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Review Article

Orthopedic manifestations of congenital muscular dystrophy subtypes in children: Emerging signatures need consolidation: a scoping review

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ABSTRACT

Our objective was to screen the literature on congenital muscular dystrophy (CMD) children/adolescents regarding the extent/nature of reporting orthopedic manifestations/deformities and to assess its *appropriateness in informing clinical practice/research*. We searched PubMed for original research on orthopedic surgical/non-surgical manifestations of CMD. Eligible articles needed to focus on orthopedic manifestations/deformities as one of the study objectives with no restrictions on study designs/types or search period. Eight hundred and thirty articles were initially identified and screened. Following the exclusion of 501 articles for disagreeing titles/abstracts, 329 were available for eligibility assessment. Two hundred and fifty-five articles were excluded for reasons. Of one hundred articles, 15 were captured manually and 11 through pre-submission searches, with 1078 patients included in the final analysis. The most common subtype was Laminin alpha-2 (*LAMA2)*-related-CMD. Orthopedic manifestations of CMD are generally underreported and insufficiently detailed. There is reliable evidence that accurate reporting of orthopedic manifestations can be a valuable clinical supplement to the complex differential diagnosis process in collagen VI-related CMD, *LAMA2*-related-CMD, *LMNA*-related-CMD, and *SEPN*[1]-related CMD (*SELENON*). For alpha dystroglycan-related CMD, there is insufficient information to delineate a subtype-specific pattern. There is emerging evidence that reporting spine surgery outcomes may facilitate orthopedic decision making. The greatest clinical/research utility was provided by articles with longitudinal, comprehensive, and correlative reporting of larger cohorts. Detailed reporting of the orthopedic phenotype of CMD in future research may further uncover its diagnostic potential.

Keywords: Collagen type VI-related dystrophies, Laminopathies, LAMA2-related congenital muscular dystrophy, Rigid spine muscular dystrophy 1, SELENON-related myopathies, Walker-Warburg syndrome

INTRODUCTION

Congenital muscular dystrophy (CMD) spans a broad category of childhood-onset genetic muscle diseases that typically manifest in varying degrees of progressive muscle weakness, floppiness, and delayed motor milestones with no definite cure. The reported prevalence rates of CMD population studies range from 0.017/100,000 to 2.5/100,000.[1-3] However, CMD subtypes express remarkable diversity regarding clinical presentation, causative genetic mutations, muscle immunostaining, brain MRI findings,[4-6] muscle MRI findings,[7] especially whole-body muscle

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MRI,[8,9] associated cardiomyopathy,[10] and abnormalities in serum creatine kinase levels.[11] The classification of CMD is evolving due to the expanding and complex genotype-phenotype correlations. Congenital muscular dystrophies can be classified according to the type of structural muscle protein deficiency, causative gene mutation, and resultant phenotype/clinical profile. Broadly, the CMD classification includes (A) Laminin alpha-2 (*LAMA2*) or early-onset *LAMA2*-related CMD. Since *LAMA2* isoform consists of chains α2, β1, and γ1, it is also labeled (laminin-211). Pathogenic mutations in the *LAMA2* gene cause early-onset *LAMA2*-related CMD. It was formerly known as merosin-deficient CMD type 1A and (B) alpha dystroglycan (DG)-related dystrophies. Pathogenic mutations in an array of genes – individually or in combination – cause Walker–Warburg syndrome, Fukuyama CMD, and muscle-eye-brain disease, among others and (C) Collagen VI-related dystrophies/CMD. Pathogenic mutations in *COL6A1, COL6A2,* and *COL6A3* genes cause severe Ullrich, intermediate, and Bethlem CMD subtypes.[11-13] Miscellaneous subtypes of CMD include rigid spine syndrome or *SEPN1*-related myopathy caused by pathogenic mutations in the *SEPN1* gene (*SELENON*; 606210). Lamin A/C (*LMNA*) or *LMNA*-related CMD is caused by pathogenic mutations in the *LMNA* gene.[14-18] This subtype belongs to a broader group known as laminopathies, which includes Emery-Dreifuss muscular dystrophy[14,19] and limb-girdle muscular dystrophy type 1B.[14] Marked cardiopulmonary insufficiency can occur in CMD.[12,20]

The CMD children share clinical manifestations common to all CMD subtypes, namely, neonatal or infantile muscle weakness, hypotonia, decreased spontaneous movements, and developmental motor delay. Disease progression eventually results in generalized contractures of the extremities and spine and compromised quality of life.[12,13,20] Conversely, certain disease-specific features can help differentiate the CMD subtypes. For example, the universal presence of white matter changes on the T2 signal of brain MRI with or without associated neurological manifestations[4,6,21] and the recent introduction of a characteristic disease signature on whole-body muscle MRI[8,9] can serve as valuable clues to the diagnosis of early-onset *LAMA2*-related CMD. However, overlapping and atypical clinical presentations of CMD subtypes[12,13,20] and other childhood-onset genetic muscle diseases such as congenital myopathies[20,22] can cause diagnostic challenges. For example, L-CMD and Emery-Dreifuss muscular dystrophy[15-18] should be strongly considered in the differential diagnosis of early-onset *LAMA2*-related CMD. In this respect, their presenting motor and orthopedic manifestations, disease severity, and prognosis bear a considerable resemblance to early-onset *LAMA2*-related CMD.[23,24]

Unlike Duchenne muscular dystrophy,[25-27] the orthopedic manifestations and outcomes of CMD subtypes have neither been widely researched nor precisely characterized in the literature.[23,28,29] Further, accurate characterization of orthopedic manifestations in CMD subtypes and their differential diagnosis may help resolve unexplained genotype-phenotype correlations respecting overlapping clinical presentations, novel genes or multiple gene associations with disease, single gene association with multiple diseases, and clinically typical cases with negative genetic testing.[14,15,30,31] We assumed that delineating the pattern of orthopedic involvement in various CMD subtypes can improve diagnostic accuracy and provide treating physiatrists, physical therapists, and orthopedic surgeons with valuable clues as to what muscle groups one should prioritize in the treatment plan and what treatment endpoints should one aim at and so forth. This topic has not been addressed previously in the literature. This scoping review aimed to screen the current literature on CMD children and adolescents, respecting the extent and precision of reporting orthopedic manifestations and its appropriateness in informing clinical practice and research.

MATERIAL AND METHODS

Identifying research questions

This scoping review was carried out in accordance with the guidelines of the PRISMA extension for scoping reviews.[32,33] The goal of this scoping review was broken down into three research subquestions, namely;

1) How often are orthopedic manifestations reported in publications on CMD children and adolescents?
2) How precise is the reporting of the orthopedic manifestations, for example, completeness and accuracy?
3) How appropriate is it in informing clinical practice and research?

The above specifics of reporting orthopedic manifestations were weighed against the standard components of orthopedic examination whenever applicable. That is history-taking and orthopedic couch examination with special emphasis on deformity/contracture characteristics. Gait analysis and motor development were not directly targeted. For clarity, the terms orthopedic manifestations and orthopedic deformities/contractures will often be used synonymously across the manuscript.

Search strategy

We searched the publications in MEDLINE through PubMed advanced search builder https://pubmed.ncbi.nlm.nih.gov/advanced/#. We performed the initial search in November 2021, and an additional search was performed on April 23, 2022 before manuscript submission to ensure the identified literature was up to date. The age filter was set to child: Birth-18 years and species set to humans. We did not include

additional search filters. Our search strategy comprised phrases, index words, and Medical Subject Headings pertinent to pathology, that is, CMD subtypes. We used the following words to indicate the three main CMD subtypes: CMD, Walker-Warburg syndrome, *LAMA2*, merosin, Bethlem, and Ullrich. We used other words in separate searches to indicate the miscellaneous and less common CMD subtypes, namely, rigid spine syndrome, *SEPN1*-related myopathy, *LMNA*-related CMD, and laminopathies. The search objective was mainly focused on recall. We screened the titles and abstracts of the initially identified articles. After making necessary omissions, we assessed the remaining articles for potential inclusion.

Moreover, we obtained the full text of the final included articles [Supplementary File S1]. A flowchart of the literature extraction process is shown [Figure 1]. We checked the reference lists of the relevant articles and reviews for additional eligible articles. We manually checked *similar* articles and *cited by* functions regarding these relevant articles.

Eligibility criteria

Articles were included if they represented original/primary research and addressed orthopedic manifestations in any subtype of CMD in a descriptive or intervention (surgical or non-surgical) setting. To be included, the article needed to focus clearly on reporting the clinical orthopedic examination/manifestations as one of the study objectives. This can occur solely or among other clinical manifestations. Simple/broad or binary referral to the presence or absence of orthopedic manifestations was not included in the analysis. This scoping review was primarily exploratory and descriptive regarding the evidence for reporting orthopedic manifestations. Thus, we considered all study designs, for example, (longitudinal vs. cross-sectional/prospective vs. retrospective) and all research types (case reports vs. case series) eligible for inclusion. Articles were also included if they investigated CMD exclusively or as a constituent of a larger cohort of genetic muscle diseases. We excluded non-peer-reviewed material, experimental or preclinical articles, and those reporting exclusively on genetic muscle diseases other than CMD as congenital myopathies.

Data extraction and synthesis of results

We extracted elementary data elements, namely, study designs and research types, patient populations (CMD subtype), and authors' disciplines of included articles. In this regard,

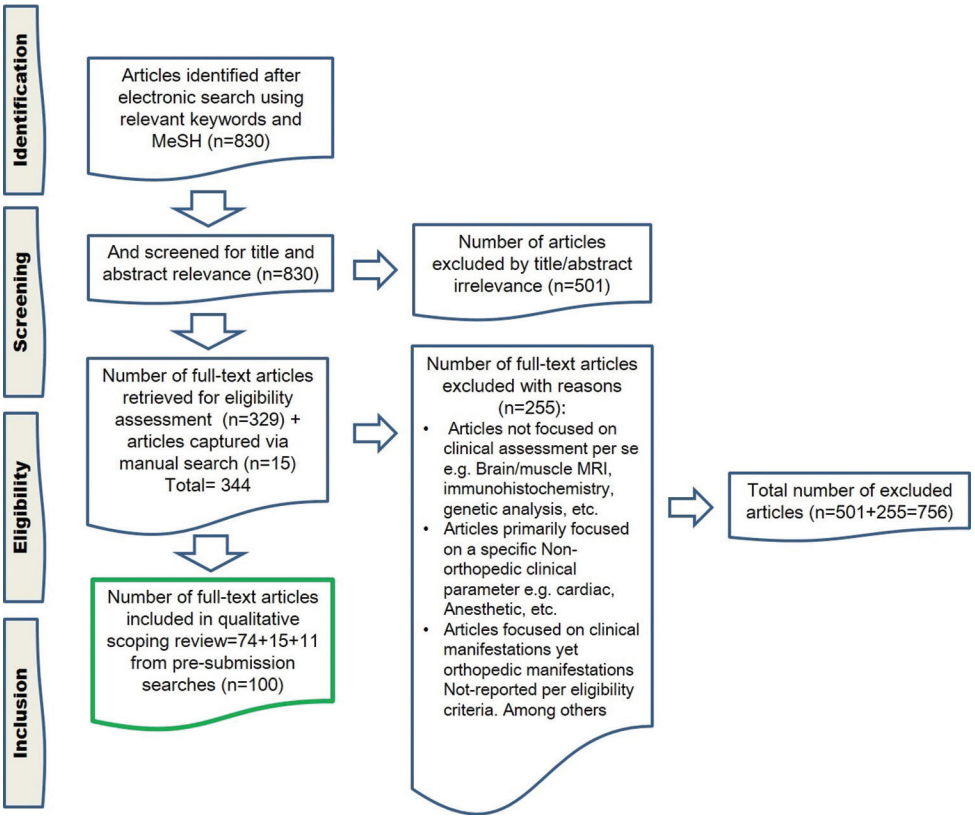

Figure 1: Flowchart of the literature extraction process. An updated search was performed before manuscript submission to ensure the identified literature was current. Detailed description of excluded articles with reasons can be found in Supplementary File S1.

we were particularly interested in identifying authors or co-authors in the discipline of musculoskeletal/orthopedics, namely, rehabilitation physicians, physiotherapists, orthotists, and orthopedic surgeons. In addition, we extracted data pertaining to the research questions, namely, (1) frequency and nature of reporting, which included qualitative or categorical reporting or quantitative as goniometric joint measurements, etc., (2) precision, which included completeness and accuracy of reporting of orthopedic manifestations, and (3) appropriateness in informing clinical practice and research. The authors performed a pilot test on screening the titles and abstracts of the initially identified articles and another on data extraction/charting of the included full-text articles. Disagreements between authors were settled by joint meetings. The final review and charting of the above data items were performed by author TAE, whereas the rest of the authors verified the data extraction/charting. We did not critically appraise the sources of evidence – articles – included in this scoping review.

RESULTS

Characteristics of sources of evidence

The 100 final articles included peer-reviewed descriptive observational research, namely, case reports of one or two patients, 47 (47%) articles or case series of affected families or unrelated patients, and 53 (53%) articles. The diagnosis was verified with the aid of genetic analysis and/or muscle biopsy immunostaining supplemented by clinical presentation and brain MRI or neuromuscular electrophysiological investigations.

Results of individual sources of evidence

The initial search for the three main CMD subtypes and the two additional searches for *LMNA*-related CMD, a subtype of laminopathies and *SEPN1*-related myopathies/CMD or rigid spine syndrome identified 830 articles, and the titles and abstracts of which were screened for any irrelevant articles. Following the exclusion of 501 irrelevant articles, 329 remaining ones were assessed for eligibility criteria. Additional articles were excluded with reasons ($n = 255$) either due to the clinical content, and consequently, the orthopedic was absent or near absent as a study objective, for example, focused on genetic analysis, muscle biopsy/immunostaining, or muscle/brain MRI features and so forth or because the articles were primarily focused on a specific *non-orthopedic* clinical parameter, for example, cardiac, anesthetic complications or because the article's clinical orthopedic content was not reported as per eligibility criteria, either solely or as one of the constituents of clinical manifestations, among other reasons [Supplementary File S1and S2]. These latter exclusions necessitated retrieval and investigation of the full-text articles, six of which were irretrievable. Among the latter exclusions were five articles that reported negative/absent orthopedic manifestations. Although this was deemed adequate reporting, they did not technically allow for evaluation of the precision of reporting. Fifteen more articles were added through manual search, as they fit the inclusion criteria. Thus, the final number of included articles in the current review was 100.[14,23,28,34-130] Of the 100 articles, two[95,96] were captured through an additional search performed on April 23, 2022, before manuscript submission to ensure the identified literature was up to date [Supplementary File S1]. Another nine articles[122-130] were captured through another pre-submission-focused search performed on May 19, 2022 [Supplementary File S1]. The latter complementary search was intended specifically to enhance the recall of articles on Walker-Warburg syndrome (alpha DG -related CMD). The total number of *patients* enrolled in these articles was 1078, distributed as follows: *LAMA2*-related CMD 399 (37%) patients, collagen VI-related CMD 132 (12%), alpha DG -related CMD 75 (7%), *SEPN1*-related rigid spine CMD/syndrome 196 (18%), and *LMNA*-related CMD 276 (26%). A flowchart of the literature extraction process is shown in Figure 1. Of the final included articles, 94 (94%) addressed clinical – non-surgical – orthopedic aspects of CMD, and 6 (6%) addressed orthopedic surgical interventions.[35-37,73,84,110] Only 26 (26%) of articles included authors affiliated to musculoskeletal disciplines, medicine or surgery; orthopedic surgery 18 articles,[28,35-37,39,40,42,48,53,73,84,87,104,105,110,117,119,125] rehabilitation medicine/therapy 7,[44,83,91,94,97,103,112] and kinetic therapy 1.[43]

Synthesis of results

Data items and extraction (charting) of included articles are shown in [Supplementary Tables S1-3] per CMD subtype. Overall, there seems to be a fairly consistent pattern of orthopedic manifestations for most of the CMD subtypes [Figure 2]. Most of the 329 articles retrieved for eligibility assessment were excluded 255 (77.5%) despite being pertinent to clinical research on CMD. The full text of the final included articles was searched for precision in reporting orthopedic manifestations (deformities or contractures) in CMD regarding anatomic localization of deformities, severity grading, symmetry, range of motion features, age at onset and course of deformity, and additional relevant information. The majority of included case series articles did not report orthopedic contractures in a correlative manner, namely, correlations between orthopedic contractures on the one side and patient's genotype, distribution and onset of muscle weakness/wasting, general motor function, and so forth on the other side. There were notable exceptions.[14,87,94] Although many of the included articles reported the overall disease progression and anatomic distribution of muscle weakness, few reported the progression and distribution of

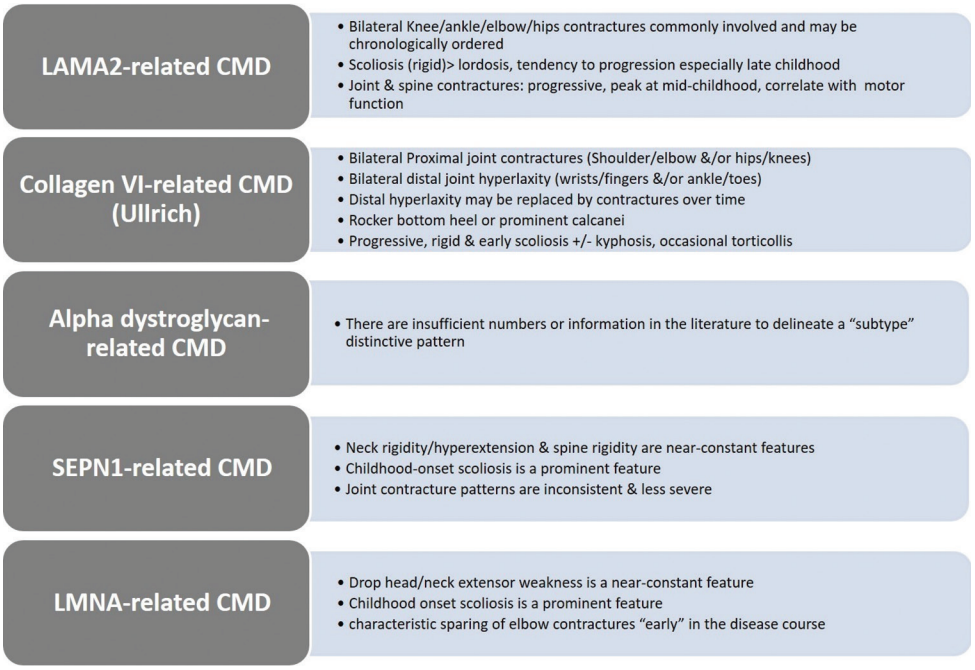

Figure 2: Graphical abstract image: General orthopedic indicators of congenital muscular dystrophy (CMD) subtypes. Indicators are based on the best available evidence and are not necessarily all-inclusive or pathognomonic. Collagen VI-related CMD indicators are most applicable to the Ullrich subtype.

orthopedic contractures particularly. There were notable exceptions.[23,94] The overall orthopedic indicators of CMD subtypes are shown in Figure 2. A proposed flowchart for comprehensive eporting of orthopedic deformities in CMD children is presented in Figure 3. We successfully contacted the authors of the included articles[111] to retrieve relevant supplementary files, which were inaccessible in the PDF versions. We unsuccessfully contacted the authors of an eligible yet excluded article[131] to retrieve supplementary files, which contained the clinical spectrum of alpha DG -related CMD in a large cohort of Chinese patients.

DISCUSSION

The fact that the vast majority of articles retrieved for eligibility assessment were excluded despite being pertinent to clinical research on CMD denotes that orthopedic manifestations in CMD are underreported both quantitatively and qualitatively. That is, these articles did not contain clinically meaningful or important orthopedic content to warrant investigation. The final articles included in our study (21.5%) yielded various qualities of reporting orthopedic manifestations. For example, articles on collagen VI CMD, Ullrich subtype reported a fairly consistent and characteristic pattern of orthopedic manifestations. A notable example is the characteristic coexistence of large/proximal joint contractures and small/distal joint laxity in these patients.[38-40,42,45] A similarly characteristic pattern of orthopedic manifestations was reported in a large cohort of *LAMA2*-related CMD, which established in addition genotype/orthopedic-type correlations[87] among others.[28,94] Additional emerging characteristic orthopedic patterns were demonstrated in large cohorts of *SEPN1*-related subtypes of CMD or rigid spine syndrome[97] and *LMNA*-related CMD.[112,113] Such an *orthopedic signature* could serve as a valuable and handy clinical differential diagnostic aid, especially if established in other subtypes of CMD. Orthopedic manifestations, particularly the chronological order of appearance of joint contractures, symmetry/laterality and degree of rigidity, need accurate reporting. For example, early appearance of elbow contractures was found to be a potentially useful diagnostic sign in patients with Emery-Dreifuss muscular dystrophy, in contrast to *LMNA*-related CMD and limb-girdle muscular dystrophy type 1B where they appeared late in the disease course[114,115,117] and so forth. The favorable intermediate-term surgery outcomes for spinal deformities secondary to CMD may prove to be another valuable decision-making tool and an indicator of responsiveness to orthopedic surgery.[35-37,73,84]

Orthopedic manifestations of neuromuscular diseases

The motor and orthopedic manifestations of genetic neuromuscular diseases are valuable clinical tools allowing for refinement of differential diagnosis,[132,133] identification of age- and disease-specific orthopedic and rehabilitation treatment endpoints,[29,134-137] informed

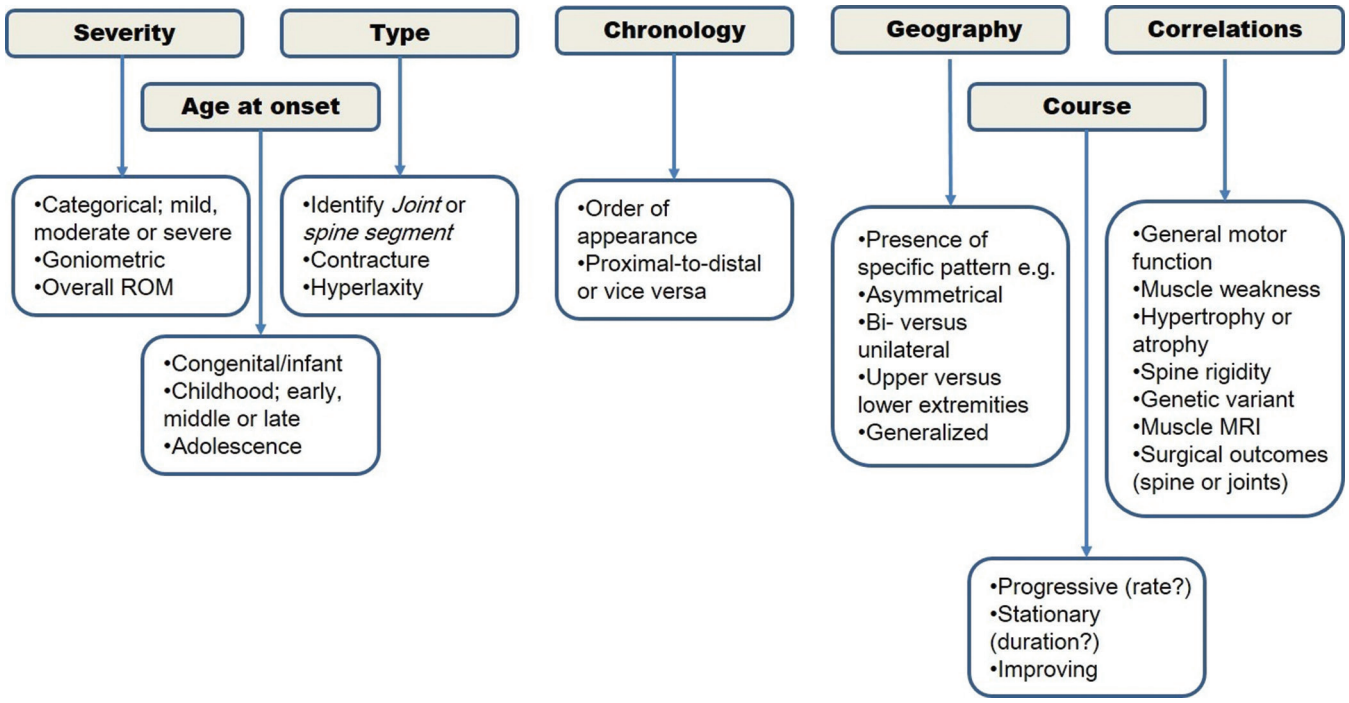

Figure 3: Proposed flowchart for comprehensive reporting of orthopedic deformities in congenital muscular dystrophy children.

surgical decision-making,[138] and assessment of efficacy of experimental therapeutics and improvement of clinical trial designs.[139] For example, emerging evidence suggests that familiarity with orthopedic manifestations can help in the differential diagnosis of Charcot-Marie-Tooth subtypes and related genetic polyneuropathies[132] and fascioscapulohumeral muscular dystrophy[133] and guide their orthopedic and rehabilitation management plans. Additional studies underscored the importance of orthopedic manifestations to the surgical decision-making in myotonic dystrophy[140] and to the monitoring of enzyme replacement therapy in early-onset Pompe disease.[137,141] The accurate description of the orthopedic manifestations of CMD subtypes[28,38-40] is particularly important to low-resource countries where diagnosis and subsequent referral to specialized centers depend highly on the physician's clinical judgment.[142]

Although experimental research on CMD subtypes is promising,[143-147] early diagnosis can facilitate supportive and system-specific management per recommended disease standards of care.[12,148] Relatedly, neglected spine deformities can accentuate cardiac[21,149-151] and pulmonary[20,152] complications.

Strengths and limitations

The strength of our study is that it mapped an underreported yet central feature in CMD children, namely, orthopedic manifestations.[148,149,153-156] Accurate and systematic reporting can provide valuable insights into the mechanisms of disease causation of the wide mutation/variant spectrum CMD subtypes. It can also establish correlative relationships between gene variants and the diverse phenotype presentations of CMD subtypes and similar genetic muscle diseases with result improvement in the genetic/molecular diagnostic yield.[22,30,31,157] The elucidation of the orthopedic manifestations in future reports can expand the phenotype/clinical profile of CMD subtypes, which can help clinicians diagnose CMD subtypes with more precision. Our study has limitations. We searched only one database. Given the ultra-specialized nature of CMD, we assumed that most research on it would be published in reputable PubMed-indexed journals. Consequently, we believe that our search should have captured at least the main bulk of relevant articles.

Further, the recall and precision of a search strategy depend on multiple variables such as the operational specifics and degree of indexing inaccuracies or delays of the electronic database and the contribution of a health information librarian to the search design among others. However, we believe that the ample amount of literature recall regarding the included number of articles and patients in this analysis has provided fairly representative material to justify meaningful conclusions, at least as far as a scoping review is concerned.

CONCLUSION

The clinical and surgical orthopedic manifestations of CMD subtypes in children and adolescents are generally underreported and insufficiently detailed in the literature. However, there is reliable evidence that accurate reporting

of orthopedic manifestations can be a valuable clinical supplement to the complex differential diagnosis process of children and adolescents with collagen VI-related, *LAMA2*-related, *LMNA*-related, and *SEPN1*-related CMD (*SELENON*). For alpha DG -related CMD, there is insufficient information to delineate a subtype-specific pattern. There is emerging evidence that reporting spine surgery outcomes may facilitate orthopedic decision-making in CMD. Predictors of high clinical and research utility were articles with longitudinal, comprehensive, and correlative reporting of larger cohorts. Detailed reporting of the orthopedic phenotype of CMD in future research may further uncover its diagnostic potential.

What does this paper add?

- Orthopedic manifestations of congenital muscular dystrophy (CMD) in children/adolescents are generally underreported and insufficiently detailed.
- There is reliable evidence that accurate reporting of orthopedic manifestations can be a valuable clinical supplement to differential diagnosis in patients with collagen VI-related, *LAMA2*-related, *LMNA*-related, and *SEPN1*-related CMD (*SELENON*).
- For alpha dystroglycan-related CMD, there is insufficient information to delineate a subtype-specific pattern.
- There is emerging evidence that reporting spine surgery outcomes may assist in orthopedic decision-making.
- The greatest clinical/research utility was provided by articles with longitudinal, comprehensive, and correlative reporting of larger cohorts.
- Comprehensive reporting of orthopedic manifestations is recommended in future research.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article and its supplementary information files.

AUTHORS' CONTRIBUTIONS

TAE conceptualized and designed the study. TAE, HA, SM, and JA contributed to data acquisition, analysis and interpretation. TAE drafted the manuscript. All authors revised the manuscript critically for important intellectual content and approved the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL

The authors confirm that this review had been prepared in accordance with COPE roles and regulations. Given the nature of the review, the IRB review was not required.

DECLARATION OF PATIENT CONSENT

Patient's consent was not required as there are no patients in this study.

USE OF ARTIFICIAL INTELLIGENCE (AI) ASSISTED TECHNOLOGY FOR MANUSCRIPT PREPARATION

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

CONFLICTS OF INTEREST

There are no conflicting relationships or activities.

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