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Review

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Rare diseases with temporomandibular joint manifestations: a systematic review

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Abstract

Background: Rare diseases (RDs) are serious often chronic progressive diseases that affect a smaller number of individuals. RDs can manifest in any region of the body and have systemic effects that are detrimental to individual health. Although RDs are individually rare, there are various debilitating disorders arising from RDs. One of the disorders that have been shown to have a negative impact on the health of RD patients is temporomandibular disorders (TMD). There is a dearth of data on the rare diseases and potential manifestations of TMD. The objective of this systematic review is to provide an overview of rare diseases and temporomandibular joint (TMJ) manifestations.

Method: The criterion for analysis of a rare disease and temporomandibular manifestations was inclusion in the Orphanet Classification of Rare Diseases and/or the National Organization for Rare Disorders (NORD)/The Genetic and Rare Diseases (GARD) databases. Only rare diseases with TMJ manifestations were recorded.

Results: A total of 54 RDs with TMJ manifestations and different TMD diagnoses were recorded. There were thirty-five studies derived from the Pubmed search, and the Orphanet input had 19 results. Overall, 13 different types of TMJ manifestations and TMD diagnoses were recorded in rare diseases.

Conclusion: TMJ manifestations associated with rare diseases are not uncommon. Healthcare professionals can play an important role in diagnosing and managing the complexity of RDs with TMJ manifestations. A

multidisciplinary approach to TMD patients with rare diseases is advisable.

Keywords: Rare diseases, temporomandibular joint, diagnosis, symptoms

INTRODUCTION

RDs, often called "Orphan" diseases, are an emerging public health priority that affects a small number of people in the population. There is currently no universal definition for RDs, with varying prevalence among different parts of the world. RDs affect fewer than 200,000 people in the United States[1], whereas according to the European Union (EU) definition, RDs affect one in 2000 people[2]. Cumulatively, there are more than 7,000 rare diseases, with approximately 80% having a genetic basis and 50%-70% with pediatric onset[3,4]. When this number is translated into the actual world, it is fairly unexpected that RDs are not as rare as universally perceived since a vast number of individuals may be suffering such rare conditions around the globe. The estimated prevalence of RDs ranges from 3.5%-5.95% globally[5]. The approximate collective number of people affected by RDs was equivalent to the population of the world's third-largest country[6,7].

There has been an overall increase in public awareness about RDs. However, exact data on RDs are often not available or incomplete as a result of various RD registrations in different national or international databases. These dispersed allocations of information make it difficult to obtain symptoms and consequences linked to specific RDs[8]. RDs can manifest in any part of the body and thus can often have systemic effects. Generally, 15% of all RDs can manifest in the orofacial region[9]. The orofacial region consists of heterogeneous hard and soft tissues that make it challenging to diagnose pain conditions[10]. One of the pain conditions which pose a global health problem is TMD. TMD are defined as a group of clinical conditions affecting the muscles of mastication, the TMJ, and the related structures[11]. The TMJ is a composite ginglymoarthrodial joint. Each TMJ is comprised of hard and soft tissue components. The hard tissue components of TMJ include the mandibular condyle, articular fossa, and articular eminence. The soft tissues include articular disc, joint capsule, synovial membranes, ligaments, and corresponding muscle attachments. It is the most frequently used joint and possesses the capacity to bilaterally move the mandible simultaneously.

TMD are frequently associated with structural and functional problems. TMD affects about 5%-12% of the general population, while some studies reported a higher incidence of TMD ranging from 25%-40%, with women having a greater risk of developing TMD conditions than men[11]. TMD affect the articulation and masticatory muscles or both. TMD can be broadly classified as articular disorders in which signs and symptoms are related to TMJ, and muscular disorders, which manifest signs and symptoms related to stomatognathic musculature. Patients with TMD frequently report pain as the primary complaint that can occur from either intra-articular structures or from an extra-articular location as referred pain from adjacent structures. Other symptoms of TMD included joint noises, impaired jaw movements, tinnitus, dizziness, cervical pain, and headaches. TMD has a multifactorial etiology and consists of various contributing factors including trauma, either physical or emotional, biological processes such as aging, postural conditions such as abnormal head and cervical position, systemic predisposition, sleep disorders, and psychosocial alterations. Genetic and sensory processing also contributes to the etiology of TMD[11]. For diagnosis of TMD, special attention should be given to the history and clinical assessment. A descriptive history is required to render TMD diagnoses and identify the contributing factors. In some cases, diagnostic imaging is needed to assess the presence, extent, stage, or progression of the disorders.

TMD symptoms vary amongst patients, for instance, patients with temporomandibular joint arthritis present to clinics with a complaint of pain, swelling, and joint noises, or they may have no symptoms at all despite progressive joint resorption. Several issues have emerged at the diagnostic level of TMD due to the heterogeneity of the disorder. The presence of comorbidities also makes this disorder more complex[12]. Like TMD, RDs are often chronic and debilitating, with adverse health outcomes. When combined, both RDs and TMD can have a detrimental influence on the individual health, psychosocial, and economic aspects of their lives[8]. Both patients and their families who suffer from RDs often face diagnostic and treatment challenges[13]. Healthcare professionals frequently grapple with constraints such as limited time, information, and resources to effectively diagnose and treat rare diseases[14,15]. Furthermore, individuals diagnosed with RDs confront substantial hurdles due to delays in treatment care and social acceptance.

Although TMD are not life-threatening, there are more significant rare clinical entities that manifest as TMD, and clinicians should be aware of these entities[15,16]. Among the potential manifestations of rare diseases, diagnoses related to TMD have scarcely been indexed, and there is no list of TMJ manifestations in rare diseases. The purpose of this review is, therefore, to explore TMD diagnosis in rare diseases, and classify TMJ manifestations in relation to their RDs. It is important to consider many potential symptoms, for instance, pain and complications relating to this region for rare diseases.

METHODS

This systematic review was elaborated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist[17].

Information sources and system behind the search criteria

The criterion for analysis of a rare disease and temporomandibular manifestations was inclusion in the Orphanet Classification of Rare Diseases and/or NORD/GARD databases. These databases cover the major definitions of rare diseases, including the EU and USA definitions of rare diseases. Only diseases defined as rare in these two databases were covered. The requirement for inclusion was the description of a Temporomandibular joint diagnosis or TMD/temporomandibular anomaly/condition/TMD symptom listed in the Orphanet or Pubmed databases. We used the "Search by Diagnosis, Clinical signs and Symptoms" function on Orphanet with the inputs: "Temporomandibular joint disorders (TMJD), joint disorders Temporomandibular, joint disorder Temporomandibular, TMD, disorder Temporomandibular, disorders Temporomandibular, TMJ disorders and TMJ disorder Anomaly of Temporomandibular joint, and Temporomandibular conditions". Search options for clinical sign(s)/symptom(s) were temporomandibular joint noises, pain, swelling, and limited mouth opening/impaired joint movement. Our relevant literature search in Pubmed used the same search as discussed in Orphanet with the following enhanced keywords: "rare disease" AND "temporomandibular joint diseases", "temporomandibular joint disease", diseases temporomandibular joint, TMJ disease as well as the input "diseases with temporomandibular manifestation" and "rare diseases with temporomandibular disorders" to cover any missed potential diseases.

Study selection

At the time of this study, there are 5,000 to 8,000 estimated number of RDs. There were 359 studies with orofacial manifestations listed in the database. All diseases recorded during the methodology described were subsequently compared with the Orphanet and NORD/GARD databases. Only diseases that appeared in either database were listed as rare diseases and continued to exist on the list. Figure 1 demonstrates search and selection process of studies with rare diseases and TMJ manifestations.

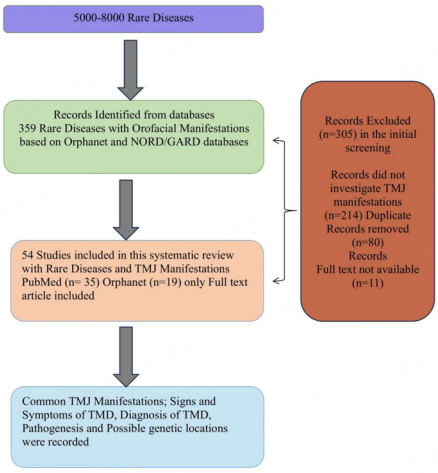

Figure 1. Showing the search and selection process of studies with rare diseases and TMJ manifestations. TMJ: temporomandibular joint.

Inclusion and exclusion criteria

For inclusion criteria, studies with rare diseases who had signs or symptoms of TMJ manifestations (joint noises, pain, and limited jaw movements/impaired joint movement) or diagnosis of TMJD/TMD or any temporomandibular conditions, anomaly and temporomandibular diseases were included. No restrictions regarding the participant's age, sex, and language of publication were applied.

Exclusion criteria were studies reporting only rare diseases or did not investigate TMJ, studies that did not provide separate data of the TMJ diagnoses, and studies with duplicated data from another included study or full text not available.

RESULTS

A total of 54 RDs with TMJ manifestations and diagnoses were recorded and included in the study. Pubmed input had 35 results, and the Orphanet input had 19 results [Table 1]. The RD-specific TMJ symptoms, the pathological mechanism (if known) that is responsible for the manifestation, and the corresponding gene locus (if known) are mentioned. The possible pathological mechanism leading to TMD is marked as "unknown" in Table 1 when it is "unknown" or "not researched" in the literature and "Not available", indicating no information on possible mechanisms related to the specific TMJ manifestation.

Of these 54 RDs, the mechanisms of the respective TMJ manifestations of five RDs is unknown. Twelve RDs are listed as "Not available", indicating no information on possible mechanisms related to the specific TMJ manifestation of the RD was identified in the study. Genetically, in the case of nine RDs, the manifestation and disease itself are considered to be "Not genetically determined". In fifteen RDs, the gene responsible for the manifestations is unknown, which implies either a lack of conclusive knowledge of specific genetic influences or a scarcity of relevant literature exploring these influences. Nine RDs had several different genetic associations, five of which involved different chromosomes. There was one RD, which had extreme variation in genetic cause for each specific case, and two other RDs, which had several non-genetic and genetic factors contributing cumulatively towards the observed phenotypic abnormalities.

13 different types of TMJ manifestations and TMD Diagnosis were reported [Table 2]. 18 RDs were diagnosed with arthralgia and myalgia. 14 RDs were diagnosed with ankylosis and TMJ arthritis. Only six

Table 1. Rare diseases with TMJ manifestations: symptoms, pathological mechanism, affected gene locations, and diagnosis

Disease name, ICD-11	TMJ manifestations/diagnosis	Possible Pathological mechanisms related to the temporomandibular manifestations	Gene, location of the disease
Acute lymphoblastic leukemia[26]	Pain/arthralgia and myalgia	TMD triggered by malocclusion in children	10q21, 7p12.2, PAX5 9p13
Aicardi-Goutières syndrome[27]	Limited jaw movements/TMJ ankylosis	Not available	TREX1, 3'-
Auriculo-condylar syndrome[28]	Limited jaw movements/TMJ Hypoplasia	Not available	Genetic variance in GNAI3, PLCB4, EDN1
Bilateral Plantar Fibromatosis[29]	Pain/arthralgia, myalgia	Not available	Unknown
Calcium pyrophosphate deposition disease[30]	Calcified deposits in the TMJ	Deposition of calcium pyrophosphate over the TMJ	Not genetically determined
Cardiocranial syndrome, Pfeiffer type[31]	Limited jaw movements/TMJ ankylosis	Not available	Unknown
Cary-Fineman-Ziter syndrome[32]	Limited jaw movements, pain/myalgia/ankylosis	Myopathy	MYMK
Chikungunya fever[33]	Pain/arthralgia, myalgia	Viral infection	Not genetically determined
Chondrosarcoma of Temporomandibular Joint[34]	Swelling, pain/arthralgia	Chondrosarcoma tumor in the TMJ causing bone destruction and joint-space widening	EXT1
Choreoacanthocytosis[35]	TMJ noises, disc disorders	Not available	VPS13A gene (9q21)
COPA syndrome[36]	Pain/Arthritis	Immune dysregulation	COPA gene-encoding COPα protein
Ehlers-Danlos syndrome, classical type [37,38]	TMJ noises, pain/arthralgia, myalgia, disc disorders	Altered structural collagens, mucosal fragility	COL5A1 or COL5A2, rare: p.(Arg312Cys) mutation in COL1A1
Ehlers-Danlos syndrome, Spondylodysplastic type[37,38]	TMJ noises, pain/arthralgia, myalgia, disc disorders	Altered structural collagens, mucosal fragility	SLC39A13
EPISODIC ATAXIA, TYPE 9[39,40]	Pain/myalgia	Not available	SCN2A gene on chromosome 2q23
Familial Mediterranean fever[41]	Pain/arthralgia, myalgia	The gene change affects the function of an immune system protein called pyrin, causing problems in regulating inflammation in the body	MEFV gene
Fibrodysplasia ossificans progressiva[42]	Permanent TMJ constriction/arthritis, pseudoankylosis	Intense fibroproliferation as a result of inflammation	ACVR1
Gorham-Stout disease[43]	Pain/TMJ arthritis/Hypoplasia	Aggressive bone reabsorption	Unknown
HOLOPROSENCEPHALY 9[44]	Asymmetry/TMJ hypoplasia	Not available	GL12 gene on chromosome 2q14
Hypoglossia or aglossia[45,46]	Limited jaw movements/TMJ ankylosis	Not available	Unknown
Hyperglossia with situs invertus[46]	Limited jaw movements/TMJ ankylosis	Not available	Unknown
Juvenile idiopathic polyarthritis, rheumatoid factor negative[47]	Pain, swelling/TMJ arthritis	Not available	Unknown
Juvenile psoriatic arthritis[48]	Pain, swelling/TMJ arthritis	Unknown	Unknown
Kawasaki Disease[49]	Pain, swelling/arthritis	Vasculitis/Inflammation	Unknown
Klippel-Feil syndrome[50]	Limited jaw movements/TMJ pseudo ankylosis	Not available	GDF6, 8q22.1 GDF3, 12p13.31 MEOX1, 17q21 MYO18B, 22q12.1 [https://www.omim.org/phenotypicSeries/PS118100]
Langerhans cell histiocytosis[51]	Pain/myalgia, arthralgia	Unknown	Not genetically determined
Lemierre syndrome[52] (NOT LISTED IN ICD-11, ICD 10:	Limited jaw movements/TMJ ankylosis	Likely a result of infection by Fusobacterium necrophorum	Not genetically determined

J03.8)			
Lethal restrictive dermopathy[53]	Limited jaw movements/TMJ ankylosis	Tightness of	Dominant LMNA gene mutation (locus 1q21.2
Loeys-Dietz syndrome type 1[54]	Limited jaw movements, asymmetry, pain, TMJ noises/myalgia arthralgia, disc disorders	TMJ limitation of movement and pain may	Heterozygous mutation in the TGFBR1 gene on chromosome 9q22
Lyme arthritis[55]	Pain, swelling/TMJ arthritis	Infection by Borrelia burgdorferi	Not genetically determined
Merosin-deficient muscular dystrophy[56]	Pain/myalgia	Deficiency or absence of laminin α2	Homozygous or compound heterozygous mutation in the laminin alpha-2 gene (LAMA2) on chromosome 6q22
Mucopolysaccharidosis type 2, attenuated form[57]	Limited jaw movements/TMJ ankylosis	GAG accumulation (glycosaminoglycans)	Gene encoding iduronate 2-sulfatase (IDS) on chromosome Xq28, missense mutations
Mucopolysaccharidosis type 2, severe form[57]	Limited jaw movements/TMJ ankylosis	GAG accumulation (glycosaminoglycans)	Gene encoding iduronate 2-sulfatase (IDS) on chromosome Xq29, apparently completely missing IDS?
Multicentric reticulohistiocytosis[58]	Swelling, pain/TMJ arthritis	Nodules in the TMJ	Not genetically determined
Multiple sclerosis[59]	Pain/TMJ arthritis/myalgia	inflammation and demyelination of different areas throughout the central nervous system	Variable
Myotonic dystrophy type 1[60]	Limited jaw movements, pain/arthralgia, myalgia	Degeneration of muscles around the facial region	heterozygous trinucleotide repeat expansion (CTG)n in the 3-prime untranslated region of the dystrophia myotonica protein kinase gene (DMPK) on chromosome 19q13
Ophthalmomandibulomelic dysplasia[61]	Limited jaw movements/TMJ ankylosis	Unknown	Unknown
Oromandibular dystonia[62]	Pain/myalgia, arthralgia	Sustained or intermittent muscle contractions	DYT-THAP1, DYT-TAF1, DYT-ATP1A3, DYT-KMT2B, DYT-PRKRA, DYT-TOR1A, DYT-CIZ1, DYT-ANO3, DYT-GNAL
Osteomyelitis[63]	TMD	Spread of malignant external otitis into temporal bone	Not genetically determined
Osteopathia Striata with Cranial Sclerosis[64]	Limited jaw movements/TMJ ankylosis	HYPERLINK [https://www.ncbi.nlm.nih.gov/medgen/331604] Unknown	WTX gene mutation
Pediatric Sjögren Disease and Sarcoidosis[65]	Pain/Arthritis	Immune-related gene	Unknown
Pigmented villonodular synovitis[66]	TMJ swelling, pain/arthralgia	Bone destruction of the mandibular condyle	Unknown
Relapsing polychondritis[67]	Pain, TMJ noises/TMJ arthralgia/DJD	inflammation, structural damage, and impaired function of cartilaginous tissues	Unknown
SAPHO syndrome[63]	Pain, limited jaw movements/TMJ ankylosis	Unknown	Multifactorial
Scedosporium apiospermum Otitis[68]	Pain/Arthritis	Infection	Fungal infection
Schwartz-Jampel syndrome[69]	Pain, TMJ asymmetry/myalgia	Not available	*HSPG2* gene
Septic arthritis[70]	Pain, swelling/TMJ arthritis	Methicillin-resistant Staphylococcus aureus infection of the TMJ	Not genetically determined
Sickle cell disease[71]	Pain, limited jaw movements, swelling/TMJ arthritis, myalgia	Vascular occlusion triggers infection	Hemoglobin genes
Synovial chondromatosis of Temporomandibular Joint[72]	Limited jaw movements, swelling, pain, TMJ noises/TMJ arthralgia, DJD	Cartilaginous metaplasia of the mesenchymal remnants of the synovial membrane	Unknown
Synovial sarcoma[73]	Limited jaw movements, swelling, pain/TMJ arthralgia	Malignant tumors of the synovial membrane	SS18 gene on Chromosome 18
Systemic Lupus	Pain, limited movements, TMJ	Unknown	PTPN22 1p13.2

Erythematosus[74]	noises /myalgia, arthralgia, disc disorders, DJD		FCGR2A 1q23.3 FCGR2B 1q23.3 CTLA4 2q33.2 TREX1 3p21.31 DNASE1 16p13
Systemic sclerosis[75]	TMJ noises, pain, limited jaw movements/myalgia, arthralgia, disc disorders, DJD	Mandibular bone resorption caused by a multifactorial process, including microvasculopathy and pressure ischaemia, secondary to thickening skin and muscle atrophy	Association with the FBN1 Gene on Chromosome 15q21.1, Association with the CTGF Gene on Chromosome 6q23, Association with the STAT4 Gene on Chromosome 2q32.2-q32.3
Tenosynovial giant cell tumor, diffuse[76]	Swelling, pain/arthralgia	Locally aggressive and proliferative tumor, bony destruction of the condyle	Unknown
Tuberculosis of the Temporomandibular joint[77]	Pain/TMJ arthralgia	Extrapulmonary TMJ infection with Mycobacterium tuberculosis	Not genetically determined
Unilateral condylar hyperplasia[78]	TMJ asymmetry/Hyperplasia	Condition etiology unknown, TMJ abnormality caused by	Unknown

TMD: temporomandibular disorders; TMJ: temporomandibular joint; DJD: degenerative joint disease.

Table 2. Number of rare diseases and TMJ manifestations

TMD Diagnosis	
18 RDs	Diagnosis of arthralgia and myalgia
14 RDs	Diagnosis of TMJ ankylosis and arthritis
6 RDs	Diagnosis of TMJ disc disorders
4 RDs	Diagnosis of TMJ DJD
3 RDs	Developmental disorders of TMD (hyperplasia)
1 RDs	Developmental disorders of TMD (hyperplasia)
1 RDs	Calcification deposits
1 RDs	TMJ constriction
1 RDs	Deviation from normal TMJ function
TMD signs and symptoms	
36 RDs	Pain is the primary symptom
21 RDs	Limited jaw movement
12 RDs	Swelling
8 RDs	TMJ noises (clicking and crepitus)
4 RDs	TMJ asymmetry

TMD: temporomandibular disorders; TMJ: temporomandibular joint; DJD: degenerative joint disease.

RDs had disc disorders and four RDs had diagnoses of degenerative joint disease (DJD). While three RDs reported TMD developmental disorders as hypoplasia of condyle, one RD had hyperplasia, one RD had calcified deposits, and one RD had TMJ constriction. However, in one RD, a deviation from normal TMJ function and structure was observed, reported as TMD. Among the signs and symptoms, 36 RDs had pain as the primary symptom, 21 RDs had limited jaw movements, 12 RDs had swelling, eight RDs reported TMJ noises, and four RDs had asymmetry, respectively.

Some of the pathological mechanisms of these RDs can be summarized into broad categories. Among the 54 RDs listed, five RDs are a result of infection by a virus or bacteria. Three different RDs are a result of varying degrees of bone reabsorption. Four RDs have their resulting TMJ manifestations due to an external, non-TMJ morphological factor inducing such manifestations. Five RDs result in a tumor in the TMJ area, causing the observed TMJ manifestations in the RDs. Three RDs have collagen defects, affecting the mucosal membrane and causing issues with their TMJ condition as a resulting consequence. Four RDs

possess muscular disorder, three being degeneration/dystrophy and one being involuntary contraction. Two RDs have excessive bone growth, one of which is an abnormal reaction to inflammation. Two RDs express glycosaminoglycan accumulation due to a lack of lysosomal enzymes. Lastly, two RDs have abnormalities with cartilage growth; one shows cartilaginous metaplasia, while the other results in impaired cartilaginous function. One specific RD, Lemierre syndrome, was not listed in the most recent edition of the International Classification of Diseases. It is, however, classified under section J03.8 (Acute tonsillitis due to other specified organisms).

DISCUSSION

To the best of our knowledge, this systematic review is the first to investigate TMJ manifestations and diagnosis in RDs using the selection criteria mentioned in the methods. Of the 5,000 to 8,000 estimated RDs[3], our study identified 54 definitive RDs with TMJ manifestation and diagnosis, representing 0.5%-0.8% of all RDs. Due to the paucity of research on rare diseases and orofacial manifestations, the comparison with other studies remains unknown. However, in a recent literature search, periodontal manifestations in RDs were reported[18]. According to Hanisch *et al.*, periodontal manifestations were determined in almost 14 percent of RD, which represents 0.95%-1.52% of all RDs[18]. Comparatively, our results place TMJ manifestations as a rarer complication among RDs than periodontal manifestations. Another study identified 106 RDs with periodontal relevant manifestations; however, the results are challenging as some of the RDs could not be found in the Orphanet classification of Rare Diseases[19].

The presentation of TMD is diverse and the symptoms may vary from mild, transient, recurrent, self-limiting to severe disabling, impacting the individual's quality of life. The pain is the primary reason patients seek treatment for TMD[20]. With the data available, our study evaluated the signs and symptoms of TMD in rare diseases. The present review reported 36 RDs with pain in the TMJ or preauricular region and muscles of mastication. In addition to pain, limited mandibular movements in 21 RDs, TMJ swelling in 12 RDs, TMJ noises in eight RDs, and TMJ asymmetry in four RDs were observed. Although TMJ noises are the most common symptoms of TMD, disc disorders and degenerative changes were not quite common in rare diseases. Furthermore, despite the fact that most RDs are syndromic and have a genetic etiology, TMJ asymmetry was also a rare clinical characteristic. The reason for this disparity is that there are only few reports in the literature on rare diseases with TMD diagnosis, and joint noises are asymptomatic and only a small percentage of affected individuals seek or require treatment.

Given the overlapping signs and symptoms among the majority of RDs and the scarcity of literature on RDs with TMJ manifestations, it is difficult to provide substantial evidence pinpointing specific TMD symptoms to particular rare diseases. Moreover, both TMD and RDs are chronic and progressive conditions, which exhibit diverse symptoms that are subjective and tend to vary over time, rendering it challenging to predict the most common symptoms. Thus, to clarify these variabilities, longitudinal studies are needed to evaluate the exact signs and symptoms and radiographic findings instead of analyzing the data.

Although TMJ manifestations are fewer in rare disease patients, it is important to recognize the signs and symptoms of TMD to enable the early diagnosis and the implementation of effective management strategies. Hence, healthcare professionals should perform a comprehensive history and complete clinical examination of each patient to understand the complexity of rare diseases with TMJ manifestations. TMD diagnosis has substantially improved over time, with the most recent diagnostic criteria for TMD (DC/TMD) being reliable and valid for most common diagnoses[20]. In this review, TMJ articular disorders including arthralgia, arthritis, disc disorders, DJD, ankylosis, and common muscle disorders such as myalgia, myositis, and other muscle disorders were classified based on the rare diseases. The most common diagnoses in the

literature search were arthralgia and myalgia, which accounted for 18 RDs. Additionally, TMJ ankylosis and TMJ arthritis were also predominant in the rare diseases. For some RDs, such as calcium pyrophosphate deposition, there is not enough data on TMD symptoms. Similarly, with conditions such as osteomyelitis, there exists a range of symptoms and diagnostic complexities. The reason for this disparity is that most of the rare disease had varied presentations or diagnostic challenges related to TMD, and most of the studies did not utilize the DC/TMD, which demonstrate excellent sensitivity and specificity in diagnosis. Hence, for many patients, the goals of therapy should be tailored towards an improved quality of life, which might be more realistic than meaningful pain reduction. An appropriate TMD management strategy should aim to alleviate the main signs and symptoms of this condition. As a result, for painful TMD, a multidisciplinary treatment approach is recommended[21].

Over the past decade, there has been tremendous progress in both TMD and RD research, especially in understanding pathogenesis, diagnosis, and management. However, there is still a lack of clarity in understanding the underlying mechanisms of TMDs and comorbid features[22,23]. Additionally, epigenetics, gene discoveries, and associated biopsychosocial models have improved our understanding of chronic painful TMD and RDs. Undeniably, a genetic diagnosis offers the potential for personalized management and yet opens another door of challenges in treatment availability and affordability. However, making a correct diagnosis is still challenging due to the heterogeneities and rarity of each RD[8,24,25].

One of the major barriers to identifying signs or symptoms and obtaining a diagnosis is the lack of knowledge of RDs. The novelty of analyzing TMJ manifestation in RDs raises the possibility of oversights in the number of RDs that actually involve TMJ manifestation. The combination of multiple databases in this study resulting in our RD yield indicates that many potential TMJ-involving RDs could exist undetected in other locations. Furthermore, RDs are usually harder to gauge due to limited literature and a lack of standardized methodologies to collect related data. Hence, patient registries are critical in tailoring evidence-based care for individuals with rare diseases and TMJ manifestations because they help to overcome the inherent challenges of rare disease research by pooling data and achieving adequate sample sizes.

LIMITATIONS

Since the present study is the first work to analyze and gather RDs with TMJ manifestations, there are several limitations to this study. The absence of electronic search using alternative keywords and comparable publications narrows possible insights into RDs that are missing from this compilation. Additionally, due to the rarity of several diseases on this list, information such as pathological mechanisms and genetic origin are still unknown. Similarly, different signs, symptoms, and diagnoses of TMD and their relationship with RDs were not explored in a uniform manner. The absence of a standard for the evaluation of TMJ manifestations introduces confusion in possible methods of categorizing different associated developments. Scattered databases and reports/articles about relevant TMJ symptoms and diagnoses in RD patients lead to inevitable omissions of certain cases. Lastly, the inconsistent definition of RD across international medical databases undermines the content of this study's collection.

CONCLUSION

There are only 54 identified RDs with TMJ manifestations. Some TMJ manifestations are common in RDs, and hence, healthcare professionals play an important role in identifying the TMD symptoms and tailoring personalized treatment plans. A multidisciplinary approach to TMD patients with rare diseases is advisable. However, making a correct diagnosis is still challenging due to the complexities of TMD and the rarity of each of the RDs. In order to mitigate these issues, patient registries are thought to be a key step that can not

only significantly improve disease classification but also contribute to developing an evidence-based personalized treatment for rare diseases with TMJ manifestations and other comorbidities.

DECLARATIONS

Authors' contributions

Design of the methodology and the search algorithm: Shrivastava M, Tian G, Ye L
Blind selection of the articles: Tian G, Ye L
Writing of the manuscript: Shrivastava M, Ye L

Availability of data and materials

All data supporting the findings of this study are available within the paper.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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