Clinical presentation of neurologic manifestations secondary to Leigh disease: a chiropractic case report

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ABSTRACT

Objective: To raise awareness and assist in recognizing the signs of neurodegenerative disorders as they are presented in a chiropractic office for assessment. This report addresses the clinical presentation, neurologic examination and a discussion about the clinical detection of neurodegenerative disorders in children. **Clinical Features:** A case of Leigh disease in a 4-month-old boy. Chiropractic care was sought for gastroesophageal reflux and difficulty feeding. Physical examination revealed hypotonia, developmental delay and abnormal cranial nerve function. **Intervention and Outcome:** Due to neurologic presentation, an immediate referral for medical evaluation was done. The child was diagnosed with Leigh disease and passed away one month later. **Discussion:** Leigh syndrome is a heterogeneous and progressive neurodegenerative disorder of infancy and childhood caused by a mitochondrial dysfunction. Central hypotonia, developmental regression or arrest, and signs of brainstem or basal ganglia involvement (respiratory and ophthalmologic abnormalities, dysphagia, ataxia, dystonia and seizures) are a classical presentation. This inherited disease is fatal and rapid medical referral is required for patients presenting this condition. **Conclusion:** Chiropractors should obtain a precise case history and perform a complete physical and neurological examination to investigate for neurodevelopmental delay or regression. Neurologic abnormalities should be quickly referred for medical investigation to identify the underlying condition.

Key words: Leigh syndrome, Leigh disease, mitochondrial disease, chiropractic, pediatric.

Introduction

Leigh Syndrome (LS), also known as subacute necrotizing encephalopathy, is a progressive neurodegenerative inherited disease. First described by Denis Leigh in 1951, this syndrome is a mitochondrial disorder[1] predominantly affecting infants and young children, and is rarely diagnosed in teens and adults.[2,3] In the majority of cases, onset of symptoms is in early childhood, typically in the first two years of life.[4] The onset of LS is often triggered by metabolic challenges such as acute infections and surgery.[5] The incidence of Leigh syndrome is approximately 1 in 40 000 births[4] but can be as high as 1 in 2000 births in French-Canadian specific sub populations such as in the Saguenay Lac-Saint-Jean area in Quebec.[6] LS represents the most common pediatric mitochondrial disease.[7,8] The estimated prevalence of LS is 2.05 cases per 100 000.[9]

LS results in a severe dysfunction in mitochondrial energy production.[10] This heterogeneous metabolic disorder presents multiple genetic causes, involving both mitochondrial and nuclear DNA gene mutations.[11,12] The modes of inheritance include autosomal recessive, x-linked recessive or maternal (mitochondrial) patterns.[13] LS neuropathology is characterised by a unique pattern of focal, bilateral and symmetric lesions in the central nervous system (CNS).[1] The lesions most commonly take the form of necrosis, demyelination, vascular proliferation and gliosis in the brainstem, diencephalon, basal ganglia, and cerebellum.[4] LS most commonly affects the brainstem.[14]

Depending on which areas of the central nervous system are involved, patients may demonstrate a wide variety of clinical presentations such as abnormal neurologic manifestations. The frequently encountered presentation of LS is characterized by:[4,6,11]

- Psychomotor delay or regression
- Muscular hypotonia
- Ophthalmologic manifestations
- Seizures
- Swallowing and sucking dysfunction
- Respiratory disturbances
- Ataxia
- Dystonia

The diagnosis is often made only after a computed tomography or magnetic resonance imaging[15] is performed. Currently, there is no cure for affected patients.[5] The prognosis is poor and the disease is fatal.[16] The median age of death is 2.4 years old[17] and the majority of cases die before the age of 5[18] with a high incidence of respiratory failure.[6] Acute respiratory failure, attributable to involvement of the brainstem or respiratory muscle weakness, is a frequent feature and occurs in 64-72% of cases.[19]

Methods
A literature search was conducted using the following electronic journal databases: PubMed, Science direct, ChiroACCESS and Index to Chiropractic literature. Other articles and books were used to provide supporting information. Publications utilized included systematic reviews, case studies and randomized controlled trials. Relevant search key words included: Leigh disease, Leigh syndrome, mitochondrial disease, mitochondrial syndrome. There were no articles or studies available on the use of chiropractic care and Leigh disease or syndrome. Articles published between 1951 and 2014 were included.

Presenting Concerns
The mother of a 4-month-old boy presented her son for chiropractic care with a myriad of complaints: difficulty feeding, poor appetite, constipation, intestinal gas, fussiness, frequent vomiting and excessive crying (high-pitch sounds). The infant was previously diagnosed by his primary care physician with gastroesophageal reflux (GER) and was prescribed a proton pump inhibitor (Prevacid (TM) (Lansoprazole) 15mg/day) which blocks the production of acid by the stomach. Concurrent with medical care, the patient received osteopathic care (non medical manual therapy) for an unspecified number of treatments. Since the infant's subjective complaints had somewhat improved but without total resolution, the mother sought care from a chiropractor with particular interest in pediatric care.

The mother reported a normal pregnancy and a full-term birth without complication. The infant's birth weight was 9 lbs 2 oz (93rd percentile) with a length of 22 in. Breastfeeding was very difficult at first so the mother was expressing milk and giving it to the infant in a bottle. She switched to a breastmilk substitute/infant formula "Good Start" after three months due to lactation issues. At this time, patient's weight dropped to 15th percentile.

Clinical Findings
Clinical evaluation included a detailed neurologic assessment examining tone, strength, and reflexes. Physical examination revealed hypotonia in active and passive muscle activity of the baby's extremities. A preferred head position in right lateral flexion was present with a normal head shape. The range of motion (ROM) of the cervical spine was without restriction.

During the neurological examination, primitive reflexes and cranial nerves evaluation revealed abnormal tongue movement (poor sucking). The blink reflex, landau and asymmetric tonic neck reflex (ATNR) were absent. A lack of visual tracking and poor eye contact were observed. Developmental milestones revealed a motor developmental delay: when prone, the infant was unable to lift his head (unable to recruit the cervical extensors and the more superficial muscles like the trapezii which are often additionally recruited in extension) and the head and shoulders could not be supported by his forearms. Multiple areas of vertebral dysfunction were identified upon palpation, specifically at C0 antero-superior, C1 lateral right, T4 posterior, T12 posterior right, with a posterior left sacrum at the S1 segment. Cranial restrictions were noted in occiput and sphenoid.

Intervention and Outcome
The child was adjusted using diversified techniques modified for an infant's gestational age and specific anatomy and physiology and no adverse events noted as a result of chiropractic adjustment. The combination of severe hypotonia, developmental delay, visual and feeding difficulties raised serious concerns about this patient's neurologic health status. The patient was immediately referred to a pediatric hospital for further assessment and testing. Clinical investigations included: biochemical laboratory investigations, swallow study, cerebral MRI, and eye, cardiac and neurologic evaluation. Results from swallow study showed evidence of aspiration with feeds and swallowing difficulties. Basal ganglia and brainstem lesion were evident on MRI. The diagnosis of mitochondrial disorder (Leigh disease) was given approximately 3 weeks after the last chiropractic consultation. The child passed away one month later. (Table 1: Timeline).

Table 1. Timeline

Date	Milestone
December 2014	Birth: feeding dysfunction, fussiness, high-pitch crying, constipation, gastroesophageal reflux.
January 2015	Osteopathic treatment: no significant improvement noted after treatments. Discontinued.
February 2015	Diagnosis (pediatrician) = GER; prescription of Prevacid with some amelioration
March- 2015	Evaluation by a chiropractor with pediatric focus. Referred immediately for medical evaluation due to neurologic presentation.
April - 2015	Pediatric hospital investigations: biochemical laboratory, swallow study, cerebral MRI, eyes, cardiac and neurologic evaluation = Diagnosis of Leigh disease
May - 2015	Death

Discussion
This case highlights the importance of adequately correlating patient symptoms with examination findings. Although the clinical presentation raised "red flags" for the presence

of a serious disease, the neurologic signs could have been missed, especially if the clinician had omitted to perform a complete pediatric neurologic exam. In fact, chiropractors do not have the necessary resources to diagnose LS. However, they can recognize symptoms indicative of a neurodegenerative disorder.

An affected child typically shows symptoms in the first 2 years of his life, including developmental delay or regression with loss of previously acquired skills.[15] Neurodegenerative symptoms include muscular hypotonia or spasticity, dystonia, seizures, ataxia, dysphagia, ptosis, abnormal eye movements such as nystagmus or slow saccades, breathing irregularities such as apnoea and psychomotor retardation, feeding difficulties leading to vomiting and failure to thrive.[11,20]

Because heterogeneous presentations can be first revealed in a chiropractic practice, it is essential that chiropractors be trained to recognize the signs and symptoms associated with LS. As primary health care providers, chiropractors need to remain current on the information pertaining to this condition in order to evaluate patients through a detailed case history and thorough physical examination including a complete neurologic evaluation[21] (Table 2) and a developmental checklist of milestones achieved at certain ages[22] (Table 3). The chiropractor's role is to detect the neurologic impairment and quickly refer the patient for further investigation.

The medical investigation for a potential diagnosis of LS is based primarily on the clinical history, the physical examination and then the laboratory parameters (blood and urine analysis). When clinical initial signs and laboratory examinations suggest a possible diagnosis of LS, cerebral MRI (T2-weight)[23] should be performed as well as other imaging techniques such as proton magnetic resonance spectroscopy (MRS).[24] Even if cerebral MRI is an effective way to identify characteristic findings of LS, biochemical analysis of muscle biopsies or, when applicable, cultured fibroblasts biopsies and genetic diagnosis are key elements to establishing genetic diagnosis and finding the causal defect.[25]

To date, there are no causative treatment options for LS.[6] However, prevention strategies can be implemented. Interdisciplinary palliative care still remains a mainstay of LS treatment to help and support problems due to brain lesions.[26] For example, ophthalmologists and audiologists should be involved in the care of affected children with problems like optic atrophy or progressive hearing loss. Home-care ventilator support for respiratory dysrhythmia and a nasogastric tube in case of dysphagia should be made available. Early intervention physiotherapy programs (exercise training) are recommended to support neurodevelopment of affected patients.[27,28] Specialized palliative care teams should be involved, providing in-home nursing and support for children and their parents.[5] The current literature contains no studies or case reports on chiropractic management. It is possible that chiropractors can be members of the team alongside other health care profession-

Table 2. Pediatric neurological examination checklist (0 to 12 months)

Posture and observation
- Flexed or extended arms and legs
- Spontaneous movement
- Asymmetric movement
- Hypotonia
- Spasticity
- Tremors
- Seizures

Primitive Reflexes

Supine:
- Rooting
- Sucking
- Palmar and plantar grasp
- Blink / Acoustic blink
- Tonic neck
- Moro
- Plantar-flexor (Babinski)

Upright:
- Vertical suspension
- Placing response
- Stepping

Prone:
- Landau
- Gallant

Cranial nerves

I.	Olfactory
II.	Optic
III.	Oculomotor
IV.	Trochlea
V.	Trigeminal
VI.	Abducens
VII.	Facial
VIII.	Acoustic
IX.	Glossopharyngeal
X.	Vagus
XI.	Spinal accessory
XII.	Hypoglossal

Deep tendon reflexes
- Patellar, Achilles, Biceps (0 to 3+)
- Clonus

** Adapted from Fysh 2002*

Table 3: Developmental milestones chart for quick office reference (0 to 12 months)

Age	Gross motor	Fine motor	Comunication	Cognitive	Social
Newborn	Moro reflex, Flexed posture	Palmar grasp reflex	Rooting and sucking reflexes, variable cries	Turns to visual stimuli (contrast, colors)	Cries when other infant cries
Two months	Holds head up 45° in prone, ATNR emerges	Holds a rattle placed in hand	Gurgles and coos	Follows objects across field of vision	Smiles, more awake during day
Four months	Head and shoulders can be supported by the forearms in prone	Brings hands together in midline, bats a toy, reaches, grasps and shakes rattle	Laughs	Plays with hands, looks for familiar objects and finds caregiver	Enjoys eye contact, calms when spoken to
Six months	Primitive reflexes gone, pulls up to sit, sits without support, rolls from prone to supine	Passes objects from hand to hand, checks objects by placing them into the mouth	Turns to voice, vocalizes to answer/babbles uses one-syllable words = "da", imitates sounds	Plays with feet, looks for dropped object, bangs objects together, recognizes own name	Facial expression, prefers familiar people, shows interest in other infants
Nine months	Postural reflexes present, rolls both ways, crawls, stands holding onto furniture	Radial-digital and raking grasp	Looks to familiar named object, inhibits to 'no', uses 2-syllable words: Mama/Dada	Object permanence, explores caregiver's face, searches for hidden toy	Attachment development established, clearly shows joy and pleasure
Twelve months	Pulls to standing position, walks holding on and/or unassisted, catches rolling ball	Pincer grasp, voluntary object release into cup, holds bottle, feeds self with fingers	Turns to name, understands several words, uses 2-3 words vocabulary, imitates clapping, waves bye-bye	Looks for object hidden, 'Cause and effect' toys	Plays Peekaboo

***Adapted from Dosman 2012 and Fysh 2002.*

als to support neurodevelopment and the well being of a child diagnosed with LS. Chiropractors could play a role with chiropractic adjustments and exercises to preserve and maximize strength, mobility and function. Further research is warranted to assess the outcomes and safety of chiropractic intervention in patients with similar presentations.

Conclusion

When evaluating a pediatric patient, chiropractors should obtain a precise history in order to investigate for delay or regression of developmental milestones, and perform a complete neurologic examination. The confluence of findings including unexplained hypotonia, neurodevelopmental delay or regression and physical neurologic abnormalities should be referred for medical investigation in order to identify the underlying condition. Outcome of a neurodegenerative condition is usually fatal and available therapies are often limited but may serve to support quality of life.

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