing spontaneous discharges as observed in EMG, suggesting that these discharges should, at least in part, propagate through the neuromuscular junction.

In our Patient #2, we made a treatment trial with corticosteroids and pregabalin, mainly to address muscle inflammation and fiber overstimulation as possible contributors to muscle weakness, with unclear results. Due to the scarcity of longitudinal data, assessing disease progression without treatment remains challenging. Most reports

Table 2. Treatment trials and therapy responses expressed in terms of the percentage of patients presenting reduction of muscle hypertrophy, symptom amelioration, and reduction of spontaneous EMG discharges.

	Hypertrophy reduction ($n = 36$)	Symptoms amelioration ($n = 37$)	EMG discharge reduction ($n = 21$)
BoNTA ($n = 13$)	90.0	91.7	100.0
Corticosteroids ($n = 11$)	62.5	80.0	50.0
Spine surgery ($n = 10$)	30.0	80.0	66.7
Antiepileptics ($n = 7$)	20.0	28.6	50.0
Root/nerve block ($n = 3$)	66.7	100.0	100.0

All values are expressed as the percentage of patients that positively responded to a certain treatment, for which the outcome is reported. Missing values for a specific outcome measure were removed from the count.
BoNTA, Botulinum Neurotoxin type A.

suggest that the phenomenon is benign and strictly localized, regardless of treatment administration. Therefore, in the absence of symptoms, it may be reasonable to withhold treatments. We believe that while our description of therapeutic outcomes may offer useful insights for symptomatic treatments, more structured data would be necessary to formulate any clear recommendations.

Association analysis

In performing this analysis, we mainly focused our attention on two aspects: (1) the presence of clinical, etiological, radiological, and histological factors associated with the occurrence of spontaneous discharges, frequently posited in literature as potential contributors to or sustainers of dysfunctional muscle hypertrophy in these individuals; (2) whether patients who showed inflammatory changes at muscle biopsy or MRI, including those classified as focal myositis, constitute a different nosologically entity altogether or belong to another end of the NMH spectrum. To achieve this, we compared patients who exhibited signs of inflammation and those who did not, among those who had undergone either an MRI (muscle edema), a muscle biopsy (inflammatory infiltration), or both of the above (see Table 3).

Regarding the first matter under investigation, we found no significant differences neither in terms of pathogenesis, nor in other instrumental or histological features,

Table 3. Baseline characteristics of NMH patients, based on the presence of inflammation on a muscle biopsy or muscle MRI.

Clinical data	NMH without inflammation $n = 49$	NMH with inflammation $n = 33$	*p*-value
Females (%)	15 (30.6)	4 (12.1)	ns
Age	46.5	45	ns
Limb			
Upper	8 (16.3)	3 (9.1)	ns
Lower	41 (83.7)	30 (90.9)	
Presumed site of injury			
Motor neuron	3 (6.3)	0 (0.0)	ns
Nerve root	34 (70.8)	29 (87.9)	
Plexus	1 (0.0)	0 (0.0)	
Nerve	10 (20.8)	4 (12.1)	
Disease duration	24	24	ns
Muscle pain	10 (21.7)	16 (48.5)	**0.016**
Weakness			
None	11 (73.3)	25 (33.3)	ns
Mild	4 (26.7)	44 (58.6)	
Severe	0	6 (8.0)	
Fasciculations, *n* (%)	19 (43.2)	8 (25.0)	ns
CPK, median	477	150	**0.006**
EMG spontaneous activity, *n* (%)			
CRD	10 (40.0)	9 (56.3)	ns
Myokimic/neuromyotonia	1 (6.3)	11 (44.0)	**0.013**
Both of the above	4.0 (12.5)	3 (18.8)	ns
Active denervation	24 (55.8)	15 (50.0)	ns
EMG remodeling, *n* (%)			
Neurogenic	39 (95.1)	23 (76.7)	ns
Myopathic	0 (0.0)	4 (13.3)	
Normal	2 (4.9)	2 (6.7)	
Muscle biopsy, *n* (%)			
Endomysial fibrosis	17 (43.6)	22 (75.9)	**0.013**
Fiber hypertrophy	32 (82.1)	23 (79.3)	ns
Internal nuclei	17 (43.6)	20 (69.0)	**0.050**
Type grouping	26 (66.7)	19 (67.9)	ns

Patients who performed at least one between muscle biopsy and muscle MRI were categorized into respective subgroups according to the presence/absence of inflammatory signs at the MRI (edema) or the muscle biopsy (inflammatory infiltrates). Continuous or discrete variables are reported as medians, while multinomial or dichotomous variables are presented as absolute numbers and percentages. *p*-values denoting statistical significance are highlighted in bold typeface. Differences between the two subgroups were assessed using either a chi-square test for association, a Fisher's exact test, or a Mann–Whitney *U* test, depending on the appropriateness of the test for the specific analysis.

between patients with or without the presence of spontaneous discharges, although it is possibly worth noting that this phenomenon was more frequent among male patients ($p = 0.001$), in muscles other than the triceps surae ($p = 0.003$), and patients reporting muscle pain ($p = 0.004$).

As for the second matter, 33 patients displayed evidence of inflammation either in their muscle biopsy or at muscle MRI examinations. We found a strong positive correlation between the presence of edema on MRI and the degree of inflammatory signs on muscle biopsy ($r_s = 0.708$, $p < 0.001$). Patients presenting signs of inflammation demonstrated many similarities to the rest of the cohort, albeit with certain distinctions. Notably, they reported a higher incidence of pain in the affected limb ($p = 0.016$) and exhibited elevated levels of CPK ($p = 0.006$). Electromyographically, descriptions of spontaneous activity typically lacked neuromyotonic and myokymic discharges ($p = 0.013$). Muscle biopsies from patients diagnosed with focal myositis more frequently displayed endomysial fibrosis ($p = 0.013$), with a nonsignificant trend toward a more frequent presence of nuclear internalization ($p = 0.050$). A more detailed description of the biopsies in these patients is reported in the chapter above (see: "MRI and muscle biopsy features").

Discussion

Neurogenic muscle hypertrophy (NMH) represents a rare late-onset complication of chronic neurogenic muscular damage of diverse etiologies. While the earliest documented cases trace back to the end of the 19th century,[69] subsequent literature on this topic has been fragmented, inadequately categorized, and often challenging to access. The primary objective of this review is to systematically compile and elucidate all reported instances, presenting the fundamental and prevailing clinical, diagnostic, and pathological attributes of this uncommon and poorly comprehended nosological entity. Despite case reports being considered the lowest level of evidence in medical research[70] and acknowledged for their inherent bias, their in-depth collection and evaluation in the context of a systematic review may play a role as hypothesis generators, especially for rare diseases.[71–75] Furthermore, the effort made in this study to depict the current state of the art on this topic, also highlighting the pitfalls due to nonstandardized definitions, can serve to create a shared vocabulary that can function as a benchmark for future case descriptions.

Clinically, NMH predominantly manifests in patients with compressive radiculopathy, causing a mild or even negligible muscular weakness, suggesting only a partial nervous injury. These individuals typically exhibit a chronic, pauci-symptomatic, and potentially misleading increase in muscle bulk within the affected limb.

Curiously, we didn't find any instances of NMH developing after a compressive neuropathy (e.g., median nerve at the wrist or ulnar nerve at the elbow), despite the high prevalence of these disorders in the general population. We speculate that this could be due to the fact that the muscles affected by these neuropathies have a much smaller muscle bulk compared to those frequently involved in this review (e.g., gastrocnemious, biceps brachii, and trapezius) while also being exposed to relatively lower workloads, possibly making hypertrophy less noticeable or significant in these cases.

A striking feature underlying most neurophysiological studies is the observation of abundant spontaneous discharges within the affected muscles, frequently occurring with so much continuity and at such amplitudes, that it hindered the analysis of voluntary muscle activity traces. On the other hand, some patients distinguished themselves by the conspicuous presence of inflammatory infiltrates at the muscle biopsy and were therefore sometimes referred to by the authors as "focal myositis."

We consider the two newly described patients as representative examples of this phenotypic spectrum, echoing the key features noted in previously published reports. Both patients presented with a history of chronic radiculopathy and focal muscle hypertrophy, sharing striking similarities in neurophysiological and radiological aspects. Despite varying degrees of inflammation observed in muscle biopsies, we posit that they both manifest features indicative of a neurogenic picture with superimposed mechanical/electrical overload, resulting in muscle fiber damage and subsequent inflammatory response.

In this context, three main themes recurred across revised literature: (1) on the origin of spontaneous EMG discharges, whether they stem from chronically damaged muscle fibers or if they have a neural generator (these possibilities are not mutually exclusive); (2) on the role of these discharges in the genesis of muscle hypertrophy, alongside with the exploration of additional potential contributing mechanisms to this uncommon manifestation, and (3) whether varying degrees of inflammatory changes observed in muscle biopsies indicate a continuum within a shared disease spectrum, or if individuals diagnosed with neurogenic focal myositis constitute an entirely distinct nosological entity.

Regarding the first inquiry, existing literature on the subject mainly refers to these phenomena as CRDs, probably also as a more conservative term, accounting for the repetitive nature of these waveforms, the absence of a clinically evident neuromyotonic phenotype, and the ambiguity surrounding the exact localization of the discharge generator. From a neurophysiological perspective,

the occurrence of spontaneous recircuiting depolarizations in CRDs is attributed to ephaptic transmission from one chronically damaged/denervated muscle fiber to an adjacent one without an intervening synapse, generating small amplitude, multi-serrated, repetitive potentials, with abnormally low jitter.[76] Because CRDs are generated and transmitted between muscle fibers, they usually persist despite NMJ blockade. A noteworthy observation within the cases we reviewed concerns the reduction of discharges in all cases treated with BoNT-A or through nerve block interventions, for which follow-up EMG data were available.[14,21,22,38,41,45,48] This response suggests that NMJs may indeed play a role at least in the initiation of these abnormal discharges,[2] thereby shifting their trigger away from muscle fibers and toward the axons, in many of these patients.

The second question involves the contribution of this aberrant electrical activity in determining muscle hypertrophy. Previous animal and human models have shown that electrical stimulation, superimposed on muscle overload, may trigger fiber damage, inflammatory response, activation of satellite cells (SCs), and consequent hypertrophy.[77] While muscle hypertrophy has been well-documented in association with myokymia and neuromyotonia,[2] attributed to the continuous electrical stimulation of fibers within the motor unit, uncertainties arise regarding its putative correlation with CRDs. Although it is conceivable that electrical recircuiting may also play a role in fiber overstimulation and consequent hypertrophy, it is important to acknowledge that in chronically partially denervated muscles, augmented workload on undamaged muscle fibers, coupled with mechanical myofiber stretch, can induce muscle fiber hypertrophy even in the absence of abnormal spontaneous activity.[8,78] Under such conditions, CRDs may not necessarily be a causative factor of neurogenic muscle hypertrophy but instead reflect the altered morphology and physiology of a diseased muscle.

Thirdly, we wanted to address the presence of inflammatory aspects observed in the muscle biopsies of many patients, so much so that some of these are referred to in the literature as "neurogenic focal myositis." To start, we found a strong positive correlation between inflammatory aspects at the muscle biopsy and the presence of T2/STIR alteration at the MRI. This correlation suggests that edema in these muscles is not exclusively a sign of acute

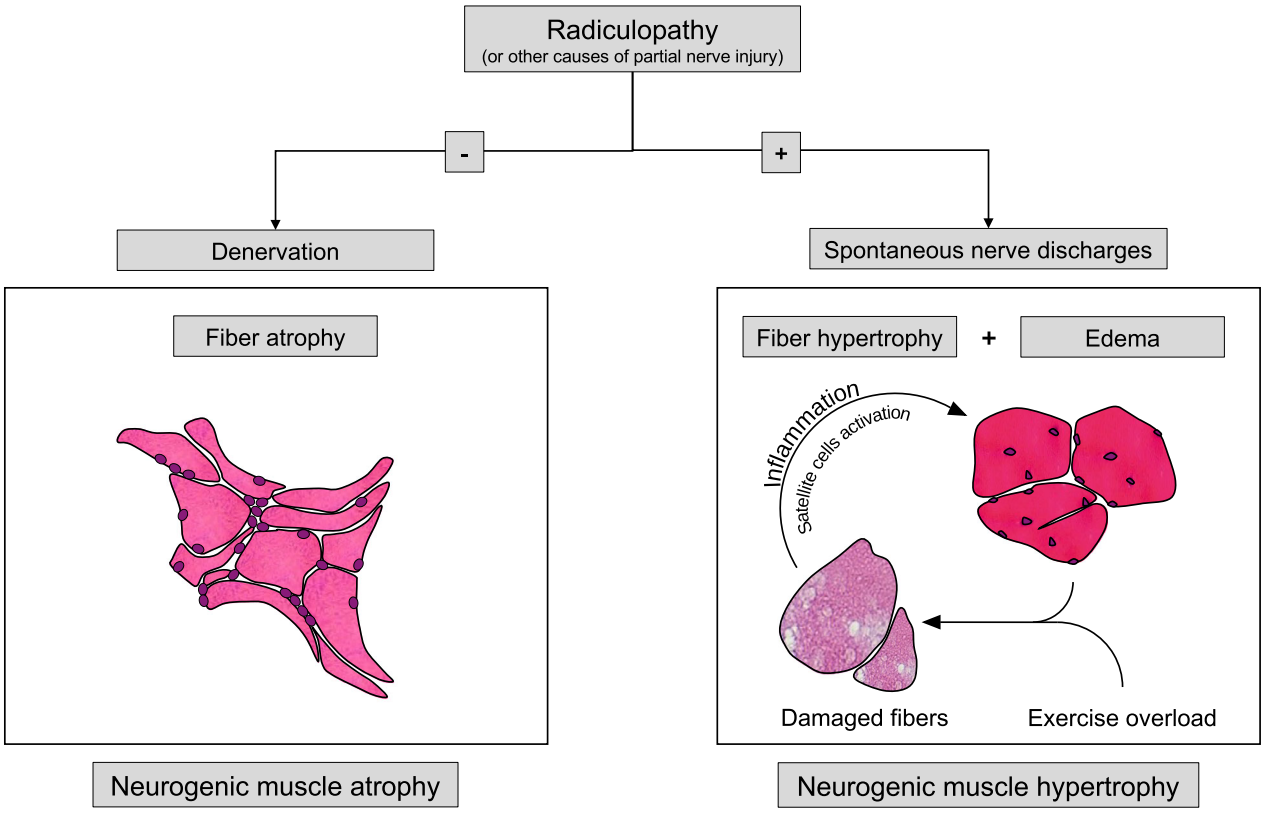

Figure 3. Schematic pathogenesis of NMH. The diagram on the left depicts the established process of muscle atrophy resulting from chronic denervation. On the right, it illustrates the proposed mechanisms responsible for generating and sustaining NMH, supported in the literature by proof of principle.

denervation,[80] but also represents genuine muscle inflammation. When comparing patients exhibiting signs of inflammation with those who did not, the similarities greatly outweighed the differences. Nonetheless, these differences laid the ground for hypotheses regarding some underappreciated aspects of this phenomenon. The scarcity of fasciculations, myokymia, or neuromyotonic discharges in focal myositis patients may hint at a more limited role of aberrant nerve stimulation in the induction of muscle hypertrophy. In addition, the high incidence of muscle pain and edema suggests an alternative pathway to muscle swelling, possibly instigated by inflammatory edema, leading to pseudohypertrophy. However, it must be noted that (1) almost all documented myositis patients also exhibited a prevalence of hypertrophic or giant muscle fibers, implying that muscle swelling is driven by genuine fiber hypertrophy, as well, and (2) the vast majority of authors described inflammatory infiltrates located near atrophied and necrotic fibers, suggesting that inflammation in these patients may be secondary to chronic muscle fiber damage. As mentioned above, previous research has already established that prolonged external electrical stimulation has the potential to induce ultrastructural muscle damage, initiating an inflammatory process and activating satellite cells.[77,81–83] Conversely, a lack of appropriate electrical stimulation, as seen in cases of partial denervation, has also been shown to exacerbate inflammation in an animal model of spontaneous myositis (SJL mouse).[84] In light of these findings, it is conceivable that inflammation may manifest, albeit in atypical circumstances, as a result of partial neurogenic muscle damage, stemming from abnormal electrical overstimulation or insufficient stimulation due to denervation (see Fig. 3). Neurogenic "focal myositis" should be considered part of a spectrum with other NMHs, where muscle inflammation assumes a subsequent and subsidiary role. While the presence of tissue inflammation can contribute to the overall functional and structural muscle impairment in affected individuals, its association with prominent neurogenic signs should not deviate from a diagnosis of chronic partial denervating muscle injury.

The present study has several limitations. The effort we exerted to depict the state of the literature on this topic is encumbered by the inherent selection bias present in case reports. In the case of association analysis between two groups (e.g., myositis vs others), the weight of this bias can heavily influence the analysis. Additionally, it should be noted that the heterogeneity of reported data cannot be managed through meta-analytic methodology due to their single-case nature. Consequently, our study cannot support any causality between the described variables, and punctual summary statistics must be considered only indicative of the available data rather than an estimation of these conditions. However, it should be acknowledged that, at the current stage, this imperfect method represents the highest grade of evidence achievable and can provide important insights to generate hypotheses that can be confirmed in a more appropriate study design setting. In this sense, the effort made in this study to create a common vocabulary and the pathogenic hypotheses we provided can serve as a starting point for collaborative studies aimed at clarifying the putative role of the mechanisms we highlighted. Lastly, our study encompassed patients with various underlying disorders, assuming a uniform mechanism for the development and manifestation of muscle hypertrophy. In reality, we may have co-categorized patients with entirely distinct diseases. Despite this potential variability, it is the homogeneity in most descriptions of these cases, also in terms of instrumental and histological aspects, that validates our review in presenting the common characteristics of an "end-stream" phenomenon. It is important to acknowledge that the exact mechanisms responsible for this phenomenon remain elusive.

With this systematic review, along with the presentation of two additional and typical NMH cases, we aimed to better describe and categorize a broad but disordered body of literature on this paradoxical presentation of a common neurological disorder, along with the pitfalls in such a diagnosis. Much remains to be investigated about the pathophysiological mechanisms that drive this specific phenotypic pattern, and whether there might be further space for therapeutic intervention.

Author Contributions

Design of the study: S. C. Previtali, M. Filippi, C. M. M. Strano, L. Bosco, Y. M. Falzone. Data collection: C. M. M. Strano, L. Bosco, C. Laurini, G. Sferruzza, C. Butera, Y. M. Falzone, B. Sorrenti, A. Ratti, L. Tufano, L. Leonardi, G. Merlonghi, S. Morino, S. Gerevini, U. Del Carro, M. Garibaldi, M. Filippi, S. C. Previtali. Data Analysis: C. M. M. Strano, L. Bosco, C. Laurini, G. Sferruzza, C. Butera, Y.M. Falzone, B. Sorrenti, A. Ratti, L. Tufano, L. Leonardi, G. Merlonghi, S. Morino, S. Gerevini, U. Del Carro, M. Garibaldi, M. Filippi, S.C. Previtali.

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Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1.

