

Atypical Young-onset Dementia in Cerebral Thromboangiitis Obliterans

A Case Report

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Abstract: Young-onset dementia (YOD, age at onset below 45 y) has a broad differential diagnosis. We describe a 41-year-old man with atypical manifestations of YOD syndrome in cerebral thromboangiitis obliterans (CTAO). Extensive antemortem workup including clinical assessment, laboratory investigations, neuroimaging, and genetic testing did not elucidate a diagnosis. Postmortem neuropathologic examination revealed cortical sickle-shaped granular atrophy, resulting from numerous remote infarcts and cortical microinfarcts that mainly affected the bilateral frontal and parietal lobe, confirming CTAO. Although CTAO is a rare cause of vascular dementia, it should be considered as one of the differentials in patients with YOD with a history of heavy smoking and presence of symmetric damages of watershed-territory on neuroimaging.

Key Words: young-onset dementia, cerebral thromboangiitis obliterans, vascular dementia

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Young-onset dementia (YOD) is defined as dementia with symptom onset before the age of 45. The differential diagnosis of YOD is extensive and includes neurodegenerative, metabolic, autoimmune, inflammatory, and infectious diseases.¹

Cerebral thromboangiitis obliterans (CTAO), also known as Spatz-Lindenberg disease, is a rare cause of vascular dementia. It is characterized by granular cortical atrophy involving multiple microinfarcts of the cortex and narrowing of the leptomeningeal vessels.^{2,3} Here, we report the unusual presentation of YOD syndrome in a 41-year-old man diagnosed with CTAO at autopsy and discuss the clinical implications of this case.

CASE REPORT

A 41-year-old right-handed man presented with a progressive gait disturbance, cognitive deficits, and personality changes. He was suspected to have had seizures at around 39 years of age but a subsequent detailed history was not obtained. At the age of 40 years, he developed sudden loss of consciousness (LOC) for 1 to 2 minutes while exercising at a fitness club. Subsequently, he developed gait disturbances and personality changes (eg, frequent anger). Although there was a brief period of gait improvement, he continued to experience several seizure attacks during sleep and recurrent LOC episodes, with gradual progression of difficulties in moving his legs and hands. He did not have a history of hypertension, diabetes, stroke, or brain trauma. He was receiving anti-epileptic drugs (AEDs). He had a 3-pack-day smoking history but had quit at the time of presentation. His mother had a history of seizures since the age of 68 years, which was well controlled with AEDs. She also had hypertension and diabetes. At age 77, she developed sudden-onset right hemianopsia associated with focal cerebral infarction in the left posterior cerebral artery territory (Supplemental Fig. 1A, Supplemental Digital Content 1, <http://links.lww.com/WAD/A362>).

Neurological examination revealed mild weakness and spasticity in the right leg, ataxia in the right arm, hyperactive deep tendon reflexes in bilateral upper and lower extremities, spastic gait, and positive Babinski sign bilaterally. The Korean version of the Mini-Mental Status Examination score was 22. The neuropsychological test showed severely impaired memory, visuospatial, language, and frontal executive functions (Supplemental Table, Supplemental Digital Content 1, <http://links.lww.com/WAD/A362>). Brain magnetic resonance imaging (MRI) showed diffuse cortical atrophy with left frontal lobe hemorrhage. His electroencephalogram findings were normal, and hence, treatment with AEDs was stopped. At the age of 42, he was admitted to a nursing hospital, and antihypertensive therapy was initiated. When he was reevaluated in our clinic at the age of 44 years, his cognitive function had further deteriorated (Korean version of the Mini-Mental Status

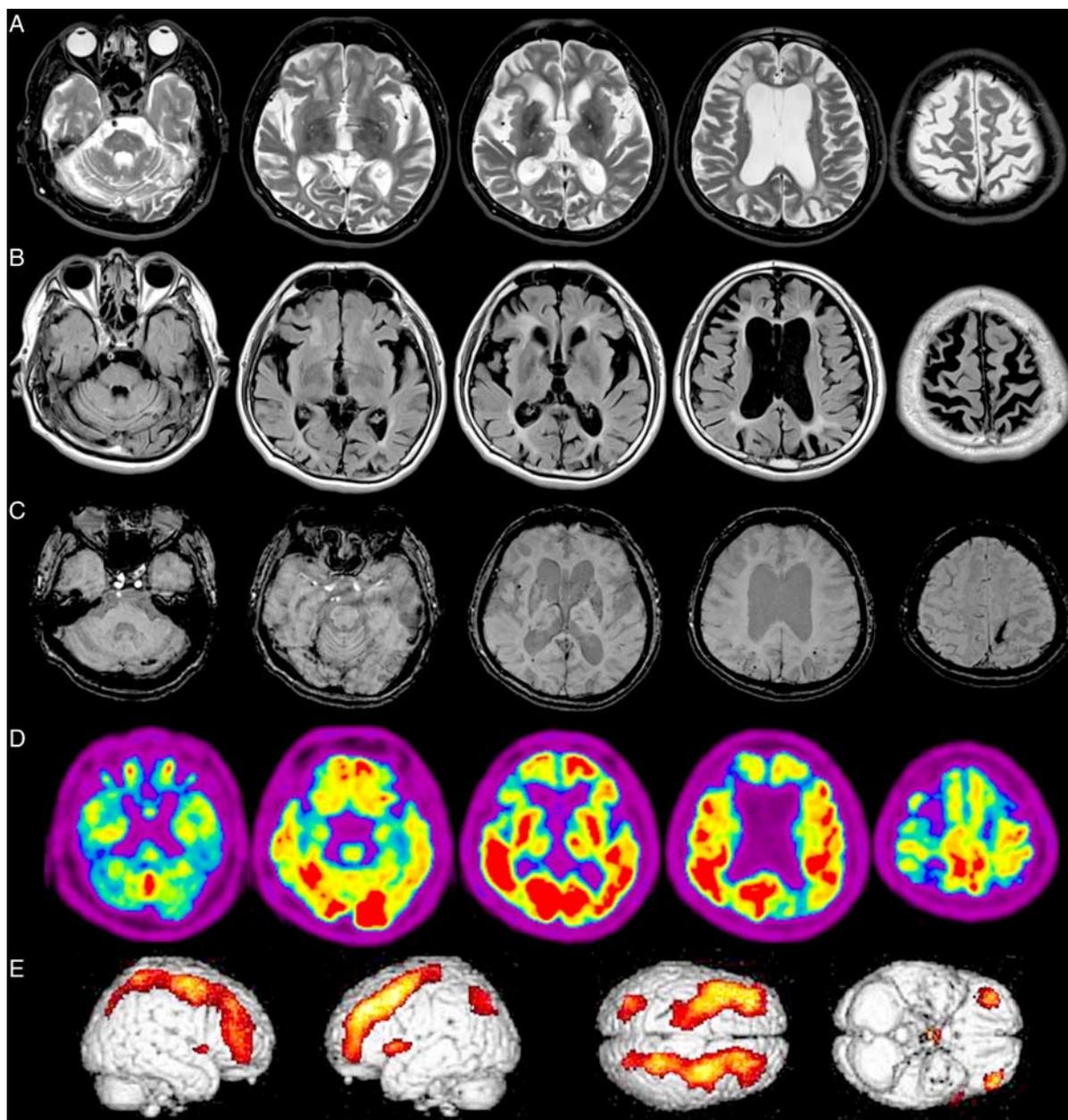


FIGURE 1. Axial T2-weighted images (A) and Fluid attenuated inversion recovery images (B) show severe cortical atrophy with multiple subcortical and cerebellar lacunes and white matter hyperintensities. Susceptibility-weighted images (C) demonstrate multiple cortical microbleeds and old hemorrhage in the left cerebellum, right lingual gyrus, and bilateral parietal cortices and left frontal cortex. ¹⁸F-fluorodeoxyglucose positron emission tomography (D) shows severe glucose hypometabolism in the bilateral frontoparietal regions. These hypometabolic regions of the patient were compared with those in 29 cognitively unimpaired controls using statistical parametric mapping positron emission tomography analysis (E), revealing hypometabolism mainly in the bilateral watershed areas of the anterior cerebral artery-middle cerebral artery territories. full color online

Examination score, 19). He showed decreased speech output, aggressiveness, and urinary frequency, and was stubborn and uncooperative. Moreover, neurological examination revealed rigidity in bilateral upper extremities, generalized bradykinesia, hemiplegic gait, and gait ignition failure. Brain MRI revealed severe cortical atrophy with multiple subcortical and cerebellar lacunes and white matter hyperintensities. Susceptibility-weighted imaging showed multiple cortical microbleeds and old hemorrhage in the left cerebellum, right lingual gyrus, bilateral parietal cortices and left frontal cortex (Figs. 1A–C). Brain MR angiography revealed

normal (Supplemental Fig. 1B, Supplemental Digital Content 1, <http://links.lww.com/WAD/A362>).

Extensive differentials were made given the history of progressive YOD with spastic gait, ataxia, several LOC episodes (suspicious seizure attacks), severe cortical atrophy with multiple lacunes, microbleeds, and old hemorrhage. Laboratory test results for progressive YOD, including complete blood count, electrolytes, chemistry, lipid profiles, liver and renal function tests, C-reactive protein, syphilis, vitamin B₁₂, folate, homocysteine, copper, ceruloplasmin, antithrombin III activity, protein C activity, fibrinogen, lupus

anticoagulant, anti-phospholipid IgG/IgM, anticardiolipin IgG/IgM, anti-SS-B, anti-SS-A, cytoplasmic anti-neutrophil cytoplasmic antibody, perinuclear anti-neutrophil cytoplasmic antibody, fluorescent antinuclear antibody, anti-dsDNA IgG/IgM, tumor markers, and paraneoplastic antibodies were normal. Erythrocyte sedimentation rates (43 mm/h, 0 to 10 mm/h) was mildly increased, however, other laboratory tests related to autoimmune or infectious diseases showed no abnormalities. Therefore, we thought it was a nonspecific finding. Echocardiography and chest and abdomen computed tomography findings were unremarkable. On the basis of these investigations, systemic differentials of YOD such as autoimmune, neoplasm, toxic-metabolic causes were excluded. Additional laboratory workup for adult-onset leukodystrophies, lysosomal storage diseases, and mitochondrial diseases including very long chain fatty acids, arylsulfatase A, hexosaminidase A/B, lactic and pyruvic acids, creatine kinase, myoglobin, nerve conduction study, and electromyogram were either normal or negative. Since his mother had a history of seizures and stroke, hereditary causes were considered in the differentials. Mutation tests for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL, *NOTCH3*), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL, *HTRA1*), adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP, *CSF1R*), Spinocerebellar ataxia 1, 2, 3, 6, 7, and Dentatorubro-Pallidolusian atrophy were negative. Because the progression of the disease course was rapid, Creutzfeldt-Jakob Disease should be ruled out. Routine cerebrospinal fluid examination was normal and cerebrospinal fluid 14-3-3 was negative. The patient had no skin lesions or hearing/vision problems. An 18F-fluorodeoxyglucose positron emission tomography scan at 45 years revealed severe glucose hypometabolism in the bilateral frontoparietal region (Figs. 1D, E).

Although extensive workup was performed, the clinical syndromic diagnosis could not be specified, and the patient continued to decline. He was wheelchair bound at age 46 and died at the age of 51 years, 12 years after symptom onset. Autopsy was performed with a 10-hour postmortem interval.

The brain weighed 1074 g. Superior aspect of brain and formalin-fixed coronal slices of the left hemisphere showed granular atrophy due to possible remote infarctions in the middle frontal gyrus, the superior parietal lobule, and some parts of the superior frontal gyrus and occipital cortex. This infarction appeared to have predominantly affected the anterior cerebral artery-middle cerebral artery (ACA-MCA)-watershed areas, which was observed as sickle-shaped granular atrophy (Fig. 2A). In the coronal sections, infarction was observed in the frontal and parietal areas as seen in the lateral view. Atrophy was also observed in the frontal subcortex and dilated frontal horn. The temporal lobe, amygdala and hippocampus were relatively preserved (Fig. 2B). Hematoxylin and eosin staining revealed that all cortical and subcortical areas were affected by remote infarctions, multiple microinfarcts, and subcortical white matter rarefaction except the frontal pole, amygdala, superior temporal gyrus, and medulla (Figs. 2C–E, G). Leptomeningeal vessels showed lots of foamy macrophages, narrowed lumen, intimal hyperplasia, and recanalization (Fig. 2F). Hyalinized subcortical vessels and loss of myelination were also detected. However, smooth muscle actin, endothelial cell lining and internal elastic lamina were relatively preserved in small-sized and medium-sized intraparenchymal arteries, although duplication of the internal elastic lamina and focal intimal hyperplasia were occasionally observed in some of them (Fig. 2H). There was no evidence of inflammatory infiltrate, or vasculitis. Immunohistochemical staining for tau, TDP, β -amyloid, and α -synuclein revealed very few tau-positive neurofibrillary tangles and gray matter threads in the dorsal raphe, locus coeruleus, and entorhinal cortex. The primary pathologic diagnosis was severe central nervous system (CNS) vasculopathy, that is, numerous remote infarcts prominently affecting the ACA-MCA border zone areas and leukodystrophy, confirming CTAO.

DISCUSSION

CTAO or Spatz-Lindenberg disease is a rare disease and is not a well-recognized cause of vascular dementia. Type 1 CTAO manifests as asymmetric infarctions

associated with proximal occlusion of the major cerebral artery, whereas type 2 involves symmetric terminal vessels causing granular atrophy in watershed areas.³ As CTAO has no standardized definition or pathognomonic histopathologic characteristics, the diagnosis may depend on exclusion of other diseases.^{4,5} In this context, a history of heavy smoking or peripheral TAO in younger patients may be a key feature in CTAO diagnosis. Although there was the absence of peripheral vascular involvement, the clinical and neuroimaging findings and pathologic characteristics showing numerous remote infarcts and cortical microinfarcts affecting bilateral frontal and parietal lobes, prominently the ACA-MCA watershed areas, without evidence of inflammatory infiltrates or vasculitis in our case exactly mirror those from previously reported CTAO type 2 cases.^{6,7} Regarding the clinical course, the patient's symptoms started approximately at the age of 39 years. Until before he stopped smoking at the age of 41 years, his clinical course somewhat rapidly progressed, but since then, the course was rather stable until he died at the age of 51 years. This was also well compatible with the "usually long duration and early transient but progressive symptoms resulting in permanent damage," the typical clinical course of CTAO.⁸

The present case has several clinical implications. Despite extensive evaluation, no etiologic diagnosis could be established before a postmortem brain autopsy. CTAO is one of differentials for vascular dementia. Although the patient's MRI showed old hemorrhage, multiple lacunes, and white matter hyperintensities, the presence of severe cortical atrophy at his age was highly suggestive of young-onset neurodegenerative dementia rather than young-onset vascular dementia attributed to, for example, cerebral amyloid angiopathy. Therefore, CNS vasculopathy could not be established as the main cause of his symptoms before the autopsy. The absence of peripheral TAO also made antemortem diagnosis difficult. Furthermore, we did not pay attention to his heavy smoking history (3-pack/day) or the 18F-fluorodeoxyglucose positron emission tomography finding of hypometabolism in the bilateral watershed regions until the autopsy. Eventually, the autopsy findings revealed CNS vasculopathy as the primary cause and explained that the transient symptoms such as the seizure and recurrent LOC episodes in the early stage could have developed due to temporary circulatory disturbances causing cerebral microinfarctions, lacunar infarctions, or transient ischemic attack. The severe cortical atrophy on MRIs might be secondary to multiple vascular lesions.

Although many CTAO cases have been reported since it was first described in 1939, the actual existence of this disease is debatable due to its unclear pathogenesis and pathologic changes.^{3,9–11} Therefore, only few cases have been recently reported, indeed only 2 cases from East Asian countries after the 2000s,^{6,12} possibly explaining the limited awareness regarding this disease among clinicians and neuropathologists.⁷ More cases of autopsy-confirmed CTAO with modern neuroimaging and neuropathologic features should be reported to clarify the pathogenesis and mechanism of this disease.

In conclusion, to the best of our knowledge, this is the first autopsy-proven CTAO case in South Korea. Even though most previously reported CTAO cases,¹² including 1 Korean case, presented with ischemic stroke with a history or evidence of peripheral Buerger disease, we suggest that clinicians should be aware of CTAO as one of differentials for young-onset vascular dementia, and that postmortem

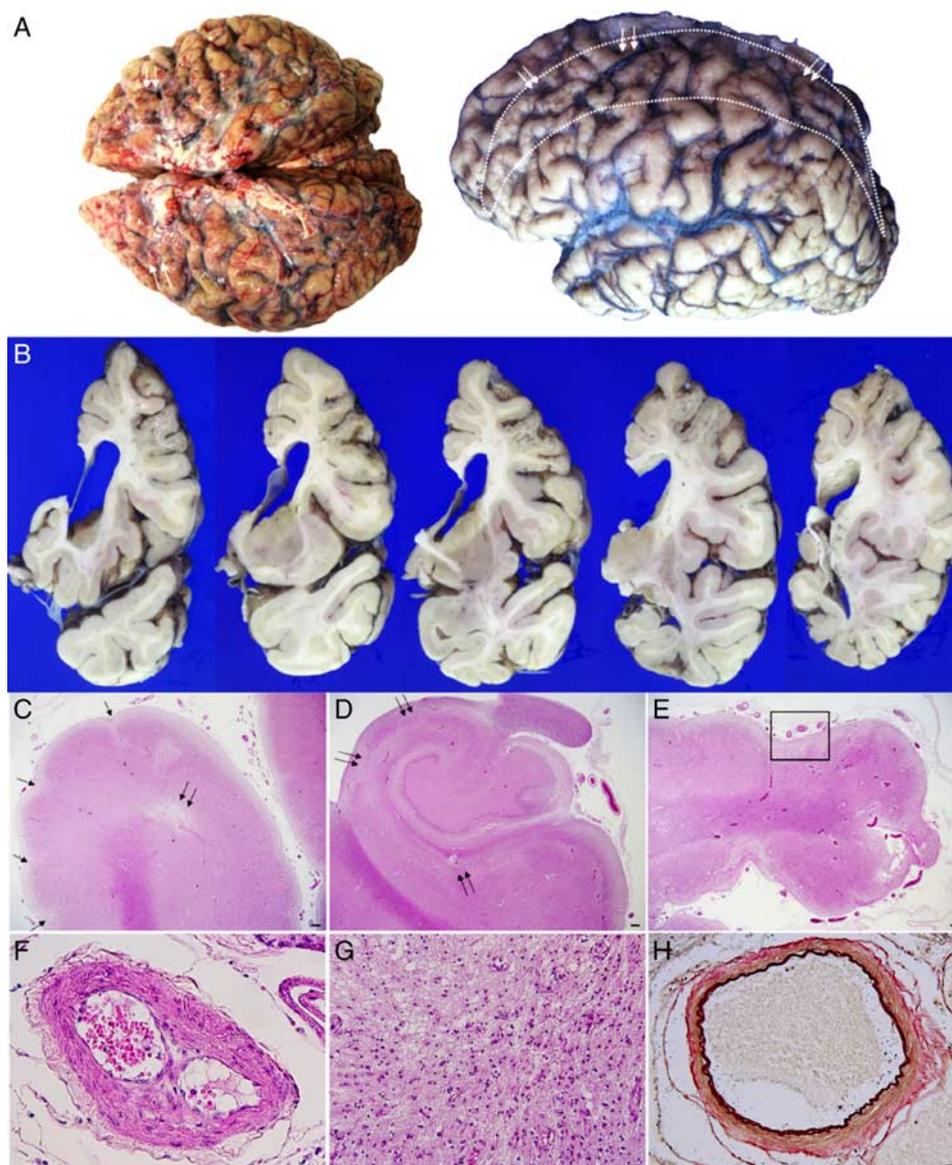


FIGURE 2. A, Sickle-shaped granular atrophy (dotted line) along the bilateral anterior cerebral artery-middle cerebral artery watershed areas (bilateral frontoparietal cortices, arrows) is seen. B, Remote cortical infarctions are noted in the frontal and parietal areas, which were the same parts seen in the lateral view. Moreover, atrophy in the frontal subcortical white matter and dilated frontal horn are observed. The temporal lobe, amygdala, and hippocampus are relatively preserved. C and D, Hematoxylin and eosin staining reveals multiple cortical microinfarctions (arrows) in the inferior frontal gyrus (C) and hippocampus (D) (scale bar = 250 μ m). E, Hematoxylin and eosin staining shows damaged frontal cortices due to multiple remote infarcts. The underlying white matter is severely affected showing rarefaction and extensive astrogliosis (scale bar = 250 μ m). F and G, Enlarged pictures of the rectangular area in (E). Leptomeningeal vessel showing lots of foamy macrophages, narrowing lumen, and recanalization (F, scale bar = 25 μ m). Infarcted area reveals severe vacuolation, astrogliosis, and neuronal loss (G, scale bar = 250 μ m). H, Intact media and internal elastic lamina are seen in a penetrating artery in basal ganglia (elastic stain, scale bar = 250 μ m). full color online

neuropathologic examination is critical for definitive diagnosis in a case with atypical presentation.

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