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Carasil: A Novel Mutation of HTRA1 Gene

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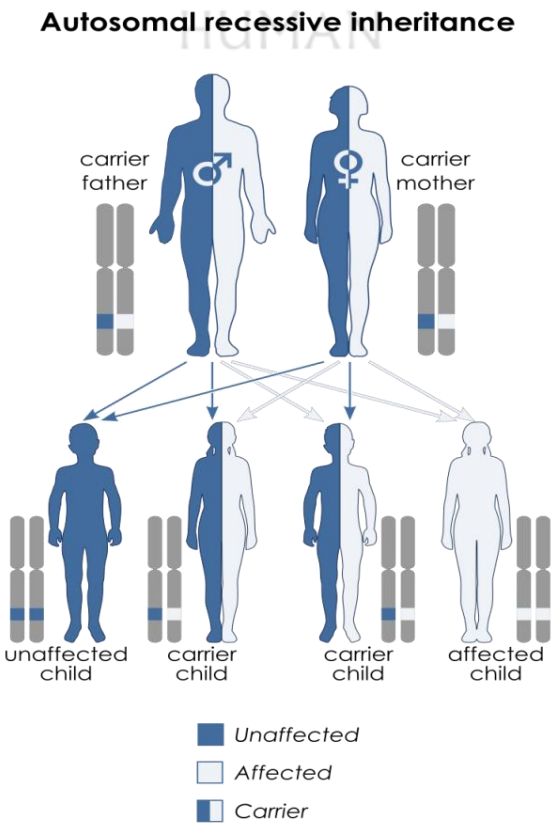
ABSTRACT

CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) otherwise known as Meada syndrome which is a rare or uncommon genetic disorder characterized by the damage to the small blood vessels in the brain. Generally, both neurological and non-neurological effects were observed. CARASIL is caused by the homozygous or compound heterozygous single gene mutation in HTRA1 gene located on the long arm of chromosome 10. CARASIL was reported by Maeda et al., in 1976. The prevalence is unknown. Roughly 50 cases were reported. Less than 10 genetically proven cases have been reported, with most of them had occurred in Japan. The exact pathophysiology of this rare disorder was not clearly understood. It may be manifested by stroke, alopecia, rigidity, poor concentration, mood changes, ataxia, unresponsiveness…etc. CARASIL is an uncommon hereditary issue with poor prognosis portrayed by the transformations in the HTRA1 quality situated on chromosome 10q(10q25.3-q26.2). This gene was located in blood vessels, skin and bone. There is no specific treatment for CARASIL. Supportive care should be given, it may be directed based on symptoms observed in particular people.

INTRODUCTION:

Stroke is a leading cause of long term neurological disability, apart from common vascular risk factors for stroke, there may be some genetic factors are also involved in the disease pattern. Monogenic (single gene) disorders may also responsible for 1% of ischemic strokes which includes CADASIL, CARASIL.CARASIL(Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) otherwise known as Meada syndrome which is a rare or uncommon genetic disorder characterized by the damage to the small blood vessels in the brain. CARASIL is caused by the homozygous or compound heterozygous single gene mutation in HTRA1 gene on the long arm of chromosome 10.CARASILwas reported by Maeda et al.,[1] in 1976 in two Japanese brothers who had rigidity, spastic ataxia and dementia.

Since then, the disease has been reported in approximately 50 patients worldwide with the majority of the patients were being from Japan and China. A few cases have been reported from Europe, Turkey,and India and have also been in the Caucasian population. It is mainly observed in consanguineous families. There is a 25%(among 4 children) chance of occurrence of the disorder in people born to both parents with carrier genes.



The disease was discovered by Fukutake and Hirayama and the term “CARASIL” was coined by Bowler and Hachinski. The onset of “CARASIL” symptoms were usually observed in early adulthood but may range from 20-40 years. Person may experiences all the symptoms before reaching 35 years of age.

ETIOLOGY:

This Genetic disorder mainly observed in consanguineous families. It is mainly related to cerebellum which controls balance and coordination which was caused by mutations in the HTRA 1 gene. This mutation is inherited as an autosomal recessive trait. Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. Recessive genetic disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one from each parent. If an individual inherits one normal gene and one abnormal gene, the person will be a carrier for the disease but usually will not show any symptoms.

There is a 25% chance of occurrence of effected child with each pregnancy born to the carrier parents. There is a 50% risk to have a carrier child with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. The risk is the same for males and females. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder[2].

EPIDEMIOLOGY:

The prevalence is unknown. Roughly 50 cases were reported. Less than 10 genetically proven cases have been reported, with most of them had occurred in Japan where on founder haplotypes have yet been found, indicating the likely existence of unreported cases[3]. The additional familial cases have been reported from Spain and China. It has been observed that one case was reported in Karnataka with similar symptoms [4].

PATHOPHYSIOLOGY:

The exact pathophysiology of this rare disorder was not clearly understood. CARASIL is an uncommon hereditary issue portrayed by the transformations in the HTRA1 quality situated on chromosome 10q(10q25.3-q26.2). This gene was located in blood vessels, skin and bone

[5]. The mutation results in the loss of HTRA1 protease activity, causing cerebral small-vessel arteriopathy. HTRA1 gene is the only gene known to be associated with CARASIL. HTRA1, a serine enzyme known to mediate cell signalling and protein degradation, plays an important role in vascular integrity, skeletal development and osteogenesis. It also modulates transforming growth factor (TGF)-β, a cytokine that promotes cell differentiation and fibrous proliferation, in response to the tissue damage [6].

CARASIL associated mutant HTRA1's loss of proteolytic activity leads to an increase in TGF—β signalling, causing degeneration of smooth muscle cells in the cerebral small vessels and angiopathy. It is likewise imagined that the up regulation of TGF-β family flagging might be in charge of non- neurological indications of CARASIL like alopecia and spine abnormalities. The findings in CARASIL most closely resemble non hereditary ischemic cerebral small vessel disease or "earthen pipe phenomenon"[7]. These highlights incorporate fibrous expansion of the intima, hyaline degeneration of the media, loss of vascular smooth muscle cells and thickening and discontinuity of the interior elastic lamina.

There is dilatation of blood vessel lumen instead of luminal stenosis the ischemic cerebrum strokes are believed to be because of the unsettling influence of autoregulatory systems for cerebral bloodstream. The discoveries are restricted to the cerebral little supply routes. CARASIL patients give early adulthood beginning of intermittent ischemic strokes and stepwise weakening of brain capacities including subjective brokenness. Clinically, the ischemic strokes look like run of the mill intense lacunar strokes, showing both pyramidal and extrapyramidal signs. Brainstem brokenness, for example, vestibular side effects, oculomotor variations from the norm, facial weakness and pseudobulbar influence might been seen.

DIAGNOSIS:

Diagnosis should be based on the presence of characteristic symptoms and image findings. The brain imaging of patients with CARASIL demonstrates lacunar infarcts on CT and MRI. Bilaterally symmetrical, periventricular white matter abnormality appears as hypodense on CT. MRI is the preferred imaging modality. The Genetic Testing Registry (GTR)[3] gives data about the hereditary tests for this condition. The determination ought to be adjusted through sub-atomic hereditary testing which distinguishes trademark changes or transformations in the HTRA1 quality.

CLINICAL MANIFESTATIONS:

CARASIL is a rapidly progressive disease manifested due to damage to the small blood vessels in the cerebellum. It brings about diminished bloodstream to the mind. Major clinical manifestations includes ischemic nonhypertensive stroke, premature baldness, progressive deterioration of brain functions and severe low back pains. Generally, both neurological and non-neurological symptoms were observed. Some patients encounters lacunar strokes and others may encounters decrease in cerebrum functions. Neurological effects incorporates Pseudo bulbar paralysis, explaining muscle tone, vestibular manifestations and ophthalmoplegia, slurred discourse, firm developments of the legs (spasticity), step unsettling influences, loss of bladder control (urinary incontinence) were additionally observed. Most influenced people encounter dynamic cerebrum harm, particularly to the white issue, which is the segment of the mind that contains myelinated nerve strands.

In the long run the turmoil causes intellectual impedance, which may incorporate memory issues, challenges settling on choices or taking care of issues, discourse troubles, shortages in ability to focus and general loss of intrigue (unresponsiveness) proceeded with intellectual decay at last outcomes in Dementia. Dementia is characterized as the dynamic loss of memory and decrease in scholarly capacities that meddles with performing routine assignments of day by day life. Additional vital side effects that have been with CARASIL incorporate scanty hair (alopecia) and degenerative in the spinal segment(spondylosis). Spondylosis starts between 10-30 years and causes backache and a herniated circle in the cervical and the lumbar locale. In spite of the fact that alopecia happens as a rule and creates before the beginning of neurological symptoms, 23% patients may creates stroke before 40 years.

SIGNS	**SYMPTOMS**
Pseudobulbar/Bulbar Paralysis	Unresponsiveness
Alopecia	Spastic Ataxia
Ophthalmoplegia	Sleeplessness
Slurred Discourse	Dementia
Lacunar Infarcts	Rigidity
Ischemic Stroke	Mood Changes

TREATMENT:

There is no specific treatment for CARASIL. Supportive care should be given [8], it may be directed based on symptoms observed in particular people. Supportive care, including emotional support and education regarding the disease, is the mainstay of management both for the patient and their families. Providing a walking aid to compensate for the gait disturbances along with medication for spasticity are also recommended. Mood stabilizers or other medication for psychiatric manifestations are suggested. Dementia can be managed according to the patient's condition. Baclofen may be given to relieve from spasticity. Anxiolytics may be given to protect from sleeplessness and mood changes. The treatment at introduced incorporates avoidances of non CARASIL related ischemic stroke, hereditary guiding, strong tend to treating dementia. The roles of antithrombotic and anticoagulant drugs in the therapeutics are still unclear.

PROGNOSIS:

Prognosis for CARASIL was very poor after the onset of neurological symptoms the disease progresses slowly over 5-20 years with average duration of illness lasting 10 years. Patients usually become bedridden for 10 years after disease onset but can live for 20-30 years with illness.

RELATED DISORDERS:

There are some disorders whose symptoms are very similar to CARASIL, they involves:

Binswanger's disease:

It is a dynamic neurological issue portrayed by atherosclerotic veins providing the white-matter and profound structures of the mind (basal ganglia and thalamus). Most patients encounter dynamic memory loss and disintegration of scholarly capacities (dementia), urinary retention or incontinence, and an unusually moderate, rearranging, precarious example of strolling, as a rule over a 5-10 year time span. Because of their vascular etiology, the indications and physical discoveries related with Binswanger's disease may abruptly compound because of stroke, balance out and afterward enhance for a concise time, yet the patient's general condition keeps on advancing as the veins turn out to be progressively deterred [10-11].

Multiple sclerosis:

It is a progressive neuroimmunologic (both the sensory system and the immunological framework are included) disorder of the focal sensory system including the cerebrum, spinal harmony and optic nerves. By methods for a system not clearly comprehended, the defensive greasy, protecting substance considered myelin sheath that covers the nerve is decimated. The provocative assaults that deliver the trademark scarring (plaques or patches) of the myelin sheath happen arbitrarily at various locales and fluctuate in force. The course of the disorder may advance, relapse, remit, or stabilize. Damage to the nerve cells may be irreversible.

REFERENCES:

1. CARASIL, a rare genetic cause of stroke in the young: Arima K, Yanagawa S, Ito N, Ikeda S. Cerebral arterial pathology of CADASIL and CARASIL (Maeda syndrome). Neuropathology 2003;23:327‑34.
2. Onodera O, Nozaki H, Fukutake T. CARASIL. *GeneReviews*. September 11, 2014; https://www.ncbi.nlm.nih.gov/books/NBK32533/..https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=199354.
3. Onodera.O.CARASIL *National Organization for Rare Disorders (NORD)*. 2016; https://rarediseases.org/rare-diseases/carasil/.
4. NavalliDevaraddi, G Jayalakshmi, Narayan R Mutalik:66(1);232-234.
5. NORD gratefully acknowledges Osamu Onodera, MD, PhD, Professor of Department of Molecular Neuroscience, Resource Branch for Brain Disease, Department of Neurology, Clinical Neuroscience Branch, Brain Research Institute, Niigata University, Japan
6. CADASIL and CARASIL:Saara Tikka Marc Baumann MaijaSiitonen Petra Pasanen MinnaPöyhönen LiisaMyllykangas MattiViitanen Toshio Fukutake:VOL24(5);SEPTEMBER-2014.
7. A CARASIL Patient from Americas with Novel Mutation and Atypical Features: Case Presentation and Literature ReviewMuhammad Ibrahimi c Hiroaki Nozaki, Angelica Lee Osamu Onodera, Raymond Reichwein, Matthew Wicklund d Mohammad El-Ghanem.
8. Nozaki H, Sekine Y, Fukutake T, et al. Characteristic features and progression of abnormalities on MRI for CARASIL. Neurology 2015;85:459-463.
9. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Genetics Home Reference (GHR). April 2011;http://ghr.nlm.nih.gov/condition/cerebral-autosomal-recessive-arteriopathy-with-subcortical-infarcts-and-leukoencephalopathy.
10. A novel mutation of the high-temperature requirement A serine peptidase 1 (HTRA1) gene in a Chinese family with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) Yan Chen1, Zhiyi He1, Su Meng1, Lei Li1, Hua Yang2 and Xiaotang Zhang: Journal of International Medical Research 41(5) 1445–1455:2013.
11. CARASIL AG Diwan, DG Bhosle, Anita Vikram, Avanti Biniwale, Satyarh Chaudhary, Bharat Patodiya: JAPI may 2012 VOL. 60.