Myopathy, lactic acidosis and sideroblastic anemia syndrome 1 (MLASA1): clinical hallmarks in a large pedigree with a novel *PUS1* R144Q mutation, remarkable response to somatropin, and review of the literature

Sideroblastic anemias (SBA) are a heterogenous group typically characterized by a large number of sideroblasts in the bone marrow. Inherited SBA are rarer then acquired SBA and can present as a syndromic disease.[1] Inherited SBA may follow an X-chromosomal, autosomal or mitochondrial mode of transmission. Careful documentation of the family history as well as the patient's symptoms and findings guide the diagnostic approach. Given the rarity of inherited SBA, phenotypic information is scarce, diagnosis is often delayed, and therapeutic approaches are unclear and mostly futile. Here we extensively describe a large pedigree of Syrian descent with two siblings demonstrating the rare hereditary myopathy, lactic acidosis and sideroblastic anemia syndrome type 1 (MLASA1) and a novel *PUS1* gene mutation, and a remarkable response of the anemia to somatropin. Consent was obtained from all patients and the study respects local ethical guidelines.

Patient 1 is a 30-year-old male who first presented to our institution at the age of 26 with a transfusion-dependent anemia. According to his family, he exhibited frailty, growth delay and exercise intolerance from birth. He completed primary school showing learning difficulties throughout the years. There were no dysmorphic signs and, up to the age of 22 years, no diagnosis had been made and no therapy given. At the age of 22, having left Syria as a refugee, he first came to medical attention in a neighbouring country because of a febrile episode. Anemia was detected. He was diagnosed with SBA and started on 2-weekly transfusions with packed red cells combined with subcutaneous iron chelation. In the following years and due to a difficult daily life, chelation was abandoned but not the transfusions.

At the age of 26, the patient arrived in Switzerland as a refugee. The patient's extreme exercise intolerance prompted a further evaluation of his SBA. His height was 150 cm and he weighed 49 kg. His medical history included infrequent diffuse abdominal pain with occasional diarrhea, a good appetite, and smoking. Laboratory analyses revealed anemia (hemoglobin, 58 g/L) with pronounced anisocytosis and microcytosis (mean corpuscular volume, 83 fL; mean corpuscular hemoglobin, 24 pg), a white blood cell count of $3.3x10^9$/L and a platelet count of $156x10^9$/L. The Quick value was 63%. Blood chemistry showed mildly elevated liver parameters and low creatine kinase and creatinine. The erythropoietin concentration was 517 U/L. Lactate levels were repeatedly elevated (3.4-12.7 mmol/L). Massive iron overload was noted, after a cumulative amount of about 500 transfusions of packed red cells: ferritin 8,225 μg/L, free serum iron 51 μmol/L, transferrin 2.13 g/L, saturation of transferrin 95.3%. Ultrasonography showed slight hepatomegaly, and elastography an increased liver stiffness at 9.2 kPa. An electrocardiogram echocardiography, audiogram and ophthalmological investigations were normal. Endocrinological analyses showed an insufficient somatotropic axis with decreased insulin-like growth factor-1 (IGF-1, 65.5 ng/mL, normal 83.6-259 ng/mL) and an insufficient increase of growth hormone after stimulation with arginine/growth hormone-releasing hormone, with otherwise unremarkable analyses of the other parts of the hypophyseal axes. Bone marrow analyses showed a hypercellular marrow with hypercellular and dysplastic erythropoiesis and megakaryopoiesis, normal myelopoiesis, and elevated iron stores with a large number of ring sideroblasts. Cytogenetic analyses were normal. Parvovirus serology was negative. Iron overload was also found in a liver biopsy showing massive intrahepatocellular and ductal siderosis and portal fibrosis with numerous septa and bridges. Investigations for the presence of thalassemia or other hemoglobin anomalies were unremarkable.

Iron chelation was restarted, first with tablets and then, while supply was difficult and compliance uncertain, with deferoxamine subcutaneously overnight with a pump system, starting with 30 mg/kg and after 3 years reducing to 20 mg/kg. Transfusions were infrequently necessary (Figure 1). Serum ferritin dropped within 3 years to 984 μg/L. Fluctuating compliance with the chelation therapy resulted thereafter in a plafond of ferritin at 1,000-1,500 μg/L. The patient continues to suffer mostly from exercise intolerance. His walking is limited to a few meters due to rapid occurrence of increasing and debilitating cramp-like pain in the legs. At the age of 33 years, he was investigated twice because of loss of consciousness; the first time, no other cause than anemia was found (hemoglobin, 60 g/L), the second time, he became unconscious while sitting over 3 hours outdoors in a chair during winter time: a markedly increased lactate of 21 mmol/L and a blood pH of 6.7 were noted (base excess of -26 mmol/L and bicarbonate at 4.6 mmol/L). Therapeutic trials with vitamin B6 300 mg/day for 3 months or coenzyme Q10 250 mg/day for 3 months were of no benefit. A wheelchair was necessary. At this time, due to low IGF-1, a trial with

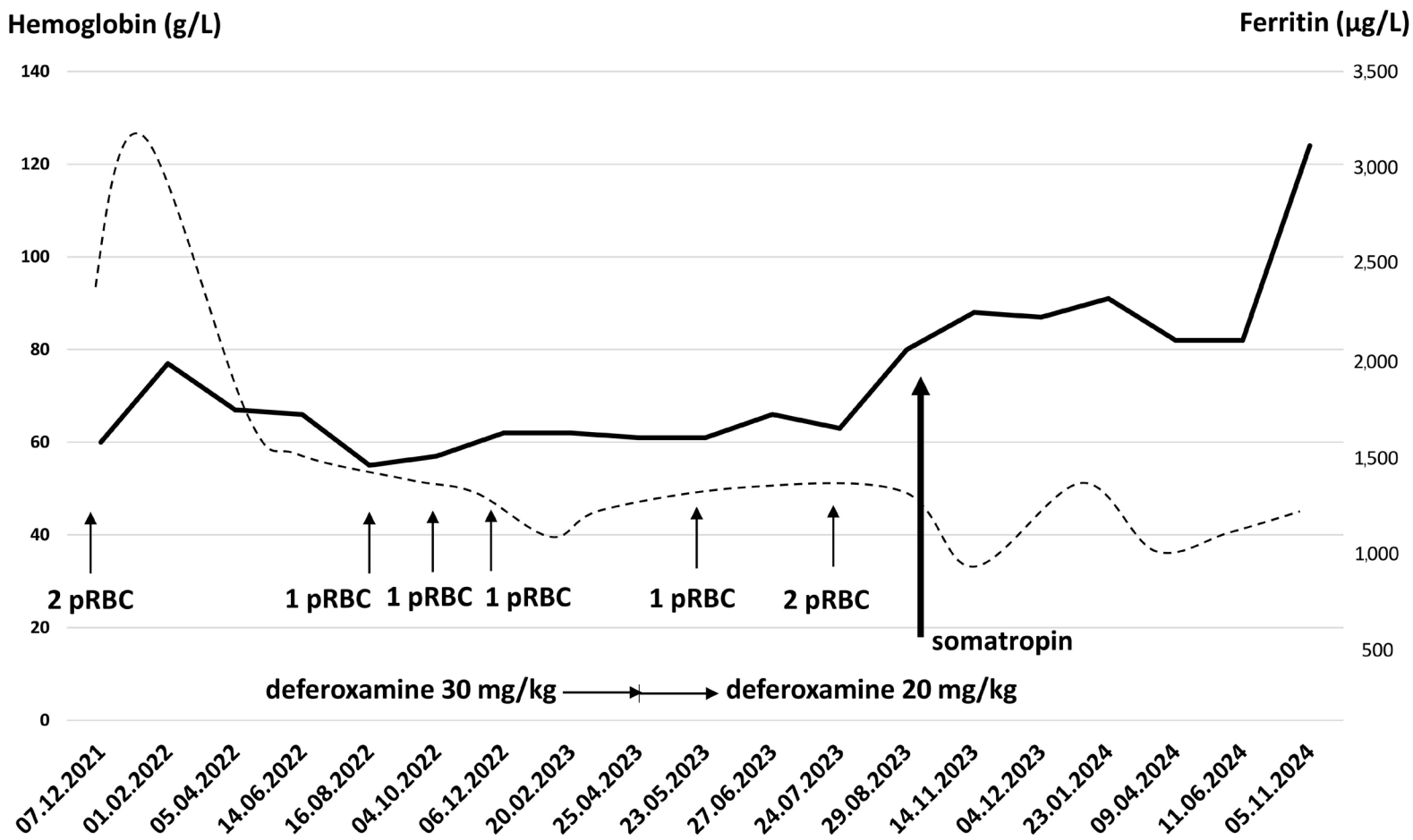

Figure 1. Time course of hemoglobin and ferritin values in patient 1 under treatment with deferoxamine and somatropin. Solid line, hemoglobin; dashed line, ferritin. pRBC: units of packed red blood cells transfused.

somatropin (Norditropin®) was started. Remarkably, since then the hemoglobin values have continuously increased and the patient is transfusion-independent.

An extensive family history was taken with the help of a translator. It revealed a similar phenotype in a female sibling (patient 2) and a consanguineous marriage of the parents (Figure 2). Patient 2 first came to medical attention at the age of 33 years during the investigations of her brother's case. She too had suffered since childhood from extreme exercise intolerance now leading to impaired walking with sore and cramping legs after 5 meters of walking, and sore and cramping arms when trying to help her mother with hanging clothes. Abdominal cramps in infancy led to investigations followed by a gluten- and lactose-free diet from the age of 4 to 15 years, without clinical improvement; current investigations could not confirm an intolerance. She too experienced presyncopes, occurring once a month and lasting for a few minutes. A postural orthostatic tachycardia syndrome was suspected, and no other cardiological or neurological etiologies were found. Sleep disturbances were noted with nightly shivering and a sensation of coldness. She also suffered from chronic, temporal headaches, at least every other day, exacerbated by exercise, lasting for hours and not responding to paracetamol, and recurrent swelling of the parotid gland every 2 weeks. Menses were unremarkable. Blood transfusions were never given. She weighs 43.8 kg with a height of 148 cm. We noted pallor, mechanical allodynia, a bilateral trochlear nerve weakness, a spleen of 12 cm, and no other pathological findings. Her hemoglobin concentration was 99 g/L, leukocytes and platelets were normal, her ferritin was 111 µg/L, erythropoietin 15.3 U/L and the hormonal axes were normal.

Remarkably, the other four siblings and their parents were of normal stature and had no medical history. We suspected a syndromic disease with autosomal recessive inheritance. Genomic DNA was extracted from EDTA-blood with the Prepito DNA Blood250 Kit. After polymerase chain reaction amplification and genetic blood DNA analysis using TWIST comprehensive exome analysis (Twist Bioscience), high-throughput sequencing (NovaSeq 6000) and Varsome Clinical v.9.3 (Sentieon-version 202010, Saphetor SA) alignment to the human reference genome GRch37hg19, a novel homozygous *PUS1* gene c.431G>A (p.Arg144Gln) mutation was detected. Targeted *PUS1* analyses were performed on buccal swabs from all family members. The inheritance is compatible with an autosomal recessive pattern (Figure 2). *PUS1* (GenBank accession #NM_025215.6) codes for pseudouridine synthase 1, a cytosolic and mitochondrial-expressed enzyme that converts uridine into pseudouridine in several transfer RNA positions by relying on secondary structure, stabilizing tRNA and increasing the efficiency of protein synthesis in both compartments.[2-4] Analysis of the crystal structure of PUS1 demonstrated the importance of arginine at position 144 in the active site cleft;[4] this arginine is highly conserved across species.[5] A missense mutation of

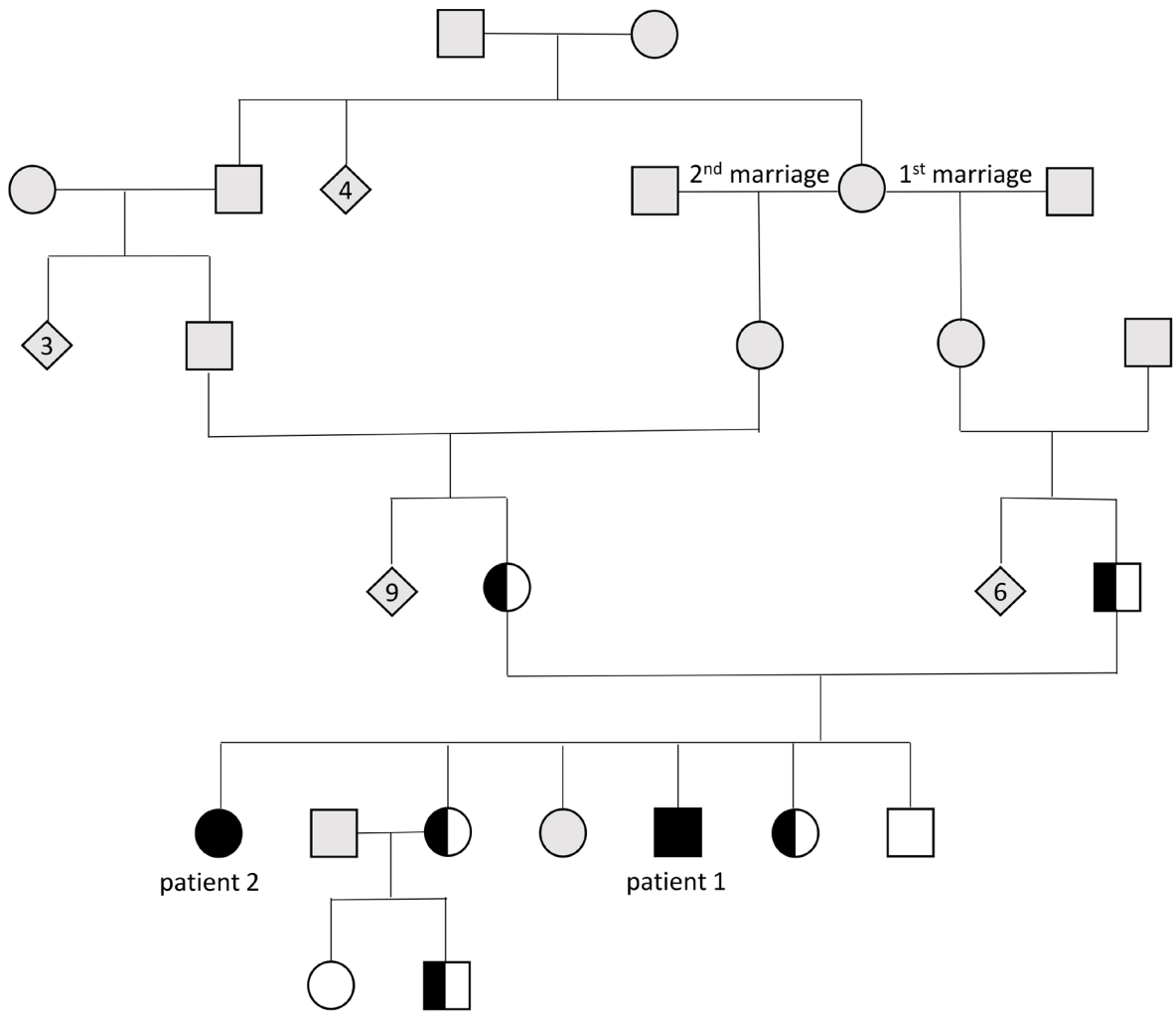

Figure 2. Six-generation pedigree of a family with hereditary myopathy, lactic acidosis and sideroblastic anemia syndrome type 1 (MLASA1). Squares represent males and circles females; diamonds stand for further siblings (with number of siblings indicated). Family members with *PUS1* mutations are marked in black (full symbol: homozygous; half symbol: heterozygous). Gray color: not tested.

this arginine to tryptophan has previously been described in three families of Iranian descent[6-8] and, thus, the present mutation arginine at position 144 to glutamine was considered pathogenic. Mutated *PUS1* defines MLASA1. We reviewed the clinical presentation of all published MLASA1 cases (*Online Supplementary Table S1*). Descriptions of a total of 18 patients have been published worldwide so far.[2,5-15] Anemia and transfusion dependency are inherent to the syndrome, as is permanent lactic acidosis. Recurrent clinical features are a failure to thrive, developmental delay, exercise intolerance, gastrointestinal symptoms and intellectual disability. Growth hormone deficiency has been reported. The myopathy shows a progressing functional decline without a plateau phase. The reported deaths have been due to respiratory failure. Within a family, the same mutation demonstrates variable penetrance. The phenotype seems to be species-specific, as muscles only were affected in a *PUS1* knock-out mouse model showing reduced exercise capacity and reduced cytochrome c oxidase activity.[3]

Therapeutic approaches using vitamin B6 or coenzyme Q10 seem to be of no benefit, as in our patients. Levocarnitine was unsuccessful too.[9] In our experience, substitution with parenteral somatropin surprisingly has shown positive effects on hemoglobin values, and the patient is transfusion-independent since the start of this therapy.

The diagnosis of MLASA1 was made when the propositus was 26 years old. Unrestricted transfusion practices had led to a significant secondary hyperferritinemia with signs of hepatopathy in laboratory, ultrasonographic and histological analyses. Awareness of the syndromic aspect of this disease with rapid and targeted investigations is important for providing appropriate counseling. Such counseling includes explaining the genetic basis of the observed physical weaknesses, the progressive myopathy associated with the disease, and the futility of most therapeutic approaches. Management of complications is the mainstay of therapy. At least in some cases of MLASA1, a trial with somatropin may improve the anemia.

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LP and RE both contributed to data collection and analysis and to manuscript redaction. RE obtained informed consent from all family members. Both authors read and approved the final version of the paper.

Data-sharing statement

Original laboratory data are available on request to the corresponding author.

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