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Intravenous Thrombolytic Therapy in Acute Ischemic Stroke: The Experience of Kütahya

Akut İskemik İnmede İntravenöz Trombolitik Tedavi: Kütahya Deneyimleri

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Abstract

Objective: Stroke is a serious cause of mortality and disability. The caregiver of the patients may be adversely affected by this situation as well. In addition, stroke has a great economic burden on healthcare. Significant improvement has been achieved in the field of diagnosis, treatment, and care in the acute phase of the ischemic stroke in recent years. Thrombolysis with intravenous (IV) recombinant tissue type plasminogen activator (r-tPA) is the main treatment option in selected patients. The aim of our study was to share the results of intravenous (IV) thrombolytic therapy applied to patients with acute ischemic stroke in our clinic.

Materials and Methods: We evaluated the clinical data of 52 patients who were admitted to our clinic with ischemic stroke within the first 4.5 hours after onset of stroke symptoms, and were treated with IV thrombolytic therapy, between the May 2014 and June 2016. Demographic characteristics and clinical data were recorded.

Results: Twenty-three of the patients were male and 29 were female. The mean age was 70.7±12.8 years (range, 41-92 years). Intracranial hemorrhage after treatment was observed in 8 patients (15.4%). Of these, 6 patients (11.5%) had asymptomatic hemorrhage, 2 patients (3.8%) had symptomatic hemorrhage. The mean score of modified Rankin Scale (mRS) was 0-1 in 16 (30.8%) patients, 2-3 in 10 (19.2%) patients, and 4-5 in 13 (25%) patients. The mean mRS score of 7 (20%) patients with total anterior circulation infarct was 0-1. The mean mRS score of 8 (57.1%) patients with partial anterior circulation infarct was 0-1. Thirteen (25%) patients died within 3 months of the treatment.

Conclusion: Intravenous thrombolytic therapy is an effective and safe treatment that is easy to administer within 4.5 hours in patients with acute ischemic stroke. This treatment increases the number of ambulatory patients and reduces disability in selected patients.

Keywords: Acute ischemic stroke, thrombolytic therapy, disability

Öz

Amaç: İnme ciddi derecede mortalite ve sakatlık sebebidir. Hastanın yanındaki bakım verenler de bu durumdan olumsuz etkilenir. Aynı zamanda sağlık ekonomisi üzerine büyük bir yük oluşturur. Son yıllarda iskemik inmeli hastaların akut dönemde tanı, tedavi ve bakımları açısından önemli gelişmeler kaydedilmiştir. Rekombinant doku plazminojen aktivatörünün (r-tPA) kullanıldığı intravenöz (İV) trombolitik tedavi bunlar arasındadır. Çalışmamızın amacı akut iskemik inmeli hastalarda, kliniğimizde uyguladığımız İV trombolitik tedavi sonuçlarını paylaşmaktır.

Gereç ve Yöntem: Mayıs 2014 ve Haziran 2016 yılları arasında inme semptomlarının başlamasından ilk 4,5 saat içerisinde kliniğimize başvuran, iskemik inme tanısı alan ve İV trombolitik tedavi uygulanan 52 hastanın klinik verileri retrospektif olarak incelendi. Demografik özellikler ve klinik veriler kaydedildi.

Bulgular: Çalışmaya alınan 52 hastanın 23'ü erkek 29'u kadın ve hastaların yaş ortalamaları 70,7±12,8 (aralık, 41-92) idi. Tedavi sonrası 8 hastada (%15,4) intrakraniyal kanama gözlendi. Bunlardan 6'sında (%11,5) asemptomatik, 2'sinde (%3,8) semptomatik kanama saptandı. On altı hastanın (%30,8) 3 ay sonraki

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modifiye Rankin Skalası (mRS) skoru 0-1, 10 hastanın (%19,2) mRS skoru 2-3, 13 hastanın (%25) mRS skoru 4-5 idi. Total anterior sirkülasyon infarktı olan 7 hastada (%20) mRS skoru (0-1), parsiyel anterior sirkülasyon infarktı olan 8 hastada (%57,1) mRS skoru 0-1 tespit edildi. Tedavi sonrası 3 aylık dönemde 13 hasta (%25) kaybedildi.

Sonuç: Akut iskemik inmede ilk 4,5 saatte r-tPA ile İV trombolitik tedavi kolay uygulanır, etkili ve güvenli bir tedavidir. Uygun hasta seçimi ile inme sonucu gelişebilecek sakatlık azaltılabilir ve bağımsız yaşayan hasta sayısı arttırılabilir.

Anahtar Kelimeler: Akut iskemik inme, trombolitik tedavi, sakatlık

Introduction

More than 80% of strokes are ischemic (1). In developed countries, acute ischemic stroke is the third most common cause of death following coronary artery disease and cancer (2). It is the most common cause of disability in adults. Expensive and long-term rehabilitation is required after stroke (1,3). For this reason, treatment of stroke in the acute phase is of great importance. Infarct formation occurs in minutes in the center of the arterial territory after occlusion of the cerebral artery. In the periphery, there is an area called "penumbra" where there is no irreversible cell death due to collateral circulation. This is the main target in the acute treatment of ischemic stroke. The goal is to recanalize the occluded artery and ensure timely reperfusion. One of the treatment strategies applied in the last 20 years is intravenous (IV) thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA). The efficacy of IV thrombolytic therapy within the first 3 hours has been demonstrated in patients with acute ischemic stroke in the National Institute of Neurological Disorders and Stroke (NINDS) study in 1995 (4). Intravenous r-tPA was approved by the Food and Drug Administration in 1996 in the United States and has been widely accepted (5). It is currently recommended that this treatment could be used within 4.5 hours after the onset of acute ischemic stroke (6). In Turkey, the drug was licensed in 2006 for use in acute ischemic stroke. From this date on, the application of IV thrombolytic therapy in our country has become increasingly widespread. However, it is still not at the desired level. The aim of our study was to investigate the patients who were admitted to our clinic between May 2014 and June 2016 with acute ischemic stroke and were treated with IV thrombolytic therapy within the first 4.5 hours after the onset of symptoms and to discuss the results in light of the literature.

Materials and Methods

We retrospectively reviewed the clinical data of 52 patients who were admitted to our clinic between May 2014 and June 2016 with acute ischemic stroke and were treated with IV thrombolytic therapy within the first 4.5 hours after the onset of symptoms. All patients were questioned according to the recommendations of the American Heart Association (AHA)/American Stroke Association guidelines 2013 (7) (Guidelines for the Early Management of Patients with Acute Ischemic Stroke) for inclusion and contraindication prior to thrombolytic therapy. Demographic and clinical features of patients who received 0.9 mg/kg (maximum 90 mg) IV r-tPA (alteplase) (10% of the calculated total dose as IV bolus and the remaining as infusion in 1 hour) were recorded, ischemic stroke classification was performed according to clinical features, and those who had computerized tomography scans before and 24 hours after treatment, and if necessary, afterwards, were included in the study. Intracranial hemorrhage causing impairment in the general condition was reported as "symptomatic", and incidentally detected hemorrhage in control scans as "asymptomatic". Intracranial hemorrhage within the first 36 hours after treatment was evaluated as an r-tPA complication. The neurologic disability of the patients after 3 months of treatment was assessed by using modified Rankin Scale (mRS) scores.

The study was approved by the Dumlupinar University of Local Ethics Committee (Decision no: 2017-9/6). Consent form was filled out by all participants.

Statistical Analysis

The mean pre- and post-treatment National Institutes of Health Stroke Scale (NIHSS) scores of all patients, symptom/needle (SN) time, and mean pre- and post-treatment NIHSS scores in patients with and without hemorrhage, and survivors and non-survivors were statistically compared.

Statistical analyses were performed using SPSS 24.0. The paired t-test was used for the comparison of means in the dependent groups, and parametric data and the non-parametric data were compared using the t-test and Mann-Whitney U test, respectively, in the independent groups.

Results

Of the 52 patients who were included in the study, 23 were male and 29 were female. The mean age was 70.7±12.8 years (range, 41-92 years). The symptom/door time was 76.7±41.6 min (range, 20-180 min), the door/needle (DN) time was 72.2±28.7 min (range, 20-135 min), and the SN time was 148.9±42.4-270 min. According to clinical features, patients were classified as follows: partial anterior circulation infarct (PACI) in 14 (26.9%) patients, total anterior circulation infarct (TACI) in 35 (67.3%) patients, posterior circulation infarct (POCI) in 1 (1.9%) patient, POCI + TACI in 1 (1.9%) patient, and lacunar infarct in 1 (1.9%) patient. Intracranial hemorrhage was observed in 8 (15.4%) patients after treatment. Asymptomatic bleeding was detected in 6 (11.5%) and symptomatic bleeding in 2 (3.8%). The mean mRS score at 3 months was 3.17±2.2 for all patients studied. The 3rd month mRS scores of 16 (30.8%) patients were 0-1, 10 (19.2%) patients were 2-3, and 13 (25%) patients were 4-5. Seven (20%) patients with TACI and 8 (57.1%) patients with PACI had a mRS scores of 0-1. Thirteen (25%) patients died after 3 months of treatment. The demographic and clinical characteristics of the patients are presented in Table 1. There were 4 (50%) patients with hemorrhage in the TACI group and 4 (50%) in the PACI group. The mean SN time and mean pre- and post-treatment NIHSS scores of patients with hemorrhage were 170±56.37 min,

14.50±5.01 (8-22), and 12.37±7.81 (1-22), respectively. The mean SN for patients without hemorrhage was 145.11±39.03 min, and the mean pre- and post-treatment NIHSS scores were 16.25±6.00 (5-26) and 12.52±7.45 (0-26), respectively. Both symptomatic patients with hemorrhage were in the TACI group and pre-treatment NIHSS scores were 22. Two (15%) non-survivors were in the PACI group and 11 (85%) were in the TACI group. The mean SN time for non-survivors was 136.15±32.79 min, and the mean pre- and post-treatment NIHSS scores were 18.53±5.29 (8-25) and 18.38±5.51 (6-26), respectively. The mean SN time for survivors was 153.20±44.78 min, and the mean pre- and post-treatment NIHSS scores were 15.12±5.96 (5-26) and 10.53±6.98 (0-22), respectively.

Mean pre- and post-treatment NIHSS scores of all patients, SN time, and mean pre- and post-treatment (24th hour) NIHSS scores in hemorrhagic and non-hemorrhagic patients, and survivors and non-survivors were compared. There was statistical significance between the mean post-treatment NIHSS scores of survivors and non-survivors ($p<0.05$). In addition, the mean pre- and post-treatment NIHSS scores of all patients were 15.9±5.8 (5-26) and 12.5±7.4 (0-26), respectively, and a comparison revealed a statistically significant decrease in the post-treatment scores ($p<0.05$) (Table 2).

Table 1. Demographic and clinical features

Age, mean ± SD (years)	70.7±12.8 (41-92)
Sex, n (%)	
Male	23 (44.2)
Female	29 (55.8)
Infarct type, n (%)	
TACI	35 (67.3)
PACI	14 (26.9)
POCI	1 (1.9)
POCI + TACI	1 (1.9)
Lacunar infarct, n (%)	1 (1.9)
Minute, mean ± SD, (min.-max.)	
Symptom/door time	76.7±41.6 (20-180)
Door/needle time	72.2±28.7 (20-135)
Symptom/needle time	148.9±42.4 (60-270)
Intracranial hemorrhage, n (%)	8 (15.4)
Symptomatic	2 (3.8)
Asymptomatic	6 (11.5)
3rd month mRS, mean ± SD	3.17±2.2
TACI mRS (0-1), n (%)	7 (20)
PACI mRS (0-1), n (%)	8 (57.1)
Total mRS (0-1), n (%)	16 (30.8)
Mortality, n (%)	13 (25)

n=52 patients, SD: Standard deviation, TACI: Total anterior circulation infarct, PACI: Partial anterior circulation infarct, POCI: Posterior circulation infarct, mRS: Modified Rankin Scale, min.: Minimum, max.: Maximum

Discussion

The primary aim of thrombolytic therapy is thrombus dissolution and maintenance of cerebral blood flow by recanalization. It was demonstrated in the NINDS study that IV r-tPA treatment was beneficial within the first 3 hours after stroke onset (4). The European Cooperative Acute Stroke Study 3 (ECASS 3), published in 2009, showed that IV r-tPA treatment within 3-4.5 hours was also effective (8). Following this study, the administration time of IV thrombolytic therapy was recommended as the first 4.5 hours in the AHA 2010 guideline (9). Approximately 2 million neurons and 14 billion synapses have been shown to disappear every minute till the time of reperfusion (10). In a study on 58,353 patients who received r-tPA, Saver et al. (11) showed that treatment 15 minutes earlier decreased mortality and intracranial hemorrhage rates, and that patients were more mobile during discharge. For this reason, although the treatment window is recommended as 4.5 hours, it is important that the treatment should be applied as early as possible. In this context, it is recommended that patients

Table 2. Symptom/needle time and mean pre- and post-treatment National Institutes of Health Stroke Scale (NIHSS) scores in patients with and without hemorrhage and survivors and non-survivors, and mean pre- and post-treatment NIHSS of all patients

	Hemorrhagic patients (n=8)	**Non-hemorrhagic patients (n=44)**	
SN time (min) Mean ± SD	170±56.37	145.11±39.03	p=0.12
Pre-treatment NIHSS Mean ± SD	14.50±5.01	16.25±6.00	p=0.44
Post-treatment NIHSS Mean ± SD	12.37±7.81	12.52±7.45	p=0.86
	Non-survivors (n=13)	**Survivors (n=39)**	
SN time (min) Mean ± SD	136.15±32.79	153.20±44.78	p=0.21
Pre-treatment NIHSS Mean ± SD	18.53±5.29	15.12±5.96	p=0.07
Post-treatment NIHSS Mean ± SD	18.38±5.51	10.53±6.98	**p=0.01**
	Pre-treatment NIHSS	**Post-treatment NIHSS**	
All patients (n=52) Mean ± SD	15.9±5.8	12.5±7.4	**p=0.001**

SN: Symptom/needle, SD: Standard deviation, NIHSS: The National Institutes of Health Stroke Scale

with stroke should be diagnosed early in emergency services and that the DN time should not exceed 60 minutes (12). In our study, all patients were treated with thrombolytic therapy within 4.5 hours of the onset of symptoms, with an average SN time of 149 min and a mean DN time of 72 min. According to the Turkish Thrombolytic Treatment Study Group, these times are 150 and 69 min, respectively (13). Although our results are similar to the mean Turkish values, it is aimed to further shorten these periods with the dissemination of public education meetings in our region and the reorganization of emergency medical personnel training.

In the NINDS study, IV r-tPA treatment was reported to be effective in all stroke types (4). In our study, pre- and post-treatment NIHSS scores of all patients were compared and a statistically significant decrease was observed in post-treatment NIHSS scores (p=0.001).

The outcome of thrombolysis in ischemic stroke depends on many factors such as thrombus type, location, length, collateral circulation, comorbid diseases, patient age, and initiation time of treatment (1). Studies show no response to IV r-tPA in patients with thrombus in large-scale proximal arteries (14,15,16). In a transcranial ultrasonography study, the rate of recanalization in the occlusion of the distal middle cerebral artery (M2) was 44.2%, 30% in the occlusion of the proximal middle cerebral artery (M1), and decreased to 6% in the distal internal carotid artery (14,16). The rate of recanalization in the occlusion of the middle cerebral artery branches is higher than that of the cervical internal carotid artery occlusion, and the prognosis is better (17,18). It has been reported that the prognosis is worse in patients with occlusion of the middle part of the basilar artery than the apex of the basilar artery, and that mortality reaches up to 80-90% (19). The size of the infarct affects the outcome of thrombolytic therapy. Recanalization can be achieved in large-sized infarcts, but the prognosis does not change and hemorrhagic complications are more frequent (17,20,21). Images of our patient with recanalized M2 occlusion after IV thrombolytic therapy are shown in Figure 1, and images of our patient with recanalized basilar artery occlusion after IV thrombolytic therapy are shown in Figure 2. Hemorrhagic complications did not develop in either patient.

The most feared complication of IV r-tPA in acute ischemic stroke is symptomatic intracerebral hemorrhage, which is associated with 50% mortality (4). Hemorrhage within the first 36 hours is associated with treatment. However, symptomatic intracranial hemorrhage in studies involving the first 4.5 hours of r-tPA does not appear to be very high. Symptomatic intracranial hemorrhage was reported to be 6.4% in NINDS, 2.4% in ECASS 3, and 7% in Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS-B), which are among the studies that form the beginning of thrombolytic therapy (4,8,22). In a multicenter study by Yaghi et al. (23), they reported that symptomatic intracranial hemorrhage developed within 4.5

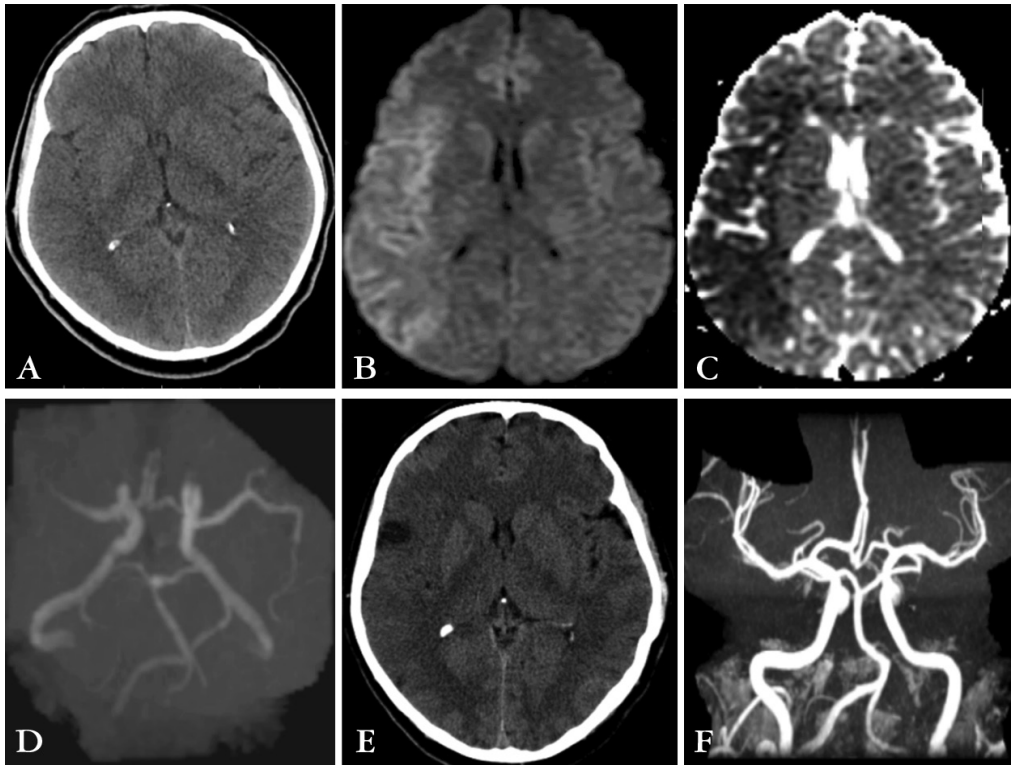

Figure 1. A 55-year-old male. On neurologic examination, the patient was somnolent, left homonymous hemianopsy, left 2/5 hemiparesis. National Institutes of Health Stroke Scale: 15, symptom/needle: 80 min. A) Normal cranial computerized tomography scan at the time of admission to the emergency department. B, C) Diffusion restriction in the right middle cerebral artery area on diffusion magnetic resonance imaging. D) Right middle cerebral artery occlusion on magnetic resonance angiography. E) A small infarct in the right parietal area on cranial computerized tomography 24 hours after treatment. F) Magnetic resonance angiogram shows recanalization of the artery (modified Rankin Scale: 0).

hours in 128 (3.3%) of 3894 patients treated with IV r-tPA and that secondary mortality rate was 52.3% (67 of 128 patients). In our study, only 2 patients (3.8%) had symptomatic intracranial hemorrhage.

The mortality rate in our study was 25% (13 patients) and none had hemorrhagic complications. Eleven (85%) of the non-survivors were in the TACI group. The mortality rate was 17% in the NINDS study, 7.7% in ECASS 3, and 11% in ATLANTIS-B (4,8,22). This rate was reported as 14.7% in the Turkish Thrombolytic Treatment Study Group (13). The high mortality rate in our study may be due to the majority of patients having TACI. In the study of Di Carlo et al. (24), 35.2% of patients with TACI were reported to have died at the end of the 3rd month.

There was no statistically significant difference between the mean SN time and mean pre-treatment NIHSS scores between the survivors and non-survivors. However, there was a statistically significant difference regarding the mean post-treatment NIHSS scores between the two groups. It is noteworthy that recanalization could not be achieved in non-survivors and that the mean post-treatment NIHSS scores did not change significantly. There were 16 (30.8%) patients with mRS of 0-1 at 3rd month. These rates were 39% and 52% in the NINDS and ECASS 3 trials, respectively (4,8). The lower rate in our study may be attributed to the fact that the majority of our patients had TACI (67.3%). Among the clinical syndromes defined for stroke, TACI is defined as the group with the worst prognosis causing the most severe disability. In a multicenter study by Di Carlo et al. (24), the authors reported that patients who survived TACI remained severely disabled (mean mRS: 2.9±1.6) at the end of the 3rd month. In our study, the number of patients with a mRS of 0-1 was 7 (20%) in patients with TACI, and 8 (57.1%) in patients with PACI. The results show that IV r-tPA treatment is more effective in distal intracranial vascular occlusions.

Conclusion

Intravenous r-tPA treatment in acute ischemic stroke is effective and safe. It is easy to apply in experienced centers. With shortening of the initiation of treatment, patients benefit more from treatment. However, as mentioned above, the rate of recanalization in the large veins is low. The benefit rates of these patients are low. Therefore, in addition to widespread use of IV thrombolytic therapy in selected patients, further efforts are needed to widen the use of other endovascular treatment options in our country.

Ethics

Ethics Committee Approval: The study was approved by the Dumlupinar University of Local Ethics Committee (Decision no: 2017-9/6).

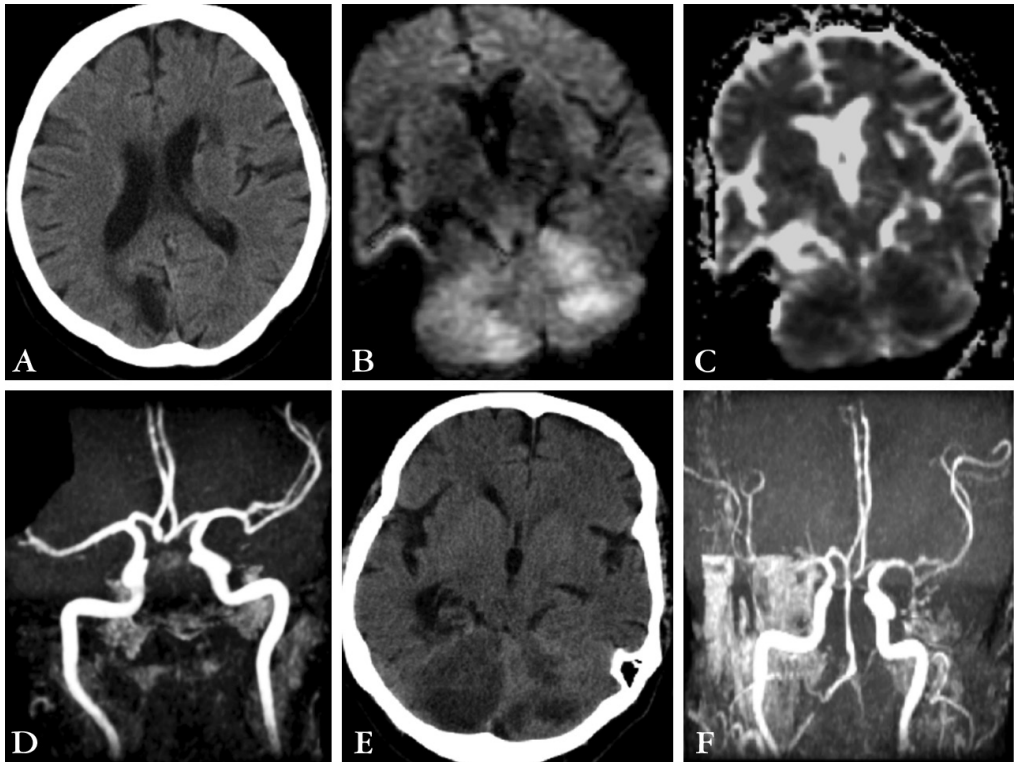

Figure 2. A 59-year-old female. On neurologic examination, the patient was somnolent, marked quadriparesis on the left side. National Institutes of Health Stroke Scale: 24, symptom/needle: 120 min. A) Chronic ischemia in the right occipital lobe and area adjacent to left ventricle on cranial computerized tomography at the time of admission to the emergency department. B, C) Bilateral diffusion restriction in the cerebellum on diffusion-weighted magnetic resonance imaging. D) Basilar artery occlusion on magnetic resonance angiography. E) Bilateral subacute infarction in the cerebellum on follow up cranial computerized tomography. F) Recanalized basilar artery on magnetic resonance angiography (modified Rankin Scale: 1).

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Authorship Contributions

Surgical and Medical Practices: H.E.A., M.Ç., Concept: M.Ç., S.C.K., Design: M.Ç., S.C.K., Data Collection or Processing: M.Ç., Analysis or Interpretation: M.Ç., S.C.K., Literature Search: M.Ç., S.C.K., Writing: M.Ç.

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