A 2020 centenary perspective on neuromuscular disorders

Stephen A Goutman, Brian Christopher Callaghan, Eva Feldman

GENETIC DIAGNOSES AND GENE-BASED THERAPIES HAVE TRANSFORMED OUR APPROACH TO NEUROMUSCULAR DISORDERS AND CREATED NEW THERAPIES TO TREAT PREVIOUSLY INCURABLE DISEASES

In August 1921, the Journal of Neurology, Neurosurgery and Psychiatry (JNNP) published a case of recurrent hypertrophic neuritis, which detailed the clinical course of a patient with a likely inherited neuropathy. Although unknown in 1921, this article foreshadowed the critical role that genetics would play in altering the course of multiple neuromuscular diseases. One year ago, we were challenged to consider the ‘most important or transformative development in neurology’ in the past 100 years and how JNNP contributed to this achievement given its broad scope. To our surprise, no nomination for neuromuscular disorders made the final list. Therefore, we wish to put forth a nomination for neuromuscular disorders. All articles cited for this nomination are published in JNNP. We contend the subspecialty of neuromuscular disorders leads the neurologic community in the most important achievements in the last 100 years: discovering the genetic aetiology of previously untreatable neuromuscular disorders and turning these discoveries into therapies.

GOUTMAN, B. C., FELDMAN, E. A. 2020. J Neurol Neurosurg Psychiatry August 2020 Vol 91 No 8

Gene-based therapies have transformed our approach to neuromuscular disorders and created new therapies to treat previously incurable diseases

GENE-BASED THERAPEUTIC TARGETS

At this writing, the GeneTable of Neuromuscular Disorders (http://www.musclegenetable.fr/index.html) lists 587 genes associated with 1042 disorders. These include 97 entries for hereditary motor sensory neuropathies, 50 for muscular dystrophies, 35 for congenital muscular dystrophies, 44 for congenital myopathies, 30 for other myopathies, 19 for distal myopathies, 6 for myotonic syndromes, 8 for ion channel muscle disorders, 29 for metabolic myopathies, 71 for motor neuron disorders and 32 for congenital myasthenic syndromes. These all represent potential targets for gene-based treatments.

Knowledge of these genes and function enabled the development and recent approval of drugs for SMA, specifically the antisense oligonucleotide nusinersen and the gene therapy onasemnogene, both of which led to not only the achievement of motor milestones in children with SMA, but also a reduction in mortality. These critical clinical achievements have led to mandatory SMA gene testing in over half of the USA and has turned a lethal neuromuscular disorder in infants into a treatable possibly curable condition. Similarly, transthyretin (TTR) amyloidosis began with identification of the underlying genetic cause and pathophysiology and evolved into a disease with multiple gene-based therapies. We have antisense oligonucleotide (ASO) and RNA interference medications that can halt or even reverse the neuropathy experienced by these patients. SMA and TTR amyloidosis are only two examples of neuromuscular therapeutics. There are currently a large number of gene therapy studies listed on ClinicalTrials.gov ranging from those for X-Linked Myotubular Myopathy (NCT03199469), Limb...
Girdle Muscular Dystrophy (LGMD) Type 2C (NCT01344798), LGMD2D (NCT01976091) and Becker Muscular Dystrophy and Sporadic Inclusion Body Myositis (NCT01519349), to name a few. These gene therapies are complemented by ASO studies for Duchenne Muscular Dystrophy (NCT00159250), Myotonic Dystrophy Type 1 (NCT02312011), SOD1 Amyotrophic Lateral Sclerosis (NCT02623699) and C9ORF72 ALS (NCT04288856). Neuromuscular disorders leads the neurological community in using our new understanding of genetic inheritance to develop and implement effective therapies.

THE NEXT 100 YEARS
What do the next 100 years hold? We will leverage the knowledge gained by treating multiple patients with the same mutation with the same drug to treat one patient with one genetic defect for a true personalised approach to neuromuscular diseases. Further, given the complexity of some neuromuscular diseases, we will harness the availability of new technology and large cohorts to find the polygenic causes of diseases where previously monogenetic causes were elusive. Next, we will better understand the interactions of our genes with the world around us—the exposome.11 This deeper understanding will in turn allow better drug targeting for multiple genes as well as any genes that are impacted by environmental exposures, a particularly relevant topic as our world experiences the COVID-19 pandemic. These therapies bring hope and allow us to envision a future where neurologists both diagnose and provide life-altering therapies for neuromuscular patients of all ages.

HAVE YOUR SAY
JNNP is asking readers to choose the most important or transformative development in neurology, neurosurgery or psychiatry in the past 100 years. To cast your vote visit our website at https://jnnp.bmj.com/pages/jnnp--100-a-centenary-of-publishing-neuroscience-achievement/. Voting closes on 15 August 2020.

Contributors  SAG, BCC and EF were involved in all aspects of the Editorial.

Funding  Support was provided by NIH NIEHS K23ES027221 (SAG) and the NeuroNetwork for Emerging Therapies at University of Michigan (BCC and ELF).

Competing interests  SAG consults with Biogen and J&J Pharma. He also serves on an ALS DSMB via Watermark Research Partners. BCC consults for a PCORI grant, DynaMed, the Immune Tolerance Network and performs medical legal consultations including consultations for the Vaccine Injury Compensation Program.

Patient consent for publication  Not required.

Provenance and peer review  Commissioned; internally peer reviewed.

REFERENCES
1 Nattrass R. Recurrent hypertrophic neuritis. J Neurol Neurosurg Psychiatry 1921;2:159–65.
2 Rosser AM, Carr AS, Devine H, et al. Peripheral neuropathy in complex inherited diseases: an approach to diagnosis. J Neurol Neurosurg Psychiatry 2017;88:846–63.
3 Kiernan MC. Milestones. J Neurol Neurosurg Psychiatry 2019;90:1189.
4 Kiernan MC. The Journal of Neurology, Neurosurgery and Psychiatry centenary milestone award 2020. J Neurol Neurosurg Psychiatry 2020;91:677.
5 Harding AE, Thomas PK, Baraitser M, et al. X-linked recessive bulbospinal neuronopathy: a report of ten cases. J Neurol Neurosurg Psychiatry 1982;45:1012–9.
6 Harding AE, Thomas PK. Autosomal recessive forms of hereditary motor and sensory neuropathy. J Neurol Neurosurg Psychiatry 1980;43:669–78.
7 Wadman RJ, Stam M, Gijzen M, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0–4. J Neurol Neurosurg Psychiatry 2017;88:365–7.
8 Kariyawasam D, Alexander IE, Kurian M, et al. Great expectations: virus-mediated gene therapy in neurological disorders. J Neurol Neurosurg Psychiatry 2020;91:849–60.
9 Farrar MA, Teoh HL, Carey KA, et al. Nusinersen for SMA: expanded access programme. J Neurol Neurosurg Psychiatry 2016;89:937–42.
10 Sekijima T, Transthyretin SY. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry 2015;86:1036–43.
11 Goutman SA, Boss J, Patterson A, et al. High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2019;90:907–12.