A Study of Seven Patients with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts qnd Leukoencephalopathy (CADASIL) in Eastern Taiwan: A Case Series with Literature Review

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Abstract

Purpose: CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is the most common cause of heritable vascular dementia. Recognizing the disease before the full-blown clinical features is challenging, so our case series high light clinical characteristics, screening tools and diagnostic process of the patients with CADASIL.

Case report: Our case series reports neurocognitive features, neuroimaging, and exemplary pedigrees of seven patients with genetically confirmed CADASIL, in which six patients presented with dementia and the other one presented with migraine.

Conclusion: Our report is the single-center experience of our hospital in eastern Taiwan, where access to medical care and genetic test is relatively limited compared to other parts of Taiwan. We had also compared the utility of Davous' CADASIL criteria and the CADASIL scale, and both can be used as sensitive screening tools before genetic tests, especially in the area with limited medical access.

Keywords: Stroke, Dementia, Neuroimaging, CADASIL, NOTCH 3 mutation

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INTRODUCTION

CADASIL refers to hereditary microangiopathy in relatively younger individuals manifesting with recurrent strokes and progressive cognitive impairment. Recognizing the disease before the full-blown clinical features is challenging. Our case series reports the single-center experience of our hospital in eastern Taiwan. We assessed the clinical characteristics of the patients and reviewed the utility of Davous' criteria and CADASIL scale as screening tools before genetic tests.

CASE SERIES REPORT

We presented seven patients with genetically confirmed CADASIL, who were assessed, diagnosed, and

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followed up at the dementia clinic in our hospital between 2014 to 2020. We retrospectively evaluated them with Davous' CADASIL criteria and CADASIL scale.

All seven patients were ethnically Han Chinese, from five families living in Eastern Taiwan. The age of onset was ranging from 41 to 60. All had no or well-controlled vascular risk factors. All except patient-5 had a familial history of stroke or cognitive impairment. Except for patient-2, all other patients had step-wise cognitive impairment, mood disorders, personality changes, and radiologic evidence of subcortical ischemic events. Patient-2 and 4 had migraines. The patient-5 could not recount the symptomatic stroke, and two patients had symptomatic intracerebral hemorrhages (ICH).

The patient-4 had heterozygous NOTCH 3 gene mutation at exon 14 (c.2149 C>T, p.R717C), and the other six patients had heterozygous NOTCH 3 gene mutation at exon 11 (c. 1630 C>T, p.R544C).

All patients except patient-2 were categorized as positive in Davous' criteria and the CADASIL scale. The clinical and neurocognitive details of the patients were in table-1 [Table-1]. Representative neuroimaging was shown in the attached figures [Figure-1]. We described the pedigrees of the two exemplary families in pedigree-1 and 2 [Pedigree-1, Pedigree-2].

Table 1. Details of clinical characteristics, neurocognitive status, the status of concurrent vascular disease, risk factors, Davous' CADASIL criteria, and CADASIL scale of the patients

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7
Clinical Characteristics of the patients							
Age of symptom onset	58	Migraine since young age	41	51	60s	58	55
Sex	Female	Female	Female	Male	Female	Male	Female
Year of diagnosis for NOTCH 3 mutation	2014	2014	2017	2015	2017	2020	2020
Gene locus	c.1630C>T p.R544C	c.1630C>T p.R544C	c.1630C>T p.R544C	c.2149C>T p. R717C	c.1630C>T p.R544C	c.1630C>T p.R544C	c.1630C>T p.R544C
Education level	University graduate	University graduate	High School Level	Occupational School graduate	Primary School-level	High School level	High School level
Ethnicity	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese
Clinical Stroke/TIA	+	-	+	+	-	+	+
History of Epilepsy or seizure	+	-	-	+	-	-	+
multiple microbleeds in MRI	-	-	+	+	-	+	+
History of Symptomatic ICH	-	-	+ basal ganglia and thalamus	-	-	+ thalamus	-
Neurocognitive status of the patients							
Attention and orientation	Impaired	Mildly poor attention	Impaired	Impaired	Impaired	Impaired	impaired

Table 1. Details of clinical characteristics, neurocognitive status, the status of concurrent vascular disease, risk factors, Davous' CADASIL criteria, and CADASIL scale of the patients (Continue)

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7
Memory	Impaired short-term memory and category fluency. Preserved long-term memory.	Preserved	Impaired short-term and category fluency. Relatively preserved long term memory	Impaired short-term and long-term memory, especially in semantic and episodic memory.	Impaired short-term memory.	Relatively preserved.	Impaired attention, short-term and long-term memory.
Visuospatial executive function	Mildly impaired	Preserved	Impaired	Impaired	Impaired	impaired	impaired
Linguistic function	Impaired	Preserved	Impaired	Impaired	Impaired	Relatively preserved	impaired
Abstraction and judgment	Preserved	Preserved	Impaired	Impaired	Impaired	Markedly impaired	Markedly impaired
CASI before or at the time of diagnosis (year of assessment)	89 (2014†)	92 (2014†)	44 (2015†)	18.3 (2009†)	43 (2017†)	56 (2019†)	Could not cooperate (2014†)
CASI at follow-up	71 (2017†)	91 (2015†)	Could not cooperate	Could not cooperate	42 (2019†)	42 (2020†)	Could not cooperate (2020†)
MMSE at the time of diagnosis	28 (2014†)	29 (2014†)	12 (2015†)	6 (2009†)	11 (2017†)	15 (2019*)	4 (2014†)
MMSE at follow- up	20 (2017†)	30 (2015†)	Could not cooperate	Could not cooperate	9 (2019†)	12 (2020†)	Could not cooperate (2020†)
CDR before or at the time of diagnosis	0.5 (2014†)	0 (2014†)	2 (2015†)	2 (2008†)	2 (2017†)	1 (2019†)	3 (2014†)
CDR at follow-up	1 (2017†)	0 (2015†)	2 (2015†)	3 (2015†)	2 (2019†)	2 (2020†)	3 (2020†)
Status of concurrent vascular diseases and risk factors							
Coronary artery diseases	-	-	-	-	-	-	-
Patency of major vessel in brain MRI	Patent	Patent	Patent	Patent	Patent	Patent	Patent
Hypertension	+	+	+	-	-	+	+
Smoking	-	-	-	+	-	-	-
Hyperlipidemia	-	-	-	-	+	+	-
Diabetes mellitus	-	-	-	-	+	+	-
Davous' CADASIL criteria‡							
Age of onset	58	Young adult	41	51	60s	58	55

Table 1. Details of clinical characteristics, neurocognitive status, the status of concurrent vascular disease, risk factors, Davous' CADASIL criteria, and CADASIL scale of the patients (Continue)

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7
Clinical findings (at least two of them)	+	-	+	+	-	+	+
Stroke like episodes	-	+	-	+	-	-	-
Migraine							
Major mood disturbances	+	-	+	+	+	+	-
Dementia§	+	-	+	+	+	+	+
Vascular risk factor	-	-	-	Mild	Mild	Mild	Mild
Family history	+ AD pattern	+ AD pattern	+ Not typical for AD pattern	+ Not typical for AD pattern	-	+ AD pattern	+ AD pattern
White matter changes in MRI	Typical lesions	Normal	Typical lesions	Typical lesions	Typical lesions	Typical lesions	Typical lesions
Clinical probability of CADASIL according to Davous' CADASIL criteria	Possible CADASIL	Negative	Probable CADASIL	Possible CADASIL	Possible CADASIL	Possible CADASIL	Possible CADASIL
CADASIL scale¶							
The score for clinical characteristics	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7
1 for Migraine	-	+	-	+	-	-	-
3 for migraine with aura	-	+	-	-	-	-	-
1 for TIA or Stroke	+	-	+	+	-	+	+
2 for TIA or Stroke onset ≤50 years of age	-	-	-	-	-	-	-
1 for Psychiatric disturbances	+	-	+	+	+	+	-
3 for Cognitive decline/ dementia	+	-	+	+	+	+	+
3 for leukoencephalopathy	+	+	+	+	+	+	+
1 for leukoencephalopathy extended to the temporal pole	-	-	+	+	+	+	+
5 for Leukoencephalopathy extended to the external capsule	+	-	+	+	+	+	+
2 for Subcortical infarcts	+	-	+	+	+	+	+

Table 1. Details of clinical characteristics, neurocognitive status, the status of concurrent vascular disease, risk factors, Davous' CADASIL criteria, and CADASIL scale of the patients (Continue)

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7
1 for Family history in at least 1 generation	+	+	+	+	-	+	+
2 for Family history in at least 2 generation	-	+	-	+	-	+	-
Total score	16	9	17	20	15	19	16

The patients were serial- numbered according to the date of genetic diagnosis.

†Year of assessment ‡Davous' CADASIL criteria

Exclusion criteria: age at onset >70 years of age, severe vascular risk factors, absence of any other cases in documented pedigree.

Probable CADASIL: Age of onset <50 years of age, at least two of clinical findings, no vascular risk, AD pattern family history, and typical white matter changes in MRIs.

Possible CADASIL: 50 to 70 years of age, at least two of less severe clinical findings, mild vascular risk, unknown or incomplete family history, atypical MRI findings.

A definitive diagnosis is by the genetic test.

§ In the original Davous' CADASIL criteria, dementia was classified into subcortical dementia for probable CADASIL and global dementia for possible CADASIL. Nevertheless, in our patients with dementia, both showed subcortical and cortical components.

¶ CADASIL scale: The total score of the CADASIL scale (ranging from 0 to 25) is obtained from the sum of each variable's score. A total score of ≥ 15 is predictive of CADASIL diagnosis and the need for a genetic test.

Footnote: At the time of genetic diagnosis in 2014, the patient-2 was 56 years of age, and she had regular follow-up at our clinic until 2019 December. As the patient-1,2 and 7 were siblings, our clinic still had informal contact with her through families of patient-1 and7 until recently. Apart from migraine history, she had no other CADASIL-related symptoms throughout the follow-up. MRI (brain) was performed at the time of genetic diagnosis for NOTCH 3 mutation, and MRI (brain) only revealed mild white matter changes in the periventricular white matter area. Formal CASI, MMSE, and CDR were assessed two times in 2014 and 2015, respectively, as mentioned above.

Abbreviations:

CASI: The Cognitive Abilities Screening Instrument, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, MRI: magnetic resonance imaging, ICH: intracerebral hemorrhage, AD: autosomal dominant

DISCUSSION

Our report is a case series of seven patients with CADASIL who had confirmed NOTCH 3 mutations. CADASIL is an autosomal dominant inherited disease of small cerebral arteries that affects middle-aged adults leading to neurocognitive impairments, subcortical strokes, migraines, and mood disorders [1,2,3]. There are a few de novo mutations [1]. Migraine is less frequent in Taiwanese patients [3].

Vascular dementia, which accounts for 16% of all dementia cases, is the second most common cause of neurocognitive impairment after Alzheimer's disease; CADASIL is the most common heritable cause of vascular dementia, which accounts for 2% of cases of lacunar stroke with leucoaraiosis in patients younger than 65 years and 11% of cases in those younger than 50 years [1,2].

Mutations of the NOTCH3 gene on chromosome 9 causing CADASIL was first reported in 1996 [1], and Taiwan reported its first case in 2004 [1,2].

NOTCH3 has 33 exons, but all CADASIL mutations occur in exons 2–24, which encode the 34 epidermal growth factor repeats (EGFR). All mutations lead to an altered odd number of cysteine residues in EGFR, leading to disrupted conformation, which causes deposition of granular osmophilic material (GOM) in close relation to vascular smooth muscle cells [1,3,5,6].

NOTCH3 mutations most commonly occur in exon 4 in United Kingdom, France, and Germany [3]. However, mutation of p.R544C in exon 11, characterized by the

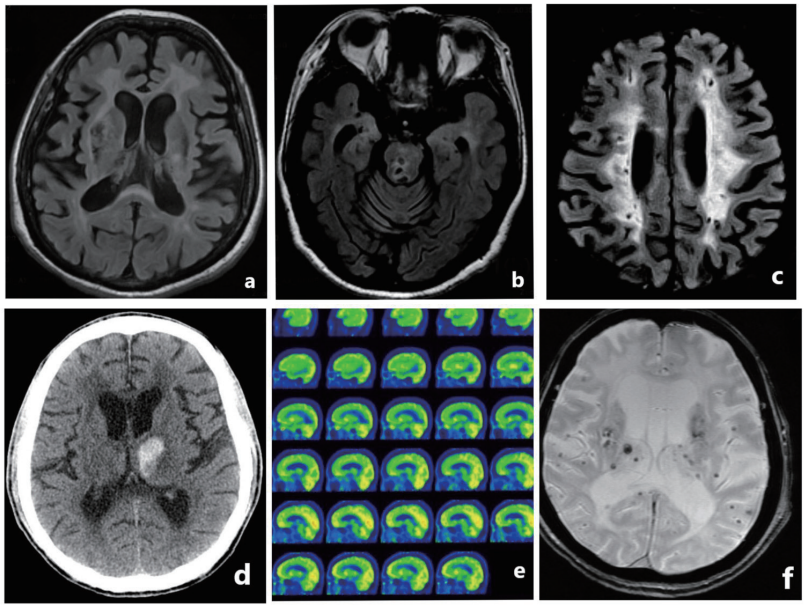


Figure 1. Representative neuroimaging of the patients. Figure- 1(a) T2 Fluid-attenuated inversion recovery (FLAIR) of magnetic resonance imaging (MRI) of the brain from patient-3 revealed white matter lesions (WMLs) with the involvement of external capsules. Figure-1(b)T2 FLAIR of the same patient's MRI brain also showing white matter lesion extending to anterior temporal pole. Figure-1(c) T2 FLAIR of MRI brain of patient-6 revealing severe white matter lesions, encephalomalacia, and brain atrophy. Figure-1(d) computed tomography (CT) brain without contrast of the same patient showing symptomatic intracerebral hemorrhage at left thalamus. Figure-1(e) the cerebral fluorodeoxyglucose-positron emission tomography (FDG PET) brain image of the same patient revealed decreased FDG uptake over the frontal cortex, insular region, anterior temporal cortex as well as right thalamus. Figure-1(f) multi-echo gradient recalled echo (GRE) T2*-weighted imaging of MRI brain revealed multiple microbleeds in patient-7 who never had a symptomatic intracerebral hemorrhage.

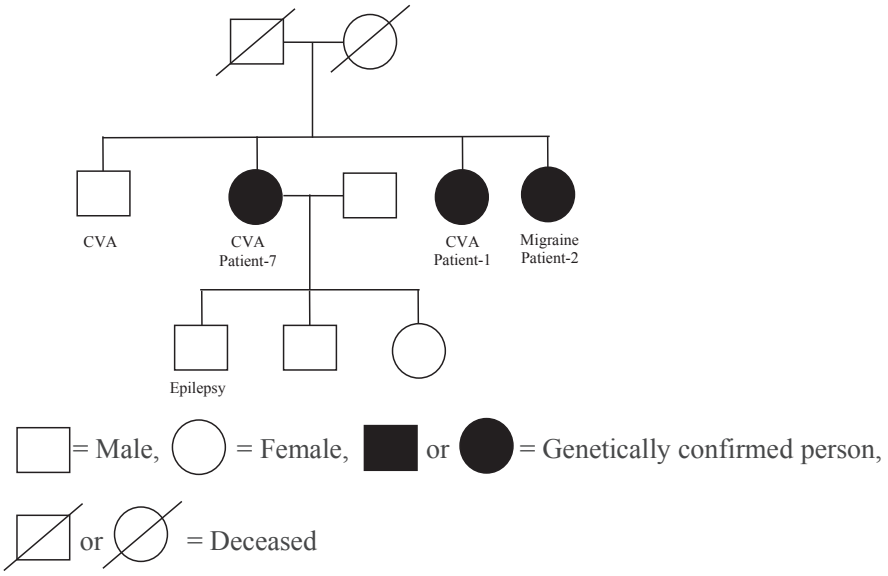
relatively late-onset but more common occurrence of cognitive decline and family history of dementia, accounts for the majority of CADASIL subjects (70%) in Taiwan, and only 1% carry p.R717C mutation in exon 14 [3,4]. Mutations in our patients reflect Taiwanese data; six out of seven patients had a mutation at p.R544C, and one patient had a mutation in p.R717C.

Transient ischemic attacks and ischemic strokes account for the most common presentations, occurring in 60–85% of clinical presentations [1]. Six patients in our study had evidence of ischemic strokes or TIA. Conventional vascular risk factors also have contributing role in Taiwanese CADASIL patients with stroke [4].

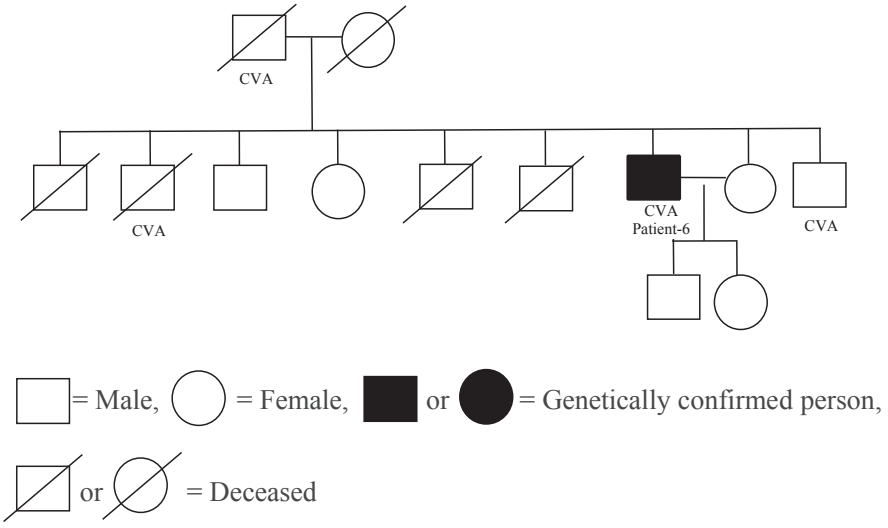
Four of our patients had multiple cerebral microbleeds (CMB), in which two patients also got symptomatic cerebral hemorrhage. CMB was present in about two-thirds of the patients with CADASIL. Multiple microbleeds (≥ 9) are significantly associated with intracerebral hemorrhagic (ICH). The number of CMB reflects functional dependency [7], and microbleeds also had two times increased risk of ischemic stroke [5]. 13.6% of patients with p.R544C mutation in Taiwan had ICHs [4]. Nevertheless, in Taiwan, ICH incidence does not differ between the R544C mutation and non-R544C mutation groups [3]. ICH was rarely reported in Caucasian patients [7].

Although previous reports revealed the proportion of moderate or severe white matter lesions in the anterior temporal pole is significantly lower in the R544C group [3], four of our patients showed white matter lesions extending to the anterior temporal region.

Genetic testing is the diagnostic test for CADASIL



Pedigree-1. Family trees of patient-1,2 and 7 (for patient identities, we have omitted details of unaffected offspring and partners). The patient-2 does not have a neurocognitive problem. The parents of the patient did not have a history of stroke or dementia.



Pedigree-2. Family trees of patient-6 (for patient identities, we have omitted details of unaffected offspring and partner).

with nearly 100% specificity and sensitivity [1,6]. A skin biopsy should be reserved for those with negative genetic tests with typical clinical and radiological findings and those with new variant mutations [1]. The finding of GOM and irregular, smooth muscle cells of small vessels on electron microscopy of skin biopsy is pathognomonic, but it has variable sensitivity [1,5,6]. NOTCH3 monoclonal antibody staining of skin samples can reveal the accumulation of NOTCH3 protein in the vessel wall, and it shows high sensitivity and specificity[1].

As the analysis of the NOTCH3 gene is costly and time-consuming, pre-genetic screening is needed

especially in the area with relatively limited access to genetic diagnosis. We had assessed Davous' CADASIL criteria and CADASIL scale in every patient [8,9]. Apart from patient-2, other patients have CADASIL scale scores of at least 15 or possible/probable results in Davous' criteria, which fulfilled the predictive criteria for selecting NOTCH 3 gene analysis.

The average age of onset in Taiwanese patients was 54 years of age, older than the global average, while males were slightly predominant [3]. Davous' criteria originally differentiated dementia into subcortical and global, but our patients with neurocognitive impairment showed mixed patterns. CADASIL scale is more straightforward, inclusive, and more applicable to our patients. The new diagnostic criteria for CADASIL were recently introduced in Japan [9]. Its criteria emphasize the white matter lesions involving temporal poles by MRI or CT along with clinical and genetic, and/or pathological criteria. Although this new diagnostic criteria for CADASIL showed high sensitivity (97.1%), it had very low specificity (7.5%)[9], and it is not yet widely validated outside of Japan.

There is no disease-modifying agent for CADASIL [1,7], although some suggest cholinesterase inhibitors and aspirin for secondary prevention [2,5,6,7].

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Declaration of patient consent:

Authors certify that the patients had provided signed informed consent.

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Conflicts of interest: Nothing to declare

REFERENCES

1. Coutinho JM, Zuurbier SM, Stam J. Declining mortality in cerebral venous thrombosis: a systematic review. Stroke. 2014;45(5):1338-41.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418.
3. Viegas LD, Stolz E, Canhao P, Ferro JM. Systemic thrombolysis for cerebral venous and dural sinus thrombosis: a systematic review. Cerebrovasc Dis. 2014;37(1):43-50.
4. Tsivgoulis G, Zand R, Katsanos AH, Goyal N, Uchino K, Chang J, et al. Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis. Stroke. 2015;46(5):1281-7.
5. Osborn AG, Hedlund G, Salzman KL. Venous Anatomy and Occlusions. In: Concannon KE, editor. Osborn's Brain. Salt Lake City, UT: Elsevier; 2017. p. 253-76.
6. Buyck PJ, Zuurbier SM, Garcia-Esperon C, Barboza MA, Costa P, Escudero I, et al. Diagnostic accuracy of noncontrast CT imaging markers in cerebral venous thrombosis. Neurology. 2019;92(8):e841-e51.
7. Dentali F, Squizzato A, Marchesi C, Bonzini M, Ferro JM, Ageno W. D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature. J Thromb Haemost. 2012;10(4):582-9.
8. Ohara T, Farhoudi M, Bang OY, Koga M, Demchuk AM. The emerging value of serum D-dimer measurement in the work-up and management of ischemic stroke. Int J Stroke. 2019: 1747493019876538.
9. Saposnik G, Barinagarrementeria F, Brown RD, Jr., Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.
10. Ferro JM, Bousser MG, Canhao P, Coutinho JM, Crassard I, Dentali F, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10):1203-13.

11. Ferro JM, Bacelar-Nicolau H, Rodrigues T, Bacelar-Nicolau L, Canhao P, Crassard I, et al. Risk score to predict the outcome of patients with cerebral vein and dural sinus thrombosis. Cerebrovasc Dis. 2009;28(1):39-44.
12. Cai H, Ye X, Zheng W, Ma L, Hu X, Jin X. Pitfalls in the diagnosis and initial management of acute cerebral venous thrombosis. Rev Cardiovasc Med. 2018;19(4):129-33.
13. Misra V, Elliott DG, Gonzalez-Toledo E, Kelley RE. Demonstration of significant resolution of cerebral sino-venous thrombosis associated with intravenous recombinant tissue plasminogen activator. J Neuroimaging. 2007;17(4):348-9.
14. Piazza G. Cerebral venous thrombosis. Circulation. 2012;125(13):1704-9.
15. Vandelli L, Marietta M, Gambini M, Cavazzuti M, Trenti T, Cenci MA, et al. Fibrinogen decrease after intravenous thrombolysis in ischemic stroke patients is a risk factor for intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2015;24(2):394-400.