Review

Orofacial Manifestations Associated with Muscular Dystrophies: A Review

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Main Points
- Patients with muscular dystrophies present alterations in growth and development as well as in orofacial morphology.
- Increased prevalence of malocclusions, of both skeletal and dental origins, characterize patients with muscular dystrophies.
- Different dentofacial characteristics are reported among patients with different types of muscular dystrophies.
- Further research is needed to clarify the orofacial phenotypic expression of muscular dystrophies.

ABSTRACT

The aim of this review is to evaluate the developmental, functional, and morphological aspects of the craniofacial complex in patients with myotonic dystrophy type 1 (DM1), Facioscapulohumeral muscular dystrophy (FSHD), and Duchenne muscular dystrophy (DMD). The degree of disease onset and severity varied from patient to patient, and most parameters indicated a greater degree of deterioration in older patients. It was found that all the muscular dystrophies studied showed altered craniofacial morphology, with malocclusion as the most consistent clinical characteristic. Particularly DM1 patients, who are the most studied, showed significant vertical aberration and post-normal occlusion. DMD patients are reported mainly with altered dental arch dimensions which influence functional capacities. Data for FSHD patients are very limited, but facial asymmetry and muscular weakness appear to be the most prominent findings. Patients with muscular dystrophies present deviations in growth and development as well as in orofacial morphology. Increased prevalence of malocclusions, of both skeletal and dental origins, characterize patients with muscular dystrophies. Different dentofacial characteristics are reported among patients with different types of muscular dystrophies. Further research is needed to clarify the orofacial phenotypic expression of muscular dystrophies.

Keywords: Genetic myopathies, myotonic dystrophy type 1, facioscapulohumeral muscular dystrophy, Duchenne muscular dystrophy, dentofacial morphology

INTRODUCTION

Muscular dystrophies are a group of hereditary degenerative diseases that affect the structure of skeletal muscles. They present related clinical symptoms, which include progressive dystrophic changes in muscle tissue. Moreover, they gradually destroy muscle cells, substituting them with connective tissue, resulting in progressive impairment of muscle strength and function. Muscular dystrophies are often characterized by atrophy in axial, facial, upper, and lower limb musculature. Other groups often affected by degenerative changes include the heart, respiratory, swallowing, and eyelid muscles.[1]

Various researchers have reported an impact of muscular involvement in the growth of the craniofacial complex.[2,3] The effects of a neuromuscular disease on the craniofacial muscles potentially disrupt both facial morphology

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and the functional aspects of dental occlusion. Although the effect of muscular weakness on the function of the craniofacial complex is reported in the literature, there are few systematic studies regarding the evaluation of such patients. Possible findings may contribute toward improvements in both the diagnostic and treatment regimens.[4]

The present review assesses the manifestations of the selected dystrophies through the prism of dentofacial science. The ultimate goal is to combine genetic testing, which verifies the presence of muscular dystrophy, with the orthodontic approach, which studies the effects on the function of the craniofacial complex, potentially leading to improved understanding of the etiology of such diseases to improve the quality of life of the patients.

MYOTONIC DYSTROPHY TYPE 1 (DM1)

Epidemiology
DM1 is one of the most common neuromuscular diseases in adults. The prevalence of the disease is 1:8000 births.[5]

Genetic Background
DM1 is inherited with an autosomal dominant pattern. The genetic locus of DM1 is localized in the long arm of chromosome 19.[6] The molecular basis of DM1 is proved to be caused by an unstable expansion of a trinucleotide repeat (CTG).[7] This repeat is localized in an untranslated area of the protein kinase gene of myotonic dystrophy (DMPK). This gene is expressed considerably in the heart, muscles, and to a lesser extent in the brain.[8]

The length of the trinucleotide repeat has been associated with the severity of the disease and the onset of the symptoms. The size of the repeats in the general population (normal individuals) mostly varies between 5 and 35 CTG. Patients with DM1 inherit a minimum of 50 repetitions, and in some cases, 2000 or more. The expansion of the trinucleotide repeat is found to be increased in consecutive generations of both female and male descendants.[9]

Clinical Picture
The dominant symptoms of DM1 include myotonia and progressive muscle weakness, especially in the face and furthermost areas of the upper and lower limbs. In addition, impairment has been reported in cardiac conductivity, smooth muscle system, hypersomnia, and cataract. In male patients, symptoms such as hair loss, testicular atrophy, infertility, and sexual dysfunction have been depicted.[10]

The weakness distribution is quite characteristic in DM1. In the early onset and frequent symptomatology, weakness of the facial musculature, eyelid ptosis, and impairment of the sternocleidomastoid muscle is included . Atrophy and degradation of temporal muscle lead to a concave shape of the temporal bone.[10] Furthermore, atrophy and degeneration of the masseter muscle have been diagnosed in patients with DM1 through an ultrasound examination.[11] Finally, the atrophy and weakness of pharyngeal muscles, resulting in a nasal tone in the patient's voice, affecting enunciation.[12]

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Epidemiology
FSHD (MIM#158900), known as Landouzy–Dejerine disease, is one of the most common forms of muscular dystrophy, with an autosomal dominant pattern, with an estimated prevalence of 1:20 000. Although it was initially reported that most of the patients affected were male, the majority of asymptomatic patients were more frequently females. Therefore FSHD is believed to affect both genders equally.[13,14]

Genetic Background
FSHD is thought to result from the abnormal expression in muscle of a gene called DUX4. Typically, DUX4 is expressed only during early embryogenesis and in the cells that develop into sperm. However, when expressed in muscle tissue, DUX4 appears to be toxic.

Linkage studies have reported the genetic locus for FSHD in the DUX4 gene on the long arm's subtelomeric region in chromosome 4 (4q35).[15] Moreover, in this area, a repeating micro-satellite array was located. The size of this repeating array depends on the number of repeats named D4Z4 with a length of 3.3 kb (16). Individuals who suffer from FSHD1 carry a reduced number of 1-10 D4Z4 repeats, while non-patients have 11-100 repeats.[16-18]

Definitive diagnosis of FSHD is facilitated only through molecular genetic testing. This can be achieved with the Southern blot technique, by determining the number of repeating D4Z4 arrays, with the use of genomic DNA, which is digested with EcoRI and hybridized with the probe p13E11.39. Numerous reports have described an inverted relationship between the severity of the clinical symptoms and the number of D4Z4 repeats, because patients with a smaller number of repeat arrays exhibit a more severe phenotype. It is worthwhile mentioning that 5% of FSHD patients do not present deletions of D4Z4 arrays (non-linked FSHD) and are considered to be related to a second phenotype known as FSHD2.[17,19]

Clinical Picture
FSHD is described as a slow and gradually progressing muscular dystrophy, with onset in the second or third decade of life. The symptoms can develop at any age, from infancy through advanced age. The most prominent symptoms are weakness of the facial and shoulder muscles, followed by ankle and medial leg musculature weakness. There have also been reports of congenital and early onset cases, with various symptoms and degrees of severity.[20]

The disease shows gradual progression, due to which it is quite common that patients do not report all of their symptoms because they consider them to be caused by other diseases or injuries. In addition, although FSHD is inherited with an autosomal dominant pattern, an adverse family history does not exclude the existence of the condition. Between 10% and 30% of cases are caused by new (de novo) mutations and by asymptomatic gene carriers, which are frequently found in families with FSHD.[15]

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DUCHENNE MUSCULAR DYSTROPHY (DMD)

Epidemiology
The estimated prevalence of DMD is estimated at 1:3300-4700 live male births.[21]

Genetic Background
DMD is an inherited myopathy, in which a genetic mutation is observed in the Xp locus, in the short arm of the X chromosome.[22] DMD is an X-linked disease caused by the absence of a protein named dystrophin, which is found more frequently in skeletal muscles and neurons in specific regions of the central nervous system.[23,24]

Clinical Picture
The initial DMD symptoms appear in childhood (usually around 5 years of age) with difficulty in walking. The most prominent symptoms include severe progressive muscle weakness in the pelvic, shoulder, upper, and lower limbs.[25]

METHODS

A literature search was conducted, including the online databases PubMed, Google Scholar, Scopus, Cochrane Library, MEDLINE, and Embase, by using the following search terms and their combinations: "Orofacial manifestations" AND "Muscular Dystrophies" OR "Genetic Myopathies," "Orofacial manifestations" AND "Myotonic dystrophy," "Orofacial manifestations" AND "Facioscapulohumeral muscular dystrophy," "Orofacial manifestations" AND "DMD." The references from the identified articles were incorporated to discover supplementary related publications.

Our inclusion criteria were the following:

1. Clinical studies based on humans only, including randomized control trials, clinical control trials, prospective or retrospective cohort studies, case reports, and case series.
2. Scientific articles written in the English language, and those in other languages were included if an English abstract was available.

Our exclusion criteria were in vitro or animal studies, and clinical outcomes based on questionnaires. Scientific articles in other languages than English, without an English abstract.

Clinical and Research Consequences
The total number of articles that met our inclusion criteria was 38. These articles were assessed and consequently reviewed.

Manifestations of DM1
The majority of research conducted regarding the manifestations of DM1 is currently related to the effects of the disease on craniofacial growth and development. Patients diagnosed with an early onset of DM1 present a hyperdivergent facial growth. A weak muscular system combined with a disrupted force equilibrium affects both the morphology of the craniofacial complex and the occlusion.[26,27] Patients with DM1 exhibit increased vertical facial growth compared to the normal population, narrower

maxilla in the transverse dimension, and deeper palatal vault.[6,26,28] Kiliaridis et al.[26] reported an increased prevalence of malocclusion in DM1 patients, such as retrognathic maxilla and mandible, anterior open bite, and posterior crossbites. These results come in agreement with those reported by other researchers.[28,29]

Gazit et al.[30] described decreased strength in the orbicularis oris muscle, tongue thrusting, and oral breathing. Also, temporomandibular joint symptoms tend to affect patients with DM1, such as disc displacement, repeated locking during opening or closing of the mouth, and clicking sounds.

As reported by various researchers, the decreased biting force of DM1 patients advocates for impaired muscle strength due to the disease.[31] The involvement of facial musculature might be the reason for the mandibular clockwise rotation, either due to gravity or due to the absence of supra-hyoid muscle support.[32] This mandibular movement consequently affects the position of the tongue and head posture. In addition, new conditions are formed around teeth in the transverse dimension. The tongue, is positioned lower in the oral cavity, following the mandibular rotation, and cannot counterbalance the forces created by the disrupted facial musculature. These newly established conditions could affect the transversal position of the teeth, reducing palatal width and causing posterior crossbite. In combination with the decreased occlusal forces, the new postural position of the mandible might contribute to over-eruption of the maxillary posterior teeth. In this case, the palatal depth increases because of the overeruption. The lower jaw may rotate even more in the clockwise direction, contributing to the increase of the angle between the mandibular plane and the palatal plane.[33]

The increased prevalence of Angle Class II malocclusion in patients with DM1 is quite possibly linked to this mandibular posterior rotation. Moreover, changes in the mandibular plane angle are in concordance with Wolff's theory (1892), which states that bone shape and structure are related to the pressure of the functional forces applied by the muscles.[34] The facial and occlusal characteristics of DM1 patients resemble the "adenoid face," where the neuromuscular adaptation contributes to a secondary backward rotation of the mandible and changing of head posture to facilitate oral breathing. Notably, in myotonic dystrophy patients, the muscular weakness is the reason which leads to the backward rotation of the mandible, contributing to oral breathing, because these patients do not present impairment of nasal breathing.[35]

Difficulties in mastication and swallowing as symptoms of DM1 have been reported in the literature.[9,29,35-37] Kiliaridis et al.[26] described that DM1 patients need 2.5-fold more time for mastication and have 2.5-fold larger mastication cycles than healthy controls. Also, they had, on average, the half-maximal biting force compared with a healthy population.[26] Swallowing difficulties are related to myotonia, muscle atrophy, and weakness, xerostomia. In more detail, cases of choking during feeding, repeated swallowing attempts, and gastroesophageal reflux have been reported.[36] Harper et al.[9] highlighted the importance

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of palatal morphology in swallowing. In combination with the mandible and tongue position, this could precipitate aspiration of food into the bronchial tree.[9] This condition could be further aggravated by the degradation of pharyngeal and esophageal muscles.[9] According to Sjogreen, congenital and childhood-onset cases of DM1 exhibit reduced facial expressiveness, apprehension, feeding difficulties, and sialorrhea compared with healthy children of the same age.[38]

Finally, in a lateral cephalometric radiography study conducted by Fotinha et al.[39] in 2018, the following findings were reported in patients with childhood-onset and congenital form of muscular dystrophy. In the sagittal plane, the ANB angle was increased, and the SNPg angle was decreased in DM1 patients. In the vertical plane, in concordance with the literature, the mandibular plane angle (ML-SN) and the intermaxillary angle (ML-PP) were increased compared with a healthy population. Moreover, a difference was noted in the anterior cranial base angle (NSBa), which was reduced in DM1 patients. It is worthwhile mentioning that in 5 years, mandibular plane and intermaxillary angles did not decrease, in contrast with the same values in unaffected subjects.[39]

Manifestations of FSHD

One of the most characteristic symptoms of FSHD is the asymmetric weakness of facial muscles. The ones who are more frequently affected are orbicularis oris, orbicularis oculi, and the zygomaticus major muscle. Facial weakness is quite evident in 25% of patients, and often the participation of facial muscles is not recognized by up to 60% of the patients themselves. The patients themselves rarely report symptoms of facial weakness, and for that reason, it is quite essential that they are assessed by the examining clinician.[20,40]

The weakness in the orbicularis oculi affects the patient's ability to close his eyelids. Many tend to sleep with their eyelids partially open and experience a conjunctiva inflammation when they wake up. When a patient with a more severe phenotype is asked to closed his eyelids Bell's phenomenon is apparent, which is an upward and outward movement of the eye. Furthermore, the lower weakness of orbicularis oculi may lead to "signe de cils," which is characterized as the eyelashes' inability to close entirely when the patient attempts to close his eyes tightly.[41,42]

The weakness in the orbicularis oris muscle results in evident asymmetry when in a rest position, which is quite prominent when the patient is asked to contract his lips or fill his cheeks with air. Tasks such as whistling, blowing a balloon, or consuming a liquid from straw could be quite challenging. In some cases, though, the upper lip might lose its mobility. The affection of zygomatic muscles contributes to the impaired ability to raise the corners of the mouth. Thus, when the patient tries to smile, his lips move in a horizontal direction producing the so-called "transverse smile," characterized as a frowning grin. In many patients with a severe clinical picture of the disease, an extended weakness of the facial muscles may lead to a "myopathic face" absent of facial expressions.[41,42]

Finally patients with FSHD present poor oral hygiene, impaired masticatory functions, decreased mouth opening, high palatal vault, narrow dental arches, and a variety of malocclusions.[43]

Manifestations of DMD

After evaluating dental casts of DMD patients, Egli et al.[44] reported a higher prevalence of malocclusion compared with the healthy controls. First of all, anterior and posterior open bites were more frequent in DMD patients. The overbite was considerably decreased in individuals with DMD, supporting the increased tendency of anterior open bites. Moreover, changes in overjet and molar relationship were not found to be of significance. During the 2-year assessment of DMD patients by Egli et al.[44] the changes that were identified as most significant were in the transverse dimension, especially the increment of inter-molar, inter-premolar, and inter-canine mandibular widths. According to the assessment of cephalometric radiographs, the ANB angle was decreased over 2 years, while NSBa was increased. The SNB angle had also reduced, but not significantly.[44]

The maximal bite force of posterior teeth, as well as the labial force, were reduced in DMD patients compared to the control group.

The healthy population presented an increase in the previously mentioned categories during the 2 years in contrast with the individuals with DMD. Regarding the masseter muscle width, no significant differences were noted between the 2 groups.

Another study conducted by Morel et al.[45] reported a tendency for an Angle class III malocclusion in older DMD patients. Overjet exhibited a significant decrease during the growth of DMD patients compared with the healthy population.[45] In addition, the transverse dimension results were in concordance with those found from Egli et al.[44] The presence of posterior crossbites was increased in DMD patients. In both upper and lower arches, an increment of the inter-molar and inter-premolar widths was reported, as well as an increase in the mandibular inter-canine distance. It is worth mentioning that inter-molar distance was considerably increased in older patients, leading to the conclusion that individuals with DMD presented progressive wider mandibular dental arches. The angular measurements of ANB and lower incisor inclinations and the lower arch depth were reduced. Finally, the values of the mandibular plane angle (ML-SN) and intermaxillary angle (ML-PP) did not present any statistically significant difference between the DMD patient and the healthy control group.[44,45]

DISCUSSION

The reviewed literature demonstrates the orofacial manifestations of 3 of the most frequent types of muscular dystrophies.

According to the existing research, young patients with congenital or childhood-onset DM1 present a differentiated craniofacial morphology and an abnormal growth pattern compared to the average population. Particularly, differences at the sagittal level were observed with retrusion of the mandible as the more

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significant. In the vertical dimension, the mandibular plane and intermaxillary angles were significantly increased in DM1 patients and did not decrease during a longitudinal assessment in a 5-year period as documented in healthy controls.[26,28] A possible explanation could be that DM1 patients have a head posture similar to individuals who present oral breathing. This fact is consistent with the findings in patients with an oral breathing pattern, who had a smaller anterior cranial base angle (NSBa) similar to the DM1 patient group.[35] The craniofacial characteristics of DM1 can possibly be linked with weakness of the masseter muscles, which could impair the oral health as well as the function of the patients.[38] Individuals with such a clinical picture might present further deterioration of their oral functions, and their diet should be accordingly adjusted.[46] Furthermore, it has been described that populations with neuromuscular diseases, and especially with DM1, present an increased prevalence of malocclusions. This tendency for malocclusions could be correlated with the deviation of the vertical dimension during the craniofacial growth and development, which is affected by masseter and hyoid muscle impairment and leads to a backward head posture. Finally, it is worth mentioning that the facial muscles' weakness may lead to a clockwise rotation of the mandible, resulting in decreased occlusal forces in the posterior teeth region. This condition could initiate the overeruption of posterior dentition, causing a deeper palatal vault, reduced palatal width, and posterior crossbite, as it has been documented.[26] DM1 affects patients from a young age, and in some instances, the deviation of the vertical dimension of craniofacial morphology could be characterized as an initial sign of the disease.

Facioscapulohumeral muscular dystrophy exhibits a progressive, gradual muscular weakness, although disease severity differs even between members of the same family. If we compare other muscular dystrophies with FSHD, it has been described that the latter possess a steady progression course. Due to alternating periods of steady progression and rapid development of muscle weakness, the anticipation of disease course is challenging. The main factors contributing to a severe phenotype are the early onset of symptoms and short repeat arrays (10-20 kb).[47] Although life expectancy is not reduced, FSHD patients should seek genetic counseling to obtain information regarding possible upcoming disease flare-ups.[20] It is already known that FSHD affects the face, shoulders, back, and leg muscles.[41] Patients frequently do not recognize the disease's symptoms and signs, highlighting the necessity of neurological clinical examination and diagnosis confirmation through genetic testing.

It has been demonstrated from current research that DMD affects both orofacial function and structure.[48-50] Phenotypes of older patients deteriorated on a larger scale than younger ones, and cases of an open bite, reduced overjet, and posterior crossbite appear at a higher prevalence. Although a significant skeletal deviation with a tendency towards an Angle Class III skeletal malocclusion was reported in the sagittal dimension, at the vertical level, no statistically significant changes were noted, despite the decreased overbite. The fact that the ANB is decreased tends to confirm the Angle Class III pattern of skeletal growth. It could be hypothesized that the impairment of orofacial function contributed as an etiologic factor in the development of malocclusions.[48-50]

The increased tongue volume, as described by van den Engel Hoek et al.,[48,51] interferes with the posterior dentition's lingual surfaces, leading to an increased inter-molar distance more prominent in the lower than in the upper arch and causing a posterior crossbite. Likewise, the increased tongue volume that might lead to interferences between the posterior dentition could also contribute to development of an open bite.[49,52,53] Moreover, in most patients, there was a buccal inclination of the posterior teeth disrupting the lower arch's parabolic shape, probably due to increased tongue volume.[48,49] It needs to be mentioned that the research by Egli et al.[44] disagrees with the findings of Matsuyki et al.,[54] where it is stated that the mandible rotates backward during growth and the patient's skull can be characterized as dolichocephalic.[44,54] Furthermore, the biting force seemed to diminish, and labial strength remained constant in DMD patients through an extended period, in contrast with the control group, where it was increased. The reason behind this difference might be the progressive weakness of the skeletal muscles.

Nonetheless, the masseter muscle's width did not change, although it is proved that a correlation exists with biting force. A possible explanation for this contradiction could be the substitution of muscle tissue with adipose and connective tissue.[55] The preservation of right occlusion and adequate muscle function for the longest possible time could be vital for an acceptable quality of life of DMD patients.

At this point, we need to highlight that not all patients with muscular dystrophies present the same manifestations in their craniofacial morphology. Comparing the existing literature regarding the orofacial characteristics of DM1 with DMD patients, the latter show a higher tendency for malocclusions, including posterior crossbites due to wider mandibular arches, anterior and posterior open bites, and a tendency for an Angle Class III malocclusion. In the vertical dimension, DMD patients do not seem to present significant deviations. On the other hand, DM1 patients present a higher tendency of deviation of vertical growth, with a clockwise rotation and a retruded position of the mandible.[26,44,45] Although both diseases are characterized by muscular weakness, the posterior crossbite's etiologic factor in DM1 patients is the narrower maxillary arch. On the contrary, posterior crossbite develops in DMD patients due to the transversal widening of the mandibular arch, caused by the reduced tension of the masseter muscle close to the molar region. This, coupled with the oversized but decreased tonicity of the tongue, leads to disruption of the force equilibrium in the oral cavity resulting in the widening of the lower jaw.

The functional matrix theory highlights the muscles' influence on the growth and development of the craniofacial complex.[56] Their impairment by a neuromuscular disease could have adverse effects on the morphology and function of the craniofacial complex, necessitating additional investigations on the topic. Future findings may aid both in clinical diagnosis and treatment planning of a patient with muscular dystrophy. Improved knowledge

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regarding the phenotypic expression of neuromuscular diseases in the orofacial region may help to particularize genotype-phenotype studies resulting in a higher quality of evidence. For example, the evaluation of facial morphology by incorporating 3D stereophotogrammetry applied by Pucciarelli et al.[57] on patients with spinal muscular atrophy demonstrated the first group of manifestations on facial soft tissues.[57] Similar assessments of the craniofacial complex could be done in various neuromuscular diseases, including muscular dystrophies, aiming at the comparison of their manifestations, facilitating more precision in diagnosis, and differentiating overlapping characteristics that frequently portray these diseases.[57]

A thorough examination of muscle weakness is strongly suggested before the start of treatment because the progressive course of the disease could convolute treatment prognosis. Clinicians, particularly orthodontists, should be very careful when patients who present muscle weakness signs inquire about treatment. It is pretty often that patients with neuromuscular diseases are not aware of their condition, even though the orofacial manifestations of the disease appear before the systemic ones, particularly at young ages. Consequently, the recognition of early neurological symptoms may be critical to the diagnosis of an underlying neuromuscular disorder and establishing a more precise treatment and post-treatment retention plan.

CONCLUSION

The findings of the present review suggest that patients with muscular dystrophies exhibit alterations in growth and development as well as in dentofacial morphology. According to numerous reports, increased prevalence of malocclusions, of both skeletal and dental origins, are strongly associated with muscular dystrophies. Nevertheless, different orofacial morphological and functional characteristics are reported among patients with different types of muscular dystrophies. Finally, future research could aim at elucidating the genotypic–phenotypic correlation in patients suffering from muscular dystrophies.

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