The Use of EMG to Diagnose Rare Genetic Disorders in Pediatric Patients

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Objectives

- General approach for electrophysiological evaluation of children with rare genetic disorders
  - Protocols for sedated vs non-sedated cases
  - Electrophysiological tools to characterize a rare genetic disorder
- Use of electrophysiological tools in clinical trials for a rare disorder
- Investigational use of electrical impedance myography in evaluating neuromuscular disorders in children
Approach to electrophysiological evaluation of children with rare disorders

Pre-evaluation considerations
Basic electrophysiological evaluation
Specialized evaluations
Reasons for Neurophysiological Evaluation in Rare Disorders

- Known genetic disorder & phenotype
- Unknown gene, unknown phenotype
- Known gene, unknown phenotype

Identify disorder

Define phenotype

Confirm disorder
Pre-evaluation of patients

• Developmental History

• Ambulatory status

• Use of assistive devices
Standard Electrophysiological Evaluations

• Motor and sensory nerve conduction studies
• Needle EMG
• (Repetitive nerve stimulation)
• (Single fiber needle EMG)
• Facial studies (Blink, facial nerve)
Autonomic testing

- QSART (QSWEAT) – Test of sympathetic post ganglionic sweat response
- Tilt table – May test if ambulatory
- Heart rate – deep breathing (HRDB) – May test if cooperative and not severe lung dysfunction
- Valsalva maneuver - Same as HRDB

QSART – In small kids, we generally perform on medial ankle and forearm rather than four sites.
Muscle Ultrasound

- Useful in localizing optimal muscle(s) for needle EMG
- Specific ultrasound characteristics can identify specific neuromuscular disorder
- May be used quantitatively to follow muscle disorder—muscle size, hyperechogenicity

Normal muscle ultrasound (Central hypotonia, possible myasthenia)

Collagen 6 muscular dystrophy – Characteristic “central cloud” in the rectus femoris
Electrical impedance myography (EIM)

• Investigational device used to evaluate qualities of the muscle through response to current flow
• Resistance and reactance are determined and phase calculated
• Most of our studies use the 50Hz Phase value
• We use 4 arm and 4 leg muscles for study

Sedated Studies

- Standard NCS protocol
  - Fibular, tibial, median (ulnar) MNCS
  - Sural & median SNCS
- Needle EMG
  - TA, Semitendinosus, biceps brachii
  - Other muscles not activated as easily
Awake studies

- Standard protocol
  - NCS dependent on clinical presentation
- Needle EMG
  - Identification of muscle by a combination of clinical exam and muscle ultrasound
Use of electrophysiological tools to characterize a rare genetic disorder

Congenital glycosylation defect-Ngly Deglycosylation Defect
N-Glycosylation Defects

• **Congenital Disorders of Glycosylation (CDG)**
  - Constellation of genetic disorders marked by errors in the glycosylation of proteins and other molecules.
  - Results in multisystem abnormalities

• **NGly1 Congenital defect in deglycosylation (NGLY1-CDDG)**
  - Associated with abnormal deglycosylation.
  - N-Glycanase, enzyme encoded by NGly1 encodes for N-glycanase-1, degrades misfolded glycoproteins produced in the endoplasmic reticulum.
  - Result in cytoplasmic accumulation of misfolded glycoproteins

(Used by permission of Dr. T. Suzuki, Gene 2016)
Clinical Findings in N-Glycosylation Defects

**Neurological Findings:**

- Global developmental delay with relative strength in socialization.
- Seizures-infantile, drop, absence, myoclonic
- Choreathetotic movement disorders
- Areflexia
- Hypotonia and weakness
- Microcephaly
- Low CSF protein and albumin
- MRI cerebral/cerebellar atrophy, WM changes

**Systemic Findings:**

- Ophthalmologic abnormalities
  - Hypolacrima/alacrima
  - Optic atrophy
- Abnormal ABR with normal hearing
- Scoliosis
- Joint hypermobility
- Liver disease
- Dysmorphic Features
- Elevated Blood Lactate w/normal CSF lactate
Evaluation of Ngly-CDDG patients

- N=11
  - Two pairs of siblings
  - Only one evaluated twice

- Demographics
  - Age 2-21 years, mean 10.2 ± 6.7 years
  - 6 females: 5 males

- Nerve conduction studies
  - Predominantly axonal sensorimotor neuropathy with some demyelinating features
  - Youngest (2y5m) had only a sensory neuropathy
  - Oldest (21y4m) had severe axonal neuropathy with many nerves unrecordable.

- EMG
  - Predominantly active and chronic neurogenic changes (may be related to motor neuron degeneration)
  - Oldest had considerable replacement of muscle with connective tissue

- Autonomic testing – shows greater loss of sweat function in leg (9/11) compared to arm (3/11) signifying a length dependent loss of sweat.

Congenital glycosylation defects

**ALG1-Axonal sm neuropathy**

**ALG13-sensory neuropathy**

**PMM2-Demyelinating neuropathy**

**ALG2-Low CMAPs**

**ALG6-Myopathy**

**ALG8-Normal**

**PIGN-Normal**

**PIGT-Myopathy**

**PIGA-sens. neuropathy**

Orphanet J Rare Dis. 2013; 8:170.
Use of electrophysiological tools in clinical trials for a rare disorder

Giant Axonal Neuropathy
Giant axonal neuropathy (GAN)

- Autosomal recessive disorder
- Age of onset – about 3 years
  - Gradual loss of ambulation
  - Frequent demise by 2\textsuperscript{nd}-3\textsuperscript{rd} decade in classic GAN due to respiratory failure
  - Milder cases with CMT type presentation
- Involvement of CNS and PNS
  - Axonal sensorimotor neuropathy with gradual loss of distal leg and hand function. There is also proximal loss of muscle and pectorial muscles
  - Cerebellar dysfunction with dysmetria, oculomotor apraxia
  - Dysarthria
  - May have optic atrophy
  - Cognitive impairment (mild, if present)
  - Scoliosis
- Hair – usually tightly coiled kinky hair
Giant axonal neuropathy

• Gene defect in mutations in the GAN gene encoding gigaxonin

• Pathology
  • Enlarged axons with disordered microtubules and neurofilaments as well as loss of myelin with onion bulb formation.
  • Abundant axon swellings and spheroids in the spinal cord, brainstem, and cerebral cortex
  • The muscle biopsy shows neurogenic findings of fiber type grouping as well as desmin accumulation.

GAN – Intrathecal gene therapy through AAV-9 vector study (NCT02362438)

• Non-randomized, phase I, escalating single dose study to assess the safety of the gene transfer vector scAAV9/JeT-GAN through intrathecal delivery to the brain and spinal cord of patients with Giant Axonal Neuropathy (GAN, OMIM No.256850).

  • Natural history study– 40 subjects (age 4-21, mean 9±3.8 years, 11 m)

  • Gene therapy – 11 subjects (age 6-14, mean 8.9±2.5 years, 4 m)
Natural history – MNC (all patients)
Natural History-EIM (all patients)
Other parameters

**Sensory NCS**
- Limited number of patients with sensory nerve responses
  - Most had 0-1 nerve present
  - One had four SNC

**Visual and Somatosensory EPs**
- SSEPs had limited reproducibility, particularly in the legs
- VEP similarly had limited ability to follow
Autonomic testing

**QSWEAT**
- Responses are generally low, particularly in the leg.

**Other ANS testing**
- Tilt table – only if ambulatory
  - Normal (no evidence of POTS)
- HRDB and Valsalva – generally older and less affected children
  - All normal
Investigational use of electrical impedance myography in evaluating neuromuscular disorders in children
Electrical impedance myography (EIM)

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In the LAMA2 and COL6 groups, there was decreased phase (p>0.0005) in the UE, LE, and 8M Avg compared to healthy volunteers. The GAN had decreased phase in the LE (p > 0.0005) and 8 MU Avg (p > 0.005) but not the upper extremity. For RYR1, phase was not significantly lower for UE, LE or 8M Avg compared to the healthy volunteers.
Resistance was significantly increased ($p > 0.05$) in the two congenital muscular dystrophy populations, COL6 and LAMA2, compared to health volunteers. RYR1 and GAN populations had resistance values remarkably close to the healthy volunteers.
Overall, reactance showed significant differences in the 8M Avg (p>0.05) compared to HV for the GAN, RYR1, and the LAMA2 but not the COL6 population. GAN and LAMA2 had significant changes (p>0.005) in the LE but not in the UE. LAMA2 had no significant differences compared to HV.
THERE ARE MANY MORE GENETIC DISORDERS WITH MULTI-TARGETED ORGAN DAMAGE AND NEURODEGENERATION. . .

WE HOPE TO HELP TO DEFINE THESE DISORDERS AND PROVIDE USEFUL OUTCOME MEASURES
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