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Historical paper

Neuromuscular disorders in Anatolia – A personal review☆

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1. Introduction

I would like to share my experience on peculiar neuromuscular disorders I have seen over the past 30 plus years in a specific region of the World, a rather complicated geography and history, Anatolia. This region of the earth is unique, because throughout the centuries the land has been occupied by many clusters of different ethnicities, as well as Moslem and other societies. Large inbred families have increased the chance of mutation emergence and maintenance. The civilizations of Anatolia go back to more than 10,000 BC. The recent discovery of Göbeklitepe, probably the first human temple dating back to at least 11,000 years which sets a clock is located in Sanliurfa, near Southeastern Turkey [1]. Some of Anatolian civilizations to follow in chrolonological order are Bronze age in northwest of Anatolia (3000–1800 BC), Hattians (2500 BC), Hittites (2000–1200 BC), Assyrian trading colonies (1800 BC), the Urartu kingdom (860–580 BC), Phrygians (750 BC), Lydians, Carians, Lycians (around 575 BC), Ionians (600–545 BC), Persian occupation (545–333 BC), Hellenistic age (333–30 BC) – the cities of Milet, Priene, Ephesus–Roman age (30BC–595 AD), Byzantian Empire (330–1453 AD), Turks from Central Asia (1071), and Ottoman Empire (until 1923) followed by modern Turkey (1923) [2–4].

According to mitochondrial DNA sequences, Anatolian populations constitute an intermediate position between Europe and Middle East [5]. This feature has also been in a recent 1001 genome project that current Anatolian populations share a chunk of European nuclear DNA [6]. So, these sequences of migrations, trade, exchange of populations over several centuries establish the genetic background and heritage.

Now, I would like to touch base to a few clinical samples as representation of how we deal with almost daily situations in a tertiary academic setting. Some disorders are typically common as elsewhere. As far as muscular dystrophies are concerned, in our practice the rough estimate would be as the following: Duchenne and Becker muscular dystrophy (DMD/BMD) 50% followed by limb girdle muscular dystrophies (LGMD) 20%, congenital muscular dystrophies (CMD) 15% (merosin deficient CMD 40%, Ullrich type CMD 40%, alpha-dystroglycan deficiencies 20%), sclerotic phenotypes such as Emery–Dreifuss muscular dystrophy (EDMD), rigid spine syndrome (RSS), and laminopathies 5%, and others such as myotonic dystrophy (DM1) 5% (personal experience). In a big adult neuromuscular center the constitution is DMD 28%, BMD 16%, DMD/BMD intermediate 5%, DMD manifesting carrier 0.7%, LGMD 14%, facioscapulohumeral dystrophy (FSH) 18%, DM1 16%, EDMD phenotype 1.5%, and oculopharyngeal muscular dystrophy (OPMD) 1,5% (personal communication, Piraye Serdaroğlu). Other neuromuscular conditions such as hereditary neuropathies, myasthenia, mitochondrial disorders, and other rare forms are not counted here.

Starting from late 1980s and early 1990s we were successful to contribute to the observation, description, definition, and genetic properties of several new clinical entities (genetic), mostly by international collaborations. Just to name a few: merosin deficient CMD [7], partial merosin deficiency [8], rigid spine syndrome [9], muscle eye brain disease [10], LGMD2K [11], LGMD2P [12], LGMD2Q [13], the POMT1 gene related CMD [14], Schwartz–Jampel syndrome [15], Marinesco–Sjögen syndrome [16], Giant axonal neuropathy [17], Charlevoix–Saguenay ataxia [18], neuropathy with GDAP1 mutations [19], muscle coenzyme Q10 (CoQ10) deficiency [20], spinal muscular atrophy and myoclonic epilepsy [21], CMD with mitochondrial changes [22], and finally inherited CD59 deficiency [23] among others. Now, I would like to mention and discuss some of these entities just briefly and their historical aspects. I have no aims to perform a state-of-the-art literature review, because this is not the scope of this short paper. I just would like to tell my own story.

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2. Merosin deficient CMD

This disorder was originally classified as "occidental type CMD" because of the original publications coming from the occident [24]. Starting from the late 1980s, we were able to diagnose a small series (I remember diagnosing 5 cases in a row, my biopsy book reflects this), and published soon thereafter [25]. The peculiar phenomenon were the white matter lucencies by cranial computed tomography (CT), which was the golden standard at the time. Despite this and limited motor achievement, usually these children have normal intellect. Independent walking was not a feature. Then, in 1993 and 1994, the protein responsible was discovered as merosin (later called laminin alpha2), the localization was around the basal lamina [26]. Gene discovery followed [7]. In the original gene search paper there were 4 families, 2 belonged to my early cohort. I am still in touch with one of these families and follow the two affected siblings who are in their early 30s. Soon after this, it was discovered that merosin was expressed *in utero* as early as 8 weeks of gestation [27]. This observation (along with genetic data) led to genetic counseling and prenatal diagnosis. This was followed by identifying cases with milder symptoms [8]. These patients had a limb-girdle distribution with relatively late onset. However, typical brain abnormalities in radiological images remained the same. Currently, merosin deficient CMD is one of the candidate conditions for gene therapy.

3. Muscle CoQ10 deficiency

In 2005 I saw two siblings who were refugees from Iraq to midland Turkey. The eldest one was a 16-year-old girl with muscle weakness, easy fatigue, exercise intolerance and falls for 8 months. There was no myoglobinuria. Her 14-year-old brother had similar symptoms. Her proximal muscle power was 3+/5 MRC with a Gowers sign of around 6 sec. Serum CK was elevated at 1484 μ/L. Working diagnosis was a limb girdle syndrome. The brother's serum CK was 2745 μ/L. However, his muscle biopsy was consistent with vacuolar myopathy, showing lipid accumulation prominent in type I fibers. Interestingly, within three weeks, we admitted two other teenage girls with the similar features and biopsy findings. One of them had increased carnitine derivatives in urine detected by Tandem mass spectrophotometry leading to electron transferring-flavoprotein dehydrogenase (ETFHD) deficiency.

Incidentally, my colleague Beril Talim was visiting her friend Rita Horvath in Munich at the time. She mentions about these cases and luckily enough Beril hears from Rita that they also have resembling cases in Germany, and they are in the current stage of formulating a diagnosis. So, a joint work was launched between Ankara and Munich. These sequences of events led to the identification of *ETFDH* mutations causing a myopathic form of muscle CoQ10 deficiency [20]. This is actually a form of glutaric aciduria type II (GA II). The muscle CoQ10 deficiency is secondary. As a matter of fact, muscle weakness in GA II was recognized as early as 1990, but the link was only established after our publication. Now, we have around 20 cases with this condition. They are physically normal without any remissions under low doses of CoQ10 and riboflavin therapy. To suspect a metabolic disease based on muscle tandem mass screening and organic acids in urine would be essential. This was previously a vague disorder [28] but now it is a well-defined one and one of those conditions not to miss [29].

4. CMD with mitochondrial changes

About 20 years ago, I saw a 7-year-old girl with severe mental retardation, head circumference less than the 3rd percentile, muscle weakness, and increased lordosis with a prolonged Gowers sign at 10 sec. Her serum CK was 1103 U/L. She also had a large atrial septal defect. So was this a Rett syndrome with myopathy? Later on other cases came along girls and boys, all sharing similar features: exclusively all with IQ/DQ under 40, muscle weakness and motor retardation, head circumference between the 3rd and 10th percentiles, normal cranial MRI and no seizures. Some of them had dilated cardiomyopathy, ichthyiosis-like changes, hearing deficit, and abnormal EEG. Muscle histology was reported compatible with myopathic/dystrophic changes, sometimes with a few COX negative fibers. My colleague Beril Talim, while investigating retrospectively clinical and pathological findings of cases from our institute's biopsy database with a student, identified a cohort with unique mitochondrial changes (giant mitochondria, mostly located towards the periphery of the fibers, causing a core-like appearance, sometimes accompanied by a few COX negative fibers) and variable dystrophic-like changes (fibrosis, fiber degeneration and regeneration). Exclusively, all cases with giant mitochondria had similar clinical features, and matched with the cases I have described above, i.e., Rett-like syndrome with myopathy and hyper CK'emia. Then, Beril reminded me of an article in which similar features were reported by I Nishino back in 1998: they had four patients in Japan with a form of congenital muscular dystrophy, all with giant mitochondria [30]. After a few years of collaboration and correspondence, this disorder was identified as a choline synthesis deficiency, actually being the first step [31]. Choline is also a major constituent of the mitochondrial inner membrane. Later on other case reports followed [32–34]. A few years ago, we were able to publish a clinical series and follow up of 15 cases [22]. As a matter of fact, this condition had originally been reported in 2006, in mice as a rostrocaudal muscular dystrophy with a defect in choline kinase beta, the first enzyme in phosphatidylcholine biosynthesis [35]. Now, this is a widely recognized genetic condition with reports coming from distant geographies [36].

5. Spinal muscular atrophy with myoclonic seizures

In the early 1990s, the late Professor Renda showed us at a grand round a family with three siblings affected similarly: a clinical course resembling spinal muscular atrophy (SMA) type III, however more progressive with patients losing ambulation several years after onset, and drug-resistant myoclonic seizures leading to dementia. All siblings expired. A similar course leading to death was additionally observed in a few other cases. In 2002 we did a literature review and noticed that there were other earlier cases, however rather vaguely described [37]. In the meantime we saw another patient, a 6-year-old boy from Istanbul. We did all investigations possible to include all progressive myoclonic epilepsy genes (such as Baltic myoclonus) available at the time, mitochondrial work-up, organic acidurias, lysosomal enzyme panels, and cranial MRI scans, which were all normal. Then I discussed our cases with Prof. Judith Melki in Paris. She suggested to perform a whole exome sequencing approach in the original triplex family, whose we had the DNA stored. She knew of other patients originating from Italy. A few months later the results were back. Interestingly, this condition was allelic to Farber disease as the mutations were in the *ASAH1* gene leading to a form of ceramide deposition [21]. So, a clinical syndrome of SMA III leading to SMA III and drug-resistant myoclonus, which in due course actually fatal is a form of Farber disease with ceramide deposition in tissues [38]. Now, there are several other reports in the literature [39]. In severe Farber disease, drug-resistant epilepsy resembling infantile spasms is not uncommon.

6. Inherited CD59 deficiency

In the early 1990s I saw this 11 mo girl with acute onset of weakness within a week. EMG denoted an axonal neuropathy. In due course she developed hemiparesis and cranial nerve involvement which showed brain stem findings. Cranial MRI was consistent with infarcts in the lentiform nuclei, and internal capsule. She then had relapsing remitting courses leading to severe scoliosis and became bed-bound. She died at 16 years of age despite ventilatory support. A few years later the family had another baby. Interestingly, she developed similar clinical features, but with brainstem stroke first followed by axonal neuropathy. A spinal MRI showed lumbar thickening and enhancement. She also had compensated hemolysis and elevated indirect bilirubin. She was partially responsive to monthly IVIg treatments. Then, a nephew was born. Starting from 6 months of age, he developed almost identical symptoms affecting the peripheral nerves and the brainstem. At this stage, we thought we should go ahead and do new generation genetics. Again this family was consulted with Prof. J Melki in Paris. In her laboratory linkage analysis followed by whole exome sequencing was consistent with a homozygous missense mutation in the CD59 gene (c.A146T:pD49V), a Sanger sequencing was confirmative. Flow cytometry showed lack of expression of CD59. Interestingly, just weeks before our observation and diagnosis, there was a large report from Israel on this clinical entity [40]. Yoram et al. described 5 infants, ages varying from 1 to 4 years of North African Jewish origin with demyelinating neuropathy and secondary axonal changes. The patients did not have CNS involvement. Actually, slightly later than this report there was a case presentation of a 7 mo Turkish baby, who was successfully treated with Eculizimab [41]. CD59 regulates complement activation cascade at the final step, inhibiting formation of the membrane attack complex (MAC [42]. Paroxymal nocturnal hemoglobinuria (PNH) is the prototype disease caused by CD59 deficiency (however only in erythrocytes). Later on, we were able to show a neonatal form of this condition in which initial symptoms arose during the first 30 days [43]. We have another report stating that Eculizimab must be the drug of choice [44]. In summary this new condition is due to chronic hemolysis, hypercoagulability, cerebral venous thrombosis or arterial strokes. The symptoms may overall respond to continuous IVIg and Eculizimab treatment. Our latest case, a 13-year-old girl is doing exceptionally well, and currently she has got a normal neurological examination under continuous drug treatment. Now in between Israeli and Turkish centers there are more than 25 cases in the preparation for publication line (personal observation and personal communication Dr. D Mevorach).

I would like to conclude by saying that the Mediterranean region is a large pool for neuromuscular mutations, where inter-community marriages still carry on substantially, especially in certain areas. This is a cultural phenomenon dating back to at least 3000 BC [45]. Apart from this, the Anatolian land is a true bridge between West and East with wars, invasions, and migrations in and out, probably why nothing is rare in this land. I think it is nice to know your history. All my efforts have been towards understanding my heritage.

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