Danon Disease with Internal Carotid Artery Occlusion Showing Good Clinical Outcome Due to Robust Collaterals

Sir,

Danon disease is a rare genetic disease characterized by cardiomyopathy, Wolff–Parkinson–White syndrome, skeletal myopathy, retinopathy, hepatosplenomegaly, and foot deformity such as pes cavus and intellectual disability. Sudden cardiac death due to ventricular arrhythmia is a well-known cause of death in Danon disease. Patients with Danon disease have a significantly increased risk of atrial fibrillation (AF) and thromboembolic events. The embolic events could be attributed to AF due to depressed diastolic left ventricular function. Cerebrovascular events in patients with Danon disease are rarely reported, but are often fatal.[1-3] Here, we describe a patient with Danon disease complicated by the left proximal internal carotid artery (ICA) occlusion that showed a favorable outcome due to robust collateral circulations.

A 20-year-old woman with a history of Danon disease visited hospital due to right-sided weakness and global aphasia. She was genetically diagnosed with Danon disease 10 years ago owing to limb muscle wasting and progressive cognitive impairment. On neurological examination, she exhibited global aphasia, right-sided hemiparesis, and diffuse muscle wasting and spasticity in all extremities. Her National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) score was 20 and 4, respectively. Electrocardiogram revealed AF with rapid ventricular response and delta waves. Chest X-ray showed cardiomegaly with thoracic scoliosis. Transthoracic echocardiography demonstrated a severe left ventricular hypertrophy and depressed left ventricular ejection fraction of 23% [Figure 1 and Video]. Diffusion imaging of the brain revealed restricted diffusion in the left basal ganglia and insular cortex. The brain computed tomographic angiogram revealed occlusion of the left proximal ICA with faint blood flow from the M2 portion of the left middle cerebral artery, mainly supplied by the posterior cerebral artery (PCA) and leptomeningeal collaterals [Figure 2]. We initiated anticoagulants and inotropics to prevent additional cardioembolism and stabilize the ventricular function in the stroke unit for the prolonged monitoring her cardiac rhythm. Her neurological signs gradually improved to a fair degree of hemiparesis with paraphasic dysarthria. After 20 days, her NIHSS and mRS score improved to 7 and 2, respectively.

Recently, embolic events have been considered a complication of Danon disease.[1-3] We reviewed the literature and found reports on six patients with embolic complications in Danon disease, including our patient. Out of the six patients, three patients had cardioembolic stroke, one had hypoperfusion infarction, one had transient ischemic attack, and one had peripheral thromboembolism.[1-3] The two previously reported cardioembolic stroke patients with Danon disease demonstrated poor clinical outcome, and there was no report on the status of their collateral circulation [Table 1]; among them, one had a severe neurological deficit and died within 5 years following a stroke and the other died within 5 days following an embolic complication.[1] In our patient, however, the reperfusion effects of collaterals appeared to protect the cortical penumbra area, leading to a good outcome.

Some of the patients with Danon disease showed arterial medial hypertrophy of vascular smooth muscle cells. This can result in diffuse vascular narrowing or atherosclerosis of the vasculature.[4] However, the vasculature of our patient did not show diffuse narrowing or atherosclerotic changes of cerebral vessels except the left proximal ICA. It is difficult to completely exclude chronic arterial occlusion or *in-situ* thrombosis such as carotid stump syndrome; the presumed stroke mechanism of our patient may be cardioembolism. Further studies including pathological evaluations should be performed to establish the pathomechanism of vasculopathy in cerebral infarction associated with Danon disease.

Table 1: Summary of the published cases of Danon disease with embolic events

Series	S/A	EF	Symptoms	Embolic event	CHA_2DS_2-VASc score	Collaterals	Outcome
Spinazzi M *et al*. 2008	M/24	30%	Aphasia, RSW	CS	1	ND	Severe deficit
	M/22	20%	Aphasia, Dysphagia, RSW	CS	1	ND	Expire
	F/48	33%	leg pain	PE	3	ND	Mild deficit
Marino M. *et al*., 2016	F/28	20%	Visual loss	Hypoperfusion	1	ND	Mild deficit
Tsuda T *et al*., 2017	F/17	76%	Transient LSW, Headache, Photophobia	TIA	0	ND	Recovery
Present case	F/20	33%	Aphasia, RSW	CS	2	posterior cerebral Leptomeningeal	Mild deficit

S/A; sex/age, E/F; ejection fraction, ND; not described, RSW; right side weakness, LSW; left side weakness CS; cardioembolic stroke, PE; peripheral embolism, TIA; Transient ischemic attack

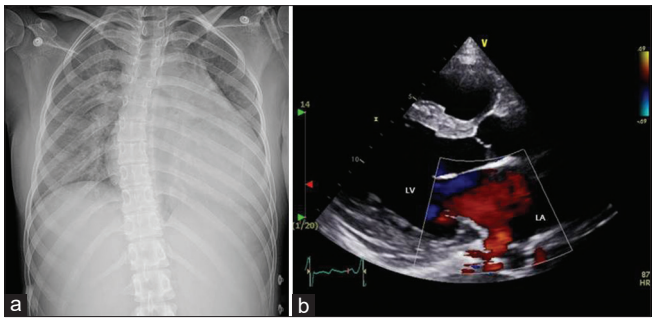

Figure 1: (a) Chest AP of the patient showed cardiomegaly and mild pulmonary congestion with scoliosis of the spine. (b) Parasternal long axis view of the transthoracic echocardiography of the patient shows an enlarged left atrium (LA), left ventricle (LV), and hypertrophied left ventricular wall

There has not been a controlled study of long-term anticoagulation among patients with dilated cardiomyopathy. The risk stratification of patients with dilated cardiomyopathy may help determine which patients will have the largest net clinical benefit from long-term anticoagulation.[5] We calculated the CHA_2DS_2-VASc score prior to embolic events of the six patients with Danon disease [Table 1].[4] Among them, three patients had the CHA_2DS_2-VASc score of 0 to 1, suggesting that no anticoagulation was recommended prior to embolic events. The majority of the patients with Danon disease appear to have an increased risk of AF, and oral anticoagulation therapy may be considered irrespective of the CHA_2DS_2-VASc score.[6]

The present case suggests that variable cerebral hemodynamic patterns can affect the prognosis of embolic complications in patients with Danon disease. To the best of our knowledge, this is the first documentation of Danon disease complicated by the left proximal ICA occlusion with the PCA and leptomeningeal collaterals resulting in a favorable outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Mi Young Lee, Bon D. Ku[1], Sang Joon An[1], Hyeyun Kim[1], Su-Jin Lee[1], Yeongln Kim[1]

Catholic Kwandong University College of Medicine, Incheon, South Korea, [1]Department of Neurology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, South Korea

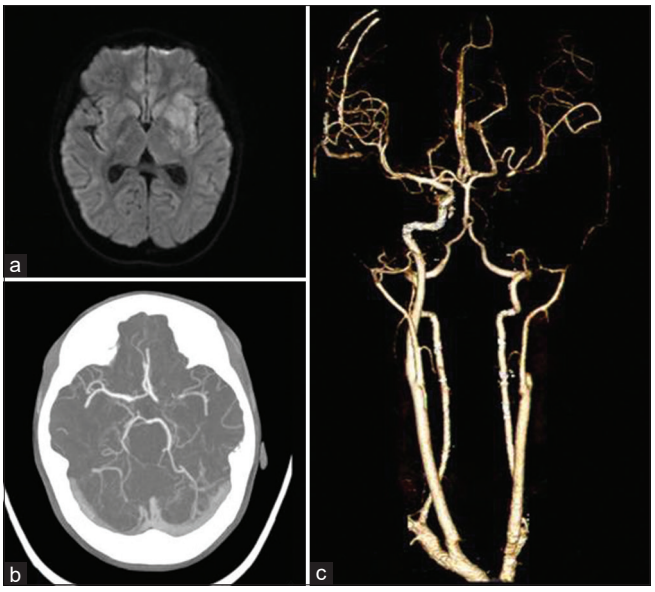

Figure 2: (a) Brain diffusion magnetic resonance image reveals a restricted diffusion area in the left basal ganglia and insular cortex (arrow). (b) Enhanced brain computed tomography (CT) image reveals the left posterior cerebral and leptomeningeal collaterals. (c) CT angiogram reveals occlusion of the left proximal ICA with blood flow from the posterior cerebral and leptomeningeal collaterals

Address for correspondence: Prof. Bon D. Ku, Department of Neurology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, 25, Simgok-ro 100beon-gil, Seo-gu, Incheon - 22711, South Korea.
E-mail: bondku34@cku.ac.kr

References

1. Spinazzi M, Fanin M, Melacini P, Nascimbeni AC, Angelini C, *et al*. Cardioembolic stroke in Danon disease. Clin Genet 2008;73:388-90.
2. Marino M, Musumeci O, Paleologo G, Cucinotta M, Migliorato A, Rodolico C, *et al*. A. Ischemic stroke due to hypoperfusion in a patient with a previously unrecognized Danon disease. Neuromuscul Disord 2016;26:890-94.
3. Tsuda T, Shillingford AJ, Vetter J, Kandula V, Jain B, Temple J. Transient ischemic attack and ischemic stroke in Danon disease with formation of left ventricular apical thrombus despite normal systolic function. Case Rep Pediatr 2017;2017:6576382.
4. Sugie K, Komaki H, Eura N, Shiota T, Onoue K, Tsukaguchi H, *et al*. A nationwide survey on Danon disease in Japan. Int J Mol Sci 2018;19:pii: E3507. doi: 10.3390/ijms19113507.
5. Koniaris LS, Goldhaber SZ. Anticoagulation in dilated cardiomyopathy. J Am Coll Cardiol 1998;31:745-8.
6. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, *et al*. Selecting patients with atrial fibrillation for anticoagulation: Stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287-92.

Video available on: www.annalsofian.org

DOI: 10.4103/aian.AIAN_244_19