A DM registry is essential to identify potential participants in clinical trials, to follow the natural history of the disease and to serve as an indicator of the effectiveness of the health care provided to the DM population. A Quebec DM population-based registry has been developed over the last 10 years. In December 2010, the Quebec DM population-based registry contained: 1183 individuals including 892 patients with DM1, 2 patients with DM2 and 145 non-affected subjects. Among these patients, 667 patients were clinically evaluated in a standardized manner. 44% of patients were male and 55% female. Patient’s distribution revealed that 3% were aged less than 18 years, 9% between 19 and 30 years, 44% between 31 and 50 years and 44% above 50 years. The congenital form represents 5% of the patients, the infantile form; 15%, the adult form 57% and late onset form 23%. The form was not determined in 6,5% of patients. The muscular impairment determined by the Muscular Impairment Rate Scale (MIRS) score shows that 28% of patients have a MIRS at 1 and 2, 27% with a MIRS = 3 and 42% with MIRS at 4 and 5. The MIRS was not available for 6,7% of the patients. The most frequent manifestations are Myotonia (80%), cataracts (56%), digestive (52%) and excessive daytime sleepiness (EDS) (50%), whereas cardiac conduction defect (27%), diabetes (13%) and thyroid (10,7%) were less frequent. Interestingly, several manifestations (thyroid, cardiac conduction defect, cholecystectomy and EDS) often occur in patients with less than the threshold of 200 CTG repeats whereas diabetes was only observed in patients with more than 800 CTG repeats in blood. Finally some manifestations (diabetes, thyroid, EDS, and patients with pacemakers) were predominantly observed in females. DM registry represents a unique source of information on the natural history of the disease, and is therefore essential for the understanding of the mechanisms of the disease.

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MYOTONIAS: POSTER PRESENTATIONS

P5.9
Muscle channelopathies: Clinical and molecular genetic studies in a cohort of Italian patients
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Clinical, electrophysiological and genetic studies are the key instruments to characterize several muscle disorders affecting ion channels, called channelopathies, such as non-dystrophic myotonias (myotonia congenita, paramyotonia congenita and sodium channel myotonias) and periodic paralysis. The aim of this study was to clinically and genetically characterize a cohort of Italian patients, affected by suspected muscular channelopathies. We recruited 31 patients with clinical and laboratory features compatible with muscle channelopathy. The patients were phenotypically classified in four groups: Periodic Paralysis (3 pts.), Paramyotonia congenita (4), Sodium Channel Myotonia (4) and Myotonia congenita (20). Molecular genetic analysis was positive in 23 out of the 31 patients, revealing: 16 patients with a mutation in the Chloride Channel gene; 2 Periodic Paralysis due to mutations in the Calcium Channel gene, and 5 mutations in the Sodium Channel gene (in particular 1 associated with Paramyotonia Congenita, 2 with Myotonia fluctuans and 2 with Potassium Aggravated Myotonia). In this group of cases, we found clear genotype-phenotype correlations, especially in patients affected by myotonia congenita. These data confirm the importance of performing detailed clinical and molecular genetic studies to better characterize patients with non-dystrophic myotonias and periodic paralysis and address a correct therapeutic approach.

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P5.11
Using fluorescence resonance energy transfer (FRET) to reveal the basis for Thomsen’s disease
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Using fluorescence resonance energy transfer (FRET) to reveal the basis for Thomsen’s disease.
Thomsen’s disease is a dominant chloride-channel-associated myotonia free of extra-muscular systemic involvement. The implicated muscle chloride channel, hClC-1, is regulated by fast gates opening and closing each pore of the dimeric channel independently and a common gate operating on both pores simultaneously. Common gating is poorly understood. Typically, in Thomsen’s disease, it is drastically affected, not only in hClC-1 channels homodimeric for the causative mutation but also in mutant-wild-type heterodimers (a dominant negative effect). Its voltage dependence is so much altered that muscle cells can never, physiologically, depolarise sufficiently to allow effective opening. Using fluorescence resonance energy transfer (FRET), we studied lateral movements of the cytoplasmic C-termini of the hClC-1 protein which appear to be functionally associated with common gating. On opening of the common gate, the C-termini of the two hClC-1 subunits that constitute the dimer approach each other more closely whereas closure is accompanied by a physical separation of the C-termini. To estimate C-terminus depth within the cytoplasm we constructed a pair of split hClC-1 fragments, the first fluorescently tagged extracellularly and the second intracellularly. They not only combined appropriately to rescue channel function but we detected positive FRET between them. This restricts each C-terminus of hClC-1 to a position close to its membrane-resident domain. Within each hClC-1 chloride permeation pore, the carboxyl side chains of glutamate residues (E232) are believed to constitute the independent fast gates. Our FRET results comparing the two single mutants E232Q (having no glutamate side chain) and C277S, with the double mutant E232QC277S, strongly suggest that fast individual pore gating and common gating are closely linked in hClC-1. We propose, therefore, that Thomsen’s disease depends on an aberrant common gate latching both fast gates closed at physiological voltages.

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P5.12
Congenital myotonia caused by mutations in the chloride channel CIC-1 in the South Moravian Region of Czech Republic
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Myotonia is known as a delayed relaxation of skeletal muscle following voluntary contraction which usually abates after repeated muscle activity. This phenomenon is caused by ion channel disorders on muscle membrane. Chloride channel (CIC1) is most frequently affected. The mutations in voltage-gated chloride channel gene CICN1 cause the disease inherited either as an autosomal dominant (Thomsen’s myotonia) or recessive (Becker’s myotonia) manner. During 2008–2010 the mutations in the chloride channel gene were found in 10 unrelated patients with myotonia. It is the third most frequent cause of myotonia in our local registry (54 patients with myotonic dystrophy type 2, 18 with myotonic dystrophy type 1, and 7 suffering from mutations in the sodium channel). All persons revealed hypertrophic muscles and warm-up phenomenon. Worsening in cold was found in seven cases and no patients have post-exercise weakness. The semi-dominant mutation c.2680C>T was found most frequently: 5 times from all 18 affected alleles. In three patients was this mutation revealed in the heterozygous combination with other recessive mutation, in one case with dominant mutation c.870C>G, and in one patient was discovered as a dominant mutation. Three times was revealed recessive mutation c.1437_1450del and two times c.1238T>G and c.220C>T. In one person we found isolated mutation c.1679T>C till this time described only in one Chinese family in semi-dominant form. Our patient is suffering from classic myotonia since childhood; his parents were clinically unaffected, but not genetically tested (died). All cases are sporadic, despite of the fact that two convincingly affected patients have only one mutated allele and another patient have the heterozygous combination of dominant and semi-dominant mutation. The majority of patients in our population could be classified as Becker’s form of myotonia congenita.

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P5.13
Spectrum of CLCN1 and SCN4A mutations in Czech patients with non-dystrophic myotonias
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The non-dystrophic myotonias are a heterogeneous group of skeletal muscle ion channel diseases that demonstrate myotonia as their common feature, in reference to a delayed muscle relaxation after voluntary or evoked muscle contraction. The non-dystrophic myotonias are caused by mutations in the genes coding the skeletal muscle chloride channel 1 (CLCN1) or the alpha subunit of voltage-gated sodium channel 4 (SCN4A). Mutations of the CLCN1 gene result in either autosomal dominant myotonia congenita (Thomsen type) or autosomal recessive myotonia congenita (Becker type). A subset of CLCN1 mutations have been found to cause both recessive and dominant myotonia. Mutations of the SCN4A gene are typically inherited as an autosomal dominant trait, regardless of the associated phenotype (paramyotonia congenita, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, potassium-aggravated myotonia, myotonia fluctuans, and congenital myasthenic syndrome). Molecular-genetic diagnostics of non-dystrophic myotonias was initiated in our laboratory in 2009. Since then, DNA diagnostics was performed in 55 unrelated patients suspected to be myotonia congenita, and confirmed in 41 of them. Mutations in the CLCN1 gene were detected in 28 patients (25 with recessive and 3 with dominant myotonia congenita), mutations in the SCN4A gene in 13 patients. We identified 20 types of CLCN1 mutations (6 mutations were novel not described previously) and 6 types of SCN4A mutations (3 mutations were novel). This work was supported by grant MSMT LC06023 and 2B08060.

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MYASTHENIC DISORDERS: POSTER PRESENTATIONS

P5.14 Challenges in diagnosis and management of a patient with severe congenital myasthenic syndrome mutated in CHRNE
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