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Case report

Title:

Adult Leigh disease without failure to thrive : a case report and review of the literatures

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Adult Leigh disease

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Abstract

Introduction:

Most Leigh disease (LD) patients die before reaching adulthood, but there are reports of 'adult LD'. The clinical features of adult LD were quite different from those in infant or childhood cases. Here, we describe a normally developed patient with adult LD, who presented with spastic paraplegia that was followed several years later by acute encephalopathy. We also conducted a systemic literature search on adult LD and integrated its various manifestations to arrive at a diagnostic procedure for adult LD.

Case report:

A 26-year-old woman presented with acute encephalopathy after spastic paraplegia. On her first admission, she exhibited bilateral basal ganglia lesion on magnetic resonance images and normal serum lactate levels. On second admission, she had acute encephalopathy with lactic acidosis and bilateral basal ganglia and brainstem lesions. A muscle biopsy revealed cytochrome c oxidase(COX) deficiency, and a diagnosis of adult LD was made. Despite treatment in the intensive care unit, she died nine days after admission.

Conclusions:

A review of the literature describing adult LD revealed that developmental delay, COX deficiency, serum lactate elevation, and basal ganglia lesions occurred less frequently than they did in children with LD. Cranial nerve disturbance, pyramidal signs, and cerebellar dysfunction were the primary symptoms in adult LD. Thus, the many differences between childhood and adult LD may be helpful for diagnosing adult LD.

Key Words:

Leigh disease, adult, mitochondrial deficits, Rahman's criteria

1)Introduction

Leigh disease (LD) is a metabolic disorder of the central nervous system usually affecting infants or children. The characteristic features of LD are developmental delay, lactic acidosis, and typical lesions in the brainstem and basal ganglia¹. LD is commonly caused by deficits in mitochondrial function, such as those involving respiratory chain complexes, ATPase 6, and components of the pyruvate dehydrogenase complex². Typical pathologic features consist of spongiform lesions, microglial and histiocytic proliferation, and vascular proliferation in the basal ganglia and brainstem. Stringent diagnostic criteria for LD in children were proposed by Rahman et al.³, which included (1) progressive neurological disease with motor and intellectual developmental delay; (2) signs and symptoms of brainstem and/or basal ganglia disease; (3) raised lactate levels in blood and/or cerebrospinal fluid(CSF); and (4) one or more of the following: (a) characteristic features of neuroradioimaging (symmetrical hypodensities in the basal ganglia on computed tomography [CT] or hyperintense lesions on T2-weighted magnetic resonance imaging [MRI]), (b) typical neuropathological changes at postmortem, or (c) typical neuropathology in a similarly affected sibling. In addition, they defined patients with a high probability of LD who did not fulfill the criteria as “Leigh-like” syndrome.

Most LD patients die before reaching adulthood, but there are reports of ‘adult LD’⁴⁻²⁸. The clinical features of adult LD were quite different from those in infant or childhood cases^{29, 30}. Here, we describe a normally developed patient with adult LD, who presented with spastic paraplegia that was followed several years later by acute encephalopathy. Furthermore, we conducted a systematic literature search on adult LD and integrated its various manifestations

to arrive at a diagnostic procedure for adult LD.

2) Case Report

A 26-year-old Japanese female was admitted to our hospital because of diarrhea and fever followed by coma. She was 162 cm in height on admission. In the past, she had asthma, a meniscal tear, chronic alveolar osteitis, and a periapical cyst. She had no family history of LD or mitochondrial diseases. She was born without any complications and had developed without mental retardation. At age 13, she was affected with spastic paraplegia five days after an asthmatic attack. At 18, she acquired a sensory disturbance of the lower extremities. At 24, she was hospitalized for a diagnostic workup of hearing loss after an asthmatic attack(1st admission). Neurological examination at that time revealed right facial palsy, sensorineural hearing loss, spastic paraplegia, hyperreflexia of the lower extremities, bilateral extensor planter response, and sensory disturbance in the lower extremities. In a laboratory test, her serum lactate level was within normal limits. Brain CT and MRI showed small bilateral lesions of the basal ganglia (Fig. 1). At age 26, she developed dysarthria and gait disturbance, and subsequently diarrhea and high fever. Three days after the onset of fever, a disturbance of consciousness with lactic acidosis had progressed and she was transferred to the intensive care unit (ICU) (2nd admission). She had deep coma, generalized hyporeflexia, and loss of the oculocephalic reflexes. Neither anisocoria nor neck stiffness were observed. She was treated with steroids, multivitamins, and coenzyme Q10 (COQ10) in the ICU. Brain CT showed diffuse cerebral swelling and edema with bilateral hypodensity in the basal ganglia and brainstem (Fig. 2). Laboratory findings (Table 1) revealed elevations of creatinine kinase

(CK), and amylase as well as lactic acidosis. CSF examination showed high CSF pressure and mild pleocytosis that did not indicate any infectious disease. A muscle biopsy revealed cytochrome c oxidase (COX) deficiency without inflammation that indicated a mitochondrial abnormality, but we did not observe strongly succinate dehydrogenase-reactive blood vessels (SSV) and ragged red fiber (RRF). She died nine days after admission. No autopsy was performed. Later, a genetic analysis of the whole mitochondrial genome and known mutations of nuclear genes (*SURF1*, *COX10*) were performed, but no mutations were detected.

3) Discussion

3-1. Systematic literature review

Search methods and results of the systematic literature review

Adult LD was defined as patients who survived longer than 18 years². We searched reports in English on Medline from 1966 to October 2009 using the MESH terms "Leigh disease" and "adult", on EMBASE from 1968 to October 2009 using "Leigh disease AND adult", and the bibliographies of the retrieved articles. We applied two concepts for the accurate diagnosis of LD: (1) the patient fulfilled all four items of Rahman's criteria for LD, or three of the four items with neuroradiological or pathological abnormalities for Leigh-like syndrome (Rahman's criteria group: RCG) and (2) the patient had an identified mitochondrial abnormality in a muscle biopsy or other procedures or gene mutations (laboratory-diagnosed group: LDG). In all, 40 reports describing 58 patients were identified (Table 2); of these 19 belong to the RCG, 24 to the LDG, and 12 patients fulfilled both sets of criteria. In the RCG, 4

patients fulfilled all 4 items of Rahman's LD criteria and 15 of them fulfilled 3 of the 4 Leigh-like items.

Characteristics and clinical manifestation

The RCG included 13 males and 6 females. The mean age of onset was 10.4 ± 10.9 years (mean $\pm$ SD). At the time of the reports, 14 of the patients were alive. Nine patients had a familial history of LD. The LDG included 12 males and 12 females. The mean age of onset was 12.7 ± 14.8 years. At the time of the reports, 18 of these patients were alive. Sixteen patients in the LDG had a familial history of LD. The proportions of each symptom in the two groups are summarized in Fig. 3-a. In both groups, the major symptoms reported were cerebellar dysfunction and lower (VII-XII) cranial nerve disturbances. In the LDG, pyramidal signs were more frequent and mental retardation was less frequent than in the RCG..

On the other hand, in children with LD, the major symptoms are mental retardation, poor feeding, swallowing difficulty, and respiratory disturbance. Ophthalmoplegia and ataxia were reported in only 35% and 31% of children with LD, respectively^{29, 30}.

Biochemical and neuroradiological features

The percentages of adult patients with elevated lactate and neuroradiological abnormalities are shown in Fig. 3-b. In laboratory examinations, elevations in lactate levels were more frequently detected in serum than in CSF; however, serum or CSF lactate levels were not described in some patients, and others had normal serum lactate levels during the uneventful phase. As the resting levels of serum lactate were often within the normal range , the lactate

stress test (LST) that measures increases in serum lactate during slight exercise may be useful for detecting elevated lactate levels in the uneventful phase^{31, 32}. In the reports that we reviewed, the LST was not performed or described.

Neuroradiological findings of basal ganglia lesions on MRI or CT were reported in only 67% of the LDG patients. On the other hand, brainstem lesions were more frequent in the LDG than the RCG. In contrast to the relatively low proportion of neuroradiological abnormalities reported in these cases, such abnormalities were present in most children with LD^{29, 33, 34}.

Muscle biopsy histology, enzymatic deficiencies, and mutations

Muscle biopsies were performed in 18 of the reported adult cases. Pathological studies comprised light microscopic assessment of frozen sections using hematoxylin and eosin (H&E), modified Gomori trichrome, succinate dehydrogenase (SDH), and COX staining. A COX deficiency was observed in only 4 patients and subsarcolemmal aggregations of abnormal mitochondria (Ragged-red fiber: RRF) were observed in 5 patients. In enzymatic analyses of muscle specimens which mainly evaluated the oxidation capacity of NADH, COX, succinate, and pyruvate dehydrogenase complex (PDHc) using standard methods^{35, 36}, decreased respiratory chain activity (NADH, COX, and succinate) was observed in 3 patients and decreased PDHc activity was observed in another.

Mutations were detected using direct nucleotide sequence of causative genes including the mitochondrial genome or those identified by positional cloning². The genetic analyses indicated that 18 patients had one or more gene mutations: the T8993C mutation was detected

in 4 patients from different families, 1 family had 4 cases of adult LD with the T9185C mutation, 3 patients in different families had a T8993G mutation, and 2 patients in the same family a G1644T mutation. There were also single occurrences of heterozygous 14459, heterozygous 14484, homozygous 3460, G13513A, and C7028T+G9547A.

COX deficiency is a typical abnormality in child LD patients with the *SURF1* gene mutation³⁷, but RRF is absent in most childhood cases^{30, 38}. Other reported means of evaluating mitochondrial dysfunction are to analyze enzyme activities in skin fibroblasts, muscle supernatants, lymphocytes, and the liver³. The major mutations known to occur in LD patients are T8993C, T8993G, T10191C, G13513A, A8344G, and A3243G in mitochondrial genes, and *SURF1* in the nuclear genome. Currently, there are 24 known mutations in mitochondrial genes and 21 in nuclear genes².

Differential diagnosis and treatment

Most of the reported cases excluded infections, autoimmune diseases, and toxins. Some cases were first misdiagnosed as multiple sclerosis and other cases were indistinguishable from Wernicke's encephalopathy. From the perspective of the basal ganglia lesions, hypoxic encephalopathy, Wilson's disease, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELAS), and neurofibromatosis type1 should be considered as differential diagnoses.

In some cases, thiamin was administered as a nonspecific treatment. Disease specific treatments consisted of Coenzyme Q10 (150-300mg/day) administered to four patients with mitochondrial abnormalities, three of which improved and the other was unchanged, and a

ketogenic diet was administered to 2 patients; both of which improved.

For children and adults, thiamin could be available for the initial treatment for LD, but its efficacy is not as well established as either coenzyme Q10 or a ketogenic diet. Currently, there is no established treatment for LD².

3-2. Conclusion

In our case, in spite of the presence of bilateral basal ganglia lesion, a diagnosis of LD was quite difficult, due to the normal lactate levels and spastic paraplegia, both are considered as atypical symptoms for LD, and the lack of gene mutations. Adult LD could not be diagnosed until a histochemical examination of the biopsy specimen revealed the COX deficiency without inflammation that indicated a mitochondrial abnormality. Using Rahman's criteria, our patient could be consistent with a "Leigh-like" syndrome. A systematic literature review revealed that adult LD was rare and its clinical manifestations were different from those of children. These differences indicate that additional investigations should be considered when LD is suspected in adults. Together with our systematic literature review, we assembled the following characteristic features of adult LD for early diagnosis:

1. History of cryptogenic thrive failure or signs of mental retardation, pyramidal signs, cerebellar disturbances, ophthalmoplegia, deafness, dysarthria, or other neurological symptoms are present.
2. Bilateral basal ganglia lesions or brainstem lesions with serum or CSF lactate elevation are present. (LST should be considered when resting lactate levels are normal .)
3. Mitochondrial abnormalities are present in muscle pathology or in biochemical analyses, or

known LD gene mutations are present.

4. Metabolic disorders, toxins, infection, multiple sclerosis, and Wernicke's encephalopathy can be excluded.

Early diagnosis and further investigations of treatments for adult LD are expected to improve its prognosis.

Figure legends

Figure 1

- a) Brain CT (left) and T2WI MRI (right) on the first admission. Brain CT showed bilateral low density areas (arrow) in the basal ganglia. MRI showed bilateral and slightly asymmetric T2 high intensity areas (arrow) in the putamen.
- b) Brain CT on the second admission. Brain CT showed diffuse parenchymal edema accompanied by typical bilateral low density areas (arrow) in the putamen and cerebellum. The putaminal lesions were larger than those seen at the first admission.
- c) Histochemical study of the muscle biopsy specimens stained for succinate dehydrogenase (left) and cytochrome c oxidase (center), and a positive control for cytochrome c oxidase (right). Succinate dehydrogenase-reactive blood vessels were not observed. Cytochrome c oxidase was completely deficient

Figure 2

- a) Clinical symptoms and signs observed in the reported cases of adult LD
- b) Laboratory data and neuroradiological abnormalities observed in reported cases of adult LD. Bars represent the percentages of total patients expressing the various symptoms and signs. RCG: Rahman's criteria group, LDG: laboratory diagnosed group.

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Table 1. Laboratory data of our case

Hematologic study		Coagulation study	
WBC	19,400/ μ l	PT	12.7 seconds
RBC	520×10^4 / μ l	APTT	34.0 seconds
Hb	15.4 g/dl	Fibrinogen	502 mg/dl
Plt	35.6×10^4 / μ l	FDP	4.0 μ g/dl
Chemical study		D-dimer	2.53 μ g/dl
TP	6.3 g/dl	Cerebrospinal fluid analysis	
T-Bil	0.3 mg/dl	CSF pressure	>400 mmH ₂ O
GOT	39 IU/l	Cell	10/ μ l
GPT	18 IU/l	Protein	60 mg/dl
LDH	370 IU/l	Glucose	89 mg/dl
CK	2053 IU/l	Muscle pathology	
Amylase	998 IU/l	SSV	negative
BUN	32 mg/dl	COX	complete deficiency
Cr	1.7 mg/dl	Gene analysis	
Na	150 mEq/l	whole mitochondrial genom	normal
K	3.9 mEq/l	<i>SURF1</i> and <i>COX10</i> mutatic	negative
Cl	102 mEq/l		
Ca	7.9 mEq/l		
Lactate	134.4 mg/dl		
Pyruvate	9.46 mg/dl		
NH ₃	55 μ g/dl		

Table 2. List of searched reports

Source	Year	Age	Alive	FH	Sex	Onset	MA	Mutation	Autopsy	Group(items*)
Feigin_1 ⁴	1969	36	No	No	M	0	No	ND	Yes	RCG
Feigin_2 ⁴	1969	30	No	No	F	28	No	ND	Yes	No(2)
Sipe ⁵	1973	32	No	No	F	5	No	ND	Yes	No(2)
Feigin_1 ⁶	1977	50	No	No	M	49	No	ND	Yes	No(1)
Feigin_2 ⁶	1977	84	No	No	F	84	No	ND	Yes	No(1)
Feigin_3 ⁶	1977	66	No	No	M	58	No	ND	Yes	No(1)
Feigin_4 ⁶	1977	58	No	No	M	58	No	ND	Yes	No(1)
Ulrich ⁷	1978	31	No	No	M	31	No	ND	Yes	No(2)
Whetsell ⁸	1978	21	No	Yes	M	6	No	ND	Yes	RCG
Kalimo_1 ¹⁰	1979	62	No	Yes	F	22	No	ND	Yes	No(1)
Kalimo_2 ¹⁰	1979	46	No	Yes	M	13	No	ND	Yes	No(2)
Kalimo_3 ¹⁰	1979	43	No	Yes	M	15	No	ND	Yes	No(1)
Ho ⁹	1979	55	No	No	F	52	No	ND	Yes	No(2)
Gray ¹¹	1984	31	No	No	F	21	No	ND	Yes	No(2)
Maso ¹²	1984	55	No	No	M	55	No	ND	Yes	No(2)
Erven_1 ³⁷	1987	25	Yes	Yes	M	3	No	ND	No	No(3)
Erven_2 ³⁷	1987	23	Yes	Yes	F	9	No	ND	No	No(2)
Erven_3 ³⁷	1987	20	Yes	Yes	F	4	No	ND	No	No(1)
Cummiskey ³⁸	1987	34	No	No	F	ND	No	ND	Yes	No(2)
Kissel ¹⁸	1987	21	No	Yes	F	21	No	ND	Yes	No(2)
Delgado ¹⁷	1987	21	No	No	M	21	No	ND	Yes	No(2)
Bianco_1 ¹⁵	1987	19	Yes	No	M	6	No	ND	No	RCG
Bianco_2 ¹⁵	1987	27	Yes	No	M	12	No	ND	No	RCG
Fulham ¹⁹	1988	32	No	No	F	32	No	ND	Yes	No(2)
Peiffer ³⁹	1988	34	No	Yes	M	9	Yes	ND	Yes	RCG
Halmagyi ²¹	1992	31	No	No	M	29	No	ND	Yes	No(2)
deVries ⁴⁰	1993	56	No	Yes	F	56	No	T8993C	No	LDG
Santorelli ⁴¹	1996	23	Yes	No	F	12	Yes	ND	No	LDG
Morris ⁴²	1996	24	No	No	M	6	Yes	ND	Yes	RCG, LDG
Chalmers_1 ²³	1997	43	Yes	Yes	F	25	Yes	G1644T	No	RCG, LDG
Chalmers_2 ²³	1997	38	Yes	Yes	M	20	Yes	G1644T	No	RCG, LDG
Suzuki ⁴³	1998	20	No	Yes	F	1	No	T8993C	No	LDG
Malandrini ⁴⁴	1998	32	No	No	M	7	No	ND	Yes	No(2)

Kumagai ²⁴	1999	38	Yes	No	F	18	Yes	ND	No	RCG,LDG
Nagashima ²⁵	1999	43	No	No	F	37	No	T8993G	Yes	RCG,LDG
Vilarinho ⁴⁵	2001	21	Yes	Yes	F	0	No	T8993C	No	RCG,LDG
Yamakawa ⁴⁶	2001	22	Yes	No	M	3	Yes	ND	No	RCG
Funalog_1 ⁴⁷	2002	33	No	Yes	M	4	No	hetrol4484	No	LDG
Funalog_2 ⁴⁷	2002	32	No	No	M	18	Yes	hetrol4459	No	LDG
Funalog_3 ⁴⁷	2002	39	Yes	Yes	M	34	No	homo3460	No	LDG
Maldergem_1 ⁴⁸	2002	29	Yes	Yes	F	0	Yes	ND	No	RCG,LDG
Maldergem_2 ⁴⁸	2002	31	Yes	Yes	F	0	Yes	ND	No	LDG
Kirby ⁴⁹	2003	36	Yes	Yes	M	ND	No	G13513A	No	LDG
Yoshinaga ⁵⁰	2003	20	Yes	No	F	0	No	T8993G	No	LDG
Goldenberg ³³	2003	22	Yes	Yes	F	14	No	C7028T +G9547A	No	RCG,LDG
Malojcic ²⁶	2004	21	Yes	No	M	ND	Yes	ND	No	RCG
Piao ²⁷	2006	32	No	Yes	M	17	No	ND	Yes	No (2)
Wick ⁵¹	2007	21	No	Yes	F	21	No	ND	Yes	No (1)
Child_1 ⁵²	2007	24	Yes	Yes	M	6	No	T9185C	No	LDG
Child_2 ⁵²	2007	22	Yes	Yes	M	3	No	T9185C	No	LDG
Child_3 ⁵²	2007	18	Yes	Yes	M	1	No	T9185C	No	RCG,LDG
Child_4 ⁵²	2007	24	Yes	Yes	F	8	No	T9185C	No	LDG
Debray ⁵³	2007	18	Yes	No	M	4	No	T8993C	No	RCG,LDG
Lekha ²⁸	2007	27	Yes	No	M	26	Yes	ND	No	RCG,LDG
Mkaouar-Rebai_1 ⁵⁴	2009	ND	ND	No	M	8	ND	ND	No	No (2)
Mkaouar-Rebai_2 ⁵⁴	2009	ND	ND	Yes	M	7	ND	ND	No	No (2)
Mkaouar-Rebai_3 ⁵⁴	2009	ND	ND	Yes	M	ND	ND	ND	No	No (2)
Sobreira ⁵⁵	2009	42	Yes	Yes	M	0	No	T8993G	No	RCG,LDG
Present case		26	No	No	F	13	Yes	ND	No	RCG,LDG

* Number of items fulfilling the Rahman's criteria, RCG: Rahman's criteria group, LDG: laboratory diagnosed group, ND: not determined, MA: mitochondrial abnormality demonstrated by muscle biopsy or other procedures, "Yes": mitochondrial abnormality exists, "No": mitochondrial abnormality was not determined or examined, FH: family history

Fig.1

a)

b)

c)

Figure 2-a

Figure 2-b