Neuromuscular Disease Update: What's of Note from 2019-2020?

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As I have constructed these in recent years, this review runs "in reverse" from skeletal muscle retrograde to the motor neuron. All studies were published in 2019 or 2020, and within one year of preparation of this bulleted syllabus. I focus mainly on management issues but there is a bit of pathogenesis mixed in. I hope the review provides a framework for some of the advances in our field in the last year.

Muscle Disease: Late-onset Pompe and enzyme replacement therapy

- Prior well-designed randomized, controlled studies have established the efficacy of enzyme replacement therapy (ERT) with recombinant human α-glucosidase in infantile and late-onset forms of Pompe disease, an autosomal recessive, previously progressive and even fatal myopathy.
- In adults, ERT has demonstrated benefits in ambulatory function and muscle strength, stabilization of pulmonary function and increased survival. However, follow-up studies through 3 years have suggested that these benefits wane with secondary decline over time.
- Late-onset patients in the initial LOTS trial have now been followed for 10 years or longer, providing better understanding of long-term benefits from ERT.
- The prospective, multicenter cohort study (class IV evidence) of 30 patients who were initially enrolled in the only randomized placebo-controlled trial or the extension study of ERT in late-onset Pompe disease found that most patients benefit long-term, but that a minority will experience decline after 3 to 5 years.[1]
- Overall, 93% of patients had initial benefit. At last follow-up (median 9.8 yrs), 52% continued to have a better than baseline 6 minute walk test or upright FVC than their baseline. There were no clear predictors for an initial or secondary response.

Muscle Disease: Pathogenesis of inclusion body myositis (IBM)

- Histologic features of myonuclei and mitochondria along with aggregation of myofibrillar cytoplasmic proteins have fed the degenerative hypothesis for IBM. Yet, an autoimmune pathogenesis remains actively argued.
- In a GWAS/big-data study of 411 muscle biopsies, including 44 of IBM, 77 with other inflammatory myopathies, 188 with other forms of myopathy (hereditary) and 106 normal muscle specimens, a signature pattern was seen for IBM, distinguishing it from others.[2]
- Highly differentiated CD8+ T-cell effector memory and killer cell lectin-like receptor G1 (KLRG1)+ cells identified in IBM. KLRG1 found in T-cells invading IBM myofibers, and these cells were also increased in IBM patient blood.
- These highly differentiated cells were poorly proliferative and are known to be resistant to immunosuppressive therapy.
- Targeting these cytotoxic T-cells has therapeutic potential in this treatment-refractory muscle disease.

Neuromuscular Disease: Social functioning and fatigue

- Chronic fatigue is the main factor in reduced social participation per 60% of surveyed neuromuscular patients.
- Aerobic exercise and/or cognitive behavioral therapy have reduced fatigue levels in a variety of neuromuscular disorders including FSH and myotonic dystrophy, mitochondrial myopathy.
- The Energetic intervention study[2] enrolled 53 patients with a variety of neuromuscular disorders in a 1:1, rater-blinded controlled trial. Intervention subjects underwent aerobic training for a total of three 30 minute sessions for 4 months in addition to energy conservation management strategy training (eight 90-minute sessions) and ten relapse prevention sessions at home.[3]
- Subjects who underwent the Energetic intervention scored significantly better on the Canadian Outcome Performance Measure (COPM) vs. controls. They also showed significant improvement

on the 6 minute walk test, depression scales and activity measures.
- Fatigue and anxiety scales did not show a significant difference between the two populations
- Overall 72% of intervention subjects had a ≥2 point improvement on the COPM vs. only 25% of control subjects, yielding a NNT of 2.3.

Myasthenia gravis: Preoperative IVIg in generalized patients undergoing procedures

- Plasma exchange and intravenous immunoglobulin both used to prepare MG patients for surgery. No prospective data on need for such preoperative therapies in well-controlled generalized MG patients.
- A double-blind, placebo-controlled randomized trial of IVIg 0.4 gm/kg x5 days vs. saline was performed in 45 generalized MG patients, 43 of whom were AChRAb+. The primary outcome was myasthenic crisis with secondary outcomes including length of stay and QMG scores. Most of the procedures were thymectomy or GI-related.[4]
- There was only one crisis episode in a 63 year-old woman with thymoma who developed bilateral pleural effusions and a left phrenic nerve palsy post-op. There were no significant differences in QMG scores or time in hospital.
- A pre-op QMG score of <8 and FVC>70% predict that MG patients will tolerate surgery without the need for preparatory IVIg.[4]

Myasthenia gravis: FcRn antagonists as new therapeutic approach

- These agents are being widely studied in immune-mediated disorders. They block the neonatal Fc receptor that normally ensures IgG homeostasis by rescuing IgG from degradation in lysosomes. FcRn antagonists lower all IgG subtypes quickly, peaking at approximately a 70% reduction, similar to plasma exchange.
- The first full report of a randomized, placebo-controlled trial of an FcRn antagonist studied efgartigimod, an IgG1 mutated Fc portion. A total of 24 patients were randomized 1:1 to efgartigimod 10 mg/kg weekly infusions for 4 weeks vs. placebo. Patients were followed through week 11.[5]
- The primary outcome was safety, and no SAEs were reported. AEs were predominantly mild and were balanced in frequency compared to placebo.
- Secondary outcomes assessed several MG outcome scales. Clinical benefit could be seen at one week that persisted on some measures through week 11. Significant separation vs. placebo was seen on the QMG at one, MG-ADL at two and MG-QOL15r at three time points during the study.[5]
- Phase 2 to 3 studies of this mechanism of action are underway for MG and other immune-mediated disorders.

Painful diabetic peripheral neuropathy: costs and complications

- A longitudinal analysis of a large commercial and Medicare claims database was used to compare costs of painful diabetic polyneuropathy (DMPN) vs. DMPN without pain and DM without neuropathy.[6] Patients were followed a median of 856 days.
- Of 360,559 total patients diagnosed with these conditions between 2010-2015, only 5% had non-painful DMPN vs. 23% with painful DMPN. So the cost differentials between painful DMPN and DM are likely underestimated.
- Baseline outpatient medication costs for painful DMPN patients were 1.67-2.13x as high than the other two patient groups.
- Painful DMPN patients were 2x as likely to receive opiates. Being on opiates increased the costs of care at 1 year by $7,000.
- Lower limb infections, amputations and falls were all significantly more likely in the painful DMPN group.[6]

Spinal muscular atrophy: real-world experience with nusinersen and combination therapy

- Between 2016 and 2019, FDA approved both nusinersen, an antisense oligonucleotide that increases full-length SMN production by altering SMN2 pre-mRNA splicing, and SMN1 gene replacement via AAV9. Combination therapy has not been formally tested.
- An Italian multicenter study assessed 12-month outcomes in 85 SMA type 1 patients ranging in age from 2 months to almost 16 years of age.[7] Sixty-one of the children had 2 SMN2 copies, 18 had 3 copies, 2 had one copy. The remainder were unknown.
- Significant group improvements in the CHOP-INTEND were seen except those starting nusinersen

after age 5 years and on the HINE-2 except those starting nusinersen after age 2 years.

- Improvement on functional scales and on parent/patient surveys were mainly in the motor domain. Less improvement noted related to gastrostomy, non-invasive ventilation and tracheostomy. Of note, an additional 7 children required gastrostomy and 2 required tracheostomy during the 12-month period.[7]
- Two infant boys presenting with hypotonia at 2 months commenced on intrathecal nusinersen loading doses at 5 to 5.5 months of age followed by the single AAV9 intravenous infusion at 9 months.[8]
- Both boys are gaining motor milestones with improved CHOP-INTEND scores, reduced BiPAP needs, enhanced functional skills per parents
- No adverse events or laboratory abnormalities were observed including platelets, LFTs.[8]
- Combination therapy is largely uncharted, with insurance coverage, treatment order implications. The potential for long-term side effects is unclear.

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