Autosomal Dominant Cerebral Small Vessel Disease in *HTRA1* Gene Mutation

Dear Sir,

Cerebral small vessel disease (SVD) is a heterogeneous group of disorders affecting small arteries, arterioles, veins, and/or capillaries of the brain. The most common symptoms seen with cerebral SVD are stroke and cognitive impairment. Brain imaging in cerebral SVD will show white matter lesions with lacunar infarct, microbleeds, and macrobleeds.[1] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common autosomal dominant (AD) monogenic SVD caused by mutation in the *NOTCH3* gene. AD SVD due to heterozygous mutation in the *HTRA1* gene accounts for 5% of AD SVD cases.[2] Hereby, we report a woman who presented with cognitive impairment, mood disturbances, migraine without aura, parkinsonism, and positive family history of strokes, headache, and cognitive impairment in three generations suggesting AD inheritance. Genetic analysis showed heterozygous mutation of *HTRA1* gene suggesting *HTRA1*-AD disease.

A 40-year-old woman presented with history of episodic headache of 3 years duration. Headache was holocranial, associated with nausea, no photophobia or phonophobia, moderate in intensity, episode lasting for 2 h, subsiding with analgesics with frequency of 2–3 per month. Headache was followed by the emergence of behavioral disturbance in the form of unprovoked aggression toward family members 6 months later. During the same time, she had two episodes of generalized tonic-clonic seizures and was started on valproic acid. She was on atypical antipsychotic for 3 months for behavioral change and showed improvement.

Two and half years later, she developed memory disturbances in the form of forgetting her daily chores, unable to dress herself, unconcerned urinary and fecal incontinence, disinhibition, and wandering behavior. There was no language or speech impairment. There was no myoclonus. She had slowness in walking with no freezing episodes. There were no falls due to postural instability or tremors in limbs. Her family history was significant for strokes, headache, and memory disturbances in 3 successive generations including her one male sibling, mother, and maternal grandfather. It started in their 40s and they died within their 50s after varying periods of bed-bound state. Systemic examination was unremarkable. Cognitive assessment was not possible as she had decreased attention span and perseverative behavior. Speech was normal. Cranial nerve assessment was normal. Motor examination showed mild rigidity in both lower limbs with brisk deep tendon reflexes. Plantar response was mute. Gait was short stepped, narrow based. Mild stooping was noted along with postural instability. Based on the clinical symptoms, family history of headache, stroke, and dementia, and examination findings, an inherited AD cerebral vasculopathy like CADASIL was considered. Routine blood investigations were normal. Serum vitamin B12, homocysteine, and thyroid hormones were normal. Brain magnetic resonance imaging (MRI) showed periventricular and subcortical T2 white matter hyperintensities sparing the external capsule and temporal lobe. Susceptibility-weighted imaging (SWI) showed multiple microbleeds in cortex and subcortical region. There was no contrast enhancement and intracranial vessels were normal [Figure 1]. Vasculitis profile and cerebrospinal fluid analysis was normal. Skin biopsy showed no amyloid deposits in blood vessels and electron microscopy was negative for granular osmiophilic material (GOM). Clinical exome sequencing showed heterozygous missense variation in exon 4 of the *HTRA1* gene (chr10:g122506818G > A; Depth: 51x) resulting in the amino acid substitution of glutamine for arginine at codon 302 (NM_002775.4) (c.905G > A) (p.Arg302Gln). The observed variation lies in the trypsin-like peptidase domain of the HTRA1 protein. The p.Arg302Gln variant (R302Q) has not been reported in the 1000 genomes, ExAC. This variant has been predicted to be deleterious by in silico tools suggesting HTRA1-AD disease. Sanger sequencing has not been done in our patient. The affected sibling, mother, and maternal grandfather were deceased.

The majority of hereditary SVD is of dominant inheritance. This includes CADASIL, high temperature requirement A serine peptidase 1 (*HTRA1*)-AD disease, collagen 4A1 and collagen 4A2 microangiopathy,[3] cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL), retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations, and pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL). Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is an autosomal recessive SVD and Fabry's disease is of X-linked inheritance.[4] AD SVD due to heterozygous mutation in the *HTRA1* gene accounts for 5% of AD SVD cases. Autosomal dominant SVD due to heterozygous mutation in the *HTRA1* gene presents with later age of stroke onset (around 60 years), cognitive impairment, and less frequent alopecia and spondylosis deformans.[4] CARASIL is caused by homozygous mutation in the *HTRA1* gene. CARASIL patients present with recurrent strokes at the age of 20 to 40 years with vascular dementia at the age of 30–40 years, premature alopecia, depression, gait disturbance, and severe back pain due to lumbar disc herniation and spondylosis deformans. Brain imaging shows diffuse WMH with lacunar infarcts and multiple microbleeds [Table 1].[5]

HTRA1 gene at the long arm of chromosome 10 (10q26) codes for a serine protease which has several domains—insulin-like growth factor binding domain, Kazal-like serine protease inhibitor domain, trypsin-like serine protease domain, and PDZ domain from the N-terminal to the C-terminal. The gene product has a role in regulating cellular proliferation. The vascular lesions may be due to

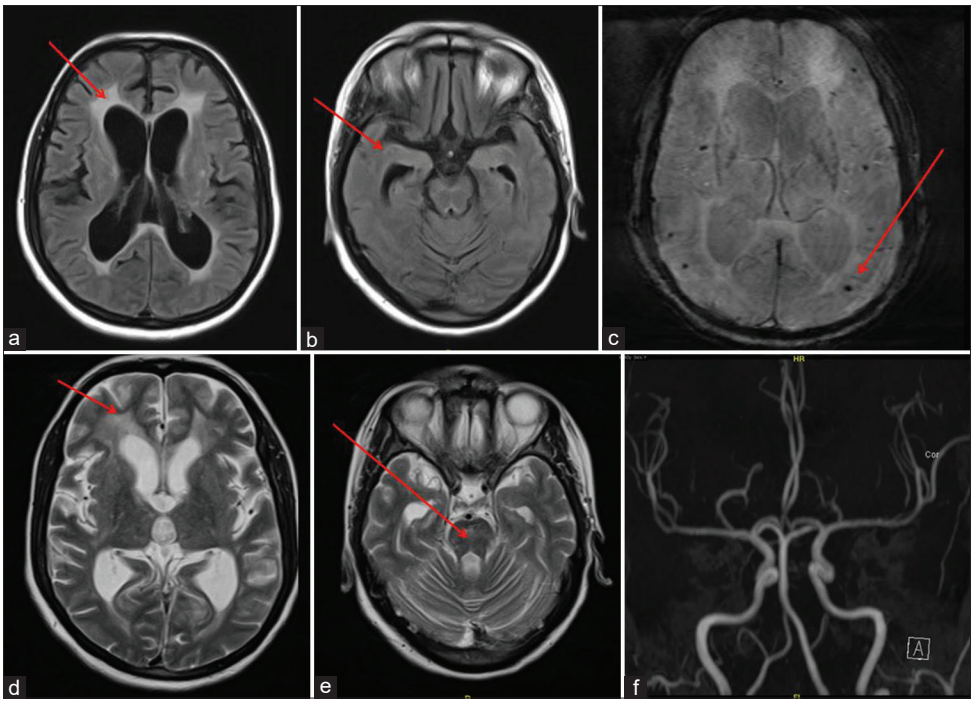

Figure 1: Brain magnetic resonance imaging (a) axial fluid-attenuated inversion recovery (FLAIR) image shows hyperintensity (red arrow) in periventricular white matter with prominent lateral ventricle sparing subcortical U fibers; (b) axial FLAIR image shows absence of signal change in anterior temporal lobe; (c) susceptibility-weighted image shows microbleeds (red arrow); (d) axial T2 image shows hyperintensity (red arrow) in periventricular white matter with prominent lateral ventricle sparing subcortical U fibers; (e) axial T2 image shows pontine hyperintense signal change (red arrow); (f) MR angiogram with normal intracranial arteries

Table 1: Clinical and radiological features of monogenic cerebral SVD

Monogenic cerebral SVD	Gene/ inheritance	Clinical features	Radiological features
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	*Notch3*/ AD	Ischemic stroke, migraine, dementia, encephalopathy, mood disorders	Lacunar infarcts, white matter hyperintensities (WMH), microbleeds, anterior temporal pole WMH
CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy)	*HTRA1*-homozygous/ AR	Ischemic stroke, dementia, mood disorders, alopecia, spondylosis deformans	Lacunar infarcts, WMHs, anterior temporal pole WMH
AD-HTRA1	*HTRA1*- heterozygous/ AD	Ischemic stroke, dementia, migraine, mood disorders, encephalopathy	Lacunar infarcts, WMHs, anterior temporal pole WMH
COL4A1/2	*COL4A1/2*/ AD	Ischemic stroke, intracerebral hemorrhage (ICH), dementia, renal/hepatic cyst, intracerebral aneurysm, retinal arteries tortuosities, cataract, focal retinal hemorrhage	Lacunar infarcts, WMHs, microbleeds
PADMAL (Pontine autosomal dominant microangiopathy and leukoencephalopathy)	*COL4A1*/ AD	Ischemic stroke, dementia	Pontine infarcts, WMH
CARASAL (Cathepsin-A related arteriopathy with strokes and leukoencephalopathy)	*CTSA*/ AD	Ischemic stroke, ICH, dementia, migraine, mood disorders, dysphagia, cramps, dry eyes and mouth, facial pain	WMH sparing U-fibers, brainstem, basal ganglia and thalamus lesions
RVCL-S (Retinal vasculopathy and cerebral leukoencephalopathy and systemic manifestations	*TREX1*/ AD	Dementia, seizures, retinal vasculopathy, Raynaud phenomenon	WMHs, large contrast-enhanced white matter lesions
Fabry's disease	αgalactosidase A/ X-linked	Ischemic stroke, ICH, cerebral venous sinus thrombosis	WMHs, microbleeds, infarcts, pulvinar sign

the dysregulation of transforming growth factor (TGF-β) signaling. TGF-β binding protein is an important component of the extracellular matrix, and substrate of proteolytic HTRA1 activity. The *HTRA1* gene mutation causes reduced

Table 2: Clinical features of published R302Q *HTRA1* mutation

Clinical features of R302Q	Nozaki *et al*. (2016) (*n*=4)	Wu *et al*., (2018) (*n*=3)	Present study (2020) (*n*=1)
Age at onset (years)	63	35	37
Stroke	Yes	Yes (*n*=2)	No
Headache	Not available	Not available	Yes
Cognitive impairment	Yes	Yes (*n*=2)	Yes
Alopecia	Yes (*n*=2)	No	No
Spondylosis deformans	Yes	No	No
Hypertension	Yes (*n*=1)	No	No

HTRA1 proteolytic activity and does not repress signaling by TGF-β causing vasculopathy.[6]

Wu *et al*. (2018) reported a family with suspected CADASIL who were *NOTCH3* gene negative. Direct sequencing showed a heterozygous missense mutation in *HTRA1* Exon4 c.905G>A p.Arg302Gln (R 302Q). Single nucleotide polymorphism (SNP) genotyping assay of the candidate gene in proband symptomatic sisters showed that *HTRA1* gene had the same SNP, suggesting that this heterozygous missense mutation is the reason for their familial SVD.[4] Donato *et al*. (2017) detected heterozygous *HTRA1* mutations in nine patients from five families with SVD. The genomic variants were p.Ser136Gly (kazal-like protein domain), p.Gly206Glu (serine protease protein domain), p.Gln151Lys (kazal-like protein domain), p.Val175Met (none), and p.Gly295Arg (serine protease protein domain). The patients were > 40 years at onset and had stroke, cognitive impairment, gait disturbances with no alopecia or spondylosis deformans.[7] Verdura *et al.* (2015) conducted a whole-exome sequencing to identify candidate genes in an AD SVD family in which known SVD genes had been excluded, and subsequently screened all candidate genes in 201 unrelated probands with a familial SVD of unknown etiology, using high throughput multiplex polymerase chain reaction and next-generation sequencing. A heterozygous *HTRA1* variant (R166L) was identified in all affected members of the index family and ten probands of 201 additional unrelated and affected probands (4.97%). They concluded that about 5% of familial SVDs are associated with deleterious heterozygous mutations of *HTRA1*. *HTRA1* mutations can be second cause of AD SVD after CADASIL.[2] Nozaki *et al.* (2016) reported four heterozygous missense mutations (p.G283E, p.P285L, p.R302Q, and p.T319I) in eight patients from 113 patients with SVD. Three mutations (p.G283E, p.R302Q, and p.T319I) were novel. Four patients had p.R302Q similar to our patient. Patients with p.R302Q had stroke, cognitive impairment in all, alopecia in two, and spondylosis deformans in all patients. *HTRA1* mutants in these manifesting heterozygotes decreased wild-type HTRA1 protease activity [Table 2].[8]

Patients presenting with familial AD SVD who are negative for *notch3* gene mutation need testing for mutation in *HTRA1* gene. *HTRA1* mutations can be second cause of AD SVD after CADASIL.[2]

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Conflicts of interest

There are no conflicts of interest.

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