EDITORIAL
Basic Appl. Myol.
7(5):307-310

Myotonic Dystrophy

Beginning in 1992, our understanding of the molecular basis of neurological disorders has expanded. A new category of DNA-triplets repeats diseases has been seen to identify a class of disorders that include now several examples (Table 1) both causing a frequent muscle disorder (Myotonic Dystrophy) and diseases with degenerations of central nervous system (CNS). An invited lecture of MDR'97 by Prof. S. DiDonato has covered the subject of unstable mutation expansions. The most common inherited ataxia, the Fredreich's ataxia, whose prevalence is estimated to be 1 in 50.000, appears to be due to a GAA triplet repeat in exon 1 of the gene mapped to 9q13-q21. In a group of various trinucleotide repeat including SCA1, SCA2, SCA3 and Huntington's Chorea, the mutation consists of CAG repeat expansion of moderate length, within coding regions of several genes, resulting in protein with expanded polyglutamine tracts that cause neuronal cell death in selective area of CNS (cerebellar cortex, brainstem, spinal cord).

Myotonic dystrophy (DM) or Steinert's disease, the most prevalent myopathy (the extimated prevalence in our region is 66 x 10"^ inhabitants or 1:15,000) is a highly variable multisystemic disease. An infantile congenital form, whose clinical features were presented at MDR'97 by Prof. C.Trevisan (mostly maternally inherited), correlates with a CTG expansion length of over 2,000 repeats. The classic adult onset form displays progressive muscle wasting, cataract, cardiac abnormalities, gonadal atrophy, insulin resistance and neuropsychiatric impairment.

Table 1. Neurological hereditary diseases with expanded trinucleotide.

Disease	Repeat	Repeats		Chromosome (coding region)
		Normal repeat N°	Range of repeats in disease	
1) Spinal and bulbar muscular atrophy (Kennedy's syndrome)	CAG	11-39	40-62	x yes androgen receptor
2) Chorea Major (Huntington's disease)	CAG	1-39	36-121	4 yes huntingtin
3) Spinocefebellar Ataxia type I	CAG	< 29-36	43-60	6p yes ataxin - I
4) Spinocerebellar Ataxia type III (Machado-Joseph disease)	CAG	13-36	49-79	14p yes
5) Dentato Rubro Pallido Lusian Atrophy	CAG	7-34	49-70	12q yes
6) Fragile X	CGG	6-54	250-4000	X no
7) Fraxe	GCC	6-25	> 200	?
8) Friedreich's Ataxia	GAA	7-22	200-1200	9q frataxin
. 9) Myotonic dystrophy	CTG	5-30	50-2900	19 no . myotonin protein kinase

The mechanism of myotonia and muscle dysfunction is bound to a selective type 1 fibers atrophy and sarcoplasmic reticulum (SR) dysfunction. In 1970 [7] with ultrastructural and biochemical studies, we demostrated that SR was preferentially affected and that the Ca^{++} uptake was lowered in DM patients with increasing muscle atrophy and weakness. In a more recent study [1], biochemical investigations confirmed a peculiar skeletal muscle SR phenotype in DM. Our results outlined a cellular process affecting slow-twitch type 1 fibers and defective expression of the slow isoform of Ca^{++} binding protein, calsequestrin.

The mechanism of this muscle dysfunction has been partially clarify. The protein product of this gene is a myotonin-protein-kinase, localized in the terminal SR cisternae of type 1 fibers as shown by immunohistochemistry by the group of Dr. Kobayashi, and a preferential involvement is likely. Similar results have been obtained by Dr. Salvatori with a different antibody [8].

Another mechanism is the shut down by the expanded poly-(A)+ mRNA or other mRNA with a negative dominant effect [10]. More recently, by two groups of investigators, it has been shown that DM CTG repeat reduces the expression of a flanking gene, a DNA hypersensitive site code DMAHP gene [3, 9].

Several endocrinological features (testicular atrophy, thyroid disorders, carbohydrate metabolism, type of pregnancy and delivery) have been studied by Prof. Mastrogiacomo and Bonanni, and the testicle myoid cells seem to be preferentially affected [4]. In their study they demonstrate that some endocrinological findings are directly correlated to the CTG expansions, while others appear to be secondarily impaired.

A beautiful review of cardiological changes in DM was done by Dr. Melacini, who confirmed and amplified the observation of correlation between involvement of specialized cardiac tissues to CTG repeat lengths, as well as the ventricular late potentials [5]. The delayed electrical transmissions through damaged myocardial areas explains the occurrence of arrhythmias; therefore careful cardiac monitoring is advised in DM patients to detect the development of atrioventricular blocks or lethal ventricular arrhythmias.

Dr. Gennarelli carried out a genotype-phenotype correlation based on clinical findings in a large group of 465 DM patients. This study demonstrates that measurement of triplet expansion in patients' lymphocytes DNA is highly valuable and accurate for prognostic assessment [2].

Cognitive dysfunction in DM and brain imaging and function was also throughly investigated. Dr. Chierichetti evaluated in 30 genetically defined DM patients the cerebral perfusion data obtained with 99m Tc-ECD SPECT and cerebral metabolism with [18-F] FDG PET. Preliminary data suggested that frontal and temporal areas are affected.

Dr. Perini studied the same 30 DM patients with WAIS test for evaluation of IQ and a more extensive neuropsychological battery. A specific deficit in attentional perfomance was found. Alteration of evoked potentials and RMN were also observed by Dr. Versino.

Altogether this supports that DM is a multisystemic disorder with somatic mosaicism and that cognitive impairment is associated with functional brain imaging alterations.

The clinical and morphological abnormalities of proximal myotonic myopathy (PROMM), a new disease with some clinical similarities to DM but no mutation expansion, were reviewed in MDR'97 by Prof. G. Meola [6], while another distinct clinical entity with cardiac arrhythmia of unknown etiology, Andersen' s syndrome, has been presented by Dr. V. Sansone who recognized this syndrome in a few cases working with Dr. Ptacek in Utah.

Channelopathies

Ion channels constitute a class of molecular protein tunnels that span the lipid bilayer of cell mebrane. About 30% of energy generated by a cell is used to mantain the gradient of potassium and sodium ion across the cell membrane. Ion channels are responsible for generating electric signals passing through the contracting muscle, the beating heart and the thinking brain. A variety of hereditary myopathies including generalized myotonia (Becker's disease), myotonia congenita (Thomsen's disease),

Table 2. Inherited muscle channelopathies.

Type Eponym	Mode of Inheritance	Ion-channel Gene	Chromosome Location
Becker's myotonia	AR	CL-CN 1	7q35
Thomsen's myotonia	AD	(skeletal muscle chloride channel)	
Myotonia levior	AD	CL-CN 1	7q35
Hyperkalemic periodic paralysis	AD	SCN4A (skeletal muscle sodium channel)	17q23
Paramyotonia congenita	AD	SCN4A	17q23
Myotonia fluctuans permanents, acetazolamide responsive			
Hypokalemic periodic paralysis	AD	CACNL1A3 (dihydropiridine sensitive calcium channel)	1q31
Malignant hyperthermia	AD	RyR1 (Ryanodine calcium channel)	19q
Central core disease	AD		
Congenital myasthenic syndromes	?	nAchR (nicotine Acethylcoline receptor s-subunit)	17p
	AD	a-subunit (slow channel)	2q

periodic paralysis, malignant hyperthermia and central core disease are associated with mutation in ion channels (Table 2).

Drug that target ion channels include calcium channel blockers (used in patients with hypertension), potassium channel blockers and anti-arrhythmic drugs. Also some diuretics (e.g. acetazolamide) have been found efficacious in the various forms of periodic paralysis.

A growing number of inheritable diseases are known to be caused by mutations in ion channel genes. Chloride channel defects include cystic fibrosis and Thomsen's congenital myotonia. Mutant sodium channels give rise to hyperkalemic periodic paralysis and paramyotonia. A dihydropiridine-sensitive calcium channel is mutated in hypokalemic periodic paralysis. Also in other CNS disorders, such as intermittent ataxia, neuronal channel proteins have been found abnormal. It is likely that this new group of disorders will increase in the near future and many mechanisms of drug action and new treatment in this field will be available.

A precise understanding of ion channel function will reveal relationship between their structure and function and should make it possible to develop new therapies for patients with these disorders.

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