

ORIGINAL ARTICLES

Epidemiology of muscular dystrophies in the Mediterranean area

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The Mediterranean countries are distinguished with their peculiar genetic pool and diversities. Recessive diseases often present with their own founder mutations. In some instances this is shared with neighboring populations. Dominant disorders in the area are increasingly recognized as health care providing systems and technology improve. Among muscular dystrophies Duchenne and Becker types constitute the major fraction in almost all societies. This is followed by various forms of limb-girdle muscular dystrophy. Congenital dystrophies and other related rare types are a matter of recognition. The identification and registry of facio-scapulo-humeral and myotonic dystrophies vary in different states.

Key words: Frequency, incidence, muscular dystrophies, Mediterranean area

Introduction

The Mediterranean Society of Myology (MSM) is formed by the following countries: France, Spain, Morocco, Algeria, Tunisia, Libya, Egypt, Jordan, Lebanon, Syria, Israel, Turkey, Cyprus, Greece, Malta, Albany, Macedonia, Bosnia, Serbia, Croatia, Slovenia and Italy (1). I delivered an invited lecture on the epidemiology of muscular dystrophies in our region for the XI Congress of the MSM held in Athens, Greece between 31 October-2 November 2013. Here I would like to summarize the overall information I had gathered.

First, I sent out e-mail messages to several colleagues around the Mediterranean basin and asked them these three questions:

What percentage of your cases are DMD/BMD, LGMD, CMD, FSH, myotonic dystrophy and others (such as mitochondrial, hereditary neuropathy)? For LGMD and CMD, can you further specify into genetic/molecular?

Is there a particular disorder that is more common in the ethnic groups? In other words, are there any clusters?

Are there any new disorders that you think is present in your area but not shown yet?

I received little reply to my last query, but for the first two questions the response was very satisfactory. These answers will be summarized here.

Actually, there has been quite few reports on the epidemiology of inherited muscle disorders around the globe. The most remarkable publication was by Emery in 1991 denoting the overall prevalence of these disorders was 1 in 3000 (2). Since then, the output of articles related has been dim.

Results

I would like to start from Spain and move in a clockwise route.

Spain: (J Colomer, personal communication) In Catalunya with 25 years of experience in a population of 7 million, 289 DMD cases followed by 89 BMD, 12 merosin deficiency, 28 LGMD2C (gamma-sarcoglycan), 2 FKRP, 21 EDMD (19 lamin A/C and 2 emerin), 7 LGMD2A, 18 collagen VI deficiency and 7 FSHD cases have been identified. Interestingly 50% of their gamma-sarcoglycan mutations is the Maghrebian form as delta521T and the remaining 50 % is the C283Y Gypsy mutation. The Gypsy limb-girdle muscular dystrophy (LGMD2), which is actually a LGMD2C presents with a homogenous phenotype. This is consistent with macroglossia and calf hypertrophy resembling in a sense to DMD. Loss of ambulation is 10-22 years after onset. Respiratory and cardiac involvement is encountered. This condition is seen in Romany Gypsies of Europe with a carrier frequency of 1:20 in certain groups (3-5). There is also a form of LGMD2A originating in Basque Country, Spain. The patients present with no contractures or calf hypertrophy. Onset is 8-15 years with patients losing ambulation 11-28 years later (6).

Italy: Italy, population wise is a diverse and rich country with lots of epidemiological data and Italian neuromuscular experts have contributed substantially with several papers. They have reported extensively on all forms of muscular dystrophies with phenotype/genotype correlation. In 1992, Merlini et al found a higher prevalence of neuromuscular disorders under age 19 than the general population pointing to medical services awareness (7). Mostacciolo et al reported the incidence of BMD as 7.2 per 100,000 male live births, which was much higher than previous figures (8). In a study to figure out the incidence of dystrophinopathies in North-West Tuscany, Siciliano et al found increase in prevalence of BMD in the year 1994 compared to the year 1981 was from 1.06×10^{-5} to 2.42×10^{-5} (9).

In Padova, myotonic dystrophy had a minimum prevalence rate of 9.3×10^{-5} inhabitants being twice as before (10). The prevalence of LGMD2A in northeastern Italy was 9.47 per million (11). Overall, the carrier frequency of this disorder in Italy was 1:103 (12). In Padova, 40 cases of FSHD were spotted in a population of 871,190 (13). Guglieri et al reported 181 cases of LGMD in 155 families (14). There were 72 cases with LGMD2A, 31 cases of dysferlin deficiency, and 32 cases with abnormal sarcoglycans. There were only four cases with alpha-dystroglycanopathy and three with caveolin deficiency. Italian cases were found to be less likely to have LGMD2I. Fanin et al were able to diagnose 77% of childhood onset and 60% of total LGMD in 550 muscle biopsies (15). There were private beta and gamma sarcoglycan mutations denoting evidence of a founder effect in Northern Italy (16). Italian investigators have also concentrated on congenital muscular dystrophy (CMD). In a population study covering the country, they have identified 160 patients with CMD, whom 92 had intellectual impairment. Alpha-dystroglycan was reduced in 73 of these 92 patients and specific mutation were found in 42 of them. There were six cases with merosin deficiency. Among these 92 cases with abnormal cognition, there were 13 cases with normal alpha-dystroglycan and merosin, so cognitive impairment was not always associated with a reduction of these two proteins (17).

The Balkans: In Slovenia, LGMD2A is about 40% of all LGMD cases (18). In Macedonia, DMD is frequent and this is followed by LGMD and CMD in order (N Algelkova, personal communication). In Serbia, this goes as DMD>CMD>LGMD order (V MilićRasic-personal communication). In Belgrade, at the end of December 2002, the prevalence of myotonic dystrophy was found as 5.3 per 100,000 population (19). In Split, Croatia, which is a town with a population of 400,000 there are registered 5 cases with DMD/BMD, 5 cases with myotonic dystrophy, 4 cases with LGMD and 2

with FSH (D Samija, personal communication). In Zagreb, there are 20 cases with DMD, followed by BMD, DMD/BMD, LGMD2, CMD and congenital myotonic dystrophy cases (N Barisić, personal communication). A specific mutation in the calpain 3 (CAPN3) gene, named 550delA has been identified on 76% chromosomes. This high frequency, along with other neighboring European countries suggests a probable founder effect (20). Disorders such as LGMD2D and merosin deficiency has been reported in Albania (21, 22).

Middle East: In Lebanon, DMD is about the same as LGMD2 or may be slightly less (M Alhdab-Barmada, personal communication). From a single center in Egypt and in a cohort of 400 patients, DMD/BMD was found as 30%, followed by LGMD 25% (dysferlin>calpain>sarcoglycan). CMD and myotonic dystrophy were rarer (N Fahmy, personal communication).

Israel: Israel is unique in the sense that there are many clusters of different Jewish ethnicities, as well as Moslem and other societies, each isolated by historical events, by country of origin and by religion. There are several large inbred families (Z Argov, personal communication). Prominent neuromuscular conditions identified or characterized in Israel could be summarized as below. LGMD2B in clusters were identified in Libyan Jewish population originating in the area of Tripoli, Italian and Spanish populations. There is also another cluster among the Jews of Caucasus region. There is a homozygous frame shift G deletion at codon 927 (2779delG) and evidence for a founder mutation. The estimated carrier frequency is 4% in this community, which is similar to carrier rate of the same condition in Libyan Jews, who have a different founder mutation specified as 1624delG (23). Recessive hereditary inclusion body myopathy (hIBM) with quadriceps sparing was initially described in Persian Jews. Later on, the same mutation was shown in other communities to include Middle Eastern Jews, Karaites and a Muslims of Bedouin and Palestinian origin with the same M712T founder mutation (24). There is also a cluster of oculopharyngeal muscular dystrophy among Bukhara Jews with a distinct founder mutation (25). A novel recessive myopathy with ocular involvement was found in 16 subjects in 8 inbred Arab families (26). Later on, this condition actually turned out to be a myosin heavy chain (MYHC) myopathy (27).

In Israel, at a pediatric setting there are registered 251 DMD cases, 33 BMD, 25 unspecified LGMD, 2 LGMD2A, 6 LGMD2B, 6 LGMD2C, 8 EDMD, 19 FSH, 8 myotonic dystrophy, 16 unspecified CMD, 7 merosin deficiency, 13 collagen VI deficiency and 1 FKRP cases (Y Nevo, personal communication).

Tunisia: Tunisia is very rich in genetic background. There has been reported 30 genetic diseases with a found-

er effect only in Tunisians. In addition, there are 51 other recessive conditions in which the founder effect is shared with African and Middle Eastern countries (28). There is a type of FKRP founder-mutation reported only from Gabes district in Tunisia (c.1364C>A) or A455D (29). About 90% of all LGMD2C cases in Tunisia carry 521delT exon 6 founder effect mutation (30, 31). In this country the frequency of LGMD2 is more than DMD. All known types of LGMD2 in Tunisia are seen in clusters of founder effects, which are also shared with other populations (F Hentati and R Amouri, personal communication). These would include 3 founder mutations for LGMD2B, 4 with LGMD2D, 2 with LGMD2I, and one with LGMD2E. In their clinic the registry of muscular dystrophies excluding CMD is: 482 LGMD2 patients (129 LGMD2C, 10 LGMD2B, 11 LGMD2D, 3 LGMD2E, 16 LGMD2I). Undermined LGMD2 is (only gamma and FKRP excluded) is 313 denoting further heterogeneity and probably new or novel conditions. They have 293 DMD/BMD cases in their cohort.

Algeria: In an adult clinic DMD/BMD constitutes 46.7% of patients. This is followed by LGMD2C 30.3%, LGMD2B 13.1%, LGMD2D 0.8%, and LGMD2A 0.8%. The ones with classical immunofluorescence normal is 8.2% (M Tazir and S Nouioua, personal communication). At a Pediatric setting, the most common neuromuscular diseases by age group are in infants spinal muscular atrophy, CMD and congenital myopathy, in later childhood; DMD and LGMD2C –with the Maghrebian founder mutation del521T (S Makri, personal communication).

Turkey: Based on mt-DNA haplotypes, Anatolian mt-DNA sequences hold an intermediate position between Europe and the Middle East (32). Mt-DNA sequencing results from 384 individuals in Anatolia showed haplotypes closer to European populations (M Özgüç and Ç Kocaefe, unpublished observations). In this country, adult and pediatric neurology clinics' registry data may vary according to age of onset, but complementing each other. In Pediatrics, DMD/BMD patients are about 50% of the volume of the neuromuscular out-patients. The remaining are: 20% LGMD2, 15% CMD (with merosinopathy 40%, collagen VI deficiency 40%), and sclerotic phenotypes 5% (B Talim and A Karaduman, personal communication). In a large adult clinic in Istanbul DMD/BMD is 46%, LGMD2 14%, FSH 18%, myotonic dystrophy 16% and EDMD phenotype 1.5% (P Serdaroğlu and F Deymeer, personal communication). Anatolian populations are diverse. There are several neuromuscular disorders which have originally described in this area with proven founder effects (33). Having said that this is not exclusive and the same mutation may be encountered in other populations as well (34). Recently, we reported a novel entity with

defective phosphatidyl-choline biosynthesis defect in a form of early-onset muscular dystrophy with mitochondrial irregularities in muscle biopsy (35). There are 2 different founder mutations in this 10-patient cohort.

Conclusion: I would like to summarize my outcome in individual points:

1. Based on several observations over decades that Mediterranean is a rich genetic pool for neuromuscular disorders. This holds true for other genetic, especially recessive disorders as well. Consanguinity rate is exceptionally high in the area, reaching about 60% in some areas of the Maghreb.
2. Overall DMD/BMD spectrum is the most frequent disorder in the region with the exception of recessive LGMDs being more prevalent in Tunisia.
3. The condition previously known as "occidental type cerebro-muscular dystrophy" which is merosin deficiency has been reported in all countries around the Mediterranean basin.
4. There exist several recessive LGMD clusters with peculiar founder effects. These would include del521T mutation in Maghreb and Spain or C283Y in Gypsies in LGMD2C. Libyan Jew dysferlinopathy with a founder mutation is different from the dysferlinopathy in Jews of Caucasus origin. The elevated prevalence of the 550delA mutation in Calpainopathy in Croatia is also unique. In the other hand, in hIBM, patients coming from apart populations of the Middle East do share the same mutation.
5. Several other clusters of recessive LGMD is commonly encountered in tribal regions in Tunisia.
6. Dominant disorders are increasingly recognized based on optimal and updated diagnostic service, such as the Italian experience in FSHD and myotonic dystrophy.
7. Anatolian populations are closer to Europeans than thought before. Mt-DNA haplotype analysis supports this view.
8. Registries vary, child cohorts differ from adults.

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Abbreviations

LGMD: Limb-girdle muscular dystrophy
 DMD: Duchenne muscular dystrophy
 BMD: Becker muscular dystrophy
 CMD: Congenital muscular dystrophy
 FSHD: Facio-scapulo-humeral dystrophy
 EDMD: Emery-Dreifuss muscular dystrophy

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