Seizures in Myoclonic Epilepsy with Ragged-Red Fibers Detected by DNA Analysis : A Case Report

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Abstract

A 19-year-old Thai woman presented with progressive ataxia and generalized tonic-clonic seizures. Later on, she developed status epilepticus. Blood was tested by molecular DNA analysis which showed A8344G mitochondrial DNA mutation associated with myoclonic epilepsy with ragged-red fibers (MERRF). We confirmed this finding in other members of this family. This is an interesting case report in Thailand of MERRF identified to have A→G transition mutation at nucleotide 8344 of mitochondrial $tRNA^{lys}$ gene without ragged-red fibers from histopathologic studies of muscle. Molecular genetic analysis in suspicious cases of mitochondrial disorders is necessary for proper management and genetic counseling.

Key word : Seizures, Ataxia, Myoclonic Epilepsy with Ragged-Red Fibers

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More than half of the cases of recurrent generalized tonic-clonic seizures in the young adult age group (18-25 years) are idiopathic[1]. However, the patients should be investigated to rule out other treatable causes such as arteriovenous malformation, brain tumor, central nervous system infection especially cysticercosis, head trauma or other metabolic causes[2].

Rare inherited metabolic disorders may cause seizures. Mitochondrial encephalomyopathies

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are clinical syndromes with a defect in the metabolic process of oxidative phosphorylation[3,4]. Their clinical manifestations are not only neurological but also the result of multiple organ involvement[5,6]. The spectrum of these syndromes was reported as Kearns-Sayre syndrome (KSS), mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic weakness, ataxia, and retinitis pigmentosa (NARP), Leber hereditary optic neuropathy (LHON) and so on[6,7]. Myoclonic epilepsy with ragged-red fibers (MERRF) is a rare mitochondrial encephalomyopathy characterized by myoclonus, myoclonic epilepsy, ataxia and myopathy with ragged-red fibers[8,9]. This is a case report of MERRF presenting with recurrent generalized tonic-clonic seizures and status epilepticus.

CASE REPORT

A 19-year-old Thai woman presented in January 1998, with a 1 year history of recurrent generalized tonic-clonic seizures. She was born at term without complications. Her development and school performance were normal. At the age of 3 years, her mother noted that she had difficulty in walking. At age 7, hearing was observed to decrease in her left ear. Her gait disturbance became increasingly worse and she frequently dropped objects during the last 2 years. She was otherwise healthy and had no previous history of head trauma. Nobody in her family had any underlying or genetic disorders.

On general examination, vital signs revealed a temperature of 37.2°C, blood pressure of 130/70 mmHg, pulse rate of 72 per minute, regular and respiration of 24 per minute. She had euphoric mood but no psychiatric symptoms. There were neither cardiopulmonary abnormalities nor hepatosplenomegaly and no deformities were detected. On neurological examination, she was alert and cooperative. Ocular movements were full with jerky pursuit, slow saccade and bilateral horizontal nystagmus. Hearing was decreased in her left ear. Knee and ankle jerks were decreased and plantar responses were flexor bilaterally. Vibration and joint position senses were impaired over both lower limbs up to the knees. She had markedly broad-based and ataxic gait. Coarse intention tremor and dysdiadochokinesis were demonstrated. Repetitive jerking of the left cheek evoked by stress was observed.

Screening tests showed no evidence of vasculitis, cardiovascular or any metabolic causes. A brain and spinal magnetic resonance imaging (MRI) revealed moderate cerebellar atrophy and mild spinal cord atrophy without white matter lesions nor abnormal calcification. Electroencephalogram was consistent with a seizure pattern. Nerve conduction study showed small amplitude of compound muscle action potentials in the upper and lower limbs and slightly slow motor conduction velocities of right median and both tibial and peroneal nerves with absence of sensory nerve action potentials of median, ulnar and sural nerves. Wechsler adult intelligence scale (WAIS) total IQ score was 77 with verbal and performance scores of 87 and 67. Audiometric findings were reported as normal speech with mild high frequency loss at 8,000 Hz.

Blood was sent for molecular DNA analysis. No triplet tandem repeats were identified for SCA2, SCA3, SCA6 and Friedreich's ataxia (FRDA) but it was positive for mitochondrial DNA (mtDNA) study. A8344G mtDNA mutation confirmed by nucleotide sequencing compatible with myoclonic epilepsy with ragged-red fibers (MERRF) was detected in this patient. Many members in the maternal lineage were identified to have the same mutation as that in this patient but in variable percentage of mutant mtDNAs. Electromyogram was normal. Muscle biopsy was taken from right quadriceps femoris. Histopathologic study did not show any structural abnormalities on electron microscopy or ragged-red fibers on Gomori trichrome stain. The patient was treated with sodium valproate to control seizures. One year later, she was admitted with status epilepticus. Muscle biopsy was repeated but ragged-red fibers were still not seen.

DISCUSSION

Clinical features of ataxia, hearing loss, sensory neuropathy and generalized seizures and MRI findings in this patient led to suspicion of either spinocerebellar ataxia (SCA) or mitochondrial encephalomyopathies. Blood was sent for molecular DNA analysis and confirmed to have A8344G mtDNA mutation associated with MERRF in the patient and other members of this family. Myoclonic epilepsy with ragged-red fibers (MERRF) is a maternally inherited mitochondrial encephalomyopathy[9] caused by transition mutation within $tRNA^{Lys}$ gene of mitochondrial DNA[10,11]. It is associated with

defect in complex I (NADH dehydrogenase) and IV (cytochrome c oxidase) of mitochondrial respiratory chain[12,13]. To date, two mtDNA point mutations have been identified at nucleotide 8344[10,11,14] and 8356[15]. Clinically, it is characterized by myoclonus, ataxia, seizures, hearing loss, dementia, myopathy, peripheral neuropathy, and muscle atrophy in the late stages. Other features include optic atrophy, strokelike episodes, cervical lipomas, pes cavus and short stature[8,9,16,22-24]. MERRF is an unusual cause of generalized tonic-clonic seizures[8,9]. However, it may manifest with other seizure types such as focal seizures, atypical absence, drop attack and status epilepticus[10,16,17,24]. Mitochondrial encephalomyopathies are a diverse group of clinical syndromes with a broad spectrum of signs and symptoms. They involve both central and peripheral nervous systems in addition to other organ systems such as visual, cardiovascular, endocrinologic, hepatic, gastrointestinal, hematologic and renal systems [5-7]. However, individual phenotypic features depend on kinds of mtDNA mutations, heteroplasmy (ratio of intracellular mixture of wild type and mutant mtDNAs) and relative mitochondrial energy supply of each organ[4,18]. These factors lead to poor correlation between genotype and phenotype including variable manifestations among members within the same family. They may cause delay in diagnosis in atypical cases. The best-known hallmarks confirming the diagnosis are ragged-red fibers on Gomori trichrome stain and cytochrome c oxidase (COX) negative muscle fibers on histochemical reaction[19,20]. Our patient had never developed myoclonus. Albeit blood was proved to have A8344G MERRF mutation, both muscle pathologic studies did not show either structural abnormalities on electron microscopy or ragged-red fibers. However, absence of ragged-red fibers cannot definitely exclude the diagnosis of myoclonic epilepsy with ragged-red fibers (MERRF) as has been previously reported[9,21-24]. In highly suspicious cases of mitochondrial encephalomyopathies, biochemical studies of respiratory chain complexes and molecular DNA analysis may facilitate the diagnosis. To the best of our knowledge, this is the first case report of myoclonic epilepsy with ragged-red fibers (MERRF) in Thailand identified by molecular DNA analysis. This type of patient should make physicians aware of an incomplete syndrome of mitochondrial encephalomyopathies. The integration of clinical features, screening tests, histopathologic findings from muscle biopsy, and molecular genetic analysis for mtDNA mutations is very important in the management and genetic counseling in suspicious cases.

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ภาวะชักในกลุ่มอาการ Myoclonic Epilepsy with Ragged-Red Fibers ซึ่งวินิจฉัยโรคโดยการวิเคราะห์รหัสพันธุกรรม : รายงานผู้ป่วย 1 ราย

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หญิงไทยอายุ 19 ปี มาด้วยอาการเดินเซซึ่งเป็นมากขึ้น ร่วมกับการชักแบบเกร็งกระตุกทั้งตัว ต่อมาผู้ป่วยมีอาการชักแบบต่อเนื่องไม่ฟื้นคืนสติ ได้ตรวจพบโดยวิธีวิเคราะห์รหัสพันธุกรรมจากเลือดของผู้ป่วย พบว่ามีการกลายพันธุ์ของ mitochondrial DNA ที่ตำแหน่ง 8344 ซึ่งเข้าได้กลับกลุ่มอาการ Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) อีกทั้งได้มีการยืนยันโดยตรวจเลือดสมาชิกคนอื่น ๆ ในครอบครัว พบลักษณะการกลายพันธุ์ที่ตำแหน่งเดียวกัน รายงานผู้ป่วยหญิงไทยรายนี้มีความน่าสนใจ เนื่องจากการวินิจฉัยโรคในผู้ป่วยรายนี้ได้จากการตรวจพบว่ามีการกลายพันธุ์ของ mitochondrial gene โดยไม่พบว่ามี ragged-red fibers จากการศึกษาทางพยาธิกล้ามเนื้อ

การศึกษาทางพันธุศาสตร์โดยวิธีทางชีวโมเลกุลในผู้ป่วยที่สงสัยกลุ่มอาการที่เกิดจากความผิดปกติของ mitochondria ถือว่ามีความจำเป็นอย่างยิ่งในการให้การรักษาที่เหมาะสม และคำแนะนำทางด้านพันธุกรรมแก่ผู้ป่วยและครอบครัว

คำสำคัญ : ภาวะชัก, เดินเซ, Myoclonic Epilepsy with Ragged-Red Fibers

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