

A Physician's Perspective on Leigh Syndrome

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Dr. Denis Archibald Leigh



- In 1951 Dr. Denis Archibald Leigh published an interesting case while working as a registrar at Maudsley Hospital in London

SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY IN AN INFANT

BY

DENIS LEIGH

From the Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London

- A 7 month old boy was admitted to King's College Hospital in 1947
- His ***developmental and feeding histories were normal*** until he:
 - stopped crying
 - became very still
 - stopped sucking
 - slept for long periods

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From the Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London

- The child was not known to have an illness but his sister was ill with a **respiratory infection** at the time his symptoms began
- Following admission, the child deteriorated rapidly
 - spiking high fevers & becoming comatose
- **Death occurred 3 days following admission**

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IN AN INFANT**

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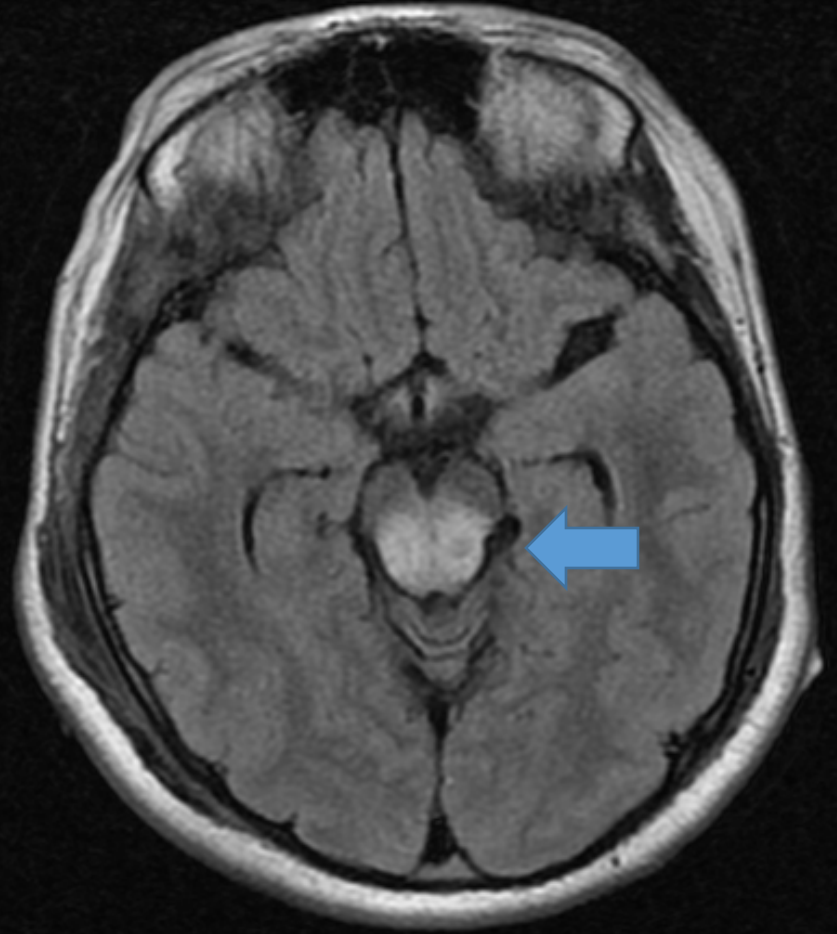
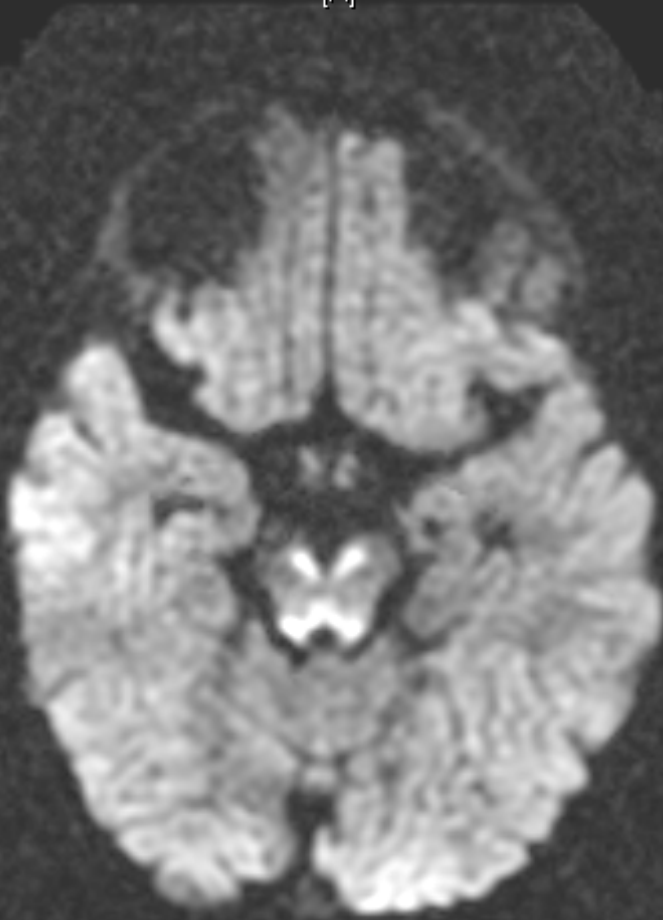
- Postmortem examination demonstrated ***bilateral symmetric necrotic lesions*** in the brain and spinal cord
- The condition he described became known as “Leigh’s disease” and ultimately evolved to become “Leigh syndrome”

Evolution of Leigh Disease

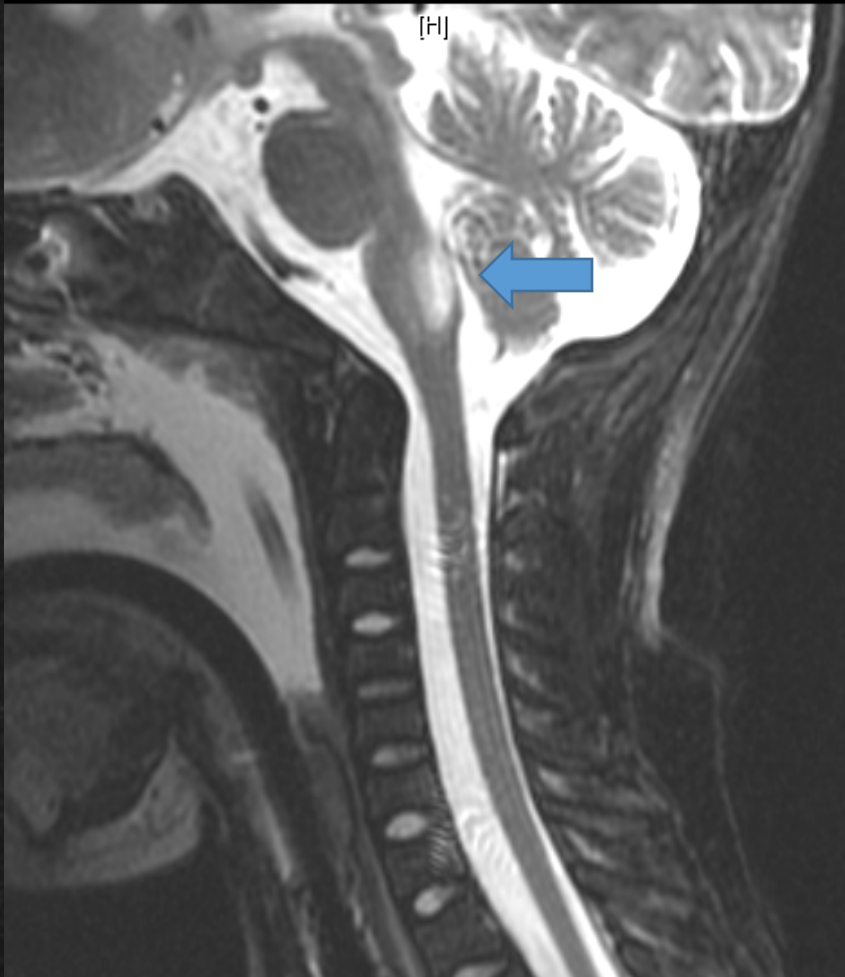
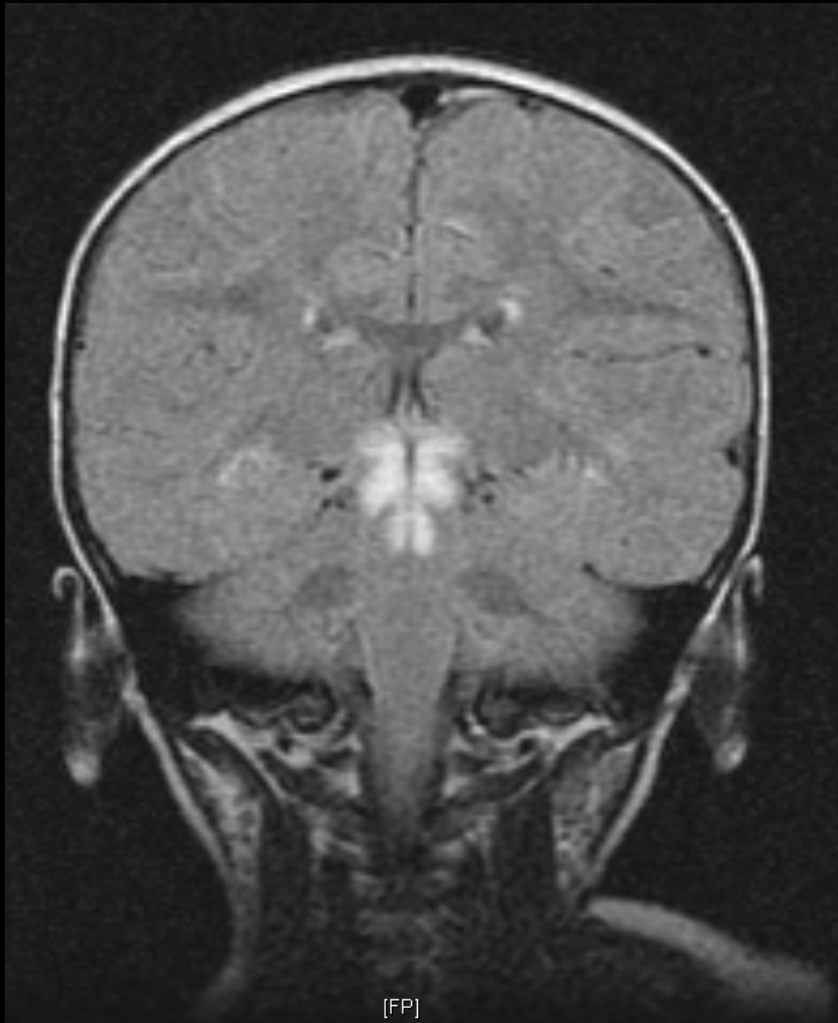
- Over 50 additional cases were described from 1951 through 1977
- As more cases were described, the clinical picture became more clear

MRI Imaging in Leigh Syndrome Midbrain

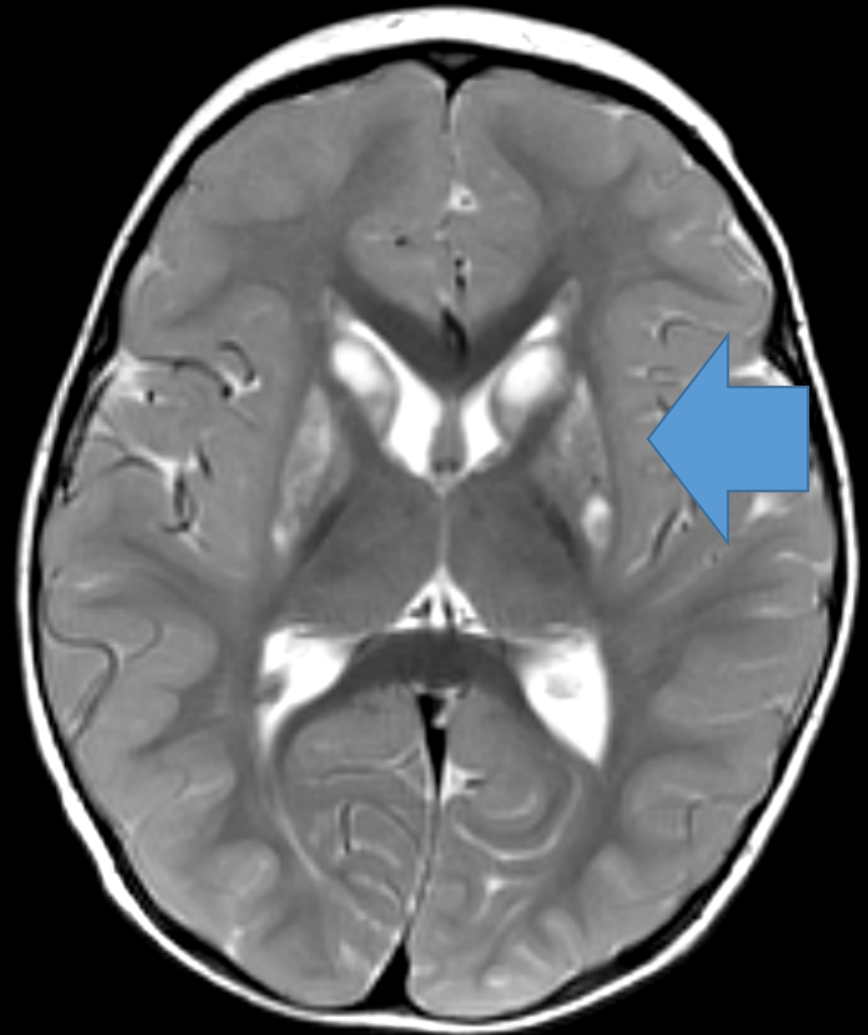
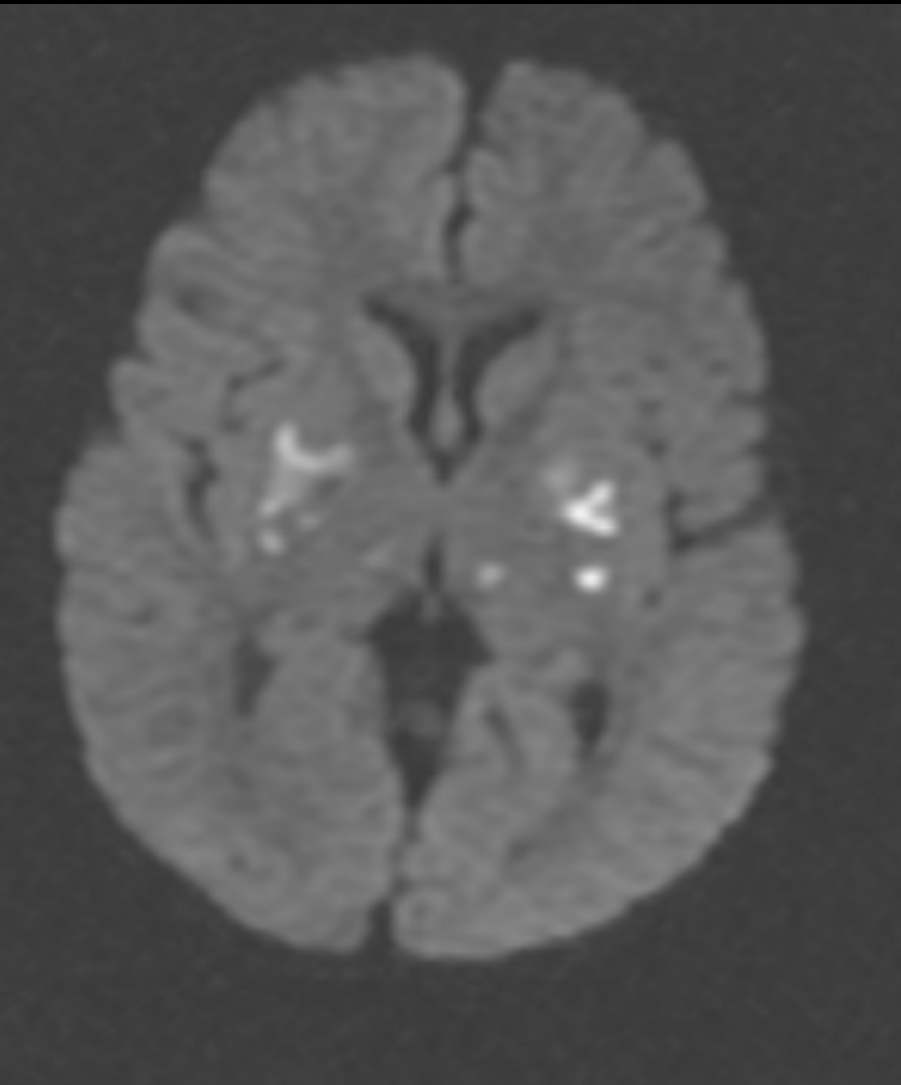
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MRI Imaging in Leigh Syndrome Lower Brainstem/Pons

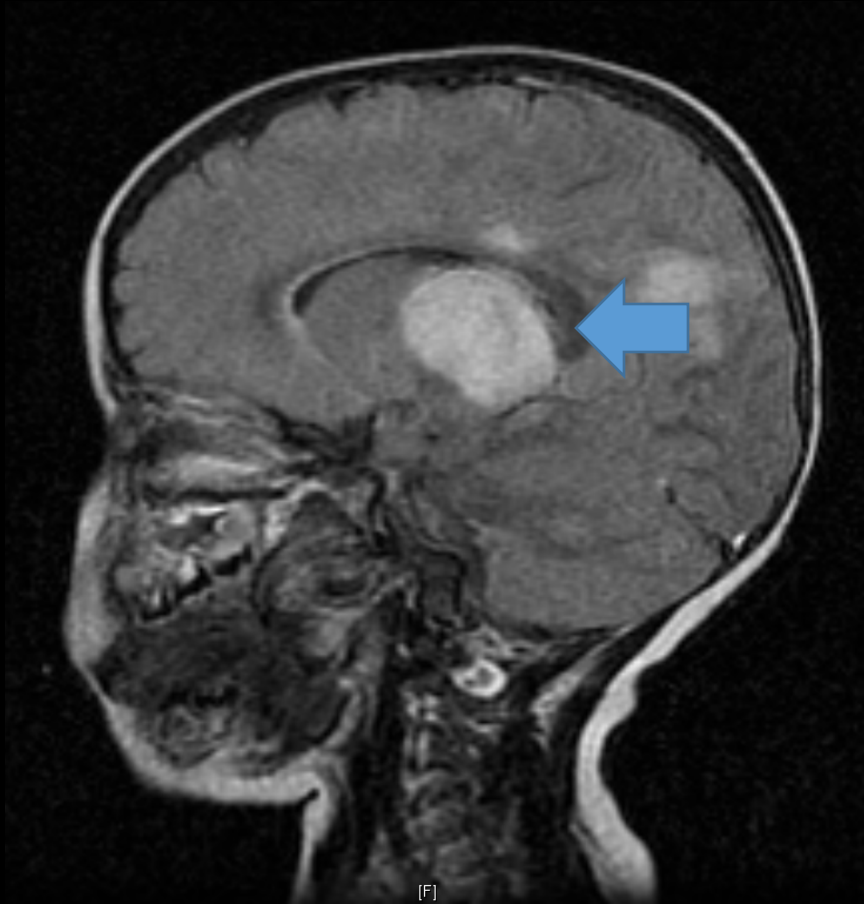
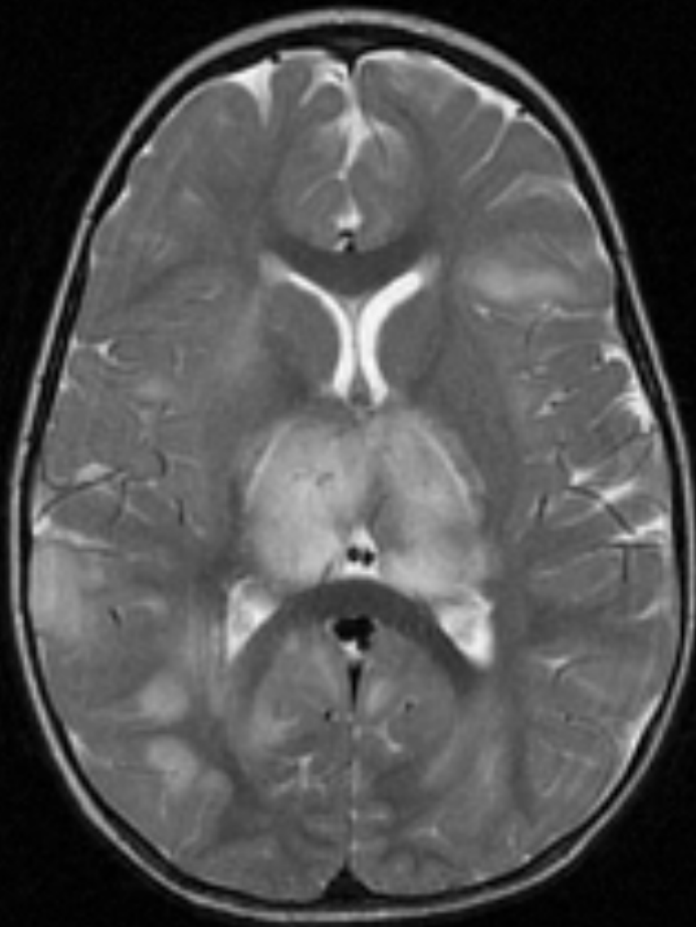


MRI Imaging in Leigh Syndrome Basal Ganglia



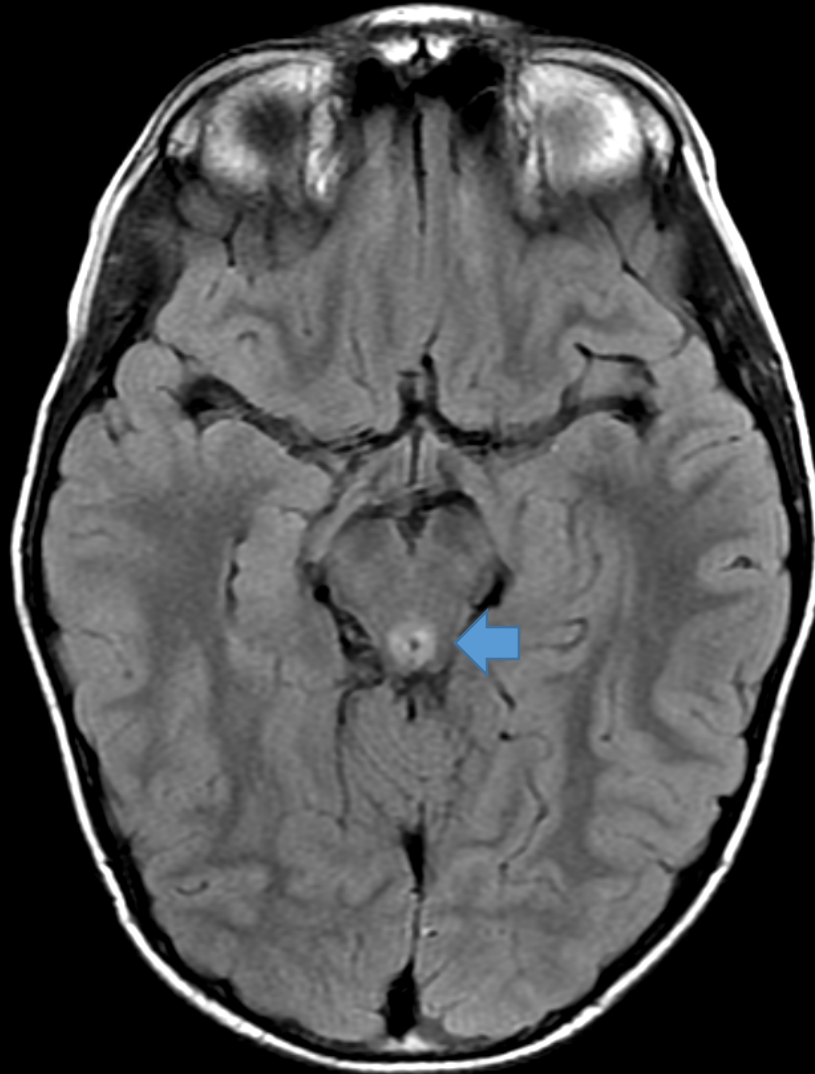
MRI Imaging in Leigh Syndrome

Thalamus



MRI Imaging in Leigh Syndrome

Periacqueductal Gray Matter



Evolution of Leigh Disease

- In most cases pregnancy and birth were normal with **normal early development**
- Onset was typically within the 1st year
- Onset was triggered by **metabolic challenges**, typically an acute febrile illness
- Onset was followed by **rapid deterioration with regression** and often death



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Febrile Illness



Brainstem Damage



Respiratory Failure



Death

Evolution to Leigh Syndrome

- In the late 1960's there were more frequent descriptions of *juveniles* and *adults*
- In the 1970's, reports began describing *lactic acidosis*
- In **1977**, Willems, et.al. reported the first finding of *mitochondrial dysfunction*, specifically dysfunction of Complex IV of the ETC

Genetics

- By now it is well known that Leigh's disease is not a single entity caused by a single defective gene
- Leigh's disease is actually a **heterogenous group of disorders** caused by multiple different genetic etiologies, typically affecting mitochondrial function
- This understanding led to a terminology shift from **Leigh's disease** (implying a single disorder) to **Leigh syndrome** (implying a set of symptoms with multiple potential etiologies)

A Definition of Leigh Syndrome

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**.

Huh?

- The truth is there's not a single definition of Leigh syndrome and the 'definition' remains a highly discussed topic among physicians and researchers
 - Do you include patients with MRI and clinical findings but who do not have genetic confirmation?
 - Do you include patients with MRI and clinical findings who have pathogenic mutations in genes that do not affect primary mitochondrial function?
 - Do you include patients who carry genes known to cause Leigh syndrome who have not yet manifested any symptoms?

How do Doctors & Researchers Classify Mitochondrial Disorders



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Phenotypic Classification

- Used to define clinical symptoms and suspected disease progression
- Acronyms
 - MELAS
 - MERRF
- Disease Names
 - Alpers
 - Leigh Syndrome

MELAS

is an acronym for

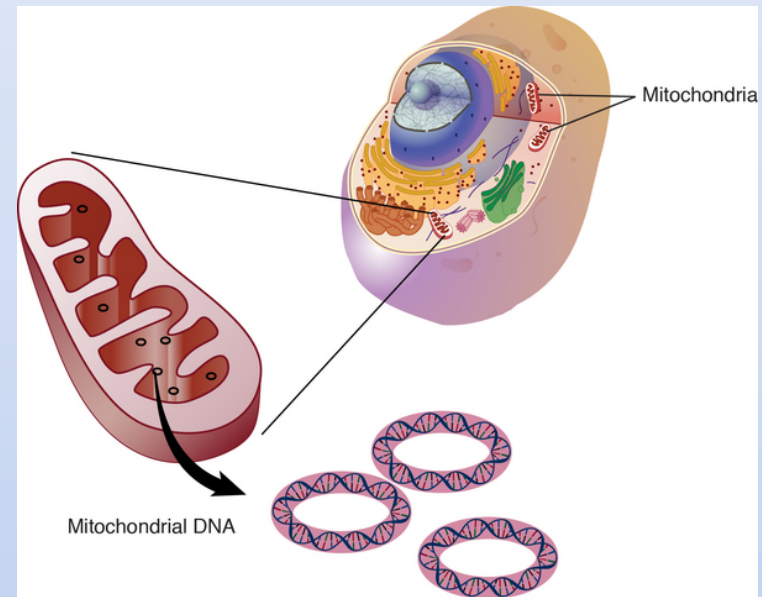
myopathy, encephalopathy,
lactic acidosis and strokelike

Genotypic Classification

- Used to describe the gene causing the syndrome
- Mitochondrial or Nuclear
- Does not necessarily imply phenotypic spectrum or give you any information about the symptoms the patient has
 - m.3243 A>G
 - POLG1
 - SURF1

Functional Classification

- Defined using functional analysis, ie, laboratory testing
 - Complex deficiencies
 - Depletion syndromes
 - Deletion syndromes



Practical Definition of Leigh Syndrome

- So the practical definition of Leigh syndrome may be different for different people, depending on why the definition is being used:
 - Clinical Care/Treatment
 - Genetic Counseling
 - Clinical Trials
 - Natural History Studies
 - Registries

Treatment

- To date there exist no definitive treatment options for patients with Leigh syndrome
- A multitude of OXPHOS cofactors and antioxidants are prescribed secondary to their potential benefits however, ***no clinical trials*** have been published demonstrating clear evidence for clinical improvement in patients



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Prognosis

- The outcome of Leigh syndrome remains poor
- The majority of affected individuals will develop sudden respiratory failure or cardiac arrest
- However, with the onset of early diagnosis and careful watching during febrile illness, more and more children with Leigh syndrome are surviving longer
- The current prognosis is unknown at this time as we do not have good natural history data for children undergoing aggressive management

Prognosis

- Those who survive often experience **neurologic sequelae** such as dystonia, chorea, or Parkinsonism affecting their quality of life
- Treatments are needed to **prolong life, cure** and also to **preserve the integrity of the brain** during the acute decompensating phase to enhance the quality of life for those who are surviving

TRiaLS

The International Registry for Leigh Syndrome

WHAT IS A REGISTRY?

- In general, a registry as a collection of information about individuals focused around a specific diagnosis or disease
- Registries can be sponsored by a government agency, a nonprofit organization, a health care facility, or a private company

RESEARCH VS. PATIENT POWERED

- Traditionally registries have been researcher-generated
- Academic institutions or research teams establish a registry for the purpose of collecting data for a specific research agenda
- These registries may be operated by a single institution or by a collaboration of multiple institutions
- They are directly associated with researchers treating the condition of interest

WHAT'S THE PURPOSE OF A REGISTRY?

- There are 2 main purposes for registries:
 - Collect basic information to connect potential subjects with clinical trials
 - Collect detailed information to learn more about a disease such as natural history or best treatments



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WHAT MAKES A GOOD REGISTRY

#1 WELL DESIGNED TECHNOLOGY

- Digital technology that allows patients to join the network and input their information in a secure, private manner
- TRiaLS is transitioning to the RedCap Platform
- The RedCap Platform provides a secure web-based location for patient information guaranteeing privacy
- It also allows for easy access of researchers to search and analyze data

WHAT MAKES A GOOD REGISTRY

#2 RECRUITMENT & PARTICIPATION

- There is a constant need for engagement with the patient community to both grow the registry membership and encourage current members to update their information
- Promotion takes a significant amount of time and effort but is critical to the success or failure of a registry
- TRiaLS utilizes the assistance of non-profit organizations such as MitoAction to assist in spreading the word on the importance of participation
- TRiaLS also sends a quarterly newsletter with useful information on the current state of Leigh syndrome to remind subjects to update their information

WHAT MAKES A GOOD REGISTRY

#3 COLLABORATION WITH RESEARCHERS

- To be effective as a data source registries must ensure that the data collected is useful
- The registry must also be able to connect their data with the appropriate researchers
- TRiaLS has a governance board composed of leaders in the field to help guide data collection and dissemination

Thank you to our governance board: Rahmat Adejumo, Amy Goldstein, Amel Karaa, Mary Kay Koenig, Lori Martin, Sumi Parikh, Phil Yeske

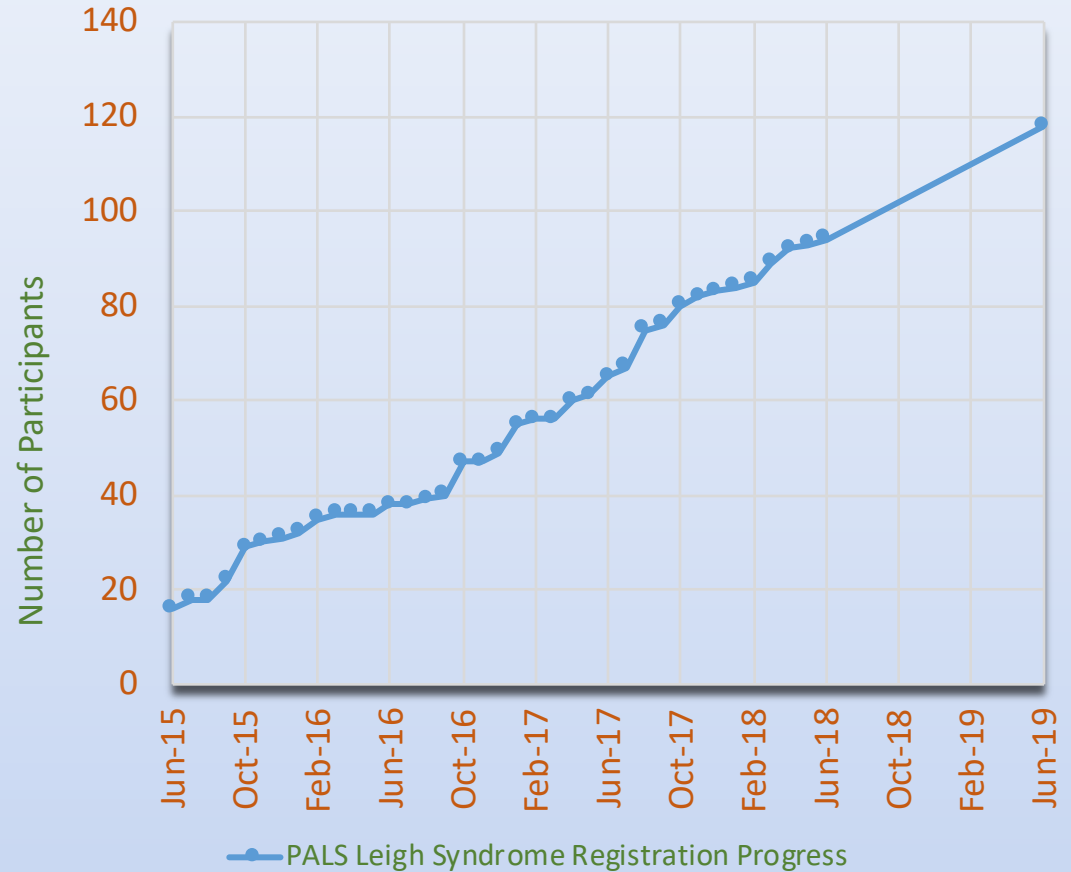
WHAT MAKES A GOOD REGISTRY

#4 PARTNERSHIPS

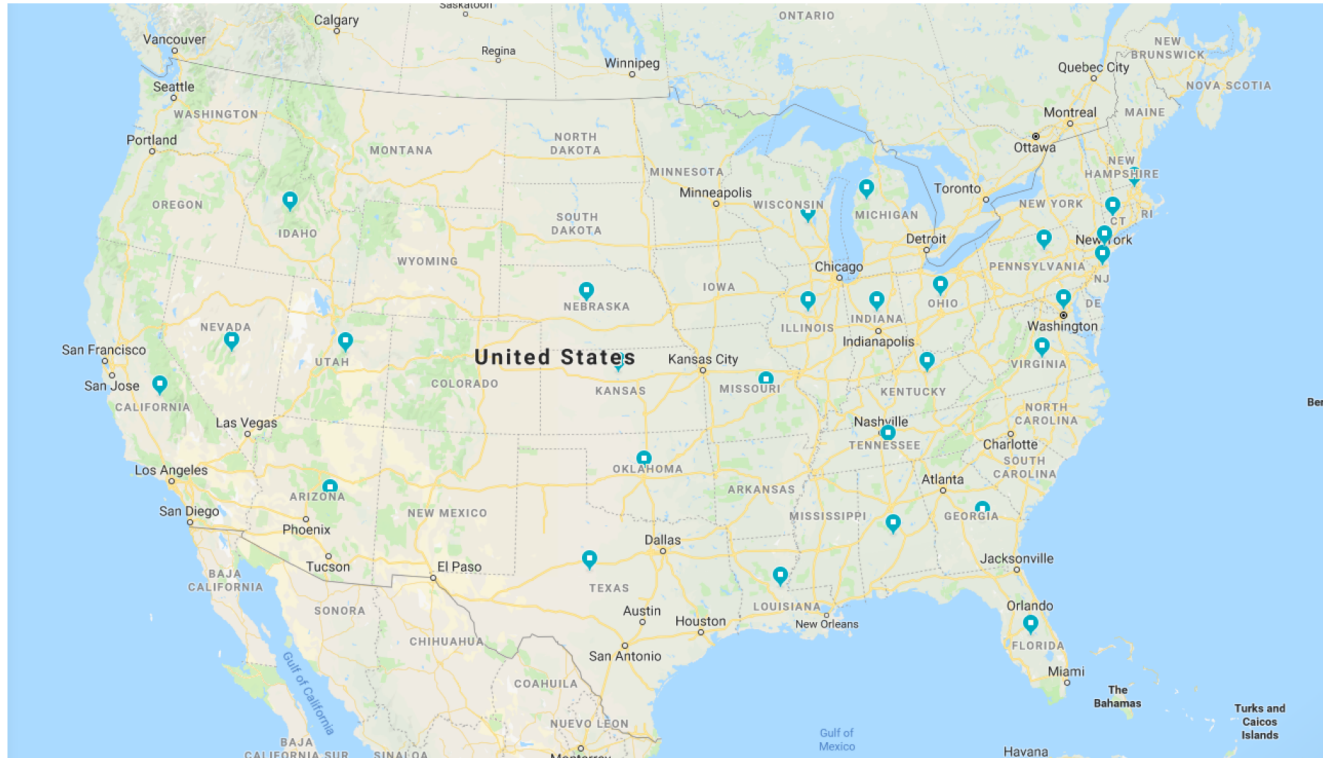
- To be successful a registry must establish collaborative relationships with similar organizations for the purpose of sharing resources, avoiding competition, and reducing the fracture of data, funds, and knowledge
- Registry competition not only increases cost it limits power by reducing the size of individual data sets decreasing our ability to draw valid conclusions for the population as a whole

So far....

- Phase I
 - Information collected
 - Contact information
 - Demographics
 - Launched June 2015

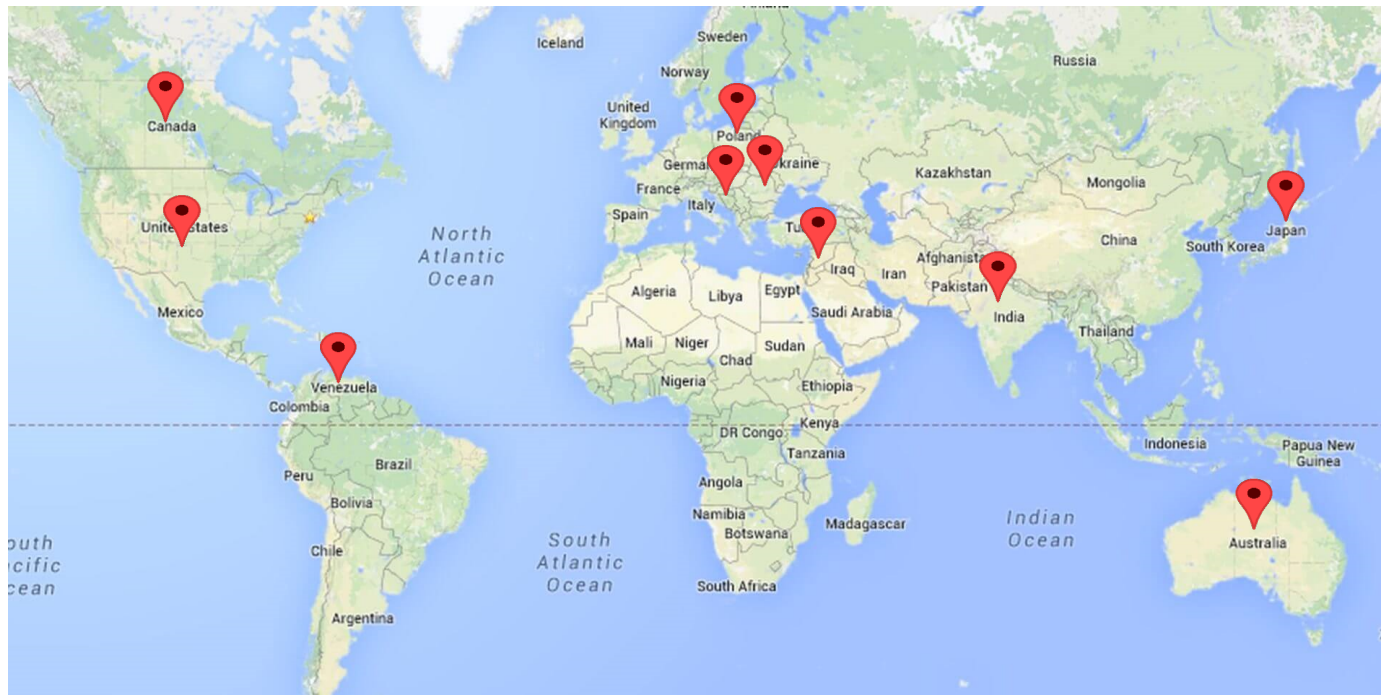


Distribution of PALS Registry participants in USA



Idaho, Nevada, Utah, California, Arizona, Texas, Oklahoma, Nebraska, Missouri, Louisiana, Alabama, Florida, Georgia, Tennessee, Kentucky, Illinois, Wisconsin, Michigan, Ohio, Indiana, Pennsylvania, Virginia, Washington DC, New Jersey, Connecticut, New York, New Hampshire

Distribution of PALS Registry participants worldwide

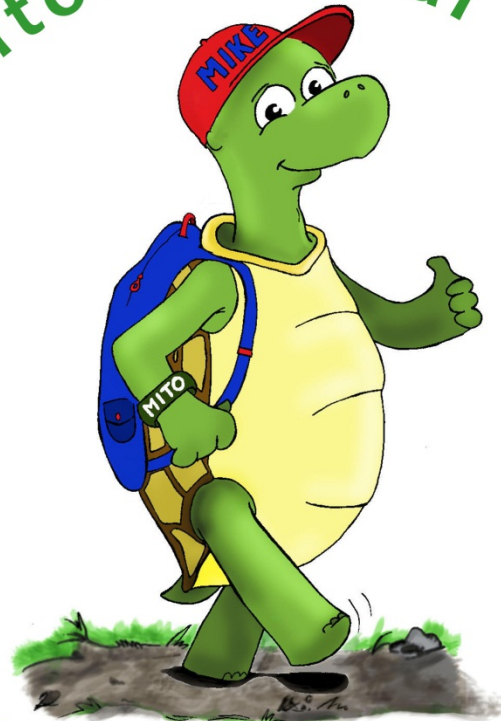


USA, Australia, Canada, Great Britain, India, Japan, Venezuela, Romania, Croatia, and Poland

Thank you 😊



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