Cortical blindness as a presentation of mitochondrial disease: A case report

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Abstract

We report a case of a 23-year-old male presenting with acute cortical blindness which developed in 3 days. He had a history of generalized tonic seizure for the last 3 years. Examination showed that the patient was confused, disoriented, and blind without other focal neurologic deficit. MRI of the brain showed a multi-stage infarction-like pattern predominately involving the cortical structures in many regions. Further investigation revealed other organ systems involvement including diabetes mellitus, hyperlipidemia, sensorineural hearing loss, hypogonadotropic hypogonadism, and an elevated serum lactate level. A diagnosis of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome was confirmed by the finding of a common mutation in the mitochondrial DNA m.3243A>G.

Conclusion: Mitochondrial disease, a rare genetic disorder, can present with common neurologic symptoms such as stroke, seizures, or diplopia. A High index of suspicion and a thorough examination of other organ systems are the keys to arriving at the correct diagnosis.

Keywords: Mitochondrial disease, MELAS, Stroke-like episode, Cortical blindness (J Thai Stroke Soc. 2020;19(2):45-51)

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รายงานผู้ป่วย: อาการมองไม่เห็นจากโรคไมโทคอนเดรีย

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บทคัดย่อ

ผู้ป่วยชายอายุ 23 ปีมาด้วยอาการตามองไม่เห็น 3 วันก่อนมาโรงพยาบาล ผู้ป่วยมีประวัติโรคประจำตัวเป็นโรคลมชักเมื่อ 3 ปีก่อน ตรวจร่างกายพบ confusion disorientation และ blindness โดยไม่พบอาการทางระบบประสาทอื่น ผลตรวจสมองด้วยคลื่นสะท้อนในสนามแม่เหล็ก พบรอยสมองขาดเลือดในหลายตำแหน่งบริเวณ cortex และจากการตรวจเพิ่มเติมพบว่าผู้ป่วยมีโรคร่วม ได้แก่ เบาหวาน ไขมันในเลือดสูง ระบบประสาทหูเสื่อม และพบกรดแลกติกในเลือดสูง ผู้ป่วยรายนี้ได้รับการยืนยันการวินิจฉัยกลุ่มโรคไมโทคอนเดรีย mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) จากผลการตรวจรหัสพันธุกรรมในไมโทคอนเดรีย พบการกลายพันธุ์ในตำแหน่ง m. 3243A>G.

สรุป โรคไมโทคอนเดรียเป็นโรคพันธุกรรมที่พบได้ไม่บ่อยชนิดหนึ่ง แต่อาจจะมาด้วยอาการทางระบบประสาทที่เจอได้บ่อยในเวชปฏิบัติ อย่างไรก็ตามหากสงสัยโรคทางไมโทคอนเดรียมาก ควรตรวจหาอาการอื่นที่เกี่ยวข้อง เพื่อนำไปสู่การวินิจฉัยได้อย่างทันท่วงที

คำสำคัญ: โรคไมโทคอนเดรีย, เมลาส, อาการโรคหลอดเลือดสมอง, อาการมองไม่เห็น (J Thai Stroke Soc. 2020;19(2):45-51)

Introduction

Mitochondrial disease refers to a group of genetic disorders characterized by a dysfunction of the mitochondrial oxidative phosphorylation. The clinical presentations are heterogeneous with the involvement of any single organ or multiple organ systems. Most often affecting the organs with the highest energy demand, such as the brain, heart, and muscles. Age of onset also varies from neonatal onset to late adult onset. Due to the fact that both mitochondrial DNA and nuclear DNA together encode over 1,500 proteins involved in the structure and function of the mitochondria, mitochondrial disease can present with autosomal dominant, autosomal recessive, x-linked, or maternal inheritance pattern[1]. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)[2] syndrome is one of the well-characterized syndromes of mitochondrial diseases. Common presentations include stroke-like episodes, encephalopathy, seizures, and lactic acidosis. Around 80% of the cases are caused by a common mutation in the mitochondrial DNA m.3243A>G in the MT-TL1 gene with a maternal inheritance pattern. MELAS can pose a diagnostic challenge because of its common neurologic presentations such as stroke-like episodes or seizures. Moreover, the variable presentations among family members, the inheritance pattern could not be easily elucidated.

Case report

A 23-year-old male presented to our clinic with progressive bilateral blurred vision, which progressed to complete blindness in 3 days. He reported having episodes of generalized tonic seizure, which started 3 years ago. The seizure was described as bilateral tonic with loss of consciousness lasting approximately 1 minute. The seizure occurred at a frequency of once every month in the first 2 years but progressed to 3-4 times per week in the last 10 months. Around the time, his mother complained that his memory had worsened and he seemed confused. For example, when his mother ordered him to buy a battery, he bought coal instead. Four months prior to this visit, his mother brought him to a hospital where he was treated with carbamazepine. He later developed Steven-Johnson syndrome around 1 week after treatment and was switched to 1,000 mg of levetiracetam per day. He did not have any seizure since and was able to carry out all daily activities by himself.

He had a normal birth with a birth weight of 2,070 grams. His gross childhood development was normal compared to his siblings. However, he had always been small compared to his peers and did not excel in school. He denied the use of alcohol, illicit drugs, or other herbal medication. He reached puberty around the age of 20. His family history is unremarkable with one younger brother and one younger sister who are alive and healthy, except for his youngest sister, who died of heart disease at three months of age.

On examination, the patient was alert but slow to respond. He was disoriented to time, place, and person. His weight was 31 kg and height 146 cm (mid-parental height = 153-173cm), BMI 14.35 kg/m^2. The arm span measured 144 cm, and the upper segment/lower segment ratio was 0.96. There was no dysmorphic feature present. Neurological examination revealed a decreased visual acuity with just light perception in both eyes. The pupils were 3 mm and reacted to light. There was no ptosis or limitation of the extraocular muscles. Other neurological examination was unremarkable. Evaluation of his genitalia was Tanner stage 4.

Investigation

Magnetic resonance imaging (MRI) study of the brain, illustrated in Figure 1 and Figure 2, revealed hyperintense T2/FLAIR (Fluid-attenuated inversion recovery) lesions mainly involving the cortex and subcortical white matter at bilateral occipital lobes and posterior right parietal lobe with some areas of restricted diffusion. There were hyperintense T2/FLAIR lesions mainly involving the cortex and subcortical white matter at bilateral frontal lobes, bilateral cingulate gyri, and anterior insular cortex without restricted diffusion. Hyperintense T2/FLAIR lesions with associated volume loss without restricted diffusion were found at bilateral parietal and temporal lobes. The magnetic resonance angiogram (MRA) study was unremarkable. The differential diagnosis of multi-stage prominent cortical lesions that did not conform to classical vascular territories includes mitochondrial diseases, ischemic strokes from cardioembolic source, metabolic encephalopathies such as hyperammonemic encephalopathy, and autoimmune encephalitis. Further investigation revealed a high serum lactate level 4.5 mol/L (0.7-2.5). EEG study showed diffuse background slowing with one episode of electrographic seizure over the left temporoparietal region lasting 25-30 seconds and periodic lateralized epileptiform discharges (PLED) plus pattern over the left temporoparietal region. Collectively, the clinical presentations, brain imaging, and laboratory findings point to stroke-like episodes as a manifestation of mitochondrial disease as the most likely diagnosis.

Figure 1. MRI brain axial view. *(A) Diffusion-weighted image (DWI). (B) Apparent diffusion coefficient (ADC) map. (C) Fluid-attenuated inversion recovery (FLAIR). The lesions at bilateral occipitoparietal regions showing increased FLAIR signal, increased DWI signal and low ADC signal consistent with a restricted diffusion (big arrows). Lesions in the frontal lobe, insular, and cingulate gyrus shows an increased FLAIR signal without restricted diffusion (increased signal in DWI without low ADC signal) (small arrows).*

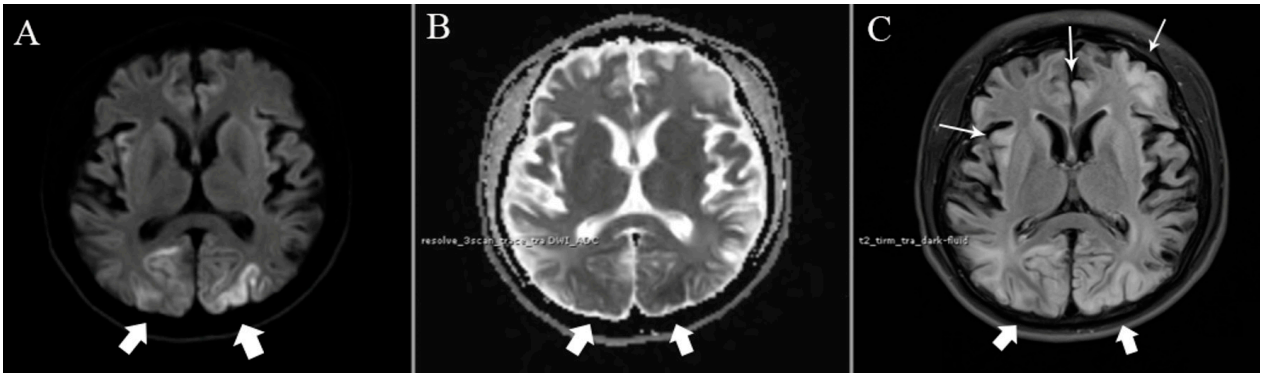
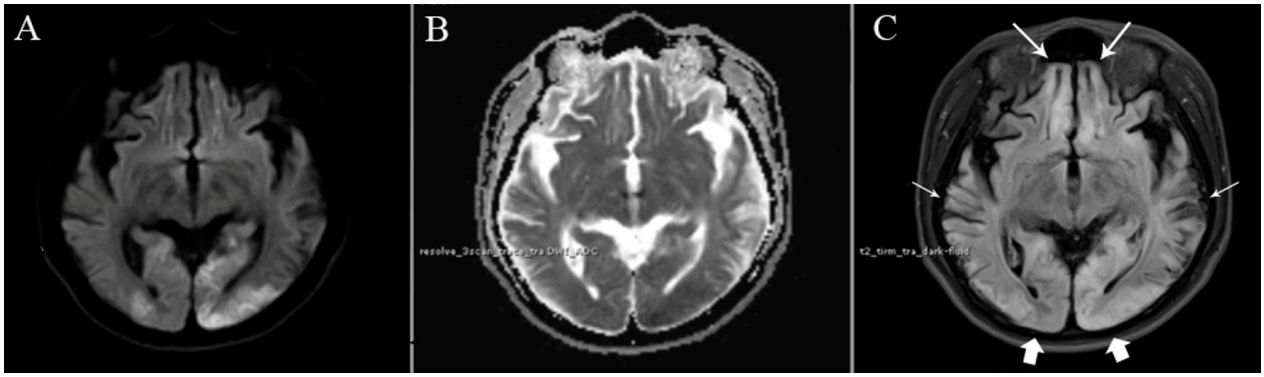


Figure 2 MRI brain axial view. *(A) Diffusion-weighted image (DWI). (B) Apparent diffusion coefficient (ADC) map. (C) Fluid-attenuated inversion recovery (FLAIR). The lesions at bilateral occipital regions showing increased FLAIR signal, increased DWI signal and low ADC signal consistent with a restricted diffusion (big arrows). Lesions in bilateral frontal and parietal regions show increased FLAIR signal with associated volume loss without changes in DWI or ADC map (small arrows).*



Further investigation into other associated conditions led to a diagnosis of diabetes mellitus, hyperlipidemia, bilateral sensorineural hearing loss, and hypogonadotropic hypogonadism. There were mildly elevated CK levels without muscle weakness or a history of exercise intolerance. The investigation into the cause of short stature revealed normal levels of growth hormone. The diagnosis of MELAS was confirmed by a genetic test revealing an m.3243 A>G mutation in the MT-TL1 gene. He was continued on long-term antiepileptic treatment and received appropriate treatment for all other associated conditions. In addition, L-arginine, coenzyme Q10, vitamin C, and vitamin E were prescribed as treatment for MELAS. The disease has largely remained inactive since then, the follow-up time was about 1 year since the last episode.

Discussion

The distinct clinical presentation of stroke-like episodes that do not conform to vascular territories makes MELAS the most likely candidate amongst mitochondrial diseases. The stroke-like lesions may resemble that of common ischemic strokes but tend to have a predilection for the occipital and parietal regions. The area of involvement is often restricted to the cortical structure with sparing of the deep white matter[3]. The mechanism underlying these stroke-like episodes is hypothesized to occur as a result of the imbalance between the excitation and inhibition of the neural networks caused by abnormalities in the mitochondrial respiratory chain which subsequently promotes neuronal hyperexcitability. The mismatch of the energy requirement of hyperexcited neurons may result in neuronal loss[4]. Interestingly, these stroke-like episodes are often associated with migraines and seizure episodes, which may imply that they share the same underlying mechanisms[5].

The failure of the mitochondrial oxidative phosphorylation process led to a chronic state of energy failure affecting organ systems and causing chronic lactic acidosis. Elevated lactate levels can often be detected in both the CSF and serum. Heteroplasmy is a phenomenon where the levels of mutant mitochondrial DNA vary between

individuals within a family and between tissues within an individual. Tissue and organ dysfunction arise when the proportion of mutant mitochondrial DNA exceeds a threshold. Therefore, the severity of organ dysfunction varies between the organ systems within an individual and family members can have varying symptoms from ranging from asymptomatic, oligosymptomatic to fully symptomatic presentations[6]. This case illustrated the phenomena of heteroplasmy within the family where the patient's mother and his siblings were asymptomatic. Moreover, heteroplasmy within an individual can be demonstrated with the variable degree of involvement between the organ systems as presented in this case where there were overt neurologic involvement, diabetes mellitus, and severe sensorineural hearing loss but mild myopathy with only mildly elevated CK levels. Short stature in MELAS is more often caused by the chronically energy-deprived state rather than growth hormone deficiency[2].

Diagnostic confirmation of mitochondrial diseases can be achieved by the demonstration of a pathogenic mutation in either the mitochondrial DNA or nuclear DNA associated with mitochondrial structure and function. In the case of suspected MELAS, a genetic test of the mitochondrial DNA may be the preferred initial choice because the majority of cases harbour a common mitochondrial DNA mutation (m.3243A>G). The whole exome sequencing or whole genome sequencing tests may be useful in cases with normal mitochondrial DNA test[2].

At present, most patients with mitochondrial diseases are treated with supportive treatment. Cocktails of dietary supplements and vitamins are frequently prescribed, such as coenzyme Q10, vitamin C, vitamin E, riboflavin, L-arginine, L-citrulline, etc. The aim is to mitigate the cellular consequences of mitochondrial respiratory chain dysfunction, albeit with modest benefit. Recent development in new treatment approaches like molecular bypass and gene therapy are being explored in mitochondrial diseases and tested in several ongoing clinical trials[2].

Conclusion

Stroke is one of the most common neurologic symptoms encountered by neurologists. Ischemic territories that does not conform to a specific vascular territory and the presence of other neurologic or systemic involvements are subtle clues that could lead to a diagnosis of mitochondrial disease. The Pattern of inheritance is most often not evident and requires thorough exploration due to the phenomenon of heteroplasmy. Despite the lack of effective treatment, accurate diagnosis in mitochondrial disorders can lead to an appropriate treatment and can help provide genetic counselling for the patient and their family.

Learning points

Mitochondrial disease is one of the rare differential diagnosis in patients presenting with stroke in the young. These stroke-like episodes often involve the cortex and spare the deep white matter. Important clues indicating an underlying mitochondrial etiology include infarction that does not conform to any vascular territory, seizure, migraine-like episode, and systemic manifestations such as diabetes mellitus, sensorineural hearing loss, ophthalmoplegia, ptosis, cardiomyopathy, myopathy, neuropathy, short stature, etc. Confirmation of the diagnosis can be made by the finding of a pathogenic mutation in either the mitochondrial DNA or the nuclear DNA associated with the structure or function of the mitochondria.

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