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Central Venous Reflux, a Rare Cause of Neurological Manifestations in Hemodialysis Patients: A Case Report and Literature Review

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Central venous disease (CVD) is a serious complication in hemodialysis patients. Neurological manifestations are rare. We describe a female with end-stage renal disease with throbbing headache accompanied by paresthesia, weakness, and abnormal posture of her right hand during dialysis sessions. Motor symptoms completely resolved after each dialysis session, although the headaches persisted for several hours. No neurological deficit was evidenced on physical examination. Digital subtraction angiography identified an incomplete thrombosis of the left brachiocephalic vein with retrograde flow in the internal jugular vein, sigmoid sinus, and transverse sinus on the left side. This case illustrates that cerebral venous congestion due to CVD can produce neurological symptoms. Furthermore, we systematically review the literature to identify the characteristics of the cases described so far. This allows clinicians to know the entity and have a high index of suspicion in a hemodialysis patient who develops neurological symptoms.

Key Words: Neurologic manifestations; Renal dialysis; Venous thrombosis; Catheterization, central venous; Vascular access devices

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INTRODUCTION

Central venous disease (CVD) is a serious complication in patients undergoing hemodialysis. It is defined as >50% lesion (stenosis or occlusion) in one of the following central veins of the chest: inferior and superior vena cava, brachiocephalic vein (BCV), subclavian vein (SCV), or internal jugular vein (IJV).[1] Its clinical presentation varies depending on the site of the injury, being more serious the closer it is to the right atrium. It typically manifests with ipsilateral upper limb and facial edema, although it can occur asymptomatically.[2] Neurological manifestations secondary to CVD are rare.[3,4] We describe a patient who presented neurological manifestations secondary to central venous reflux due to throm-

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botic occlusion of the left BCV. We also performed a systematic review of the literature.

CASE REPORT

A 51-year-old female presented with a 3-month duration of throbbing headache, of moderate to severe intensity, located in the frontal and retroocular region, without nausea or vomiting. It got worse during dialysis sessions and interfered with her activities of daily living. She also complained of paresthesia, weakness, and abnormal posture of her right hand during headache episodes. Motor symptoms completely resolved after each dialysis session, although the headaches persisted for several hours. No neurological deficit was evidenced on physical examination. Her past medical history includes arterial hypertension and chronic renal failure secondary to focal segmental glomerulosclerosis. Six years ago, she had a deceased donor kidney transplant. Due to the rejection of the transplant, she required hemodialysis through a central venous catheter (CVC) in the right IJV for 7 months. Then, an arteriovenous fistula (AVF) was performed in her left upper limb, and she undergoes hemodialysis through this access until now.

Brain tomography and magnetic resonance imaging did not show acute lesions or signs of intracranial hypertension (optic nerve sheath hydrops, reduced pituitary height, optic disc protrusion, or optic nerve edema). The fundus examination was normal. Magnetic resonance angiography showed high signal intensities of the sigmoid sinus, transverse sinus, and inferior petrosal sinus on the left side due to venous reflux (Fig. 1A–D). Digital subtraction angiography (DSA) ruled out intracranial AVF and identified an incomplete thrombosis (75%) of the left BCV (Fig. 1E). Delayed venous phase images of DSA showed reverse venous flow in the IJV, sigmoid sinus, and transverse sinus on the left side (Fig. 1F). The patient was not eligible for endovascular treatment due to the difficulty of making a new venous access. The decision was to start anticoagulation with complete resolution of symptoms after 3 months of follow-up.

DISCUSSION

We described a hemodialysis patient who developed neurological symptoms due to thrombotic occlusion of the left BCV. The estimated incidence of CVD in patients undergoing hemodialysis ranges from 16% to 50%. However, the presence of neurological symptoms is rare and nonspecific.[5,6] In Table 1[1-20], we summarize the cases of neurological manifestations secondary to CVD reported so far. There is no sex prevalence with a mean age of 55.4 years (standard deviation [SD] ±14.1). Cardiovascular risk factors were identified in 14 out of 23 patients, with arterial hypertension being the most frequent factor (50%), and the average time of hemodialysis was 7.1 years (SD ±3.4).

The etiology of CVD is multifactorial. However, CVC placement has been associated with an increased risk of CVD, even after its removal. SCV access has up to 4 times the risk compared to IJV for the development of this pathology.[2] As well as our patient, CVC placement was described in 6 out of 23 of the reported cases.

In patients without a history of endoluminal devices, hemodynamic abnormalities could explain the development of CVD. Turbulent blood flow due to the presence of AVF would damage the vessel wall, stimulate the development of neointimal hyperplasia, and cause stenosis. Shunts located on the left side are associated with an increased risk of stenosis or thrombosis due to anatomical causes (left BCV is located between the sternum and pulsating aorta, which contributes to stenosis).[5,6]

Among the reported cases, 14 patients (60.9%) had an AVF, 7 (30.4%) had an arteriovenous graft, and in 2 cases (8.7%) the type of shunt was not specified. The mean time from AVF creation to symptoms onset was 4.5 years (SD ±4.2), and in 65.2% of patients (15/23), including the present case, the shunt was located in the left upper limb.

Previous studies have found associations between venous reflux and neurological manifestations. Retrograde flow caused by CVD (especially BCV) could cause alteration of the cerebral venous drainage, affect the circulation of the cerebrospinal fluid, and develop intracranial hypertension.[6,7] Headache attacks in our patient could be explained by this mechanism. On the other hand, intracranial venous congestion decreases cerebral perfusion pressure, which leads to a reduced supply of brain nutrients and potentially causes a hypoxia-like condition and affects neuronal function.[8,9] This is some of the currently available evidence about the pathophysiology of central venous reflux as a cause of neurological signs and symptoms. Among the patients described, occlusion/thrombosis prevailed over stenosis as a more frequent central lesion, and in the majority of them (87%) there was

BCV involvement. The most frequent symptoms and signs were: headache (60.9%), motor deficits (21.7%), cranial nerve involvement (17.4%), and sensory symptoms (4.3%).

Change of flow direction could also lead to increased cerebral venous pressure, causing ischemia (due to altered cerebral perfusion pressure) or bleeding.[1,8,10] A brain lesion was present in 30.1% of reported cases at symptoms onset, which included 3 cerebral infarctions and 3 intraparenchymal hemorrhages. We did not identify brain lesions in our case.

The diagnosis of CVD is based on clinical and imaging findings. A high index of suspicion is necessary for this pathology, where DSA is the gold standard for the diagnosis of this disease due to its greater sensitivity compared to other imaging methods.[10]

Symptoms can be reversible if CVD is treated early. Treatment options include percutaneous transluminal angioplasty (PTA), stenting, and surgery. PTA with a dilatation balloon is the current mainstay of treatment and should be performed

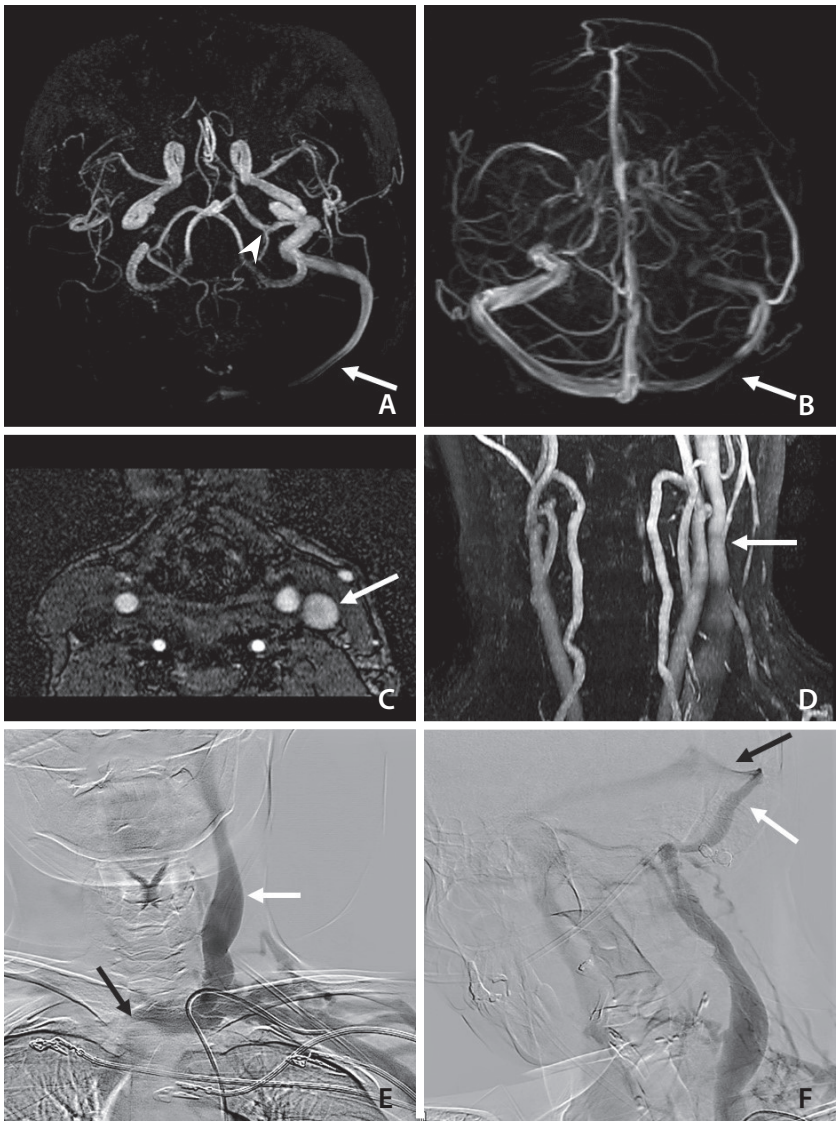

Fig. 1. (**A**) Brain time-of-flight (TOF) magnetic resonance angiography (MRA) shows reflux venous flow in the sigmoid sinus, transverse sinus (white arrow), and inferior petrosal sinus (arrowhead) on the left side. (**B**) Brain TOF magnetic resonance venography shows reflux venous signals in the left transverse sinus (white arrow). (**C**, **D**) Neck TOF MRA demonstrates retrograde flow in the left internal jugular vein (IJV) (white arrow). (**E**) Digital subtraction angiography (DSA) after injection in the left brachial artery shows reflux venous flow in the left IJV (white arrow) and incomplete thrombosis of the left brachiocephalic vein (black arrow). (**F**) Delayed venous phase images of DSA show retrograde flow in the IJV, sigmoid sinus (white arrow), and transverse sinus (black arrow) on the left side.

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Table 1. Existing case reports of neurological complications due to central venous disease in hemodialysis patients

Study	Sex/ age (y)	Length of HD (y)	Previous CVC	CVC location	Previous renal transplant	AV shunt type/limb	Shunt usage time	Neurological manifestations	Central venous disease	Treatment	Evolution
Lal et al. (1986)[10]	M/62	3	Yes	Right SCV	No	AVF/right upper limb	1 year	Decreased visual acuity, diplopia, retro-ocular throbbing headache, transient amaurosis	Right BCV stenosis	AVF ligation	Complete resolution of symptoms in 6 weeks
Molina et al. (1998)[11]	M/74	5	Yes	Right and left SCV, right IJV	No	AVF and AVG/ bilateral	6 months	Decreased visual acuity, headache, blurry vision	Bilateral BCV stenosis	AVF ligation	Complete resolution of symptoms
Varelas et al. (1999)[12]	F/58	NR	Yes	Right SCV	No	AVF/right upper limb	NR	Diplopia, right hemicranial headache, bilateral sixth nerve palsy	Right BCV stenosis	Angioplasty+stent placement	Resolution of ophthalmoplegia in 24 hours
Hartman et al. (2001)[13]	F/59	8	NR	NR	Yes	AVF/left upper limb	5 years	Headache, gait disturbance, memory loss	Left BCV stenosis	AVF ligation	Resolution of hydrocephalus and symptoms in one week
Chang et al. (2004)[14]	F/50	3	NR	NR	No	AVF/left upper limb	3 years	Intermittent headache, retro-ocular pressure	Left BCV stenosis	Balloon angioplasty	Resolution of symptoms and papilledema in 3 months
Cuadra et al. (2005)[15]	F/57	NR	Yes	NR	Yes	AVG/right upper limb	NR	Headache, blurry vision	Right IJV, SCV, and axillary vein stenosis	AVG occlusion	Visual acuity was not recovered in the left eye
Nishimoto et al. (2005)[7]	F/62	9	NR	NR	No	AVF/left upper limb	9 years	Headache, seizures	Left BCV thrombosis	AVF ligation	Immediate resolution
Cleper et al. (2007)[5]	F/13	10.5	NR	NR	Yes	AVF/left upper limb	2 months	Right amaurosis, seizures	Right BCV and SCV occlusion	AVF ligation and creation of new access failed	The patient died
Watson and Russo (2007)[16]	F/36	NR	NR	NR	No	AVF/left upper limb	NR	Headache, blurry vision	Left BCV occlusion	Recanalization of the left BCV	Complete resolution of symptoms
Nishijima et al. (2011)[17]	F/47	5	NR	NR	No	AVF/left upper limb	5 years	Right hemiplegia, headache, seizures	Left BCV occlusion	AVF ligation	Dramatic recovery from motor deficit
Saha et al. (2012)[18]	F/53	3	NR	NR	No	AVG/ left upper limb	NR	Headache, lethargy	Left IJV stenosis	AVG occlusion	Complete resolution of symptoms
Samaniego et al. (2013)[6]	M/50	11	NR	NR	No	AVG/right upper limb	2 weeks	Headache, left homonymous hemianopia, encephalopathy	Left BCV occlusion	AVG occlusion	Full recovery one week later

Table 1. Continued

Study	Sex/ age (y)	Length of HD (y)	Previous CVC	CVC location	Previous renal transplant	AV shunt type/limb	Shunt usage time	Neurological manifestations	Central venous disease	Treatment	Evolution
Herzig et al. (2013)[3]	M/73	NR	NR	NR	No	AVF/left upper limb	NR	Headache, blurry vision, seizures	Left BCV thrombosis	AVF ligation	Full recovery 2 days later
	F/67	NR	NR	NR	No	NR	NR	Right arm monoparesis, Involuntary movements of the right arm	Left BCV stenosis	Angioplasty+stent placement. Recanalization of the stent	Incomplete recovery with recurrence at seven months. Complete recovery four months after the second intervention
Salama et al. (2014)[4]	F/40	NR	NR	NR	No	AVF/left upper limb	NR	Tinnitus, proptosis of the left eye	Left BCV occlusion	Angioplasty+stent placement	Recovery of symptoms in 24 hours
Prasad et al. (2015)[2]	M/47	NR	NR	NR	No	AVG/ left upper limb	NR	Right hemiparesis, altered mental status	Left BCV occlusion	Angioplasty+stent placement	Recovery of symptoms in the following days
Simon et al. (2014)[19]	M/65	NR	Yes	Right IJV	No	AVF/ Bilateral	NR	Decreased visual acuity, headache, blurry vision, tinnitus	Right BCV thrombosis	Angioplasty	Headache recovery in 24 hours. Visual acuity improved at 5 months
Mackay and Biousse (2015)[9]	F/60	NR	NR	NR	No	AVF/right upper limb AVG/left upper limb	AVF NR AVG 3 days	Headache, blurry vision	Right SCV stenosis	Withdrawal of AVG. Ventriculoperitoneal shunt	Complete resolution of symptoms in 4 weeks
Kim et al. (2018)[8]	F/71	7	NR	NR	No	AVG/ left upper limb	7 years	Throbbing headache	Left BCV occlusion	Balloon angioplasty	Complete resolution of symptoms
	F/63	10	NR	NR	No	AVG/ left upper limb	10 years	Seizures	Left BCV occlusion	Delayed treatment for sepsis	The patient died
Haruma et al. (2020)[1]	M/53	4	NR	NR	No	AVF/left upper limb	4 years	Right hemiparesis, altered mental status, seizures	Left BCV stenosis	Angioplasty+stent placement	Symptom improvement without recurrence of stenosis
Iguchi et al. (2020)[20]	F/73	14	NR	NR	Yes	AVG/ left upper limb	NR	Aphasia	Left BCV stenosis	AVG occlusion	Complete resolution of symptoms in one month
Caiza-Zambrano et al. (current study)	F/43	8	Yes	Right IJV	Yes	AVF/left upper limb	5 years	Abnormal right hand posture, retro-ocular headache, paresthesia	Incomplete left BCV thrombosis	OAC	Complete resolution of symptoms in three months

M, male; F, female; HD, hemodialysis; CVC, central venous catheter; SCV, subclavian vein; IJV, internal jugular vein; BCV, brachiocephalic vein; AV, arteriovenous; AVF, arteriovenous fistula; AVG, arteriovenous graft; NR, not reported; OAC, oral anticoagulants.

only if there is a clinical indication (arm or face swelling).[4] Balloon dilation for a narrow lesion found incidentally without symptoms accelerates the growth of the lesion. All the current treatment options will lead to recurrent stenosis or occlusion requiring multiple repeat interventions to maintain patency, but the risk of vessel rupture may increase.[2]

Other options may be decongestion of the cerebral venous system by closing the active vascular access, but an alternative vascular access should be insured to continue renal replacement therapy.[6,11] Ligation/occlusion was performed in half of the reported patients, and less frequently (39.1%) when they underwent PTA. Twenty patients had good outcomes with a disappearance or clear improvement of symptoms after treatment.

Due to the location and type of lesion, our patient was not eligible for endovascular treatment. AVF ligation was not possible because the patient did not have another adequate venous access for a new AVF placement. Our patient represents the first reported case of neurologic manifestations secondary to CVD with complete resolution of symptoms after oral anticoagulants therapy. We have no evidence about medical therapy for secondary prevention for CVD. Further randomized controlled trials of currently available treatment options with long-term follow-up are essential in the future to develop adequate treatment algorithms.

Central venous reflux due to CVD is a serious complication in patients undergoing hemodialysis. Neurological manifestations are infrequent; therefore, this entity requires a high index of suspicion in those patients under hemodialysis who present neurological symptoms. Moreover, anticoagulation could be considered as an alternative treatment in special cases.

Fund
None.

Ethics Statement
This case report was approved by the Institutional Review Board (British Hospital Institutional Bioethics Committee) and conducted according to the criteria set by the declaration of Helsinki. Written informed consent for publication of her details was obtained from the patient.

Conflicts of Interest
The authors have no conflicts to disclose.

Author Contributions
Concept and design: FCZ, CMP, SG, and PB. Analysis and interpretation: FMG, MBB, MF, and MS. Data collection: FMG, MBB, FL, MF, and MS. Writing the article: FCZ, CMP, SG, and PB. Critical revision of the article: SG, CR, RR, and MFP. Final approval of the article: CR, RR, MFP, and PB. Statistical analysis: FL and MF.

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REFERENCES

1. Haruma J, Escalard S, Smajda S, Piotin M. Left temporal hemorrhage caused by cerebral venous reflux of a brachio-brachial hemodialysis fistula. *Neuroradiology* 2020;62:1341-1344
2. Prasad V, Baghai S, Gandhi D, Moeslein F, Jindal G. Cerebral infarction due to central vein occlusion in a hemodialysis patient. *J Neuroimaging* 2015;25:494-496
3. Herzig DW, Stemer AB, Bell RS, Liu AH, Armonda RA, Bank WO. Neurological sequelae from brachiocephalic vein stenosis. *J Neurosurg* 2013;118:1058-1062
4. Salama GR, Farinhas JM, Pasquale DD, Wertenbaker C, Bello JA. Central venous occlusion mimics carotid cavernous fistula: a case report and review of the literature. *Clin Imaging* 2014;38:884-887
5. Cleper R, Goldenberg-Cohen N, Kornreich L, Krause I, Davidovits M. Neurologic and ophthalmologic complications of vascular access in a hemodialysis patient. *Pediatr Nephrol* 2007;22:1377-1382
6. Samaniego EA, Abrams KJ, Dabus G, Starr R, Linfante I. Severe venous congestive encephalopathy secondary to a dialysis ar-

teriovenous graft. *J Neurointerv Surg* 2013;5:e37
7. Nishimoto H, Ogasawara K, Miura K, Ohmama S, Kashimura H, Ogawa A. Acute intracranial hypertension due to occlusion of the brachiocephalic vein in a patient undergoing hemodialysis. *Cerebrovasc Dis* 2005;20:207-208
8. Kim CH, Kang J, Choi DS, Park JH. Intracranial venous reflux caused by occlusion of the brachiocephalic vein mimicking dural arteriovenous fistula. *World Neurosurg* 2018;120:438-441
9. Mackay DD, Biousse V. Hemodialysis graft-induced intracranial hypertension. *Neurol Clin Pract* 2015;5:494-497
10. Lal SM, Twardowski ZJ, Van Stone J, Keniston D, Scott WJ, Berg GG, et al. Benign intracranial hypertension: a complication of subclavian vein catheterization and arteriovenous fistula. *Am J Kidney Dis* 1986;8:262-264
11. Molina JC, Martinez-Vea A, Riu S, Callizo J, Barbod A, Garcia C, et al. Pseudotumor cerebri: an unusual complication of brachiocephalic vein thrombosis associated with hemodialysis catheters. *Am J Kidney Dis* 1998;31:E3
12. Varelas PN, Bertorini TE, Halford H. Bilateral ophthalmoplegia and exophthalmos complicating central hemodialysis catheter placement. *Am J Kidney Dis* 1999;33:966-969
13. Hartmann A, Mast H, Stapf C, Koch HC, Marx P. Peripheral hemodialysis shunt with intracranial venous congestion. *Stroke* 2001;32:2945-2946
14. Chang S, Masaryk TJ, Lee MS. Optic nerve edema: complication of peripheral hemodialysis shunt. *Semin Ophthalmol* 2004;19:88-90
15. Cuadra SA, Padberg FT, Turbin RE, Farkas J, Frohman LP. Cerebral venous hypertension and blindness: a reversible complication. *J Vasc Surg* 2005;42:792-795
16. Watson RR, Russo C. Upper extremity arteriovenous dialysis fistula resulting in cavernous sinus arterialized blood flow. *AJNR Am J Neuroradiol* 2007;28:1155-1156
17. Nishijima H, Tomiyama M, Haga R, Ueno T, Miki Y, Arai A, et al. Venous cerebral infarction in a patient with peripheral hemodialysis shunt and occlusion of the left brachiocephalic vein. *J Stroke Cerebrovasc Dis* 2011;20:381-383
18. Saha MK, Hamieh T, Larkin B, Mcmillan W. Cerebral hemorrhage due to internal jugular vein stenosis in a hemodialysis patient. *Clin Exp Nephrol* 2012;16:345-349
19. Simon MA, Duffis EJ, Curi MA, Turbin RE, Prestigiacomo CJ, Frohman LP. Papilledema due to a permanent catheter for renal dialysis and an arteriovenous fistula: a "two hit" hypothesis. *J Neuroophthalmol* 2014;34:29-33
20. Iguchi T, Harada M, Kurihara S, Ichikawa T, Satoh S, Kobayashi M. Neurological symptoms due to intracranial venous congestion in a hemodialysis patient with arteriovenous shunted flow. *Kidney Int Rep* 2020;5:2097-2101