Spectrum of inherited myotonias and periodic paralyses

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ABSTRACT

Objective: To study the spectrum of inherited myotonias and periodic paralyses in Saudi Arabia.

Methods: Forty nine patients with electromyography confirmed myotonic disorders and periodic paralysis were seen at King Khalid University Hospital between January 1985 and January 1998. Data was analyzed and available patients reassessed in order to document fully the various clinical features and ascertain the diagnosis and mode of inheritance.

Results: There are 11 patients with Thomsen's disease; 21 patients with Becker's disease, most of them had an early onset of 2-3 years; 12 patients with myotonic dystrophy; and 5 Filipino patients with periodic paralyses, 3 of them with associated thyrotoxicosis.

Conclusion: The spectrum of these disorders is similar to that described in western reports, apart from 2 main differences. First, is the clear predominance of Becker's disease (45%) which has a lower age of onset. This is probably the result of the high local consanguinity rate. Secondly is the absence of periodic paralysis in Saudis, while some patients had associated thyrotoxicosis, which is well recognized in Far East populations. These disorders are poorly studied in Saudi Arabia and deserve further epidemiological and genetic assessment.

Keywords: Myotonias, periodic paralyses, channelopathies, epidemiology.


Myotonia dystrophica (MD) is an autosomal dominant disease of variable clinical features, which include typical facies, distal muscular weakness and wasting, myotonia and widespread systemic manifestations including cataract, frontal baldness, cardiac conduction, endocrine disturbances and dementia. Myotonia congenita (MC) is either inherited as an autosomal dominant (AD) disorder (Thomsen's disease), characterized by early childhood onset and good prognosis, or as an autosomal recessive (AR) disorder (Becker's disease), also known as generalized myotonia and is characterized by a later childhood onset (4-12 years) with typical fluctuating weakness on exertion and eventual development of persistent weakness, with a tendency for progression with age. Recently, these disorders were classified together, while periodic paralyses (PP), which is characterized by episodic generalized paralysis with and without myotonia, were grouped under metabolic myopathies. However, the recent enormous advances in the field of pathophysiology and genetics of these disorders has led to a major rewriting of their nosography, with the introduction of a new term: the channelopathies. Myotonia congenita, PP and paramyotonia congenita are now classified under channelopathies, because their clinical pictures are manifestations of chloride, sodium or calcium channel mutations. Myotonia dystrophica, on the other hand, is not included within this new group, because it is not due to a specific primary channelopathy.

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So far, these disorders have not been studied in any detail in Saudi Arabia, and in view of the high consanguinity rate in this country, some significant variations were expected, especially in relation to the autosomal recessive variety.\textsuperscript{11}

This study is intended to fulfill this gap, by describing the spectrum of these disorders and their clinical and genetic features.

\textbf{Methods.} Data of 49 patients seen at King Khalid University Hospital, which is one of the main tertiary referral centers in the Kingdom who presented between January 1985 and 1998, with the diagnosis of myotonia associated disorder or periodic paralysis were analyzed. All available patients and members of their families were reassessed and had detailed history and clinical examination, stressing especially on the following points: severity of myotonia estimated from the duration of "warm up" period, and the degree of interference with daily activity; the association of myotonia with cold and exercise; the severity of muscle weakness if present and its relation to exertion and its association with muscle wasting or hypertrophy; and whether periodic paralysis is present or not. Myotonia was labeled as mild if it does not interfere with any activity; moderate if only severe exertion such as sports and running are affected while daily activities and work are not; and severe if it interferes with everyday activities such as dressing, bathing, walking and or work. All patients should have electromyographic (EMG) confirmation of myotonia, and available parents also should undergo EMG screening. Other tests including creatine kinase (CK) measurements and muscle biopsy were analyzed. Finally, family pedigrees were outlined, and mode of inheritance defined. Sporadic cases of MC were considered to have AR inheritance, as de novo mutation of AD/MC has not been documented anywhere.\textsuperscript{12} Progression of the disease was estimated by inquiring into the deterioration of different functional abilities the prolongation of "warm up" period and the subjective assessment of worsening of symptoms.

\textbf{Results.} There were 2 families with AD/MC, which included 5 males and 6 females, age range 6-75 years and age of onset 9 months - 2 years. Myotonia was mild in most patients, and power was normal in all of them. Noticeable muscular hypertrophy, associated with moderate myotonia was noted in 2 patients only. There was no functional limitation in any patient including jogging, but not competitive running.

There were 7 families with AR/MC, 15 males and 6 females (ratio 2.5:1), age range 4-32 years and age of onset 2-17 years. However, if 2 single patient families were excluded, the age of onset will be 2-3 years in 80\% of the patients (5 families). Typical, mainly lower limb hypertrophy was noted in the majority, being more marked in males. Weakness of variable degrees was present in all patients, but tended to be generally of similar severity in the same family. Most patients were restricted from sport but were able to maintain essential activities and work. In only one patient, it was severe enough to affect every daily life activity and school attendance. Progression of the disease appears to continue in most patients until late 20\'s and early 30\'s. The eldest patient is 43 years old and her symptoms which are of modest severity, appear to have been stable for the past 10 years.

There were 5 families with MD (12 patients), 8 males and 4 females (ratio of 2:1), age range 24-46 years and age of onset 4-30 years. If one patient with early onset is excluded it will be 11-30 years. The commonest clinical features noted were frontal baldness, ptosis, cataract and wasted neck and distal muscles. It also included diabetes mellitus in one patient and azoospermia in another.

Myotonia was mild in all AD/MC patients; requiring treatment in less than half of them, while all patients with AR/MC required treatment. Utilized medications included quinidine, phenytoin, verapamil, procainamide and acetazolamide. Mexiletine was effective in most patients not responding well to other medication (17\%). Three patients with AR/MC reported a decline in the initial satisfactory effect of mexiletine despite reaching 1000mg total dose.

Finally there were 5 patients with hyperkalemic PP. All of them were males from the Philippines aged from 24-36 years. None of them were noted to have myotonia, and 3 had associated thyrotoxicosis, the treatment of which successfully prevented the recurrence of PP. Data on these patients however, was limited, as contact could not be made with any of them. No case of PP in Saudis was detected. Also no patient with paramyotonia was noted.

\textbf{Illustrative case.} A 28 year old Saudi man presented with difficulty in initiating all types of voluntary movements. He walked at the age of one year but by the age of 2 he was noted to have difficulty in walking, as his muscles became stiff and required some time before reaching normal walking speed. He could not run properly and was unable to participate in sport activities at school. This progressed with time and currently he needs up to 2 minutes to "warm up" (about 15 steps or 8 stair steps). However he can still walk for more than 10 kilometers non-stop. This problem is encountered in performing all activities including writing for which he needs about 30 seconds to "warm up". A similar period is necessary again after only a few minutes of rest. His symptoms apparently tended to worsen when he was under stress but not in cold weather. He also complained of some weakness in hand grip and the upper limbs in general. He has ten other
affected relatives (Figure 1a). On examination, his mini-mental test was normal as well as cranial nerves, cerebellar and sensory systems. He had relatively thin arms and hands but his thighs and calf muscles were hypertrophied, similar to but more severe than his younger brother who was 17 years old (Figure 1b). Also severe wasting of his extensor digiti minimi is noted in comparison with his brother. Myotonia was clearly demonstrable after handgrip (Figure 1c). He had weak upper limbs, more so distally (4/5 MRC scale) and normal power in lower limbs. Deep tendon reflexes were normal. Electromyography showed typical myotonic discharges and normal motor units. Creatine kinase and muscle biopsy were normal. He was diagnosed as AR/MC (Becker’s disease), and was tried on the following medications with no significant effect: phenytoin, quinidine, acetazolamide and verapamil. He is currently on mexiletine, which gave significant initial improvement but tended to wear off gradually. Other family members provided a very similar history and clinical picture, apart from the finding that the affected female patient showed only mild muscular hypertrophy. All of them are leading near normal lives including work, however none are or were able to participate in any sport activity.

**Discussion.** In view of this study’s results, MD appears to be less common than MC in Saudis, which contrasts with worldwide figures. However this discrepancy is most likely factitious, and does not reflect the true prevalence of these disorders. This is partially because MD is probably under-diagnosed, which is a long recognized fact, as it tends to present in most patients with only subtle weakness or myotonia. On the other hand, it is very likely that MC is relatively more common in this society, a conclusion already supported by the results of a local population-based epidemiological study. Within the limitation of the small number of patients in Al Rajeh et al study, the probable prevalence of MC in the Saudi population exceeds by many folds, the worldwide overall prevalence of 10 x 10⁻⁶, estimated by Emery. In view of our results, the most likely cause of this increased prevalence of MC in the Saudi population, is the higher occurrence of the AR variety of MC in comparison with the AD variety, with a ratio of 2:1. This finding is not unexpected, as higher prevalence of AR inheritance is already well recognized in many other inherited disorders studied in this country. This is mainly a result of the very high consanguinity rate of 60-80% encountered in the Saudi population.

The other significant finding in this study is the absence of any case of PP in Saudis, which is unlikely to be due to under-diagnosis, as the clinical picture of these disorders is usually very characteristic. This is further supported by the absence of any case of PP in the study of Al Rajeh et
al or local case reporting. The fact that all patients are Filipinos is consistent with the well recognized predilection of thyrotoxicosis-associated PP in Far Eastern populations.18,19

Most clinical features in our patients resembled those described in other populations. A significant variation however, is the lower age of onset of most patients with AR/MC of 2-3 years compared with 4 years being the lowest age of onset observed in western reports. None had any significant exaggeration of their symptoms in cold weather, which may be related, at least partially to the relatively mild and short winter in this country. The main clinical features including age of onset and severity of symptoms appear to be very similar in all affected members in the same family, while it tended to vary in different families. AD/MC patients in general had minimal functional limitation with tendency to respond well to medications. Function in all AR/MC patients was affected significantly. Most were unable to participate in any sport activity but were able to work normally. In one patient only, the disease was severe enough to interfere with everyday activities of life and school attendance. Response to treatment in MC/AR patients was generally unsatisfactory which resembles experiences elsewhere. A wide range of agents were utilized to control myotonia. Mexiletine proved very helpful in 27% of patients who did not respond well to other medications. This is similar to the experience of Ponget and Servatrice, who found that all their patients who were refractory to phenytoin, obtained a good response from mexiletine. However our patients reported a large drop in its efficacy within a few months.

The overall prognosis is similar to that noted in western reports. All patients with Thomsen's disease were able to lead a normal life with no evidence of significant progression until late age, which is 75 years in our eldest patient. The picture however is different in Becker's disease, where disability tended to progress with age until the 3rd-4th decades of life. This is consistent with Sun and Streib's observation that progression of the disease halts after about 30 years of age.12

Despite the enormous advances in the genetics of these disorders, no such study has yet been carried out in this country. Myotonia congenita of both types is due to chloride channel dysfunction with an allelic genetic defect on chromosomes 7. Sodium channelopathies include paramyotonia and hyperkalemic PP which are localized to chromosome 17,18. While hypokalemic PP is a calcium channelopathy, and is localized to chromosome 1, MD on the other hand is not due to a primary channel dysfunction. Apparently, MD gene codes for a cAMP-dependent protein kinase, termed myotonia-protein kinase, which modulates ion channel function.4,10

In conclusion, this study has outlined the spectrum of inherited myotonic disorders and periodic paralyses in this country. AR/MC (Becker's disease) apparently occurs relatively more commonly than described in the west, probably as a result of the high rates of inbreeding in this community. Periodic paralysis on the other hand is very rare. These results, however, need further verification, through a national multicenter effort. In view of the promising potential of gene therapy, this should include genetic studies especially on AR/MC.21

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References


