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A CASE REPORT ABOUT CADASIL: MUTATION IN THE NOTCH 3 RECEPTOR

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ABSTRACT

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a rare autosomal dominant genetic disease characterized with recurrent stroke, migrainous headache, cognitive deficits, and psychiatric symptoms associated with mutations in the NOTCH 3 gene on chromosome 19. Here, we report a case of CADASIL who presented with left sided weakness, recurrent strokes and the diagnosis was established by the findings of head magnetic resonance images revealing characteristic white matter lesions and a mutation in the NOTCH 3 gene.

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INTRODUCTION

CADASIL is an autosomal dominant arteriopathy associated with mutations in the NOTCH 3 gene on chromosome 19 (Scheid *et al*., 2006; Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Tang *et al*., 2005; Opherk *et al*., 2004; Hassan and Markus, 2000; Dichgans, 2007; Bowler, 2005; Caeiro and Ferro, 2006). Clinical manifestations include recurrent cerebral ischaemic episodes, progressive cognitive deficit, migraine with aura, dementia, and psychiatric symptoms (Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Tang *et al*., 2005; Opherk *et al*., 2004; Hassan and Markus, 2000; Dichgans, 2007; Bowler, 2005; Caeiro and Ferro, 2006). The neurological symptoms often develop between the 3rd and 6th decades. Head magnetic resonance image (MRI) often discloses diffuse white matter lesions, small subcortical lacunar infarcts, and cerebral microhemorrhages (Scheid *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Opherk *et al*., 2004; Hassan and Markus, 2000; Charlton *et al*., 2006). Electron microscopy evaluations of skin or smooth muscle biopsy specimens may show the characteristics of CADASIL, that are specific accumulation of granular osmophilic material (GOM) in the basal lamina (Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Hassan and Markus, 2000; Dichgans, 2007). The diagnosis of CADASIL is established by the detection of mutations in the NOTCH 3 gene. This report aimed to discuss neurological and radiological characteristics of CADASIL through evaluation of a patient diagnosed with this rare disease.

Case Report

A 43 year old male patient presented to us with chief complains of left upper and lower limb weakness for past 3 days .Weakness was sudden in onset, non progressive and started simultaneously on upper and lower limb.

- The patient is non diabetic and non hypertensive.
- He is a non smoker and non alcoholic.
- He had similar episode of weakness in the year 2008.

- His MRI finding showed acute lacunar infarct in right thalamus.
- Multiple chronic lacunar infarcts in bilateral ganglio-capsular regions,pons,bilateral corona radiata and centrum semiovale with foci of blooming posteriorly in left ganglio capsular region
- Diffuse cerebral and cerebellar atrophy
- Extensive leukoencephalopathy involving bilateral cerebral and cerebellar hemispheres as described.

- The serum B 12 was low -**171pg/ml.**
- The homosysteine level was high **-24.07umol/l**
- The results of other routine hematological ,biochemical and hormonal studies were normal.
- The diagnosis of CADASIL was based on the presence of recurrent stroke,clinical and head MRI findings and detection of NOTCH 3 gene mutation.

DISCUSSION

CADASIL is a hereditary vasculopathy affecting the small arteries and arterioles of the brain and other tissues (Scheid *et al*., 2006). It was first described in 1977 in a case with hereditary multiinfarct dementia syndrome, followed by several reports of cases with autosomal dominant genetic stroke and dementia (Scheid *et al*., 2006; Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Tang *et al*., 2005; Opherk *et al*., 2004; Hassan and Markus, 2000; Dichgans, 2007; Bowler, 2005; Caeiro and Ferro, 2006; Charlton *et al*., 2006; Orlacchio and Bernardi, 2006; Dichgans *et al*., 1998; Schroder *et al*., 2005; Chabriat *et al*., 1999; van Den Boom *et al*., 2002; Lesnik Oberstein *et al*., 2001; Chabriat *et al*., 1995; O'Sullivan *et al*., 2001). CADASIL syndrome is the first detected form of vascular dementia with a genetic-origin (Dichgans, 2007). It is also one of the common hereditary forms of stroke (Coto *et al*., 2006). The incidence of CADASIL in general population is thought to be higher than estimated (Coto *et al*., 2006; Dichgans, 2007). The onset of the disease is usually between the ages of 30 and 60 years (Opherk *et al*., 2004). Eighty-five per cent of the patients experience recurrent strokes and transient ischemic attacks (Opherk *et al*., 2004). The first stroke usually occurs in the ages of 35-45 years (Tuominen *et al*., 2001). Recurrent strokes may result in motor disability, pseudobulbar palsy, and urinary incontinence (Buffon *et al*., 2006; Gurumukhani *et al*., 2004; Opherk *et al*., 2004). The patient may become bed-ridden in time and has a mean life expectancy of 65 years (Hassan and Markus, 2000). Cognitive changes may develop after 35 years of age. However, in 70-80% of the patients, marked cognitive deficit develops parallel to the increased burden of lesions at about 60 years of age and is followed by dementia (Liem *et al*., 2007; Charlton *et al*., 2006; Dichgans *et al*., 1998). Cognitive decline may be progressive as well as stepwise with acute episodes (Buffon *et al*., 2006). In 30-50% of the patients, migraine attacks occur and are usually with aura (Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Tang *et al*., 2005; Opherk *et al*., 2004; Hassan and Markus, 2000; Dichgans, 2007; Bowler, 2005). Migraine attacks generally present a few years before the first vascular event (11). Patients with CADASIL may also show behavioral anomalies and psychiatric disorders (Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004, Tang *et al*., 2005; Opherk *et al*., 2004; Hassan and Markus, 2000; Dichgans, 2007). Psychiatric symptoms vary from mild personality disorders to severe depression and mania (Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006). The onset of migraine and psychiatric symptoms is usually in the early phases of the disease (Tuominen *et al*., 2001; Hassan and Markus, 2000) and in some families, they are the dominant clinical findings (Hassan and Markus, 2000). Ten per cent of CADASIL patients suffer epileptic attacks, and in some, subclinical polyneuroptahy has been reported (Opherk *et al*., 2004; Hassan and Markus, 2000; Dichgans, 2007; Bowler, 2005; Schroder *et al*., 2005; Chabriat *et al*., 1999). In a series of 45 patients, the incidence rate for subcortical events was 84%; for progressive or stepwise subcortical dementia accompanied by pseudobulbar palsy, 31%; for migraine with aura, 22%; and mood disorders accompanied by severe depression attacks, 20% (Chabriat *et al*., 1995). Subclinical retinal lesions (Opherk *et al*., 2004) and rarely, hearing loss have been reported in some cases (Scheid *et al*., 2006). Hyperintense areas are observed in the subcortical white matter of CADASIL patients on T2-weighted sections of cranial magnetic resonance images (Scheid *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Opherk *et al*., 2004, Hassan and Markus, 2000; Charlton *et al*., 2006). In addition, 2/3 of the subcortical lacunar infarcts and rarely microhemoorahges in the thalamus may be observed (Scheid *et al*., 2006; Buffon *et al*., 2006; Liem *et al*., 2007; Coto *et al*., 2006; Gurumukhani *et al*., 2004; Opherk *et al*., 2004; Hassan and Markus, 2000; Charlton *et al*., 2006; 18,19).

On head MRI, involvement of the white matter of the anterior temporal lobe and external capsule are characteristic (Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Opherk *et al*., 2004 Dichgans, 2007; Bowler, 2005). Hyperintensities in the white matter of the anterior lobe have been reported to provide high sensitivity (90%) and specificity (100%) rates for the diagnosis of the disease (O'Sullivan *et al*., 2001). External capsule involvement is less specific and may be observed in the early phase of the disease (Gurumukhani *et al*., 2004). In some patients, the corpus callosum was also involved (Gurumukhani *et al*., 2004). The frontal lobes have the highest burden of lesions in the white matter, followed by the temporal and parietal lobes (Chabriat *et al*., 1999). Characteristic MRI findings may be observed in asymptomatic individuals with mutations in the NOTCH 3 gene (Liem *et al*., 2007; Hassan and Markus, 2000), and in just about all of the mutant gene carriers, pathologic MRI findings are observed in the 3rd decade (Scheid *et al*., 2006). Cerebral angiography results are normal because of the small size of the involved arteries, the images of which cannot be obtained (Bowler, 2005). Angiography has not been recommended for CADASIL patients because of increased risk of complications (Bowler, 2005). Because the disease systemically affects the vascular structure, the result of the peripheric biopsy evaluation is often positive. In the electron microscopy evaluation of the smooth muscles and skin specimens, GOM may be detected (Gurumukhani *et al*., 2004; Tuominen *et al*., 2001; Hassan and Markus, 2000; Dichgans, 2007). Although evaluation of the skin biopsy is a common procedure, the results of almost half of the studies are false negative (Bowler, 2005). Muscle biopsy studies, however, have a higher sensitivity (Bowler, 2005) The disease develops due to the mutations in the NOTCH 3 gene on chromosome19. This gene codes a large transmembrane receptor that is expressed in the arterial smooth muscle cells and has a role in the arterial development (Coto *et al*., 2006; Gurumukhani *et al*., 2004; Dichgans, 2007; Bowler, 2005).

The treatment of CADASIL is symptomatic. Literature presents no specific studies on the use of acetilacidic acid in CADASIL patients. Nevertheless, it has been recommended for the treatment of CADASIL because it is a general antiaggregant agent used in cerebrovascular disease prophylaxis (Opherk *et al*., 2004). In addition, recommendations have been made for CADASIL patients to avoid risk factors for ischemic cerebrovascular diseases (Opherk *et al*., 2004). In conclusion, particularly in young adult patients with no vascular risk factors, mild clinical findings, but a familial history of stroke and characteristic lesions on MRI, CADASIL should be suspected, and mutations in NOTCH 3 gene should be investigated.

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