

## The Evolution of Leigh Syndrome

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Dr. Mary Kay Koenig joined the Department of Pediatrics, Division of Child & Adolescent Neurology at The University of Texas Medical School at Houston in July of 2007. Dr. Koenig is an internationally renowned Child Neurologist with expertise in Tuberous Sclerosis Complex and Mitochondrial Medicine. She received her undergraduate degree in Biochemistry from the University of Texas in Austin, her master's degree in Microbiology from Southwest Texas State University in San Marcos, and her medical degree from St. Georges School of Medicine. Dr. Koenig completed her residency in Pediatrics at the University of Texas Medical Branch in Galveston and her fellowship in Child Neurology at the University of Texas Medical School in Houston. Dr. Koenig is currently a tenured Associate Professor of Pediatrics and the Endowed Chair of Mitochondrial Medicine. Dr. Koenig serves as the Director for the University of Texas Neurometabolic and Mitochondrial Center of Excellence, the Director for the Leigh Syndrome Clinic, the Co-Director for the University of Texas Tuberous Sclerosis Center, and the Co-Director for the University of Texas Lysosomal Storage Disease Center.

Dr. Koenig regularly presents abstracts at national meetings, has authored over 40 peer-reviewed publications, and contributed four book chapters. She conducts active clinical research programs in Tuberous Sclerosis Complex, Mitochondrial disease, Neurometabolic disease, and Leigh Syndrome working with a team of clinical research specialists including a junior faculty member and 4 research coordinators.

Dr. Koenig is an active speaker, regularly educating her peers at local, national, and international conferences. She serves on the boards of the Mitochondrial Medicine Society and the Tuberous Sclerosis Alliance Professional Advisory Board. She is currently Chair of the Department of Defense United States Medical Research and Material Command Congressionally Directed Medical Research Programs' Tuberous Sclerosis Research Program Integration Panel and was previously a member of the Eunice Kennedy Shriver National Institute of Child Health & Human Development Pediatrics subcommittee. Dr. Koenig is an editorial member of the Journal of Child Neurology and serves as an ad hoc reviewer for many other world-renowned scientific journals. In addition to her clinical and research responsibilities, Dr. Koenig has a passion for educating and mentoring new residents and junior faculty members.

## Slide 1: Introductions

[Lori Martin explains People Against Leigh Syndrome and discloses that Dr. Koenig is her son's doctor.]

Thank you Lori, it has been my privilege to get to know boys like Lori's son and girls too. Our goal here is both to help find a cure but also to improve the quality of life (and the longevity) in children who have this condition. What I would like to do today is talk to you about Leigh Syndrome. I'm going to start by talking about the history of Leigh Syndrome and where we have come over the years because I think it does help us understand this condition and helps us understand what we do know and what we don't know about Leigh Syndrome.

**Slide 2:** . . We are going to go to the first slide where we are going to talk about Dr. Denis Archbald Leigh. Obviously he is the namesake for Leigh Syndrome. Received his medical degree in 1947.

- ,subsequently, presented 7-month-old. Served as military medical officer and Consultant to the British Army until 1980.
- Specialized training in neurology but interestingly he didn't practice neurology and instead focused his career in psychiatry.
- **Slide 3:** In 1951, pretty soon after he finished medical school, Dr. Leigh published an interesting case while working as a registrar at Maudsley Hospital in London.
- The condition he described became known as "Leigh's Disease" and ultimately evolved to become "Leigh Syndrome".

## Slide 4: *Subacute Necrotizing Encephalomyelopathy in an Infant*

We are going to review the actual case that Dr. Leigh presented:

SA 7-month-old boy was admitted to King's College Hospital in 1947. His developmental and feeding histories were completely normal until the age of five months. His parents noted at five months he:

- Stopped crying
- Became very still
- Stopped sucking

- Slept for long periods

He The child was not known to have an illness but his sister was ill with a respiratory infection when the symptoms began. Following his admission, the child deteriorated rapidly. He passed away three days following admission.

**Slide 6:** *Subacute Necrotizing Encephalomyelopathy In an Infant*

Post-mortem examination (autopsy) demonstrated bilateral symmetric necrotic lesions in the brain and spinal cord. These lesions were on both sides of the brain; they looked the same on both sides; and they were necrotic (which means that the tissue itself was dying). This was really interesting because this wasn't typical to see in a seven-month-old baby.

- Slide 7: -Over 50 additional cases were described from 1951 to 1977. These cases were almost identical.
- Each case was diagnosed postmortem via pathologic examination or autopsy where someone looked at the brain.

Slide 8: As more cases were described, the clinical picture became more clear.

Early on in the description of Leigh syndrome:

Children had normal early development followed by subacute onset of:

- Feeding difficulties
- Psychomotor retardation (slowing of the brain and body)
- Disturbances in the state of consciousness (sleeping too much or not interacting the way they should)
- Abnormalities of eye movements
- Ataxia (off balance wobbly feeling)
- Muscular weakness

Although the disease begins insidiously, (subacutely, it didn't (typically) happen in one day. It (typically) happened several days or weeks) the patient's condition deteriorated rapidly with children dying from acute respiratory failure.

**Slide 9:**

In the late 1960's, there were more frequent descriptions of juveniles and adults with the pathologic features on postmortem examination. consistent with Leigh's Disease and patients were divided into 3 categories:

- Infantile onset (Classic Form). Onset >18 years
- Sudden death (in sleep) secondary to respiratory failure
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The majority of the information available even today on adult-onset Leigh Syndrome is in the pathology literature (in the literature for people who perform autopsies) because these patients still have a tendency to present with sudden death during sleep. **Slide 10:**

In the 1970's, the etiology remained elusive however the suspicion for a metabolic derangement (disease) persisted and reports began describing lactic acidosis (high levels of lactic acid) in patients.

**Slide 11:** The association between febrile illness, acute brainstem damage, and respiratory failure also became more clear. A child would be okay, but they weren't severethen they would get a febrile illness and they would have acute damage followed by respiratory failure, ultimately would lead to death

**Slide 12:**

Prior to the availability of magnetic resonance imaging, diagnosis remained exclusively pathologic, i.e., made on postmortem examination (looking at the brain). MRI became available in the 1980's shifting Leigh's Disease to a diagnosis that could be made pre-mortem through clinical findings, such as recognizing patterns on MRI scans. This allowed them to diagnose before the child passed away.

**Slide 13:** MRI Imaging in Leigh Syndrome – Midbrain

These are the specific findings that can be seen on the MRI scan. I know most of you guys aren't used to looking at MRI scans, but these are actually pretty striking. It is the white tissue that is not normal, and I put an arrow there so we all know what we are looking at. So ne of the areas where we see abnormalities is the midbrain. What I want you to see is that the brain is divided into two halves and what you notice in Leigh Syndrome very specifically, is that it is symmetric looks the same on both sides. There are not very many neurological conditions that produce a finding like that. The other thing that is really notable is that this is in the middle, or the midline of the brain. So you have bilateral (on both sides), symmetric (looking the same), midline lesions. And that is one of the very common characteristic of Leigh Syndrome.

**Slide 14:** MRI Imaging in Leigh Syndrome - Lower Brainstem/Pons Again, the common areas are the midbrain, ou also see this in the lower brainstem and the pons.

**Slide 15:** MRI Imaging in Leigh Syndrome - Basal Ganglia

You can see this in the basal ganglia. Slide. Slide

### **Slide 16:** MRI Imaging in Leigh Syndrome –Thalamus

You can see the thalamus, and the areas around the thalamus.

### **Slide 17:** MRI Imaging in Leigh Syndrome - Periaqueductal Gray Matter

You see what is called the periaqueductal gray matter. This is a very small little piece of brain that surrounds something called the cerebral aqueduct in brainstem. It is very, very important in regulating a lot of automatic central nervous system functions.

### **Slide 18:** MRI Imaging in Leigh Syndrome – Cerebellum

Other areas are the cerebellum. The cerebellum is often called little brain. It is in the back part of your brain and it controls balance. .  
Syndrome, but

### **Slide 19:** MRI Imaging in Leigh Syndrome - White Matter

On occasion you can see changes in white matter. And again you will notice these are not necessarily as symmetric as what we see in the deeper structures or the midline structures, but it is seen in quite a few patients who have Leigh Syndrome.

**Slide 20:** Spectroscopy Also seen in Leigh Syndrome patients are excessive amounts of lactic acid in abnormal tissue. With MRI spectroscopy, (Slide 20) excessive levels can be visualized, obviating the need to sample tissue to obtain the levels.

The last imaging slide you see is what we call spectroscopy. , and this is a special sequence that is done on MRI scanning, where we look for different chemical peaks inside the brain and the blue arrow there is pointing to something that should not be there this is a lactic acid peak. In a lot of patients with Leigh Syndrome we see in the abnormal tissue that there will be excessive amounts of lactic acid. With the MRI, we are able to recognize that without actually having to sample the tissue to obtain the lactic acid levels.

### **Slide 21:** Clinical Features

Pre-mortem diagnosis allowed for an expanded understanding of the clinical features:

- In most cases pregnancy and birth are normal with normal early development.
- Onset is typically within the 1st year.

- Onset is triggered by metabolic challenges such as an acute infection. . n: When you get an infection your body works very hard to fight the infection off, and in order to do that it requires extra amounts of energy; for most of us we are able to do that very well but for children with Leigh Syndrome they don't have that extra energy reserve and that produces a stress on their body from a metabolic standpoint resulting in a metabolic challenge which can often trigger a rapid deterioration in the child's condition).
- Onset is followed by rapid deterioration.

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Even as the clinical picture became more concrete, the etiology remained elusive (we still didn't know what was causing it).

- In 1977, Willems, et.al., reported the finding of mitochondrial dysfunction, specifically dysfunction of Complex IV of the ETC, in a child with Leigh's Disease.
- Although several follow-up reports confirmed mitochondrial dysfunction in Leigh's Disease, but interestingly, this suggestion was widely disregarded, and people didn't believe that mitochondrial system dysfunction could cause this syndrome. **Slide 23:** In 1979, De Vivo, et.al. reported the finding of pyruvate dehydrogenase deficiency in a child with clinical Leigh's disease. PDH research led to a moderately effective treatment (for some children) involving dietary modification that is widely used today.

PDH deficiency remained the suspected cause (the only cause) of Leigh Syndrome from 1979 until 1992. Most children didn't respond to the ketogenic diet so it still remained a kind of a conundrum as to what was really going on. **Slide 24:** In 1992, Nagai, et al, published a cohort of patients with Leigh Syndrome and was the first to re-direct the etiology of Leigh Syndrome back to the mitochondria.

What he found when he looked at his patient was that the biochemical defects in Leigh's are heterogeneous and that the etiology may also be heterogeneous. He was the first person to suggest that perhaps there wasn't just one cause, but that could be multiple different causes that could be resulting in the same condition. **Slide 25:** Genetics Since Dr. Nagai's reporting it has now become clear that Leigh's disease is not a single entity caused by a single genetic condition.

- Leigh's Disease is a heterogeneous group of disorders caused by multiple different metabolic derangements affecting terminal oxidative metabolism and impairing energy production.
- The common features of Leigh Syndrome seem to be the clinical features as well as the involvement of the mitochondria and mitochondrial dysfunction in these conditions.

### **Slide 26-29**

The next four slides are going to show you just a few of the genes that we know are related to Leigh Syndrome. This was probably put together a few years ago so there are several more genes that could be added to this list now. But I think it brings the point home that this is not a single genetic disease, it is multiple genetic diseases, all producing similar symptoms.

### **Slide 30: Leigh's Disease vs. Leigh Syndrome**

As the concept of a heterogeneous disorder became more accepted, the terminology shifted from Leigh's disease (implying a single disorder) to Leigh Syndrome (implying a set of symptoms with multiple potential etiologies)

This may seem like a small distinction to a lot of people but in the medical world, this is actually a big distinction. When you call something a disease, that means it's a single disorder. There is one cause, one outcome, one set of symptoms. We know that is not what we see in patients with Leigh's. There are multiple causes, there are even multiple different symptoms. It has now been renamed Leigh Syndrome. A syndrome is a set of symptoms that can have multiple different causes, and it does provide a lot of information, but it also helps us understand that it is not just one condition. So we tend to use the term Leigh Syndrome in modern treatment.

The outcome of Leigh syndrome remains poor at this time. The majority of affected individuals die from sudden respiratory failure. However, with the onset of early diagnosis and careful watching during febrile illness, more and more children with Leigh syndrome are surviving longer. As of yet we do not know what adulthood holds for these complicated kids, but we do believe that the medical stresses decrease the older you get, and therefore the risk for decompensation and ultimately for death decrease somewhat with age. That is a very general statement regarding a very complex set of diseases. . . **Slide 32: Leigh Syndrome: Serial MR Imaging and Clinical Follow-up**  
Dr. Arii was trying to determine if we could figure out which patients were at risk to develop respiratory failure based on their MRI features. In 2000, Arii et al. investigated eight patients with Leigh syndrome (three months to 12 years of age) to determine if respiratory failure could be predicted on the basis of clinical characteristics or findings on serial/repeated longitudinal MRI images of the brain.

- They found that fatal respiratory failure was unpredictable from clinical or neuroradiologic findings
- Brain stem lesions are associated with the loss of respiratory control however the time at which these lesions develop is unpredictable

Keep in mind that even though this is a negative study, which means it didn't find the answer we were hoping for, it does still provide a lot of information, which tells us to stop looking there and start looking somewhere else.

### **Slide 33: Treatment**

To date there really exist no good treatment options for patients with Leigh Syndrome. We are hoping to change that, but right now we don't really have anything concrete.

A multitude of OXPHOS cofactors and antioxidants are prescribed (because we believe that they should help) secondary to their potential benefits. However, no definitive trials have been published demonstrating clear evidence for clinical improvement in patients.

Just because we don't have the studies, doesn't mean they don't work. Most of these substances are nontoxic and we do recommend our patients try them. Some patients do report clinical benefit, and I do believe that in some cases, clinical benefit is clear.

- CoQ10
- L-carnitine
- Alpha-lipoic acid
- Creatine
- Biotin
- Thiamine
- Riboflavin

### **Slide 34: Treatment**

We also recommend that newly diagnosed patients should all receive a trial of high dose biotin (10-20 mg/kg) and thiamine (100-300 mg) if their Leigh syndrome is genetically undiagnosed. There is a condition called biotin responsive basal ganglia disease (BBGD), which is one of the types of Leigh Syndrome, and again there is a genetic test for this, and if you have had genetic testing for your Leigh Syndrome you have had this test done. If you have BBGD, then treatment with biotin and thiamine can stave off the decompensations or sometime even improve the condition of the child.

For all children, malnutrition should be corrected. Malnutrition is very common in Leigh Syndrome they present some degree of mild malnutrition if not more severe. As noted above, for those children with a PDH deficiency (Pyruvate dehydrogenase deficiency) a ketogenic diet should be initiated. Please remember, a ketogenic diet is not appropriate for most child with Leigh Syndrome, only for those with a PDH deficiency, and then only in conjunction with your doctor.

### **Slide 35: Proton Magnetic Resonance Spectroscopy to Study the Metabolic Changes in the Brain of a Patient with Leigh Syndrome**

look at a compound called dichloroacetate in patients with Leigh syndrome. He administered this orally to them and what was also noticed very clearly was that the lactic acid level in both the blood and the spinal fluid improved. What was also very impressive was that the child's symptoms did not improve and the MRI did continue to show progressive disease. Dichloroacetate is typically not recommended anymore for patients with Leigh Syndrome or other forms of mitochondrial disease. because it can cause some very severe side effects.

Again, the clinical study that was done did not show benefits, so reducing the lactic acid did not prevent the progression of the disease. In 1999 Takahashi et.al. reported dichloroacetate normalized the lactate levels in both blood & CSF of patients with Leigh syndrome • However, symptoms did not improve and MRI showed progressive disease

**Slide 36: Treatment**

Thus, while early case reports and pre-clinical data suggested that DCA might be an effective treatment for lactic acidosis, clinical trials found no clinical benefit of DCA.

- Additional trials have shown that subjects developed progressive, irreversible neuropathy while taking DCA
- The DCA story highlights the importance of clinical trials in drug development

**Slide 37: Efficacy of Idebenone for Respiratory Failure in a Patient with Leigh Syndrome: A Long-Term Follow-up Study**

- Idebenone is a synthetic analog of CoQ10 with improved absorption and bioavailability. Haginoya reported a case in 2009 Slide of the successful treatment of a single patient with Leigh Syndrome using idebenone (. The patient's brainstem function improved after idebenone administration) suggesting this might be worth trying in patients with Leigh Syndrome. Again, this is one of those supplements, one of those theoretical compounds that may be of benefit and I just wanted to point out that no follow-up studies have been performed that confirmed that this is effective. However, this is a substance that is pretty non-toxic and might be worth considering or trying in your patient or for your children.

,Slides.

**Slide 38: Beneficial Effect of Pyruvate Therapy on Leigh Syndrome due to a Novel Mutation in PDH E1 Gene**

In 2012, Koga et.al. published a report of a single case treated with sodium pyruvate

The patient was an 18-month-old child - noted on DOL 3 to have lactic acidosis. Development was poor with the child never learning to hold his head, sit, or crawl. In infancy, the child developed infantile spasms (seizures) that evolved to Lennox-Gastaut syndrome.

At 18 months of age, the child was started on sodium pyruvate.

**Slide 39: Beneficial Effect of Pyruvate Therapy on Leigh Syndrome due to a Novel Mutation in PDH E1 Gene**

actate, pyruvate, and alanine levels decreased significantly (improved). There were no adverse effects noted.

Development began to occur with the child rolling over and smiling 3 months after initiation of therapy. Six months after starting therapy, the EEG normalized and seizures resolved. Although promising, the authors recognize that this therapy needs evaluation by randomized double-blind placebo-controlled study.

Just because it worked for one child, it might not work for everybody else. There maybe something different and there was no information provided about the child's genetic background to know whether or not this is more generalized. But I do think that some of these single case reports are very exciting.

**Slide 40:** *EPI-743 Reverses the Progression of the Pediatric Mitochondrial Disease - Genetically Defined Leigh Syndrome*

A study from Italy (not too long ago I don't have the publication date here) investigated the use of EPI- 743 in ten children with Leigh SyndromeSlides. All exhibited a reversal of disease progression regardless of the genetic determinant or disease severity. T There were no significant drug-related adverse events reported. Treatment was brief, for an average of five months.

**Slide 41:** Treatment (with EPI-743)

There is an ongoing randomized, placebo-controlled, double-blind clinical study investigating the utility of EPI-743 in children with Leigh Syndrome in the United States. There are still many children with Leigh Syndrome who are on this trial and we are waiting for the definitive results to come out talking about whether or not this was effective and whether or not this treatment is something that will be available to other children.

**Slide 42:** *mTor Inhibition Alleviates Mitochondrial Disease in a Mouse Model of Leigh Syndrome*

In 2013 Johnson et.al. administered a medicine called rapamycin to mice with Leigh SyndromeSlide. The rapamycin treated mice demonstrated:

- Delayed onset of neurological symptoms,
- Reduced neuroinflammation (nervous system inflammation) and

A lack of development of the characteristic brain lesions. The mechanism (why this worked) of rescue remains unknown..

I know that people are still looking into the use of rapamycin and other medicines like that, for potential treatment in humans.

**Slide 43:** Current Understanding:

A Multicenter Study on Leigh syndrome: *Disease Course and Predictors of Survival* (Study in Sweden)

- Natural history study of 130 patients with clinically defined Leigh syndrome. Slide. Symmetrical lesions in one or more areas of the CNS (central nervous system) including the basal ganglia, diencephalon, brainstem, cerebellum, and spinal cord. These are the characteristic MRI findings from the Leigh Syndrome. did not have to have a genetic diagnoses. In fact that is one of the things that they looked at.

I will say that this is currently our best understanding of the clinical situation regarding Leigh syndrome.

**Slide 44:** Current Understanding: *A Multicenter Study on Leigh syndrome: Disease Course and Predictors of Survival* (Study in Sweden)

Onset typically occurs between three and 12 months of age with disease progression and death within two years.

- Later onset and slower progression however, have been reported

One of the things that became very clear though is that not all children born with Leigh Syndrome had normal early development. A lot of them ha

- Motor delay
- Hypotonia (low muscle tone)
- Cognitive impairment and/or progressive cognitive loss
- Brainstem dysfunction: respiratory abnormalities, swallowing dysfunction, ophthalmological manifestations, and abnormal thermoregulation (difficulty with temperature control)

**Slide 45:** Current Understanding: *A Multicenter Study on Leigh syndrome: Disease Course and Predictors of Survival* (Study in Sweden)

Dr. Sofou's group found that this condition could be inherited as a mitochondrial, X-linked, or autosomal recessive condition.

- Slight male preponderance (78 males, 52 females)
- Parental consanguinity in 31 patients (the parents were first cousins or more closely related than that)

- 15% were born early
- 80% of pregnancies were uneventful
- 23% had abnormal signs at birth: hypotonia, cardiac complications, lactic acidosis, feeding/sucking problems, dysmaturity, hypoglycemia, hyperbilirubinemia, hyperammonemia, seizures, hypertonia, contractures, dysmorphic features

**Slide 46:** Current Understanding: *A Multicenter Study on Leigh syndrome: Disease Course and Predictors of Survival* (Study in Sweden)

The other thing that was really important about this study was that they were able to identify findings that occur outside of the central nervous system. This is really important because when physicians get so focused on in the central nervous system, they forget that other parts of the body can be involved.

Extra-CNS findings that occur with Leigh syndrome:

- Polyneuropathy
- Myopathy
- Diabetes
- Short stature
- Hypertrichosis (more hair than other people)
- Cardiomyopathy (heart failure)
- Anemia
- Sleep disturbances
- Renal failure (kidney problems)
- GI dysfunction (difficulty feeding)
- Failure to thrive
- Hearing loss
- Retinitis pigmentosa (visual loss)
- Cranial nerve palsies
- Scoliosis

These comorbid conditions or extraCNS findings are things that doctors should be looking for because they could again potentially affect the child's quality of life as well as their ability to survive a metabolic stressor such as an illness.

**Slide 47:** Current Understanding: *A Multicenter Study on Leigh syndrome: Disease Course and Predictors of Survival* (Study in Sweden)

Another important finding: 25% of patients had normal lactate levels. . Often children will have normal lactic acid levels at rest, and then they can go up during times when they have stress.

Only 44% had abnormal muscle histology. . In the muscle biopsies that were done, less than half of the children had any findings on the muscle, and that is hugely important and we typically do not recommend muscle biopsies for children who have Leigh

syndrome because there is at least a 50% chance it will be normal and it is not going to change our understanding of the child's condition.

Other important findings:

- 70% had abnormal ETC (electron transfer chain) analysis on the muscle biopsy
- Genetic etiology was confirmed in 59%
- 41% (a large group) were unable to identify a genetic mutation
- 38% with nDNA (nuclear DNA mutations)
- 21% with mtDNA (mitochondrial DNA mutations)

People ask me all the time, 'Well if the genetic test comes back negative, do you still have this condition?'. The answer to that is . Those 41% of children still have Leigh Syndrome, it is still a genetic etiology for them it is still caused by an abnormal gene. We just don't know what gene yet. But probably in the next years we will be able to identify the genetic change in those children. But a lack of genetic identification does not change the fact that you have the disease.

**Slide 48:** Current Understanding: *A Multicenter Study on Leigh syndrome: Disease Course and Predictors of Survival* (Study in Sweden)

The median age at death was 2.4 years (range from one month to 21 years). .

- The elapsed median (average) time from onset to death was 1.8 years
- Main cause of death was respiratory complications (51.0%)

**Slide 49:** Current Understanding: *A Multicenter Study on Leigh syndrome: Disease Course and Predictors of Survival* (Study in Sweden)

The authors found the following findings to be associated with poorer survival:

- Age of onset below or equal to 6 months
- Seizures
- Failure to thrive
- Hospitalization in an ICU (intensive care unit)
- Genetically verified disease, and
- Brainstem lesions on neuroimaging

**Slide 50:** - Bar Graph

This is my very favorite slide of this entire presentation. This is a slide showing how many papers have been published per year on Leigh Syndrome, Leigh's Disease, or subacute necrotizing encephalomyelopathy. If you look back all the way to the left it

says 1951 and there is a little blue bar there that says, just one. That was the very first case that was published in the medical literature by Dr. Leigh back in 1951. What I want you to notice is how dramatically increased the number of publications have come in the last 60 years. In 2013 there were over 35 individual papers published on Leigh Syndrome in the medical literature. I do need to update this slide because that has persisted and it is becoming more and more of interest in the medical community. That is how we find answers. That is how we find treatments. We start understanding, learning more, and sharing this information with other physicians and other researchers around the world.

### **Slide 51: Modern Definition of Leigh Syndrome**

According to Online Mendelian Inheritance in Man (OMIM), Leigh Syndrome is defined as:

*An early-onset progressive neurodegenerative disorder with a characteristic neuropathology consisting of focal, bilateral lesions in one or more areas of the central nervous system, including the brainstem, thalamus, basal ganglia, cerebellum, and spinal cord. The lesions are areas of demyelination, gliosis, necrosis, spongiosis, or capillary proliferation. Clinical symptoms depend on which areas of the central nervous system are involved. The most common underlying cause is a defect in oxidative phosphorylation (or mitochondrial function.)*

Online Mendelian Inheritance in Man is one of the most widely used genetic references by physicians in the country.

### **Slide 52: Febrile Illness > Brain stem Damage > Respiratory Failure > Death**

The original belief that a febrile illness leads to brain stem damage which leads to respiratory failure which leads to death still holds. SlideWe still recognize this association: an otherwise stable child will develop some sort of febrile illness which produces an enormous metabolic stress on their body which causes acute or rapid damage to the brain. When the brain stem becomes damage it results in respiratory failure and respiratory failure can rapidly lead to death. So it is important to try and keep your kids healthy, try to get aggressive treatment if they become sick. antibiotic We typically will admit our children to the hospital for any fevers to try and decrease their metabolic stress as well as monitor them. If the child develops respiratory failure in a hospital, there is a higher likelihood of survival then if it happens at home. . . . .

e. . .

### **Slide 53: THE (INTER)NATIONAL LEIGH SYNDROME REGISTRY**

I am going to leave you with that and I am going to turn things over to Lori Martin and she is going to talk to you a little bit about our registry that we have developed here and how excited we are about it.

**Lori Martin:** My name is Lori Martin I am the Director of People Against Leigh Syndrome (PALS) and I am excited to be on the call.

#### **Slide 54: What is the PALS Leigh Syndrome Patient Registry**

I would like to share a little bit of a personal perspective of why this is so important, and why I chose to spend all of my free time trying to help watch this. When our son was first diagnosed, I still can go back right into that room where we were told. It will forever be ingrained in my memory, like I am sure all of you have that memory as well. I think one of the things that I was left with feeling was 'So what? What do you mean there is no treatment that do you mean there is no cure his is unacceptable his is just not okay this is our child'. This is the hardest thing I have ever had to understand, what's next? I needed a next. I needed to understand the process of the disease, what it looks like, when my child might die, what he might die of. These are very intense conversations and there are just no answers. That is part of why this patient registry is so important because we have the chance to collect information about children who currently have Leigh Syndrome, and try and help others in the future understand this disease progression. So that way, it may not be one of us on this call that walks into the doctor's office and we get an answer, exactly what the future looks like and what it holds but we might be able to pay it forward in some way by helping others not go through that same conversation in the future. So that is the premise behind a lot of this. We are trying to help gather and register anybody with a clinical or genetic testing confirmation of Leigh syndrome.

What is the PALS Leigh Syndrome Patient Registry?

- An electronic database for people with Leigh syndrome with self-directed questionnaires.
- The registry is accessible to all people across the U.S. and the world.

What is its purpose?

- To collect demographic, clinical and quality of life information on people diagnosed with Leigh Syndrome

We do not share this information. It is protected. We have gone through quite a bit of research to find the correct platform, as well as the safest spot for all of our information. The platform it is used on is a widely used medical community platform that has all those HIPAA rules -- we have got that box checked.

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## **Slide 55: How Will this Registry Benefit People with Leigh Syndrome:**

Data from the registry will help the medical community to bridge gaps in our knowledge about Leigh Syndrome. We are bridging the gaps between what we as parents know about what is happening in our homes, what is happening when we take our child to the doctor and what we are told. And we have to find a way to come together and bridge that information gap so that we can help doctors who have gone to school and have access to these types of research projects and things we may not have access to at home, to help us figure out some sort of way to predict complications and hopefully prevent complications from happening and improve the quality of life for our children, and ultimately improve the survival.

Not only will it help us break that information gap of what is happening with all of these amazing kids, but it is also going to help pharmaceutical companies design clinical trials and that means a treatment one day. It connect us quicker to these clinical trials so when there is a clinical trial that comes out, we can work with that pharmaceutical company to provide, if that patient has chosen, we can work with them to provide access immediately to patients who would be interested in doing a clinical trial. Ultimately it will advance treatment.

Information taken from a larger pool of patients will allow us to:

- Better understand the natural history of Leigh syndrome
- Predict complications
- Prevent complications
- Improve quality of life
- Improve survival
- Design clinical trials
- Connect patients to clinical trials
- Advance treatment

Visit [www.PeopleAgainstLeighs.org](http://www.PeopleAgainstLeighs.org) to join the registry or learn more.

## **. Slide 56: So Far – Phase I**

- We all have our favorite slides and the things we are most excited about sharing, and I think this is probably one of my favorite slides. I don't know how many of you know them almost 90 people with Leigh syndrome, maybe you live in a city or a state or a country where you don't know a soul. But there are almost 90 of us in this patient registry, which I think is just amazing. We have watched this to collect information and demographics, that is where we started so, who is the population, where do they exist, and how can we start building a relationship with them and

connecting with them? We would encourage, if you don't have the time to do Phase II, to at least go in for Phase I and share your information.

#### Phase I:

- Information collected
  - Contact information
  - Demographics
  - Beta-tested March 2015
- Launched June 2015 participant's

#### **Slide 57:** So Far – Phase II

We launched Phase II last June. This is that next step the in-depth collection of medical history, your family history, quality of life and then, what are your interests as far as research and clinical trial. So if you have not had a chance to sign up for the registry I would encourage each of you to do so. You can go online to have an FAQ online to where you can read more. Our website is [peopleagainsteighs.org](http://peopleagainsteighs.org). We are also on Facebook we can find us there and get engaged.

#### Phase II

- Information Collected
  - Medical history
  - Family history
  - Quality of life
  - Research participation
- Launched in June 2017

#### **Slide 58:** Distribution of PALS Registry Participants in USA

Just to show you a little snapshot of where we are at in the United States, our distribution of participants, and just because you see one dot, for example in Texas, it takes about a whole day just to get out of our state, so we are not just one dot, it is many, many participants in Houston and same thing for the other states you see.

#### **Slide 59:** Distribution of PALS Registry Participants Worldwide

Our worldwide distribution of participants, Japan, Australia, India, Italy, and so on, you see where the dots are.

#### **Slide 60:** Thank You

I would just encourage each of you to consider joining the PALS registry, so that we can really join forces together as a patient community. I also wanted to let you all know that

there is it is not associated with PALS a it is just a private, closed Facebook group for parents with Leigh syndrome. It is online and run by an amazing human being and mom to a child who has Leigh syndrome and she has really worked to make this group be really meaningful, so that way we can all get to know each other. So if you are on Facebook, it is a private group for Leigh Syndrome families and I think you can find that through a simple search and Heather can help you join the group and get to know everybody. Thank you for your time today and I am betting there are a lot of questions.

**MaryBeth Hollinger:** Thank you, that information was just information, I learned new things. I did not realize there were three slides worth of mutations that all play into this syndrome. I agree, I love the slides that show that more and more effort, passion, science is being directed, with outcomes, with papers, and (with) research and that to me is so hope inspiring. I have been watching Dr. Miller and Dr. Klein's study through Bioelectro and EPO-743 and really hope that they get those finishing touches and final approval so that medication will go forward. I do have many questions.

Let's start with a question from North Carolina:

*"Should a child with Leigh Syndrome be kept away from public places, especially schools, for fear of illness and that decompensation and potentially respiratory failure that you mentioned?"*

**Dr. Koenig:** That is a really good question and a really hard one to answer. We know that people with mitochondrial disease and that does include children and folks with Leigh Syndrome, have differences in their immune function, and that has not been quite delineated yet but there are some people doing studies on this, I am going to put in a plug for Peter McGuire and the NIH. He has a study (a mini-study) where he is looking at immune function in people with mitochondrial disorders including Leigh Syndrome. So we believe that at least in some children with Leigh Syndrome there is an increased risk to develop infections, they have an increased susceptibility.

So what I would like to do with every patient I have with Leigh Syndrome is I would like to put them in a little bubble, and I would like to leave them there with a big jar of antibiotic hand gel and I would like to tell them to never get anywhere near anyone. But as you can imagine, that doesn't really lend to a very good quality of life.

So that question that I answer with my patients is always very individual, and it has to do with more with quality of life than anything else. We know that there is a risk, being around other people to get sick, but there are things you can do to mitigate that risk. You can not let strangers touch them. They actually make little signs you can put on a child's stroller or car seat that says "Please don't touch me without asking my mother", because people like to touch babies. We recommend carrying hand gel with you. We recommend leaving any place where anyone is coughing, sneezing, or otherwise looks ill. We recommend trying to keep sick people away from your child. But in the setting of quality of life it is important for them to be out in the world and be around other people.

And I will just say one last thing about that, and that is that if you are concerned that if your child does get sick from other people, having an evaluation by an immunologist would not be a bad idea.

**MaryBeth Hollinger:** Thank you, I agree. Sometimes is not just child with Leigh Syndrome. but I work with a family who has a baby with Leigh syndrome and a little preschooler. So there is that pulldo we let that preschooler go out into the world and bring back germs? It is a big balance. There is a lot to be said by just basic germ management, and stripping your clothes off when you come in from preschool and washing and making sure you brush your teeth at night.

How about this one from your neck of the woods:

*“Can other diseases cause brain lesions similar to what is found in Leigh syndrome? Is the MRI diagnostic or are more tests needed?”***Dr. Koenig:** The short answer to that is yes, but the long answer is not very many. There are only a very few subset of conditions that can cause lesions like this in the brain. With ost neurologist and neuroradiologist are very familiar with these types of lesions and the differential associated with that or the different things that can cause it. So I would definitely work with a neurologist to define those things but there are a few other things that can do this.

**MaryBeth Hollinger:** This next question is definitely broad and on people’s minds, it is about gene therapy:

*“We are hearing gene therapy for other diseases and what is the likelihood for come to play for something like Leigh syndrome?”***Dr. Koenig:** Gene therapy is a really exciting field and I am very, very, optimistic about the future with gene therapy. But I do want to say that right now, it is not working as well as we would like. I think there are some situations where there have been some amazing strides and advances but I believe there is still a long way to go with the research before it is readily available. One of the issues we do have with Leigh Syndrome is that again it is not a single genetic disease, so typically when we are looking at gene therapy for a disease, it is targeted to a particular genetic defect. So again I don’t want to take away anyone’s optimism because I do believe that we should be optimistic, but I don’t’ think we are quite there yet. I think it is something we all need to be keeping our eye on though.

**MaryBeth Hollinger:** I agree, it is tough when it is rare and has so many defects. They have to develop the vectors and the ways to get those genes in there. I am hoping that once the more common genetic defects are handled, it will just be a cascade of ‘Oh we can apply this science to many different defects.’

**Dr. Koenig:** I agree with that.

**MaryBeth Hollinger:** Rick is asking and I think this is important, because I know you made the point of it being very cautious with beginning a ketogenic diet so I will bring this up again:

*“Can a ketogenic diet be harmful for Leigh syndrome patients who do not have the PDH deficiency?”*

**Dr. Koenig:** Yes.

**MaryBeth Hollinger:** I just wanted you to reiterate that. Perfect. Definitely any attempts at a ketogenic diet should be done very carefully under close supervision, and I know many babies are hospitalized for that and just to check their ketones and to make sure they gain weight etc. So we definitely want to make sure that we get that point across very clearly.

This one I am not so sure about, maybe you can decipher it a little bit:

*“Which gene defect could be BBGD which I think is biotin thiamine responsive basal ganglia disease?”*

**Dr. Koenig:** Yes, it is caused by a mutation of the SLC19A3 gene.

**MaryBeth Hollinger:** We will move on to Jessica if you have time for one more.

*“How can we spread awareness to ERs, first responders, schools and communities?”*

Because she is feeling where she is, nobody knows anything about this disease or syndrome.

**Dr. Koenig:** That is a great question. When I started here a little over ten years ago one here knew anything about mitochondrial diseases and especially nothing about Leigh Syndrome. And I will tell you now if you walk into our emergency room and you tell them you have Leigh Syndrome, they have a protocol very person in the ER knows what to do you are the first person back and you get taken right to your room. This has been a lot of effort on the part of not myself but a whole team full of people.

What needs to happen is increased education. I am in a major city with a medical school, I spend a lot of time educating students and residents about this condition. So no one walks out of my medical school without knowing what Leigh Syndrome is. Those people don't stay here, most of them go other places, like some of them go to small towns and some of them go to other cities, and they take that knowledge with them. It takes a long time for that knowledge to get disseminated because they have to pass it on to the people who are already there. I may educate a first year medical student and it is eight years before they are out in medical practice.

What we recommend for a lot of children with metabolic and mitochondrial diseases and especially Leigh Syndrome is that you go to the ER, sometime when it is not an emergency, some time when they aren't so busy, in the mornings, during the weekdays. Meet with the ER Director and tell them what your child has. Bring them some printed information on Leigh Syndrome and let them know this is what is going to happen.

If your child is following with a neurologist or a geneticist, they should provide you with what we call a protocol letter. There are samples of those on some of the support websites. The Mitochondrial Medicine Society, I believe, has a sample letter that you can access. What it does is that it details what your child's condition is and what they should do in the event of an emergency. That one little piece of just having that protocol letter is often very helpful and most physicians want to know about your child's condition. They just don't and they don't have time. So by engaging with them and interacting with them in a non-urgent time frame, it does help provide that information to them. Other things you might consider would be visiting fire stations, who might send ambulances to your house in the event of an emergency, and give them information. We also do recommend a lot of our children wear medic alert bracelets, and that has been very helpful.

**MaryBeth Hollinger:** I do like the proactive approach and I know that in any emergency, everyone's adrenaline is flowing and they are a little less able to take in tons of information, not maybe in an ER because they are used to it, but a first responder time of information but if you do catch them, a school or a fire station, ambulance company, while they are not in an emergency state, they are much more receptive to that opportunity to learn about your child and they will want to. Even that protocol letter, we also have some, keep it right on file in the ER as well as on yourself or in your child's backpack. That way it gives just a little bit more credibility instead of you handing them something and saying 'Hear follow this' to say 'Oh it is actually on file in your ER', they have a little bit more ownership, and we have found they are more likely to follow that plan without question.

**Dr. Koenig:** One of the things too that lots of parents have said to me is 'I don't know where the letter is, or I don't have it with me, every time there is an emergency I don't have it with me.' One thing I know everyone has with them all the time is their phone, and I would suggest to do is take a picture of it. You can always email it to somebody if they need to see it bigger.

**MaryBeth Hollinger:** Very good idea and I know I do the same for our medication list and few others, 'Oh I forgot that paper, oh I have a copy, let me email it you' and they are like 'great' so that works; that is a good idea I never thought of it for the protocol letter.

Thank you so much. It is a little after one and I know you have had a very busy morning so I want to thank both you and the PALS group for joining us for this presentation I know we have all learned quite a bit and we are ready to step out and spread that

awareness. You can also use many of the advocacy groups, whether PALS or MitoAction or whomever to help with getting information and ways to disseminate it so that the world starts to learn about these more rare diseases that aren't seeming as rare anymore.

**Dr. Koenig:** Thank you so much for having us. We really have enjoyed being able to share.

**MaryBeth Hollinger:** I totally appreciate it and you guys have a good rest of your day, and thank you to all of your listeners for calling in. The few remaining questions I will get to you guys and give an answer, and we will see you next week for our regularly scheduled supported group.