UTHealth
The University of Texas
Health Science Center at Houston
Medical School

Children's
MEMORIAL
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Hospital

Leigh Syndrome

Mary Kay Koenig, MD
Leigh Syndrome Clinic Director
University of Texas Medical School at Houston

UT Mitochondrial
Center of Excellence

Dr. Denis Archibald Leigh

- Received his medical degree in 1947
- Served as a military medical officer and Consultant to the British Army until 1980
- Specialized training in neurology but focused his career in psychiatry

Dr. Denis Archibald Leigh

- In 1951 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”

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 the age of 5 months when he:
  - stopped crying
  - became very still
  - stopped sucking
  - slept for long periods

SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY IN AN INFANT

BY

DENIS LEIGH

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***

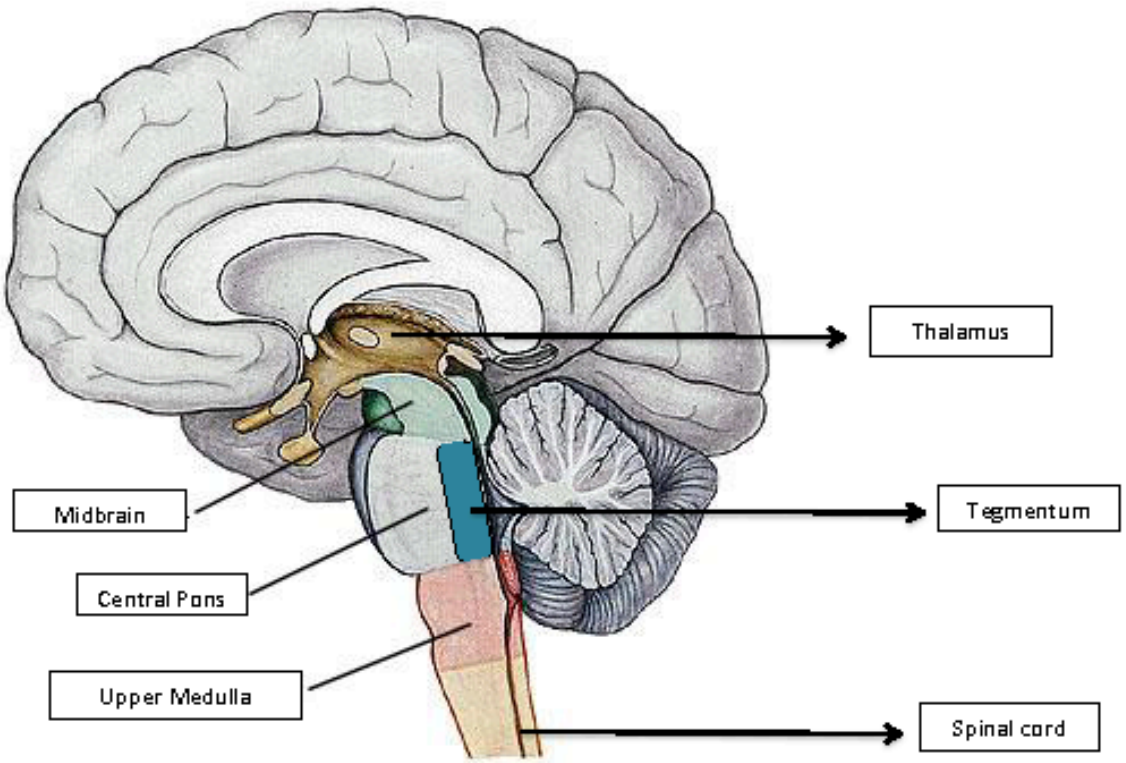
SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY IN AN INFANT

BY

DENIS LEIGH

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

- Postmortem examination demonstrated ***bilateral symmetric necrotic lesions*** in the brain and spinal cord



Evolution of Leigh Disease

- Over 50 additional cases were described from 1951 through 1977
- Each case was diagnosed ***postmortem*** via pathologic examination

Evolution of Leigh Disease

- As more cases were described, the clinical picture became more clear
- Children had ***normal early development*** followed by subacute onset of:
  - feeding difficulties
  - psychomotor retardation
  - disturbances in the state of consciousness
  - abnormalities of eye movements
  - ataxia
  - muscular weakness
- Although the disease ***begins insidiously,*** the patient's condition ***deteriorates rapidly*** with children dying from ***acute respiratory failure***

Evolution of Leigh Disease

- In the late 1960's there were more frequent descriptions of juveniles and adults with the pathologic features of Leigh's disease and patients were divided into 3 categories:

Infantile onset

- onset < 1 year of age
- death by 2 years

Juvenile onset

- onset after 4 years
- death in 5-10 years

Adult onset

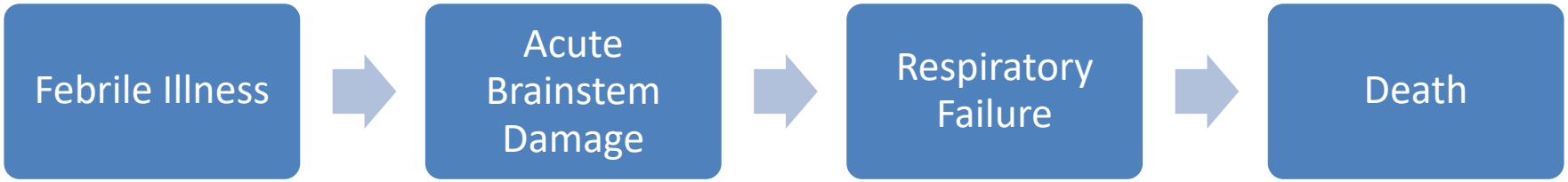
- onset >18 years
- sudden death secondary to respiratory failure

Evolution of Leigh Disease

- In the 1970's, the etiology remained elusive however the ***suspicion for a metabolic derangement*** persisted and reports began describing ***lactic acidosis*** in patients

Evolution of Leigh Disease

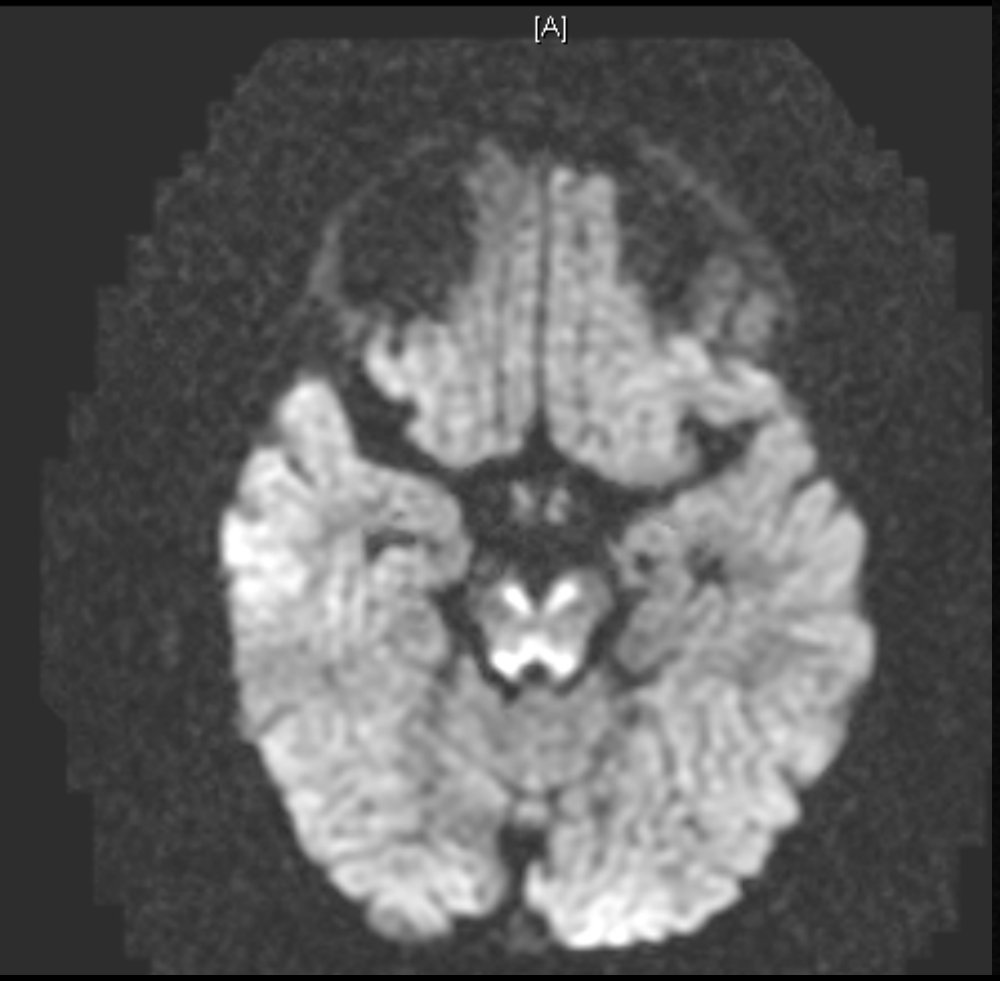
- The association between febrile illness, acute brainstem damage, and respiratory failure also became more clear

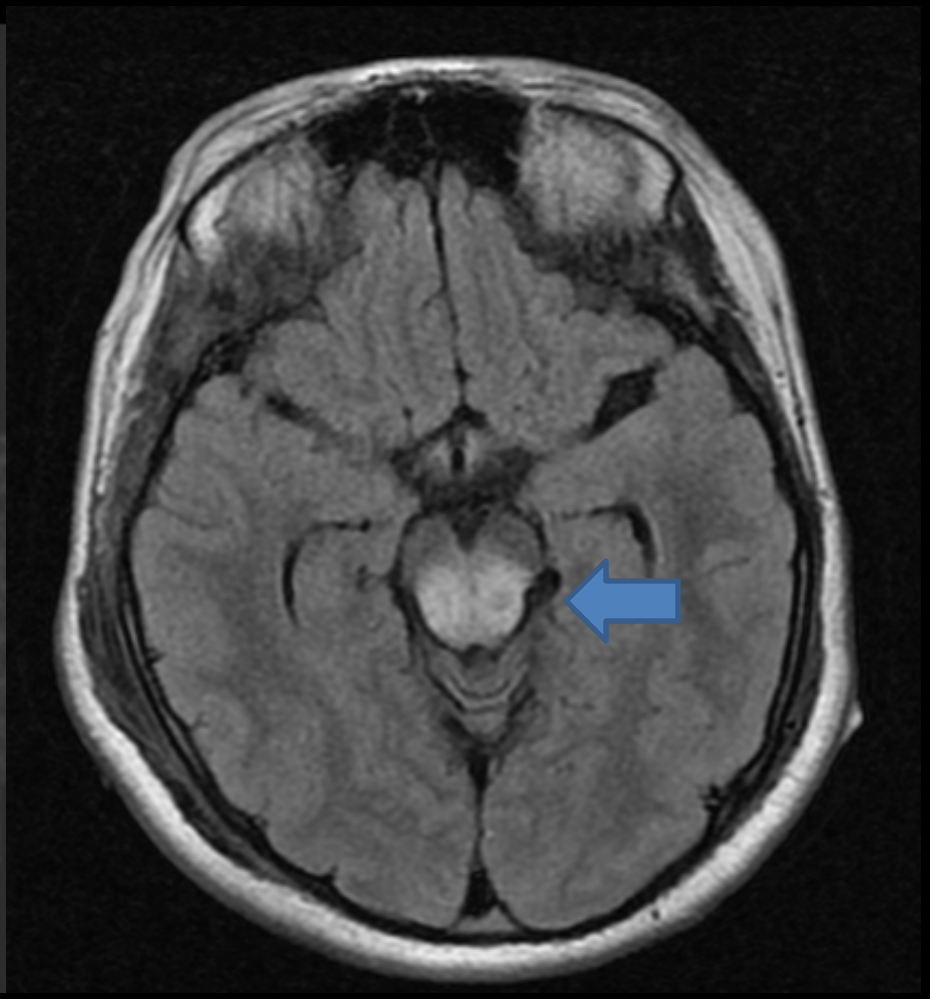


Pre-Mortem Diagnosis

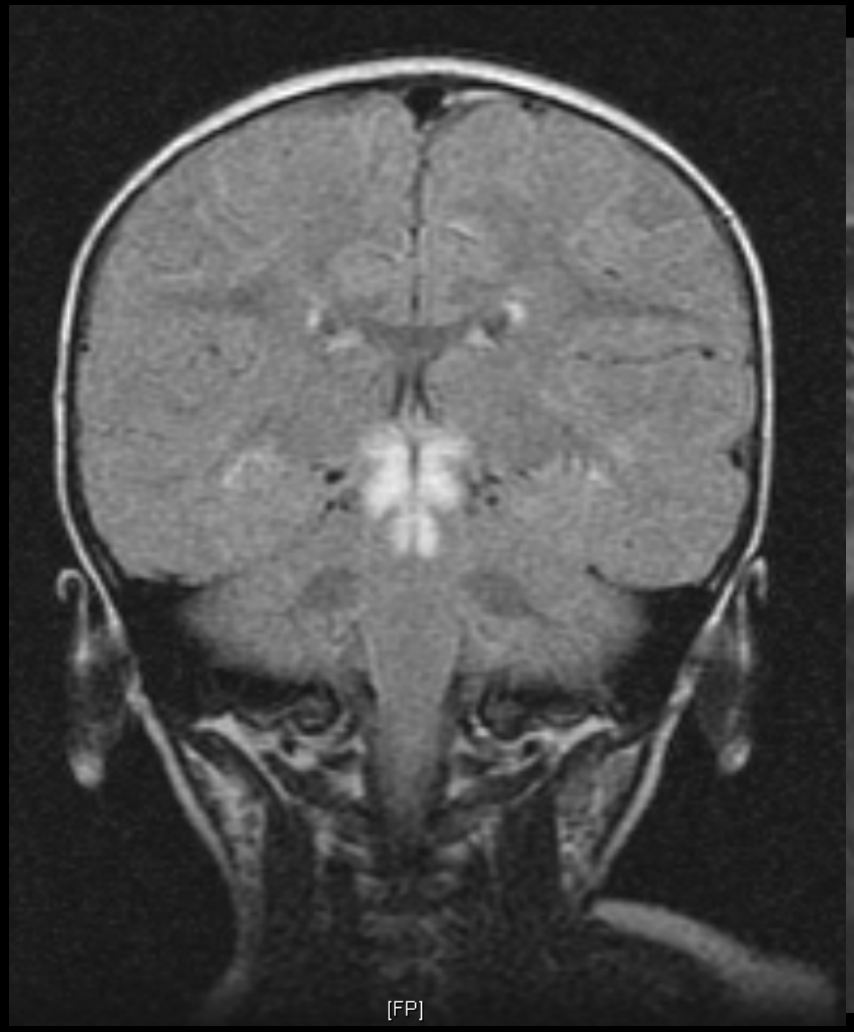
- Prior to the availability of magnetic resonance imaging, diagnosis remained exclusively pathologic, ie, made on postmortem examination
- ***MRI became available in the 1980's*** shifting Leigh's disease to a diagnosis that could be made pre-mortem through clinical findings

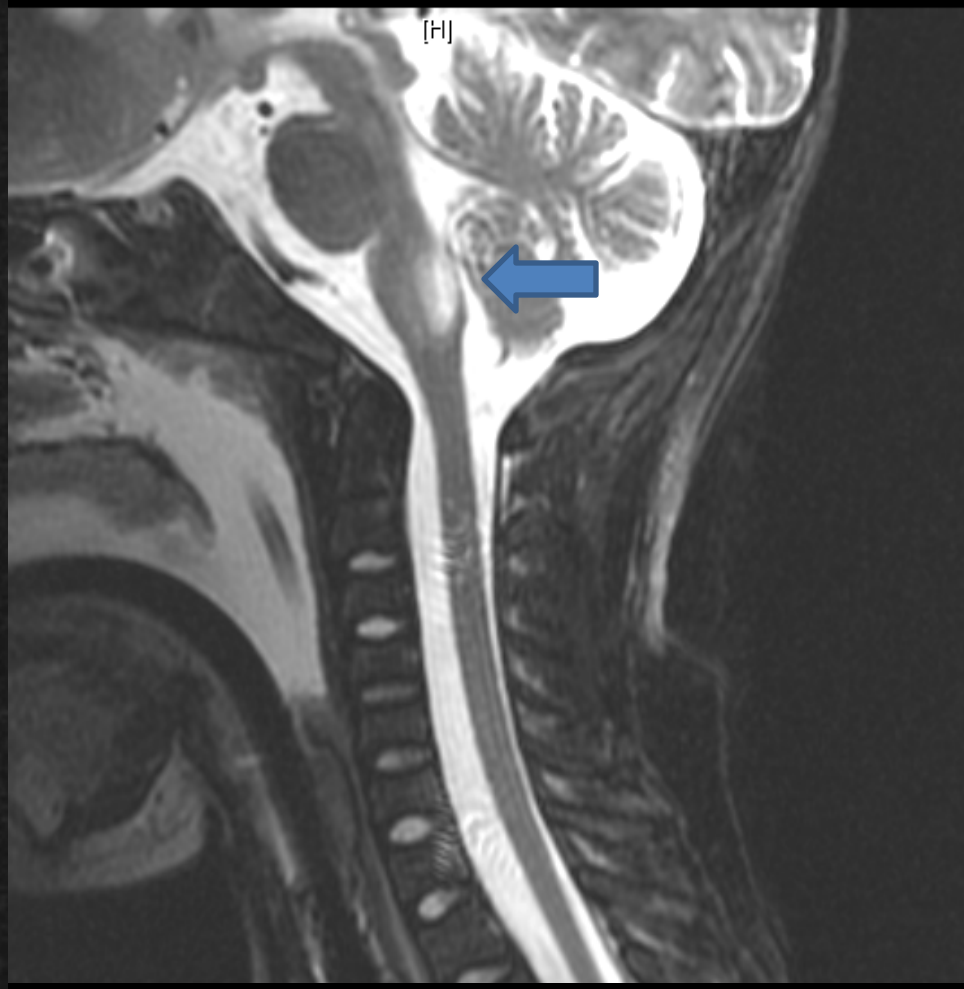
MRI Imaging in Leigh Syndrome
Midbrain



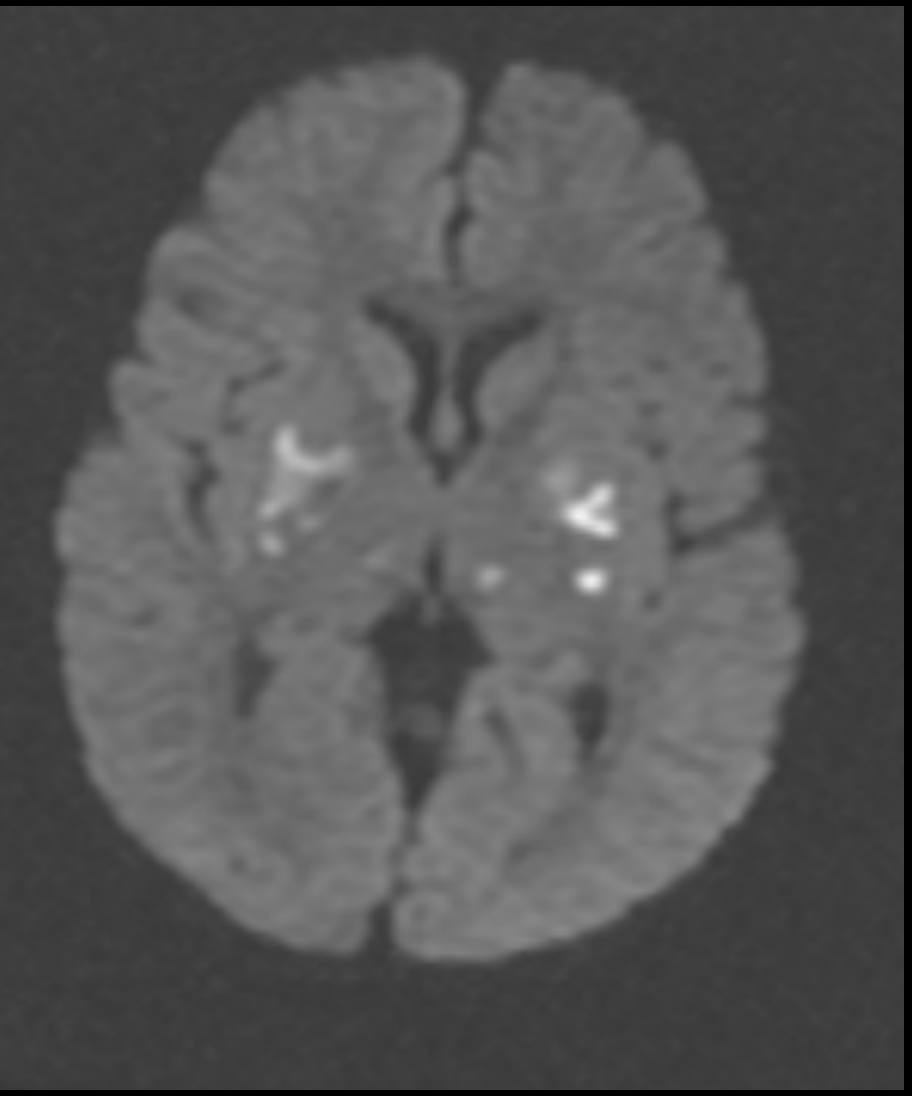


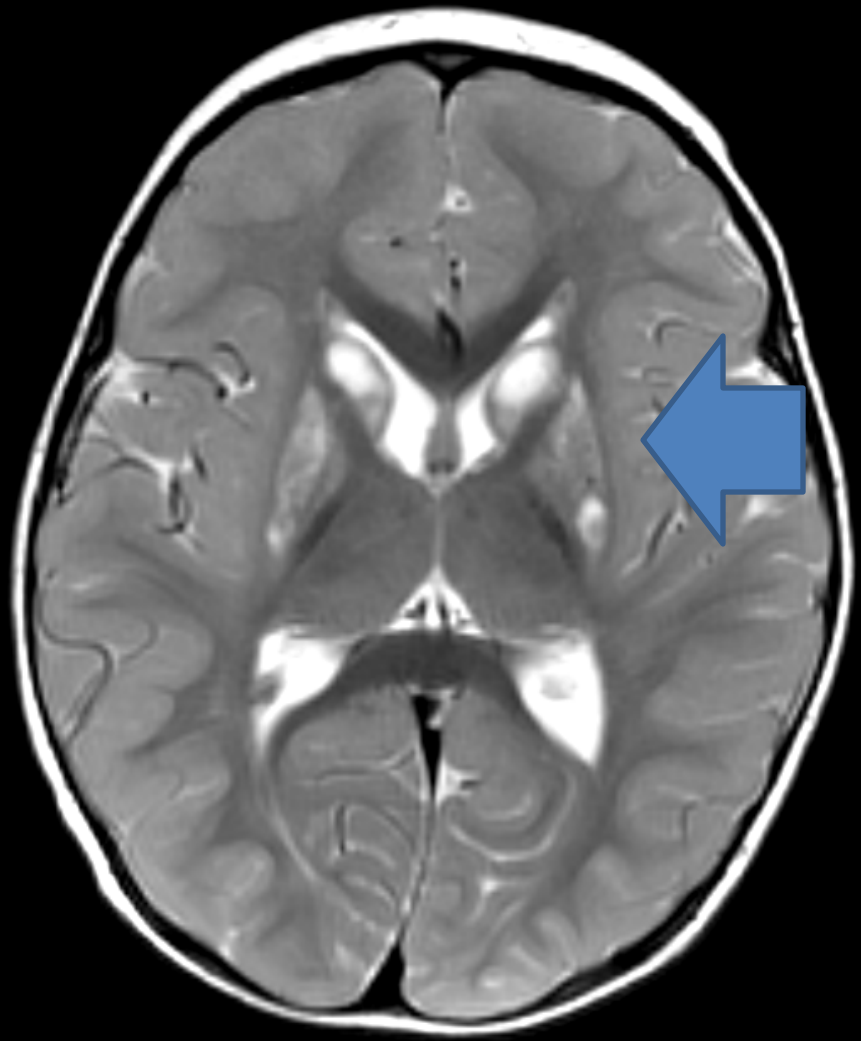
MRI Imaging in Leigh Syndrome
Lower Brainstem/Pons



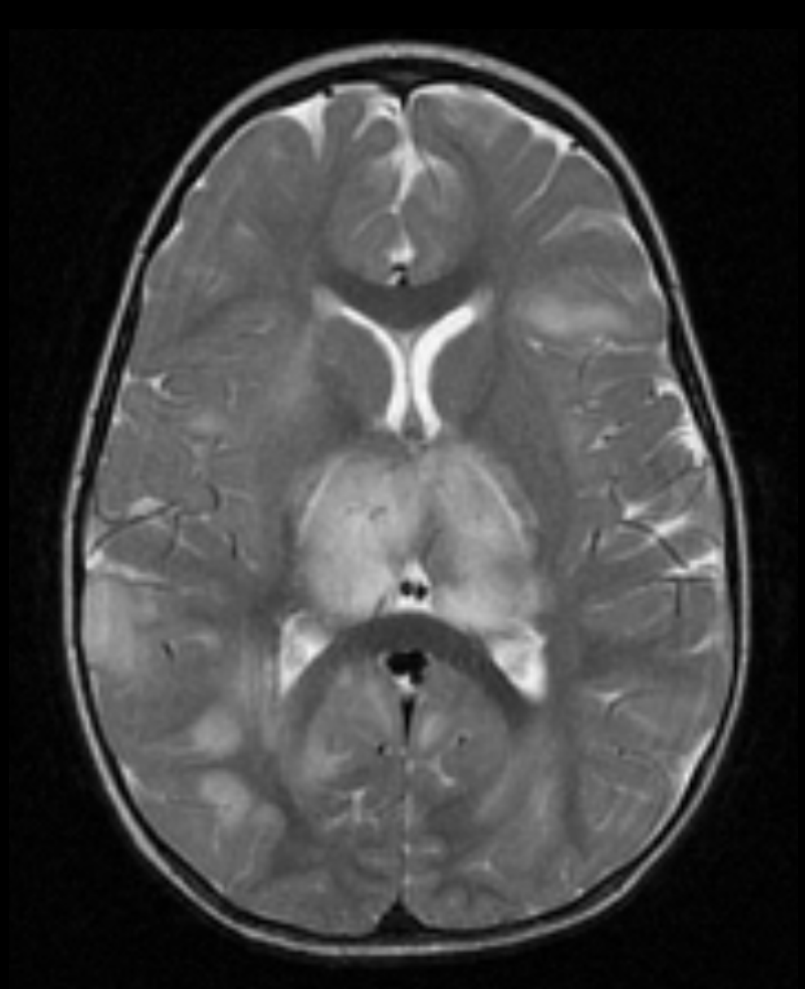


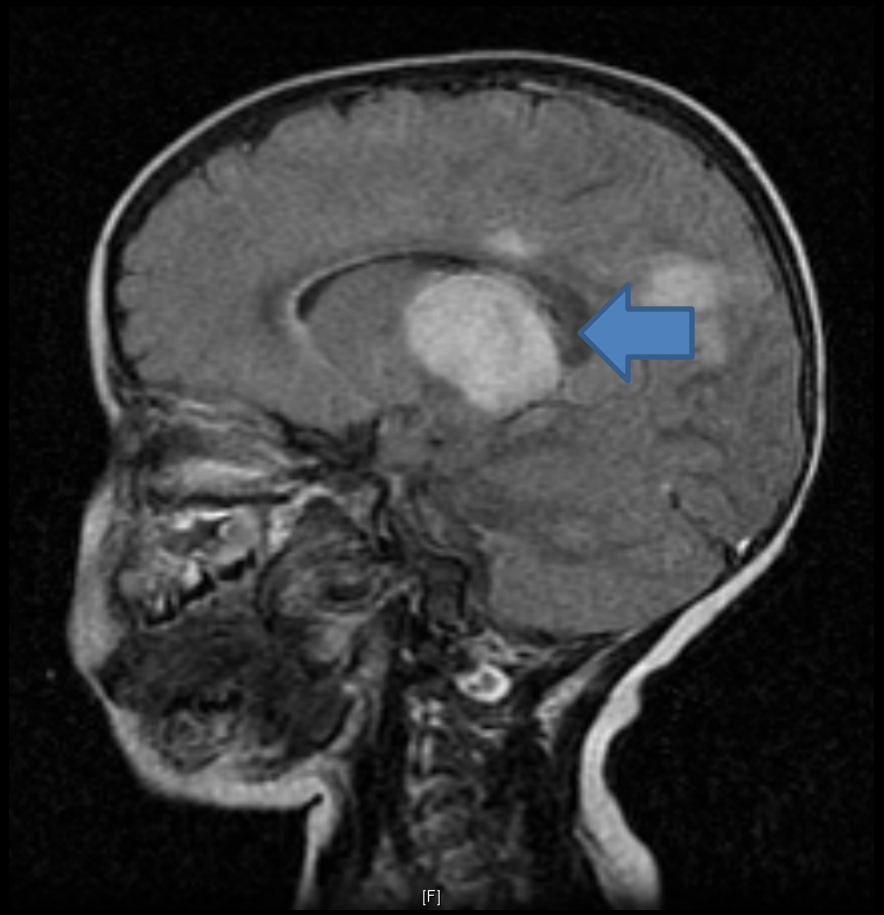
MRI Imaging in Leigh Syndrome
Basal Ganglia



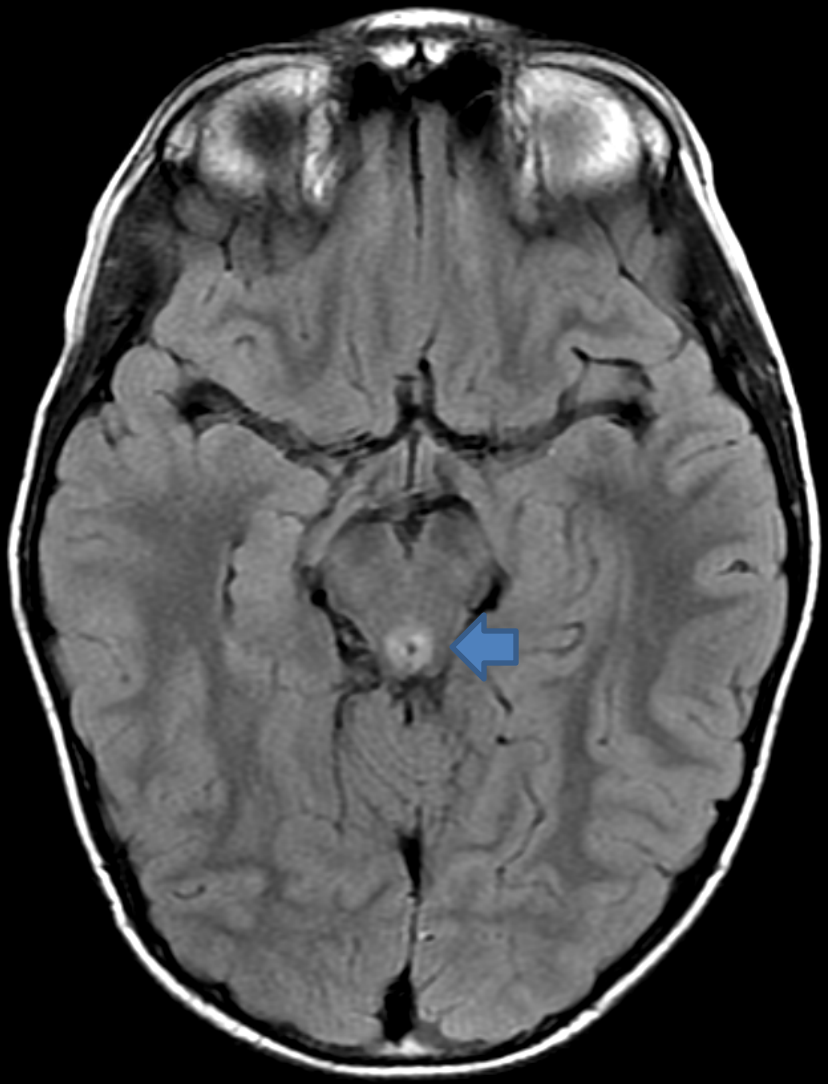


MRI Imaging in Leigh Syndrome Thalamus

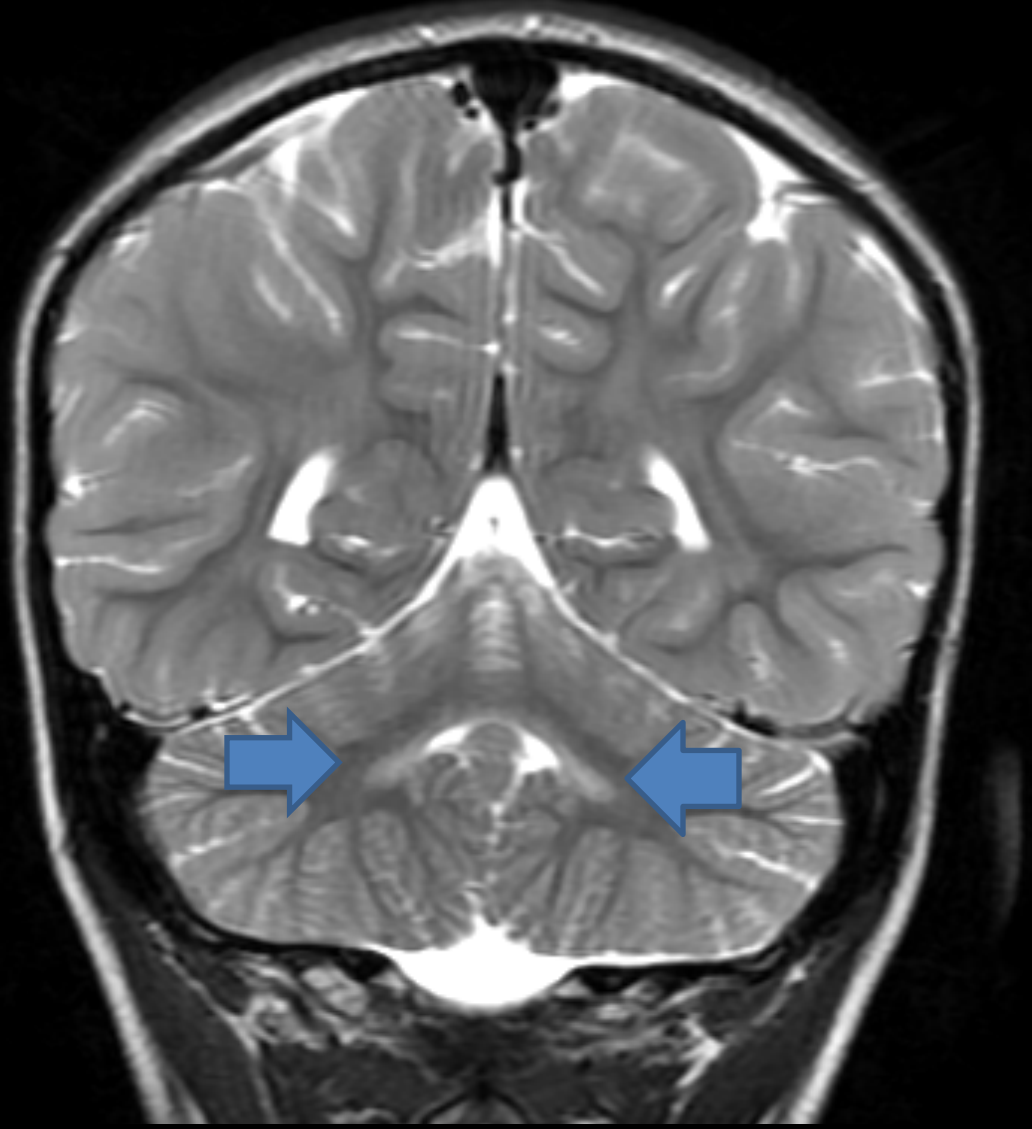




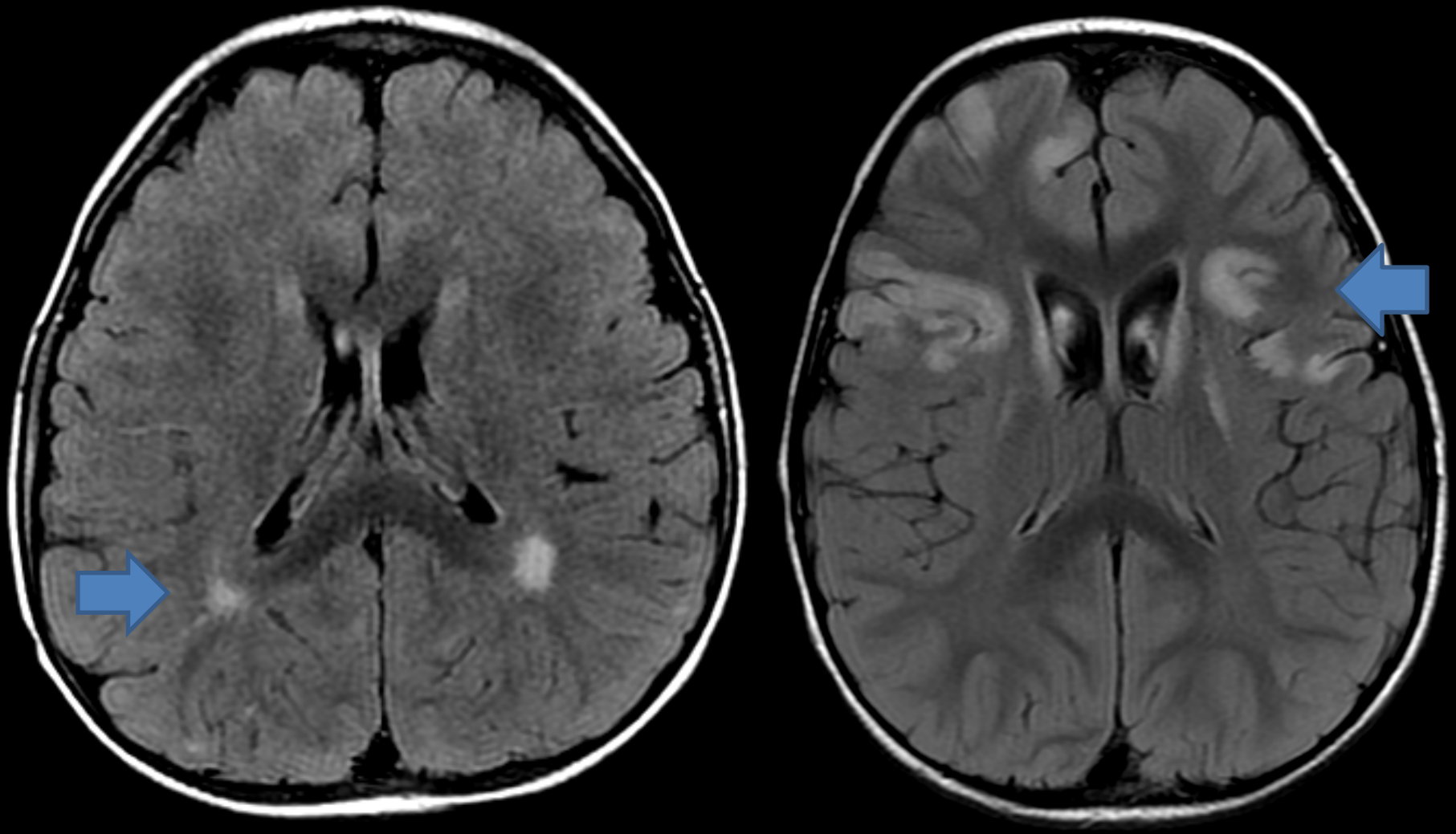
MRI Imaging in Leigh Syndrome
Periacqueductal Gray Matter



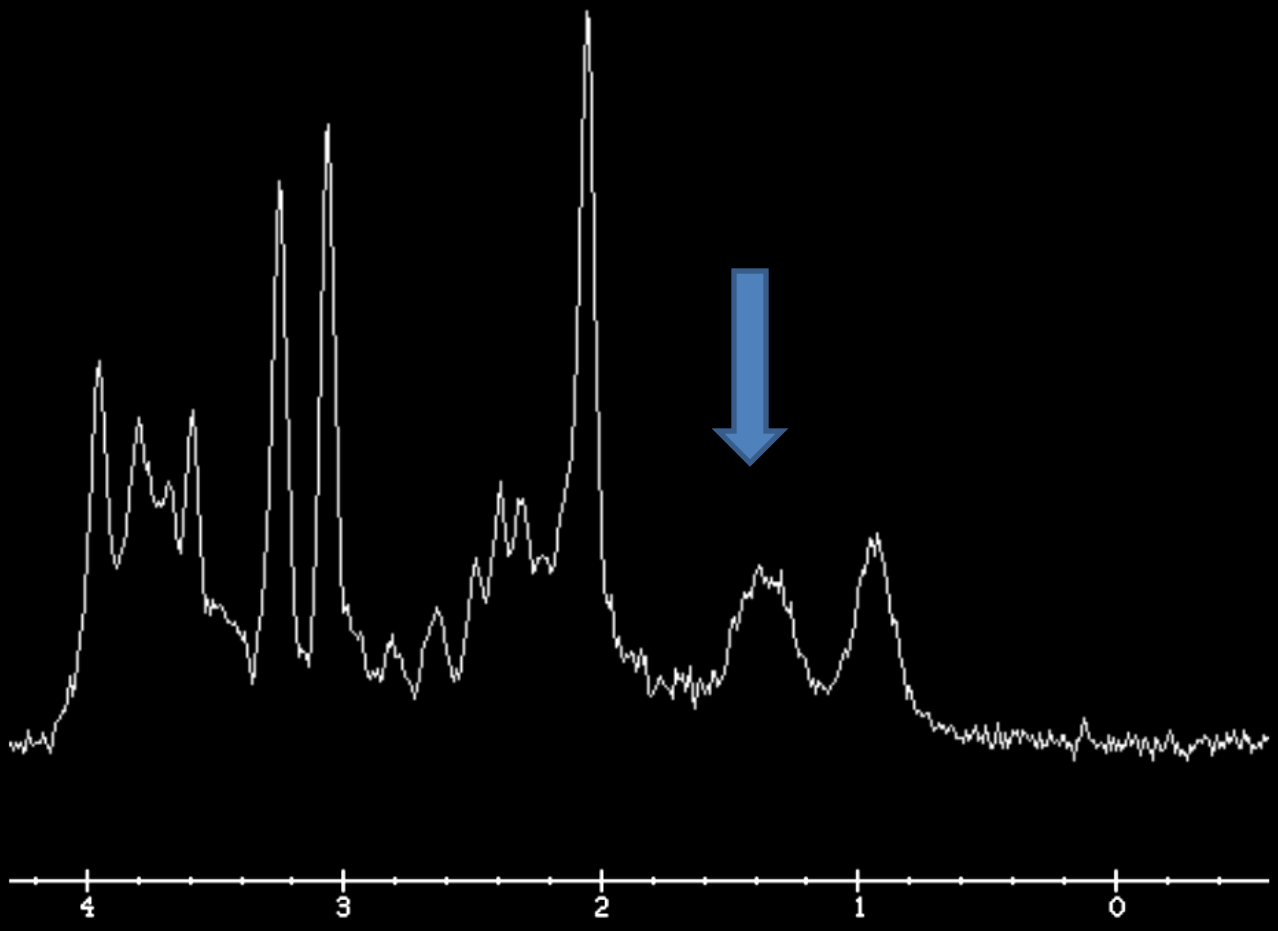
MRI Imaging in Leigh Syndrome Cerebellum



MRI Imaging in Leigh Syndrome
White Matter



Spectroscopy



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
  - onset is followed by rapid deterioration

Leigh's Encephalomyelopathy in a Patient With Cytochrome c Oxidase Deficiency in Muscle Tissue

J. L. Willems, Ph.D., L. A. H. Monnens, M.D., J. M. F. Trijbels, Ph.D., J. H. Veerkamp, Ph.D., A. E. F. H. Meyer, M.D., K. van Dam, Ph.D., *and* U. van Haelst, M.D.

From the Departments of Pediatrics, Biochemistry, and Pathology, University of Nijmegen, and the Departments of Pathology and Biochemistry, University of Amsterdam, The Netherlands

- Even as the clinical picture became more concrete, the etiology remained elusive
- 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, ***this suggestion was widely disregarded***

Defective activation of the pyruvate dehydrogenase complex in subacute necrotizing encephalomyelopathy (leigh disease)

Dr Darryl C. Devivo MD, Morey W. Haymond MD, Kathleen A. Obert BS, James S. Nelson MD, and Anthony S. Pagliara MD[1,2]

Annals of Neurology
Volume 6, Issue 6, pages 483–494, December 1979

- 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 involving dietary modification that is widely used today
- ***PDH remained the suspected cause of Leigh syndrome from 1979 until 1992***

Leigh Encephalopathy: Histologic and Biochemical Analyses of Muscle Biopsies

Toshiro Nagai, MD*†, Yu-ichi Goto, MD*, Taro Matsuoka, MD*, Ryouichi Sakuta, MD*, Etsuo Naito, MD‡, Yasuhiro Kuroda, MD‡, and Ikuya Nonaka, MD*

- 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***
- His paper suggested that the biochemical defects in Leigh's are heterogenous and that the etiology may also be heterogenous

Genetics

- 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 **heterogenous group of disorders** caused by multiple different metabolic derangements affecting terminal oxidative metabolism and impairing energy production

Table 2. Mutations in mitochondrial genes causing maternally inherited Leigh syndrome

Mutation	ML (%)	Gene	NOP
3460G>A	Homoplasmic	*ND1*	1 patient
4681T>C	Na	*ND2*	1 patients
10158T>C	85	*ND3*	2 patients
10191T>C	80-90	*ND3*	2 patients
10191T>C	Na	*ND3*	1 patient
10191T>C	>98	*ND3*	1 patient
10191T>C	50	*ND3*	1 patient
10197G>A	Variable	*ND3*	3 pedigrees
11984T>C	Na	*ND4*	1 patient
12706T>G	>90	*ND5*	1 patient
12706T>C	60	*ND5*	1 patient
12706T>C	43	*ND5*	1 patient
12706T>C	Na	*ND5*	1 patient
13511A>T	Low	*ND5*	1 patient
13513G>A	50	*ND5*	3 patients
13513G>A	90	*ND5*	1 patient
13513G>A	42-70	*ND5*	6 patients
13513G>A	Na	*ND5*	2 patients
13514A>G	90	*ND5*	1 patient
14459G>A	>95	*ND6*	1 patient
14459G>A	40	*ND6*	1 patient
14484T>C	70	*ND6*	1 patient
14487T>C	80	*ND6*	1 patient
14487T>C	95	*ND6*	1 patient
14487T>C	86	*ND6*	2 patients
14600G>A	Homoplasmic	*ND6*	1 patient
9537Cins	Homoplasmic	*COX III*	1 patient
9547G>A	Na	*COX III*	1 patient

8993T>C	Na	*ATPase6*	1 pedigree
8993T>C	19-95	*ATPase6*	6 pedigrees
8993T>C	>95	*ATPase6*	1 patient
8993T>C	Na	*ATPase6*	1 patient
8993T>C	>95	*ATPase6*	2 patients
8993T>C	Na	*ATPase6*	2 patients
8993T>C	Variable	*ATPase6*	56 pedigrees
8993T>C	Na	*ATPase6*	1 patient
8993T>G	95-99	*ATPase6*	1 patient
8993T>G	Na	*ATPase6*	1 patient
8993T>G	53-91	*ATPase6*	1 pedigree
8993T>G	Na	*ATPase6*	1 patient
8993T>G	90-98	*ATPase6*	1 patient
8993T>G	Variable	*ATPase6*	56 pedigrees
8993T>G	Na	*ATPase6*	1 patient
8993	0-95	*ATPase6*	3 pedigrees
9176T>C	Homoplasmic	*ATPase6*	1 patient
9176T>C	Homoplasmic	*ATPase6*	1 patient
9176T>G	>95	*ATPase6*	2 patients
9185T>C	>90	*ATPase6*	Several
1644G>T	Na	*tRNA(Val)*	1 pedigree
8344A>G	Na	*tRNA(Lys)*	1 pedigree
8344A>G	Na	*tRNA(Lys)*	2 patients
8344A>G	Na	*tRNA(Lys)*	Na
8344A>G	Na	*tRNA(Lys)*	1 patient
8344G>A	Na	*tRNA(Lys)*	56 pedigrees
3537Tins	>92	*tRNA(Trp)*	1 pedigree
3243A>G	Na	*tRNA*	1 patient
3243A>G	Na	*tRNA*	1 patient
3243A>G	Na	*tRNA*	1 patient
3243A>G	Variable	*tRNA*	56 pedigrees
8363G>A	Na	*tRNA(Lys)*	1 patient

Table 3. Mutations in genes of nuclear genome (nDNA) causing Leigh syndrome or Leigh-like syndrome

Mutation/Gene	Protein	NOP
Complex I		
NDUFS1	RC I subunit	2
NDUFV1	RC I subunit	3
NDUFV1	RC I subunit	1
NDUFV2	RC I subunit	Series
NDUFS1, NDUFV1	RC I subunit	6
NDUFS2	RC 1 subunit	Three families
NDUFS3	RC 1 subunit	1?
NDUFS4 (AQDQ)	RC I subunit	1
NDUFS4 (AQDQ)	RC I subunit	3
NDUFS4 (AQDQ)	RC I subunit	1
NDUFS7	Assembly factor	2
NDUFS8	TYKY subunit of complex I	1
Complex II		
SDHA	Succinate dehydrogenase	1
SDH	Flavoprotein subunit	1
SDH	Flavoprotein subunit	1
Complex IV		
COX15	Enzyme for hem synthesis	1
SURF1	Assembly factor	24
SURF1	Assembly factor	8 families
SURF1	Assembly factor	1
SURF1	Assembly factor	1
SURF1	Assembly factor	1
SURF1	Assembly factor	1

SURF1	Assembly factor	3
SURF1	Assembly factor	7
SURF1	Assembly factor	3
SURF1	Assembly factor	1
SURF1	Assembly factor	25
SURF1	Assembly factor	2
SURF1	Assembly factor	1 family
SURF1	Assembly factor	43
SURF1	Assembly factor	1
Coenzyme Q		
CoQ	CoQ	1
PDSS2	CoQ	1
Pyruvate dehydrogenase complex		
PDHc	E1 alpha-subunit (X-chrom)	
PDHc	E1alpha subunit	6
PDHc	E1alpha subunit	1
PDHX1	E3 binding protein	1
Others		
EFG1	Elongation factor G1	1
EFTu	Elongation factor Tu	1
LRP130	Transcriptional coactivator	0
SUCLA2	Succinyl-CoA ligase*	12
BTD	Biotinidase	1

Leigh's Disease vs. Leigh Syndrome

- As the concept of a heterogenous 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)

Prognosis

- The outcome of Leigh syndrome remains poor
- ***The majority of affected individuals die from sudden respiratory failure***
- 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

Leigh Syndrome: Serial MR Imaging and Clinical Follow-up

Junko Arii and Yuzo Tanabe

- In ***2000***, Arii et.al. investigated ***8 patients*** with Leigh syndrome (3 months to 12 years of age) to determine if respiratory failure could be predicted on the basis of clinical characteristics or findings on longitudinal MR 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

Treatment

- To date there exist no good treatment options for patients with Leigh syndrome
- A multitude of OXPHOS cofactors and antioxidants are prescribed secondary to their potential benefits however, ***no definitive trials*** have been published demonstrated clear evidence for clinical improvement in patients
  - CoQ10
  - Alpha-lipoiic acid
  - Biotin
  - Riboflavin
  - L-carnitine
  - Creatine
  - Thiamine

Treatment

- Newly diagnosed patients should all receive a trial of high dose biotin (10-20 mg/kg) and thiamine (100-300 mg) in case they have biotin responsive basal ganglia disease (BBGD)
- Malnutrition should be corrected
- Ketogenic diet in PDH deficiency

Proton magnetic resonance spectroscopy to study the metabolic changes in the brain of a patient with Leigh syndrome

Satoru Takahashi*, Junichi Oki, Akie Miyamoto, Akimasa Okuno

Department of Pediatrics, Asahikawa Medical College, 4-5-3-11 Nishikagura, Asahikawa 078-8510, Japan

- 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

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

Short communication

Efficacy of idebenone for respiratory failure in a patient with Leigh syndrome: A long-term follow-up study

Kazuhiro Haginoya [a,b,*], Shigeaki Miyabayashi [c], Masahiro Kikuchi [d], Akira Kojima [e], Katsuya Yamamoto [f], Kiyoshi Omura [g], Mitsugu Uematsu [b], Naomi Hino-Fukuyo [b], Soichiro Tanaka [a], Shigeru Tsuchiya [b]

- ***Idebenone*** is a synthetic analog of CoQ10 with improved absorption and bioavailability
- Haginoya reported a case in ***2009*** 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
- ***No follow-up studies have been performed***

Beneficial effect of pyruvate therapy on Leigh syndrome due to a novel mutation in PDH E1α gene

Yasutoshi Koga [a,*], Nataliya Povalko [a], Koujyu Katayama [a], Noriko Kakimoto [a], Toyojiro Matsuishi [a], Etsuo Naito [b], Masashi Tanaka [c]

[a] *Department of Pediatrics and Child Health, Kurume University Graduate School of Medicine, 67 Asahi Machi, Kurume, Fukuoka 830-0011, Japan*
[b] *Department of Pediatrics, School of Medicine, Tokushima University, Tokushima 770-8501, Japan*
[c] *Department of Genomics for Longevity and Health, Tokyo Metropolitan Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015, Japan*

- 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 that evolved to Lennox-Gastaut syndrome
- At 18 months of age, the child was started on sodium pyruvate

Beneficial effect of pyruvate therapy on Leigh syndrome due to a novel mutation in PDH E1α gene

Yasutoshi Koga [a,*], Nataliya Povalko [a], Koujyu Katayama [a], Noriko Kakimoto [a], Toyojiro Matsuishi [a], Etsuo Naito [b], Masashi Tanaka [c]

[a] Department of Pediatrics and Child Health, Kurume University Graduate School of Medicine, 67 Asahi Machi, Kurume, Fukuoka 830-0011, Japan
[b] Department of Pediatrics, School of Medicine, Tokushima University, Tokushima 770-8501, Japan
[c] Department of Genomics for Longevity and Health, Tokyo Metropolitan Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015, Japan

- Lactate, pyruvate, and alanine levels decreased significantly
- There were no adverse effects
- Development began to occur with the child rolling over and smiling 3 months after initiation of therapy
- 6 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***

EPI-743 reverses the progression of the pediatric mitochondrial disease—Genetically defined Leigh Syndrome

Diego Martinelli [a], Michela Catteruccia [b], Fiorella Piemonte [b], Anna Pastore [a], Giulia Tozzi [b], Carlo Dionisi-Vici [a], Giuseppe Pontrelli [c], Tiziana Corsetti [d], Susanna Livadiotti [c], Viktoria Kheifets [e], Andrew Hinman [e], William D. Shrader [e], Martin Thoolen [e], Matthew B. Klein [e], Enrico Bertini [b], Guy Miller [e,f,*]

- A study from Italy investigated the use of ***EPI-743*** in children with Leigh syndrome
- All exhibited a reversal of disease progression regardless of the genetic determinant or disease severity
- There were no significant drug-related adverse events reported
- Treatment was for an average of 5 months

Treatment

- 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

Science
AAAS

mTOR Inhibition Alleviates Mitochondrial Disease in a Mouse Model of Leigh Syndrome

Simon C. Johnson *et al.*
Science **342**, 1524 (2013);
DOI: 10.1126/science.1244360

- Johnson et.al. administered a medicine called ***rapamycin*** to mice with Leigh syndrome
- The rapamycin treated mice demonstrated
  - delayed onset of neurological symptoms
  - reduced neuroinflammation and
  - a lack of development of the characteristic brain lesions
- The mechanism of rescue remains unknown

Current Understanding

A multicenter study on Leigh syndrome: disease course and predictors of survival

Kalliopi Sofou[1*], Irenaeus F M De Coo[2], Pirjo Isohanni[3,4], Elsebet Ostergaard[5], Karin Naess[6], Linda De Meirleir[7], Charalampos Tzoulis[8,9], Johanna Uusimaa[10,11], Isabell B De Angst[2], Tuula Lönnqvist[3], Helena Pihko[3], Katariina Mankinen[12], Laurence A Bindoff[8,9], Már Tulinius[1] and Niklas Darin[1]

- Natural history study of 130 patients with clinically defined Leigh syndrome
- Symmetrical lesions in one or more areas of the CNS including the basal ganglia, diencephalon, brainstem, cerebellum, and spinal cord

A multicenter study on Leigh syndrome: disease course and predictors of survival

Kalliopi Sofou[1*], Irenaeus F M De Coo[2], Pirjo Isohanni[3,4], Elsebet Ostergaard[5], Karin Naess[6], Linda De Meirleir[7], Charalampos Tzoulis[8,9], Johanna Uusimaa[10,11], Isabell B De Angst[2], Tuula Lönnqvist[3], Helena Pihko[3], Katariina Mankinen[12], Laurence A Bindoff[8,9], Már Tulinius[1] and Niklas Darin[1]

- Onset typically occurs between 3 and 12 months of age with disease progression and death within 2 years
  - Later onset and slower progression have been reported
- CNS:
  - motor delay
  - hypotonia
  - dyskinesia
  - ataxia
  - cognitive impairment and/or progressive cognitive decline
  - akinesia
  - dystonia
  - brainstem dysfunction: respiratory abnormalities, swallowing dysfunction, ophthalmological manifestations, and abnormal thermoregulation

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Kalliopi Sofou[1*], Irenaeus F M De Coo[2], Pirjo Isohanni[3,4], Elsebet Ostergaard[5], Karin Naess[6], Linda De Meirleir[7], Charalampos Tzoulis[8,9], Johanna Uusimaa[10,11], Isabell B De Angst[2], Tuula Lönnqvist[3], Helena Pihko[3], Katariina Mankinen[12], Laurence A Bindoff[8,9], Már Tulinius[1] and Niklas Darin[1]

- Inherited as mitochondrial, X-linked, or autosomal recessive
- Slight male preponderance (78/52)
- Parental consanguinity in 31 patients
- 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

A multicenter study on Leigh syndrome: disease course and predictors of survival

Kalliopi Sofou[1*], Irenaeus F M De Coo[2], Pirjo Isohanni[3,4], Elsebet Ostergaard[5], Karin Naess[6], Linda De Meirleir[7], Charalampos Tzoulis[8,9], Johanna Uusimaa[10,11], Isabell B De Angst[2], Tuula Lönnqvist[3], Helena Pihko[3], Katariina Mankinen[12], Laurence A Bindoff[8,9], Már Tulinius[1] and Niklas Darin[1]

- **Extra-CNS findings that occur with Leigh syndrome:**
  - Polyneuropathy
  - Myopathy
  - Diabetes
  - Short stature
  - Hypertrichosis
  - Cardiomyopathy
  - Anemia
  - Sleep disturbances
  - Renal failure
  - GI dysfunction
  - Failure to thrive
  - Hearing loss
  - Retinintis pigmentosa
  - Cranial nerve palsies
  - Scoliosis

A multicenter study on Leigh syndrome: disease course and predictors of survival

Kalliopi Sofou[1*], Irenaeus F M De Coo[2], Pirjo Isohanni[3,4], Elsebet Ostergaard[5], Karin Naess[6], Linda De Meirleir[7], Charalampos Tzoulis[8,9], Johanna Uusimaa[10,11], Isabell B De Angst[2], Tuula Lönnqvist[3], Helena Pihko[3], Katariina Mankinen[12], Laurence A Bindoff[8,9], Már Tulinius[1] and Niklas Darin[1]

- 25% of patients had normal lactate levels
- Only 44% had abnormal muscle histology
- 70% had abnormal ETC analysis
- Genetic etiology was confirmed in 59%
  - 38% with nDNA
  - 21% with mtDNA

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- The median age at death was 2.4 years (range from 1 month to 21 years)
- The elapsed median time from onset to death was 1.8 years
- ***Main cause of death was respiratory complications (51.0%)***

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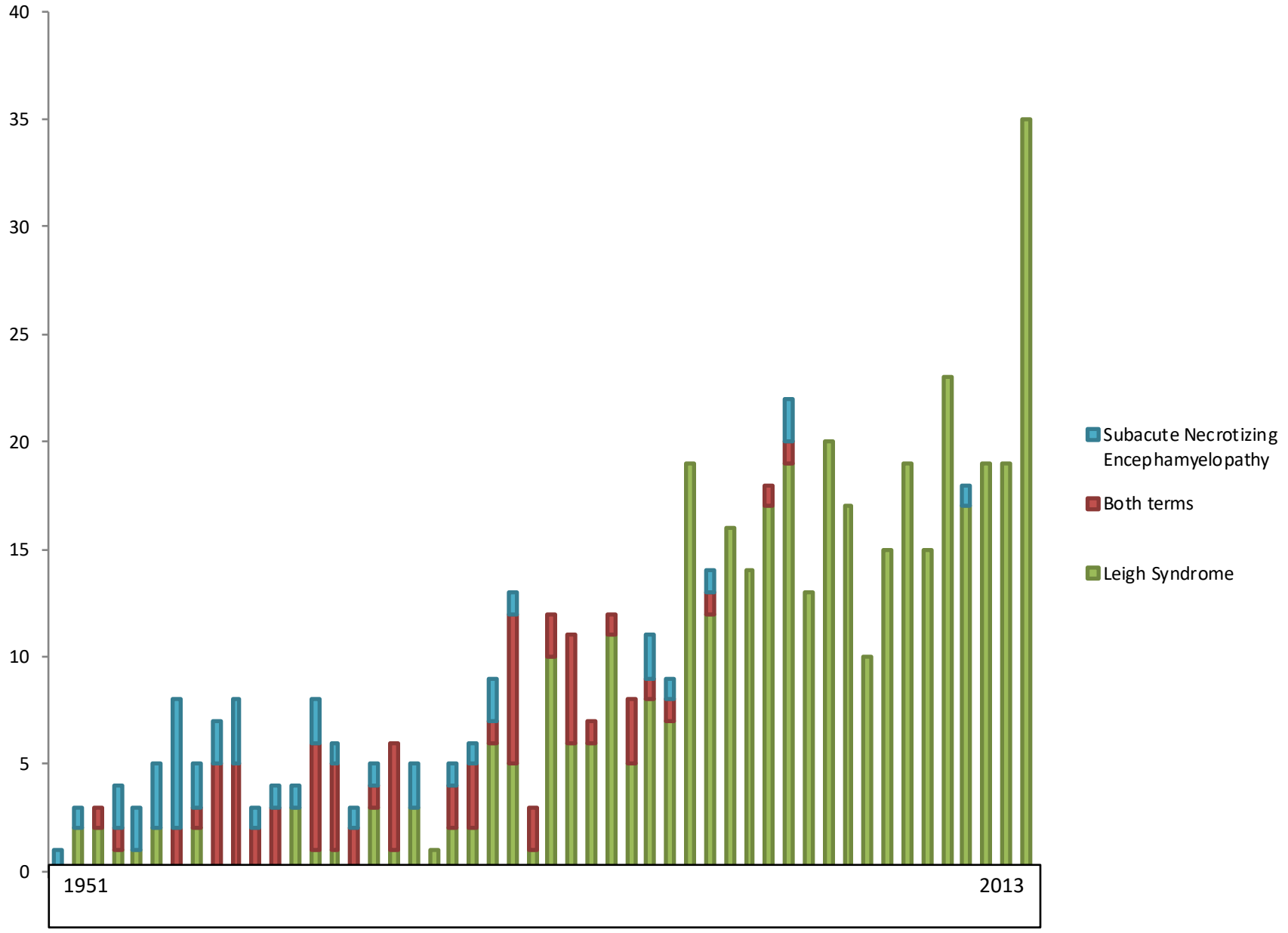
- The authors found the following findings to be ***associated with poorer survival***:
  - age of onset below or equal to 6 months
  - seizures
  - failure to thrive
  - hospitalization in an ICU
  - genetically verified disease, and
  - brainstem lesions on neuroimaging


40
35
30
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20
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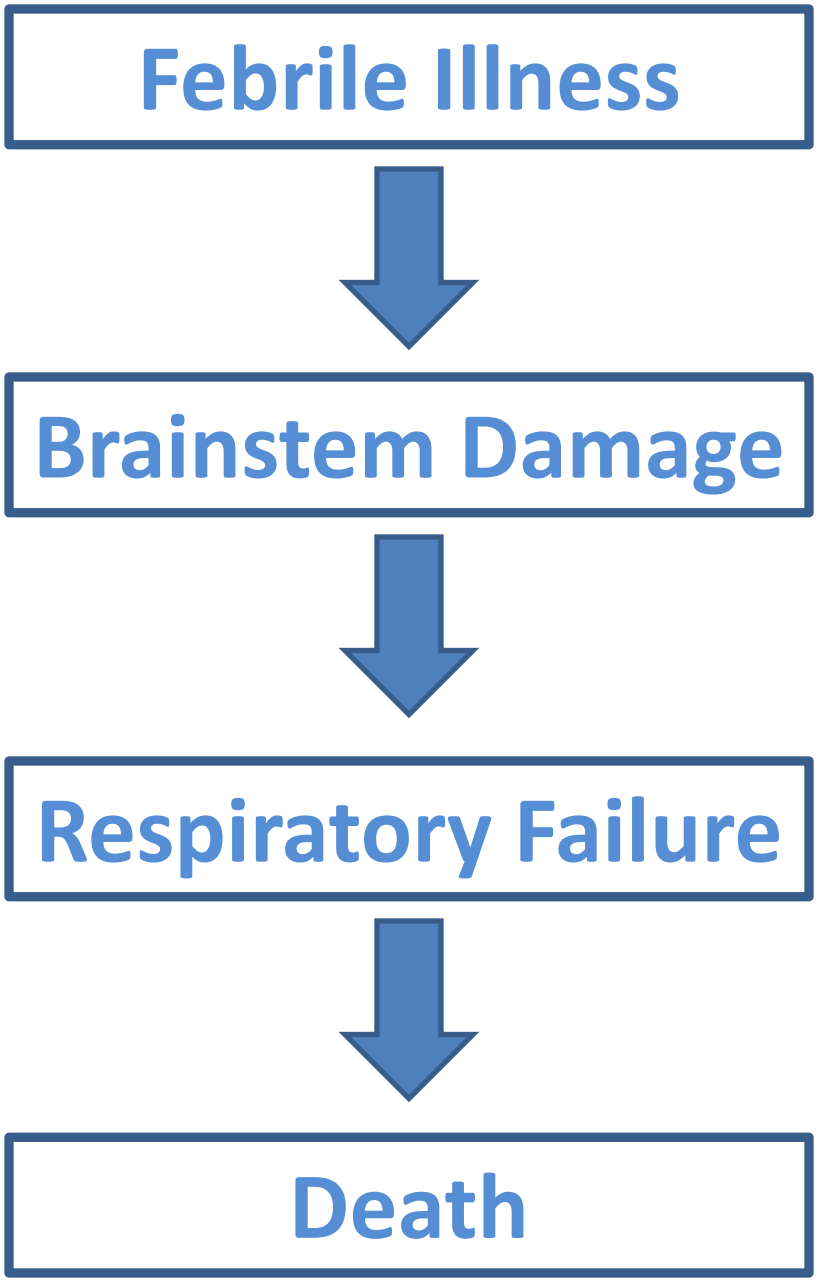
1951
2013
Subacute Necrotizing Encephamyelopathy
Both terms
Leigh Syndrome

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.


Febrile Illness
Brainstem Damage
Respiratory Failure
Death

THE (INTER)NATIONAL LEIGH SYNDROME REGISTRY

UT MITOCHONDRIAL CENTER
PEOPLE AGAINST LEIGH'S 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 IT'S PURPOSE?

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

PALS
PEOPLE AGAINST LEIGH SYNDROME

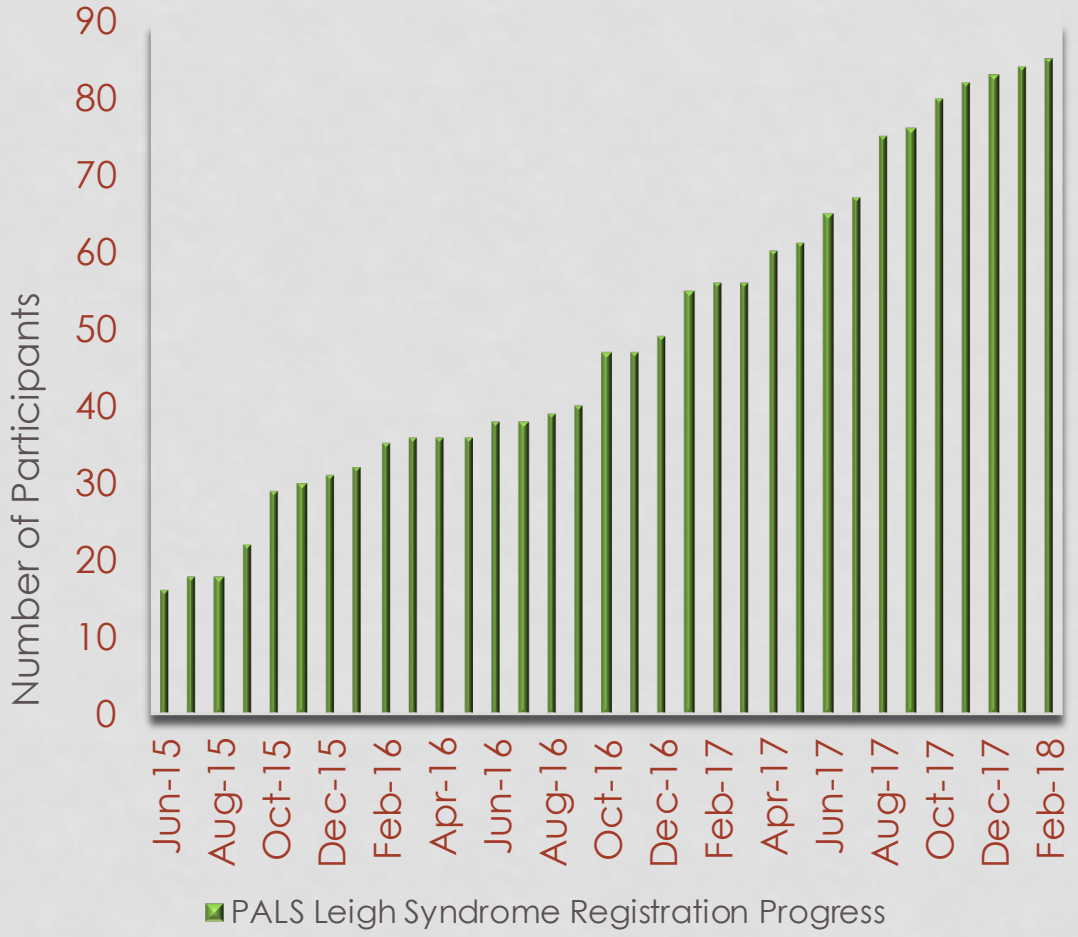
HOW WILL THIS REGISTRY BENEFIT PEOPLE WITH LEIGH SYNDROME:

- Data from the registry will help the medical community to bridge gaps in our knowledge about Leigh syndrome
- 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 to join the registry or learn more.

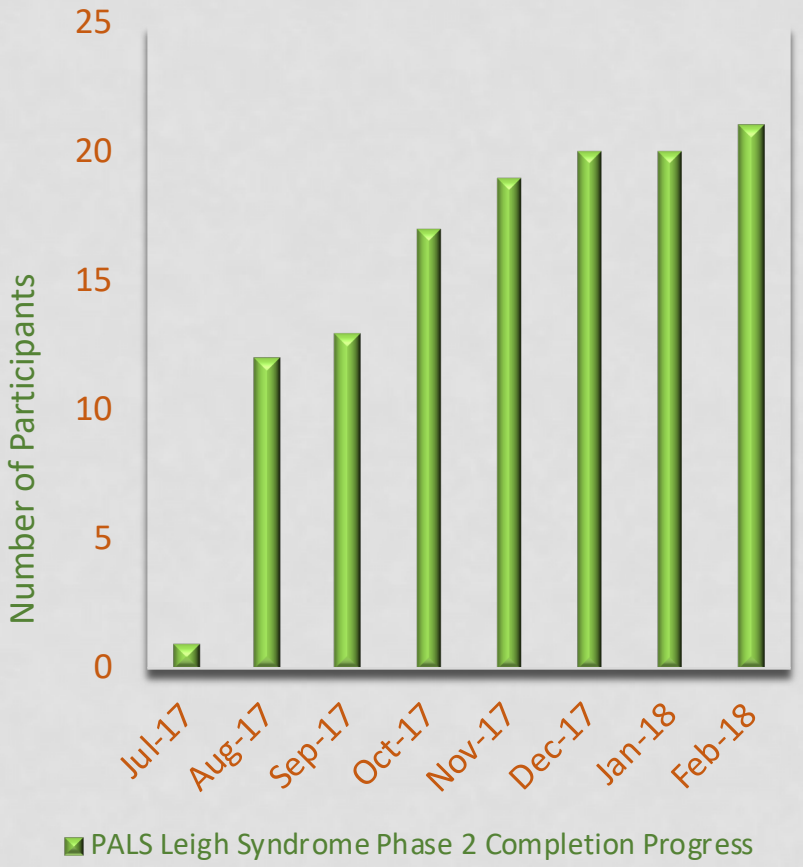
SO FAR….

- Phase I
  - Information collected
    - Contact information
    - Demographics
  - Beta-tested March 2015
  - Launched June 2015

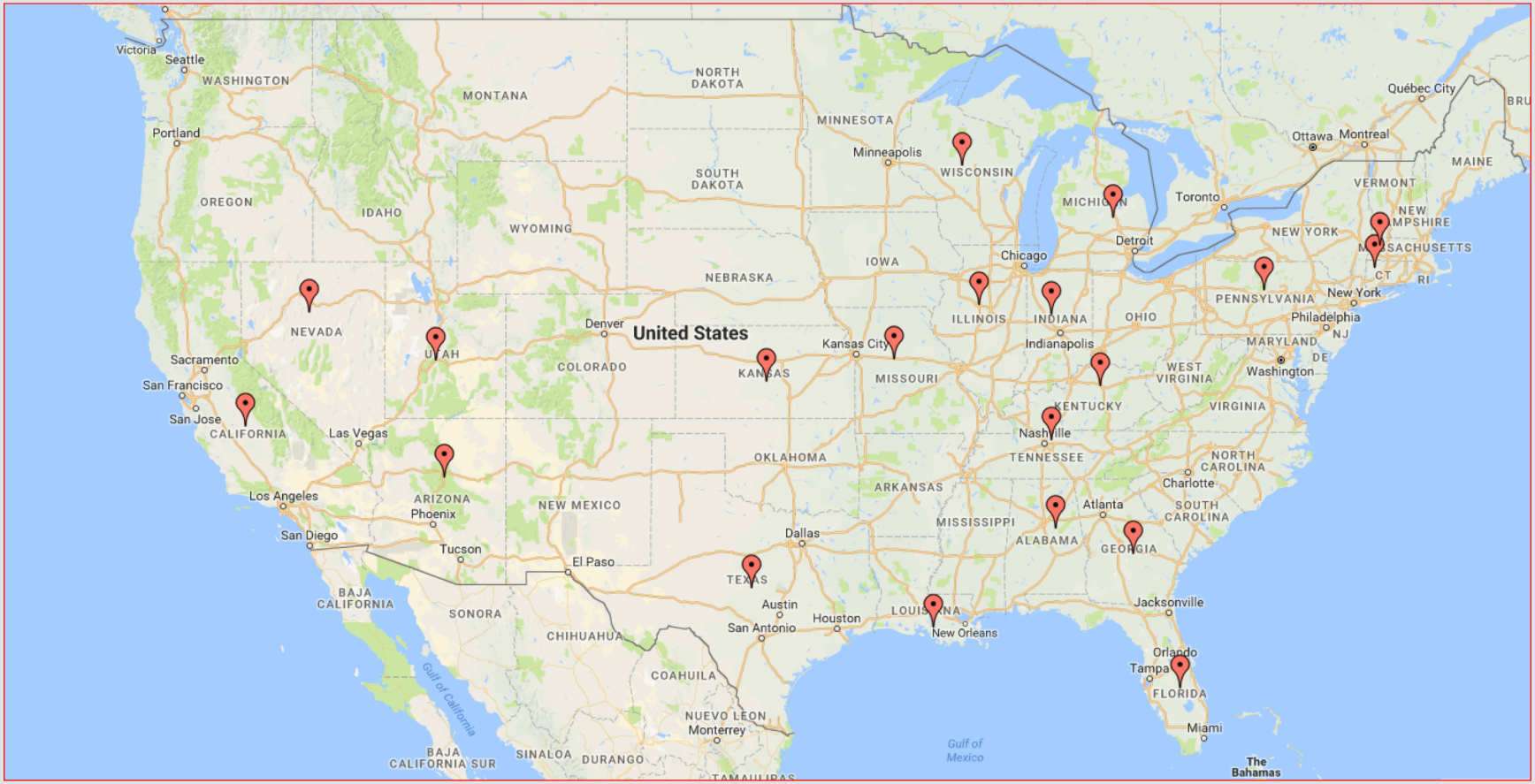


SO FAR….

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



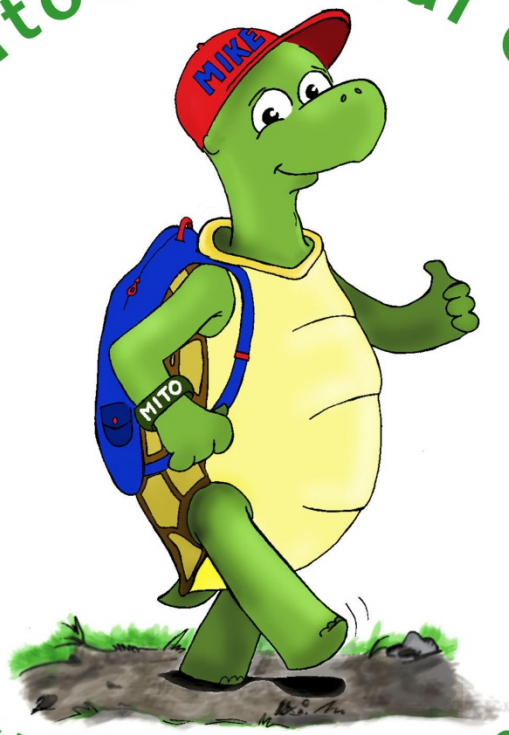
DISTRIBUTION OF PALS REGISTRY PARTICIPANTS IN USA



DISTRIBUTION OF PALS REGISTRY PARTICIPANTS WORLDWIDE

Thank you ☺

UT Mitochondrial Clinic



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