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Research Article

Subacute necrotizing encephalomyelopathy (Leigh syndrome) in pediatric patients: a retrospective study

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ABSTRACT

Background: The clinical manifestations of Leigh Syndrome (LS) are heterogeneous and its diagnosis is often based on information acquired from multiple levels of inquiry. To identify LS, Oral Glucose Lactate Stimulation Test (OGLST) and Magnetic Resonance Spectroscopy (MRS) have been used as additional tools for evaluation of this metabolic disorder. The objective of the study was to report the clinical manifestations, neuroimaging assessments, and multidisciplinary approaches of lactate in pediatric patients with LS.
Methods: We performed a retrospective charts review of pediatric patients with LS, which underwent the investigations using laboratory tests and Magnetic Resonance Images (MRI)/MRS of the brain.
Results: The distributions of the lesions on the MRI of the brain studies were as the following: basal ganglia (7/8), brainstem (7/8), and cortex (3/8). Despite all of the patients showed disorient neurological manifestations and symmetrical lesions over the basal ganglion and brainstem on MRI, elevated levels of serum lactate were detected in 6 of 8 patients by either random serum sample obtained for lactate or OGLST. Subsequently, the remaining 2 cases were demonstrated with lactate peak over the affected areas by MRS. Cranial MRS showed lactate duplex and decreased N-acetylaspartate/creatine ratio over the affected areas in the 5 of 6 patients.
Conclusions: The study shows the importance of multidisciplinary approaches in the diagnosis of LS. Approach of LS may not only depend on the elevation of the value of random serum lactate but also can be further aided by OGLST or MRS to evaluate metabolic disorder in such patients.

Keywords: Leigh syndrome, Mitochondrial disorder, Lactate, Oral glucose lactate stimulation test, Magnetic resonance spectroscopy

INTRODUCTION

Leigh syndrome (subacute necrotizing encephalomyelopathy, LS) is a rare neurological disorder characterized as symmetrical lesions in one or more areas of central nerve system, including basal ganglia, thalamus, brainstem, cerebellum or spinal cord observed at autopsy.[1,2] Since its early description, LS had been proved to be not only genetically but also clinically heterogeneous. The definite diagnosis of LS had been made as a result of autopsy demonstrating the symmetrical involvement of basal ganglia and brain stem.[1,3] The diagnostic criteria of LS have been suggested of encephalopathy, characters in brain Magnetic Resonance Imaging (MRI), and biochemical abnormalities with lactemia.[4] Elevated lactate levels in plasma or Cerebral Spinal Fluid (CSF) present in patients with LS; however, not all the LS patients have the presence of lactemia in the acute onset of the disease.

Therefore, the sensitivity and specificity of the use of lactemia for the diagnosis of LS remains varied.[5,6]

To identify LS, an Oral Glucose Lactate Stimulation Test (OGLST) has been suggested to determine whether it could be used as an alternative method for screening patients with suspected mitochondrial disease.[7]

Magnetic Resonance Spectroscopy (MRS) has been used as an additional tool for evaluation of the pyruvate oxidation disorders, but absence of direct demonstration of a mitochondrial dysfunction. The various imaging modalities of MRI and MRS allow multiple independent detection procedures that can give important anatomical and metabolic clues for diagnosing abnormal value of lactate.[8,9]

The purpose of this study was to report 8 pediatric cases series, including 2 siblings, and to review the findings of laboratory tests and neuroimages when assessed the pediatric patients with LS or Leigh-Like Syndrome (LLS). Here we also discussed the role of MRS on the providing additional information to support diagnostic suspicion of this disease.

METHODS

We performed a retrospective charts review of patients with LS or LLS who had admitted to the hospital. The patients must fulfilled the following criteria for LS: (1) progressive neurologic disease with motor and intellectual developmental delay; (2) signs and symptoms of brain stem and/or basal ganglia dysfunction; (3) elevated lactate levels in the blood and/or CSF; and (4) one or more of the following: (a) characteristic features of LS on neuroimaging (symmetrical hyperintense lesions in the basal ganglia and/or brain stem on T2-weighted MR images); (b) typical neuropathological changes at postmortem examination; or (c) typical neuropathological findings in a similarly affected sibling.

Based on clinical history, patients were excluded if the presence of previous perinatal insult, hypoxia, or central nervous system infection, which was confirmed by all of the patients with negative finding of pleocytosis, protein or glucose on the analysis of CSF. All of the patients underwent biochemical and metabolic investigations, including liver function tests, blood amino acids and urinary organic acids. On OGLST, patients were required to fast and rest for at least 6 hours before the test. Glucose was administered orally using 50% glucose/water solution at a dose of 1.75 g/kg. Blood samples then were drawn from a retained heparinized venous line at 0, 30, 60, 120 & 180 minutes, respectively, and were measured for lactate and glucose levels.

MRI was conducted in all patients in acute stage upon admission. All imaging examinations were performed with 1.5-Tesla Magnetic Resonance (MR) imagers (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany, or Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, WI, USA), equipped with high-performance 3-axis gradient systems. The scan protocol included T1-weighted, T2-weighted, fluid attenuation inversion recovery and diffusion-weighted imaging. Coronal and transaxial cranial images were performed using T2-weight spin-echo sequences and conventional inversion recovery sequences.

After MRI was performed, a volume of interest for MRS was positioned on the axial MRI with one or multiple regions within the affected areas. All spectra were reviewed with a special interest in lactate levels elevation and evaluated by comparing amplitudes of the resonance signals. Peak amplitude was determined by assuming a Lorentzian line shape and evaluating the baseline noise standard deviation.

RESULTS

Eight patients diagnosed as LS or LLS aged from 3 months old to 3 years and 8 months old were enrolled into this study. Of them, five presented with clinical features in infancy and the remaining three in early childhood (Table 1).

The majority of the initial presentations of neurological symptoms were conscious change, hypotonia/ataxia and respiratory failure needed ventilator support. Outcomes of the patients were frustrated, including two patients expired and five patients subsequently developed severe handicapped on follow-up. The patient 2 presented with typical features of LS and died of respiratory failure; however, her younger brother presented only mild, occasional ataxia and high signal of brain stem lesions on MRI with persevered basal ganglia (Figure 1).

Laboratory tests, including complete blood cell count, electrolytes, and ammonia, all were within normal limits in all of the patients. Neither pleocytosis nor CSF lactate levels was identified. Skeletal muscle biopsy for light and electron microscopic examinations was unremarkable of the subjects. Elevated levels of serum lactate were detected in six of eight patients by either random serum specimen obtained for lactate or OGLST (Table 2).

All the patients showed symmetrical, focal high-signal intensities of T2-weighted MRI over the basal ganglion, brainstem, especially putamen (Figure 2). The distributions of the lesions on the MRI studies were as the following: basal ganglia (7/8), brainstem (7/8), and cortex (3/8). Subsequently, cranial MRS showed lactate duplex and decreased *N*-acetylaspartate/creatine ratio (NAA/Cr) in five patients (5/6). The cases (case 1 and 8), with neither lactemia nor positive OGLST, showed a positive lactate peak over the affected areas in the MRS.

Table 1: Demographics, clinical features and outcome of patients with LS or LLS.

Patient	1	2	3	4	5	6	7	8
Age of onset	2Y	3Y8M	2Y11M	4 M	6 M	3 M	4 M	5 M
Gender	F	F	M	M	M	F	M	M
Neurological symptoms								
Conscious change/lethargy	+	+	–	+	+	+	+	–
Headache	–	–	+	+	–	–	–	–
Ataxia/hypotonia	A	A	A	H	H	H	H	H
Ophthamoplegia	+	–	–	+	–	–-	–	–
Respiratory failure	+	+	-	+	+	+	+	+
Dysarthralgia	+	+	+	–	–	–-	–	+
Seizures	–	–	–	+	–	+	+	+
Family history	–	Sibling of case 3	Sibling of case 2	Retarded uncle	–	–	Elder sister died of unknow cause	–
Outcome (year)	Mental regression, spastic quaplegia (5Y)	Expired (3Y9M)	Unstable gait (4Y)	Expired (5M)	Mental regression, spastic quaplegia (2Y)	Floppy, Respiratory failure with tracheotomy (1Y)	Mental regression, spastic quaplegia (1Y)	Mental regression, spastic quaplegia (3Y)

LS: Leigh syndrome; LLS: Leigh-like syndrome; +: Positive; –: Negative, M: Male; F: Female; A: Ataxia; H: Hypotonia

Table 2: Laboratory results and MRI/MRS in patients with LS or LLS.

Patient	1	2	3	4	5	6	7	8
Lactemia								
Random lactate (>20 mg/dl)	Negative (11.5)	Positive (72.0)	Positive (20.2)	Negative (15.4)	Negative (10.0)	Positive (24.5)	Positive (83.4)	Negative (11.0)
OGLST	Negative	–	Negative	Positive	Positive	–	–	–
MRI								
Cortex	Temporal lobe	NP	NP	Temporal lobe	NP	Temporal lobe	NP	NP
Basal ganglia	Putamen/ caudate nucleus/ thalamus	Putamen/ globos pallidus	NP	Putamen/ globos pallidus	Putamen/ globos pallidus/ caudate nucleus	Thalamus	Putamen, thalamus	Putamen, caudate, lentiform nucleus
Brain stem	Cerebellum/ midbrain/ medulla	Cerebellum/ midbrain	Pons/ cerebellum	Midbrain	Midbrain	Midbrain	Midbrain	NP
MRS	Lactate doublet	–	NP	Lactate doublet	Lactate doublet	Lactate doublet	–	Lactate doublet
Molecular survey	mtT8597TC,	–	NP	–	–	mtT10191C	T8993G	–

LS: Leigh syndrome; LLS: Leigh-like syndrome; OGLST: Oral glucose lactate stimulation test; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NP: No particular finding; –: Not done

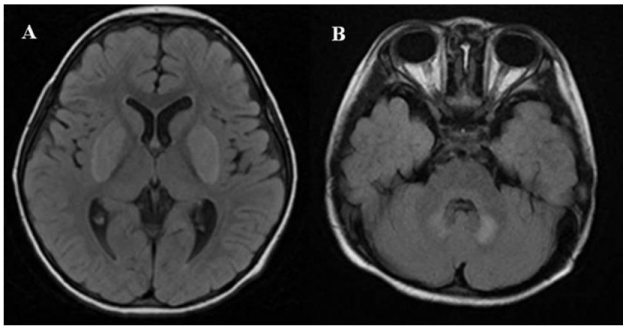

Figure 1: MR images of case 2 and case 3 during the acute phase. 1A) Case 2: A 2-year-old girl suffered from conscious disorientation, unstable gait and respiratory failure upon admission. T1-weighted images showed symmetrical high signal intensities in the putamen, globus pallidus, midbrain and cerebellum. 1B) Case 3: A sibling of case 2 suffered from occasional unstable gait at the age of two years old. T1-weighted images showed symmetrical high signal intensities in the cerebellum, pons and preserved basal ganglia.

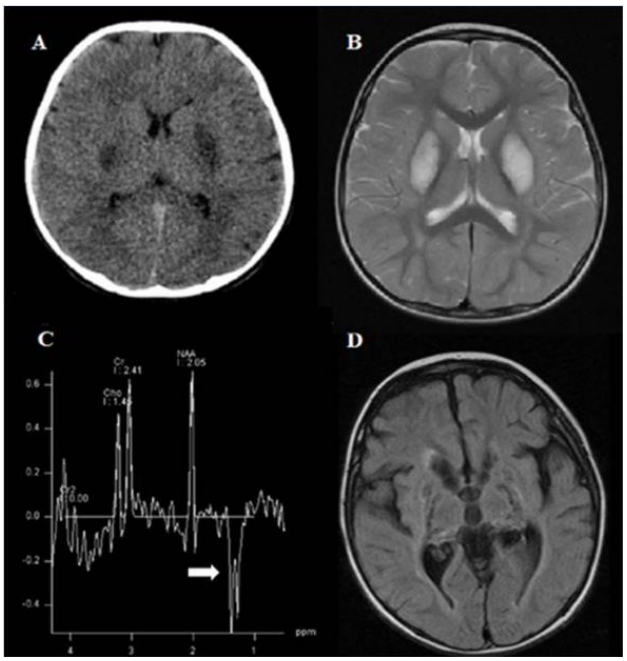

Figure 2: Serial images of case 1 with CT, MRI and MRS. 2A) Initial axial CT scan of brain showed symmetrical decreased densities in bilateral lentiform nuclei, especially bilateral putamen. 2B) MRI of case 1: Axial T2-weighted images (TR = 3990 ms; TE = 101 ms) showed symmetrical T2 prolongation with high signal intensities in the putamen. 2C) Proton MR spectroscopy (TE = 135ms) of the left putamen showed a large lactate peak (arrow), consistent of mitochondrial dysfunction with anaerobic glycolysis. 2D) On day 30, MRI showed diffuse enlargement of cerebral surface sulci and cisterns. The bilateral basal ganglia became encephalomalacia with complete hemorrhagic necrosis and cystic change.

DISCUSSION

Generally, LS is classified as a mitochondrial disorder with subsequent diverse neurological abnormality. However, in addition to mutations in mitochondrial genes, the mutations in nuclearly encoded genes will cause lactemia resulting from disturbed oxidation-reduction potential of the respiratory chain.[10,11] Mutated mitochondrial DNA usually occurs together with wild type of mitochondrial DNA within a mitochondrial or cell, a condition as heteroplasmy.[12] The diverse genetic model and different heteroplasmy rate cause manifestations clinically heterogeneous in severity.

Table 3: Assessment of mitochondrial diseases for lactate level by provocation test and MRS.

Authors	Case No.	Positive	Sensitivity (%)	Literature (Year) and reference No.
Lactemia for LS				
Medina et al.	9	8	88.9	1990[13]
Arii et al.	8	8	100.0	2000[6]
Chae et al.	16	8	50.0	2008[5]
Tsai et al.	8	4	50.0	This study
Lactate provocation test for MD				
Chi et al.	11	8	72.7	1992[7]
Finsterer et al.	18	26	69.2	1998[16]
Finsterer et al.	54	37	68.5	2000[14]
Finsterer et al.	155	103	67.0	2002[15]
MRS of brain for MD				
Lin et al.	8	5	67.5	2003[19]
Branchi et al.	15	12	75	2003[9]
Chi et al.	14	12	85.7	2011[8]

MRS: Magnetic resonance spectroscopy: LS: Leigh syndrome; MD: Mitochondrial diseases

There is no single algorithm for diagnosing mitochondrial disorders. Several diagnostic methods have been applied to help clinicians detect mitochondrial disorders earlier. Assessments of lactate level in mitochondrial diseases were summarized in Table 3. For mitochondrial disorder, the elevation of lactate in LS ranged from 50% to 100%.[5,6,13] To provoke lactemia in mitochondrial disorders, the sensitivity and specificity of OGLST for lactate provocation were 72.9% and 91.7%, respectively, which revealed acceptable positive values in the assessment of LS.[7] In the current study, there were 4 of 8 cases showed negative of lactemia, and the case 4 and 5 were subsequently proved the elevation of serum lactate by lactate stimulation test. The provocation test, with a sensitivity of 70%, to assess the impaired oxidative metabolism in mitochondrial disorders was proposed as an alternative method for screening mitochondrial disorders before determining whether a muscle biopsy should be performed.[7,14-16] This simple, noninvasive test

can helps to facilitate approach and differential diagnosis of such disorders that need for further investigation.

With the increasing availability of MRI for patients with acute encephalopathy, more patients with LS are being recognized at the earlier stage. In addition, MRS supplies additional information to conventional imaging and helps to identify *in vivo* biochemical state on a variety of brain compounds, which facilitate to give insight into the physiopathology of brain lesions in metabolic disreses.[17] In a series study, a high level of lactate was shown by MRS that correlated well with other makers in mitochondrial disorders.[9] The combination with MRI is useful in screening patients for metabolic disorders based on the detection of increased cerebral lactate.[18] Accurately determining the change of lactate by means of MRS are related to the concentration of lactate, requiring >0.5 mmol/L, and brain lactate levels may rise during stages of metabolic imbalance. Therefore, the ideal timing to perform a MRS should be during the stages of clinical exacerbations. Moreover, MRS revealed lactate peaks during deterioration of the disease course may be related to the severity of disease. In contrast, previous study has shown that MRS does not always show elevated lactate level allowing for the assessment of mitochondrial disorders.[19] The lack of lactate abnormalities may reflect insufficient lactate concentrations for detection, temporary fluctuations in lactate concentrations, or failure to interrogate the proper region. Even if not specific, it has been suggested to draw a metabolic map and demonstrate metabolic abnormities even in areas of the brain that appear to be normal in MRI of the brain.[17] On the contrary, lactate was never found in brain that appeared normal MR images reflect the specificity in identification mitochondrial diseases.[9] In the current study, the case 4, 5, and 6 had the positive results in either random serum lactemia or OGLST, their MRS subsequently displayed lactate doublet. Moreover, despite the case 1 and 8 presented with typical clinical manifestations and neuroimages of LS but who did not have lactemia in random serum sample and in OGSLT, their MRS still displayed a map with lactate doublet which demonstrated an evidence of anaerobic oxidation *in vivo*.

In our cases series, the case 2 manifested as typical LS with typical basal lesions and expired of respiratory failure. Her younger sibling (case 3) also suffered ataxic gaits at the age of 2 years, and his MRI findings showed symmetrical cerebellum and mid brain lesions with preserved putamen. The issue of siblings of the index patients with LS has rarely been reported.[3] Ronchi et al.[20] described the clinical and molecular features of a novel pedigree, where LS developed in two siblings. The proband was a young woman with unusual adult-onset LS. In contrast to our report, the brother died at the age of 7 years and was subsequently autoptically confirmed of LS. It implied that siblings with similar symmetrical lesions over basal ganglia/brain stem might suggest the presence of metabolic disorders.

Limitations of this report include its retrospective design and small sample size. Only three cases were demonstrated by mitochondrial molecular evidence of LS. There was no control to compare the MRI/MRS result in assessment of LS in the study. These may pose a selection bias. Neither long term follow-up data nor serial MR images were obtained in the study. The reported cases may be too small to make a firm conclusion. Further prospective studies with larger cohorts are warranted.

CONCLUSION

The clinical manifestations and neuroimages of LS are heterogeneous; and a history of typical neuropathologic findings in a similarly affected sibling should be considered as such a genetic disorder. The laboratory tests including lactate value in LS are usually variable despite typical brain images with symmetrical lesions over basal ganglia and brain stem. Therefore, OGLST may benefit in the assessment of such metabolic disorder and MRS can substantially help in the assessment of the impaired oxidative metabolism of brain.

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