CONGENITAL MYASTHENIAS AND MYOTONIC DISORDERS

P.12.1
Diagnostic pitfalls in congenital myasthenic syndromes in children: Clinical experience in an academic neuromuscular centre
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Congenital myasthenic syndromes (CMSs) cover a group of heterogeneous disorders in which the neuromuscular transmission is affected. As clinical features, like tiredness and weakness in a young child, are rather a specific and do not always guide towards a CMS, the diagnostic studies leading to a diagnosis can be very challenging.

We describe our diagnostic work up and show our struggles in eight children suffering from tiredness, exhaustion and muscle weakness. Common diagnostic pitfalls, causing delay in diagnosis and treatment, are the lack of specificity of clinical features, false negative electromyography (EMG) results, non-specific changes in muscle histology and technical drawbacks of invasive testing in young children. We discovered five mutations in the CHRNE gene, two in the RAPSYN gene and one mutation in DPAGT1, so finally DNA confirmed diagnosis of CMS was made. We started with medications what considerably improve the quality of life.

Clinicians are urged to perform tailored genetic testing guided by clinical features. CMSs are highly treatable and early initiation of treatment can considerably improve the quality of life of patients with a CMS.

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P.12.2
Dominant distal myopathy due to slow channelopathy
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Slow channel syndrome, first recognized by Engel in 1982, has distinct phenotypic features, dominant inheritance, selective weakness of cervical scapular and finger extensor weakness, ophtalmoparesis. Histochemical findings show type 1 fibers preponderance, small group of atrophic fibers of either fiber type, increased fiber size variability, tubular aggregates.

We examined 3 biopsies in 3 patients (2 males – 55 years and 66 years, 1 female – 61 years) presenting a dominant distal myopathy with variable age at onset (from second to third decade). The patients had ophtalmoparesis, upper limb extensor, forearm and finger weakness and distal myopathy with a progressive slow course.

The woman had also some difficulty in anterior tibial flexor muscle but also atrophy of forearms muscles. Electrophysiology on single stimulus of ulnar nerve showed repetitive CMAP.

The genomic wide linkage analysis identified 3 regions co-segregating with the disease in chromosome 1, 13, 17. Next generation sequencing showed in all patients a known mutation in epsilon-subunit of AChR receptor and a mutation in phospholipase. Muscle showed mild changes consisting in atrophic fibers, mostly of type 2, some fiber type grouping, central nuclei and ring fibers. Such fibers are consistent with abnormal regeneration. We suggest the occurrence of mutations involving both AChR receptor and phospholipase might concur in determining a new distal phenotype with permanent weakness.

Our family was previously diagnosed as myotonic dystrophy or distal myopathy. The presence of the histochemical findings of both myopathy and neuromyopathy were present. We suggest the possibility of calcium overload due to prolonged open time of the AChR channel with a preynaptic component might determine a distal neuro-myopathy with slow evolution and muscle rearrangement due to a muscle fiber degeneration and functional denervation.

The slow channel mutation should be searched in families with permanent distal weakness.

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P.11.21
Bioanalysis of a double blind, placebo-controlled clinical phase 2 study of drisapersen for the treatment of boys suffering from Duchenne muscular dystrophy and comparison to clinical outcome results
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Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disorder, ultimately lethal, caused by the absence of dystrophin protein due to mutations of the dystrophin gene. Drisapersen is a 2'-O-methyl-phosphothioate oligo designed to skip exon 51 in the dystrophin pre-mRNA for the treatment of DMD. Here we report the pharmacodynamic results of a double blind, placebo-controlled clinical study of drisapersen.

Subjects with DMD and a dystrophin mutation correctable by exon 51 skipping were randomized to 2 drisapersen dosing regimens or matched placebo (2:1) and dosed subcutaneously for 48 weeks. Muscle biopsies were obtained from either the anterior tibialis or quadriceps prior to treatment and at 24 weeks after first dose.

The restoration of dystrophin at the sarcolemma was studied by immunofluorescence and semi-automated image analysis. Precision cut cryosections of the muscle biopsies before and after treatment were stained with antibodies against dystrophin and spectrin protein and the resulting images were computationally analysed using customised software to measure sarcolemmal dystrophin intensity in individual fibres. Exon 51 skip induced by drisapersen and the expression of dystrophin in muscle homogenate was evaluated by quantitative RT-PCR and Western blot analysis (WBA), respectively. Drisapersen levels were measured using quantitative ELISA methodology, in plasma and muscle tissue. Using immunofluorescence, semi-automated analysis and defined criteria, it was possible to detect changes in dystrophin membrane intensity (mean and quantile values) in the muscle fibre population after treatment with drisapersen.

Drisapersen was also observed to induce skip of exon 51 by RT-PCR and dystrophin expression by WBA. This pharmacodynamic data was compared to the primary clinical outcomes including the 6 Minute Walk Distance (6MWD) over 24 weeks, and secondary outcomes included 6MWD at 48 weeks and the North Star Ambulatory Assessment.

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