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Clinical Reasoning: A 17-Year-Old Girl With Progressive Cognitive Impairment

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Abstract: A 17-year-old girl presented with a long history of cognitive impairment, personality and behavioral changes, dysarthria, and paroxysmal lower-extremity weakness. She was initially suspected of having mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) because of stroke-like symptoms, such as episodic lower extremity weakness, as well as abnormal brain MRI findings of generalized cerebral atrophy, extensive high intensity lesions in the cortex and subcortical white matter on FLAIR images, decreased N-acetyl aspartate (NAA)/creatine (Cr) ratio, and a lactate peak in the focal area on spectrum images. However, there were no relatives with similar presentations in the family of the patient. The whole mitochondrial genome and whole exome sequencing did not suggest pathogenic mutations, and no abnormalities were found in the blood or cerebrospinal fluid lactate levels. In this case, we detail the clinical manifestations, diagnostic workup, and imaging findings. This case highlights the importance of the assessment of cognitive function and the relevant differential diagnoses in an adolescent with cognitive impairment.

Section 1

A 17-year-old Chinese right-handed girl presented with worsening memory for six years. Six years ago, her academic performance dropped dramatically due to short-term memory loss, trouble concentrating, and agitation. Her symptoms progressed from forgetting appointments and asking the same question to being unable to recall

time and place. Three years ago, she developed episodic weakness in both lower extremities (more severe on the left side), causing unstable walking and paroxysmal falls. She experienced fatigue and drowsiness, and one year ago, slurred and repetitive speech. Occasionally, she had drooping eyelids bilaterally and choked while drinking water. She became increasingly nervous, as well as cried more readily and experienced difficulties with communication. She was diagnosed with a psychiatric disorder without improvement after antipsychotics.

Questions for consideration:

1. What is the localization for her presentation?
2. What is the differential diagnosis?
3. Which investigations would you perform?

Go to Section 2

Section 2

Progressive memory loss may involve the cerebral cortex, thalamus, hippocampus, and medial temporal lobe. Dysarthria and weakness of the lower extremities may involve the pyramidal tract. Personality and behavioral abnormalities may include the frontotemporal lobe and limbic system. Congenital diseases and acquired diseases, such as hereditary causes, infectious diseases, metabolic and toxic encephalopathies should be considered.

Four months prior, the patient's brain MRI revealed extensive cortical atrophy (**Figure 1A**) and high intensity in the cortex and subcortical white matter (**Figure 1B**) without enhancement. MR spectroscopy demonstrated a decreased N-acetyl aspartate(NAA)/creatine (Cr) ratio and lactate peak in the focal area (**Figure 1C**), thus leading to a suspected MELAS diagnosis. However, serum lactic acid levels and muscle biopsy results were normal without pathogenic mutations detected in either the mitochondrial genome or on whole exome sequencing.

The patient's condition did not improve after four months of Coenzyme Q and multivitamins. In our department, neurological examination revealed poor memory and attention, mild dysarthria, normal pharyngeal reflex, muscle strength and tone in all four limbs, inability to walk straight, and positive Babinski's sign on the left side. The Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores were out of 12/30 and 19/30, respectively. Electroencephalography reveal single slow spike-wave complexes in the left prefrontal lobe, but electromyographic findings were normal.

Questions for consideration

1. What is MELAS?
2. What clinical tests and investigations suggest a diagnosis of MELAS?
3. Can the patient be diagnosed with MELAS?

Go to Section 3

Section 3

MELAS is a maternally inherited disorder caused by mutations in mitochondrial or nuclear genes, causing stroke-like episodes, dementia, epilepsy, lactic acidemia, myopathy, recurrent headaches, hearing impairment, etc[1]. Imaging demonstrates high T_2 signal in the cerebral cortex that is not limited to arterial regions. Serial imaging reveals that these lesions migrate over time and appear atrophied, and NAA/Cr on MRS is decreased with an increased lactate peak[2].

The patient's episodic lower-extremity weakness suggested a possible stroke-like episode. Dysarthria[3], ptosis[4], personality, and behavioral changes[1] can also be observed in MELAS patients. MRI displayed generalized cerebral atrophy and a high lactate peak on MRS. Some studies have shown that Coenzyme Q and multivitamins can treat mitochondrial diseases[1,5]. However, mitochondrial gene tests, muscle biopsies, blood lactic acid levels, and hereditary family history were negative.

Questions for consideration:

1. How does this information change your differential diagnosis?
2. What other diagnostic workup would you order?

Go to Section 4

Section 4

Hereditary and non-genetic disorders were suspected. The differential was broadened to include tuberous sclerosis, cerebral autosomal-dominant/recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL/CARASIL), neuronal intranuclear inclusion disease (NIID), fragile-X syndrome, and other genetic disorders with cognitive and psychiatric symptoms. Physical examination did not reveal hypopigmented macules or angiofibromas. Whole-exome sequencing results were normal. NIID was excluded from the muscle biopsy.

For non-genetic diseases, metabolic, toxic, infective, and autoimmune etiologies were suspected. Thyroid ultrasound and thyroid function tests were normal as was tandem mass spectrometry for organic acids, amino acids, and acylcarnitine. Biochemical tests for arylsulfatase A, galactocerebrosidase, galactosidase, hexosaminidase, and metabolic screening were normal. The patient had no history of toxic exposures. For limbic encephalitis, the patient refused polymerase chain reaction for viral, paraneoplastic, and autoimmune encephalitis antibodies.

Given the patient's young age of onset, evidence of possible congenital disease, particularly the parents' medical history, was pursued. Further history-taking revealed that both of her parents had a history of syphilis for many years. Although they were treated after being diagnosed with syphilis, they were rarely retested for syphilis antibodies later. Further laboratory tests of the patient revealed positive rapid plasma regain (RPR) and Treponema pallidum particle agglutination assays (TPPA) tests. Based on a positive finding for her blood syphilis antibodies, neurosyphilis was suspected. A lumbar puncture revealed positive fluorescent treponemal antibody absorption (FTA-ABS), TPPA, and RPR tests, with elevated leukocyte counts and protein levels (**Table 1**). Tests for human immunodeficiency virus 1 and 2 antibodies were negative. The patient had no history of sexual activity or drug use. The diagnosis of neurosyphilis was established.

Questions for consideration:

1. Can a neurosyphilis diagnosis explain all patient's symptoms?
2. What subtype of neurosyphilis does this patient have?
3. How would you manage this patient?

Go to Section 5

Section 5

Neurosyphilis is a chronic infectious disease caused by invading Treponema pallidum into the cerebrospinal fluid. Neurosyphilis is divided into early (asymptomatic neurosyphilis and syphilitic meningitis), early or late (meningovascular syphilis), and late forms (general paresis and Tabes dorsalis)[6]. Syphilitic meningitis was excluded because the patient had no headache, meningismus, photophobia, or cranial nerve palsies[6]. Meningovascular syphilis and tabetic neurosyphilis were excluded without brain ischemia or spinal cord injury lesions[6]. General paresis mainly manifests as progressive dementia, psychiatric syndromes, personality changes, manic delusions, tremors, and dysarthria (characterized by halting and syllabic repetition)[6]. Although the possible signs of late neurosyphilis such as Argyle-Robertson pupils, Romberg's sign and posterior spinal involvement were not present in the neurological examination, the diagnosis of general paresis was clear based on the patient's decreased cognitive function, personality and behavioral abnormalities, and abnormal laboratory testing. Penicillin was administered for two weeks, and her MOCA score improve from 12 to 19 and her MMSE score from 19 to 24. The patient's orientation to time and space as well as her ability to communicate also improved. No Jarisch-Herxheimer reaction developed. A second lumbar puncture was performed, and the results can be found in **Table 1**. We recommended a neurological examination and lumbar puncture after 3 months, but the patient was lost to follow-up.

Discussion

Syphilis is a highly contagious, sexually and transplacentally transmitted disease caused by Treponema pallidum (T. pallidum). In 2016, over 6.3 million new syphilis cases were diagnosed globally[7]. Syphilis screening is important for low- and middle-income countries, but pregnant women in some rural and poor areas of China are not tested because of cost and transportation problems[8].

Our patient denied engaging in sexual activity, but her parents had syphilis for decades. Congenital syphilis was suspected because her mother had no prenatal care or treatment for syphilis before delivery. Only a few patients with congenital syphilis of juvenile general paresis have been reported in the last century[9].

Clinical manifestations of neurosyphilis are mainly related to the injury's location. In earlier stages of infection, T. pallidum affects the meninges, cerebral vessels, and CSF, causing meningeal and meningovascular syphilis. General paresis and tabetic neurosyphilis occur in the late stages. Neurosyphilis can present with ocular and auditory abnormalities[10], and syphilitic gummas[11].

A neurosyphilis diagnosis depends on neurological symptoms and signs, as well as serum and CSF testing for T. pallidum. No specific radiological neurosyphilis manifestations have been identified, but generalized cerebral atrophy and foci of increased signal intensity are common on brain MRI[12]. Contrast enhancement, cerebral infarction, and edema are also commonly seen on brain MRI[13]. A few

neurosyphilis cases with bilateral temporal lobe high signal intensity, mimicking herpes simplex virus and limbic encephalitis, have been reported.

For assessing cognitive function in late adolescents, an appropriate scale covering a wide range of cognitive domains is lacking. MoCA has been increasingly used in recent years for cognitive assessment in late adolescents (aged ≥14) due to its facile administration in clinical settings, wide coverage of domains necessary for cognitive assessment in adolescents, and sensitivity in detecting mild cognitive deficits[14]. The MMSE is suitable for analyzing cognitive function in children and adolescents ages four and older [15]. Our patient was very close to adulthood and was about to graduate from high school; therefore, we chose to use the MoCA and MMSE.

This interesting case highlights the presentation of congenital syphilis and neurosyphilis in an adolescent and highlights the importance of cognitive function and the relevant differential diagnoses in an adolescent with cognitive impairment.

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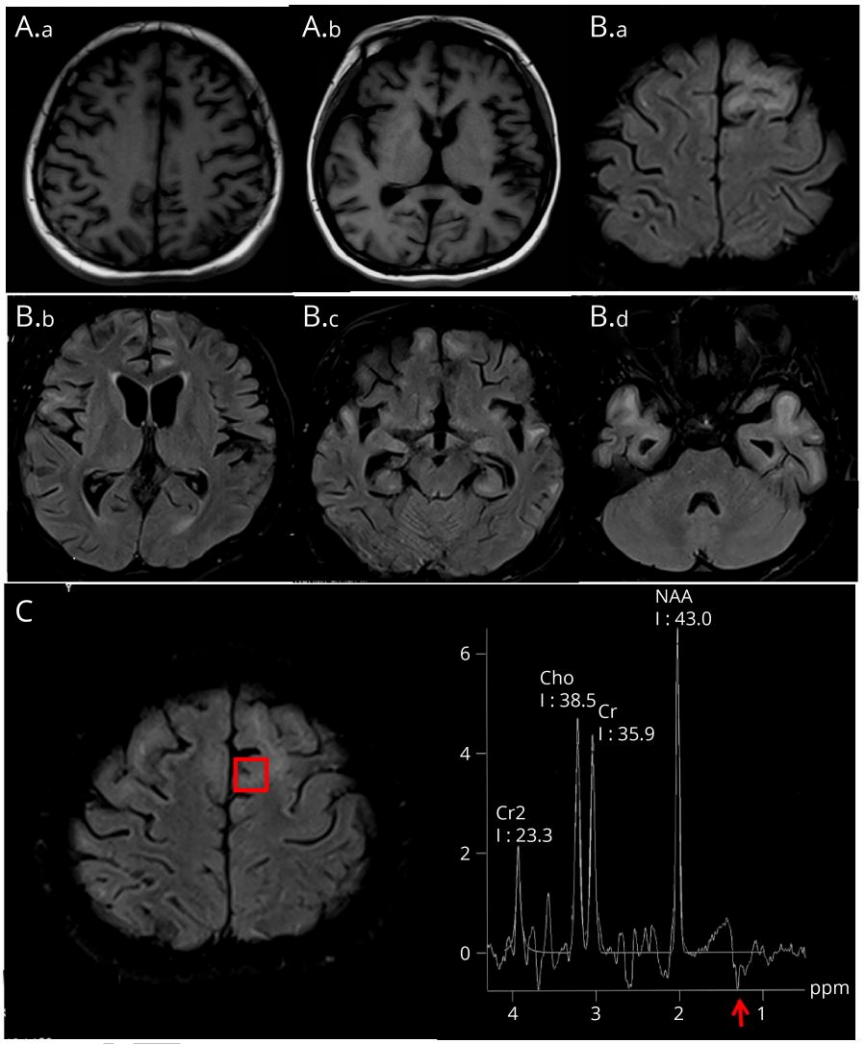
Figure Legends

Figure 1. Abnormalities of brain MRI.



T_1 MRI sequence revealed extensive cortical cortex atrophy(A). Fluid-attenuated inversion recovery (FLAIR) sequence showed multiple cortical and subcortical white matter hyperintense signal changes, mostly within the left frontoparietal and bilateral temporal lobes (B). MR spectroscopy demonstrated a decreased NAA/Cr ratio and lactate peak (arrow) in the focal area (C).

Table 1Values of cerebral spinal fluid (CSF) and blood before and after treatment.

Values	Berore treatment (2018.6.29)	After treatment (2018.7.17)	Reference range
CSFvalues			
Pressure (mmH_2O)	175	120	80 ~ 180
Protein (mg/dL)	96.9	56.6	15 ~ 45
Leukocyte ($\times 10^6$ /L)	60	10	0
Erythrocyte ($\times 10^6$ /L)	10	12	0 ~ 5
Glucose (mmol/L)	2.3	2.3	2.5 ~ 4.4
Chloride (mmol/L)	128	127	120 ~ 130
CSF culture	No growth	No growth	No growth
FTA-ABS IgG	Reactive	Non-reactive	Not detected
FTA-ABS IgM	Non-reactive	Non-reactive	Not detected
RPR tier	1:8	1:2	Not detected
TPPA	Reactive	Reactive	Not detected
Blood values			
FTA-ABS IgG	Reactive	Reactive	Not detected
FTA-ABS IgM	Reactive	Weakly reactive	Not detected
RPR tier	1:128	1:64	Not detected
TPPA	Reactive	Reactive	Not detected

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