Case Report

Stroke-like lesions in mitochondrial disease may resemble ischemic stroke

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Abstract

The patient is a 73-y-male who was referred after a fall without losing consciousness or secessus. Clinical exam revealed disorientation, ophthalmoparesis, hemianopia to the left, left hemineglect, hypoacusis, quadruparesis, general wasting, generally reduced tendon reflexes, mild rigor, occasional myoclonic jerks of the right lower limb, and ataxia of the left lower limb. Cerebral magnetic resonance imaging (MRI) showed a stroke-like lesion (SLL), generalized atrophy, white matter lesions, and ponsgliosis. The previous history was positive for diabetes, hypoacusis, arterial hypertension, hyperlipidemia, vitamin-D deficiency, cataract, esophageal adenocarcinoma, histiocytoma, Barrett esophagus, hiatal hernia, colonic polyps, and lactic acidosis. Based upon this phenotypic spectrum, lactic acidosis, and the cerebral MRI, a mitochondrial disorder (MID) was diagnosed. This case shows that a MID may be missed for years, that an SLL may be easily mixed up with ischemic stroke; and that the initial manifestation of an SLL may be a fall.

Keywords: Epilepsy, fall, MELAS, multisystem, stroke-like episode

Introduction

Stroke-like episodes (SLEs) are the hallmark of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS).[1] They occasionally also occur in other mitochondrial disorders (MIDs).[2] The morphological equivalent of a SLE on multimodal magnetic resonance imaging (MRI) is the stroke-like lesion (SLL).[3] As SLLs are specific for MIDs, their presence indicates a MID, as in the following case.

Case Report

The patient is a 73-year-old Caucasian male, height 172 cm, weight 73 kg, who was referred after a fall in his kitchen at 4 h in the morning without losing consciousness or secessus. A computed tomography (CT) scan of the brain on hospital day-1 (hd1) only showed atrophy and basal ganglia calcifications. However, cerebral MRI on hd8 revealed a hyperintensity on diffusion-weighted imaging (DWI), and partially also on apparent diffusion coefficient (ADC) in an occipitotemporal distribution not confined to a vascular territory, features suggesting an SLL [Figure 1]. In addition to the SLL, cerebral MRI showed generalized atrophy, leukoencephalopathy, and gliosis of the pons. Despite the evidence for an SLL, the cerebral lesion was misinterpreted as ischemic stroke. *Electroencephalographies (*EEGs) on hd14 and hd18 revealed a focal, right parietal-central nonconvulsive status epilepticus (NCSE), why treatment with levetiracetam (1000 mg/d) was initiated. The SLL occurred under therapy with edoxaban, given after thrombosis of the left subclavian vein 2 months earlier. Lung CT showed pleural effusions bilaterally. Pneumonia was detected, and cefuroxime was begun.

The previous history was noteworthy for diabetes since age 40 y, smoking until age 52 y, resection of a nuchal hemosiderotic histiocytoma located over thoracic vertebra-1 at age 62 y, bilateral hypoacusis, arterial hypertension, hyperlipidemia, and vitamin-D

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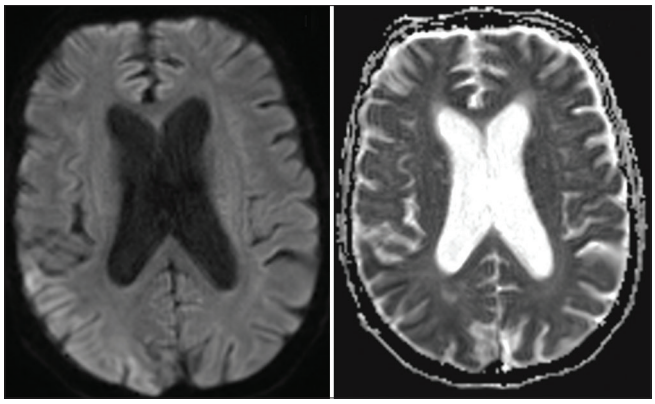

Figure 1: Multimodal, cerebral MRI of the presented patient shows a typical stroke-like lesion in the right occipital-temporal region, which was hyperintense on DWI and isointense on ADC

deficiency since at least age 70 y, cataract surgery bilaterally at age 72 y, adenocarcinoma of the distal esophagus treated with transthoracic resection of the esophagus with pulling up of the stomach and adjuvant chemotherapy pre- and post surgery at age 72 y. Additionally, Barrett esophagus, hiatal hernia, colonic polyps, and steatosis hepatis were found. Three months later, a syncope in the context of hypoglycemia occurred. Serum iron levels were low. Since then, recurrent lactic acidosis despite discontinuation of metformin with a maximal value of 8.1 mmol/L (n, <1.8 mmol/L) and QT-prolongation to 534 ms, thrombosis of the left subclavian vein, hypomagnesemia, hypocalcemia, and hypokalemia became evident. The family history was positive for diabetes (mother, brother) and short stature (mother).

Clinical neurologic exam at age 73 y revealed disorientation, ophthalmoparesis particularly for vertical movements, hemianopia to the left, neglect for the left side, severe hypoacusis, quadruparesis, general wasting, generally reduced tendon reflexes, mild rigor on the upper limbs, contracture of the left shoulder, occasional myoclonic jerks of the right lower limb, and ataxia of the left lower limb. Blood tests revealed anemia, hypocalcemia, hypomagnesemia, a HbA1c of 6.6, a pro brain natriuretic peptide (BNP) of 2137 ng/L (n <241 ng/L), and elevated lactate 2.4 mmol/L. Parameters for infectious disease or epilepsy were negative. The patient refused further work-up for a MID since he was transferred to a nursing home. His last medication included levetiracetam, amlodipine, lisinopril, atorvastatin, esomeprazol, amylase, lipase, protease, calcium, potassium, triazolam, edoxaban, spironolactone, and erythropoietin.

Discussion

The patient is interesting for an SLE manifesting as fall, hemianopia, hemineglect, and NCSE, for misinterpretation of the corresponding SLL as ischemic stroke, and that the MID remained undetected for 32 y after the initial manifestation of diabetes. Arguments in favor of the diagnosis MID are the SLE, lactic acidosis, basal ganglia calcification, brain atrophy, leukoencephalopathy, the cataract, hypoacusis, ophthalmoparesis, quadruparesis, extrapyramidal manifestations (rigor), diabetes, the two malignancies, steatosis hepatitis, heart failure, QT-prolongation, and arterial hypertension. All these features have been previously reported in association with MIDs.[1,4,5] Particularly, the SLL is highly suggestive of a MID. SLEs/SLLs occur most frequently in MELAS but occasionally also in other MIDs, such as myoclonic epilepsy with ragged-red fibers (MERRF), chronic progressive external ophthalmoplegia (CPEO), Kearns–Sayre syndrome (KSS), Leber's hereditary optic neuropathy (LHON), Leigh syndrome, Saguenay-Lac-Saint-Jean cytochrome-c oxidase (SLSJCCOX) deficiency, *POLG1*-related MIDs, triple-H syndrome, CoQ-deficiency, or mitochondrial multiorgan disorder syndrome (MIMODS).[2] In the few cases in which a SLE has been reported in apparently nonmitochondrial disease,[2] the MID was most likely unrecognized or subclinical.

SLLs in the acute stage are characterized by dynamic expansion of a hyperintensity on T2, fluid- attenuated inversion recovery (FLAIR), DWI, and perfusion-weighted imaging (PWI), as decreased oxygen extraction on oxygen extraction fraction (OEF) MRI, as hypometabolism on fluoro-2-deoxyglucose positron emission tomography (FDG-PET) and not confined to a vascular territory.[3] SLLs occur spontaneously or are triggered. Triggers of SLLs may be infections, seizures, ischemia, stress, or drugs. The trigger of the SLE in the presented patient remains speculative, but possibly it was triggered by chemotherapy or pneumonia. The fall as the initial manifestation of the SLE is unusual and has not previously reported, but the further course with hemianopia, hemineglect, and NCSE are common findings. Possibly, the fall was due to a seizure, frequently associated with SLEs.

The case is relevant for primary care physicians as it shows that delineation between ischemic stroke and SLL is crucial already at the onset of the clinical manifestations. As the therapeutic management of ischemic stroke and SLLs is entirely different between the two, it is important not to mix them up. The earlier both conditions are correctly diagnosed, the better will the outcome be. Early treatment of a SLL with L-arginine or L-citrulline, antiepileptic drugs, antioxidants, or steroids is important to prevent the expansion or recurrence of the lesion. Red flags for diagnosing an MID with SLEs are the multimodal cerebral MRI, lactic acidosis, and progressive multimorbidity.

Limitations of the study were that no muscle biopsy and no biochemical investigations had been carried out, that no magnetic resonance spectroscopy (MRS) had been carried out, and that the suspected MID was not genetically confirmed.

This case shows that a MID may be misdiagnosed for years, that a SLL may be easily mixed up with ischemic stroke; and that the initial manifestation of a SLE may be a fall. Differentiating between ischemic stroke and a SLL is of paramount importance for the therapeutic management and outcome. SLLs are pathognomonic for MIDs, while the occurrence of a SLL should prompt extensive diagnostic work-up for a MID.

Key points

Mitochondrial disorders are easily missed as they frequently manifest with multisystem manifestations behind which the single cause is often not evident

If mitochondrial disorders manifest with a stroke-like episode, they are frequently mixed up with ischemic stroke

The initial manifestation of a stroke-like episode may be simply a fall

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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