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Letter to the Editor: New Observation

Acute Fatal Leukoencephalopathic Presentation of CADASIL

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Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease caused by mutations in *NOTCH-3* gene.[1] Core clinical symptoms include stroke, cognitive decline, psychiatric disturbances, and migraine with aura1. Here, we describe an unusual presentation of CADASIL.

A 60-year-old man presented with waxing and waning neurological symptoms over 6 weeks. He initially presented to another center with a 1-day history of acute-onset headache, blurring of vision, unsteadiness of gait, and drowsiness. He showed partial improvement over a week.

After 4 weeks, he worsened with increasing headache, blurring of vision, recurrence of drowsiness, and walking difficulty requiring support to walk with additional features of bladder and bowel incontinence. He was treated along the lines of idiopathic intracranial hypertension with acetazolamide but had no improvement and was referred to our institute. His history was significant for hypertension, acute-onset headache, and unilateral cerebellar symptoms 3 years back (Fig. 1a: brain MRI). He was suspected to have stroke and treated with aspirin, atorvastatin, and amlodipine and made a complete functional recovery over 3 months. There was no history of exposure to illicit drugs or toxic substances. There was no family history of stroke, migraine, cognitive decline, or other neurological illness.

On examination, he was drowsy, disoriented to time and place, obeying simple commands with hypophonic speech. His blood pressure was 140/80 mmHg. Visual acuity was hand movements, and fundus examination revealed grade IV papilledema with hemorrhages and venous stasis retinopathy.

There was bilateral sixth cranial nerve palsy. He was able to move all limbs against gravity with mild spasticity, brisk tendon reflexes, and extensor plantar response. He needed support to walk with a tendency to fall backward. The clinical possibilities of toxic, immune-mediated (demyelination: MOG, ADEM, autoimmune, and paraneoplastic), metabolic, and infective causes were considered.

Investigations revealed normal hemogram, serum electrolytes, ammonia, lactate, thyroid, hepatic, and renal function tests. Serology for HIV and VDRL were negative, and ESR was mildly elevated. Brain MRI revealed diffuse expansile T2/FLAIR hyperintensities in the periventricular, deep, and subcortical white matter involving U fibers, pons, external capsule, and temporal lobe (Fig. 1b and c). CSF opening pressure was 200 mm of H2O (while on treatment with mannitol) with four cells (lymphocytes), glucose: 70 (normal range: 40–70mg/dl), and protein: 50 (normal range: 15–45mg/dl). Vasculitis profile (ANA, ANA profile, p-ANCA, and c-ANCA), anti-thyroid-peroxidase, anti-aquaporin-4 IgG and anti-myelin-oligodendrocyte-glycoprotein IgG antibodies, autoimmune encephalitis profile (NMDA, CASPR2, LGI1, and AMPA1), urine toxic screening for nicotine, hippuric acid, antihistamine, cannabis, opiates, barbiturates, and benzodiazepines were negative. His paraneoplastic neuronal antibody profile (Anti-Hu, Anti-Ri, Anti-Yo, Anti-CV-2, Anti-PNMA2, Anti-PNMA1, Anti-amphiphysin, PCA-2, Anti-Tr, Anti-MAG, Anti-GAD65, Anti-Zic4, Anti- titin, Anti-Recoverin, and Anti-Myelin) demonstrated Anti-SOX1 antibody 1+ positive (insignificant unless there is a clinical correlation). CT chest and abdomen didn't reveal any evidence of malignancy. Given the history of stroke and MRI features suggestive of leukoencephalopathy, *NOTCH-3* gene analysis was carried out which revealed pathogenic heterozygous missense variation c.397C>T(p. Arg133Cys) in exon 4 of the *NOTCH-3* gene (chr19:15303053G>A) and confirmed the diagnosis of CADASIL.

He was treated with antihypertensies, aspirin, atorvastatin, oral glycerol, and intravenous mannitol. He had a persistent headache with periods of worsening and vomiting. Diminution of vision was status quo. Later, he was treated with steroids (intravenous methylprednisolone 5 grams) in view of CADASIL coma. There was a transient improvement in headache and sensorium (alertness improved). However, during the 10th week of illness, his sensorium progressively deteriorated (drowsy and then stuporous), and he succumbed to the illness in the 11th week. Severe brain edema resulting in uncal herniation was suspected as the cause of death.

Brain autopsy revealed diffuse cerebral edema with uncal herniation and midbrain hemorrhages. Histopathology revealed sclerosed vessels with irregular thickening, folded mura, and perivascular hemorrhage along with focal perivascular mononuclear inflammation, perivascular and diffuse reactive glial and microglial changes (leukoencephalopathy changes) (Fig. 2).

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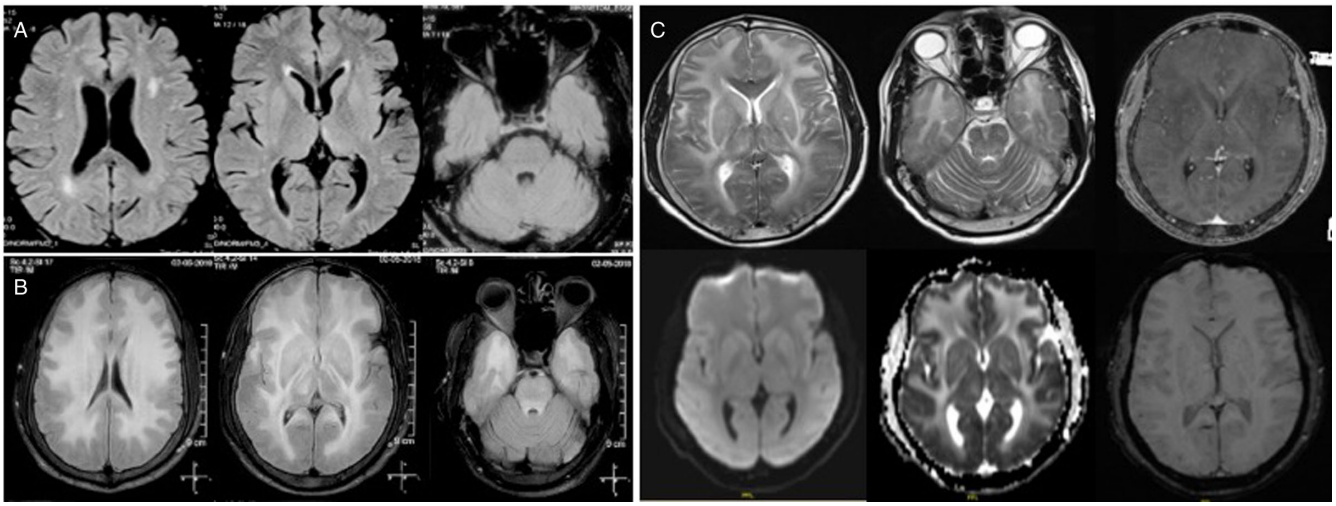

Figure 1: Sequential MR images of the patient. ***a***: FLAIR axial images of initial MRI (June 2015) showed nonspecific discrete subcortical and deep periventricular frontoparietal white matter hyperintensities. ***b***: MRI at second presentation (May 2018) revealed diffuse cerebral edema with extensive, symmetric white matter hyperintensities involving U fibers, anterior temporal lobes, external capsules, basal ganglia, brainstem, and cerebellar hemispheres (not shown). ***c***: MRI at our institution (June 2018) revealed persistence of symmetric expansile, white matter hyperintensities with no enhancement. There was no evidence of diffusion restriction or blooming (lower row).

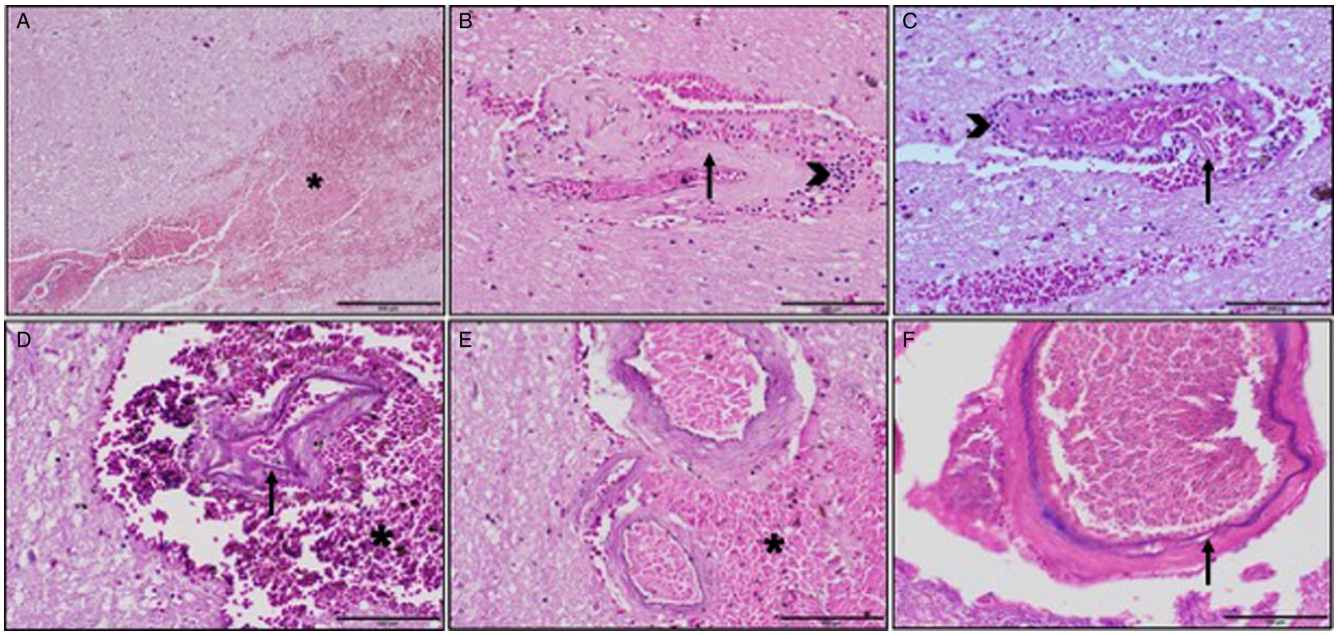

Figure 2: Histopathology of brain. ***a***: Microphotograph showing brain parenchyma with a large area of hemorrhage (asterix) and a congested blood vessel [hematoxylin and eosin (H & E) staing visualized at x40 magnification]. ***b***, ***c,*** and ***d***: Microphotograph showing brain parenchyma with a blood vessel displaying folded mura (arrow) and perivascular hemorrhage (asterix) and lymphocytic infiltration (arrow head) [H & E × 200]. ***e***: Microphotograph showing brain parenchyma with a large area of hemorrhage (asterix) and a congested blood vessel [H & E × 200]. ***f***: Microphotograph showing a cerebral blood vessel with uneven wall thickness, folding, and duplication of the internal elastic lamina (arrow) [H & E × 200].

Unfortunately, ultrastructural examination by electron microscopy could not be done.

Newly proposed diagnostic criteria for CADASIL by the Japanese Group (2017) requires the presence of white matter lesions on imaging, exclusion of leukodystrophy, and presence of either *NOTCH-3* mutations involving exon 2–24 on genetic analysis or granular eosinophilic material on electron microscopy for the definitive diagnosis of CADASIL.[2] Our patient had known disease-related pathogenic *NOTCH-3* mutation[3] and fulfilled definite criteria. However, histopathological findings were nonspecific but consistent with CADASIL.

Acute encephalopathy-like presentation sometimes referred to as "CADASIL-coma" is reported in 8%–10.3% of CADASIL.[4,5] These patients presented with reversible recurrent encephalopathy lasting 7–14 days associated with confusion, headache, and seizures on the background history of migraine with aura.[4–6] Our patient presented with an unusual progressive disease course with

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headache, vision impairment, papilledema, and encephalopathy leading to death over 11 weeks. A similar presentation was described earlier, in a patient with headache and raised ICP; however, she recovered fully.[7]

CADASIL is reported to have both brain atrophy and brain swelling. Brain swelling correlates with the episodes of migraine in these patients. Cerebral edema can be attributed to damage to vascular endothelium and temporary dysfunction of the blood–brain barrier in CADASIL7. We hypothesize that each episode of headache adds to cell death and brain swelling during acute episodes, finally resulting in brain atrophy in the long run. There was initial recovery from the encephalopathy within a week in our patient; however, he again worsened within 4 weeks. The presence of hypertension, recurrent episodes of encephalopathy in a short span, and progressive diffuse cerebral edema leading to herniation may be responsible for the fatal course in our patient.

The conventional MRI features of CADASIL including multifocal/confluent subcortical white matter lesions, involvement of anterior temporal lobes, external capsules, and periventricular and frontoparietal regions are well established.[4,5] Focal brain edema in a few and diffuse brain edema in one patient with CADASIL coma, are described.[7] Acute toxic leukoencephalopathy (ATL) is characterized by cerebral white matter injury on diffusion-weighted imaging.[7] To the best of our knowledge, this is the first case which closely resembled features of ATL on imaging, but there was no diffusion restriction.

Thus, imaging features of diffuse leukoencephalopathy without diffusion restriction or blooming in an acute encephalopathy-like illness may give clue to the diagnosis of CADASIL in an appropriate clinical scenario after excluding the relevant causes.

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Competing interests. None of the authors has any conflict of interest to disclose.

Statement of authorship. AH: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data.

DVS: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data.

BN: drafting/revision of the manuscript for content; major role in the acquisition of data; and analysis or interpretation of data.

KK: revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data.

PG: drafting/revision of the manuscript for content and analysis or interpretation of data.

RK: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data.

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