Epileptic Seizure as An Uncommon First Symptom in CADASIL with a Novel Likely Pathogenic Mutation

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Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the monogenic disease caused by the mutation of the NOTCH3 gene. The previous reports identified that migraine with aura, subcortical stroke, cognitive decline, and psychiatric disorders were the common presentation of CADASIL. We reported recurrent focal onset seizure as an atypical presentation in a CADASIL with a novel pathogenic missense variant (heterozygous, c.922G>A, p.Gly308Ser) in exon6 of NOTCH3 gene.

Keywords: CADASIL, seizure, NOTCH3 mutation

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the monogenic disease caused by the mutation of the gene on the chromosome 19 encoding the protein named NOTCH3.[1] This transmembrane protein plays major roles in controlling cell differentiation and it mainly expressed in vascular smooth muscle cells. The pathophysiology explaining how Notch3 mutation cause the vascular pathology was not well clarified. However, the main mechanism of the disease involved the arterial circulation led to ischemic injury. The common clinical presentations include migraine with aura and stroke in the early stage.[2] With silently progressive disease course, multiple subcortical cerebral infarction and leukoencephalopathy led to disruption of the subcortical circuit which may produce slowly progressive cognitive decline and neuropsychiatric symptoms.[2]

Although it is not listed in the classic symptoms, epileptic seizure occurs in the minority ranging

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between 5% and 11% of CADASIL patients.[3,4] In addition, the epileptic seizure is often accompanied by a stroke event and it is rarely presenting as an initial symptom.[5,6] This case report illustrated the CADASIL patient who developed seizure as a first symptom.

Case report

A 41-year-old right-handed man presented with a history of 6-month recurrent focal onset seizure. He observed a synchronized involuntary tonic posture of the right arm and legs following with the rhythmic jerking which lasted for 5 minutes and preserved awareness. No headache, nausea, vomiting, weakness or abnormal sensory symptoms was noticed. Three days later, the same symptoms occurred and it draw his health concern to a medical visit. The initial computed tomography (CT) of the brain revealed unremarkable. He was prescribed phenytoin 350 mg orally per day. Two weeks after, he developed an acute onset right hemiparesis and right facial palsy. The CT scan of the brain revealed significant edematous subcortical lesion involving the left frontal region. He was treated with oral prednisolone and recovered to the normal baseline within 2 weeks. However, he also continued the oral prednisolone for 3 months.

Three weeks prior to the visit, he developed focal onset with secondary generalized tonic-clonic seizure starting at the right arm and leg. No residual neurological deficit was observed. One week prior to the visit, he could not control the conjugated eye movement to the right side. No diplopia, ptosis and visual disturbance was noted.

The physical examination showed restricted right lateral gaze control which was correctable by the vestibulo-ocular reflex. The visual acuity, color, pupillary response and fundoscopic examination was within normal limits. The other cranial nerve function was also normal. No motor weakness, sensory disturbance and limbs ataxia was observed. All deep tendon reflex revealed 2+ and gait was normal. The general physical examination was also unremarkable.

The magnetic resonance imaging of the brain demonstrated the edematous subcortical lesion at the left dorsolateral frontal region which was correlated with the anatomic localization. The lesion revealed hyperintense in T2W and FLAIR sequence with the adjacent cortical swelling irrespective to the vascular territories. No diffusion weighted imaging (DWI) restriction and gadolinium enhancement was detected. In addition, confluent white matter lesion with sign of volume loss was also noted at the right anterior temporal region. The magnetic resonance angiography of the brain revealed abnormal circumferential thickening at bilateral middle cerebral arteries suggesting underly vasculopathy.

The complete blood count, ESR, CRP was within normal limits. The serological test for ANA, Anti-MPO, Anti-PR3, Anti-HIV, HBsAg and anti-HCV were negative. The temporal artery biopsy was performed to exclude the small possibility of vasculitis showed negative result. The cerebrospinal fluid was within normal limits and the serum lactate level was 7.3 mg% (normal range 4.5-18).

The NOTCH3 gene sequencing disclosed the heterozygous, likely pathogenic missense variant, c.922G>A in exon6 (p.Gly308Ser). In correlation with the clinical-radiological features and the NOTCH3 genetic, the patient was diagnosed cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Discussion

Apart from the classic recognized clinical features of migraine, stroke, dementia and neuropsychiatric problems, the clinical spectrum of CADASIL is extremely diverse. The atypical features of CADASIL and exhibit in either the peripheral nervous system including neuropathy and myopathy, or the central nervous system involving spinal cord syndrome, coma, parkinsonism and seizure.[7] The prevalence of epileptic seizure in CADASIL ranged between 5% and 11% in the previous reports.[3,4] Most of the seizure cases had experienced stroke prior to the seizure occurrence.[6] The onset of seizure in correlation with the CADASIL disease course often found to be a late presentation.[3] Therefore, developing seizure as a first presenting symptoms was considered rare and often misled to other possible differential diagnosis besides CADASIL.

The seizure semiology in CADASIL in the previous reports was mainly the focal onset seizure with or without secondary generalized tonic-clonic seizure and self-limited which was consistent with our case.[6,8,9] However, developing a life-threatening status epilepticus could possible occur.[10] The electroencephalography often discloses a focal epileptiform discharge which correlated to the focal structural brain lesion.

The correlation between genotype and phenotype of CADASIL is not clear due to the limited number of the reports. However certain genotypic features may suggest the preferential phenotypic characteristics. The association between the lower median age at death and the mutation type of p.Cys174Tyr and p.Cys117Phe was found among German population. In addition, the p.Cys117Phe mutation was also correlated with a lower median age at onset of stroke.[11] However, the genotypic correlation of the seizure presentation in CADASIL was not well studied. The mutation among CADASIL presenting with seizure showed a heterogeneity, for example, p.R544C, p.Arg182Cys and p.Cys446Tyr.[6,8,12] To the update data, the likely pathogenic missense variant, c.922G>A in exon6 (p.Gly308Ser) shown in our case has not been previously reported. This mutation may be considered as a novel mutation.

To summarize, this case report demonstrated the epileptic seizure as an unusual first clinical presentation in a patient with CADASIL. Recognizing a wide spectrum of clinical features may avoid misdiagnosis of this rare disease.

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