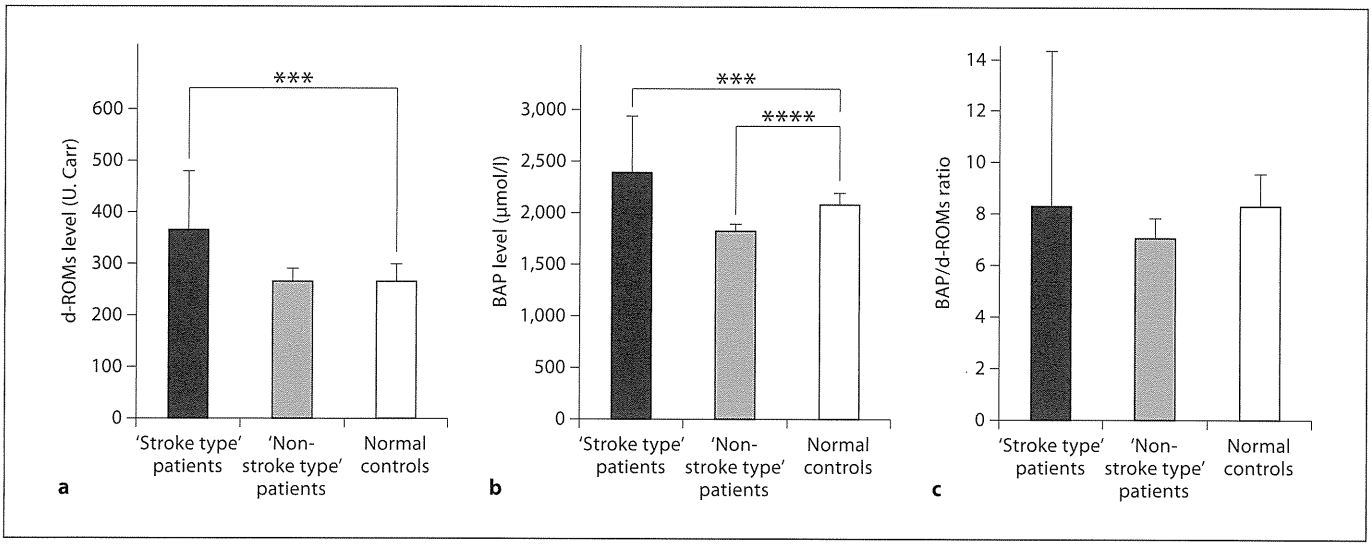

Fig. 2. The mean d-ROMs (**a**) and BAP (**b**) levels and mean BAP/d-ROMs ratio (**c**) in the 'stroke type' patients (black), 'non-stroke type' patients (grey) and controls (white). *** $p < 0.01$, **** $p < 0.001$, according to the Dunn test. Bars indicate mean ± SD.

(259.1 ± 42.0 U. Carr; $p < 0.005$) (fig. 1a). In particular, the mean d-ROMs level of the 'stroke type' patients (361.0 ± 119.6 U. Carr) was significantly greater than that of the controls ($p < 0.01$) (fig. 2a). Meanwhile, the mean d-ROMs level of 'non-stroke type' patients (261.5 ± 28.0 U.Carr) demonstrated no significant differences compared with those of the controls and 'stroke type' patients (fig. 2a).

The mean BAP level of all patients (2,258.9 ± 517.7 μmol/l) was not significantly different compared with that of the controls (2,057.6 ± 149.5 μmol/l) (fig. 1b). However, compared with the controls, 'stroke type' patients (2,428.9 ± 523.1 μmol/l) demonstrated significantly high BAP levels ($p < 0.01$), and 'non-stroke type' patients (1,834.0 ± 59.2 μmol/l) demonstrated significantly low BAP levels ($p < 0.001$) (fig. 2b). There was no significant difference between 'stroke type' patients and 'non-stroke type' patients in terms of the mean BAP levels.

The mean BAP/d-ROMs ratio of all patients (7.87 ± 5.05) was significantly lower than that of the controls (8.13 ± 1.30; $p < 0.02$) (fig. 1c). However, there were no significant differences among the controls and patient groups (fig. 2c).

There was no relationship between the functional status evaluated by performance status rating and the d-ROMs level or BAP level or BAP/d-ROMs ratio.

Discussion

In the present study, the d-ROMs and BAP tests were applied to evaluate the redox states in serum of patients carrying A3243G. These tests demonstrated that oxidative stress represented by the d-ROMs levels was increased and redox balance represented by the BAP/d-ROMs ratios was decreased (tendency for oxidation) in the patients compared with those of the controls (fig. 1). These findings suggested that an imbalance of redox states due to mitochondrial dysfunction affects the pathogenesis in patients carrying A3243G.

In the 'stroke type' patients in particular, both d-ROMs levels (oxidative stress) and BAP levels (antioxidant activity) were increased compared with those of the controls (fig. 2a, b). In vitro studies previously demonstrated that A3243G enhances ROS generation leading to oxidative stress [7–10], and enhanced oxidative stress is proportional to mitochondrial dysfunction [7, 23]. In the present study, all of the 'stroke type' patients have been treated with antioxidants, and 8 out of 10 patients were also treated with an oral administration of L-arginine. Although serum antioxidant activity may be increased by antioxidants and L-arginine therapy, serum oxidative stress was still increased in 'stroke type' patients. Increased oxidative stress even with increased antioxidant activity suggested a severe deterioration of mitochondrial function in patients with a history of stroke-like epi-

sodes, and that oxidative stress plays a crucial role not only in the brain lesions of stroke-like episodes [11, 12] but also systemically in these patients. In other words, a history of stroke-like episodes indicates that patients who have these episodes are exposed to underlying oxidative stress.

In the 'non-stroke type' patients, the mean d-ROMs level (oxidative stress) was not significantly different compared with that of the controls (fig. 2a). Meanwhile, the BAP levels (antioxidant activity) were significantly decreased (fig. 2b). Only 1 of 4 patients was treated with antioxidants, and antioxidant therapy may not affect antioxidant activity in 'non-stroke type' patients. These findings may reflect that antioxidants are consumed in order to prevent increase of oxidative stress in these patients. In addition, the difference of profiles in redox states between 'stroke type' and 'non-stroke type' suggested phenotypic diversity in patients carrying A3243G.

In the present study, we presented redox states in the serum of patients carrying A3243G using the d-ROMs and BAP tests. Rapid evaluation of redox states in serum has been difficult to date. To assay oxidative stress in serum, the spin trap method using electron spin resonance (ESR) has been the most reliable method [24]. However, performing ESR is cumbersome, thus it is difficult to apply this method in clinical practice. The d-ROMs test can evaluate oxidative stress in serum by measuring oxides due to hydroperoxides, and this test has been validated by ESR [25]. Likewise, each endogenous antioxidant can be measured, but there has been no method estimating the whole activity of endogenous antioxidants in serum to date. The BAP test provides a reliable indicator of the antioxidant activity in serum by measuring the ability to reduce ferric to ferrous ions [15]. Moreover, the d-ROMs and BAP tests only need a small amount of blood, and require only 15 min for measurement. Therefore, these methods are prompt and reliable, and suitable for evaluating redox states in patients.

Previous studies using postmortem organs or positron emission tomography imaging have demonstrated regional enhancement of oxidative stress in the brain lesions of stroke-like episodes and the heart lesions of cardiomyopathy in patients carrying A3243G [11–13]. Although enhanced oxidative stress due to A3243G has been proven in these lesions, systemic oxidative stress in patients carrying A3243G has not been evaluated to date. The present study demonstrated a systemic and underlying imbalance of redox states in these patients.

The present study has some limitations. (1) The 'non-stroke type' group included only 4 patients. (2) The mean age of 'non-stroke type' patients was likely older than that of 'stroke type' patients. (3) The 'stroke type' group included only 2 of 10 patients with cardiomyopathy or diabetes, which might affect the systemic redox states. (4) All of the 10 'stroke type' patients received antioxidant therapy, but only 1 of the 4 'non-stroke type' patients received antioxidant therapy. (5) This study did not show any significant difference in either value of oxidative stress or antioxidant activity between the 'stroke type' and 'non-stroke type' groups. (6) The possibility that the 'non-stroke type' patients in this study will also subsequently develop stroke-like episodes cannot be ruled out. Further studies are necessary to confirm our preliminary results.

Taken together, the d-ROMs and BAP tests clearly demonstrated an abnormality of redox states in patients carrying A3243G. In particular, enhanced oxidative stress in patients with a history of stroke-like episodes may reflect severe mitochondrial dysfunction, which would contribute to the emergence of stroke-like episodes. In addition, in patients without stroke-like episodes, consumption of antioxidant activity may indicate latent oxidative stress. These findings suggested that patients carrying A3243G are always exposed to underlying oxidative stress, and further antioxidant therapy would be beneficial to prevent an intensification of the symptoms.

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Disclosure Statement

The authors report no conflicts of interest.

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Original article

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

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Abstract

Leigh syndrome (LS) is a progressive untreatable degenerating mitochondrial disorder caused by either mitochondrial or nuclear DNA mutations. A patient was a second child of unconsanguineous parents. On the third day of birth, he was transferred to neonatal intensive care units because of severe lactic acidosis. Since he was showing continuous lactic acidosis, the oral supplementation of dichloroacetate (DCA) was introduced on 31st day of birth at initial dose of 50 mg/kg, followed by maintenance dose of 25 mg/kg/every 12 h. The patient was diagnosed with LS due to a point mutation of an A–C at nucleotide 599 in exon 6 in the pyruvate dehydrogenase E1α gene, resulting in the substitution of aspartate for threonine at position 200 (N200T). Although the concentrations of lactate and pyruvate in blood were slightly decreased, his clinical conditions were deteriorating progressively. In order to overcome the mitochondrial or cytosolic energy crisis indicated by lactic acidosis as well as clinical symptoms, we terminated the DCA and administered 0.5 g/kg/day TID of sodium pyruvate orally. We analyzed the therapeutic effects of DCA or sodium pyruvate in the patient, and found that pyruvate therapy significantly decreased lactate, pyruvate and alanine levels, showed no adverse effects such as severe neuropathy seen in DCA, and had better clinical response on development and epilepsy. Though the efficacy of pyruvate on LS will be evaluated by randomized double-blind placebo-controlled study design in future, pyruvate therapy is a possible candidate for therapeutic choice for currently incurable mitochondrial disorders such as LS.

Keywords: Leigh syndrome; PDH E1α mutation; Pyruvate; Lactic acidosis; Therapy

1. Introduction

LS, originally reported as subacute necrotizing encephalomyelopathy by Dr. Denis Leigh in 1951 [1], is an early-onset progressive neurodegenerative disorder characterized by developmental delay or regression, lactic acidosis, and bilateral symmetrical lesion in the basal ganglia, thalamus, and brainstem [2]. The clinical presentations of the disease are heterogeneous, due to the severity of biochemical defects caused by mutations in both nuclear and mitochondrial genes involved in energy metabolism. Though many molecular defects are reported to be associated with LS [3], the underlying gene defects remain unidentified in nearly half of the patients [4,5]. Since LS is associated mainly with the respiratory chain deficiency, there is no established treatment except for a limited number of patients such as those with thiamine-responsive pyruvate dehydrogenase deficiency [6], or those with defects in the biosynthetic pathway of coenzyme Q [7]. We have proposed that pyruvate has a therapeutic potential for mitochondrial diseases, because: (a) pyruvate can stimulate the

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glycolytic pathway by reducing the NADH/NAD ratio in the cytoplasm, (b) pyruvate can activate PDHC by inhibiting pyruvate dehydrogenase kinase, and (c) pyruvate can scavenge hydrogen peroxide by non-enzymatic reaction [8]. Recently, we reported that pyruvate produced a slightly favorable change in the plasma lactate and pyruvate levels in LS with cytochrome c oxidase deficiency [9]. In the present report, we describe a clinical experience of pyruvate therapy in a child with LS having PDH deficiency caused by a novel mutation in PDH E1α gene.

2. Patient and methods

2.1. Patient

The 5-years-old boy, presented as severe psychomotor retardation with severe lactic acidosis, was born weighing 1797 g at full term gestational age as the second child of unconsanguineous parents. He was transferred to neonatal intensive care units because of fatal distress with the severe lactic acidosis. The concentrations of lactate and pyruvate in blood were 6–10 times higher than normal range, with normal lactate/pyruvate ratio (Table 1). He was under respiratory care with medication of severe metabolic acidosis. Aminogram of his plasma showed an elevated alanine concentration of 1.82 mM (normal range, 0.21–0.52). Since he was showing continuous lactic acidosis, the oral supplementation of DCA was introduced on 31st day of birth at initial dose of 50 mg/kg, followed by maintenance dose of 25 mg/kg/every 12 h. Though he showed severe floppy infant, his mechanical ventilation has been terminated at the 45th day of birth, and starting oral administration of ingredient nutrient. Although the concentrations of lactate and pyruvate in blood were

Table 1
Biochemical parameters during therapy with none, DCA, or pyruvate.

	None ($n = 8$)	DCA therapy ($n = 12$)	Pyruvate therapy ($n = 10$)
Lactate (mM) (normal: 0.03–0.17)	9.6 ± 0.54	8.6 ± 2.63	5.28 ± 1.73[a,b]
(Range: minimum–maximum)	(8.70–10.10)	(3.56–12.70)	(2.73–7.75)
Pyruvate (mM) (normal: 0.003–0.10)	0.69 ± 0.13	0.61 ± 0.19	0.42 ± 0.13[a,b]
(Range: minimum–maximum)	(0.49–0.82)	(0.31–0.93)	(0.26–0.68)
L/P ratio (normal: 10–15)	14.5 ± 3.10	14.2 ± 2.12	12.6 ± 1.52
(Range: minimum–maximum)	(10.6–18.7)	(11.5–17.9)	(10.5–15.1)
Alanine (mM) (normal: 0.21–0.52)	1.7 ± 0.28	1.13 ± 0.27[a]	0.77 ± 0.38[a]
(Range: minimum–maximum)	(1.11–1.82)	(0.76–1.51)	(0.39–1.42)

All date are presented as mean ± SD during each treatments.
Lactate, pyruvate L/P ratio, and alanine were analyzed the significance between periods of none, DCA and pyruvate therapy using the two-tailed Mann–Whitney *U*-test. *P* value less than 0.05 showed significant.
[a] It showed significance between none and DCA or pyruvate therapy.
[b] It showed significance between DCA and pyruvate therapy. *n*: number of measurements.

Table 2
Entire clinical course and symptoms.

	Clinical course		
	None	DCA	Pyruvate
Study periods	1 month (1 m)	17 months (2–18 m)	58 months (1 year 6 months–6 years 4 months)
Hospitalization (day)	31	124	3
Emergency visit (time)	0	14	4
Diagnosis by EEG	Infantile epilepsy	West syndrome or Lennox–Gastaut syndrome	Lennox–Gastaut syndrome
Convulsion			
Frequency	15 or more/days	18 or more/days	2–3/months
Duration	5–15 s/Epilepsy	5–20 s/Epilepsy	5–10 s/Epilepsy
Series formation	None	Series formation	No series formation
Anticonvulsants	Phenobarbital 20 mg/kg/day	Carbamazepine 10 mg/kg/day Valproate 10–15 mg/kg/day Clobazam 1.0 mg/kg/day Zonisamide 2–4 mg/kg/day	Carbamazepine 10 mg/kg/day Valproate 15 mg/kg/day Clobazam 1.5 mg/kg/day Zonisamide 2–4 mg/kg/day
JMDRS	58	58	57
Developments	Severe floppy infant Respiratory care	Cannot head control Cannot sit alone Cannot rolling over Floppy infant Eating mainly by S-tube	Floppy infant Head control (21 months) Rolling over (42 months) Sit alone (56 months) Eating mainly by mouth

slightly decreased by DCA, his clinical conditions were deteriorating progressively. He could not fix the head control, and roll over at 6 months of age. He was diagnosed with West syndrome at 6 months-old because of his intractable generalized convulsions. Though he received two types of anti-convulsants as shown in Table 2, his convulsion did not stop and showed several seizures a day with series formation. Brain MRI on 7-months-old showed a premature myelination and atrophy in frontal lobe with callosal hypoplasia, and brainstem abnormality. He showed severe floppiness, loose head control, inability to sit alone and roll over, feeding difficulty, and no significant words at the age of 18 months-old. His EEG pattern changed to Lennox–Gastaut syndrome at that time (Fig. 1A). Nerve conduction velocity in both motor and sensory nerve showed low amplitude with delayed velocity indicating severe neuropathy. At this point, we thought that severe neuropathy seen in the patient may caused by the severe adverse effects of DCA, since he received the DCA supplementation for more than 17 months period. Because of the severe neuropathy, we decided to terminate the DCA at his age of 18 months-old, and after received written informed consent, we started the oral supplementation of sodium pyruvate at 0.5 g/kg/day TID. Three months later, he started to roll over and showed the facial expression of happiness and sadness. He could start to chatter and swallow the liquid food. Six months after starting pyruvate supplementation, he had almost no epileptic seizure and was demonstrated the significant improvement by EEG (Fig. 1B). The entire clinical course is summarized in Fig. 2 and Table 2.

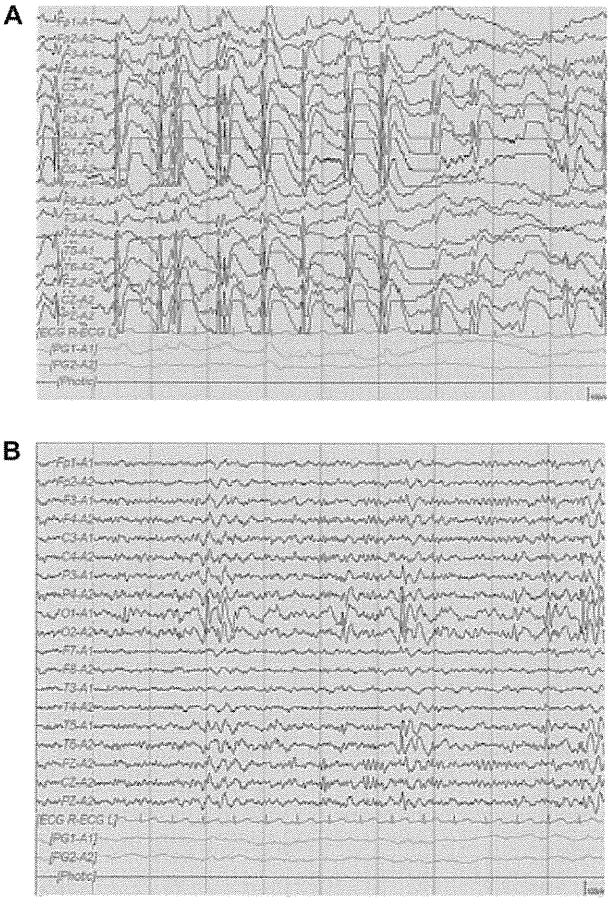

Fig. 1. (A) EEG taken at 18 months old. A grossly abnormal inter-ictal EEG showed continuous, high-amplitude, sharp-slow-waves or spike-slow-waves indicating a multifocal and generalizing sharp-slow-wave-discharges at 1.5–2.5 Hz. Patient showed intractable epilepsy with 15–20 times a day of grandmal, and/or myoclonic type seizure. (B) EEG taken at 36 months old. An abnormal inter-ictal EEG pattern showed with continuous, sharp-slow-waves or spike-slow-waves. However it showed low-amplitude and less multi-focality. Patient showed no grandmal or myoclonic type seizure by daily base frequency.

The lactate and pyruvate concentrations in cerebral spinal fluid were 8.23 mM, and 1.26 mM under the period of DCA therapy, and 4.61 mM and 0.68 mM under the period of pyruvate therapy (Fig. 2).

2.2. Lactate, pyruvate, L/P ratio and alanine determination

In order to investigate the energy state of patient in each time period of therapy, we measured the plasma level of lactate, pyruvate and aminogram including alanine, 8 times in the periods of 31 days with free of DCA and pyruvate, 12 times in 17 months during DCA therapy, and 10 times in 58 months during pyruvate therapy. Analysis of amino acids was performed on protein-free extracts of fresh plasma using described methods.

2.3. Enzyme assays

The PDHC activity in cultured skin fibroblasts was assayed using two different concentrations of TPP (0.4 and 1104 mM) after the activation of PDHC using DCA as previously described [10].

2.4. Genetic analysis

Mutation analysis of the E1α gene, a major cause of PDHC deficiency, was performed using genomic DNA from cultured skin fibroblasts. For the genetic analysis of the 11 exons of the E1α gene, the individual exons were amplified using primer pairs and conditions as described previously [11].

2.5. Statistical analysis

Statistical analysis of the biochemical data including lactate, pyruvate, L/P ratio, and alanine was performed using two-tailed Mann–Whitney *U*-test or Student's *t*-test. A value of $P < 0.05$ was considered as statistically significant.

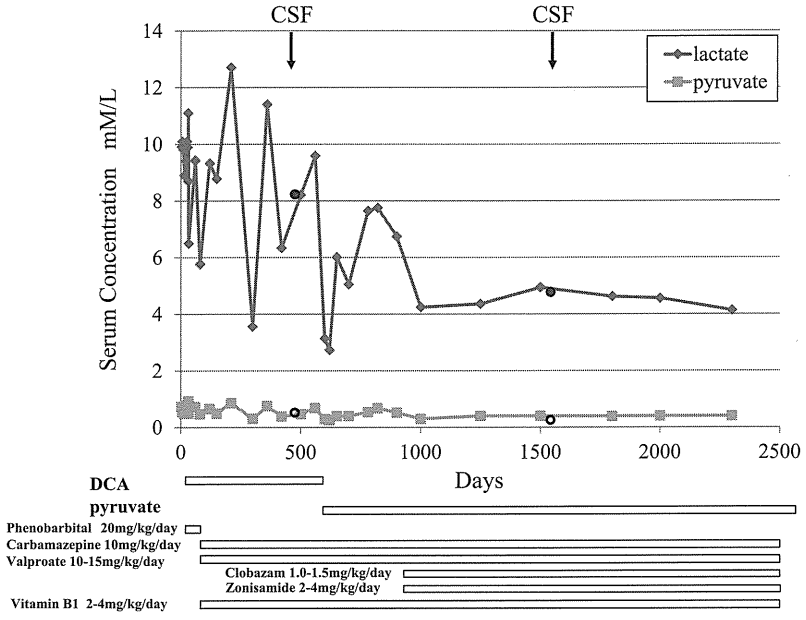

Fig. 2. Entire clinical course.

3. Results

Since patient showed lactic acidosis with normal lactate/pyruvate ratio, we measure the PDHC activity in cultured skin fibroblasts cells. The PDHC activity was 0.94 in the presence of DCA and 0.4 mM TPP (normal: 4.07 ± 0.68 nmol/min/mg protein). Mutation analysis of PDH E1α subunits revealed a point mutation of an A–C at nucleotide 599 in exon 6, resulting in the substitution of aspartate for threonine at position 200 (N200T). Though this mutation has not been reported before, we considered it as the responsible gene defect in this patient because; (1) no other mutations were found in entire PDH E1α gene, (2) conserved amino acid in different species, (3) mother has the mutation in hemizygous condition, and (4) no same mutation found in 50 normal females.

The laboratory data before, and after the treatment by DCA, and after pyruvate treatment are shown in Table 1 and Fig. 2. The concentration of lactate and pyruvate in blood before the treatment was 51–58 times higher than normal range, with normal lactate/pyruvate ratio (Table 1). The concentration of alanine was also increased 2.1–3.5 times higher than normal range. After the treatment by DCA, though the concentration of lactate and pyruvate showed no significance, the concentration of alanine was significantly decreased. The patient showed intractable seizures, and decreased the activity of daily living. After the treatment by pyruvate, the concentration of lactate and pyruvate were significantly decreased in comparison with those without therapy, and with DCA treatment, with significantly decreased level of alanine (Table 1 and Fig. 2). The concentrations of lactate and pyruvate in the CSF were also significantly decreased with significantly decreased plasma level of alanine (Fig. 2).

4. Discussion

LS, the most dominant sub-type of mitochondrial disorders in children, are clinically more severe and patients usually die before the first decade of the life. In another words, LS showed the most severe cytopathy among subtypes of mitochondrial disorders. Therapeutic target of mitochondrial angiopathy is now on-going of L-arginine as an investigator-mediated clinical trial on MELAS [12]. However there are no clinical trial of therapeutic approach for mitochondrial cytopathy especially LS. Since the severe adverse events of DCA reported in 2006 [13], the new therapeutic drugs to prevent or improve the mitochondrial cytopathy or lactic acidosis have to be developed as a substitute for DCA.

In the present study, we reported a patient with LS caused by a novel PDH E1α mutation who responded to pyruvate administration for 3 years period. Pyruvate therapy significantly decreased the lactate, pyruvate and alanine levels, showed no adverse effects such as severe neuropathy seen in this patient under the DCA therapy, and had better clinical response on development and epilepsy. It was reported that pyruvate percolates through the blood brain barrier via monocarboxylate transporters and provides an excellent energy state for neurons and astroglia [14]. As shown in our patient (Fig. 2), pyruvates decreased lactate and alanine levels not only in blood but in CSF, and improved the electroencephalogram in our patient, suggested that pyruvate

may pass through blood-brain barrier and improve the metabolic condition in the brain in our patient. We have proposed that pyruvate has a therapeutic potential for mitochondrial diseases, because: (a) pyruvate can stimulate the glycolytic pathway by reducing the NADH/NAD ratio in the cytoplasm [8], (b) pyruvate can activate the pyruvate dehydrogenase complex (PDHC) by inhibiting the pyruvate dehydrogenase kinase [8,9], and (c) pyruvate can scavenge the hydrogen peroxide by a non-enzymatic reaction [15]. Pyruvate improved the hemodynamic condition by intracoronary infusion in patients with congestive heart failure [16,17], or the neurological recovery following cardiopulmonary arrest and resuscitation [18]. In our patient, we determined the daily supplement of pyruvate by the presence of diarrhea as adverse effects or by the capacity of amount of oral administration. In our patient, daily administration of sodium pyruvate resulted in 0.5d/kg/day TID. The exact pharmacological mechanisms why serum pyruvate is also decreased after the pyruvate therapy, have to be clarified in future study, by using proteome analysis or comprehensive multiple analysis of total cell metabolism.

Considering the progressive nature of LS, pyruvate may prevent the neurodegeneration and lactic acidosis in our patient. Though the efficacy of pyruvate on LS will be evaluated by randomized double-blind placebo-controlled study design in future, pyruvate therapy is a possible candidata for therapeutic choice for currently incurable mitochondrial disorders such as LS.

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Ⅴ．ミトコンドリア病ハンドブック

ミトコンドリア病ハンドブック

国立精神・神経医療研究センター病院　遺伝カウンセリング室

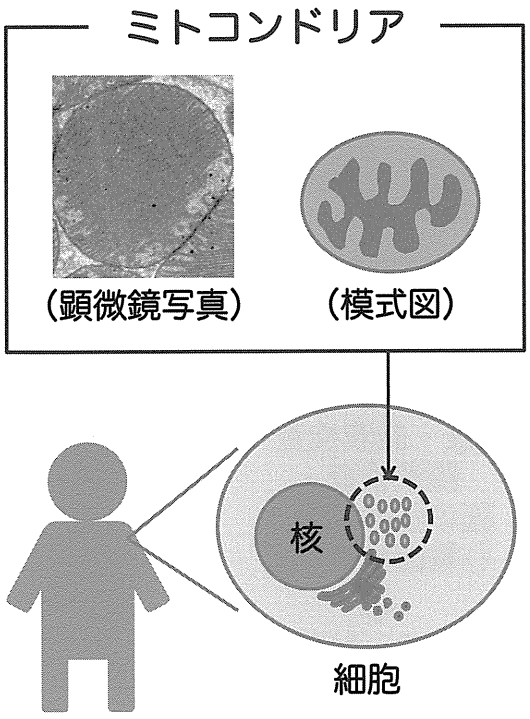
もくじ

はじめに

このハンドブックは、ミトコンドリア病をもつ患者さんとそのご家族に、
病気への理解を深めるときの参考としていただくために作成しました。
各項目について、イラストと文章での説明があります。
イラストは、医療者から当事者の方へ説明するときの資料として、
文章は、当事者の方がご自身で読んで理解するときの補足説明として、
利用していただけるようになっています。
分かりにくいところがあれば、医療者へお尋ねください。
また、ミトコンドリア病の症状は多様ですので、
すべての患者さんには当てはまらない内容もたくさん書かれています。
病気とうまく付き合っていくためには、
それぞれの状況に合わせて対応することが大切ですので、
ご自身の病気については、担当の医療機関等でよくご相談ください。

ミトコンドリアとミトコンドリア病

ミトコンドリア



《細胞内での働き》

エネルギーの合成

活性酸素の発生

アポトーシス

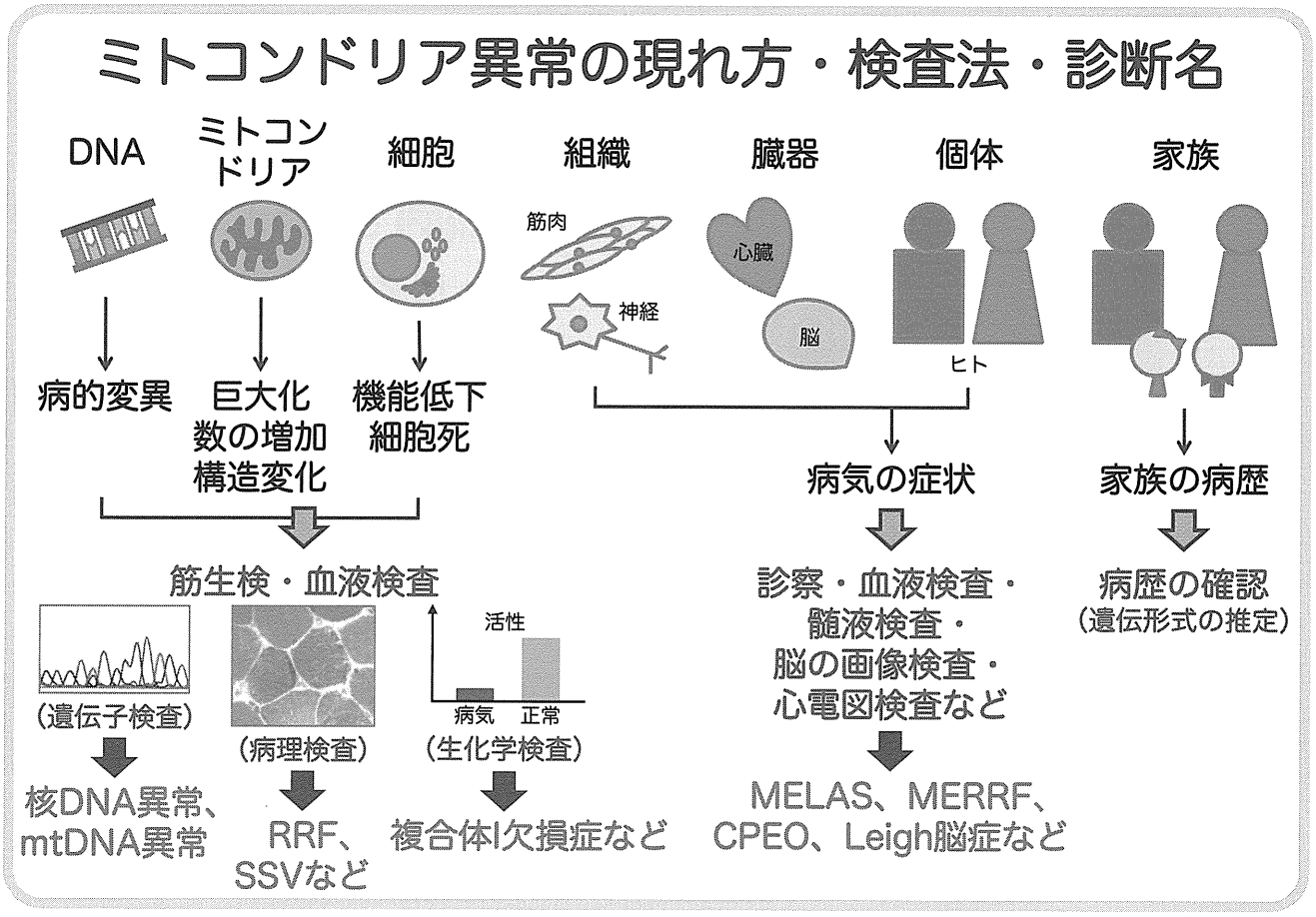
カルシウムの貯蔵

感染の防御

ミトコンドリアの異常
→ ミトコンドリア病

私たちの体は、たくさんの細胞でできています。
その細胞の一つ一つの中にミトコンドリアは存在しています。
一つの細胞に数百個のミトコンドリアが入っていて、
細胞に必要なエネルギーを作り出しています。
そのため、ミトコンドリアに異常が生じると細胞の働きが悪くなり、
さまざまな症状が現れます。これがミトコンドリア病です。
体のどこのミトコンドリアに異常が生じるかによって症状は異なります。

また、ミトコンドリアは、活性酸素の発生、アポトーシス（細胞死）、
カルシウムの貯蔵、感染の防御などにも関わっていて、
ミトコンドリア病以外のさまざまな病気にも関与しています。



ミトコンドリアの異常を調べる検査には多くの種類があります。
どの検査でどのような異常が見つかるかによって、
ミトコンドリアの異常はさまざまな形で現れます。
たとえば、設計図であるDNAには、
病気を引き起こす変化（病的変異）が起きます。
DNAに病的変異があるミトコンドリアは、大きさや数、構造が変化し、
そのミトコンドリアをもつ細胞は、機能が低下したり、死んだりします。
そして私たちの体のさまざまな部分（臓器）に症状となって現れます。
DNAは先祖から代々受け継がれるものなので、
家族の中に同じような症状をもつ方がいる場合もあります。

特定疾患治療研究事業

ミトコンドリア病の認定基準（1）

（1）主症候

① 進行性の筋力低下、又は 外眼筋麻痺を認める。

② 知的退行、記銘力障害、痙攣、精神症状、失語・失認・失行、痙攣、強度視力低下、一過性麻痺、半盲、・皮質盲、ミオクローヌス、ジストニア、小脳失調などの中枢神経症状のうち、1つ以上を認める。

③ 心伝導障害、心筋症などの心症状、糸球体硬化症、腎尿細管機能異常などの腎症状、強度の貧血などの血液症状、中等度以上の肝機能低下などの肝症状のうち、１つ以上を認める。

（1）①から③のうち1項目以上かつ（2）①から⑤のうち2項目以上→確実
（1）①から③のうち1項目以上かつ（2）②から⑤のうち1項目以上→疑い

ミトコンドリア病は、平成21年（2009年）10月に、
国の難病対策の一つである特定疾患治療研究事業の対象に認められました。
この事業は、一定の条件を満たす病気を対象に、
その患者さんの医療費を助成し、原因の究明や治療法の開発などに向けた
調査研究を推進しようとする制度です。

ミトコンドリア病の患者さんであると認定されるためには、
定められた認定基準を満たす必要があります。
具体的には、主症候（主な症状）として、筋肉、中枢神経、心臓、腎臓、
血液、肝臓のいずれかに症状があることが要件となります。

特定疾患治療研究事業

ミトコンドリア病の認定基準（2）

（2）検査・画像所見

① 安静臥床時の血清又は髄液の乳酸値が繰り返して高い、又はMRスペクトロスコピーで病変部に明らかな乳酸ピークを認める。

② 脳CT/MRIにて、梗塞様病変、大脳・小脳萎縮像、大脳基底核、脳幹に両側対称性の病変等を認める。（画像検査所見）

③ 筋生検 又は 症状のある臓器でミトコンドリアの形態異常を認める。（病理検査所見）

④ ミトコンドリア関連酵素の欠損又はコエンザイムQ10などの中間代謝物の欠乏を認める。（生化学検査所見）

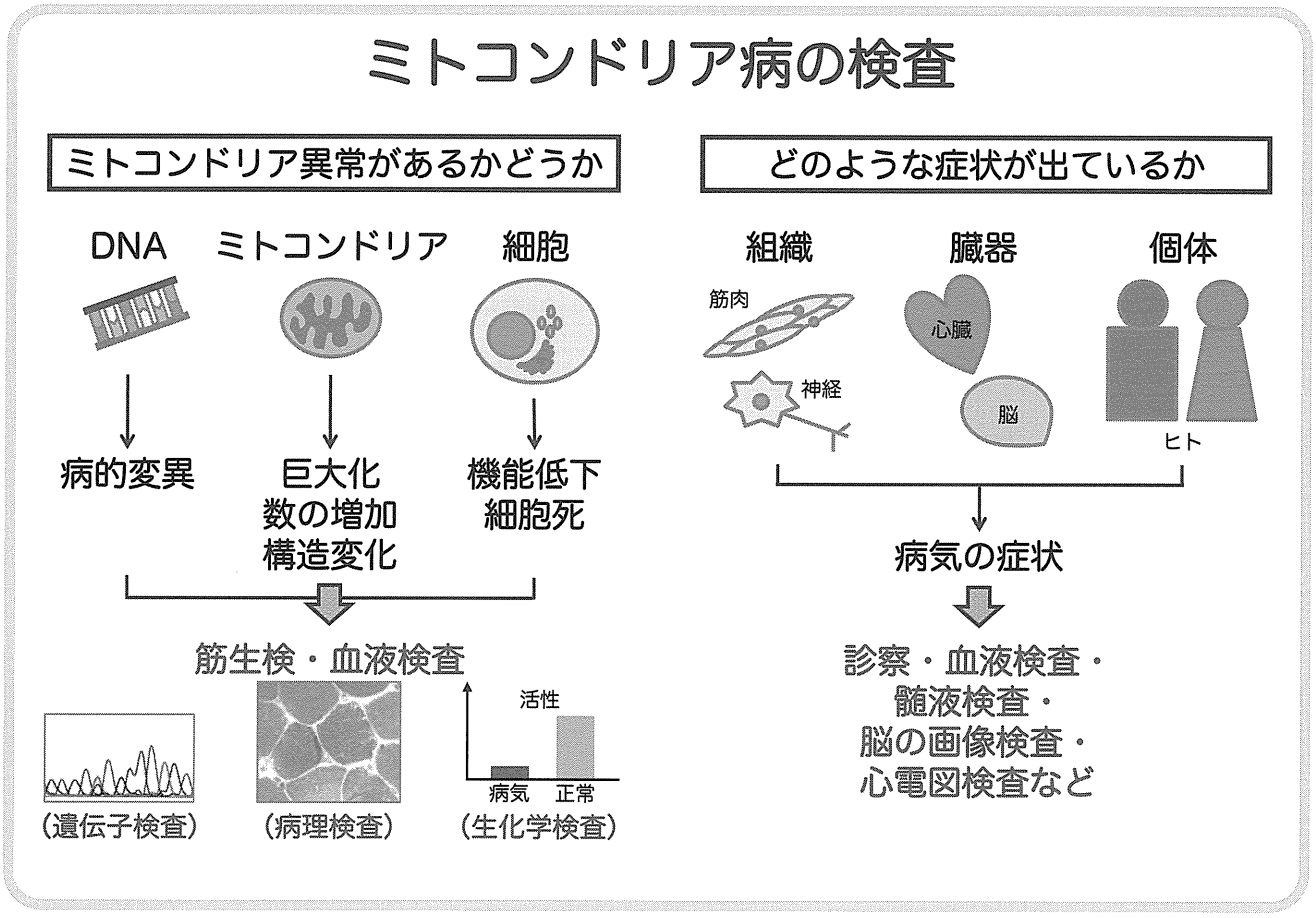
⑤ ミトコンドリアDNAの質的、量的異常、またはミトコンドリア関連核遺伝子変異を認める。（遺伝子検査所見）

（1）①から③のうち1項目以上かつ（2）①から⑤のうち2項目以上→確実
（1）①から③のうち1項目以上かつ（2）②から⑤のうち1項目以上→疑い

主症候に加え、検査で異常な所見が認められるかどうかも基準となります。
どのような所見がいくつ見られるかによって、
「確実」と「疑い」に分類されます。

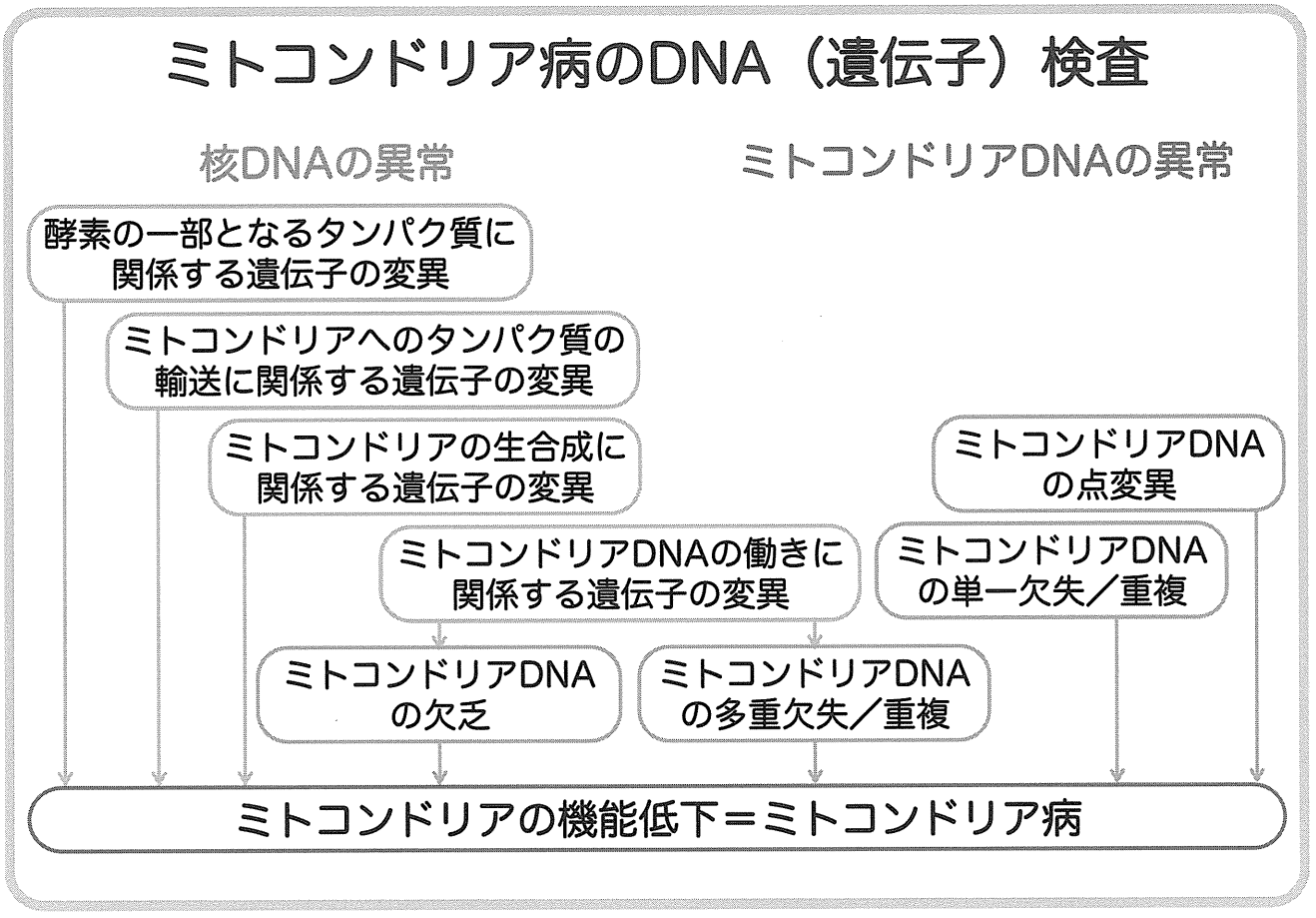
ミトコンドリア病の認定を受けるためには、
「臨床調査個人票」と呼ばれる診断書が必要となりますので、
主治医の先生にご相談ください。

ミトコンドリア病の検査



ミトコンドリア病の検査は、その目的によって大きく二つに分けられます。
一つは、どのような症状が出ているかを調べるための検査（右）です。
脳の画像検査や心電図検査などを行い、
さまざまな臓器に異常があるかどうかを調べます。

もう一つは、ミトコンドリアの異常を調べるための検査（左）です。
筋生検や血液検査で採取した検体を用いて、
DNA（遺伝子）検査、病理検査、生化学検査を実施します。
これによって、ミトコンドリアのDNA、形、働きを詳しく調べることが
できます。



DNA（遺伝子）検査は、筋生検や採血によって採取した細胞から
DNAを取り出して、特定の遺伝子に病的変異があるかどうかを調べます。
病的変異が見つかれば、それが症状の原因であるということが分かります。
ミトコンドリア病の原因となるDNA（遺伝子）の異常は、
核DNAの場合とミトコンドリアDNAの場合があります。
どちらのDNAにどのような異常が生じているかによって、
その由来や次世代への遺伝の仕方が異なります。