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Chronic anemia as a manifestation of MELAS syndrome

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INTRODUCTION

Myopathy, encephalopathy, lactacidosis and stroke-like episodes (MELAS)-syndrome is a heterogeneous respiratory-chain-disorder (RCD) due to point mutations in mitochondrial genes (m.583G>A, m.1642G>A, m.3243A>G, m.3252A>G, m.3260A>G, m.3271T>C, m.3291T>C, m.5814A>G, m.9957T>C, m.13513G>A), due to mtDNA deletions, or due to nDNA mutations, such as in POLG1.[1] Like most of the RCDs, MELAS is a multi-system disease, involving the brain, peripheral nervous-system, eyes, endocrine glands, heart, guts, kidney, or dermis.[2] Involvement of the bone marrow, manifesting as hy- pochrome, and microcytic anemia, has been only occasionally described.[2-5]

CASE REPORT

The patient is a 37years-old HIV-negative female with a history of: increased blood sedimentation rate since childhood; hypochrome, microcytic anemia since age 6y; episodes of migraine-like headache and partial visual-field defects since age 30y; epilepsy with complex partial seizures (optic hallucinations, kakosmias, dysgeusia) and occasionally generalized seizures since age 32y; hypergammaglobulinemia, first noted at age 32y; recurrent episodes of double vision, ptosis, and chronic sinusitis requiring surgical intervention. The history was negative for thrombotic microangiopathy, recurrent abortions, or ischemic stroke.[6] The family history was noteworthy for a presumed RCD in her sister, who died at age 19y from cerebral edema after a seizure, but had also developed migraine, aseptic pleocytosis, encephalopathy, slight anemia, and cerebral calcifications since age 17y.

Neurologic examination of the index-patient revealed short stature (160 cm), mild cognitive impairment, bilateral ptosis, sore neck muscles, small constant left-sided visual-field-defects, and reduced Achilles-tendon-reflexes. Resting lactate, pyruvate, homocysteine, and urinary acids were normal but lactate-stress-testing was abnormal. Needle electromyography of the right brachial biceps muscle was myogenic. Muscle biopsy revealed single atrophic fibers but was otherwise normal. Nerve biopsy was non-informative. The electroencephalogram (EEG) showed continuous theta-delta-activity over the left hemisphere and paroxysmal activity (sharp waves) over the left frontotemporal projections. Visually-evoked-potentials (VEPs) were slightly abnormal on the left side. Cerebral magnetic resonance imaging (MRI) revealed an extensive hyperintensity on T2-weighted images over the left parieto-tempo-ro-occipital region, sparing the cortex. The lesion was not confined to any vascular territory and typical for a stroke-like lesion. It disappeared after five years. Hyperintense lesions were also visible in the C. nuclei caudati and deep and periventricular white matter. MR-spectroscopy showed a reduced N-acetyl-aspartate-peak and an increased lactate-peak. Screening for the m.3243A>G and the m.8344A>G mtDNA mutations was negative. Despite the absence of these mutations MELAS-syndrome was diagnosed, based upon the synopsis of the individual and family history, clinical neurologic examination, blood chemical investigations, EEG, VEPs, the MRI, and the MR spectroscopy.

Revision of previous blood cell counts, available between age 27y and 37y, revealed chronic, hypochrome, and microcytic anemia throughout the years (Table 1). Iron parameters, determined at age 31y, revealed a serum iron of 27 µg/dL (n, 40-150 µg/

dL), transferrin of 182 mg/dL (200-360 mg/dL), transferrin saturation of 11% (n, 16-45%), and a ferritin level of 467 ng/mL (n, 10-120 ng/mL). At age 37y these values amounted to 12 µg/dL, 275 mg/dL, 3%, and 30.3 ng/mL respectively. Reticulocyte counts and thyroid function tests were normal. She had repeatedly received iron substitution during this period, resulting in normalization of the iron parameters, without effect on the anemia. Occasionally, mild thrombocytosis was noted in the absence of concomitant acute or chronic infection. Gastroscopy and colonoscopy were normal. There was no indication for hemolysis. Renal function parameters, amylase, lipase, electrolytes, immunoglobulines, and liver enzymes, in particular creatine-kinase, were normal whenever determined, as well as vitamin-B12 and folic acid levels. Rheuma-factors, anti-streptolysin-O titer, and anti-nuclear antibodies at age 35y were negative. Anti-phospholipid-antibodies determined at age 32y were negative. The HbA was 97.4%, the HbF 0%, and the HbA_2 2.4%. There was no hemoglobinopathy and genetic investigations excluded a thalassemie. The erythropoietin serum level was normal. The patient refused to undergo a bone marrow aspirate for further diagnostic work-up. At age 37y she was on a regular therapy with lamotrigine and lorazepam.

DISCUSSION

In addition to what the acronym represents, typical features of MELAS include epilepsy, migraine, confusion, hypothalamo-pituitary dysfunction (growth retardation), polyneuropathy, pigmentary retinopathy, hearing loss, hypertrophic cardiomyopathy, arrhythmias, intestinal pseudo-obstruction, diabetes, or chronic renal failure.[1] In the presented case MELAS-syndrome manifested as short stature, migraine-like

Table 1. Blood cell counts over a period of 11 years. Reduction of particularly hemoglobin, hematocrit and mean cell volume were attributed to the mitochondrial disorder.

AD Reference limits	Erythrocytes 4.0-5.2 /pl	Hemoglobin 12-16 g/dL	Hematocrit 38-48%	MCV 84-100fl	Thrombocytes 140-440 G/l
27	4.9	9.1*	30.5*	62*	432
27	4.8	8.7*	29.4*	61*	436
27	5.04	10.6*	33*	65*	393
28	5.31	11.4*	38	72*	429
30	4.98	11.9*	36*	72*	338
32	4.35	11.1*	33.4*	76.8*	474*
32	4.7	11.9*	36.2*	76.9*	450*
33	4.74	12.7	37.9*	79.9*	395
33	4.2	11.3*	34.2*	81.2*	322
33	3.99*	10.8*	32.8*	na	337
34	3.62*	10.0*	29*	80*	315
34	4.0	10.4*	31.8*	79.4*	391
34	4.43	11.0*	35*	79*	401
34	4.78	11.9*	36.8*	76.9*	325
34	4.22	10.3*	32.5*	77.2*	282
34	4.67	11.4*	36*	77*	382
34	4.59	11.1*	34.6*	75.4*	445*
35	4.42	10.7*	32.7*	73.9*	404
35	4.45	10.8*	32.8*	73.6*	352
35	4.63	11.3*	34.3*	74*	519*
35	4.49	10.9*	33.2*	73.6*	387
36	4.73	10.7*	33.2*	73.9*	403
36	3.98*	9.0*	28.0*	70.3*	331
36	4.54	10.1*	31.0*	69*	361
37	4.95	10.4*	34.0*	69*	413
37	4.74	10.1*	33.0*	70*	392
37	4.59	9.8*	31.0*	68*	446*
37	4.78	10.1*	32.0*	67*	436

AD: Age at determination. MCV: Mean corpuscular volume. na: Not available. *: Abnormal result.

headache, epilepsy, and recurrent stroke-like episodes. MELAS is associated with the heteroplasmic mtDNA transition m.3243A>G in the $tRNA^{Leu(UUR)}$ gene in about 80% of the cases. The second most frequent mtDNA mutation causing MELAS is the m.3271T>C transition also in the $tRNA^{Leu(UUR)}$ gene. Other MELAS-associated mtDNA point mutations affect the tRNA(Phe), tRNA(Val), tRNA(Lys), COXII, COXIII, ND1, ND5, or rRNA genes.[7] The genotype-phenotype correlation of the m.3243A>G mutation is poor since it has been detected also in several patients with maternally-inherited progressive external ophthalmoplegia, Kearns-Sayre-syndrome, maternally-inherited diabetes and deafness, Leigh-syndrome, cluster headache, isolated myopathy, cardiomyopathy, renal failure, or pancreatitis.

Arguments for anemia as an additional manifestation of MELAS-syndrome are that

1. Anemia is a typical feature also of other RCDs, such as Pearson-syndrome, Kearns-Sayre-syndrome, mitochondrial myopathy, lactic acidosis and sideroblastic anemia (MLASA), X-linked sideroblastic anemia and X-linked sideroblastic anemia with ataxia. or a number of non-syndromic RCDs.[8]
2. All other causes for hypochrome, microcytic anemia, such as chronic bleeding, malignancy, iron deficiency, thalassemia, celiac disease, systemic lupus erythematodes, or lead intoxication were excluded.[6,9] An antiphospholipid syndrome with hemolytic anemia was excluded since lactate dehydrogenase, bilirubine, and anti-phospholipid antibodies were normal.
3. Iron substitution improved serum iron levels but not anemia.
4. Slight anemia was also present in her sister who also suffered from MELAS and died during an intractable epileptic state.
5. Anemia had started already in childhood together with growth retardation and persisted throughout the following years (Table 1).

MLASA was excluded since the patient also presented with stroke-like episodes and epilepsy and did not exhibit microcephaly or facial dysmorphism.[3,10] Malabsorption of the oral iron substitution was excluded as the cause of anemia since the patient did not have a gastro-intestinal problem and since iron levels increased after substitution. There was also no chronic infection, which could explain anemia. Most likely, the underlying MELAS mutation impaired the intra-mitochondrial iron-metabolism.

Thrombocytosis is more frequently reactive than autonomous (neoplastic).[11] Conditions resulting in reactive thrombocytosis include infections, immunological disease, malignancy, acute bleeding, hemolysis, rebound to thrombocytopenia, trauma, iron deficiency, or post-splenectomy state.[11] In the presented patient occasional thrombocytosis was assumed to have been reactive resulting from anemia, since the above mentioned conditions were excluded and since thrombocytosis has been only rarely reported as a feature of RCDs.[12] An argument against a causal relation between anemia and thrombocytosis is that anemia was not associated with the thrombocyte count at each determination. Lamotrigine and lorazepam were excluded as causative since these drugs have not been reported in association with thrombocytosis. Limitations of this report are that the patient did not consent with bone marrow aspiration, that iron metabolism was investigated only two times, and that the causative mutation could not be detected.

This case shows that MELAS can be associated with chronic, non-transfusion-dependent, microcytic, and hypochrome anemia and reactive, mild thrombocytosis. Physicians should be aware that anemia may be a feature of MELAS syndrome, non-responsive to oral iron substitution.

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