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ORIGINAL ARTICLE

Dysferlinopathies: phenotypic study of a Moroccan series of 28 cases

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Introduction. **Dysferlinopathies are a spectrum of autosomal recessive muscular dystrophies caused by mutations in the dysferlin gene (DYSF), leading to heterogeneous phenotypes, mainly limb-girdle muscular dystrophy type 2R (LGMDR2) and Miyoshi distal myopathy (MMD1). In Morocco, dysferlinopathies accounted for 18% of all limb-girdle muscular dystrophies, ranking second after sarcoglycanopathies.**

Methods. We retrospectively analyzed 28 confirmed cases, diagnosed either by dysferlin deficiency or DYSF mutation.

Results. The median age at examination was 25,5 years (21-33). Twelve patients (43%) were female, and 19 (68%) had consanguineous parents. The proximodistal phenotype was predominant (50%), followed by LGMDR2 (39%) and MMD1 (11%). Selective biceps brachii involvement was observed in 68% of patients. Seven patients (25%) showed hypertrophy of the extensor digitorum brevis muscle, and two (7%) presented with severe genu recurvatum. In addition to dystrophic lesions, muscle biopsy revealed inflammatory infiltrates in 15 cases (58%), leading to an initial misdiagnosis of inflammatory myopathy in two cases. Dysferlin deficiency confirmed the diagnosis in 26 cases, while two others had homozygous DYSF variants. Four patients received corticosteroids, with clear improvement in only one. Overall, disease progression was slow, although two patients lost ambulation at the ages of 26 and 32. Regular physical activity appeared to have a beneficial effect in most patients.

Keywords: dysferlin, miyoshi myopathy, limb-girdle muscular dystrophy, LGMDR2

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Introduction

Dysferlinopathies are autosomal recessive inherited muscular dystrophies, caused by mutations in the DYSF gene, which encodes dysferlin, a skeletal muscle protein involved in membrane repair and regeneration [1]. Several clinical phenotypes have been associated with dysferlin deficiency, most commonly limb-girdle muscular dystrophy R2 (LGMDR2) and distal Miyoshi myopathy type 1 (MMD1). LGMDR2 describes a phenotype with predominant proximal weakness in the lower and upper limbs at presentation, and was previously called LGMD2B before the recent consensus review of LGMD nomenclature [2]. MMD1 is characterized by predominantly distal lower limb weakness at disease onset [3]. Additional phenotypes have also been described, including proximodistal presentation, distal anterior compartment myopathy, and asymptomatic hyperCKemia. Many studies have reported that a high proportion of patients had good physical performance prior to symptom onset, suggesting that intensive exercise may act as a disease-triggering factor [4]. As the disease progresses, clinical features tend to overlap, with muscle weakness extending both proximally and distally. Consequently, phenotypic distinctions are most evident at disease onset but become less discernible over time [5]. Early onset in young adults, slow progression, elevated creatine kinase (CK) levels, and muscle inflammation are the cardinal signs of this disease. Among the various limb-girdle

muscular dystrophies, dysferlinopathy is particularly likely to be confused with inflammatory myopathy, reported in approximately 25% of cases [6]. The demonstration of dysferlin deficiency in muscle tissue, and the identification of pathogenic variants in the DYSF gene, are the key diagnostic tools for dysferlinopathy. All types of DYSF variants have been reported, including missense, nonsense, deletions, insertions, and splicing mutations, but no clear genotype-phenotype correlation has been established [7]. In the present series, we describe the clinical features of 28 patients with dysferlinopathy from 26 Moroccan families.

Patients and methods

We retrospectively collected clinical and paraclinical data from all patients diagnosed with dysferlinopathy, who were followed up in the neuromuscular disease consultation at the Department of Clinical Neurophysiology, Hospital of Specialties, Rabat, Morocco, between January 2004 and January 2024. Inclusion criteria comprised the absence of dysferlin expression in muscle immunohistochemistry and/or the presence of pathogenic variants in the DYSF gene in either the patients or their family members diagnosed with dysferlinopathy. Demographic information, such as date of birth, gender, and consanguinity status were collected. Symptom duration was calculated as the interval in years between the initial visit and the reported onset of muscle weakness.

All patients underwent a thorough neuromuscular evaluation using the Medical Research Council (MRC) scale, as well as respiratory and cardiac assessments at baseline and during follow-up visits. Additional data analyzed included creatine kinase (CK) levels, electromyography (EMG), muscle biopsy results, and molecular genetic testing. Disease progression was assessed in patients with available follow-up data, using MRC scale and functional abilities scores (Tab. I). Ambulatory status was evaluated with the Modified Walton-Gardner-Medwin Scale (WGM), a validated 10-point functional scale commonly used in muscular dystrophies. This scale ranges from grade 0, indicating normal ambulation including running and climbing stairs, to grade 10, representing complete dependence and being bedridden. Upper limb function was assessed using the Brooke Upper Extremity Scale, which evaluated arm mobility on a 6-grade scale (0-5), where grade 0 corresponds to full arm function and grade 5 indicates no useful arm movement.

Statistical analysis was performed using Jamovi software (2.0.0). Quantitative variables are presented as mean ± standard deviation or median with interquartile range, depending on their distribution. Frequencies were reported for categorical variables. Normality was assessed using the Shapiro–wilk test, and statistical significance was set at $p < 0,05$.

Table I. Functional abilities Scores.

The Modified Walton and Gardner-Medwin Scale (WGM)	Description
Grade 0	Pre-clinical. All activities
Grade 1	Walks normally. Unable to run freely
Grade 2	Defect in posture or gait. Climbs stairs without using banister
Grade 3	Defect in posture or gait. Climbs stairs only with banisters
Grade 4	Walk without assistance. Unable to climb stairs
Grade 5	Walk without asisstance. Unable to rise from chair
Grade 6	Walks only with calipers or other aids
Grade 7	Unable to walk. Sits erect in a chair. Able to roll wheelchair
Grade 8	Can sit up in bed, but not stand
Grade 9	Unable to sit erect without support
Grade 10	Confined to bed. Requires help for all activities

Brooke Upper Extremity Scale	Description
Grade 0	Full arm function; raises arms above head
Grade 1	Can raise arms above head, but with difficulty
Grade 2	Cannot raise arms above head, can reach mouth
Grade 3	Cannot reach mouth, but can hold a pen or utensil
Grade 4	Some arm movement, but cannot bring hand to mouth
Grade 5	No useful arm movement

Results

Twenty-eight patients from 26 Moroccan families met the inclusion criteria. Clinical data are listed in Tables II and III. The median age at examination was 25,5 years [21–33]. Twelve patients (43%) were female and 19 (68%) had consanguineous parents. Half of the patients had at least one affected family member. The median age at symptoms onset was 18 years [16–25], and the median diagnostic delay was 6 years [4-9].

Lower limb weakness was the initial symptom in all patients. Isolated difficulty in standing on tiptoes was observed in three patients at disease onset. The other patients had difficulty in walking, jumping, climbing stairs, or rising from the floor. Four patients reported myalgia, and one reported pain and exercise intolerance, all associated with persistent muscle weakness. Muscle weakness and atrophy were globally symmetrical in all patients. At the first consultation, symptoms had already spread to the upper limbs in 13 patients (46%), with selective involvement of the biceps brachii in 19 patients (68%), while the deltoid and other arm muscles were relatively spared. Tendon reflexes were absent in the lower limbs in 10 patients and in all four limbs in 3 patients. Seven patients (25%) showed hypertrophy of the extensor digitorum brevis muscle, and two (7%) had severe genu recurvatum (Fig. 1). The LGMDR2 phenotype was identified in 11 patients (39%), with early proximal weakness and atrophy, whereas only 3 patients (11%) started with MMD1 phenotype. However, in 14 patients (50%), it was not possible to distinguish between the two phenotypes due to simultaneous proximal and distal onset;

Table II. Clinical Data of the study sample at diagnosis in patients with Dysferlinopathy (N = 28).

Patient	Gender	Age at onset	Age at diagnosis	Phenotype	MRC Hamstrings	MRC distal foot muscles	MRC Biceps	CK level (UI/L)	Deformity	Inflammatory Infiltrate	Diagnostic tools
1	M	33	37	Proximal	2	5	5	5250		No	Complete absence of Dysferline in IHC
2	F	20	28	Proximodistal	2	2	5	14286		Yes	
3	M	20	23	Distal	3	1	5	4200	Cavus feet	No	
4	F	18	24	Proximodistal	3	3	5	7432		No	
5	M	18	22	Proximodistal	2	2	5	10700	Coxa vara	No	
6	M	25	32	Proximodistal	3	2	5	3839		No	
7	M	25	28	Proximodistal	4	4	4	409	Genu recurvatum		
8	M	14	24	Proximal	5	5	5	4334		No	
9	F	17	21	Distal	3	2	4	6190		No	
10	M	31	57	Proximal	4	5	4	505	-	No	
11	M	25	39	Proximal	3	5	5	7030		Yes	
12	M	32	40	Proximodistal	4	5	5	10420	Genu recurvatum	No	
13	F	16	25	Proximal	4	5	4	900	Winged Scapula/ Lumbar hyperlordosis	No	
14	M	12	14	Proximodistal	5	5	5	4837		No	
15	F	20	26	Proximodistal	3	4	4	1841		Yes	
16	M	14	38	Proximal	3	5	3	239		Yes	
17	M	18	21	Distal	3	1	5	20000		Yes	
18	M	17	28	Proximal	2	5	4	2155	Lumbar hyperlordosis	Yes	
19	F	12	18	Proximodistal	4	4	5	9648	Cavus feet	Yes	DYSF mutation (c. 3191G > A p.Arg1064His)
20	M	15	21	Proximodistal	3	2	5	6400		Yes	Complete absence of Dysferline in IHC
21	F	14	19	Proximodistal	3	4	5	5694			
22	F	41	49	Proximal	4	5	4	341	Scoliosis	Yes	
23	F	18	30	Proximal	2	5	2	5351	Lumbar hyperlordosis	Yes	
24	F	18	19	Proximal	3	5	4	6000		Yes	
25	F	17	25	Proximodistal	1	1	4	4120		Yes	
26	M	16	21	Proximodistal	2	3	4	8000	Scoliosis	Yes	
27	M	26	37	Proximal	3	5	3	348		No	
28	F	19	28	Proximodistal	4	5	5	3260		Yes	DYSF mutation (c.4200dup p.Ile1401HisfsTer8)

MRC: Medical Research Council scale

IHC: Immunohistochemistry

these cases were therefore classified as a proximodistal phenotype, which was the most frequent in our cohort (Fig. 2). The median age at examination was 35 years for patients with a proximal phenotype, 25 years for proximodistal, and 21 years for distal presentation ($p = 0.02$). Serum CK levels at diagnosis were consistently elevated (10-35 x normal). EMG showed a myopathic pattern with short motor unit and abundant spontaneous activity.

Twenty-six patients underwent muscle biopsy; most often retrieved from the deltoid muscle. Histological analysis revealed dystrophic lesions in 23 patients (88%). Inflammatory infiltrates by mononuclear cells were observed in 15 patients (58%), two of whom were initially misdiagnosed as inflammatory myopathy. Immunohistochemical results of all 26 samples showed complete absence of dysferlin. Additional proteins were tested using anti-dystrophin antibodies 1, 2, and 3 in all patients; anti-sarcoglycan antibodies against a, b, g and d subunits in 24 patients; and anti-merosin antibodies in 6 patients, all showing normal expression (Fig. 3). In two patients, genetic testing identified homozygous pathogenic variants in the DYSF gene: one missense variant (c. 3191G > A p. Arg1064His) and one nonsense variant (c. 4200dup p. Ile1401HisfsTer8).

Of the 28 patients, only 15 were regularly followed up for a median of 4 years [3-9] with a median disease duration of 13 years [11-15]. The

Table III. Statistical results at diagnosis in Dysferlinopathy (N = 28).

Epidemiological, clinical and laboratory data	Total patients (n = 28)
Age at diagnosis	25 [21-33]
Age at onset	18 [16-25]
Diagnosis delay	6 [4-9]
Gender Male Female	 16 (57%) 12 (43%)
Consanguinity of parents	19 (68%)
Familial cases	14 (50%)
Onset by difficulties in standing on tiptoes	3 (11%)
Onset by proximal lower limb deficiency	11 (39%)
mixed proximal and distal onset	14 (50%)
Myalgia	4 (14%)
Exercise intolerance	1 (3,6%)
Biceps involvement	19 (68%)
Hypertrophy of extensor digitorum brevis	7 (25%)
Genu recurvatum	2 (7%)
CK levels	10-35 x N
Needle EMG Spontaneous activity at rest Myopathic recruitment at muscle contraction Polyphasic MUP with low amplitude and short duration	 16 (57%) 28 (100%) 28 (100%)
Muscular biopsy Dystrophic aspect Inflammatory infiltrates	26 (92%) 23 (88%) 15 (58%)
Absence of Dysferlin staining at muscle biopsy (performed in 26 cases)	26 (100%)
DYSF mutation (Performed in 2 patients)	2 out of 2
Normal transthoracic ultrasound	28 (100%)
Normal spirometry	28 (100%)

Abbreviation: CK: Creatin kinase; EMG: Electromyogram; MUP: Motor unit potential.

Continuous variables are expressed as median (interquartile range), and categorical variables as percentages



Figure 1. Genu recurvatum in patient with Dysferlinopathy (Patient 7). He maintained cycling ability for many years despite genu recurvatum deformity.

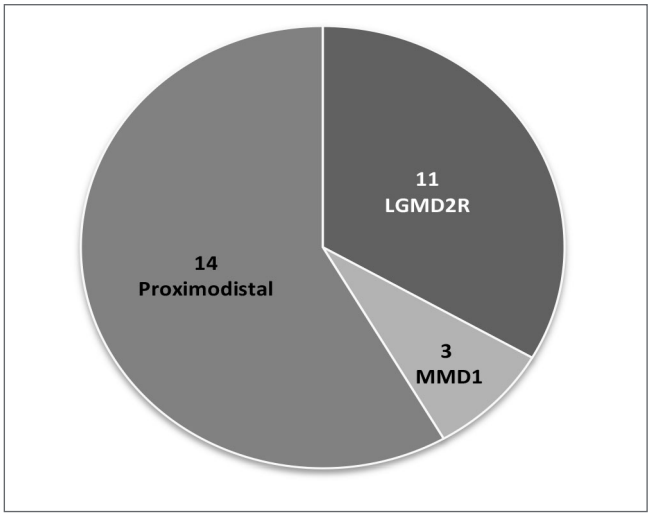


Figure 2. Distribution of dysferlinopathy phenotypes in the study cohort (N = 28).

remaining patients were not followed up in our department, because they had initially been referred only for muscle biopsy. Most patients showed improvement with physical rehabilitation, as documented by stable or increased muscle strength on the MRC scale and preserved functional motor abilities. This beneficial effect was particularly evident during the COVID-19 pandemic, when most patients experienced a transient decline in motor abilities due to interruptions in regular physical activity. Four patients received oral prednisone, with heterogeneous outcomes. One patient improved significantly and maintained a normal gait, with only minor difficulty running after seven years of disease progression (Patient 24). Notably, this patient had an acute onset and prominent inflammatory infiltrates on muscle biopsy. Two other patients (Patient 19 and 28) maintained the same WGM scores of 2 and 3, over 13 years. In contrast, the last patient (Patient 22) experienced a marked score worsening from 3 to 6, requiring bilateral assistance for ambulation six years after diagnosis.
Overall, disease progression was slow. No patient had cardiac or respiratory impairment at the last visit.
Five patients retained the ability to walk and climb stairs (corresponding to lower grades on the WGM Scale), six patients were able to walk but unable to climb stairs (Grade 4), two required bilateral supports for ambulation (Grade 6), and two had lost independent ambulation and were using a full-time wheelchair after 8 ± 2 years from diagnosis. At a mean age of 29 ± 3 years. No difference in the WGM scores was observed between the proximal and proximodistal phenotypes (p = 0,13). The median score in patients with muscle inflammation was 4.5 versus 3.5 in those without inflammation.
The progression of lower limb function according to the WGM Scale in the 15 patients with regular follow-up is shown in (Fig. 4), at baseline, after 1 year, after 4 years, and at the last follow-up. Data for patients receiving corticosteroid treatment are also presented.
Concerning upper limb function, assessment using the Brooke Upper Extremity Scale at last examination (Fig. 5) showed that three patients had normal function (grade 0), four had mild difficulty raising their arms (grade 1), five were unable to raise their arms above the

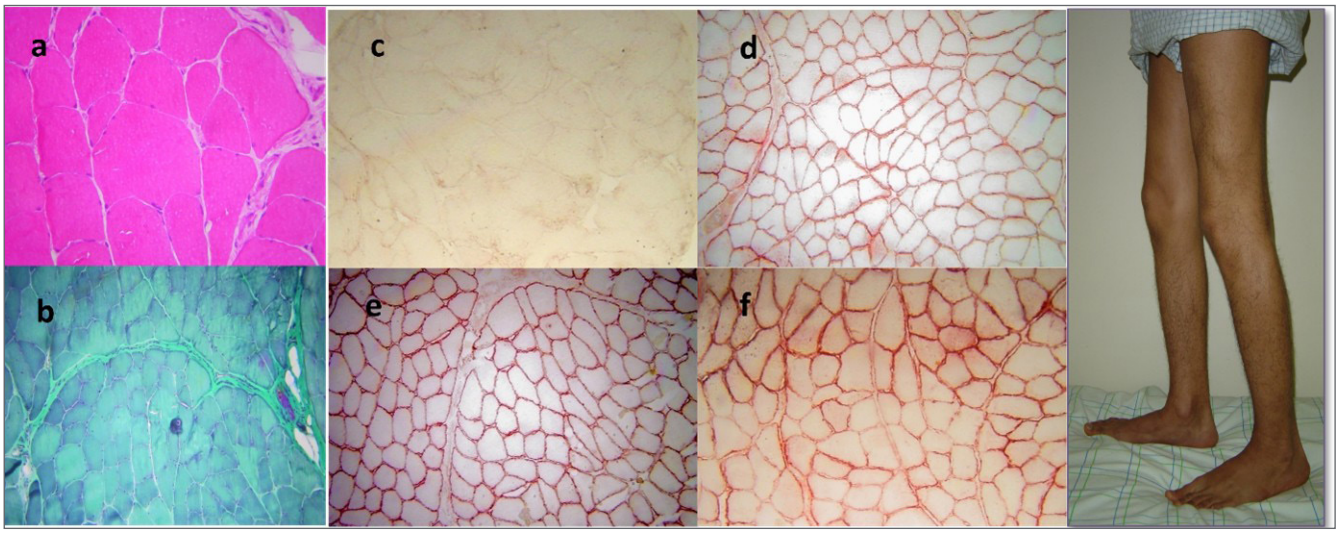


Figure 3. Deltoid muscle biopsy findings in patient with Dysferlinopathy showing subtle dystrophic signs (a): Hematoxylin and eosin (b): Gomori's trichrome with no dysferlin staining (c) while alpha sacroglycan (d), gamma sarcoglycan (e) and dystrophin 3 (f) staining are normal (Patient 20).

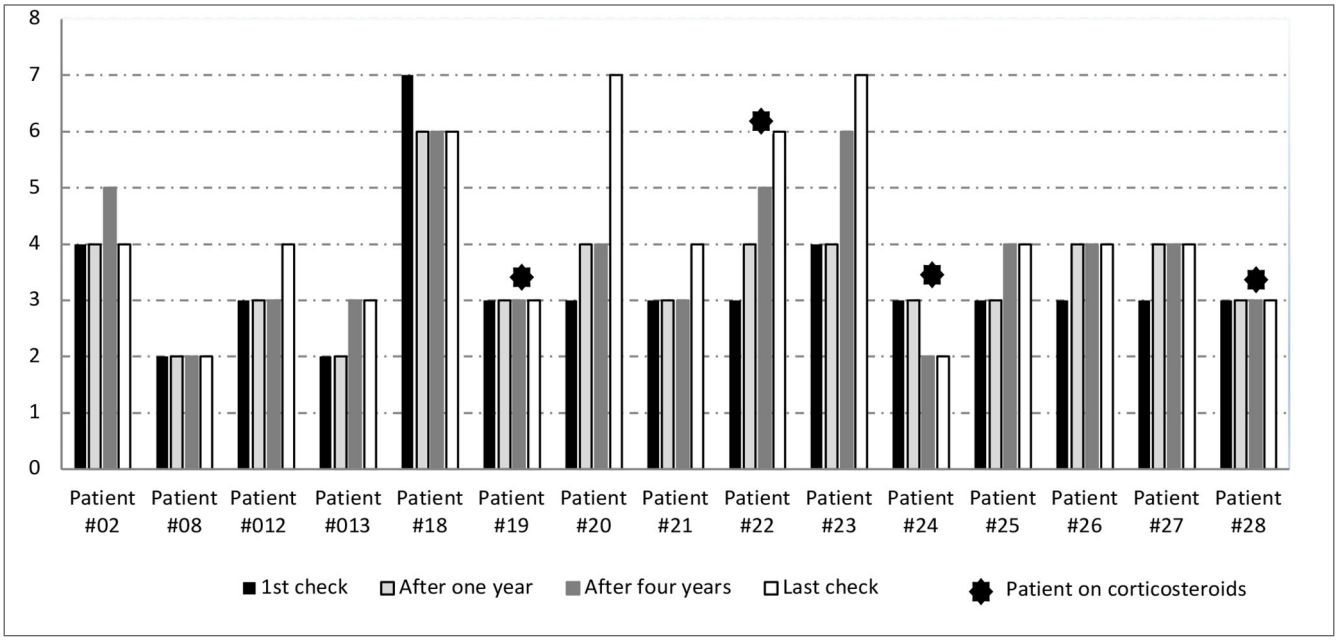


Figure 4. Evolution of The Modified Walton and Gardner-Medwin Scale (WGM) of 15 patients with dysferlinopathy during observation period.

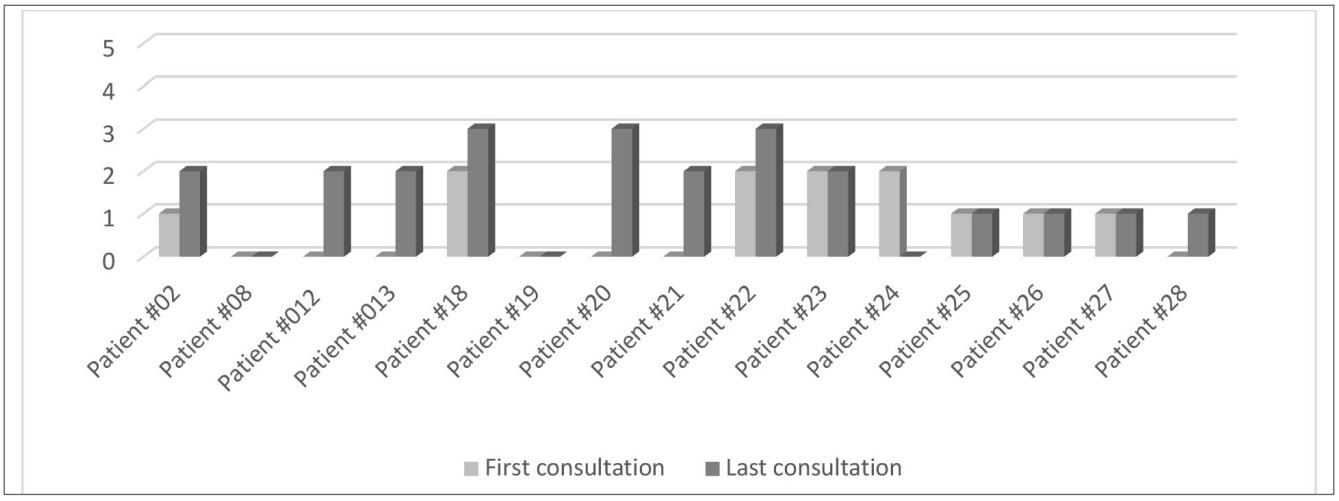


Figure 5. Evolution of the Brooke Upper Extremity Scale of 15 patients with dysferlinopathy.

head but could reach the mouth (grade 2), and three could not reach the mouth but could hold a pen or utensil (grade 3). No patients were observed in grades 4 or 5.

Discussion

Dysferlinopathies refer to a group of autosomal recessive muscular dystrophies characterized by marked clinical heterogeneity. Mutations in the DYSF gene were first identified in patients with early adult-onset distal myopathy or Miyoshi myopathy, and limb-girdle muscle dystrophy 2R. Since then, the clinical spectrum has expanded to include a wide range of phenotypes, including those with atypical ages of onset, abnormal proximodistal, axial, or anterior distal topography of early lesions, as well as pseudo-metabolic presentation and asymptomatic hyperCKemia [8].

In our cohort, the classic phenotypes MMD1 and LGMDR2 accounted for only half of the cases. Fourteen patients (50%) could not be clearly classified into either group, as they showed at onset a mixed pattern of proximal and distal lower limb weakness. On the other hand, we did not observe any cases of distal anterior compartment myopathy or asymptomatic hyperCKemia. A high proportion of proximodistal phenotype has also been reported in a Tunisian series of 20 patients with dysferlinopathy, categorized into five phenotypes: Limb-girdle muscular dystrophy (35%), proximodistal phenotype (35%), Miyoshi myopathy (10%), distal myopathy with anterior tibial onset (DMAT) (10%), and asymptomatic HyperCKemia (10%) [9]. The predominance of the proximodistal phenotype in our cohort, as well as in the Tunisian series, may reflect specific DYSF pathogenic variants, marked clinical heterogeneity, and population-specific genetic backgrounds. Intermediate or mixed patterns may not fit classical classifications, and differences in assessment criteria could also contribute to this higher frequency.

Dysferlinopathy can begin at any age, from birth to the seventh decade, although it most commonly manifests in young adults [10,11]. In our study, we did not find a significant association between age at onset and clinical phenotype. However, distal and proximodistal phenotypes appeared to be diagnosed earlier than proximal forms (distal: 21 years; proximodistal: 25 years *vs.* proximal: 35 years), with this difference reaching statistical significance ($p = 0,02$). A recent study involving 48 patients with late-onset dysferlinopathy (≥ 30 years) showed a high prevalence of atypical phenotypes, including camptocormia and exercise intolerance [12]. In addition, some authors have suggested a potential association between muscle inflammation and the proximodistal phenotype [6]. In our cohort, 8 out of 15 patients with inflammation exhibited a proximodistal phenotype, although this was not statistically significant ($p = 0,63$). Moreover, the clinical phenotype was relatively homogeneous among members of the same family, although intrafamilial phenotypic variability has been reported in other studies [13]. Cardiac and respiratory involvement are usually absent in most patients [14]. However, recent evidence suggests that subclinical involvement may be present in several patients requiring routine cardiopulmonary surveillance. In a recent report of 188 patients followed over three years; 24-30% had respiratory impairment defined by forced vital capacity (FVC) < 80% of predicted value, and 58% had atrial conduction abnormalities, particularly P-wave changes on surface ECG [15]. Therefore, the authors recommended annual or biannual FVC measurement and routine assessment of cardiac rhythm via peripheral pulse palpation.

Analysis of dysferlin protein expression is fundamental to confirm the diagnosis of dysferlinopathy. However, molecular analysis of the DYSF gene is even more desirable, as it definitively establishes that the dysferlin deficiency is primary and not secondary to mutations in other related genes. In this respect, Matsuda et al. reported that patients with caveolin-3 mutations may exhibit reduced dysferlin immunostaining. This reduction is typically patchy, partial, and of different intensity compared to that seen in true dysferlinopathies. Their study demonstrated co-immunoprecipitation of dysferlin and caveolin-3 proteins using either anti-dysferlin or anti-caveolin-3 antibodies in normal human muscle biopsies, suggesting a functional interaction between the two proteins [16]. In our study, the diagnosis was mainly based on the complete deficiency of dysferlin expression on muscle immunohistochemistry. Genetic confirmation was obtained in only two patients, in whom homozygous pathogenic variants in the *DYSF* gene were identified. for the other patients, genetic testing could not be performed due to limited resources.

The clinical differential diagnosis of dysferlinopathy primarily includes other types of muscular dystrophies, as they may present with a similar clinical picture. However, dysferlinopathy can often be distinguished by a set of distinct phenotypic peculiarities, including atrophy of the posterior leg compartment with genu recurvatum deformity, hypertrophy of the extensor digitorum brevis muscle, and selective involvement of the biceps brachii with the “Bulge” sign in the upper limbs. The combination of some of these features is strongly suggestive of dysferlinopathy, particularly in young adults with high CK levels [5]. Furthermore, dysferlinopathy is probably the most common myopathy to be confused with inflammatory myopathy, due to shared features such as sporadic cases, possible myalgia, subacute onset, elevated serum CK levels, similar EMG changes, and inflammatory infiltrates on muscle biopsy [17]. This was the case for two of our patients, in whom the initial diagnosis of inflammatory myopathy was reconsidered given minimal or absent response to immunosuppressive therapy and the presence of atypical features, particularly distal muscle impairment with marked weakness and atrophy of the medial gastrocnemius. Similar diagnostic challenges were reported in two Iranian patients, who were initially misdiagnosed with polymyositis but later confirmed to have dysferlinopathy through a screening with Western blot followed by DNA analysis of dysferlin gene [18]. In a cohort of 40 patients with dysferlinopathy, 10 (25%) were initially misdiagnosed as polymyositis [6]. Another study reported six patients who fulfilled Bohan and Peter’s criteria for at least probable idiopathic polymyositis, but were later found to have genetic myopathy. Among these, four patients had *DYSF* mutations, one had a *RYR1* mutation, and one had a *GNE* mutation consistent with Nonaka distal myopathy [19].

The natural course of dysferlinopathy is highly variable, making clinical trials more challenging. Some patients maintain mobility for many years, while others may experience more rapid progression. An international multicenter study reported that 30% of patients remained mildly or moderately affected 30 years after symptom onset, whereas a comparable proportion developed severe disability after 17 years

of disease duration [20]. Similar to other reports, we observed few patients with severe disease progression in our series. The two most severely affected patients, one with a proximal phenotype and the other with a proximodistal phenotype, progressed to complete loss of ambulation after 14 and 11 years from symptom onset, respectively, while upper limb involvement remained mild to moderate. No significant association was found between phenotype and progression. Similarly, the presence of muscle inflammation did not correlate with functional abilities in our cohort. Furthermore, cases of asymptomatic hyperCKemia suggest that elevated CK levels do not necessarily predict future muscle weakness, highlighting the importance of considering dysferlinopathy even in minimally symptomatic individuals [21].

There is currently no curative treatment for dysferlinopathies. Corticosteroids and other immunosuppressive agents have been considered as potential therapies due to the presence of marked inflammation in muscle biopsy. Yet, results remain disappointing. In a German clinical trial assessing the course of dysferlinopathy on deflazacort, patients did not improve during the treatment period. In contrast, there was a trend toward worsening of muscle strength, which recovered after stopping the drug during the wash-out period [22]. Lerario et al. reported two cases of dysferlinopathy in whom rituximab, a B-cell depleting agent, seemed to improve limb-girdle and grip strength [23]. Furthermore, the beneficial effect of alternate-day low-dose prednisone was reported in a female patient treated for 17 years [24]. In our cohort, we employed the same prednisone protocol in four patients with severe myalgia, showing heterogeneous outcomes. The first patient showed a significant improvement, maintaining a normal gait with only mild difficulty running after 7 years of disease progression. In this patient, the favorable response may be related to the prominent inflammatory features observed at disease onset. However, given the overall lack of evidence supporting corticosteroid efficacy in dysferlinopathy, this observation should be interpreted with caution. Two other patients retained stable functional abilities over 13 years. In contrast, the fourth patient worsened shortly after corticosteroid initiation.

In addition, functional rehabilitation with moderate activity has played an important role in preserving motor abilities in most patients. A particularly interesting experimental study investigated the effects of long-term exercise in dysferlin-deficient mice, The results showed that concentric and isometric exercise, such as swimming, improved muscle strength and reduced muscular degeneration. On the other hand, eccentric exercise induced by long-term wheel running worsened the dystrophic process. The authors explained this worsening by the fact that membrane damage occurs more frequently and more severely during eccentric/lengthening contractions than during isometric or concentric/shortening contractions. This mechanism may help explain the large proportion of patients practicing various sports or being very active prior to the onset of symptoms [25].

Conclusion

Dysferlinopathies rank second in frequency after sarcoglycanopathies and account for 18% of all limb-girdle muscular dystrophies in Morocco. This study provides new insights into the phenotypic spectrum of dysferlinopathies in North African patients, particularly highlighting the high prevalence of the proximodistal presentation and the variable response to corticosteroid therapy. In parallel, our findings emphasize the important role of functional rehabilitation in preserving functional abilities in most patients. These observations underscore the need for early recognition, individualized management strategies, and improved access to genetic testing to enhance diagnostic accuracy and clinical care in this population.

Conflict of interest statement

The authors declare that they have no conflicts of interest related to this study.

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None.

Authors contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Ethical considerations

This retrospective study was conducted in accordance with institutional ethical standards at the Hospital of Specialties, Rabat, Morocco. Written informed consent was obtained from all patients or their legal guardians.

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