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Historical paper

Neuromuscular disorders in Israel: A model country for ethnic clusters ☆

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Introduction

Israel is a relatively young country (established in 1948) with a total population of about 8 million. Grossly, there are about 75% Jews and 21% Arabs with Israeli nationality residing in Israel. Although there is currently a relatively high rate of inter community marriages between different Jewish historical ethnic origins and to a lesser degree among Arabs, characteristic communities can still be delineated according to country/region of origin. Consanguineous marriages rate is declining but according to a study in 1991 (the last available) it was still practised among Jews (1.2–9.2% in various communities) and Arabs (at least 20%) [1]. This situation creates the basis for the relatively high frequency of various Mendelian hereditary diseases, as recorded by the Israeli National Genetic Database created in 2006 [1]. Among those disorders there are several neuromuscular diseases which will be reviewed in this review based on my invited Meryon Lecture (Oxford UK, 2012).

1. Israel population general characteristics

I will try to characterize the various Israeli communities in general terms, as relevant to the topic of this review, avoiding any stigmatization or current political issues.

The Jewish population in Israel has numerous historical origins. Two broad terms are widely used in the medical literature: Ashkenazi Jews and Sephardic Jews. It is estimated that about 50% of the Jewish Israeli population is Ashkenazi and the other half is 'non Ashkenazi'. A more focused look at the history of the various communities makes it clear that the above-mentioned general terms do not represent 'true' ancestry.

1.1. Ashkenazi Jews

In today's reference to Ashkenazi Jews it is customary to include all Jews of European origin, be it West or East Europe, as Ashkenazim. However, this general approach is misleading as the various Jewish communities in Europe have different ancestors. Originally the Ashkenazi Jews were a small community residing in Germany (Rhine area) and the north of France (ASHKENAS is the name of Germany in old Hebrew) around 1000 CE. This community slowly spread to central Europe and Western Europe (including England). After the 1492 CE total expulsion of the Jews from Spain, where a very prosperous community existed for several centuries, many fled to Western and central European countries and mixed with the 'original' Ashkenazi community. The large Jewish community in Eastern Europe started in the 12th century with its main growth progressing from the 16th century. The Eastern European communities of Poland and Russia have different origins and cultural characteristics compared with the original Ashkenazi Jews of the Rhine valley. Thus, despite sharing many religious and cultural characteristics one should be careful in using this term in genetic evaluations of diseases. Some common hereditary disorders do not have similar prevalence in various Ashkenazi communities. As mentioned, consanguinity was less common in the European Jews, compared with the Middle Eastern Jews (probably about 1.2% in Israel in 1991).

1.2. Sephardic Jews

Currently, it is customary to use the term Sephardic for Jews originating in Islamic-ruled countries, but again diversity in this group is prominent. Originally the 'true' Sephardic Jews resided in Spain (SEPHARAD is the Hebrew name for Spain) and flourished under the Islamic rule of the Iberian peninsula (before the Christians took over). During the spreading conquest of the Islam after the 7th century AD many old and 'new' communities were under Islamic rule in North Africa and the Middle East. In fact at the end of the 7th century AD 90% of world Jewry was living in Islamic-

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ruled countries. The main centers were the old Babylonian region (Iraq and Persia), Egypt, Syria and Lebanon and the Spanish community. The Spanish Jewry spread to North Africa and the Byzantine area, especially after their expulsion in 1492. The old historical Middle Eastern Jews, some relate to early settlement in the 7th century BC, remained isolated in many regions. Thus, when referring to the Sephardic Jews one should be more specific, for instance the North African Jewish community and the isolated communities in old Persia and in Yemen share very little genetic background. In some isolated communities consanguinity was unavoidable as Jews were culturally prohibited to marry outside their religion. In some communities marrying inside the family was practiced, probably to preserve the family assets.

1.3. Israeli Arabs

The Arab population is composed of around 80% Muslim (mostly of Sunni type), 12% Christians (both Catholics and Orthodox) and the rest are Druze and few other minorities. The Muslim group is not homogeneous in origin. The majority originates from local rural agricultural communities and mostly define themselves as Palestinians Arabs. Historically many inhabited specific neighboring villages and belonged to 'tribal clans' defined as HAMULA. The other large community is Bedouin, people of nomad society (mostly from the Arab Peninsula) that differ from Palestinians in term of ethnic source. The Bedouins inhabit mostly the south of Israel. The Druze community belong to a special sect that emerged from the Shiite Islam around the 11th century AD. They reside mostly in the north of Israel. There is very little, if at all, inter marriages between these various communities.

2. Models for ethnic neuromuscular disease clusters in Israel

Four disorders which have a founder mutation in Jewish or Arab specific clusters will present the various models for ethnic clusters that could be relevant to other countries with similar population profile. These clusters were also crucial in defining the faulty gene of these world-wide hereditary myopathies. The fifth model is that of community specific mutations.

2.1. Model 1: Recessive disorder in an ancient closed community – dysferlinopathy in Libyan Jews

The Libyan Jewish community has roots in the 3rd century BC. Repeated growth and expulsions through the centuries resulted in a small, very closed community centered around Tripoli. Today the size of this community residing in Israel is estimated to be about 50,000. The community is well known in the neurological field because of their high incidence of the dominantly inherited Creutzfeldt Jakob disease due to a specific prion protein mutation. However, for several decades it became evident that there were numerous patients with limb girdle muscular dystrophy with a recessive inheritance pattern in this community. By mid 1990s a large inbred Libyan Jewish family with a recessive LGMD and features of Miyoshi myopathy was linked to chromosome 2. This family together with additional 7 families with similar clinical features were an important contributor to the identification of the desferlin gene in 1998 [2]. This was in fact the first identified ethnic cluster of dysferlinopathy with a clear founder mutation (1624delG). This mutation has a high carrier rate of at least 4.3% with an estimated prevalence of disease of 1:1300 adults in this community [3]. All known clinical features of dysferlinopathy were recognized in this ethnic cluster, such as equal numbers of distal (Miyoshi) versus proximal (LGMD) onset patients (including sibs with divers onset patterns), unusual features like initial affliction of the tibialis anterior (and not the posterior muscle group) and transient isolated biceps weakness when spreading to the upper limbs. Milder forms were also identified within this community making the issue of genotype-phenotype correlation of lesser importance in this group, since they all are homozygous for the same founder mutation.

Interestingly, in an even smaller Jewish community which was very isolated through history in the Caucasus mountain area, another founder mutation (2779delG) was found in 2007 with an estimated carrier rate of 4% [4].

2.2. Model 2: Recessive myopathy with a regional founder mutation – the GNE story

The dysferlin story in Libyan Jews is typical for a recessively-inherited myopathy in a closed, well-defined small community. In contrast, the story of GNE myopathy (also known as hereditary inclusion body myopathy, HIBM, or quadriceps-sparing myopathy) presents a different model of the spread of recessive founder mutation in a wider geographical and ethnic distribution. The condition was first identified in several families of Persian (Iranian) Jews in early r1980′s [5]. By mid 1990s it was linked to chromosome 9p1-q1 region and already then it became clear that it is not limited to Iranian Jews, but was also present in Jews from neighboring Middle Eastern countries (e.g. Iraq, Afghanistan) [6]. Because of the unique clinical feature of preservation of quadriceps power through the disease course, we were able to identify patients with this condition in the Karaite community originating from Egypt (the Karaites are a very small Jewish sect that departed from mainstream Judaism around the 11th century). By then the disease site was narrowed to a 700 kb segment in the 9p1-q1 region, and all patients seemed to carry the same haplotype. When the causative gene was identified (GNE) [7] all patients were found to carry the same founder recessive mutation (by previous nomenclature: M712T, current new nomenclature M743T [8]). Surprisingly, few Muslim Arab families (both of Bedouin and of Palestinian origin) were found to have the same condition due to the same founder mutation. More so, several families from the various religious origins with the same mutation were found to carry the same founder haplotype.

The origin and spread of this founder mutation/haplotype are unclear. We initially estimated the mutation to be at least 1300 years old (the time of Islam emergence when Jewish and Islam mixed marriages were forbidden by both religions) [9]. However, preliminary calculations (unpublished) suggest that this mutation is about 100 generations old (about 2500 years). If fully confirmed this will time the age of the emergence of the mutation to the kingdom of Persia, during the reign of king Cyrus. This monarch who ruled practically the whole Middle Eastern region issued a decree allowing various deported peoples to return to their homeland. The Jews were specifically mentioned and indeed returned to Israel to build their second temple. They could have brought with them the mutation to the region at that time explaining the wide ethnic distribution of this founder mutation. In this case myology and history seem to go hand in hand [10]. Unlike in Japan and other Asian countries where numerous mutations (few of those are probably founder mutations) cause GNE myopathy (also known there as distal myopathy with rimmed vacuoles, DMRV [11,12]) the vast majority of more than 170 patients diagnosed in Israel carry the M743T founder mutation. This enables the clinician to ascertain a definite diagnosis of this condition by direct mutation testing. Thus, this is a 'regional disease' and we refer to the founder mutation as Middle Eastern. It is very common in the Persian (Iranian) Jewish community (carrier rate of about 5%), which still has high rate of consanguineous marriages (around 9% as recorded in 1991) [1]. As a result family trees in this community may sometimes suggest a dominant inheritance pattern of this myopathy. In one of our early recognized families with 7 patients of 3 generations, 15/17 recorded marriages were consanguineous and only the clinical pattern of quadriceps sparing indicated that this is a pseudodominant pattern. Only 6/67 GNE families identified in Israel carry different mutations (belonging to Jewish families from Rumania, Poland and India or Palestinian Muslims). Jewish patients with the Middle Eastern mutation present all the known variability spectrum of disease severity, suggesting again the minor role of the founder mutation in determining the phenotypic expression [13].

2.3. Model 3: Dominant myopathy in a small community – OPMD in Bukhara Jews

Oculopharyngeal muscular dystrophy (OPMD) is traditionally associated with the French-Canadian community of the Quebec region. The dominantly inherited genetic defect underlying this condition in this community was discovered in 1998, and the estimated prevalence in the French Canadian community is 1:1000 adults [14]. The same defect in the *PABPN1* gene (a GCN triplet repeat expansion) was also recognized in the very small Jewish community originating from Bukhara [15]. Bukhara is a town in the mountain region in Uzbekistan and Jews lived there for at least 800 years. Currently most of them reside in Israel, the estimated community number is 60,000–70,000 people. Because of religious and cultural isolation, consanguineous marriages were unavoidable and the estimated prevalence of OPMD is the highest in the world (1:700 in the adult population) [15]. Since OPMD is a late onset disease, marriages between pre symptomatic heterozygous subjects have also occurred due to the small size of this Jewish community. This resulted in homozygous ('double dominant') patients, a rare feature seemingly unique to this community. At least six such patients were recorded and they, as expected, present a more severe form of OPMD with earlier onset and shorter survival. Furthermore, an unrecognized feature of this disease was revealed in these homozygous patients- early dementia and psychotic manifestations [16]. Interestingly, a defect in a chromosomal 'neighboring' gene led to a significant association of OPMD with a recessively-inherited retinal disease [17] thus the homozygous patients may have another feature.

2.4. Model 4: Recessive myopathy in one village – MYH2 related ophthalmoplegia

A unique disorder of very slowly progressive external ophthalmoplegia without ptosis was recognized in one small Arab village (Abu Gogh, close to Jerusalem, with about 7000 inhabitants). The disease starts probably in late childhood although most patients are unaware of it till adult life. The ocular motility impairment is associated with mild limb weakness and scoliosis [18]. About 20 such patients were already identified, belonging to several different families. However, a more extensive genealogy evaluation revealed that they all belong to the same Muslim 'tribal clan' (HAMULA). This religiously mixed Arab village has a long history: it was a Christian village till the 15th century and then became a primarily Muslim village. Since all patients belonged to the same Muslim HAMULA, a recessive disorder could be predicted. The condition was similar to a dominant disorder due to a defect in the MYH2 gene reported from Sweden [19]. Only when it became clear that a defect in this gene (*MYH2*) could also lead to a recessive disease with similar features, was this condition re-evaluated in the Abu Gosh cluster. Indeed, a homozygous mutation (a single base deletion, technically missed in an initial sequencing study) was identified in all the patients [20]. This neuromuscular disorder is typical for the distribution of rare inherited disease according to place of residence in old Arab villages in Israel. Currently no such patient has been diagnosed outside this village in Israel.

2.5. Model 5: Community specific mutations of known conditions

As in any country, numerous hereditary neuromuscular disorders have been identified in Israel. These include both pediatric and adult diseases. However, some conditions have characteristic mutations in specific communities. If such communities are present outside Israel, recognition of its specific mutation may be helpful for the diagnostic procedure. Two such examples are worth mentioning:

phosphofructokinase deficiency which is probably more prevalent in Ashkenazi Jews (worldwide, not only in Israel) with specific mutation [21]. Likewise a specific Ashkenazi mutation has been identified in children with nebulin defects [22]. Similarly a local identifiable community may have a specific syndrome with a unique genetic defect. A cluster of congenital myasthenia with facial deformities was identified three decades ago in Iraqi Jews living in Israel [23]. The gene defect was identified only in 2003 as a unique mutation in the E-box of the rapsin gene [24]. Knowledge of such community specific mutations can facilitate the diagnosis in relevant clinical presentations, especially when genetic testing via exome screening is not available.

3. Discussion

Israel is a model country for studies of ethnic clusters of hereditary disorders. This of course is not unique to Israel but the variability seems unusual because of its population history. Several local communities have large inbred families, and the tradition of consanguineous marriages over generations in some of them facilitated the persistent presence of various disease mutations. Although the rate of consanguinity is decreasing, it is still relatively high in some Jewish and Arab communities. Historically, these communities were isolated thus increasing the chance of creating a founder effect. Modern research and the creation of the Israeli National Genetic Database in 2006 [1] are important factors in recognizing the various neuromuscular (and other) hereditary diseases typical for each community (for more information see the free Golden Helix- Israel web site). In 2014 >1500 entries were registered in the national database, divided almost equally between Jews and Arabs. As already mentioned, the pattern of founder mutation distribution is different among Jews and Arabs residing in Israel, as exemplified in the neuromuscular field. While in Jews it is mainly in historically isolated populations that emigrated to Israel, in Arabs it is primarily limited to a single village or tribal clan.

There are some social and medical aspects related to the existence of community clusters of hereditary diseases, which we observed in the neuromuscular field. In two examples of recessive myopathies we identified in Israel (dysferlinopathy in Libyan Jews and GNE myopathy in Middle Eastern Jews), a wide range of clinical spectra was observed. This suggests that even in a rather homogeneous community with a single founder mutation, the characterization of genotype-phenotype correlation mostly fails. Various onset patterns (Miyoshi, LGMD and anterior peroneal syndromes) and age of onset were observed in the Libyan Jewish dysferlinopathy cluster. Disease severity was markedly variable in the Persian Jewish GNE community: few patients became severely quadriparetic in their third decade of life and few others were still ambulatory in their sixth decade of life. Onset ranged from late teens to mid 40s. These observations support the recent conclusion from a world GNE registry that mutation type has a modest effect on clinical severity in GNE myopathy [13].

Another unique result of community clusters is the different disease pattern observed in the homozygous patients with the dominant OPMD mutation. Not only did the severity of the condition increase, but new features emerged. The most imported one is the brain involvement (cognitive decline and behavioral changes), which was unrecognized in the heterozygous patient communities. This may indicate that *PABPN1* (the defective gene) has a role in brain function. The retinal involvement in these patients is due to a physically associated, recessive gene defect, which suggests that a chromosomal segment rather than an isolated mutation was at the basis of this founder effect. A similar situation exists in GNE Middle Eastern cluster, where a founder haplotype of about 700 Kb containing the GNE gene was identified.

One of the major aspects of ethnic clusters of neuromuscular disorders we observed is the fear of stigmatization. This is of course not only a feature of myopathies and affects the social attitudes of the families and community toward genetic counseling. In Israel a pre marriage screening program for Tay Sachs disease in the Ashkenazi community has been very effective in prevention of this condition [1]. More recently screening for spinal muscular atrophy (SMA) was introduced for all communities and the impression of clinicians is that new cases of type 1 SMA are very rare. Both programs are supported by the National Medical Insurance. Screening for GNE and dysferlin founder mutations in the relevant communities is much less practiced. It is offered to relevant community members as part of family planning counseling, but at their own expense.

In summary, when faced with a new patient with an as yet undiagnosed neuromuscular disease, it seems important to know his background. The general rule of ‘know your patient population’ may make the diagnostic process much easier, especially in countries where immigration is frequent. Also, for history aficionados (like me) this adds yet another aspect to the practice of medicine.

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