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Review Article

Carasil and htra1: an early adulthood syndrome

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Article History	Abstract
Received on: 29-06-2021 Revised on : 11-07-2021 Accepted on : 29-08-2021	Cerebral Autosomal Recessive Arteriopathy Subcortical Infarcts Leukoencephalopathy (CARASIL), is an autosomal recessive disorder inherited by two copies of an abnormal gene from some trait, one from each parent. Person with this disorder may have a change in deep white matter in brain; and this disorder can be characterized by damage to small blood vessels in brain. Increasing muscle tone, slurred speech, stiff movement of legs, gait disturbance, spondylosis, sparse hair are the major symptoms. But the ultimate cause of this disorder can lead to loss of memory, cognitive impairment. This disorder can be caused in early adulthood i.e., between 20-40 years of age. CARASIL has first reported in Japan, later occurred in China and Caucasian population. A neurological disorder named Binswanger's disease (BD) and chronic immunological disorder multiple sclerosis are main different alternation of this disease. Mutation requires the high temperature resultant, A serine peptidase 1 causes CARASIL, so it is a serine protease. Serine protease HTRA1 is an enzyme that in humans is encoded by HTRA1 gene. HTRA1 protein is composed of four distinct protein domains. This is located on the long (q) arm of chromosome 10 in a region known as 10q26.
Keywords Arteriopathy, Leukoencephalopathy, Binswanger's disease, Mutation, polymorphism	
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Introduction

A rare disease is a group of disease that affects a small percentage of the population. The World Health organization says that a disease is said to be rare when the number of people affected is less than 6.5 - 10 per 10,000 people [1]. For most rare diseases, common knowledge such as cause of disease, disease symptoms, etc. is unknown. Genetic diseases are the most common type of rare diseases. The term orphan disease is used as a synonym for rare disease as such diseases also lack in resources and availability of treatment. Funding required for clinical research is low as orphan drug development is of less interest by pharmaceutical

industries. New generation of targeted therapy is in progress, and the products developed will be useful for therapy of smaller number of patient group [2].

Cerebral Autosomal Recessive Arteriopathy Subcortical Infarcts Leukoencephalopathy (CARASIL). It is an extremely rare disorder reported in Chinese and Caucasian populations; described in Japanese medical literature. Scientist and researchers claim that this disorder is difficult to be diagnosed so that true frequency of this disease can't be determined [3].

It is an autosomal recessive disorder characterized by damage to small blood vessels (arteriopathy). This damage causes too little blood to survive. Tissue death

(infarcts) can occur in outer layer of brain (subcortical) [4]. This condition leads to ultimate loss of key connection between brain cells that function as normal due to reduced blood flow and tissue death. The recessive condition may cause changes in HTRA1 gene, which involves formation of new blood vessel and cases arises due to undiscovered mutations in gene. Symptoms of CARASIL are a result of limited blood flow of brain, often resulting in dementia [3]. The other major symptoms are, decreased mental ability, changes in behavior, change in personality, confusion, stiffness in legs, difficulty in walking, increased muscle tone, stroke episode, muscle spasm, slurred speech, loss of bladder control, difficulty in controlling facial muscles and speaking, Patchy hair loss and Inflammation of spine [5].

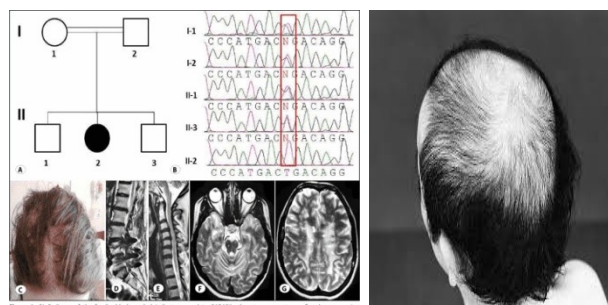


Figure:1 Mutation in the HTRA 1 gene in a patient with degenerated spine as a component of CARASIL syndrome: - A) pedigree of the family; black symbols indicate complete CARASIL phenotype; parents are first degree cousins. B) sequencing of all family members in exon six of HTRA1 revealed c.1108 C>T transition, leading arginine to stop codon (R370X) and causing truncation in the protein. C) the proband showed alopecia. D) cervical spine degeneration midsagittal MRI E) lumbar degeneration and artifacts because of undergone stabilization operation. F, G) brain axial sections revealed wide spread white matter changes involving anterior temporal lobes, centrum semi ovale, and brain stem collapse.[7] **Figure: 2** CARASIL from discovery to gene identification: Diffuse baldness in a 33-year-old man with CARASIL [7].

Causes and risk factor

CARASIL caused by the mutation of HTRA1 gene. It is an autosomal recessive trait inherited from parents to an offspring. This is so rare that only 50 cases have been identified, mostly seen in Japan and China. The reported cases have been more affected in men than in women. A subtype of CARASIL, condition which follow autosomal dominant inheritance known as CADASIL. HTRA1 gene mutation decreases the function of normal HTRA1 gene

inherited from another parent, dominant trait causes men and women equally. CARASIL can be identified in early adulthood nearly 30, while CADASIL could be diagnosed by the time of 40 (LATER ADULTHOOD). CADASIL patients may also be at high chance of heart attack [6,7].

Diagnosis

These conditions usually begin with physical exam and review of patient's medical history and symptoms, MRI finding mode of inheritance, laboratory results. The condition of disease can be positively diagnosed through genetic mutation. The presence of diffuse white matter lesion on MRI extending to temporal poles, causes acute low back pain, premature baldness. Absence of optic nerve and spinal cord involvements, absence of known vascular risk factors are seen in critical cases. Certain leukodystrophy associated with dermatologic or skeletal disorder in young adulthood [8,9].

Treatment

There is no specific treatment for CARASIL. the symptoms of each individual vary each other and medication is given focusing on this. Supportive care including emotional support, practical assistance, genetic counseling is also done for the patients and relatives [8]. These patients need physical and occupational therapy as a part of treatment.

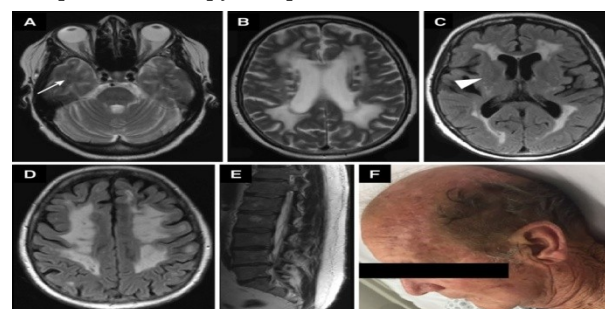


Figure.3 Typical clinical and neuroimaging features of CARASIL. Axial brain MRI disclosing marked diffuse leukoencephalopathy on T2-weighted (A,B) and FLAIR images (C,D) affecting mainly the periventricular and deep white matter. Only mild hyperintensity is seen in right temporal lobe (white arrow) and absence of marked signal changes are depicted in the external capsules (white arrow-head), differentiating it from the classic neuroimaging pattern described in CADASIL. (E) Lumbar spine MRI showing mild degenerative vertebral spondylosis on T2-weighted image. (F) The patient's marked baldness [8].

Related disorders There are some related disorders as Binswanger's disease (BD) and Chronic immunological

disorder multiple sclerosis. Binswanger's disease is a progressive neurological disorder causes deposition of fatty material on inner walls of arteries supplying the white matter of the brain. Thereby results in memory loss, dementia, urinary urgency, unsteady walking pattern; which lasts for five to ten years of time [8,9]. This on certain condition worsen due to stroke and improves a little later. Multiple sclerosis is a disease which commonly affect both nervous system and immunological system, it also affects spinal cord and optic nerve. The production of patches of myelin sheath randomly on multiple sites vary intensively. So that disease become advance or stabilize. Damage to nerve cells may be irreversible [10,11].

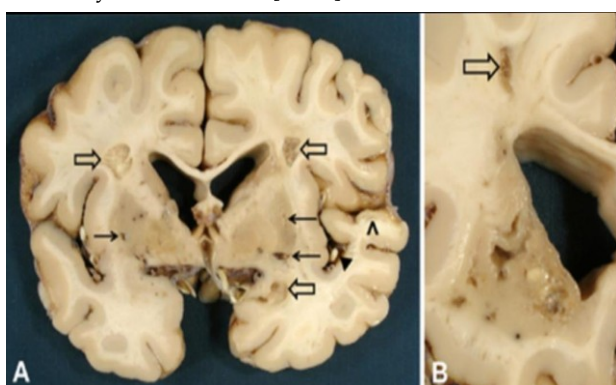


Figure 4: Three old infarcts of moderate size in cerebral white matter (open arrows) and smaller lacunar infarcts in putamen bilaterally (arrows) in a 65-year-old female CADASIL patient with p.Arg133Cys Notch3 mutation. Note the relatively spared cortex except for the ischemic lesion in temporal cortex (arrowhead) because of atherosclerotic occlusion of a middle cerebral artery branch [black triangle; (A)]. In this same patient's caudate nucleus, the lesions are more severe than in putamen. In the WM of the centrum semiovale, there is another small cystic infarct [open arrow; (B)]. Lateral ventricles in both (A) and (B) are widened because of ischemic tissue loss[9].

Case Studies On Carasil

A 37-year-old woman from Sri Lanka was referred. Her Family didn't have anyone with neurological disorders up to that point, however her parents were cousins. At the age of 11, the patient had patchy hair loss and a spastic-ataxic-gait was seen at the age of 28. After an interval of 3 years, the patient then suffered from bipolar personality disorder, short-term memory disturbance and loss of concentration [12]. Un-steady gait caused her to be wheel chair-bound at early 2019. First diagnosis was hereditary spastic paraplegia. Exome-sequencing was carried out due to

leukoencephalopathy and cavernomas. Examination of the genes CCM2, KRIT1, PDCD10, COL4A1, COL4A2, NOTCH3, and HTRA1 was conducted. The missense variant c.1022G>T in the HTRA1 gene was in homozygous state, causing amino acid change p.Gly341Val [11]. This was not present in exome variation databases and was also uncommon in patients with CARASIL it was initially classified as class 3 VUS (variant of unknown significance), but later due to categorization of ACMG, homozygosity of such a rare variant is correspondent to the consanguinity of the patient's parents. This showed CARASIL as a plausible diagnosis symptoms were similar with leukoencephalopathy, dementia, spasticity, and rapid disease progression [13]. Acute worsening The patient had progressive somnolence. The first plausible hypotheses were stroke. CT and MRI scan showed no large acute cerebral infarction. Electrocardiogram showed a significant elevation in troponin T but didn't show ST-elevations. Hence, a non-ST-segment elevation myocardial infarction was diagnosed [14,15].

Neurological examination

The patient was diagnosed with severe cognitive impairment and was getting easily aggressive and agitated. There was a central facial paralysis on the left side. The patient had average to severe spastic tetra paresis. Deep sensation were interrupted in both legs [10,16].

Radiological findings

The patient went through 3-Tesla MRI of the brain and spine. White matter hyperintensities were found on fluid attenuated inversion recovery and on T2-weighted imaging. Lacunar infarcts were found in the thalamus, basal ganglia, deep white matter. Incomplete "arc-shaped" lesions were found from pons region to middle cerebellar peduncles. MRI of spine showed multilevel disc degeneration and spondylosis deformans in cervical and lumbar spine [10,16].

Cardiological findings

The coronary arteries were calcified and altered severely. Severe stenosis of the proximal ramus interventricular is anterior (RIVA) and chronic occlusion of median RIVA and right coronary artery. The distal RIVA were filled with collaterals. Hence, the patient was also diagnosed with severe CAD [10].

Mutations In Htra1 Gene

The high temperature requirement A (HTRA) group of proteins are serine proteases. Four mammalian HTRA proteins has been found, HTRA 1-4. Human HTRA1 is

situated on chromosome 10q26. HTRA1 identified substrates such as collagen II, clusterin, biglycan, fibronectin, fibromodulin, vitronectin, aggrecan, decorin are extracellular matrix (ECM) proteins, inducing the critical role of HTRA1 in ECM homeostasis. HTRA1 gene causes the production of an enzyme called Serine protease. The HTRA1 enzyme causes lysis of many other types of proteins. This enzyme also binds to transforming growth factor-beta proteins and inhibits their capacity to send chemical signals. Altered expression of HTRA1 is causing a variety of diseases such as age-related macular degeneration, cancer, and Alzheimer's disease [17,18]. Inactivating mutations in HTRA1 gene has been recently linked to CARASIL, a hereditary white matter disease distinguished by subcortical infarcts with non-hypertensive cerebral small vessel arteriopathy, spondylosis, and alopecia. HTRA1 gene regulates the extracellular matrix proteoglycans degradation [19,15]. Overexpression of HTRA1 can change the Bruch's membranes structural integrity, causing invasion of choroidal vessels, abnormal vascularization. HTRA1 mutant proteins found in symptomatic carriers and identified that they weren't able to cause formation of trimers or were having mutations in the LD or L3 domain. The mutant HTRA1s with such properties are presumed to cause inhibition of trimer-dependent activation cascade. Wild type protease activity are inhibited by mutant HTRA1s [12,20].

Case Report of Mutation in HTRA1

Finding the clinical features, frequency, spectrum of HTRA1 mutations in a Taiwanese group with SVD.

Methods

Mutational analysis of HTRA1 were performed on a group of 337 unrelated patients and sequencing 222 subjects with SVD after excluding those having a NOTCH3 mutation.[13]

Results

Seven novel heterozygous mutations in HTRA1 were found, including p.Gly120Asp, p.Ile179Asn, p.Ala182Profs*33, p.Ile256Thr, p.Gly276Ala, p.Gln289Ter, and p.Asb325Thr. Each of these were found in 1 single index patient [16,21]. 7 index cases and 2 affected siblings having a heterozygous HTRA1 mutation, the clinical problems included lacunar infarction, intracerebral haemorrhage, cognitive decline, and spondylosis from fifth to sixth decade of life. In the 9 patients, 4 had psychiatric symptoms such as delusion,

depression and uncontrollable behaviour. 3 had leukoencephalopathy in the anterior temporal poles and 2 patients were having alopecia [18, 22].

Conclusions

CARASIL which is an autosomal recessive genetic disorder can harm an individual in their early adulthood. It is inherited from the abnormal genes caused to small arteries and to the specific area of deep brain in higher function; tissue loss due to lack of oxygen where small arteries get blocked destruction to myelin an oily substance covers and protects the nerve fibers in CNS. The diagnosis and physical examination of a patient is done by analysing the patient's medical history, symptoms, MRI findings... There is no specific treatment for this normally the medication is given based upon the symptoms seen. As per the case studies neurological examination, radiological findings, cardiological findings are done for the purpose of diagnosis. HTRA1 group of protein are serine proteases. The mutant HTRA1s with such properties are presumed to cause inhibition of trimer dependent activation cascade. HTRA1-related SVD and Sporadic SVD clinical and neuroradiological features are similar. These findings widen the mutational spectrum of HTRA1 and spotlight the pathogenic part of heterozygous HTRA1 mutations in SVD

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