
Article abstract—We studied a patient with somatic growth failure with easy fatigability, myopathy with mitochondrial abnormality, increased lactate and pyruvate in blood and CSF, mental retardation, seizure, myoclonus, deafness, cerebellar ataxia, and blindness with macular degeneration and optic atrophy. Pathologic findings included multiple brain infarctions and massive calcification in the basal ganglia. Biochemical studies of isolated mitochondria revealed decreased oxygen consumption in skeletal muscle, diaphragm, and brain, suggesting an abnormality in the respiratory chain.

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Mitochondrial encephalomyopathy with lactate-pyruvate elevation and brain infarctions

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There have been several reports of patients with lactic acidemia and abnormal mitochondria. They can be classified into two groups, ie, one with mainly weakness and wasting of skeletal muscle without brain lesions, and another group with encephalomyopathy. Shapira et al¹ used the term "mitochondrial encephalomyopathy" to encompass the following: Kearns-Sayre syndrome, trichopoliodystrophy (Menkes' kinky hair syndrome), subacute necrotizing encephalomyelopathy (Leigh's syndrome), Alper's disease and other progressive poliomyopathies, Canavan's disease (van Bogaert-Bertrand type spongy degeneration of white matter), the cerebrohepato-renal syndrome of Zellweger, and myoclonus epilepsy syndrome with "ragged red fibers".

Case report. This boy had a normal birth and development, but he was always thin and short, and had chronic intermittent vomiting with acetonuria after age five. He attended elementary school without problems. At age 10, he had limb weakness and seemed to fatigue easily after exercise. Intellectual performance gradually deteriorated. At age 13, he had generalized convulsive seizures that were intractable. There were exacerbations of unsteady gait and myoclonic seizures. His hearing gradually diminished, and he had intermittent tinnitus. He was the second of two children. There was no known consanguinity, and no other members of his family or close relatives had similar symptoms.

On general physical examination at age 14, he was asthenic, 19.5 kg in weight, and 134 cm in height. He had a high palate. A systolic ejection murmur was audible at the apex. There was no cardiomegaly. The liver and spleen were not enlarged. His IQ was 88, but comprehension seemed good. Except for slightly nasal speech, there were no cranial nerve abnormalities. There was diffuse wasting and weakness of all limb muscles. He could rise from a squatting position only with assistance.

Sternocleidomastoid and periorbital muscles were also weak and wasted. Reflexes were generally decreased. Sensation was normal. The heel cords were tight. He had unsteadiness of gait due to truncal ataxia. Bilateral horizontal nystagmus was noted. Visual acuity was almost normal, ocular movement was full, and fundoscopic findings were unremarkable.

Routine hematologic studies, urinalysis, serum proteins, urea nitrogen, uric acid, serum creatine and creatinine, serum electrolytes including Ca and P, serum cholesterol and lipids, fasting blood sugar, arterial blood pH, and serologic reactions were all normal or negative. Liver, renal, thyroid, and parathyroid function tests were normal. Serum enzymes were likewise normal except LDH, which was 562 units (normal, 50 to 400), and CK 55 units (normal, less than 35). Electrocardiograph showed occasional monofocal ventricular premature contractions. However, there was no abnormal finding by phonocardiography and echocardiography. Roentgenograms of the chest, skull, vertebrae, and long bones showed normal configurations. Respiratory function tests indicated poor respiratory reserve suspected to be due to weakness of the intercostal muscles. Bilateral moderate hearing loss of the

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sensorineural type was detected by audiogram. CSF examination disclosed normal pressure, protein, sugar, and cell content. An electroencephalogram showed diffuse slow background activity with paroxysmal spike and wave complexes, as well as focal slow waves mainly over the right posterior area. CT demonstrated diffuse cerebral atrophic changes with secondary ventricular dilatation, and enlargement of ambient and supracerebellar cisterns and cerebellar valliculae, suggesting atrophy of the brainstem and cerebellum, especially the vermis. In addition, symmetrical high density areas, suspected to be calcifications, were present bilaterally in the caudate nucleus, globus pallidus, and dentate with no enhancement. EMG was consistent with myopathy with low voltage and short-duration potentials. Motor nerve conduction velocities were normal. Chromosomal analysis demonstrated a normal male karyotype. Quantitative measurement of amino acids (including alanine) in serum, urine, and CSF was normal, and urinary organic acids, analyzed by gas-liquid chromatography and gas chromatographic mass spectrometry, were normal. Lysosomal glycosidase activities in leukocytes, including β -N-acetyl-hexosaminidase A and B, β -galactosidase, β -glucuronidase, α -glucosidase, α -mannosidase, and arylsulfatase A were all normal.

Lactate and pyruvate. Lactate and pyruvate levels were high in venous blood, CSF, and urine. In the venous blood that was obtained during resting basal state, lactate was 38.9 mg% (normal controls, $n = 29$; 9.43 ± 2.75), pyruvate was 0.97 mg% (normal controls, $n = 29$; 0.46 ± 0.21), and lactate/pyruvate ratio was 40.1. In the CSF, lactate was 42.9 mg% (normal controls, $n = 57$; 11.1 ± 2.4), pyruvate was 1.41 mg% (normal controls, $n = 26$; 0.56 ± 0.19), and lactate/pyruvate ratio was 30.4. In the urine obtained in the early morning, lactate level was 152.4 μ g/mg of creatinine (normal, 20 to 80), and pyruvate level was 137 μ g/mg of creatinine (normal, 20 to 100). Venous lactate and pyruvate levels showed normal response after ischemic exercise, as did venous lactate, pyruvate, glucose, and free fatty acid levels after an oral 50g-glucose-tolerance test. Activities of 11 glycolytic enzymes and metabolites, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase activities in the pentose phosphate pathway were normal in erythrocytes. ATP, ADP, AMP, and NAD contents in erythrocytes were also normal. Blood thiamine level, transketolase activity, and thiamine pyrophosphate effect in erythrocytes also showed normal values.

Treatment and clinical course. Daily intravenous injection of 300 mg of thiamine tetrahydrofurfuryl disulfate (TTFD) for 7 days did not affect venous lactate and pyruvate. After daily oral administration of 1,500 mg of TTFD and 180 mg of lipoic acid, the level of venous pyruvate became normal (0.78 mg%, after 7 days; 0.49 mg%, after 14 days), but lactate did not change. Clinical symptoms did not improve.

The patient was treated with vitamins and anticonvulsants. He failed to gain weight, and the clinical manifestations fluctuated with exacerbations after febrile illness and remissions. He was often readmitted to the hospital. He lost weight and became totally deaf. He had visual difficulty that could not be corrected with glasses; at age 17 there was bilateral macular degeneration and slight optic atrophy. The macular lesion was a well demarcated white-yellow circular spot resembling an egg yolk, and definitely different from a cherry red spot. At age 18, after a common cold, he died.

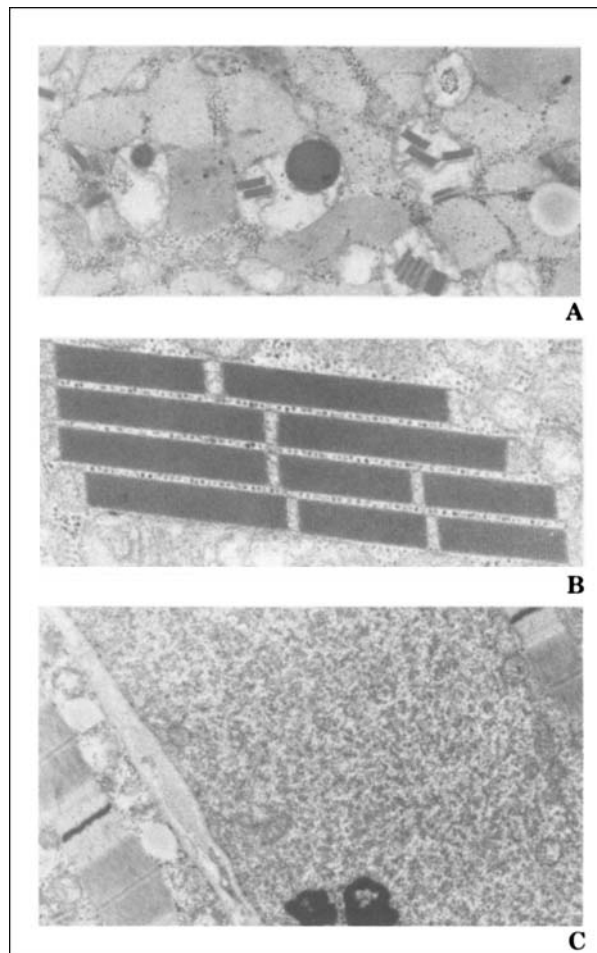


Figure 1. (A) Abnormal mitochondria with paracrystalline inclusion. Note the abnormal dense bodies and increased glycogen granules in mitochondria (original magnification $\times 40,000$). (B) Longitudinal view of paracrystalline inclusion in the pool of mitochondria of the subsarcolemmal area (original magnification $\times 64,000$). (C) Accumulated glycogen in subsarcolemmal space. Note the increased lipid droplets in the adjacent fiber (original magnification $\times 17,000$).

Pathologic and histochemical studies. Muscle (Quadriceps). Muscle fibers ranged from 15 to 60 μ m in diameter, with a slight increase in the number of internal nuclei. Many fibers were degenerating, and some were regenerating or necrotic. With the NADH dehydrogenase stain, areas of increased or decreased oxidative enzyme activity were observed in 20% of fibers, which represented "ragged red fiber" with the modified trichrome stain. With the myosin ATPase, the distribution of histochemical fiber types was preserved. Acid phosphatase activity was high in some fibers. The most prominent ultrastructural change was the presence of abnormal accumulations of mitochondria in the sarcoplasm. Many abnormal mitochondria contained paracrystalline inclusions, and some contained homogenous dense bodies. There were abnormal accumulations of glycogen in the muscle fibers, especially in the subsarcolemmal spaces, intermyofibrillar spaces, and between the accumulated mitochondria.

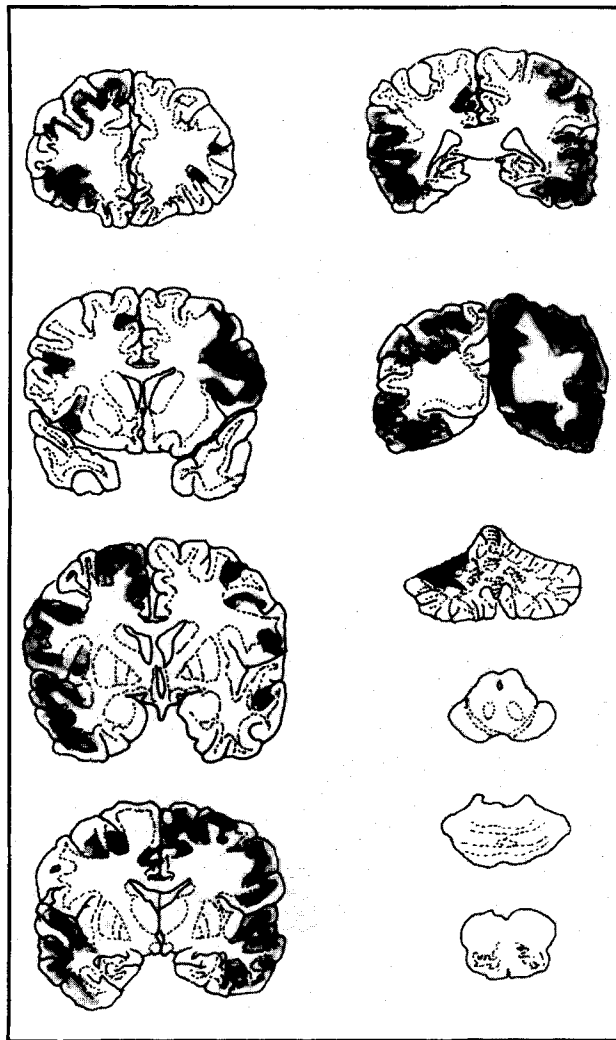


Figure 2. Schematic distribution of brain infarctions. Solitary and continuous foci of infarctions are distributed in both hemispheres, more diffusely in the occipital lobes. The lesions do not correspond to territories of main and focal vascular supply.

Glycogen particles were also found in some mitochondria. Occasionally, lysosomes containing dense material were also observed. In addition, the number of lipid droplets was often increased (figure 1 A, B, and C).

Autopsy studies. The brain weighed 1,150 g and appeared atrophic, especially in the cerebellum and brainstem. On coronal section, solitary and continuous foci of infarction were seen in the cerebral cortex (figures 2 and 3). The cortical lesions were seen in both hemispheres, more diffusely in the occipital lobes, regardless of vascular supply. There were small cystic cavities in the right occipital cortex and dorsal surface of the cerebellar hemispheres. Subcortical white matter was often involved, but deep white matter and subcortical nuclei appeared normal. The spinal cord was well preserved. Histochemically, the cerebral lesions stained poorly, with dilated perivascular and pericellular spaces. Severe atrophy of nerve cells, vesicular enlargement of astrocytic nuclei, slight increase of capillary endothelial cells, and poor staining of myelin sheaths were seen in these foci and also in surrounding areas to a

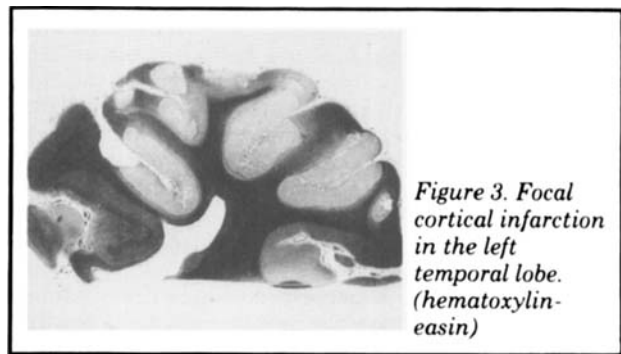


Figure 3. Focal cortical infarction in the left temporal lobe. (hematoxylin-eosin)

lesser degree. Destruction products and astrocytic proliferation were not observed in fresh lesions. Together with the fresh lesions, old but more circumscribed foci with neuronal loss, astrocytic proliferation, and capillary overgrowth were also observed. Older lesions with small cavity formations were seen in the occipital and cerebellar cortices. Massive calcifications were seen in the caudate, pallidum, internal capsule, lateral thalamic nuclei, and dentate nucleus. Fine and coarse mineral granules were deposited in and around the capillary and arterial walls or scattered diffusely, though nerve and glial cells were not affected. In the subthalamic nucleus, substantia nigra, and red nucleus, fine mineral deposits were also seen; otherwise, they were unremarkable. Occasional nerve cells in the pontine nucleus, dorsal nuclei in the medulla, and reticular nuclei showed central chromatolysis and swelling of perikarya. Slight loss of nerve cells and glial proliferation were seen in the olivary nucleus. No significant change was seen in the spinal cord, peripheral nerves, and retina, though a slight decrease of nerve fibers and gliosis were observed in the optic tracts. Electronmicroscopic observation of the acoustic nerve did not disclose any abnormality.

Postmortem biochemical studies. Human tissues, heart (left ventricular muscle), kidney (renal cortex), liver, skeletal muscle (right biceps muscle), diaphragm, cerebral cortex, and cerebellar cortex, were obtained at autopsy within 90 minutes of death, frozen immediately on dry ice, and stored at -80°C until use. The enzymes of pyruvate metabolism were assayed as follows: α -keto acid dehydrogenase complex and component enzymes,² pyruvate carboxylase,³ phosphoenolpyruvate carboxykinase,⁴ and lactate dehydrogenase.⁵ A piece of each tissue was also kept on ice for 12 hours after death. Mitochondrial fractions of tissues, except brain, were prepared by the modified method of Hogeboom et al.⁶ Brain mitochondrial fractions were prepared by the method of Stahl et al.⁷ Oxygen consumption was measured polarographically at 30°C with Clark type oxygen electrode,⁸ and protein was determined by a biuret method.⁹ About 10% tissue homogenate was prepared with 0.02 M potassium phosphate buffer (pH 7.4) by an automatic operation of Polytron Type PT-10 at 16,000 rpm, for 30 seconds under cooling. Whole homogenate was immediately subjected to pyruvate carboxylase assay, and the rest of homogenate was subjected to one freezing-thawing cycle for solubilization of the other enzymes associated with pyruvate metabolism.

The enzymes of pyruvate metabolism in heart, kidney, liver, skeletal muscle, diaphragm, cerebral cortex, and cerebellar cortex were normal specimens collected at biopsy or autopsy. The oxygen consumption rates of skeletal muscle, diaphragm, and brain mitochondrial fractions were signifi-

Table. Oxygen consumption in mitochondrial fraction

Patient	Cardiac muscle	Kidney	Liver	Skeletal muscle	Diaphragm	Cerebral cortex	Cerebellar cortex
-Q _{O₂}	398.7	612.6	415.6	23.7	35.8	10.8	36.5
Relative ratio (other tissue Q _{O₂} /heart Q _{O₂})	1.00	1.54	1.04	0.06	0.09	0.03	0.09
Control							
Relative ratio* (other tissue Q _{O₂} /heart Q _{O₂})	1.00	2.18	1.08	0.30	0.74	1.37 - 0.59	

- Q_{O₂} is expressed as nmol/min/g wet weight tissue.
 * The value was cited from Biochemists Handbook, (Long C, ed. London: E & FN Spon Ltd., 1961:795-810).
 The reaction mixture (3 ml) contained 0.15 M KCl, 0.005 M MgCl₂, 0.005 M potassium phosphate buffer (pH 7.4), 0.003 M sodium succinate, and 1.2 to 13.8 mg of mitochondrial protein. Reaction was started by addition of the substrate.

cantly less than heart, kidney, or liver (table). Oxidative phosphorylation of mitochondria could not be investigated.

Discussion. This patient had growth failure, easy fatigability after exercise, and increased lactate and pyruvate in blood, CSF, and urine, and myopathy with abnormal mitochondria. In addition, he had mental retardation, generalized seizure, myoclonus, severe nerve deafness, cerebellar ataxia, blindness with macular degeneration and optic atrophy, and basal ganglia calcifications. Pathologically, widespread cortical infarcts did not correspond to the territories of the main blood vessels, and there was no evidence of thromboembolism. Nerve cells in the Sommer's sector of the Ammon's horn, striatum, tectal region of the brainstem, and Purkinje's cells outside of ischemic foci were preserved. It seemed unlikely that the multiple infarctions were due to deficient oxygen supply or repetitive convulsions. Calcification of basal ganglia was also prominent, but parathyroid function was normal. In "idiopathic" cases, calcification is mainly in the globus pallidus,¹¹ but in our patient the massive calcifications were distributed not only in the globus pallidus but also in the caudate, internal capsule, lateral thalamic nucleus, and dentate nucleus.

Similar cases have had no consistent symptoms, and suggest that they do not indicate a single disease but that there are several different disorders which are strongly suggestive of a metabolic derangement. Eighteen reported cases have had evidence of mitochondrial encephalomyopathy associated with elevation of lactate or pyruvate.¹²⁻²² Cerebral manifestations included mental retardation,^{15-17,19,20,22} seizures,^{12,15,17-21} myoclonus,^{13,15,20,21} ophthalmoplegia,¹⁶ retinal pigmentation,^{14,16,22} blindness,^{14,15,18,20-22} hemiplegia suggested to be due to cerebral vascular accident,^{15,17,18} and

basal ganglia calcification.^{15,17-19} Diagnosis has sometimes been based on the pathologic findings in the brain, sometimes on clinical manifestations, and sometimes on biochemical abnormality in muscle. The exact relationships among these disorders have not been established.

The clinical features in our patient were similar to those in the myoclonic epilepsy syndrome with ragged red fibers.^{13,20,21} In those cases, however, the cardinal manifestations were myoclonic jerks and cerebellar ataxia resembling Ramsay-Hunt syndrome. In one case,²⁰ there were neuronal degeneration with marked gliosis, demyelination, and axonal degeneration in the cerebral cortex and some nuclei, and striking abnormalities of the Purkinje's cells with formation of numerous axonal torpedoes and abnormal dendrites in the cerebellum. These findings differed from those in our patient. Bogousslavsky et al²³ described a 26-year-old man with clinical manifestations similar to those in our patient (short stature, bilateral deafness, ataxia, dementia, lactic acidosis, multiple cerebral infarcts, and calcification). They attributed the infarcts to an accompanying cardiopathy that might have caused ischemia or embolism. Multiple areas of infarction in our patient did not correspond to vascular territories, and this mechanism probably differed from the usual thrombotic or embolic process. Macular degeneration was another feature of our patient. This lesion was a well demarcated white-yellow circular spot that resembled an egg yolk, and differed from the cherry red spot of lipid storage disease. The macular finding was similar to that in Best's or Stargardt's macular dystrophy,²⁴ which differed clinically from our patient.

The abnormality of lactate and pyruvate suggested a biochemical disorder of mitochondrial metabolism. There was no evidence or clinical history of hypoxia, ischemia poisoning with exogenous toxins, or intake of oral hypoglycemics, which might

impair pyruvate oxidation. Thiamine deficiency was also ruled out by blood thiamine level, transketolase activity, and thiamine pyrophosphate effect in erythrocytes.²⁵ High CSF lactate and pyruvate contents were noted. CSF lactate is independent of blood lactate, and is an indicator of brain metabolism.²⁶ The cerebral degeneration in this patient was probably due to the primary brain pathology rather than the blood change. Since some genetic disorders of carbohydrate metabolism cause similar syndromes, we measured all enzyme activities and intermediate metabolites of the glycolytic pathway and the main enzymes of the pentose phosphate pathway in erythrocytes, but all enzyme activities and metabolites were normal.

This patient had somatic growth failure, fatigability, and exacerbation of neurologic symptoms after exercise or infection, ie, after hypermetabolism, as well as the increased levels of lactate and pyruvate. These manifestations suggest a disorder of energy metabolism. In postmortem samples, oxygen consumption was decreased in skeletal muscle, diaphragm, and brain, implying a defect of mitochondrial respiration, although the primary site was not disclosed.

Four mitochondrial respiration chain deficiencies have been reported to affect NADH oxidase, cytochrome b, cytochrome c oxidase (aa_3), or cytochrome $aa_3 + b$ in combination. Patients with a defect of NADH oxidase show a variety of clinical features. Four adults²⁷⁻²⁹ had no cerebral signs or symptoms. The clinical features were confined to skeletal muscle, with weakness, wasting, and exercise intolerance. In one fatal case of Alper's disease,³⁰ there was easy fatigability, ataxia, and myoclonus. In two cases of the cerebrohepatorenal syndrome of Zellweger,³¹ infants died before 7 weeks. One 46-year-old man had limb weakness, dementia, optic atrophy, impaired eye movement, and dystonia.²²

Cytochrome b deficiency has been found in four patients. One 46-year-old man had ataxia, dementia, and limb weakness. His 16-year-old son had the same symptoms, and impaired eye movement, ptosis, cataracts, retinitis pigmentosa, myoclonus, and generalized seizures.³² One 38-year-old man had myopathy without cerebral symptoms,³³ and one 48-year-old woman had limb weakness, ataxia, myoclonus, confusion, retinal pigmentary degeneration, and basal ganglia calcification.²²

Patients with cytochrome c oxidase (aa_3) deficiency and combined cytochrome deficiency ($aa_3 + b$) showed a rapid progressive course^{14,34-38} involving skeletal muscle, brain, liver, and kidney. The relationship between clinical and biochemical abnormality has not been established. Different biochemical deficiencies may produce identical clinical phenotypes, the same enzymatic deficiency may have different phenotypical expressions, or an additional unknown biochemical abnormality might cause the variety of clinical features.

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References

- Shapira Y, Harel S, Russell A. Mitochondrial encephalomyopathy: a group of neuromuscular disorders with defects in oxidative metabolism. *Isr J Med Sci* 1977;13:161-4.
- Koike M, Keike K. Biochemical properties of mammalian 2-oxo acid dehydrogenase multienzyme complexes and clinical relevancy with chronic acidosis. *Ann NY Acad Sci* 1982;378:225-35.
- Atkin BM, Utter MF, Weinberg MB. Pyruvate carboxylase and phosphoenolpyruvate carboxylase activity in leukocytes and fibroblast from a patient with pyruvate carboxylase deficiency. *Pediatr Res* 1979;13:38-43.
- Ballard FJ, Hanson RW. Phosphoenolpyruvate carboxylase and pyruvate carboxylase in developing rat liver. *Biochem J* 1967;104:866-71.
- Okabe K, Hayakawa T, Hamada M, Koike M. Purification and comparative properties of human lactate dehydrogenase isoenzymes from uterus, uterine myoma and cervical cancer. *Biochemistry* 1968;7:79-90.
- Hogeboom GH, Schneider WC, Pallade GS. Cytochemical studies of mammalian tissues. I. Isolation of intact mitochondria from rat liver: some biochemical properties of mitochondria and submicroscopic particulate material. *J Biol Chem* 1948;172:619-35.
- Stahl WL, Smith JC, Napolitano L, Basford RE. Brain mitochondria. I. Isolation of bovine brain mitochondria. *J Cell Biol* 1963;19:293-307.
- Estabrook RW. Mitochondrial respiratory control and the polarographic measurement of ADP:O ratios. In: Estabrook RW, Pullman ME, eds. *Methods in enzymology*, vol 10. New York: Academic Press, 1967:41-57.
- Layne E. Spectrophotometric and turbidimetric method for measuring proteins. In: Colowick SP, Kaplan NO, eds. *Methods in enzymology*, vol 3. New York: Academic Press, 1957:447-54.
- Lowenthal A, Bruyn GW. Calcification of the striopallidodentate system. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology*, vol 6. Amsterdam: North-Holland Publishing 1968:703-29.
- Koller WC, Cochran JW, Klawans HL. Calcification of the basal ganglia: computerized tomography and clinical correlation. *Neurology (NY)* 1979;29:328-33.
- Hackett TN, Patrick BS, Bray F, Ziter FA, Nyhan WL, Creer BS. A metabolic myopathy associated with chronic lactic acidemia, growth failure and nerve deafness. *J Pediatr* 1973;83:426-31.
- Tsairis P, Engel WK, Kark P. Familial myoclonic epilepsy syndrome associated with skeletal muscle mitochondrial abnormalities. *Neurology (Minneapolis)* 1973;23:408.
- Monnens L, Gabreels F, Willems JL. A metabolic myopathy associated with chronic lactic acidemia, growth failure and nerve deafness. *J Pediatr* 1975;86:983.
- Shapira Y, Cederbaum SD, Cancilla PA, Nielsen D, Lippe BM. Familial poliodystrophy, mitochondrial myopathy and lactic acidemia. *Neurology (Minneapolis)* 1975;25:614-21.
- Lou HC, Reske-Nielsen E. Progressive external ophthalmoplegia: evidence for a disorder in pyruvate-lactate metabolism. *Arch Neurol* 1976;33:455-6.
- Hart ZH, Chang CH, Perrin EVD, Neerunjun JS, Ayyar R. Familial poliodystrophy, mitochondrial myopathy and lactic

- acidemia. *Arch Neurol* 1977;34:180-5.
18. Britton DE, Pellock JM, Eiben RM. Acute hemiplegia of childhood, lactate-pyruvate acidemia and mitochondrial disorder. *Ann Neurol* 1977;2:265.
 19. Markesbery WR. Lactic acidemia, mitochondrial myopathy and basal ganglia calcification. *Neurology (NY)* 1979;29:1057-61.
 20. Fukuhara N, Tokiguchi S, Shirakawa K, Tsubaki T. Myoclonic epilepsy associated with ragged-red fibers (mitochondrial abnormalities): disease entity or a syndrome? *J Neurol Sci* 1980;47:117-33.
 21. Fitzsimons RB, Clifton Bligh P, Wolfenden WH. Mitochondrial myopathy and lactic acidemia with myoclonic epilepsy, ataxia and hypothalamic infertility: a variant of Ramsay-Hunt syndrome. *J Neurol Neurosurg Psychiatry* 1981;44:79-82.
 22. Morgan-Hughes JA, Hayes DJ, Clark JB, et al. Mitochondrial encephalomyopathies: biochemical studies in two cases, revealing defects in respiratory chain. *Brain* 1982;105:553-82.
 23. Bogousslavsky J, Perentes E, Deruaz JP, Regli F. Mitochondrial myopathy and cardiomyopathy with neurodegenerative features and multiple brain infarcts. *J Neurol Sci* 1982;55:351-7.
 24. Walsh FB, Hoyt WF. The macular dystrophies. In: Walsh FB, Hoyt WF, eds. *Clinical Neuro-ophthalmology*. Baltimore: Williams and Wilkins, 1969:889-95.
 25. Kuriyama M, Yokomine R, Arima H, Hamada R, Igata A. Blood vitamin B₁₂, transketolase and thiaminpyrophosphate (TPP) effect in beriberi patients, with studies employing discriminant analysis. *Clin Chim Acta* 1980;108:159-68.
 26. Posner JB, Plum F. Independence of blood and cerebrospinal fluid lactate. *Arch Neurol* 1967;16:492-6.
 27. Morgan-Hughes JA, Darveniza P, Landon DN, Land JM, Clark JB. A mitochondrial myopathy with a deficiency of respiratory chain NADH-CoQ reductive activity. *J Neurol Sci* 1979;43:27-46.
 28. Land JM, Morgan Hughes JA, Clark JB. Mitochondrial myopathy: biochemical studies revealing a deficiency of NADH-cytochrome b reductase activity. *J Neurol Sci* 1981;50:1-13.
 29. Busch HFM, Scholte HR, Arts WF, Luyt Houwen IEM. A mitochondrial myopathy with a respiratory chain defect and carnitine deficiency. In: Busch HFM, Jennekens FGI, Scholte HR, eds. *Mitochondria and muscular diseases*. Beeststergwaag, The Netherlands: Mefar BV, 1981;207-11.
 30. Gabreels FJM, Prick MJJ, Renier WD, et al. Progressive infantile poliodystrophy (Alper's disease) associated with disturbed NADH-oxidation, lipid myopathy and abnormal muscle mitochondria. In: Busch HFM, Jennekens FGI, Scholte HR, eds. *Mitochondria and muscular diseases*. Beeststergwaag, The Netherlands: Mefar BV, 1981;165-71.
 31. Goldfischer S, Moore CL, Johnson AB, et al. Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. *Science* 1973;182:62-4.
 32. Spiro AJ, Moore CL, Prineas JW, Strasberg PM, Rapin I. A cytochrome-related inherited disorder of the nervous system and muscle. *Arch Neurol* 1970;23:103-12.
 33. Morgan-Hughes JA, Darveniza P, Kahn SN, et al. A mitochondrial myopathy characterized by a deficiency in reducible cytochrome b. *Brain* 1977;100:617-40.
 34. French JH, Sherard ES, Lubell H, Brotz M, Moore CL. Trichopolydystrophy. I. Report of a case and biochemical studies. *Arch Neurol* 1972;26:229-44.
 35. Willems JL, Monnens LAH, Trijbels JMF, et al. Leigh's encephalomyelopathy in a patient with cytochrome c oxidase deficiency in muscle tissue. *Pediatrics* 1977;60:850-7.
 36. Van Biervliet JPG, Bruinvis L, Ketting D, et al. Hereditary mitochondrial myopathy with lactic acidemia, a De Toni Fanconi-Debre syndrome and a defective respiratory chain in voluntary striated muscles. *Pediatr Res* 1977;11:1088-93.
 37. DiMauro S, Mendell JR, Sahenk Z, et al. Fatal infantile mitochondrial myopathy and renal dysfunction due to cytochrome-c-oxidase deficiency. *Neurology (NY)* 1980;30:795-804.
 38. Heiman-Patterson TD, Bonilla E, DiMauro S, et al. Cytochrome-c oxidase deficiency in a floppy infant. *Neurology (NY)* 1982;32:898-901.

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