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A REVIEW OF CEREBRAL AUTOSOMAL RECESSIVE ARTERIOPATHY WITH SUBCORTICAL INFRACTS AND LEUKOENCEPHALOPATHY (CARASIL)

FATHIMA SHAJAHAN[1], PRASOBH.G. R[2], SOUMYA. R.V[3],JULIA.J.J[4]

[1]FIFTH YEAR DOCTOR OF PHARMACY STUDENT, SREEKRISHNA COLLEGE OF PHARMACY AND RESEARCH CENTRE,PARASSALA,THIRUVANANTHAPURAM,KERALA,INDIA

[2]PRINCIPAL OF SREEKRISHNA COLLEGE OF PHARMACY AND RESEARCH CENTRE,PARASSALA,THIRUVANANTHAPURAM, KERALA,INDIA

[3]ASSOCIATE PROFESSOR, DEPARTMENT OF PHARMACY PRACTICE, SREEKRISHNA COLLEGE OF PHARMACY AND RESEARCH CENTRE,PARASSALA,THIRUVANANTHAPURAM, KERALA,INDIA

[4]ASSISTANT PROFESSOR, DEPARTMENT OF PHARMACY PRACTICE, SREEKRISHNA COLLEGE OF PHARMACY AND RESEARCH CENTRE,PARASSALA,THIRUVANANTHAPURAM, KERALA,INDIA

ABSTRACT

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a single-gene disorder caused by mutations in the HTRA1 gene, which codes for HtrA serine peptidase/protease 1. (HTRA1). CARASIL, along with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, is the second known genetic form of ischemic, nonhypertensive, cerebral small-vessel disease with an identified gene (CADASIL). The exact prevalence of CARASIL is currently unknown, but approximately 50 patients have been reported to date, the majority of whom were from Japan and two from China. Because no founder haplotype has been identified genetically, the disease is expected to be more widespread. The most common clinical manifestations of CARASIL are ischemic stroke or progressive deterioration in brain function.

KEY WORDS: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; ischemic stroke; alopecia; spondylosis deformans; small-vessel disease; HTRA1

INTRODUCTION

Cerebral small-vessel disorders (SVDs) represent a significant disease burden in Japan and other developed countries. Lacunar infarction, intracerebral haemorrhage, and vascular dementia are common symptoms of SVDs. Although hypertension, dyslipidemia, and diabetes mellitus are well-known risk factors for SVDs, various hereditary or idiopathic SVDs have also been found. [1-3]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy are two of them. (CADASIL) is the most frequent single-gene disease of the cerebral small arteries and was the first to be genetically discovered. CADASIL is caused by gene mutations in the Notch3 gene.[4] The disorder was initially documented in Europe more than 30 years ago, but the abbreviation "CADASIL" did not appear until the early 1990s, when the causative gene mutations were discovered. Several young adult patients (with or without familial occurrence) with symptoms similar to CADASIL in nonhypertensive arteriopathy were documented in the Japanese literature during the same time period. In 1995, I and a colleague studied 17 Japanese patients with early adult-onset arteriosclerotic leukoencephalopathy accompanied by unusual extraneural symptoms such as alopecia and lumbago/spondylosis deformans, finding that the illness was potentially autosomal recessivemode.5 Bowler and Hachinski6 suggested the moniker "cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)" based on the disorder's recessive inheritance and similarities to CADASIL.

Recurrent stroke or gradual decrease of motor abilities, cognitive deficiency, and the aforementioned systemic symptoms are the major clinical signs of CARASIL. Although CARASIL is extremely uncommon, two siblings were recently reported from China, the first outside of Japan. [7] This condition is likely to be more common because no founder haplotype has yet been discovered. [8]

This review describes CARASIL's historical background, epidemiology, typical clinical symptoms, neuroimaging, pathology, genetics, and therapy.

Although just a few genetically verified instances have been published to date, our group's clinical and pathological/neuroradiologic criteria have been used to identify about 50 individuals.[11] This review focuses mostly on the latter clinical instances.

EPIDEMIOLOGY

CARASIL's actual prevalence is unknown; to far, roughly 50 individuals have been recorded, with all but two coming from Japan. [19] Two siblings from a Chinese family were recently mentioned. [7] Because no founding haplotype has been discovered genetically, CARASIL is predicted to be found more extensively. [8] The age of onset of encephalopathy ranges from 20 to 45 years (mean, 32 years), which is younger than the age of onset of CADASIL (45 years) and Binswanger's disease (BD) (50-60 years). Alopecia develops early, in the second decade, and bouts of severe low back pain occur about the same time as encephalopathy develops. [9] In early studies, the typical duration of disease was up to 10 years, while survival for as long as

20-30 years has been reported. Recently, a life expectancy of 20-30 years has been recorded, albeit practically all of these patients became bedridden within 10 years of start. Males are more afflicted than females (a male:female ratio of 3:1 in clinically definite cases and 1.3:1 in all instances, including suspected cases). Consanguinity occurs in nearly half of all afflicted families.

CLINICAL FEATURES

The cardinal clinical symptoms of CARASIL include ischemic stroke or gradual degradation of brain functions, progressive dementia, premature baldness/alopecia, and bouts of severe low back pain or spondylosis deformans/disk herniation.

ISCHEMIC STROKE OR STEPWISE DETERIORATION

The most prevalent symptom of CARASIL is a typical lacunar stroke, which mostly affects the basal ganglia or brainstem. This happens in around half of the patients; the other half see a gradual decrease in brain function. According to BD, some individuals experience a protracted plateau phase. [21] Pseudobulbar palsy; pyramidal and extrapyramidal signs such as hyperreflexia and (rigido-) spasticity; brainstem signs such as vestibular symptoms, ophthalmoplegia, and facial palsy; and gait difficulties owing to leg weakness and/or ataxia are examples of neurologic signs and symptoms.Convulsions occur in certain patients.[14] A patient of ours suffered from advanced brain haemorrhage.[1]

COGNITIVE DEFICITS

Cognitive deficiency is the second most common symptom in CARASIL, occurring in nearly all patients who acquire dementia by the age of 30-40 years. Patients begin with forgetfulness and progress to calculating problems, temporal disorientation, personality changes, emotional incontinence, and severe memory impairment, eventually manifesting abulia (lack of spontaneity) and apallic syndrome (akinetic mutism). There are no brain focal symptoms (e.g., aphasia, apraxia) or aberrant behaviour (e.g., stereotypy, day-night sleep inversion). Personality changes, such as irritability and emotional lability, are sometimes noticeable even at the outset or early stages of the disorder, but depression does not generally emerge. CARASIL's cognitive abnormalities differ from those of cortical dementias (e.g., Alzheimer's disease) and subcortical dementias (e.g., progressive supranuclear palsy, Huntington's disease), and hence may be distinguished be classified as white matter dementia.[2]

PREMATURE BALDNESS/ ALOPECIA

Alopecia is the most common first symptom, occurring in nearly 90% of CARASIL patients and usually as early as puberty. It has been reported that a sibling has white matter illness but does not have alopecia. 26 Hair loss is limited to the scalp; there is no visible hair loss on the body. The baldness is widespread and not limited to the frontal or parietal areas (Fig 1). Miscel laneous dermatological signs have been observed keratosis and ulcers, xeroderma, pigmentary nevus, and dry skin with sclerema.[1]

DEFORMANS ACUTE LUMBAGO/SPONDYLOSIS

Acute middle to lower back pain (lumbago) affects roughly 80% of CARASIL patients, with onset between the ages of 20 and 40. Spondylosis deformans and/or disc degeneration in the cervical and/or thoracolumbar spine are seen on MRI and X-ray. Myelography revealed that an obstruction was frequently observed between the lower thoracic and upper lumbar sections of some of the patients mentioned in early studies, which is higher than the most typical locations of lumbar disc herniation.[5] Arachnoid adhesion and neurinoma (suspected) were the orthopaedic postoperative diagnosis in two of our patients.[18]Kyphosis, ossification of osteoarthritis in the elbows and/or knees are further skeletal abnormalities reported in certain patients.

ADDITIONAL MANIFESTATIONS

One CARASIL patient also had nasopharyngeal squamous cell cancer, which was discovered 4 years after the beginning of encephalopathy.[22] Another patient developed opticneuritis as well as retinal vascular abnormalities. In severe illness stages, two individuals acquired minor arteriosclerosis in the eyes.[19] CARASIL has not been associated with chronic persistent arterial hypertension in any patient. Routine laboratory tests are often noncontributory. In the individuals studied, serum very-long-chain fatty acids, serum and urine amino acids, and leukocyte lysosomal enzymes were all normal.[5]

BRAIN IMAGING

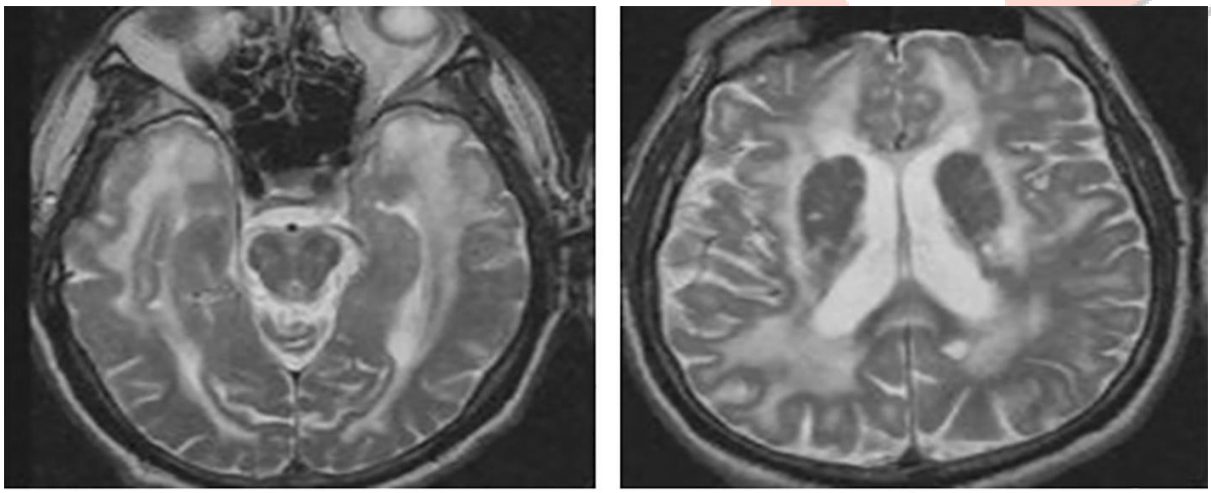

FIGURE:1 The patient's MRI shows scattered confluent HSI areas in the cerebral white matter that stretch to the anterior temporal lobe, internal and external capsules, and minor lesions in the basal ganglia and brainstem.

Even in the early phases of CT scans revealed diffuse homogenous white matter alterations in all studied individuals and tiny foci with softening in roughly 50% of patients. A 33-year-old guy with CARASIL has diffuse baldness.There was mild to severe dilatation of the lateral ventricles and cerebral sulci.[5] About a quarter of the patients exhibited modest regions of poor attenuation in the pontine base, indicating Wallerian degeneration of the cortico-descending pathways but not lacunes.[5] White matter high-signal intensity (HSI) lesions and numerous lacunar infarctions in the basal ganglia and thalamus are the most common brain MRI findings in CARASIL patients. In virtually all patients, T2-weighted MRI scans revealed HSI lesions in the

white matter, more often in the periventricular and deep white matter than in the superficial white matter (U-fibers).[6] In the absence of deep infarcts, HSI lesions begin to show diffusely and symmetrically in the subcortical white matter by the age of 20 years, suggesting that white matter alterations predate the onset of neurologic symptoms. These injuries then spread into the basal ganglia, thalamus, brainstem, and cerebellum are all involved. Some individuals have involvement of the anterior temporal lobes and external capsules, which are early symptoms of CADASIL. Although the evolution of MRI alterations in CARASIL is not extensively established, MRI/CT white matter abnormalities tend to develop homogeneously from the early stage30, whereas those in CADASIL appear to be punctiform or nodular at first and only subsequently create confluent lesions.[11] Cerebral angiography revealed no substantial abnormalities in nearly half of the individuals evaluated, while the remaining patients exhibited aberrant results consistent with arteriosclerosis.[5] Single photon emission computed tomography revealed decreased cerebral blood flow in several areas of the brain, including the unilateral frontal lobe, bilateral frontal cortex, and diffuse subcortical region, as well as in the cerebellum.[18]

PATHOLOGY

CARASIL is characterised histopathologically by severe arteriosclerosis, primarily in small penetrating arteries, with no granular osmiophilic materials or amyloid deposition. The cerebral white matter and basal ganglia are the most affected by arteriosclerotic changes.[7] Characteristic features include fibrous intimal proliferation, hyaline media degeneration, loss of vascular smooth muscle cells, thickening and splitting of the internal elastic lamina, and concentric narrowing of the lumen. Some patients have abnormal segmental dilatation of the small arteries.[12] Small arteries in periodic acid-Schiff preparations are occasionally stained homogeneously as a result of exudative changes, but never with the granular appearance characteristic of CADASIL's granular osmiophilic materials. The small arterial changes in the cerebral medullary and leptomeningeal arteries are intense, resulting in multifocal, confluent, or diffuse.[6]

GENETICS AND MOLECULAR PATHOGENESIS

Molecular Pathogenesis and Genetics HTRA1 is the only gene that has been linked to CARASIL.[2] There are no known phenotypes associated with HTRA1 gene mutations. A single-nucleotide polymorphism in the HTRA1 promoter region that homGenetics and Molecular Pathogenesis HTRA1 is the only gene that has been linked to CARASIL. There are no known phenotypes associated with HTRA1 gene mutations. Age-related macular degeneration has been identified as a single-nucleotide polymorphism in the promoter region of HTRA1 for which homozygosity for the AA genotype increases the risk of wet (neovascular) age-related macular degeneration.[6,8] In 5 families with CARASIL, genome-wide linkage analysis revealed a link to a 2.4-Mb region on chromosome 10q containing the HTRA1 gene20. HTRA1 is a transcription factor.

DIAGNOSIS

Smooth muscle and vascular endothelial cells. Hereditary hemorrhagic telangiectasia is caused by decreased TGF-b signalling caused by TGF-b receptor mutations, whereas Marfan's syndrome and related illnesses are caused by increased TGF-b signalling. [9]Hereditary ischemic cerebral SVDs may be added to the list of illnesses linked to TGF-b signalling imbalance. Alopecia and spondylosis, the other two essential clinical characteristics of CARASIL, have also been connected to dysregulation of the suppression of signalling by TGF-b family members. Transgenic mice with excessive levels of bone morphogenetic protein (BMP)-4, BMP-2, and TGF-b experience hair loss or slow hair follicle formation. Bone formation, repair, and regeneration are well-known processes regulated by members of the BMP family[10]

MANAGEMENT

There is currently no effective treatment for CARASIL patients. Genetic counselling, supportive care, and medications for dementia and secondary prevention of ischemic stroke are among the primary treatments.[22] However, the effects of antiplatelet agents and anticoagulants in these patients are unknown.

A medication that combines the biological components stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) improves cognitive performance in CADASIL patients by boosting brain blood vessel density and facilitating neural network remodelling.[23,7,15]

STEM CELL FACTOR(SCF)

Stem cell factor is an early-acting hematopoietic cytokine that most likely operates constitutively to promote the proliferation and survival of pluripotent progenitor cells while also increasing their sensitivity to lineage commitment and differentiation in response to lineage-specific cytokines.[9] Mast cell proliferation and activation can also be induced by stem cell factor. Stem cell factor has shown synergy with other hematopoietic cytokines in vitro and in vivo. Stem cell factor has been proven in clinical studies to mobilise peripheral blood progenitor cells and, when paired with G-CSF, to enhance the quantity of peripheral blood progenitor cells collected.[23] Stem cell factor treatment has been well tolerated when administered in lower dosages and with antihistamine and beta-agonist premedication. Phase III trials are now underway to demonstrate the effectiveness of stem cells Cell factor in methods for extracting peripheral blood progenitor cells.[5,10] Future therapeutic uses may include adult and paediatric marrow failure, ex vivo expansion and manipulation of hematopoietic progenitor cells, and therapy of skin pigmentation problems.

GRANULOCYTE COLONY STIMULATING FACTOR(G-CSF)

Granulocyte colony-stimulating factor (G-CSF or GCSF), also known as colony-stimulating factor 3 (CSF 3), is a glycoprotein that stimulates bone marrow to manufacture and release granulocytes and stem cells into the circulation[24]. It functions as a cytokine and hormone, as well as a sort of colony-stimulating factor, and is generated by a variety of organs. Filgrastim and lenograstim are pharmacological analogues of naturally occurring G-CSF. G-CSF also promotes neutrophil precursor and mature neutrophil survival, proliferation, differentiation, and function.[16,9]

CONCLUSION

CARASIL is a genetic disease that affects the cerebral small vessels, spine, and hair follicles. To date, four causative mutations in the HTRA1 gene have been identified. Mutant HTRA1 is thought to contribute to the pathogenesis of CARASIL by inhibiting signalling by TGF-b family members. Although it is the second most common hereditary cerebral SVD in Japan, this condition has never been reported outside of Asia. Because no founder haplotype has been identified genetically, CARASIL is expected to be found more widely. The phenotypic presentation of CARASIL's neurologic and neuroimaging features is similar to that of BD and CADASIL but differs in terms of underlying vasculopathy, mode of inheritance, and extraneural symptoms. CARASIL, like CADASIL, is a forerunner.

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