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Review Article

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Mitochondrial Encephalomyopathy Masked By "Cerebral Infarction"

Analysis of A Case of Delayed Mitochondrial Encephalomyopathy with Hyperlactic Acid and Apoplexy - Like Onset

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Keywords: Mitochondrial Encephalomyopathy; Apoplexy Attack; Hyperlactatemia

Case Description

The patient, male, 49 years old, was admitted to our hospital due to "blurred vision for 3 days worse than before".3 days prior to the hospital patients with no obvious incentives in his eyes to the left side is not clear from the previous increase, with the right side of the headache, obscures vision is characterized by absence of vision to the left of both eyes, walk tilt, easy to hit objects, the right side of the headache is acerbity keenly feel, at that time did not attach importance to it, not treatment, no obvious improvement in symptoms, then to the hospital emergency line head CT no bleeding, "Cerebrovascular disease" was included in the Department of Neurology. During the course of onset, there was no dizziness, nausea and vomiting, palpitation or feeling of stepping on cotton. Since the onset of the disease, Poor spirit, poor sleep, good diet, normal defecation.

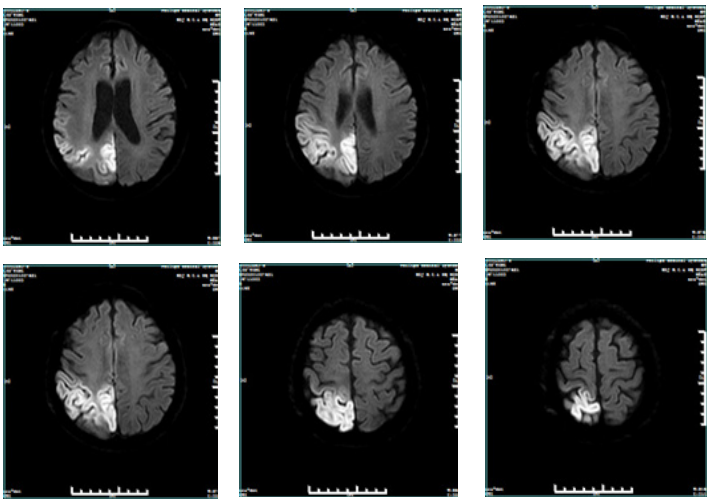
Past history: intermittent headache for 7 years; Diabetes history of 3 years, long-term subcutaneous injection of insulin asparagus (early 14 IU late 16 IU), self-reported good blood glucose control; Neurological deafness for 2 years; Cerebral infarction occurred one year ago, with left visual field defect; cerebral infarction occurred again one month ago, without obvious sequelae; The history of intestinal obstruction for 5 months has been cured; Denied a history of infectious diseases such as hepatitis and tuberculosis; Denied the history of surgical trauma and blood transfusion; Denied a history of drug or food allergies; Have a history of vaccination; Smoking for 30 years; Short stature; My father was in good health, and my mother died of progressive mental decline for 5 years.

Physical examination: blood pressure 130/80mmHg, heart rate 80beats/min, regular, abdomen soft, no edema in both lower extremities. Nervous system: Consciousness clear, words are normal, bilateral pupil equicongruent circle, pupil light reflex, eyeball move freely in all directions, left homotypic hemianopia of both eyes, no central facial tongue paralysis, limbs limb muscle strength level 5, bilateral muscle tone is normal, bilateral limbs tendon reflex (+ +), coarse needle pain not seen obvious abnormity, bilateral body rotation test is normal, Eyes closed and difficult to stand (-). Bilateral finger-nose test and hehe-knee tibial test were stable. Left Babinski's sign (+), no neck stiffness, Kernig sign (-), and Brudzinski's sign (-). The drinking water experiment in depression field was Grade 1, with ADL score of 95, NIHSS score of 3, MRS score of 1 and Essen score of 2. Blood test on admission indicated: WBC 11.36×109/L, RBC 4.27×1012/L, HGB 143g/L, PLT 223.0×109/L, ALT 39U/L, AST 24U/L, ALB 37.3g/L, UREA 7.1mmol/L, CREA 43.7mmol/L, GLU 11.16mmol/L, CK 1211.6U/L, MYO 231.9ng/mL, ctnI <0.012ng/mL, TG 0.71mmol/L, CHOL 3.2mmol/L. DWI of the head suggested cerebral infarction in the right paraoccipital lobe and softening lesion in the right temporal paraoccipital lobe. No abnormalities were observed in head MRA and head and neck CTA.ECG suggested sinus rhythm. The color ultrasound of the heart showed no abnormality.

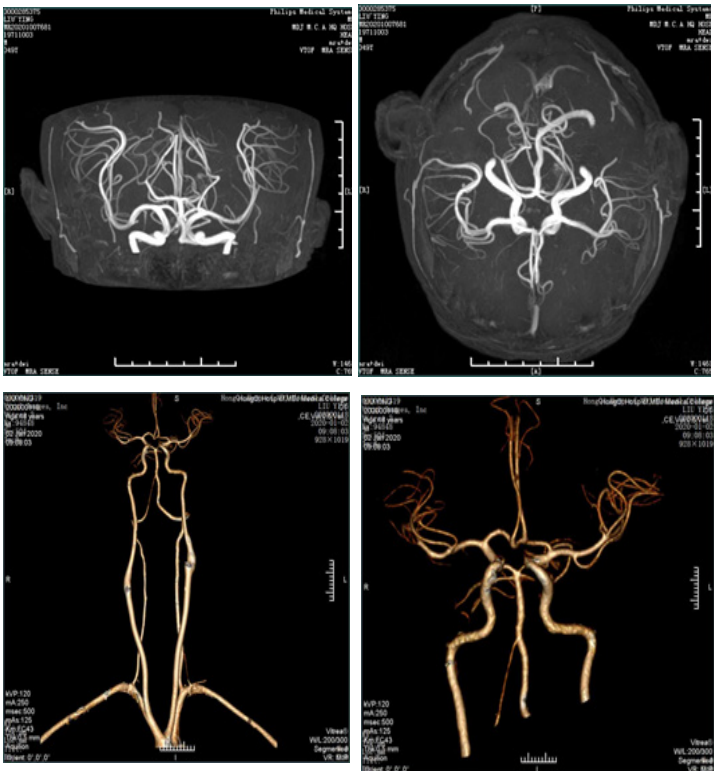
Primary diagnosis: multiple cerebral infarction; Type 2 diabetes.
Therapeutic schedule: secondary nursing care, diabetes diet, improvement of related examinations, anti-platelet aggregation, lipid regulation and plaque stabilization, improved collateral circulation, blood circulation and blood stasis improvement.

The patient's condition suddenly worsened on the 7th day after admission, with movement disorder in the left limb. Physical

examination showed blood pressure of 100/60mmHg, muscle strength of the left limb was level 4, and the rest physical examination was the same as before. The patients were given volume enlargement and enhanced lipid-lowering therapy, and the lace sign was found on NMR DWI after reexamination.



The DWI of the review head is shown in the figure above



Head MRA and head and neck CTA are shown in the figure above

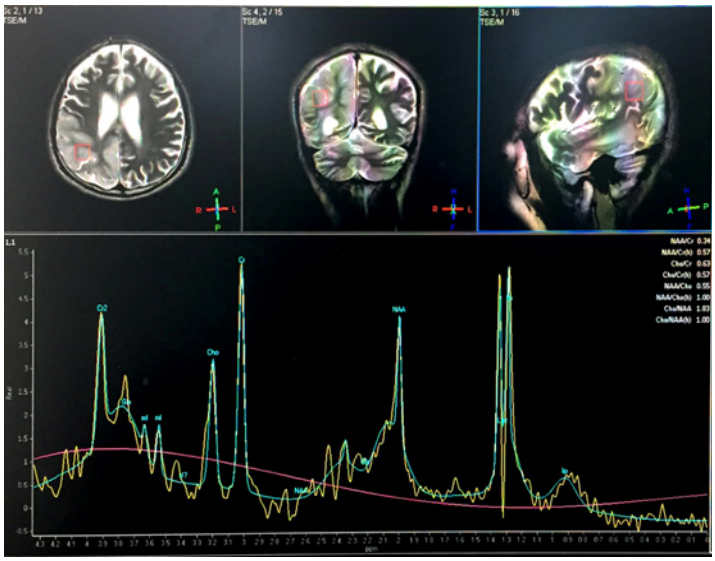
Condition Analysis

The patient was middle-aged male with apoplexy like onset. Smoking for 30 years, diabetes for 3 years, 2 times of cerebral infarction history; He was admitted to the hospital because of "blurred vision for 3 days worse than before". CT indicated low density shadow in the brain, and DWI indicated cerebral infarction, which was temporarily identified as cerebrovascular disease.

However, the following points should be considered: 1. the infarct site of the patient involved the temporo-parietal occipital lobe, involving the internal carotid artery and vertebral basilar artery system. NMR indicated that the infarct area presented lace-like signs, and the lesion was cortical, which did not conform to the vascular regional distribution of the cerebral infarction lesion; 2. The patient had two previous histories of cerebral infarction, but no history of hypertension, normal blood lipids, head MRA and head and neck CTA suggested good vascular conditions, and no history of heart disease such as atrial fibrillation, and no abnormal heart color ultrasound, so the possibility of cerebral thrombosis and cerebral embolism was relatively small;3. Refer to the history, family history of the patient, her mother died 5 years due to the progressive mental decline history, history of diabetes, nerve deafness patients with gastrointestinal tract disease history, history of headache, stroke history, history of cortical hemianopia, and patients with short stature, family v. patients since the first started to progressive intellectual impairment after cerebral infarction.

Based on the above, the monistic explanation was used to consider the patient as a "stroke-like episode" of mitochondrial encephalomyopathy.

Therefore, the arterial blood was taken from the patient and the lactic acid was determined by blood gas analysis. Meanwhile, the head was examined by Magnetic resonance spectroscopy (MRS). The results were as follows: blood lactic acid was 1.4mmol/L in resting state, 2.5mmol/L after exercise, and 1.9mmol/L again after 10 minutes' rest. MRS a significant LAC peak and lactic acid deposition in the cerebrospinal fluid. Lac peak slightly increased, NAA peak slightly decreased, and Cho peak slightly increased, suggesting neuronal damage and lactic acid deposition in the anterior cingulate gyrus region. NAA peak decreased, MI peak decreased, and Lac peak increased in the right parietal lobe lesions, suggesting neuronal damage in the lesion region, obvious lactic acid deposition and hypoxia in the brain tissue.



Magnetic resonance spectral analysis indicated elevated lactic acid

Magnetic resonance spectral analysis indicated elevated lactic acid According to the Expert Consensus on Diagnosis and Treatment of Mitochondrial Cerebromyopathy with Hyperlactic Acid and Stroke-like Attack in China, the patient was considered to be very likely to have Mitochondrial Cerebromyopathy with Hyperlactic Acid and Stroke-like Attack, and genetic examination and muscle biopsy were recommended, but the patient refused. The patient was given energy supplement and symptomatic supportive treatment, and the patient was discharged after symptom relief.

Disease Characteristics

Mitochondrial diseases are usually a group of genetic diseases characterized by dysfunction of oxidative phosphorylation of mitochondrial respiratory chain caused by mitochondrial DNA or nuclear DNA defects. Abnormal mitochondria cannot produce enough energy to meet the needs of various organs, leading to multiple organ dysfunction. Meanwhile, lack of energy can also stimulate the proliferation of mitochondria in the smooth muscle of small vessels and endothelial cells, leading to impaired blood perfusion in the microvascular system of organs [1]. Some patients with mitochondrial diseases often show a range of clinical characteristics, including "mitochondrial encephalopathy, mitochondrial encephalomyopathy, mitochondrial neuropathy, mitochondrial myopathy", Mitochondrial encephalomyopathy also includes mitochondrial encephalomyopathy with hyperlactic acid and stroke-like seizures (MELAS), myoclonic epilepsy with broken red fibers (MERRF), Kearns-Sayre syndrome (KSS), and mitochondrial neurogastroenteric encephalomyopathy (MNGIE) [2].

Main features of mitochondrial encephalomyopathy with hyperlactic acid and stroke-like episodes (MELAS)

Mitochondrial encephalomyopathy with hyperlactic acid and stroke-like episodes (MELAS) is a matrilineal genetic disease with a male to female ratio of about 1.5:1. Most of the diseases occur in children and young adults, and rarely occur after 40 years of age [2]. MELAS is a multi-organ disease with a wide range of manifestations, including stroke like episodes, dementia, epilepsy, lactic acid, myopathy, recurrent headache, hearing impairment, cortical blindness, diabetes, and short stature [1]. A few patients may be accompanied by retinopathy [3] and gastrointestinal disorders [4]. Patients generally die 5-10 years after onset [2].

Related tests involved in the diagnosis of MELAS

Laboratory Inspection

Most patients with MELAS will have elevated lactic acid, and the lesions involved in different organs may have abnormal corresponding indicators. For example, patients with skeletal muscle involvement generally have slightly elevated creative kinase. In patients with renal involvement, proteinuria can be found on routine urine. Elevated transaminase can be observed in patients with liver damage [2]. At the same time, it has been pointed out that the combination of lactic acid test and oxygen saturation test has high specificity and sensitivity for the screening of MELAS [5]. It has also been pointed out that through the ATP analysis system of luciferase luminescence reaction, it can be found that cerebrospinal fluid ATP is negatively correlated with disease activity and reflects the therapeutic effect, indicating that cerebrospinal fluid ATP may also be used as a new monitoring index for MELAS [6].

Imaging and Other Examinations

The typical imaging features of MELAS are that the lesion does not distribute according to the classical vascular supply area, and fluctuates, migrates, and even disappears over time (hence the name "stroke-like"). The common manifestations of cranial CT are bilateral basal ganglia and thalamus calcification, and the strok-like lesions are mostly located in the paraoccipital cerebral cortex. Deep gray matter such as thalamus may also be affected, while the cranial blood vessels are usually normal [7]. Magnetic resonance spectroscopy (MRS) analysis of MELAS encephalopathy showed a decrease in aspartic acid and an increase in lactic acid, but when the lesion gradually progressed to atrophy, the lactic acid level did not increase, or even decreased, so the monitoring of cerebral lactic acid level of MRS could also be an effective marker of efficacy [8].

Oxygen extraction fraction (OEF) is the proportion of blood oxygen that a tissue receives from the bloodstream to maintain functional and morphological integrity. Due to abnormal mitochondrial function in MELAS patients, the oxygen utilization rate of the brain will be reduced, leading to a decrease in OEF, so the quantitative analysis of OEF can reflect the functional state of the brain mitochondria [9]. At the same time, it has been pointed out that the severity and mutation load of MELAS are negatively correlated with arterial and cerebrovascular responsiveness, and are proportional to frontal cerebral blood flow. These indicators can further understand the cerebrovascular hemodynamic changes of MELAS, and can be used as non-invasive prognostic indicators [10].

Electron Microscopy and Pathological Biopsy

Under electron microscope, crystallized inclusion bodies in muscle fiber mitochondria can be clearly seen as a "parking lot" arrangement, which is a typical characteristic of MELAS [11]. Histological and pathological biopsy of the muscle of MELAS patients revealed that 80% to 100% of the patients had RRF phenomenon in the muscle, which means that the abnormal aggregation of mitochondria in muscle fibers, especially under the membrane of muscle fibers, showed red color and a sense of fragmentation on the modified Gomori staining. It is caused by insufficient cell energy supply, compensatory mitochondrial hyperplasia and large number of aggregation due to mitochondrial dysfunction [12]. At the same time, studies have shown that about 84.8% of MELAS patients can see the blue color of abnormal mitochondria aggregation in muscle fibers or under muscle fiber membrane on SDH staining, namely RBF phenomenon. Another hihiopathological feature of MELAS is the observation of excessive mitochondrial hyperplasia in SDH stained intramural vascular smooth muscle and endothelial cells, which is called strong SDH reactive vessels, namely SSV phenomenon [11]. Bennett et al. [13] have pointed out in the report that about 85% of MELAS patients can develop SSV phenomenon, which has the same diagnostic value as RRF and RBF phenomenon.

Gene

Detection of gene mutation sites is the gold standard for the diagnosis of MELAS. In recent years, nearly 20 kinds of MELAS-related mtDNA point mutations have been found in the tRNALEU

(UUR) region, such as A3243G, A3252G, T3271C, T3291C, G3959A, A3995G, etc. Among them, 80%-90% of mtDNA A3243G mutations can be used for the preliminary screening of MELAS, and mutations at this site are associated with the diversity of stroke-like episodes [14]. The second most common mutation is mtDNA T3271C, and the single base deletion in this mutation is associated with retinal dystrophy in MELAS patients [3].

Diagnosis and Differentiation of Diseases

Diagnose

The diagnostic criteria for MELAS are as follows [15] :

A: Core evidence
1. Have a stroke-like attack (a)
2. Craniocerebral imaging findings are limited to cortical and/or subcortical lesions that do not conform to single vascular domination, and the lesions can be completely or partially reversible by follow-up review
[B] Supporting evidence
1. At least one of the following clinical manifestations: cognitive/mental disorders, seizures, sensorineural deafness, diabetes, short stature, hair abnormalities, exercise intolerance, gastrointestinal dysfunction, cardiomyopathy/cardiac conduction abnormalities, nephropathy, etc
2. Significant blood/cerebrospinal fluid lactic acid increase or MRI showing focal/cerebrospinal fluid lactic acid peak
3.≥2 stroke-like attacks
4. The clinical manifestations of the family members are 1 or more B (supporting evidence), item 1, and conform to the maternal inheritance
C: Confirmatory evidence
1. Evidence of mitochondrial abnormality in skeletal muscle biopsy pathology:detected by Modified Gomori trichrome staining found irregular red edge fibers (b) , and/or small vessels with abnormal activity of succinate dehydrogenase detected by deep staining of muscle fibers and/or succinate dehydrogenase, or abnormal mitochondria detected by electron microscopy
2. Genetic testing detected clear mitochondrial encephalomyopathy with hyperlactic acid and stroke-like episodes associated with mitochondrial DNA or nuclear DNA pathogenic mutations
Note: a: includes headache with or without vomiting, seizures, hemianopia or cortical blindness, aphasia, partial sensory disorder or hemiplegia;b: irregular red edge fiber >2%;Diagnosis of mitochondrial encephalomyopathy with hyperlactic and stroke-like episodes: A (at least 1 item) +C (at least 1 item); Mitochondrial encephalomyopathy is likely to be associated with hyperlactic and stroke-like episodes: A (at least 1 item) +B (at least 2 items); Possible mitochondrial encephalomyopathy with hyperlactic and stroke-like episodes: A (at least 1 item) +B (at least 1 item); Suspected diagnosis of mitochondrial encephalomyopathy with hyperlactic acid and stroke-like attacks: A (both are true)

Identify

MELAS syndrome is often identified with the following diseases: viral encephalitis, brain tumor, brain infarction, glucocorticoid reaction encephalopathy, cerebral small vasculitis, Moya disease, venous thrombosis, and reversible encephalopathy after epilepsy, methyl malonic acid hematic disease, high blood ammonia, other causes of ataxia with epileptic seizures, chronic gastrointestinal diseases [2].

Treatment

General and Symptomatic Treatment

Patients should eat more foods containing high calorie, low fat and multivitamin. For patients with diabetes, subcutaneous insulin injection is usually required to control blood glucose [1]. At the same time, regular exercise can improve the exercise ability of patients with MELAS and other mitochondrial myopathy. It has been reported that endurance training can induce the transfer of normal mitochondrial template from satellite cells to mature muscles, which may reduce heterogenous mutations [16].

Metabolic Treatment

At present, coenzyme Q10, Edibenzoquinone, vitamin and L-arginine are mainly used for clinical treatment. Double-blind studies [17] have shown that intravenous injection of L-arginine in the acute phase can improve the symptoms of stroke-like episodes, and oral administration of L-arginine in the acute phase can reduce the frequency and severity of stroke-like episodes. Meanwhile, L-arginine therapy may also improve other clinical symptoms of MELAS, including muscle weakness, exercise intolerance and lactic acidosis [18]. L-arginine therapy is beneficial in the treatment and prevention of MELAS.

Avoiding Triggers

In addition to avoiding infection, overwork, mental stimulation, and more attention should be paid to the use of relevant drugs. During the treatment of MELAS, attention should be paid to avoiding the use of mitochondrial toxic drugs, otherwise it will aggravate the mitochondrial energy metabolism disorder. For example, valproic acid may lead to the deterioration of MELAS patients or cause new epileptic seizures in clinic, so valproic acid should be avoided in the treatment of epileptic seizures [19]. Also, attention should be paid to avoiding the use of other antiepileptic drugs that may affect mitochondrial metabolism, including phenobarbital, carbamazepine, phenytoin sodium, oxcarbazepine, gabapentin, etc. [20]. Meanwhile, since MELAS is prone to lactic acidosis, metformin should be avoided in patients with diabetes [21].In addition, statins can reduce endogenous synthesis of coenzyme Q10, and should also be avoided in the treatment of hyperlipidemia [22].

Discussion and Outlook

MELAS usually manifests in early life and rarely in adulthood. According to literature reports, only about 1%-6% of patients are older than 40 years old at the time of consultation [23]. Here, we describe the case of a 49-year-old man who initially misdiagnosed symptoms of MELAS as recurrent ischemic stroke. Based on our case study, we conclude that in the presence of recurrent stroke-like episodes and atypical stroke-like imaging, we should consider the possibility of MELAS even at older ages, and perform appropriate

radiological and biochemical tests, and ultimately genetic analysis. Most importantly, because early intervention may improve prognosis, this late onset of MELAS underscores the importance of rapid diagnosis at the first visit.

After diagnosis, patients with MELAS should be managed multidisciplinary, including genetics, neurology, cardiovascular medicine, nephrology, ophthalmology, and endocrinology, as well as a comprehensive evaluation of multiple organs, regular follow-up of patients, monitoring of disease progression and screening for potential complications. Future research should investigate the mechanisms of the disease at the cellular level, as well as highlight advanced MRI techniques and new attempts at gene therapy for targeted therapies.

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