MRI for acute neurologic complications in end-stage renal disease patients on hemodialysis

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ABSTRACT

Acute cerebrovascular disease is one of the most frequent causes of mortality and morbidity in patients on long-term hemodialysis therapy. Early recognition of cerebrovascular events improves the prognosis and quality of life of end-stage renal failure patients. This paper reviews the magnetic resonance imaging features of acute neurological findings in patients with end-stage renal failure.

Key words: • magnetic resonance imaging • end-stage renal disease • hemodialysis

Hemodialysis is the most frequently administered therapy for end-stage renal disease (ESRD) patients, and acute cerebrovascular disease is one of the most frequent causes of morbidity and mortality in patients on long-term hemodialysis (HD) treatment (1). Neurological examination alone is usually not sufficient to distinguish the underlying pathologies. Magnetic resonance imaging (MRI) of the brain is the most valuable and frequently used diagnostic method. Early diagnosis of cerebrovascular diseases is important for prognosis and quality of life in ESRD patients (1, 2). The purpose of this paper is to discuss acute neurological manifestations in symptomatic hemodialysis patients based on brain MRI findings.

Acute cerebrovascular manifestations in HD patients develop for the following reasons: a) disease processes, such as hyperparathyroidism, systemic hypertension, hyperlipidemia, chronic uremia, fluid-electrolyte imbalance, and immune system abnormalities; b) HD therapy (i.e., dialysate fluid); and c) both disease processes and HD therapy (e.g., bleeding diathesis and HD duration) (3).

The most frequently encountered cerebrovascular disorders in ESRD patients are cerebral infarction, intracerebral hemorrhage, posterior reversible encephalopathy syndrome (PRES), osmotic demyelinization syndrome (ODS), cerebral infection, sinus vein thrombosis (SVT) and dialysis disequilibrium syndrome (Table).

Cerebral ischemia and infarction

Cerebrovascular events are a major cause of mortality in ESRD patients. Many studies report a four to ten times greater incidence of strokes in ESRD patients compared to the general population (4).

Atherosclerosis, uremia, increased lipoprotein-A levels, advanced age, smoking, and hypertension are the primary risk factors for silent cerebral infarctions (SCI) in hemodialysis patients (3–5). SCI is an important risk factor for stroke and is caused by occlusion of the small, deeply penetrating cerebral arteries. In many patients, SCI manifests in the form of lacunar infarctions or subcortical infarctions (5).

Radiological findings using conventional MRI are usually normal for the first eight hours of SCI. During the acute stage, the T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences reveal an increase in intensity, swelling of gyri, effacement of sulci, absence of arterial flow void, and intravascular contrast enhancement following intravenous contrast administration (Fig. 1). Changes in the diffusion-weighted (DW) MRI signal intensity can be detected within minutes of the arterial occlusion. Acute infarcts have low apparent diffusion coefficients (ADCs) compared to the non-infarcted brain regions. On the other hand, the infarction area displays a large signal in DW images.

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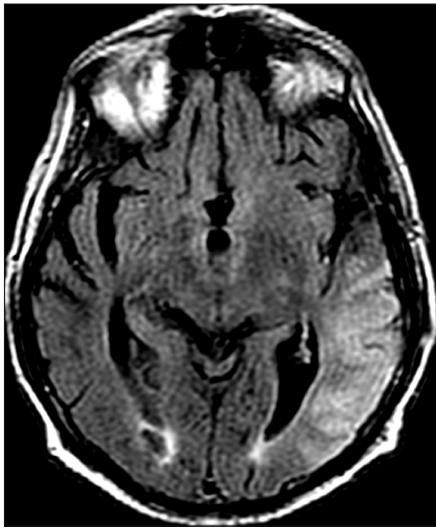
Figure 1. Axial FLAIR MR image obtained 24 hours after ictus, showing hyperintense edematous gyri and sulcal obliteration in the temporoparietal lobe, consistent with recent infarction.

Intracerebral hemorrhage

There is a high incidence of intracerebral hemorrhage in hemodialysis patients (4, 6). In the general population, the underlying cause of intracerebral hemorrhage is atherosclerosis, the same underlying cause of SCI. ESRD patients bear an increased risk of atherosclerosis. Hence, the incidence of both SCI and intracerebral hemorrhage is increased in ESRD patients. Hemodialysis patients are at greater risk of bleeding because of anticoagulant therapy (e.g., heparin and low molecular weight heparins), defective platelet adhesion, anemia and inadequate control of hypertension. A hemorrhage may be intraparenchymal, subdural, epidural, or subarachnoid.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome's clinical presentation includes seizures, severe headaches, and mental and visual changes. The characteristic neuroradiological lesions are located in the posterior (i.e., parietooccipital lobes) white matter and may involve the overlying gray matter. Hypertensive encephalopathy is a neurological syndrome that presents the same symptoms and imaging findings as the other causes of PRES. Sudden increases in blood pressure and subsequent renal failure are the most frequent etiologies described in the literature (7). In addition, immune suppression using cyclosporine-A and tacrolimus, eclampsia, and the use of various cytotoxic agents may also cause PRES. An acute hypertensive attack was the primary trigger for PRES in most of the cohort studies conducted. When an acute increase in blood pressure exceeds the autoregulatory capacity of the central nervous system (CNS) vessels, regions of vasoconstriction and vasodilatation develop, typically at the arterial boundary zones. This is followed by a breach of the blood-brain barrier, causing a transudation of fluid and a petechial hemorrhage (7). Notably, some of the cases studied were normotensive (8). The uremic milieu of ESRD has also been proposed as an independent triggering agent (9).

The posterior brain involvement can be explained by the weaker auto-regulatory mechanisms in the posterior cerebral vasculature due to relatively few sympathetic innervations (7, 10). The clinical and neuroradiological reversibility of this syndrome is well known, but recurrence of PRES is very rare (11). If the initial trigger redevelops, the same vasogenic response is likely to be generated in the CNS vasculature.

On MR images, the bilateral symmetrical edema in the parietooccipital region, supplied by the posterior cerebral circulation, is hyperintense on T2-weighted and FLAIR sequences and hypointense on T1-weighted sequences (Fig. 2). The calcarine fissure and paramedian lobe are generally not affected. The high signal intensity in

Table. Acute neurological complications and MRI findings in end-stage renal disease patients

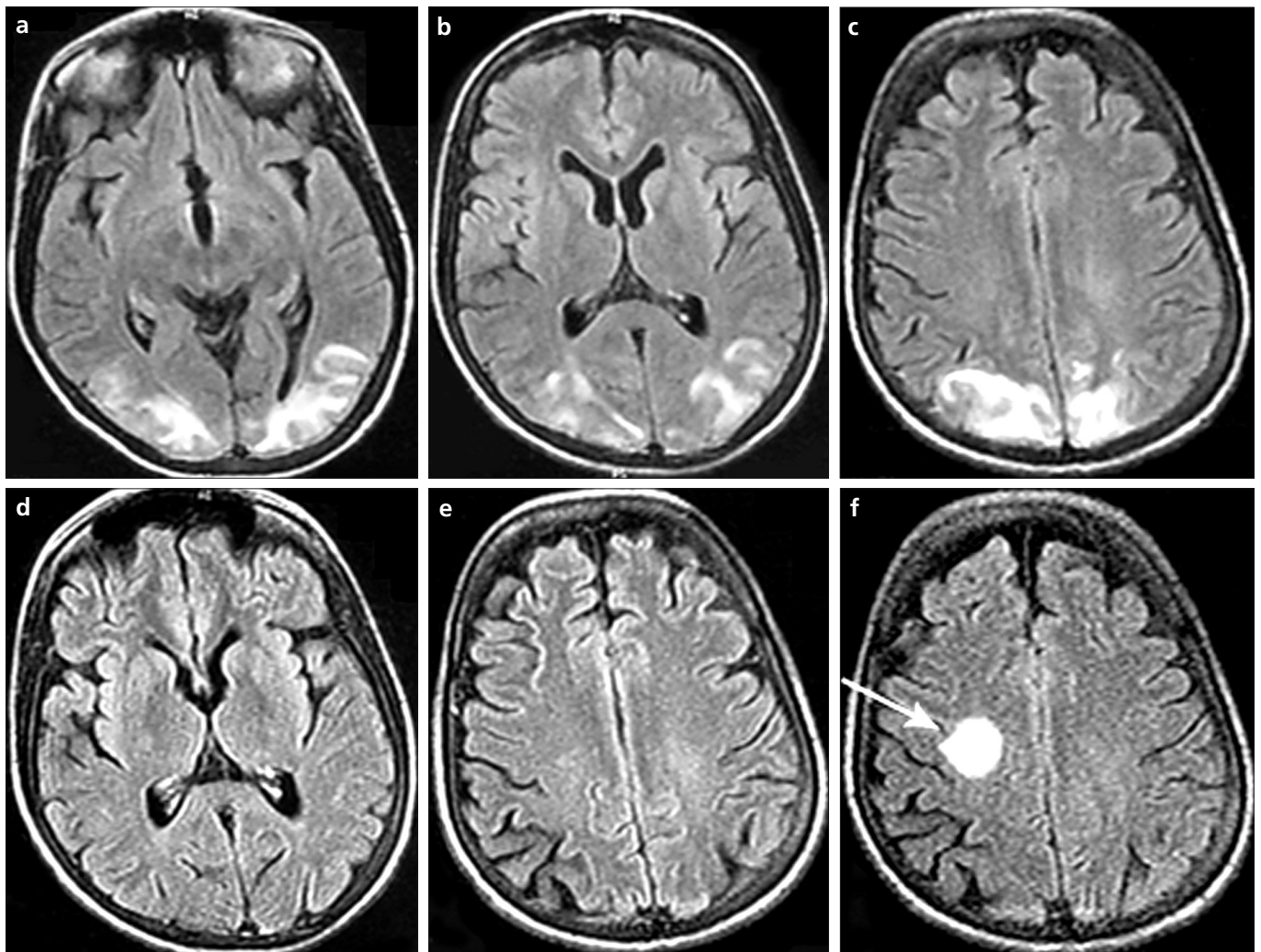| Acute neurological complications in end-stage renal disease patients	MRI findings
Cerebral infarction	Intensity increase in the territory of the arterial supply, T2-weighted and FLAIR sequences; low signal in ADC, high signal in DWI
Intracerebral hemorrhage	
Intraparenchymal	Isointense on T1-weighted sequences; low central and high peripheral signals on T2-weighted sequences
Subdural	Crescent-shaped, iso-/hypointense on T1-weighted sequences; low signal on T2-weighted sequences
Epidural	Biconvex, isointense on T1-weighted sequences; high signal on T2-weighted sequences
Subarachnoid	Subarachnoid space hyperintensity on FLAIR images
Posterior reversible encephalopathy syndrome	Bilateral parietooccipital region hypointense on T1-weighted sequences and hyperintense on T2-weighted and FLAIR sequences; high ADC, and low DWI signal
Osmotic demyelination syndrome	Pontine and/or extrapontine areas have symmetric increased signals on T2-weighted and FLAIR sequences
Cerebral infections	Hypointense on T1-weighted sequences; hyperintense on T2-weighted sequences; contrast enhancement following intravenous contrast administration
Gadolinium persistence in the cerebrospinal fluid	Hyperintensity in the subarachnoid space on FLAIR images
Sinus vein thrombosis	Increased dural sinus signal on T1-weighted and T2-weighted sequences
Dialysis disequilibrium syndrome	Cerebral edema (hypointense on T1-weighted sequences; hyperintense on T2-weighted sequences), particularly in posterior parietooccipital regions

Figure 2. a–f. Axial FLAIR MR images **(a–c)** show symmetrically-located, bilateral, hyperintense lesions in the parietooccipital regions affecting the cortex and subcortical white matter. On the follow-up MR image **(d, e)**, the edema has completely resolved. On axial FLAIR MR image obtained **(f)** six weeks later, there is a 2-cm edematous lesion at the right centrum semiovale *(arrow)*, consistent with recurrent PRES.

the ADC maps is high in PRES. The signal intensity of the lesion is normal or decreased in DW MR images. The vasogenic edema of PRES (i.e., low signal on DW MR images) is differentiated from cytotoxic edema, which indicates an acute cerebral infarct (i.e., high signal in the DW images).

Osmotic demyelination syndrome

Osmotic demyelination syndrome is a clinicopathological entity that results in convulsions and a change in consciousness and is characterized by pontine and extrapontine region edema and demyelination. The processes that cause the edema and demyelination are unknown. However, a rapid correction of chronic hyponatremia, which is a change in abnormal blood gases also referred to as "fluid-electrolyte imbalances", is known to frequently

cause ODS. In addition, direct osmotic changes and the uremia-related accumulation of metabolites in hemodialysis patients may cause a sudden fluid transfer from the extracellular brain areas into the brain cells (i.e., edema) and demyelination, resulting in ODS (12). This uremia-related accumulation of metabolites is the most important mechanism in the development of ODS in ESRD patients.

Cranial MRI findings, both in the general population and in ESRD patients, have revealed primarily symmetric pontine lesions with increased signals on T2-weighted, proton density-weighted, or FLAIR images (Fig. 3). In addition, lesions may also involve the pontine and/or extrapontine areas, basal ganglia, bilateral thalamus, cerebral peduncles, and corticomedullary junction of the cerebrum and spinal

cord. The involvement of the cerebellar peduncles has been reported in a few rare cases (13).

Cerebral infections

Uremic patients have both humoral and cellular immune deficiencies. Lymphocytopenia and lymphocyte function disturbances are also often encountered in cerebral infections. Both T and B cells are affected, as well as nonspecific cells (i.e., granulocytes and phagocytes). In addition to a decrease in chemotaxis and an insufficient inflammatory response, the cell-mediated (i.e., delayed-type) hypersensitivity response is deficient (14). Iron overload, elevated levels of intracellular calcium, and hemodialysis treatment are known to contribute to the development of an infection. The uremic toxins that accumulate in the
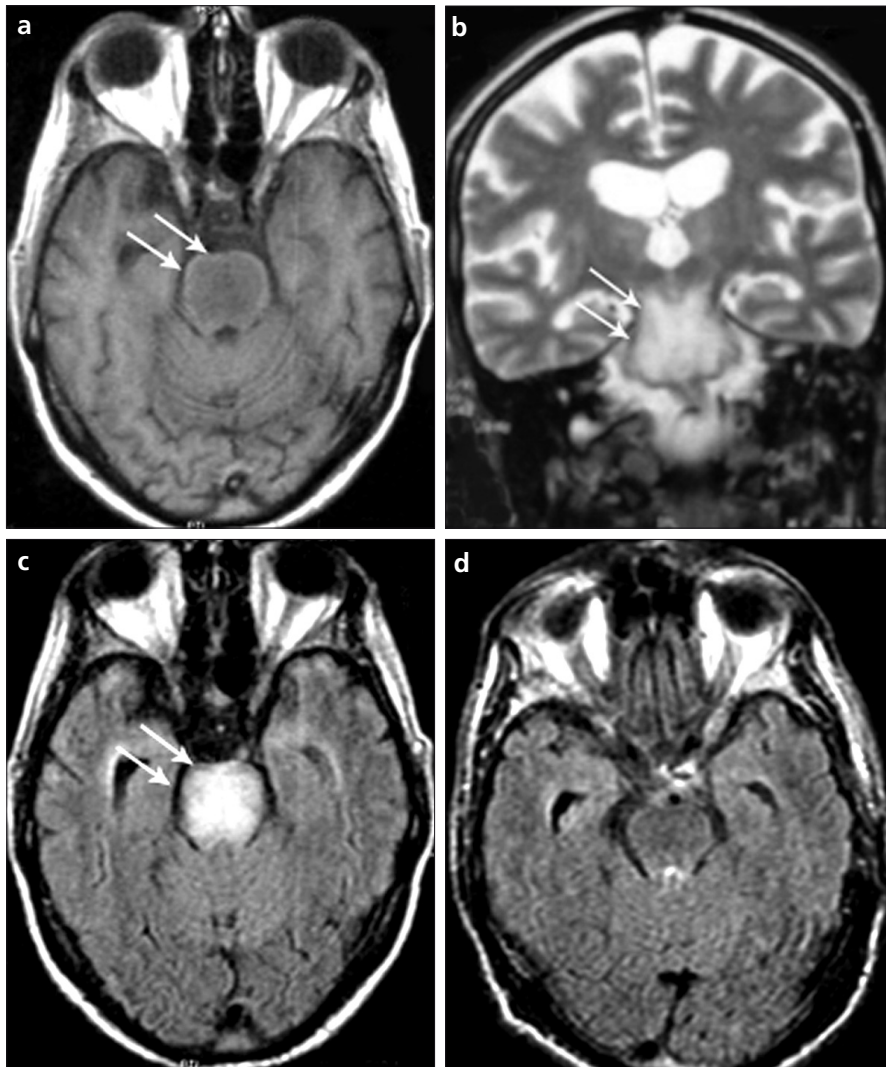
blood serum of uremic patients also inhibit the nonspecific immune system. ESRD patients are more susceptible to infections, but it is not clear why viral infections are less frequently encountered than fungal and bacterial causes (Fig. 4) (14).

Persistence of gadolinium in the cerebrospinal fluid

The persistence of gadolinium in the cerebrospinal fluid (CSF) is the cause of an increased signal intensity in the subarachnoid space, observed in the T1-weighted and FLAIR MR images following intravenous gadolinium administration (Fig. 5). This may lead to diagnostic confusion, predominantly of pathologies causing a protein increase in the CSF (e.g., infection, hemorrhage, and neoplasia) and of cases of renal failure in which renal elimination of gadolinium is prolonged, and gadolinium is thus excreted into the CSF. The abnormal increase in the plasma concentration of gadolinium, distributed into all of the extracellular body compartments, causes gadolinium to diffuse through the permeable and semi-permeable membranes. The tight junctions of the endothelium in the cerebral capillaries form a selectively permeable structure. The cerebral choroid plexus and the ocular ciliary body contain fenestrated capillary endothelium. This fenestration may be one possible site for diffusion of the contrast agent. The circumventricular structures are other sites where gado-

Figure 3. a–d. Axial T1-weighted **(a)**, coronal T2-weighted **(b)**, and axial FLAIR **(c)** MR images show edema in the central pons *(arrows)* and preservation of the tegmentum and ventrolateral aspects of the pons. Axial FLAIR MR image **(d)** repeated six weeks later shows that the lesion has completely resolved.
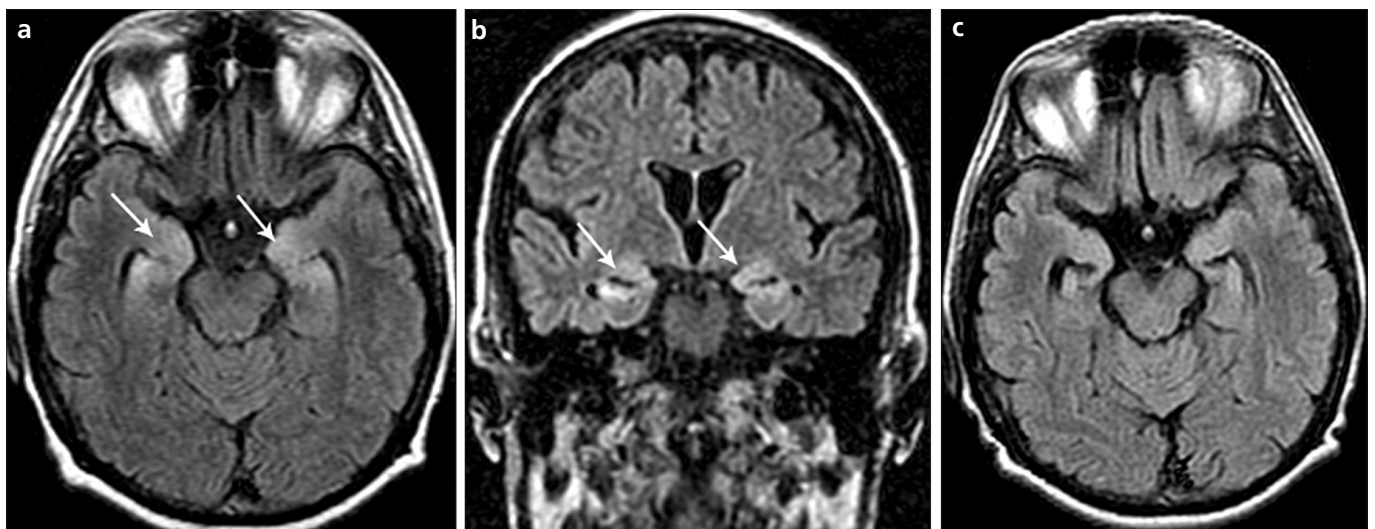

Figure 4. a–c. Axial **(a)** and coronal **(b)** FLAIR MR images of a 57-year-old woman with a high fever and delirium show high signals in the hippocampal and parahippocampal areas bilaterally *(arrows)*. On the follow-up axial FLAIR MR image **(c)**, high signals in the hippocampal and parahippocampal areas have completely resolved.
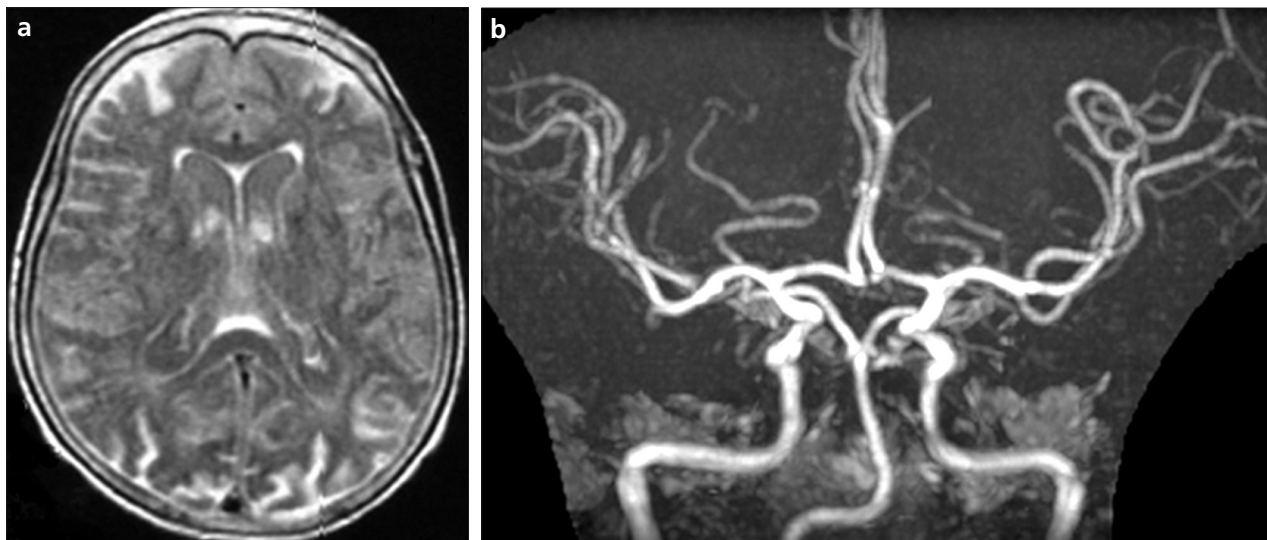
Figure 5. a, b. Axial FLAIR image (a) obtained three days after intravenous gadolinium administration demonstrates a significant, diffuse increased signal intensity within the subarachnoid space and the ventricles because of a delay in the clearance of the gadolinium chelate. The same-day MR angiography (b) was normal.

linium may move along an osmotic gradient, prolonging the elevation of the plasma concentration (15).

Gadolinium accumulation in the subarachnoid space is a potentially under-recognized phenomenon and may cause some confusion in diagnosis. Thus, accumulation should be differentiated from other possible causes, such as bleeding, infections, and complications from electrolyte alterations in ESRD patients. This knowledge would likely prevent diagnostic errors and unnecessary interventions (16).

Sinus vein thrombosis

ESRD patients also have predisposing factors that lead to sinus vein thrombosis. Cerebral venous sinus thrombosis is a rare but potentially dangerous disease. Clinical presentations involve different parts of the cerebral venous system. Initial symptoms include a headache of varying severity, raised intracranial pressure, and cerebral venous infarcts, which are frequently hemorrhagic and may lead to seizures, neurologic deficits, disorders of consciousness, or death.

A computed tomography (CT) scan is usually the first diagnostic assessment performed in an emergency situation. Although a CT scan can detect a spontaneously hyperdense thrombosed sinus at times, it usually shows nonspecific changes, such as hypodensities, blood, and contrast enhancement; in up to 30% of cases, the CT scan findings are normal. The present "gold standard"
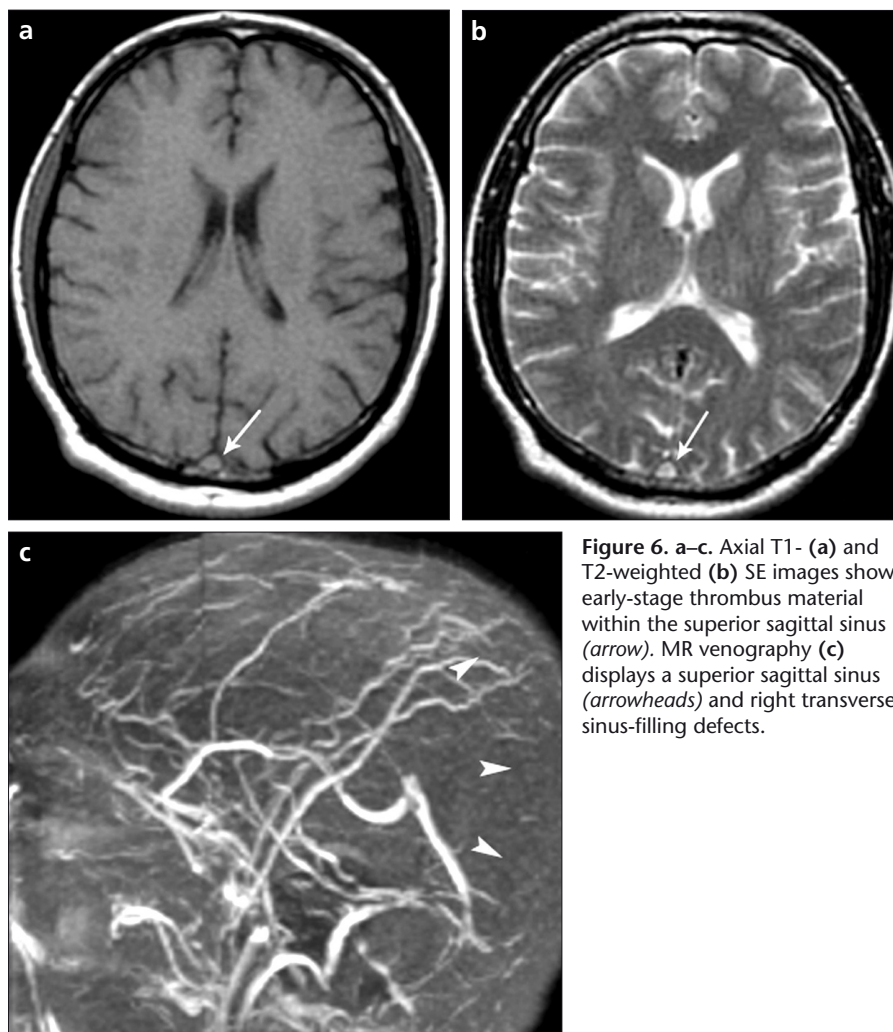

Figure 6. a–c. Axial T1- (a) and T2-weighted (b) SE images show early-stage thrombus material within the superior sagittal sinus (arrow). MR venography (c) displays a superior sagittal sinus (arrowheads) and right transverse sinus-filling defects.

for the diagnosis of SVT is no longer cerebral angiography but MRI, which displays the thrombosed sinus as an increased signal on both T1- and T2-weighted imaging (Fig. 6). The signal characteristics will vary depending on

the time at which the MRI was performed in relation to the onset of the thrombosis. A MR venography is, nevertheless, indicated in the very early (i.e., before day 5) or late (i.e., after 6 weeks) stages when a false-negative result from MRI may occur or whenever a routine MRI shows equivocal signs. Although MRIs and MR venograms are now the preferred imaging methods, a conventional angiogram may be necessary for patients with cortical vein involvement or equivocal MRI studies (17).

Dialysis disequilibrium syndrome

Dialysis disequilibrium syndrome is an acute neurological disorder that occurs in patients receiving hemodialysis. Clinical features include headache, nausea, blurry vision, hypertension, seizures, and coma (18). It is most often seen in patients undergoing rapid hemodialysis during one of the initial treatments. The diagnosis is one of exclusion; uremia, hyponatremia, hypoglycemia, stroke, and subdural hematoma must be excluded first. While there is no definitive diagnostic test, many authors agree that the clinical presentation is the result of cerebral edema, a direct result of dialysis treatment. The pathophysiology and description of this edema have been controversial (18). Increased levels of cerebral edema, particularly in the posterior parietooccipital regions, have even been documented by MRI in patients on hemodialysis who have no neurological symptoms (19).

In conclusion, acute cerebrovascular events, which are the most frequent cause of morbidity and mortality in ESRD patients, have various clinical manifestations. In ESRD patients, MRI is a valuable assessment method that aids in the early diagnosis of acute cerebrovascular events.

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