

# CASE REPORT

## MLASA SYNDROME: A CASE REPORT

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### **Abstract**

Mitochondrial myopathy, lactic acidosis, and sideroblastic anemia (MLASA) syndrome is a rare autosomal recessive disorder of oxidative phosphorylation and iron metabolism. The association between myopathy and sideroblastic anemia was initially reported in 1974. Here we report an 8.5 year old boy with normal cognitive function, suffering from chronic progressive weakness in his lower extremities, inability to walk and palor. Microcytic sideroblastic anemia, mild lactic acidosis and inflammatory myopathy (myositis) in muscle biopsy was detected and treated; the response to corticosteroid therapy and rehabilitation was excellent and the patient was ambulatory after four months.

**Keywords:** Sideroblastic anemia, Mitochondrial myopathy, Lactic acidosis

### **Introduction**

Although rare, sideroblastic anemia, one of microcytic anemias, is still seen in children; in all cases of the disease, impaired heme synthesis leads to accumulation of non-heme iron in RBC mitochondria surrounding the nucleus instead of cytoplasmic ferritin, ringing the red cell nucleus and thus the formation of “ringed sideroblasts” (1). Association of myopathy, lactic acidosis and sideroblastic anemia was initially reported in 1974 and, following that, in 1994(2,3). The last case, the seventh, was reported in 2005 (4). In one case reported in 1995, irregular, enlarged mitochondria with paracrystalline inclusions were seen on electron microscopy of the patient’s muscle specimen, but DNA examination showed no deletions in the mitochondrial DNA, such as that seen in syndromes of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (MELAS) or myoclonic epilepsy associated with ragged-red fibers (MERRF); hence it was considered to be a new mitochondrial syndrome (5).

Progressive muscle weakness during childhood, onset of sideroblastic anemia around adolescence, basal lactic acidemia, and myopathy are hallmark features of a new syndrome known as mitochondrial myopathy, lactic acidosis, and sideroblastic anemia( MLASA) syndrome (6) which, in turn, is due to mutations in the nuclear-encoded pseudouridine synthase1 (PUS1) gene (4). This gene encodes the enzyme PUS1 that is known as pseudouridylylate tRNAs (7).

Linkage analysis and homozygosity testing of two Iranian families with MLASA syndrome localized the candidate region to chromosome 12q24.33. Hence it can be proposed that deficient pseudouridylation of mitochondrial tRNAs is an etiology of MLASA (8,9). Multiple deletions of mtDNA in two brothers with sideroblastic anemia and mitochondrial myopathy and in their asymptomatic mother, have been

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reported from Spain (3).

**Case report**

A previously well, 8.5 year old boy, weighing 18 kg., referred to the pediatric neurology clinic with a history of progressive weakness, pallor and inability to walk. The first child of unrelated parents, he was a second grade student of primary school and had no past history of fever, rash or drug usage. Family history was also negative.

Six months earlier, his problems had begun as a mild weakness in the proximal area of his lower extremities, and had since progressed 2 months later to him losing his walking ability, while suffering from mild weakness in his upper proximal extremities.

On examination, he was alert, pale and with mild bilateral ptosis; organomegaly was detected on abdominal exam, with the liver touching 2-3 cm below the right costal margin, and the spleen, 3-4 cm below the left. A neurological exam showed the cranial nerves to be intact; muscle power was 2/5 in the distal lower, 2/5 in the proximal upper and 3/5 in the distal upper extremities. Mildly flexion contractures were seen in the legs; DTR was hypoactive and plantar reflexes were down. Laboratory findings of the patient are given below:

Hb = 8.1 gr/dL (11.5 – 15.5), MCV =54.3 fL (77-95)	RDW = 27.5 % ( 10-14 ), reticulocytes= 4.5%
Ferritin = 93 µg/L (7- 140 )	Iron= 63 µg/dL (22-184), TIBC = 312 µg/cc(250-400)
ESR= 15mm/hr, CRP = negative	Serum Lactate = 35 mg/dL (0-20)
SGPT = 160 U/L (< 40 ), SGOT =107 U/L (< 40 )	CPK = 3715 U/L (5-130), Aldolase =12.2U/L(1.2-8.8 )
Serum LDH = 2452U/L(150-500)	ABG =mild metabolic acidosis

ANA & anti-ds-DNA were negative and C<sub>3</sub>, C<sub>4</sub>, C<sub>50</sub>, PTH, TFT, Hb electrophoresis and echocardiography were normal as well. In electrodiagnosis, NCV was normal but EMG was suggestive of a myopathic process. A bone marrow biopsy showed erythroid hyperplasia and excess ringed sideroblasts (figure1).

Muscle biopsy showed perivascular infiltration of lymphocytes in muscle fascicles, indicating inflammatory myopathy or myositis ( figure2).

The patient was treated with vitamin B<sub>6</sub>, folic acid and 1.5 mg/kg/day oral prednisolone; rehabilitation and regular physiotherapy was initiated simultaneously. Two months later, muscle enzymes returned to normal levels and lower extremity contractures disappeared but Hb was still 9.5 gr /dl, for which reason the daily corticosteroid dosage was reduced to 0.5 mg/kg. Eventually, after 4 months of treatment, he regained his walking ability and was able to return to school. A 3-year follow up still showed mild proximal weakness of the lower extremities and microcytic anemia.

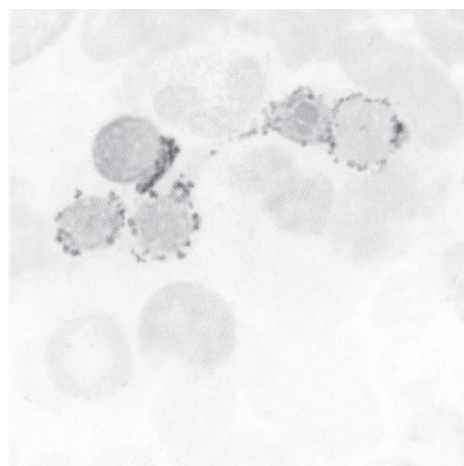


Figure 1: A bone marrow biopsy showed erythroid hyperplasia and excess ringed sideroblasts.

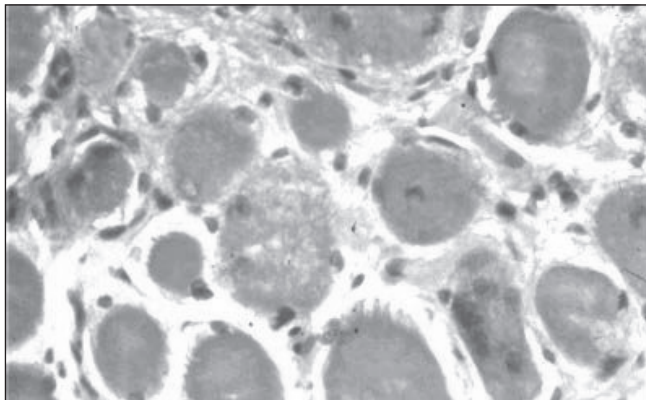


Figure 2: Muscle biopsy showed perivascular infiltration of lymphocytes in muscle fascicles, indicating inflammatory myopathy or myositis.

### Discussion

In this case, suspicions of a mitochondrial disease arose following severe weakness and reduction in grip strength in the upper and lower limbs, bilateral ptosis, sideroblastic anemia and lactic acidosis. Mitochondria are one of the largest organelles of the cell; their primary function is oxidative phosphorylation (generation of the high-energy phosphate bond in ATP by phosphorylation of ADP) (10).

Mitochondriopathies should be considered in any patient with unexplained progressive multisystem disorder. These diseases usually show a chronic, slowly progressive course and present with multi-organ involvement with varying onsets, anytime between birth and late adulthood. Systems frequently affected in mitochondrial cytopathies are the peripheral nervous system (myopathy, polyneuropathy, lactic acidosis), brain (leukoencephalopathy, calcifications, stroke-like episodes, atrophy with dementia, epilepsy, upper motor neuron signs, ataxia, extrapyramidal manifestations, fatigue), endocrine disorders (short stature, hyperhidrosis, diabetes, hyperlipidaemia, hypogonadism, amenorrhoea, delayed puberty), heart (impulse generation or conduction defects, cardiomyopathy, left ventricular non-compaction heart failure), eyes (cataract, glaucoma, pigmentary retinopathy, optic atrophy), ears (deafness, tinnitus, peripheral vertigo), guts (dysphagia, vomiting, diarrhea, hepatopathy, pseudo-obstruction, pancreatitis, pancreas insufficiency), kidney (renal failure, cysts) and bone marrow (sideroblastic anaemia) (11).

The diagnosis of mitochondrial disease is made on the basis of biochemical assays, mitochondrial enzymes, mtDNA mutation analysis and evaluation of structural details of mitochondria by electron microscopy.

Mitochondrial myopathy, lactic acidosis, and sideroblastic anemia (MLASA syndrome) is a rare autosomal recessive disorder of oxidative phosphorylation and iron metabolism causing sideroblastic anemia, myopathy, and in some cases, mental retardation. The patient presents with weakness and anemia in late childhood and may become dependent on blood transfusions (6). The association of mental retardation and dysmorphic features, reported in some cases, were not found in our patient (4,5).

Although in progressive mitochondrial myopathy, muscle weakness is mainly proximal and the upper extremities tend to be more affected, in our case, major muscle weakness was observed in the lower extremities (10).

Since mitochondrial disease mimics polymyositis and inflammatory myopathy, therefore in the differential diagnoses of myositis, mitochondrial myopathies should be considered (12).

Some patients with mitochondrial myopathies showed transient muscle strengthening and lowering of elevated muscle enzymes with corticosteroid therapy, (10,13) but there are no reports on the therapy in MLASA syndrome. In the case reported, oral prednisolone improved muscle weakness in the patient effectively, and returned and maintained CPK to normal levels. This continuing effectiveness might be a result of the drastic role played by corticosteroid therapy in treating myositis or other unknown causes; this however needs more diagnostic mitochondrial investigations.

Five cases, from three families of the aforementioned patients, were products of consanguineous Jewish-Iranian parents with autosomal recessive inheritance and mutations in the nuclear-encoded pseudouridine synthase I (PUS1) gene (4,7,8), however multiple deletions of mtDNA were reported in two Spanish brothers (3).

To conclude, our patient was the child of non-relative parents, making genetic study and mtDNA mutation analysis in patients and parents, therefore more imperative.

## References

1. Richard E. Behrman, M.Kliegman, B.Jenson. Other microcytic anemia .Nelson textbook of pediatrics,W.B Saunders, 2004, 17th edit,pp.1616.
2. Rawles JM, Weller RO. Familial association of metabolic myopathy, lactic acidosis and sideroblastic anemia. *Am J Med* JUN, 1974; 56 (6 ):891-7.
3. Casademont J, Barrientos A, Cardellach F, Rötlg A, Grau JM, Montoya J, et al. Multiple deletions of mtDNA in two brothers with sideroblastic anemia and mitochondrial myopathy and in their asymptomatic mother. *Hum Mol Genet* 1994 Nov;3(11):1945-9.
4. Zeharia A, Fischel-Ghodsian N, Casas K, Bykhovskaya Y, Tamari H, Lev D, et al. Mitochondrial myopathy, sideroblastic anemia, and lactic acidosis: an autosomal recessive syndrome in Persian Jews caused by a mutation in the PUS1 gene. *J Child Neurol*, 2005 May;20(5):449-52.
5. Inbal A, Avissar N, Shaklai M, Kuritzky A, Schejter A, Ben-David E4, Shanske S, et al. Myopathy, lactic acidosis, and sideroblastic anemia: a new syndrome. *Am J Med Genet*. 1995 Jan 55(3):372-8.
6. Casas KA, Fischel – Ghodsian N. Mitochondrial myopathy and sideroblastic anemia. *Am J Med Genet*. 2004 Mar 1;125(2):201-4.
7. Patton JR, Bykhovskaya Y, Mengesha E, Bertolotto C, Fischel-Ghodsian N. Mitochondrial myopathy and sideroblastic anemia (MLASA): missense mutation in the pseudouridine synthase 1(PUS1) gene is associated with the loss of tRNA pseudouridylation. *J Biol Chem*. 2005 May 20;280(20):19823-8.
8. Bykhovskaya Y, Casas K, Mengesha E, Inbal A, Nathan Fischel-Ghodsian N. Missense mutation in pseudouridine synthase 1 (PUS1) causes mitochondrial myopathy and sideroblastic anemia (MLASA). *Am J Hum Genet*. 2004 June; 74(6): 1303–1308.
9. Casas K, Bykhovskaya Y, Mengesha E, Wang D, Yang H, Taylor K, et al . Gene responsible for mitochondrial myopathy and sideroblastic anemia (MSA) maps to chromosome 12q24.33. *Am J Med Genet* 2004 May ;127(1):44-9.
10. John H. Menkes, *Metabolic disease of the nervous system*, John H. Menkes, HarveyB. Sarnat, Child Neurology. Philadelphia: Lippincot 6 th ed; pp:135- 147, 2000 .
11. Finsterer J. Mitochondriopathies. *Eur J Neurol* Mar;11(3):163-86, 2004 .
12. Corrado A, Cantatore FP, Serlenga L, Amati A, Petruzzella V, Lapadula G. Mitochondrial disease mimicking polymyositis : a case report .*Clin Rheumatol* 2002 Sep ; 21(5):411-4.
13. Fujimoto S, Ueyama H, Mita S, Kumamoto T, Tsuda T. A case of chronic progressive external ophthalmoplegia presenting as inflammatory myopathy. *Rinsho Shinkeigaku* 1998 Mar ; 38(3):228-32.