Marinesco-Sjogren syndrome with reduced cytochrome c oxidase in muscle.

Kodama, S ; Komatsu, M ; Miyoshi, M ; Nakao, H ; Sakurai, T ; U, M

Kobe J. Med. Sci. 38, 245/254, August 1992

MARINESCO-SJÖGREN SYNDOROME WITH REDUCED CYTOCHROME C OXIDASE IN MUSCLE

SOICHI KODAMA,[1] MIKIO KOMATSU,[1] MARI MIYOSHI,[1] HIDETO NAKAO,[1] TAKASHI SAKURAI,[1] AND MAN U[2]

1) Department of Pediatrics, Himeji Red Cross Hospital, Tatsuno-cho, 5-30-1, Himeji, 670 Japan
2) Department of Pediatrics, Kansai Medical University, Fumisono-cho 1, Moriguchi, 570 Japan

INDEXING WORDS

Marinesco-Sjögren syndrome, cranial MRI, muscle biopsy, ^{1}H-NMR of urine

SYNOPSIS

The present study deals with the sisters of Marinesco-sjögren syndrome without parental consanguinity. Cranial MRI of sisters in a 0.5T superconducting magnet revealed the cerebellar hypoplasia or atrophy, especially in vermis and tonsils with dilatation of IVth ventricle. Microscopic findings of muscle biopsy indicated moderate variation of fibers with phagocytosis, rimmed vacuoles and no ragged red fibers with markedly decreased cytochrome C oxidase activity. ^{1}H-NMR study of urine indicates the secondary decreased turnover rate in urea cycle due to high concentration of 3-hydroxy-n-butyrate.

INTRODUCTION

The Marinesco-Sjögren syndrome (MSS) is a rare autosomal recessive disorder characterized by mental retardation, hypotonia, bilateral cataracts and cerebellar hypoplasia resulting in ataxia, dysarthria, nystagmus and tremor [1,7,8]. Recently, cranial CT scan in the patient

Received for publication: August 7, 1992
Authors' names in Japanese: 児玉荘一, 小松幹夫, 三好麻里, 中尾秀人, 桜井 隆, 禹 満

with MSS revealed cerebellar atrophy or hypoplasia [4]. The muscle biopsy specimen from the patient with MSS revealed muscle fiber necrosis followed by regeneration and focal myofibrillar degeneration, rimmed vacuole and scattered fibers with histochemical characteristics of ragged red fibers with decreased or negative cytochrome C oxidase (CCO) activity [2,3,6]. The study deals with the sisters (5 and 3 years old) of MMS (without parental consanguinity), who indicated typical findings of brain MRI and muscle biopsy specimen.

SUBJECTS

Case 1 (1/2) is the elder sister who was born after normal pregnancy and delivery with a weight of 2500 g. By 6 months of age, her developmental milestones were slow. She was not able to hold up her head well until 5 month-old. She was able to speak some words at 2 years old, while she can not stand alone at present. Bilateral cataracts were pointed out at 3-year old. Intelligence quotients are 30 in motor function and 50 in verbal function. Neurological examination in eleder sister revealed that there was hypotonia in all muscle, tendon reflexes greatly diminished, speech was slow, and signs of ataxia and nystagmus were unclear. Her younger sister (2/2) is 3 years old who was born after normol pregnancy and delivery with a weight of 2570 g. Her developmental milestones were similar to those of elder sister, except that acute cataract developed in both eyes and were treated surgically at 3 years old.

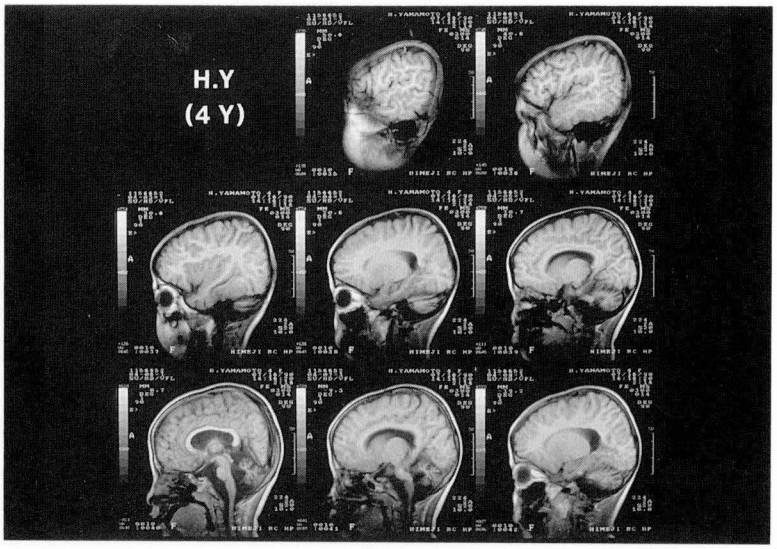
RESULTS

1. Laboratory data on admission

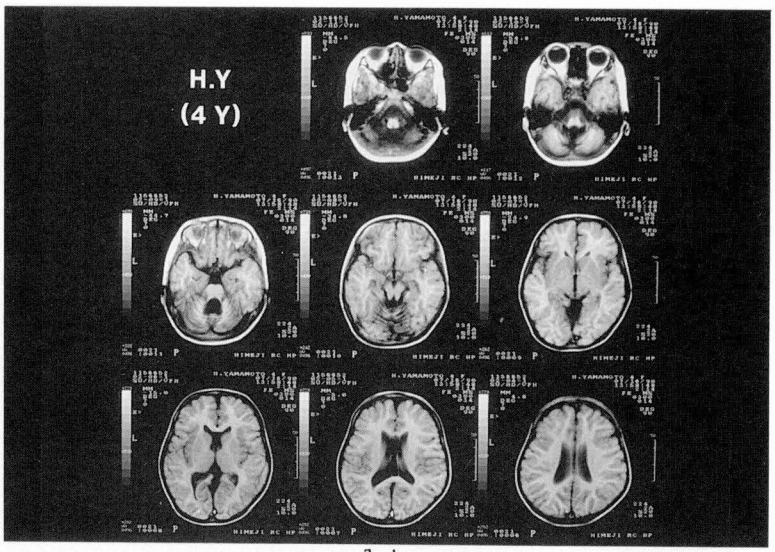
Routine blood and urine tests in sisters gave normal results. The activities of serum LDH, GOT, GPT and CPK and concentration of NH_3, lactate and pgruvate were within normal ranges in sisters.

2. EEG and cranial MRI findings

EEG at sleep (stage 1~4) was within normal range in sisters. Cranial MRI of the sisters in a 0.5 T superconducting magnet (MRT-50-A-SE, Toshiba Medical co, Japan) revealed the cerebellar hypoplasia or atrophy, especially in vermis and tonsils with dilatation of IVth ventricle and moderately in hemispheres, as shown in Fig. 1,2. In elder

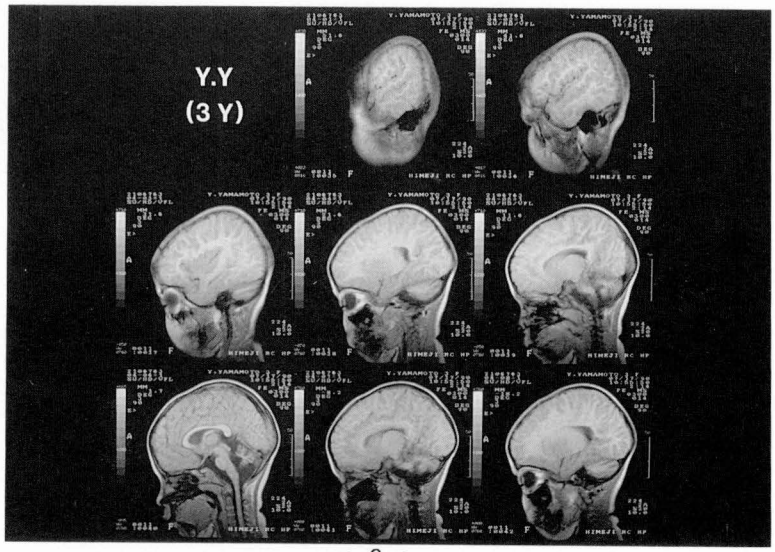


1-a

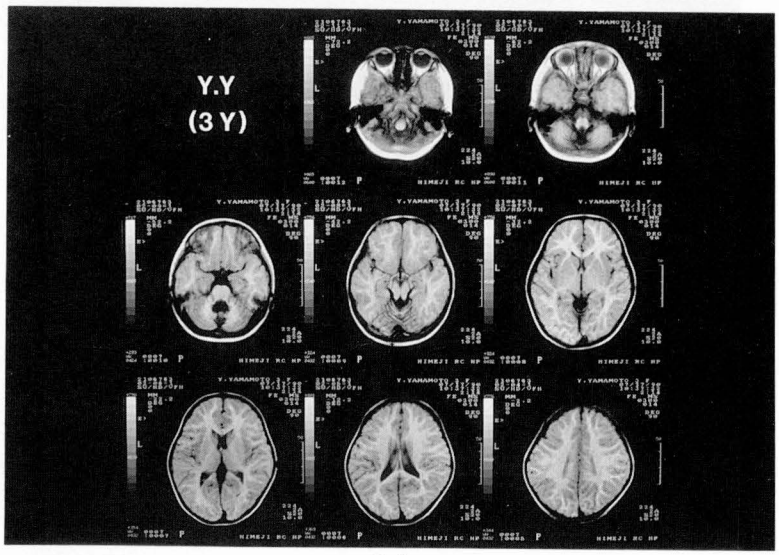


1-b

Fig.1. Cranial MRI (SE500/20) of elder (H.Y.): Non contrast MRI scans of sagittal (a) and axial (b) demonstrate the cerebellal hypoplasia or atrophy with dilatation IVth ventricle.



2-a



2-b

Fig.2. Cranial MRI (SE 500/20) of younger sister (Y.Y.): Non contrast MRI scans of sagittal (a) and axial (b) demonstrate the same findings as elder sister.

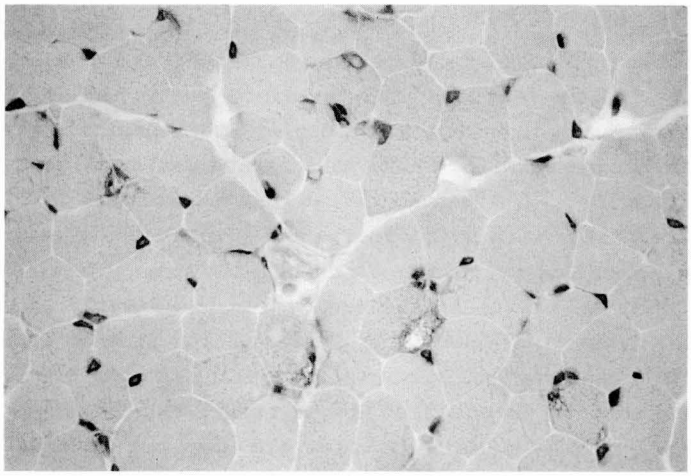
sister, cavum verga was pointed out with normal MRI of cerebrum, while in young sister, no malformation was found out with normal MRI of cerebrum.

3. Microscopic findings of muscle biopsy from biceps in eleder sister

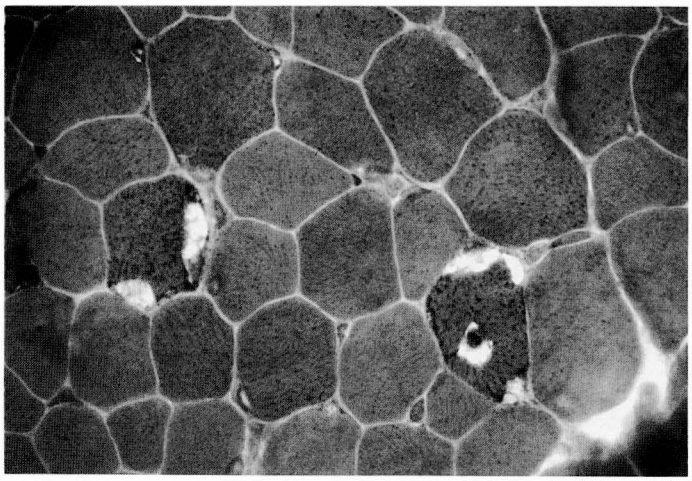
Serial frozen sections were stained with hematoxyln-eosin, modified Gomori trichrome and a battery of bistochenical methods. On hematoxylin-eosin staining, there is moderate variation in fiber size measuring from 10-20 μm in diameter as shown in Fig. 3-a. There are a few necrotic fiber with phagocytosis and several regenerating fibers which have basophilic cytoplasm. A number of fibers (2-3%) have small vacuoles. Fibrous tissue in the endomysium is slightly increased in amount. The fibers with centrally placed nuclei are not increased in number. Inflammatory cellular infiltration is not seen. Muscle spindles are intact. On modified Gomori trichrome staining, there are no ragged red fibers. Small vacuoles are rimmed by purple-red tiny granules (rimmed vacuoles) as shown in Fig. 3-b. On NADH staining, intermyofibrillar networks are disorganized in approximately 10% of fibers. On ATPase staining, Type 1, 2A, and 2B fibers comprise 41%, 35%, 21% respectively and some type 2C fibers are scattered. Type 2b fibers are slightly small in diameter. On PAS staining, there are no fibers with strongly positive granules. On oil-red 0 staining, lipid droplets are slightly increased in endomysium. On SDH staining, there is no ragged red fiber nor strongly positive vessels. On acid phospahtase staining, several fibers have high enzyme activity and the rimmed vacuoles occasionaly have high enzyme activity as shown in Fig. 3-c. On CCO staining, almost all fibers have markedly decreased CCO activity except for intrafusal fibers as shown in Fig. 3-d. There are no definite abnormalities on other stains including Ach-E, AMP deaminase, nonspecific esterase, phosphofructokinase and menedionelinked α-glycerophosphate dehydrogenase (MAG).

4. ^{1}H-NMR (Proton nuclear magnetic resonance spectroscopy) study of urine

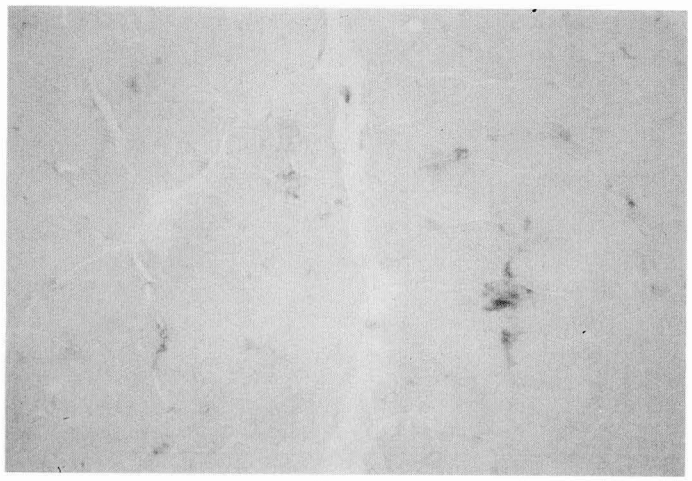
0.7 ml of urine was placed in a 5 mm diameter NMR tube and 0.07 ml of D_2O (Deuterium oxide) containing 3-(trimethylsilyl)-2,2,3,3-tetradeutero-propionate (TSP-d4, σ=0.0) was added, to act as a chemical shift reference. ^{1}H-NMR spectra were measured with a Varian VXR-500 spectrometer at 499.8 Mhz. The transients of 32-160 each with 90 pulses



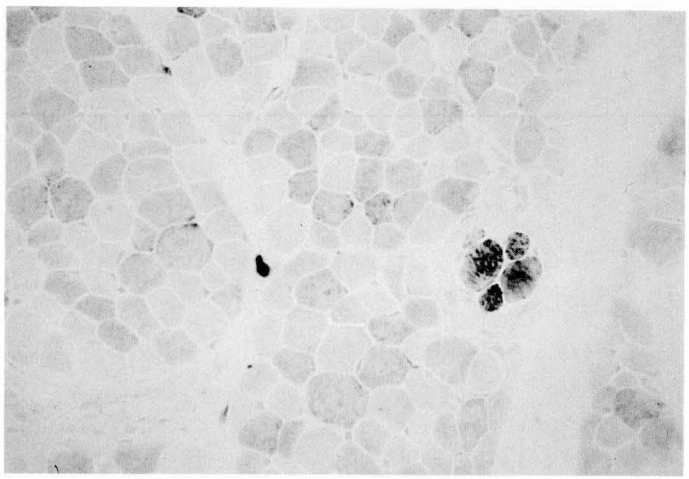
3-a



3-b

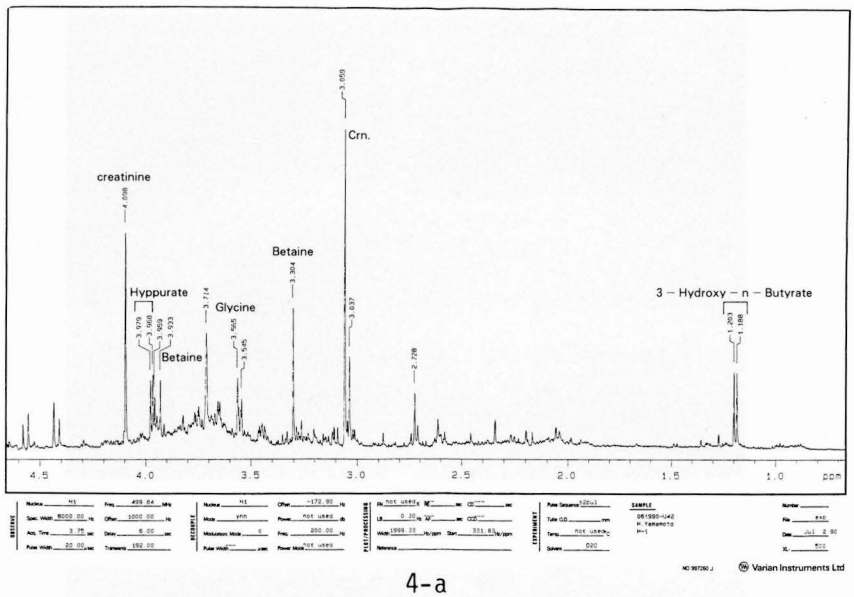


3-c

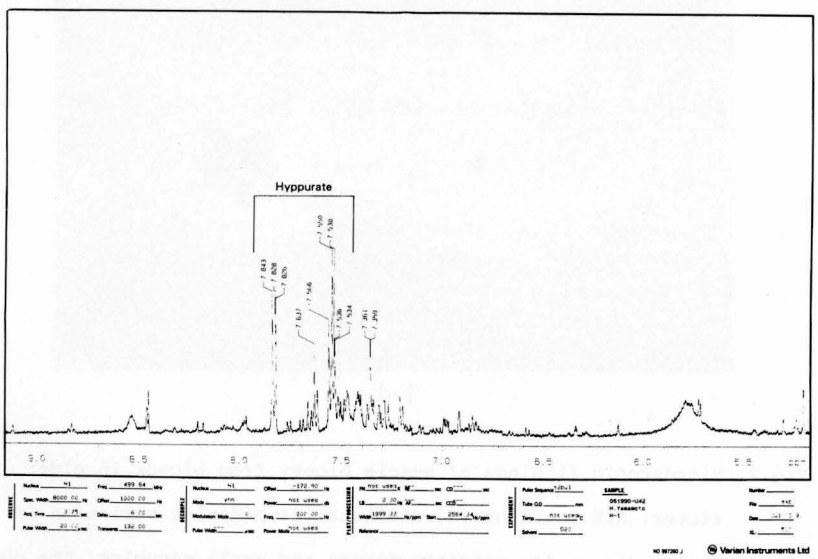


3-d

Fig.3. Microscopic findings of muscle biopsy from biceps in elder sister: H&E staining (a) demonstrates moderate variation in finder size,a few necrotic fibers and small vacuoles. The mGt staining (b) demonstrates no ragged red fibers but small rimmed vacuoles. Acid phosphatase staining (c) demonstrates rimmed vacuoles with high activity CCO staining (d) demonstrate markedly decreased CCO activity.



4-a



4-b

Fig.4. ^{1}H-NMR study of urine. The high concentration of 3-hydroy-n-butyrate is indicated in (a), and large amounts of hyppurate (b) are excreted.

were accumulated. During a relation delay of 6s the H_2O/DHO signal was suppressed by homogated decoupling. The raio of urinary metabolites/ creatinine concentration (mol/mol) obtained by NMR was calculated [5]. The results of elder sister was shown in Fig. 4. The high concentration of 3-hydroxy-n-butyrate (0.23 mol/mol crn) in urine probaly depends on the acceleration of β-oxidation in fatty acid. The increased excretion of glycine (0.19 mol/mol crn) and hyppurate (0.16 mol/mol crn) indicates the secondary decreased turnover rate in urea cycle due to high concentration of 3 hydroxy-n-dutyrate [5]. The same results was obtained in the younger sister.

DISCUSSION

There have been few reports of pathological examination of central nervous system in MSS [7,9]. The specific finding of MSS was a marked atrophy of cerebellum especially in cerebellar hemisphere and vermis without any malformation. The microscopic findings revealed the almost total loss of purkinje and granule cells with astrocytic gliosis. In addition the findings of cerebellem, pons and medulla showed the nerve cell loss and gliosis. The clinical symptoms of central nervous system probably depend on the microscopic findings. In our cases, cranial MRI revealed the remarkable atrophy of cerebellum in hemisphere and vermis, and the findings of cranial MRI were consistent with the autopsied findings previously reported [7,9].

According to Goto et al [3], muscle fibers undergo degeneration in two major way: 1. mucle fiber necrosis with invasion by phagocytes in which extracellular components probably influx into sarcoplasm through the defective salcolemma as seen in progressive muscular dystrophies and inflammatory myopathies;2. focal degeneration of myofibrils and organells followed by autophagic phenomen (rimmed vacuole formation) in which lysosomal enzymes such as phosphatase and cathepsins are activated. These phemomenon are found in the specimen of muscle biopsy in the elder sister. The scattered CCO-deficient fibers as like as those of some kinds of muscle diseases have been recognized in the patient. However, mitchondrial change of MSS is probably a secondarily induced phenomen [3].

The pathogenesis of cataracta in the patients was not clarified, since their serum Ca and P level, intact, C- and N- terminal PTH (parathyroid hormone) level, and calcitonin level were within normal

range. The result of ^{1}H-NMR study in urine may indicates that primary metabolic disorder was not existent in MSS.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. I. Nonaka and his colleagues in Division of Ultrastructural Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, for determination of microscopic findings of muscle biopsy.

REFERENCES

1. Andersen, B.: Develop. Med. child neurol. 1965. 7. 249-257. Marinesco-Sjögren syndrome: Spinocerebellar ataxia, congenital cataract, somatic and mental retardation.
2. Borud, O., Aasly, J. and Lindal, S.: Genetics of Neuromuscular Disorders.1989, 135-139. Alan R. Liss Inc. Mitochondrial myopathy in six patients with Marinesco-Sjögren syndrome.
3. Goto, Y., Komiyama, A., Tanabe, Y., Katafuchi, Y., Ohtaki, E. and Nonaka, I.: Acta Neuropathol. 1990, 80: 123-128. Myopathy in Marinesco-Sjögren Syndrome: an ultrastructural study.
4. Herva, R., L. von Wendt, W. von Gurvor, Saukkonen, AL. and Leisti, J.: Neuropediatrics. 1987, 18. 164-169. A syndrome with juvenile cataract cerebellar atrophy, mental retardation and myopathy.
5. Kodama, S., Sugiura, M., Nakao, H., et. al.: Acta paediatr Jpn. 1991, 33. 139-145. ^{1}H-NMR studies of urine in propionic acidemia and methylmalomic acidemia.
6. Komiyama, A., Nonaka, I. and Hirayama, K.: J. Neurol. Sci. 1989, 89. 103-113. Muscle pathology in Marinesco-Sjögren syndrome.
7. Mahloudji, M., Amirhakimi, GH., Haghighi, P. and Khodadoust, A.A.: Brain. 1972, 95. 675-680. Marinesco-Sjögren syndrome.
8. Marinesco, G., Draganesco, S. and Vasiliu D.: Encephale. 1931, 26. 97-109. Nouvelle maladie familiale caractérisée par une cataracte congénitale et un arrêt du développement somate-neuro-psychique.
9. Todorov, A.: J. genet. Hum. 1965, 14. 1-30. Le syndrome de Mairnesco-Sjögren.