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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

# Clinical Characterization of Inherited Erythromelalgia Due to Sodium Channel Mutations

*By Joshua Weaver, MD*

*Assistant Professor of Clinical Neurology, Weill Cornell Medical College.*

**Dr. Weaver reports no financial relationships relevant to this field of study.**

SYNOPSIS: A detailed non-interventional clinical study of patients with inherited erythromelalgia who carry gain-of-function mutations of voltage-gated sodium channel Nav1.7 further characterized pain phenotypes in this disorder and showed wide variability of pain symptoms.

SOURCE: McDonnell A, Schulman B, Ali Z, et al. Inherited erythromelalgia due to mutations in SCN9A: Natural history, clinical phenotype and somatosensory profile. *Brain* 2016;139:1052-1065.

Inherited erythromelalgia (IEM) is a rare pain syndrome genetically linked to dominant gain-of-function mutations of the SCN9A gene encoding the voltage-gated sodium channel Nav1.7. Patients with IEM experience episodic pain, erythema, and swelling of the distal extremities and face, and attacks often are triggered by exertion and exposure to heat.

From a database of IEM subjects maintained at the Yale University Department of Neurology, 13 patients with clinical erythromelalgia who carried one of four distinct gain-of-function mutations of Nav1.7 were consented and enrolled in this study. Information was obtained regarding pain and psychological symptoms, family history, and treatments. Quantitative sensory testing (QST) was performed in one affected and one unaffected body site. Since there are known links between Nav1.7 and odor perception, olfaction threshold testing was obtained. Subjects then completed a 12-week diary recording pain symptoms during and between pain attacks.

All subjects reported IEM signs and symptoms by the second decade of life, with the majority of subjects reporting onset in the first decade. A clinical diagnosis

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Neurology [ALERT]

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was obtained anywhere from one to 20 years after the onset of pain symptoms. The most common symptoms included reddening, swelling, and heat in the distal extremities. Four subjects reported facial pain. Disease progression was split almost evenly among the subjects, with five reporting worsening, four reporting improvement, and four reporting stable symptoms over time.

There was considerable variability noted in pain symptoms across all subjects and between subjects with the same genetic mutation. The severity of pain ranged from 1 to 10 on a numerical rating scale, generally with more severe pain noted during an attack (mean 5.7 across subjects) compared to pain felt between attacks (mean 2.69). The mean number of attacks ranged from 0.9 to 15.3 per week. This variability also was seen within family groups having the same mutation type. The duration of pain attacks ranged from 5 minutes to 17 hours.

Many pharmacologic therapies were reported, usually with modest results at best. Acetylsalicylic acid was tried by 11 of 13 subjects, with six reporting a positive ("some" to "good") response and five reporting no response. Two subjects reported a modestly beneficial response to carbamazepine in terms of reduction of severity and frequency of pain attacks. Non-pharmacological treatments were used most often and included ice, cold air, or immersion of affected extremities in cold water; most patients reported this to be the most effective form of treatment. Pain triggered by heat and exercise was reported by all subjects, but two also reported worsening of pain with exposure to cold. No trigger was identified for about one-third of all attacks recorded.

Based on psychometric questionnaire scoring, seven subjects had anxiety and four had depression; these scores correlated with pain severity between attacks. Pain catastrophizing was seen in only three of 13 subjects. Olfaction threshold testing was normal. QST profiles showed reduced detection of temperature in affected sites and hyperalgesia in unaffected sites, suggesting small fiber nerve dysfunction.

## ■ COMMENTARY

Prior to the discovery of the link between IEM and Nav1.7 mutations about a decade ago, patients with clinical erythromelalgia symptoms were studied, but no verification of genetic mutation status was possible. In the last decade, multiple mutations have been described and partially clinically characterized. This study is the first systematic review of patients with IEM and known sodium channel gain-of-function mutations.

Faber et al reported a link between gain of function mutations in Nav1.7 and small fiber neuropathy.[1] This study also suggested an association between small fiber neuropathy and erythromelalgia based on QST results. Analyzing intraepidermal nerve fiber density via skin biopsy in patients with IEM may help better characterize these findings. There was substantial variability reported in the number, duration, and severity of pain attacks both between and within mutation subtypes. Careful characterization of pain phenotype will be important in pursuing clinical trials for therapeutic agents in this disorder. Future trials assessing the efficacy of sodium channel blockers as well as gene therapy will be of particular interest. ■

## REFERENCE

1. Faber CG, Hoeijmakers JG, Ahn HS, et al. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. *Ann Neurol* 2012;71:26-39.

ABSTRACT & COMMENTARY

# Relationship Between Spikes and Seizures Using an Implantable Intracranial Detection Device

***By Kimberly Pargeon, MD***

*Assistant Professor of Clinical Neurology, Weill Cornell Medical College*

**Dr. Pargeon reports no financial relationships relevant to this field of study.**

SYNOPSIS: The authors report the preliminary findings for an implantable ambulatory intracranial recording device for seizure detection in 15 subjects. One of the primary findings was that spike rate significantly changed prior to seizures in nine of 15 subjects. Six of these subjects showed a significant *decrease* in spiking prior to ictal onset, whereas the remaining three showed a significant *increase* in spiking and these three subjects had the best seizure prediction results.

SOURCE: Karoly PJ, Freestone DR, Boston R, et al. Interictal spikes and epileptic seizures: Their relationship and underlying rhythmicity. *Brain* 2016;139:1066-1078.

With the growing concern for sudden unexpected death in epilepsy patients (SUDEP) and other comorbidities associated with intractable epilepsy, one of the latest trends in epilepsy research is seizure prediction and detection. With it, there has been a proliferation of so-called seizure detection devices, particularly ones that can be worn or used at home. Many of these devices focus on physiological changes, such heart rate changes, electrical activity in muscle, and galvanic skin resistance changes.[1] Since many at risk for SUDEP have nocturnal seizures, pressure mats, as well as video and infrared devices, have been used. So-called seizure alert dogs also have been reported, although data are mixed. More recently, there have been collaborations with many companies for "wearable" devices, such as watches.[2] The concern for many of these devices is that there may be some false positives and that not all of the detected events require evaluation or treatment.

The present study focuses on an implantable intracranial device for spike and seizure detection, which is not commercially available in the United States. Seattle-based NeuroVista makes the device, which is being tested clinically in Australia. The device is composed of two intracranial leads implanted subdurally and unilaterally in the seizure onset zone based on scalp electroencephalogram .[3] These are connected to a telemetry unit placed subcutaneously under the clavicle. The telemetry unit sends data via a wireless signal to a handheld device, which can produce signals, either audio or visual, to indicate whether the patient has a low, medium, or high likelihood of having a seizure.

For the initial study, 15 patients with medically refractory partial epilepsy, having two to 12 partial seizures per month, were enrolled and implanted from three centers in Melbourne, Australia, from March 2010 to June 2011.[3] During the data collection phase, spikes were identified using a complicated algorithm for automated spike detection, which erred of the side of over-detection, and were validated with expert review of randomly selected one-hour segments. Seizures were identified using a previously validated automated seizure detection algorithm, subjects' seizure diaries, and device audio recordings, all of which were then verified by expert investigators.

One of the primary findings was that nine of 15 subjects showed a significant change in spike rate prior to seizures, suggesting a relationship between spiking and seizure activity. However, for three of these patients, the spike rate increased, and for the remaining six, the spike rate decreased. The three patients who had the increased spike rate also had the best seizure prediction results. In addition, subjects with high rates of seizures did not necessarily demonstrate high rates of interictal spiking. Thus, the authors could not conclude that spikes directly promoted or inhibited seizure activity, but suggested that seizures and spikes likely share some common regulatory mechanisms. This was further supported by another key finding, which suggested common circadian variations affecting both spikes and seizures, particularly related to sleep for many patients. Other cyclic patterns were noted and, interestingly, the only subject to show a monthly cycle for spike rate was male, while four of the female subjects showed peaks at intervals of less than a month, usually between 1 to 3 weeks. In general, the relationship between spikes and seizures appeared to be subject-specific.

## ■ COMMENTARY

Although the authors have produced some promising initial results, use of this device for seizure detection and prediction may be limited for several reasons. First, in reviewing the original paper by Cook et al, all patients had a refractory *partial* onset epilepsy with a localized epileptic onset zone,[1] whereas many patients at risk for SUDEP have poorly controlled convulsive seizures, which can be from either from partial or generalized epilepsies. Second, this device, which is not approved in the United States, is invasive, costly, and requires implantation of electrodes in the epileptic onset zone, which needs to be clearly localized. Thus, in a patient with poorly localized or lateralized epilepsy, it may be of limited usefulness. The authors also report that the relationship between spikes and seizures was subject-specific, so the spiking pattern prior to seizures would need to be individually determined to improve seizure prediction and would vary across individual patients. In fact, the limited data from this study suggest that those with increased spiking prior to seizures may be the most ideal candidates for implantation of this device as a seizure detector. ■

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3. Cook MJ, O'Brien TL, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: A first-in-man study. *Lancet Neurol* 2013;12:563-571.

ABSTRACT & COMMENTARY

# Carpal Tunnel Syndrome: Everything You Want To Know, and More

*By Michael Rubin, MD*

*Professor of Clinical Neurology, Weill Cornell Medical College*

**Dr. Rubin reports no financial relationships relevant to this field of study.**

SYNOPSIS: Carpal tunnel syndrome can be reliably diagnosed, only with nerve conduction studies, and this test should be performed before any invasive treatments are initiated.

SOURCE: American Academy of Orthopaedic Surgeons. Management of Carpal Tunnel Syndrome: Evidence-Based Clinical Practice Guideline. www.aaos.org/ctsguideline. Published Feb. 29, 2016.

Based on a comprehensive review of current scientific and clinical information, the American Academy of Orthopedic Surgeons recently published an encyclopedic tome spanning 982 pages, outlining, in detail, new guidelines for the diagnosis, investigation, and treatment of carpal tunnel syndrome (CTS).

Body mass index and repetitive hand/wrist movements are risk factors strongly associated with CTS, whereas perimenopausal age, rheumatoid arthritis, gardening, and assembly line and computer work are some of the factors moderately associated with increased risk of CTS. Taken alone, age, gender, diabetes, bilaterality of symptoms, or worsening at night are weakly or poorly associated. Only a limited association was found between CTS and distal radial fracture or dialysis. Hormone replacement therapy and oral contraceptive use are not associated with CTS. Thenar muscle atrophy is the only clinical sign strongly associated with CTS, but its absence does not rule it out. All other physical signs and maneuvers, taken alone, are poor or weak indicators of CTS, including the Phalen or reverse Phalen sign, Tinel sign, thenar weakness, Luthy sign (where, due to thumb abduction weakness, the skinfold between the thumb and index finger does not wrap tightly around a cup), or flick maneuver (where patients vigorously shake their hand or hands, and symptoms of suspected CTS resolve immediately, or shortly thereafter).

Apart from obtaining a history and performing a physical examination, standard nerve conduction studies are the only recommended test for diagnosis. Ultrasound and magnetic resonance imaging of the wrist are not routinely recommended.

Strong evidence indicates that splinting the wrist and methylprednisolone injections are beneficial, whereas magnetic therapy is not. Nonsteroidal anti-inflammatory agents, diuretics, gabapentin, and pyridoxine appear to be no better than placebo, but oral steroids and ketoprofen phonophoresis show benefit. Compared to placebo, therapeutic ultrasound and laser therapy can be effective, but surgical release shows the strongest evidence of benefit at 6 and 12 months compared to nonoperative approaches, with endoscopic carpal tunnel release possibly showing additional short-term benefits in terms of earlier pain relief and earlier return to work. Other than carpal ligament release, no additional benefit appears to accrue from additional neurolysis, tenosynovectomy, epineurotomy, or ligament-lengthening procedures. Local anesthesia is preferred over intravenous regional anesthesia, due to longer postoperative pain relief. Buffered rather than plain lidocaine is the preferred anesthetic, due to less injection pain. Aspirin may be continued perioperatively. Routine preoperative antibiotics, supervised physical therapy, and postoperative immobilization appear to be of no benefit.

## ■ COMMENTARY

Surprisingly, pregnancy and its association with CTS were not mentioned in this guideline. Among 639 pregnant women, 34% (n = 219) reported symptoms of CTS. Even after adjusting for age, body mass index, depression scores and parity, CTS was significantly associated with higher levels of fluid retention compared to those who did not report CTS symptomatology, and, during the third trimester, had an independent negative effect on sleep.[1] Although CTS is found in 4% of the general population, it is nine times higher in pregnancy. Vitamin D deficiency was also omitted. It is significantly more common in patients with CTS, compared to normal controls, and although lower vitamin D levels do not correlate with symptom severity, functional status, or pain score, patients with CTS should have their vitamin D levels measured and normalized where appropriate.[2] ■

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1. Meems M, Truijens S, Spek V, et al. Prevalence, course and determinants of carpal tunnel syndrome symptoms during pregnancy: A prospective study. *BJOG* 2015;122:1112-1118.
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ABSTRACT & COMMENTARY

# Differentiating Sarcoidosis from Neuromyelitis Optic in Patients with Transverse Myelitis

***By Jai S. Perumal, MD***

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**Dr. Perumal reports she receives grant/research support from Genzyme Corp., and is on the speakers bureau for Biogen Idec, Genzyme Corp., Acorda Therapeutics, and Teva Pharmaceuticals.**

SYNOPSIS: Based on a retrospective analysis of 71 patients with an neuromyelitis optica spectrum disorder (n = 37) or sarcoidosis (n = 34), whose initial presentation was longitudinally extensive transverse myelitis (≥ 3 vertebral segments), the authors report clinical, radiologic, and laboratory findings that help distinguish one from the other.

SOURCE: Flanagan EP, Kaufmann TJ, Krecke KN, et al. Discriminating long myelitis of neuromyelitis optica from sarcoidosis. *Ann Neurol* 2016:79:437-447.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. NMO spectrum disorder (NMOSD) is diagnosed in patients with optic neuritis or transverse myelitis who have the NMO IgG antibody. The typical longitudinally extensive (≥ 3 vertebral segments) spinal cord lesions in NMOSD help differentiate this condition from multiple sclerosis along with other clinical, radiologic, and laboratory features. But transverse myelitis in the context of other immune-mediated diseases like sarcoidosis, systemic lupus erythematosus, and Sjogren's disease can have a very similar appearance to NMOSD. Sarcoidosis can mimic NMOSD and is often an underdiagnosed cause of longitudinally extensive transverse myelitis, especially since the initial or the only clinical presentation of sarcoidosis can be myelopathy. The authors undertook a study to examine clinical, radiologic, and laboratory features that can help distinguish sarcoidosis from NMOSD.

Adult patients (≥ 18 years of age) who had a diagnosis of NMOSD or sarcoidosis and whose initial presentation was longitudinally extensive transverse myelitis were included in the study. Thirty-seven NMOSD and 34 sarcoidosis patients were included in the analysis. NMOSD was diagnosed if 1) the first myelitis was characterized by a T2 hyperintensity that spanned ≥ 3 vertebral segments; 2) there was seropositivity for NMO IgG ab (AQP4 Ab); and 3) there were adequate clinical data. Sarcoidosis was diagnosed if 1) the first myelitis was characterized by a T2 hyperintensity that spanned ≥ 3 vertebral segments; 2) there was pathological confirmation of sarcoidosis at time of myelitis; and 3) there were adequate clinical data. Similarities and differences in demographics, clinical presentations, radiologic features, and laboratory findings were analyzed.

Statistically significant clinical and laboratory findings that were more likely to indicate NMOSD were female sex, presence of optic neuritis, episodes of intractable nausea and vomiting, paroxysmal tonic spasms, and coexisting systemic autoimmunity, either clinical or serologic. Similarly, findings that were more suggestive of sarcoidosis were presence of constitutional symptoms, longer median time to worst deficit during an acute event, and longer time from onset of symptoms to diagnosis. Although cerebrospinal fluid (CSF) pleocytosis and elevated protein were common in both, it was more suggestive of sarcoidosis. Hilar adenopathy was exclusive to sarcoidosis and seen in 73% of patients who had a CT of the chest. CSF hypoglycorrhachia and elevated angiotensin-converting enzyme also were seen exclusively in sarcoidosis patients but were seen only in 11% and 18% of patients, respectively. With regard to radiologic findings, the distribution of lesions in the spinal cord or the length of the individual lesions did not show a statistical difference between the two groups. However, subpial gadolinium enhancement and persistent gadolinium enhancement for more than two months were more common in sarcoidosis, while ring-enhancement was more common in NMOSD, than in sarcoidosis.

Among the 34 patients who were confirmed as having sarcoidosis, the initial diagnosis was sarcoidosis in 32%; in the others, one or more of the following causes for the transverse myelitis, in decreasing order of frequency were NMOSD, transverse myelitis not otherwise specified, tumor, and multiple sclerosis. Among the 37 NMOSD patients, the initial diagnosis was one or more of the following: NMOSD in 22, transverse myelitis not otherwise specified in eight, tumor in three, multiple sclerosis in three, and gastrointestinal disease in one.

The authors concluded that sarcoidosis can present initially with longitudinally extensive transverse myelitis, and these patients often are misdiagnosed as having

NMOSD or idiopathic transverse myelitis. This could potentially explain the delay in diagnosing sarcoidosis compared to NMOSD, due to a lack of specific or sensitive serologic or CSF markers and the need for pathological confirmation before making a diagnosis of sarcoidosis. They have shown factors that are more suggestive of sarcoidosis vs. NMOSD that can raise clinical suspicion and initiation of appropriate workup, including imaging and biopsy, that can lead to the correct diagnosis. A correct diagnosis is important, because the clinical course and treatment of sarcoidosis is different from NMOSD.

■ COMMENTARY

Sarcoidosis is one of the causes of longitudinally extensive transverse myelitis along with NMOSD. The initial presentation of sarcoidosis can be transverse myelitis, and a diagnosis of sarcoidosis is frequently made after a delay or is missed in patients with longitudinally extensive transverse myelitis. Often, sarcoidosis is wrongly attributed to NMOSD or one of the other inflammatory conditions. The authors have shown clinical, radiologic, and laboratory findings that are more suggestive of sarcoidosis than of NMOSD. Since the disease course and treatment of these conditions are different, it is important for clinicians to be clinically vigilant to factors that are more suggestive of one diagnosis vs. the other so that the correct diagnosis can be made in a timely fashion and appropriate treatment initiated. ■

ABSTRACT & COMMENTARY

# Leigh Syndrome: Insights and Implications from Advances in Next-generation Sequencing


***By Eric Mallack, MD, MBE, and Barry E. Kosofsky, MD, PhD***

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**Dr. Mallack and Dr. Kosofsky report no financial relationships relevant to this field of study.**



SYNOPSIS: Leigh syndrome is a genetically heterogeneous neurodevelopmental disorder. The application of next-generation sequencing has enabled a deeper understanding of the diverse nature of the genetic and molecular etiologies that give rise to the shared clinical phenotype of Leigh syndrome.


SOURCE: Lake NJ, Compton AG, Rahman S, et al. Leigh syndrome: One disorder, more than 75 monogenic causes. *Ann Neurol* 2016;79:190-203.

Leigh syndrome (LS) is the most common disease of mitochondrial energy production in children. Symptoms often present after illness or infection following a brief period of normal development. Patients undergo developmental delay, often followed by regression, associated with hypotonia, dystonia, ataxia, and progressive ophthalmological disease. Radiographically, lesions develop in the bilateral basal ganglia and brainstem, with evidence of elevated cerebrospinal fluid (CSF) lactate detected by magnetic resonance spectroscopy. At the biochemical level, LS results from impairment in any of the five multiprotein complexes in the oxidative phosphorylation pathway, in the electron carrier coenzyme Q10 (CoQ10), or in the pyruvate dehydrogenase complex (PDHc). Death usually occurs in infancy or early childhood.

The majority of known mutations disrupt nuclear-encoded proteins and are of autosomal recessive (or X-linked) inheritance. A minority of mutations are found in maternally inherited mitochondrial DNA (mtDNA), for which heteroplasmy becomes a large determinant in phenotypic severity, with higher mtDNA mutation burden resulting in more significant disease expression. The application of next-generation sequencing (NGS), specifically massively parallel sequencing (MPS), has allowed for identification of 30 new genetic causes of LS in the past 5 years. Advanced sequencing has provided a refined understanding of the genotype-phenotype correlation in LS, and has also uncovered novel mechanisms by which pathogenic mutations give rise to LS, summarized in this review as follows.

## NUCLEAR-ENCODED GENES

Complex I deficiencies are the most common cause of LS, and are predominantly characterized by mutations in NADH dehydrogenase (ubiquinone) Fe-sulfur protein 4 (NDUFS4), NDUFV1, and NDUFS1, all giving rise to an early-onset, severe form of disease. However, mutations in 15 other nuclear-encoded genes and five additional mitochondrial encoded genes comprising Complex I subunits give rise to less severe and more variable phenotypes.

Mutations in the Complex II subunit SDHA are responsible for two separate LS phenotypes: one a severe infantile presentation with early death, the other a milder course, with preservation of cognitive ability and survival into childhood.

Complex III and CoQ10 mutations account for a small percentage of LS. Individuals with Complex III assembly factor TTC19 mutations develop neuroimaging abnormalities consistent with LS. Patients with CoQ10-deficient LS have variable response to supplementation, with some surviving into adulthood, while others with a PDSS2 mutation do not respond.

Mutations in SURF1 impair Complex IV assembly and are the single largest genetic cause of LS, with more than 200 cases reported in the literature. Although mutations in this gene cause a clinically and biochemically homogenous phenotype, a subset of patients exhibit atypical neuroradiological features more consistent with leukodystrophy or cerebral atrophy.

Multiple disease genes that cause LS, including SCO2, LRPPRC, ETHE1, SERAC1, and AIFM1, additionally exert their effects via secondary mechanisms at the cellular level. For example, LRPPRC mutations not only affect Complex IV, but also have been found recently to have post-transcriptional and translational affects, which in turn affect ATP synthase. They disrupt mitochondrial energy function at the nucleic acid level and via more global dysregulation of oxidative phosphorylation. ETHE1 gives rise to the LS phenotype by causing secondary dysfunction to Complex IV via sulfur accumulation. Similar mechanisms hold for patients with ECHS1 and HIBCH mutations. SERAC1 and apoptosis-inducing factor AIFM1 mutations reduce the structural stability of the mitochondrial membrane, thus leading to mitochondrial energy failure.

## MITOCHONDRIAL-ENCODED GENES

Further genetic heterogeneity is introduced by mutations in mtDNA, including SUCLA2, SUCLG1, MTND3, MTND5, and MTATP6, genes encoding structural components of Complexes I, III, IV, and V. Such mtDNA mutations will lead to a combined oxidative phosphorylation deficiency and, subsequently, the LS phenotype.

Despite being different clinical entities, shared mutations in MTTL1 and MTTK exist between LS and two distinct syndromes: mitochondrial encephalopathy lactic acidosis and strokelike episodes (MELAS) and myoclonic epilepsy with ragged red fibers (MERRF). Conversely, there are Leigh-like syndromes that phenotypically overlap with MERRF and MELAS resulting from mutations in MTND5 and MTND3.

A new class of mutations affecting a nuclear-encoded mt-tRNA modifying enzyme, mitochondrial methionyl-tRNA formyltransferase required for mitochondrial translation, provides a novel mechanism for nuclear-mitochondrial interaction via translational regulation, which gives rise to LS.

## ■ COMMENTARY

The authors' detailed review categorizing more than 75 mutations known to cause LS provides a 21st century view of a disease first described in 1951. By applying the power of NGS sequencing, our knowledge of the genetic and molecular heterogeneity contributing to a single clinical, radiographic, and pathologic disorder has been richly elucidated. Conversely, despite providing a unified biochemical understanding of LS as a disorder of oxidative phosphorylation, the authors highlight the variability in the phenotypes attributable to particular genotypes evident for a number of specific mutations. The application of NGS will undoubtedly lead to the discovery of additional genetic causes of LS, underscoring the complex array of proteins and cellular processes vulnerable to genetic disruption.

The authors additionally demonstrate that a mutation in a particular gene can result in both variable severity of disease, as well as different disease phenotypes altogether. Mutations of SURF1, resulting in Complex IV deficiency, also give rise to clinical and neuroradiological findings highly atypical of LS. Similarly, mutations in MTND5 are responsible for both LS and MELAS, two distinctly different diseases. In terms of disease severity, SDHA-encoded mutations in Complex II-associated LS are responsible for both mild and severe courses of the disease. As a result, clinicians increasingly will be required to look more closely for clinical, and when available preclinical, evidence of the functional significance of the individual mutations identified in their patients. Likewise, such detailed information may be of therapeutic significance, as some LS-causing mutations can respond to treatment with vitamins and cofactors.

This review also expands our understanding of molecular pathogenesis of LS from the primary affected pathway — in this case the electron transport chain and PDHc — to include novel mechanisms at the broader cellular level. For example, the transcriptional dysregulation induced by LRPPRC mutations impact cellular function more globally, likewise broadening the phenotype of LS. Similar logic applies for secondary mechanisms that disrupt the primary pathway, in this case sulfur or toxin accumulation seen in ETHE1, ECHS1, and HIBCH mutation-induced LS, which affect cell viability via dysregulation of factors responsible for the apoptotic pathway.

The authors have provided a higher resolution insight into the genetic, molecular, biochemical, and cellular basis of LS. By doing so, they have illustrated how powerful

advances in next-generation sequencing will exponentially enhance our ability to understand both the molecular reductionism, as well as phenotypic complexity of mitochondrial energy disorders, specifically, and genetic disease, in general. ■

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## CME QUESTIONS

1. **Which of the following is reported as the most effective form of treatment in inherited erythromelalgia?**
   a. Acetaminophen
   b. Acetylsalicylic acid
   c. Carbamazepine
   d. Immersion of limb in cold water
   e. Mexiletine

2. **For patients implanted with an intracranial seizure detection device, which spiking pattern, prior to seizures, was most likely to predict seizure onset?**
   a. Decreased spiking
   b. Increased spiking
   c. No change in spiking
   d. Mixed – for some seizures, it was increased, and for others, it was decreased

3. **Which of the following statements is true regarding carpal tunnel syndrome?**
   a. Body mass index and repetitive hand/wrist movements are risk factors strongly associated with carpal tunnel syndrome.
   b. Perimenopausal age, rheumatoid arthritis, gardening, and computer work are moderately associated with increased risk of carpal tunnel syndrome.
   c. Taken alone, age, gender, diabetes, or worsening at night are weakly or poorly associated with carpal tunnel syndrome.
   d. Thenar muscle atrophy is the only clinical sign strongly associated with carpal tunnel syndrome.
   e. All of the above

4. **Which of the following is not a feature of myelitis that is caused by sarcoidosis?**
   a. Systemic constitutional symptoms
   b. Cerebrospinal fluid pleocytosis
   c. Hilar adenopathy on chest CT
   d. Positive anti-Aquaporin antibodies
   e. Elevated angiotensin-converting enzyme

5. **Leigh syndrome describes a clinical disorder that is caused by over 75 different gene mutations.**
   a. True
   b. False

## [IN FUTURE ISSUES]

Eating Disorders in Neurological Disease

# Neurology Alert

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| 4. pain | O A | O B | O C |
| 5. peripheral neurology | O A | O B | O C |
| 6. stroke | O A | O B | O C |
| 7. trauma | O A | O B | O C |
| 8. basic neuroscience | O A | O B | O C |
| 9. Alzheimer's disease | O A | O B | O C |
| 10. Parkinson's disease | O A | O B | O C |
| 11. multiple sclerosis | O A | O B | O C |
| 12. pathophysiology | O A | O B | O C |

**13. What other topics would you like to see discussed in *Neurology Alert*?** _____

_____

_____

**14. Are the articles in *Neurology Alert* written about issues of importance and concern to you?**

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

**15. Are the articles in *Neurology Alert***

O A. Too short O B. Too long O C. About right

**16. What type of information not currently provided in *Neurology Alert* would you like to see added?** _____

_____

_____

**Please rate your level of satisfaction with the items listed.**

| | A. excellent | B. good | C. fair | D. poor |
|---|---|---|---|---|
| 17. quality of newsletter | ○ A | ○ B | ○ C | ○ D |
| 18. article selections | ○ A | ○ B | ○ C | ○ D |
| 19. timeliness | ○ A | ○ B | ○ C | ○ D |
| 20. quality of commentary | ○ A | ○ B | ○ C | ○ D |
| 21. clearness of abstracts | ○ A | ○ B | ○ C | ○ D |
| 22. overall value | ○ A | ○ B | ○ C | ○ D |
| 23. customer service | ○ A | ○ B | ○ C | ○ D |

**24. To what other publications or information sources about neurology do you subscribe?**

_____

_____

**25. Including *Neurology Alert,* which publication or information source do you find most useful, and why?**

_____

_____

**26. Which website(s) related to your position do you use most often?**

_____

_____

**27. Please list the top three challenges you face in your job today.**

_____

_____

**28. Please describe your work place:**

○ A. private practice ○ B. hospital ○ C. government institution ○ D. research

○ E. Other _____

**29. Has the information in *Neurology Alert* changed your clinical practice?**

○ A. yes
○ B. no

If yes, how? _____

_____

**Contact information** _____

_____