



The Diagnosis and Treatment of Cerebral Venous Thrombosis

Serebral Venöz Sinüs Trombozunda Tanı ve Tedavi

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Abstract

Cerebral venous sinus thrombosis involves thrombosis of the dural sinuses and/or cerebral veins. It constitutes 0.5-1% of all strokes and usually affects young individuals. It is slightly more common in young women due to pregnancy, puerperium, and oral contraceptive use. Patients usually present with headache or focal neurologic deficits. The superior sagittal sinus is most frequently affected sinus. Variations in venous anatomy, such as atresia/hypoplasia of the sinuses or asymmetric drainage of the sinus, may mimic sinus thrombosis. In general, magnetic resonance imaging is more sensitive than computed tomography in the detection of cerebral venous sinus thrombosis at each stage. Anticoagulants are the first preferred group of drugs in the treatment.

Keywords: Anticoagulation, thrombosis, venous sinus

Öz

Serebral venöz sinüs trombozu, dural sinüslerin ve/veya venlerin trombozunu içerir. Tüm inmelerin %0,5-1'ini oluşturur ve genellikle gençlerde görülür. Gebelik, puerperyum ve oral kontraseptif kullanımı nedeni ile genç kadınlarda biraz daha fazla görülmektedir. Hastalar genellikle baş ağrısı veya focal nörolojik defisit nedeni ile başvurur. En sık superior sagittal sinüs etkilenir. Sinüslerin atrezisi/hipoplazisi, asimetrik sinüs drenajı gibi venöz anatomideki varyasyonlar sinüs trombozunu taklit edebilir. Genel olarak manyetik rezonans görüntüleme kullanımı bilgisayarlı tomografi kullanımına göre trombozun tüm dönemlerinde tanı için daha duyarlıdır. Tedavide ilk tercih edilecek ilaç grubu antikoagülanlardır.

Anahtar Kelimeler: Antikoagülasyon, tromboz, venöz sinüs

Introduction

Venous sinus thrombosis (VST) is one of the rare causes of ischemic stroke. Recent developments in imaging techniques and increased awareness of this disease have enabled diagnosis of more cases. It has an annual incidence of 0.2-1.2 cases per 100.000 persons (1,2,3). The vast majority of ischemic strokes are of arterial origin, and venous strokes account for only 1% of all strokes (1). It can be seen in all age groups, but is more common in the newborn and children than in adults. Although there is no sex predominance in children and the elderly, it is 3 times more common in women (age 20-35 years) than in men during early adulthood (4,5). The

most important cause for this difference is additional risk factors such as pregnancy, puerperium, and oral contraceptive use (6,7). The average age of diagnosis of VST is 39 years (8). Only 8% of patients are aged over 65 years (9). The prognosis of VST is usually good, even though it can be fatal.

Cranial Venous Sinuses

The veins of the brain are found in the subarachnoid space, they do not have muscle tissue and valves, and they drain into the cranial venous sinuses (Figure 1). Venous sinuses are anatomic cavities formed by layers of the dura and they do not contain vessel

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walls. Sinuses, which are classified into two groups as superficial and deep, eventually merge and form the internal jugular vein. In this anatomic structure, the arachnoid membrane (villi) protrudes into the dural sinus by perforating the dura in some areas and causes a protrusion. These structures are called arachnoid granulations and they are just extensions of the arachnoid membrane, which causes the release of cerebrospinal fluid (CSF). The most common locations are the superior sagittal sinus and the transverse sinus. The function of arachnoid granulations is to provide CSF drainage into venous sinuses when necessary in terms of intracranial pressure dynamics. Arachnoid granulation tissue is a normal anatomic structure, but it causes filling defects on radiologic images and may be erroneously interpreted as VST if due attention is not paid.

Two systems have been identified related to the distribution of dural venous sinuses. The superficial system includes the superior sagittal sinus and cortical veins, and the deep system comprises the transverse (lateral) sinus, vein of Galen, straight sinus, and sigmoid

sinus. They all merge distally to form the internal jugular vein and join in the systemic circulation (Figure 2).

Symptoms

Although symptoms vary according to the location of the VST, the most common symptom is headache. The severity of headache can increase over days and can become unbearable. Patients may describe these headaches as the most severe they have ever felt. Besides symptoms such as nausea, vomiting, and blurred vision, VST may lead to focal neurologic deficits such as hemiparesis, speech disorders, and visual field defects, and different levels of disorders of consciousness such as confusion and coma. The symptoms can be acute or subacute, and can increase in days to weeks. Focal or generalized epileptic attacks and status epilepticus may occur. Epileptic attacks are more common in VSTs than in other ischemic strokes.

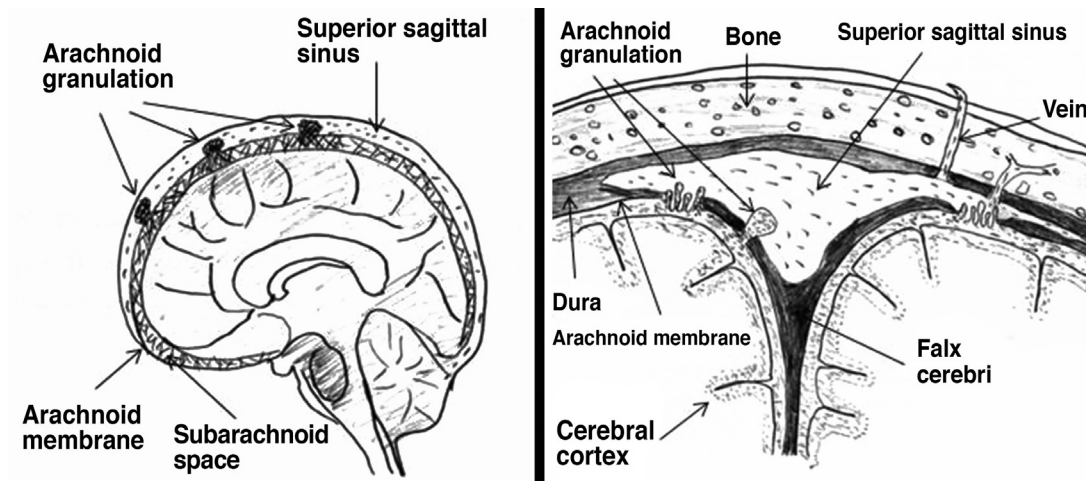


Figure 1. Arachnoid membrane covers the whole brain and forms the cerebrospinal fluid-draining protrusions, also known as arachnoid granulations, by perforating the dura in certain areas and protruding into venous sinuses. Cerebral veins drain into the venous sinuses between the layers of the dura and start the cerebral venous system. Figure is adapted by (27,28).

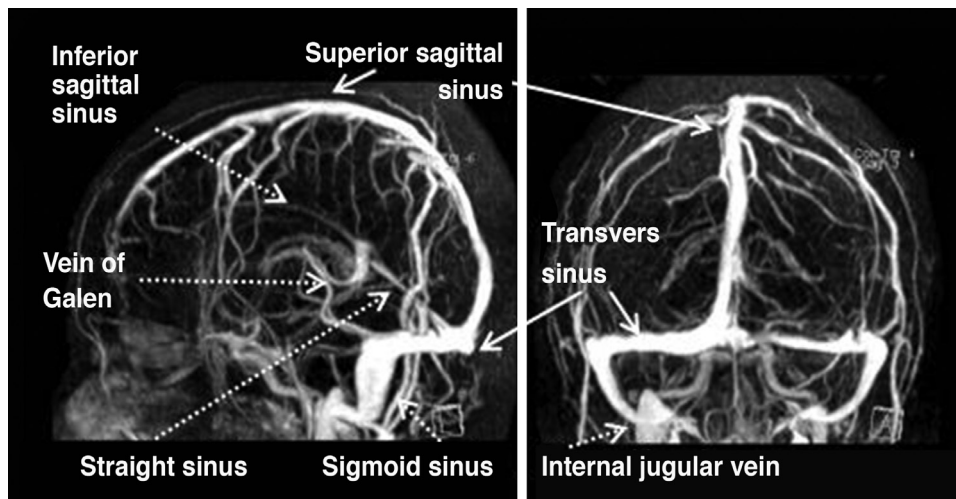


Figure 2. Cerebral veins and venous sinuses on sagittal and coronal slices in cranial magnetic resonance imaging

The location of the sinus thrombosis is decisive in the clinical presentation; the most commonly seen is thrombosis of the superior sagittal sinus (10). Headache and papilledema due to increased intracranial pressure is in the foreground in thromboses of this sinus. The involvement of cranial nerves, pain in the mastoid region and ears, and symptoms of ear infection can be observed in the transverse sinus thrombosis. Oculomotor palsy and orbital pain are at the forefront of cavernous sinus thrombosis (11,12). Homonymous hemianopsia, contralateral weakness, epileptic seizures, and aphasia due to involvement of cortical veins may be observed. Thalamic and basal ganglia infarct due to involvement of the internal cerebral vein, vein of Galen, and straight sinus, and related symptoms may occur in approximately 16% of cases (13,14).

Etiology

The most important risk factors for VST are blood flow stasis, vessel wall changes, and changes in blood content, also known as the classic Virchow triad. An underlying cause can be found in approximately 80% of cases (Table 1). It can be seen both during puerperium and pregnancy in young women (6). Twenty-seven to fifty-seven percent of all pregnancy-related ischemic strokes are due to VST (15,16). Oral contraceptive use and coagulation disorders are important causes. Connective tissue diseases and inflammatory bone diseases are risk factors (17). Genetic factors such as Factor V Leiden mutation, hyperhomocysteinemia, deficiency of protein C, protein S, and antithrombin 3, and prothrombin gene mutations are responsible in 10-15% of cases (18,19).

Cancer-induced hypercoagulability causes susceptibility to VST (20). Antiphospholipid and anti-cardiolipin antibody positivity was found in 5.6% of cases (8).

The etiologic factors are infections in about 8% of cases (1). Infections of the ears, sinuses, mouth, face, and neck regions cause VST owing to their close proximity.

Infections (regional, intracranial, systemic)
Head trauma
Malignancies
Connective tissue diseases
Behcet's disease
Sarcoidosis
Inflammatory bone disease
Coagulation disorders
Endocrine causes
Pregnancy, puerperium
Oral contraceptive use
Hereditary causes
Cardiac disorders
Dehydration
Inactivity

Pathology

There are two important underlying mechanisms in the pathology of VST. One of the mechanisms is parenchymal ischemic injury and the other is increased intracranial pressure. The capillary perfusion pressure in brain tissue decreases due to a pressure increase in the venous system following venous thrombosis. The increase in venous and capillary pressure leads to blood-brain barrier disruption, flow of fluid through the interstitial space, and vasogenic edema. If the pressure increase persists, venous hemorrhages occur with rupture of the venous capillaries. Increased pressure in vascular compartments adversely affects cerebral blood flow by decreasing cerebral perfusion pressure and brain damage increases with the development of cytotoxic edema (21).

The other mechanism is related to the blockage of CSF flow. CSF transport is normally through the superior sagittal sinus via the arachnoid granulations. When the sinus is occluded by a thrombus, CSF passage decreases and intracranial pressure increases gradually. Increased intracranial pressure is seen mostly in superior sagittal sinus thromboses.

Diagnosis

The diagnosis primarily requires a clinical suspicion and is confirmed through radiologic demonstration of thrombosis. The primary diagnostic method is cranial imaging. Superior sagittal and transverse sinus thromboses are the most frequent thromboses in such analyses. The involvement rates are given in Table 2.

Severe headache, which is the most important symptom indicating increased intracranial pressure, is seen in 90% of cases, and it worsens gradually within days to weeks. Although increased CSF pressure, protein level, and cell count is observed in some patients with VST, lumbar puncture is not diagnostic. However, it can be used for differential diagnosis of other pathologies that can cause headache (8). There is no specific serologic marker to confirm the diagnosis of VST; however, routine complete blood count, biochemistry panel, and prothrombin time analyses are suggested. Although high serum D-dimer levels support the diagnosis, normal values do not exclude the diagnosis.

Radiologic Imaging

There are 3 main aims of cranial imaging performed in order to exclude the suspicion of VST:

1. To demonstrate the presence/absence of variation (agenesis, atresia, asymmetry) in sinuses
2. To determine the location of the VST

Venous structure	%
Cortical veins	17
Superior sagittal sinus	62
Transverse (lateral) sinus	45
Straight sinus	18
Deep venous system (Galen)	11
Internal jugular vein	12

3. To detect the presence/absence of parenchymal damage (infarct, hemorrhage)

Anatomic variations such as sinus hypoplasia/atresia, asymmetric sinus drainage, arachnoid granulation, and sinus septa can imitate sinus thrombosis in radiologic examinations in many cases (22). In several studies, cranial magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) revealed partial or total agenesis of the transverse sinus in 20% of subjects and transverse sinus asymmetry in the absence of any pathology in 49% (23,24). The features of 3 modalities that can be used in the diagnosis of sinus thrombosis are given below.

Computed Tomography

Computed tomography (CT) is the most widely used primary imaging modality with easy accessibility. Unenhanced CT does not have an important diagnostic role. It is not adequate for demonstrating sinus variations and ischemic changes. The most important finding is the hyperdense appearance of the thrombosed cortical vein or dural sinus, which can be visualized in 1/3 of cases (Figure 3, 4). Thrombosis of the posterior portion of the superior sagittal sinus leads to a hyperdense appearance of the sinus on unenhanced CT and this finding is called the "delta sign". No contrast can be visualized in the middle of the sinus on contrast-enhanced CT due to thrombosis, but a rim of contrast enhancement can be seen. This contrast filling defect finding is called the "empty delta sign" (Figure 5) (25).

Magnetic Resonance Imaging

Cranial MRI is more sensitive than CT in the diagnosis of VST. Although the ideal method in the diagnosis was previously catheter angiography, cranial MRI and MRV are currently the main diagnostic methods (26). We can detect the presence of sinus variations or thrombosis on non-contrast-enhanced MRI with T2, T1, fluid-attenuated inversion recovery (FLAIR) analysis in the axial, coronal, and sagittal planes. Most of the time, the standard 5-mm thick sections performed in almost all centers in our country are adequate for gathering information about the sinuses while

paying attention to artifacts. It is important to know the normal appearance of the sinuses, and on which sequence and in which plane to search for the anatomic location of sinuses on cranial MRI. In general, we can obtain satisfactory information about venous sinuses on T1, T2, and FLAIR sequences in the axial, coronal, and sagittal planes without venography (Figure 6, 7, 8).

The first thing to determine on cranial MRI, as mentioned above, is the presence of sinus variation. The continuity of the sinus should be followed in subsequent sections with necessary adjustments, and the right/left symmetry should be examined carefully. Sinus atresia should be investigated thoroughly on all sequences in all planes. If suspicions cannot be resolved, thinner sections can be obtained, and contrast agent can be used to analyze venography and post-contrast T1 examinations.

MR venography is often used to confirm the diagnosis of thrombosis. However, as shown in Figure 7, venography alone can also be confusing. If the other sequences are not taken into consideration and diagnosis is made only using venography, misinterpreting atresia/agenesis for thrombosis is extremely easy. One common mistake, as seen in Figure 8, is mistaking arachnoid granulation tissue for thrombosis (27,28).

The demonstration of isointense or hyperintense fullness, which may vary according to the stage of period of within the sinus on T1, T2 and FLAIR sequences is an important finding for detecting whether the sinus is thrombosed. Confirmation of the same finding with other sequences, and ensuring the exclusion of artifacts and arachnoid granulation supports the diagnosis. If necessary, filling defects in sinuses can be visualized using both contrast-enhanced T1 sequences and venography. FLAIR and T2 sequences may demonstrate venous infarct, parenchymal hemorrhage or subarachnoid hemorrhage secondary to thrombosis (Figure 9, 10, 11). One of the most important distinguishing features of venous infarctions is the discordance between the region of infarction and the region of arterial blood supply.

Gradient echo and susceptibility-weighted imaging (SWI) sequences are basically susceptible to hemorrhage and calcification. However, each sequence is also used for visualizing the intravascular

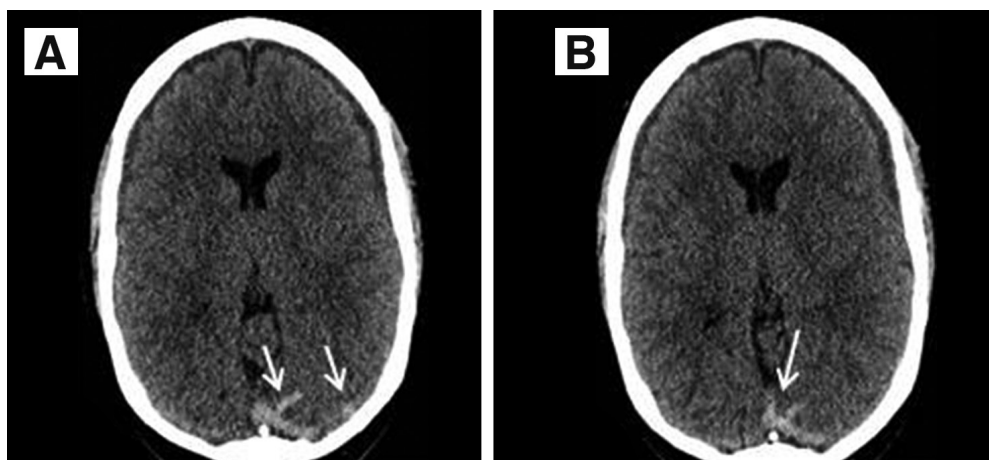


Figure 3. Hyperdense appearance of sinus thrombosis at the junction of superior sagittal sinus and transverse sinus in unenhanced axial computed tomography examination

thromboses. Thromboses in arteries, veins or the dural sinus cause hypointensity (29).

Contrast-enhanced venography unquestionably confirms the diagnosis of thrombosis. The diffusion sequence can demonstrate

ischemic changes, and gradient echo and SWI sequences can easily demonstrate hemorrhage.

The worst approach in the use of MRI for the diagnosis of venous thrombosis is to assume that MRV as the decisive sequence.

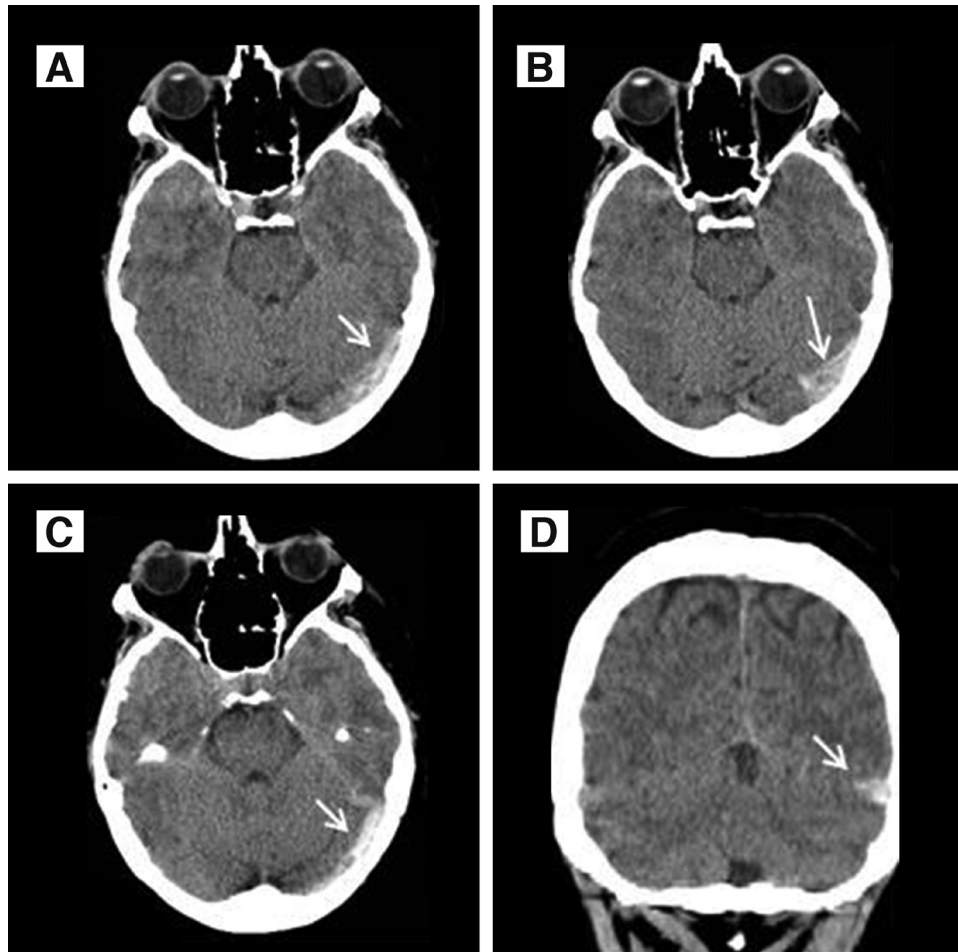


Figure 4. Hyperdense appearance consistent with left transverse sinus thrombosis on (A, B, C) axial and (D) coronal slices in unenhanced cranial computed tomography examination

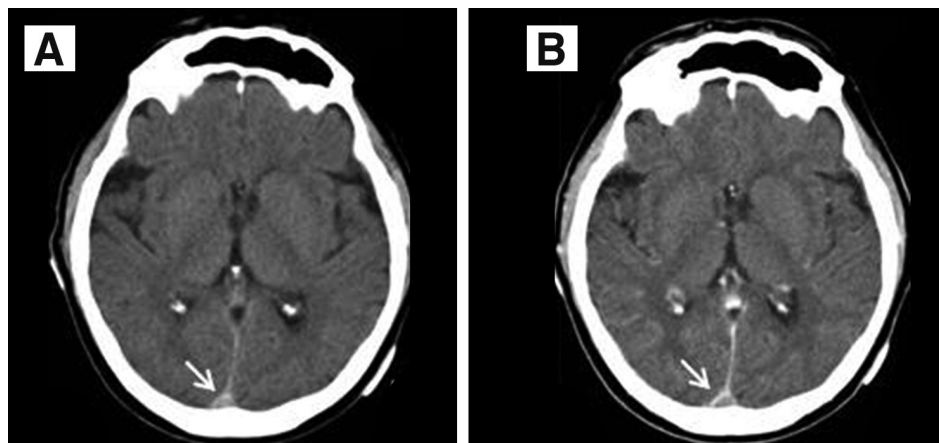


Figure 5. Hyperdense appearance “delta sign” at the posterior segment of superior sagittal sinus in unenhanced axial cranial computed tomography images (A), contrast filling defect “empty delta sign” due to thrombosis at the same location in contrast-enhanced computed tomography images (B)

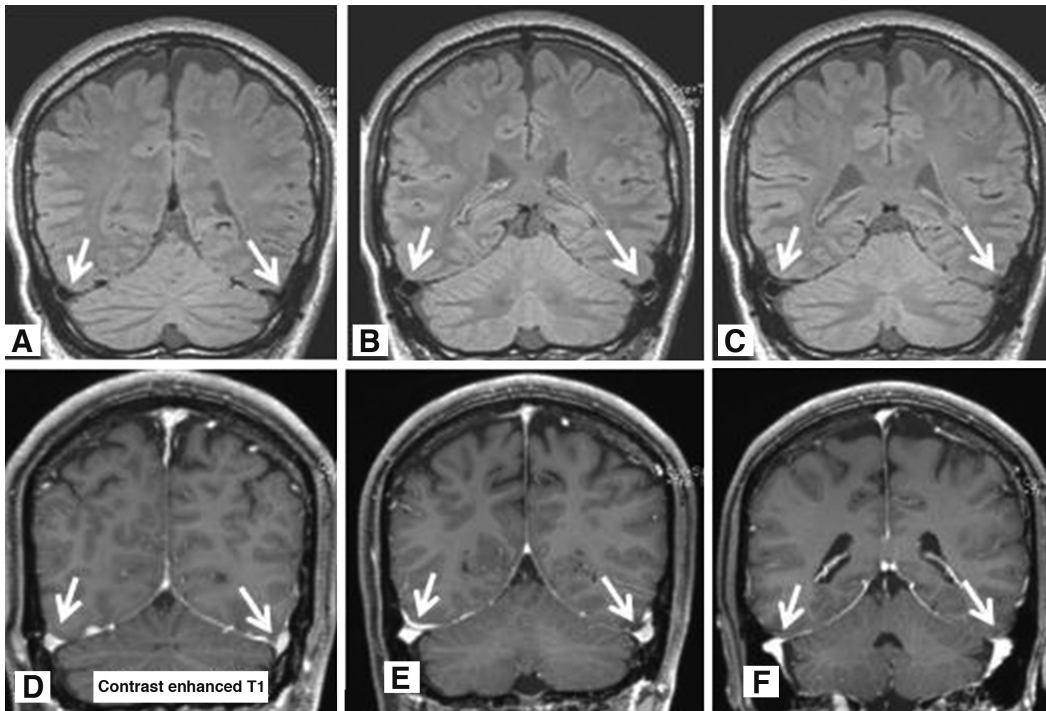


Figure 6. Normal appearance of the sinuses on coronal slices in cranial magnetic resonance imaging. Unenhanced T1 (A, B, C), contrast-enhanced T1 examinations (D, E, F)

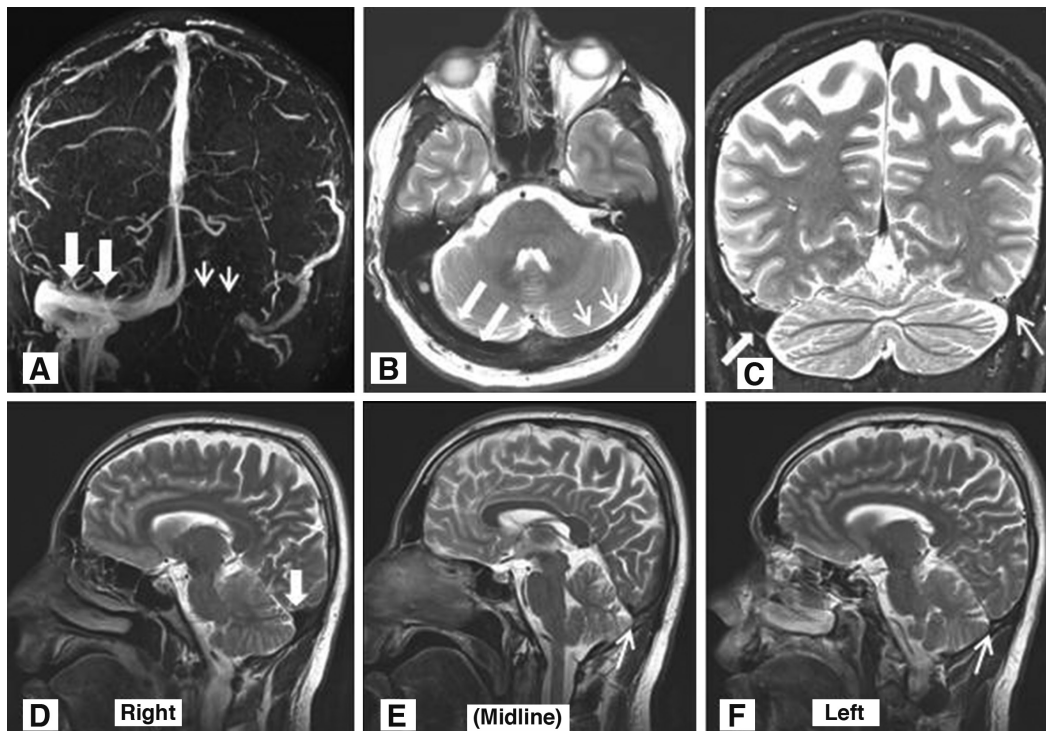


Figure 7. Although the right transverse sinus (thick arrow) is visualized, the left transverse sinus (thin arrow) cannot be visualized due to atresia in (A) venography, (B) axial T2, (C) coronal T2, (D, E, F) sagittal T2 images. Note: In this case, venography demonstrated only the absence of flow in the left transverse sinus. It did not provide information about thrombosis or atresia, which might be the reason for the lack of flow. Atresia on the left side could only be determined after conventional axial, coronal and sagittal examinations. The lack of flow in the transverse sinus has been shown to be due to atresia rather than thrombosis.

The transverse sinus is not visible in three cases in Figures 7, 8, and 9 on MRV, but there is thrombosis in only one case. The most important aspect of venography is that it can visualize the presence/absence of filling defects in the venous sinuses accurately. However, the most important problem in this investigation is that it does not provide sufficient information about the cause in cases where venous sinuses cannot be totally visualized. As it is often the case, the diagnosis of thrombosis or agenesis that may cause the total filling defect in the venous sinus is made by examining sequences other than venography.

Magnetic resonance black-blood thrombus imaging is a new MRI sequence that will be used in the diagnosis of VST in the future. Its sensitivity for the diagnosis of thrombosis in a small series of patients was found as 97.4% (30). Although it is not available for routine use and there are as yet insufficient related studies, this non-contrast-enhanced study will be a first-line sequence used in VST diagnosis in the future.

Digital Subtraction Angiography

Digital subtraction angiography (DSA) is rarely needed during the diagnostic stage because MRV and CT venography provide sufficient information in most of cases (31). If a decision cannot be made with other venography methods and/or an endovascular intervention is considered, DSA can be performed in VST. The

cortical veins can be better displayed during the venous phase in DSA in cases in which cortical veins cannot be demonstrated well with MRI.

Treatment

Treatment should be initiated urgently following confirmation of the diagnosis. If there is a specific underlying factor that leads to thrombosis, factor-targeted therapy should be started immediately and problems such as infection, inflammation, epileptic attacks, and dehydration should be immediately treated. Anticoagulation is the main treatment. The efficacy of anticoagulation has been shown in two randomized controlled trials (32,33). There are no studies showing the efficacy of aspirin or other antiplatelets.

The general consensus is for the treatment of CVST is to anticoagulate all patients (34,35,36). Low-molecular-weight heparin was found to be superior to unfractionated heparin (37). It has been shown that recanalization starts after 3 months and increases within the first 12 months at various rates (38). It has been suggested that anticoagulation should be continued for 6 months with vitamin K antagonists after the acute phase (22,39,40).

A relationship between recanalization rates and the location of thrombosis was also shown. Higher rates of recanalization in deep cerebral veins and cavernous sinuses, and lower rates of recanalization in the transverse sinus were found (41). Recurrence

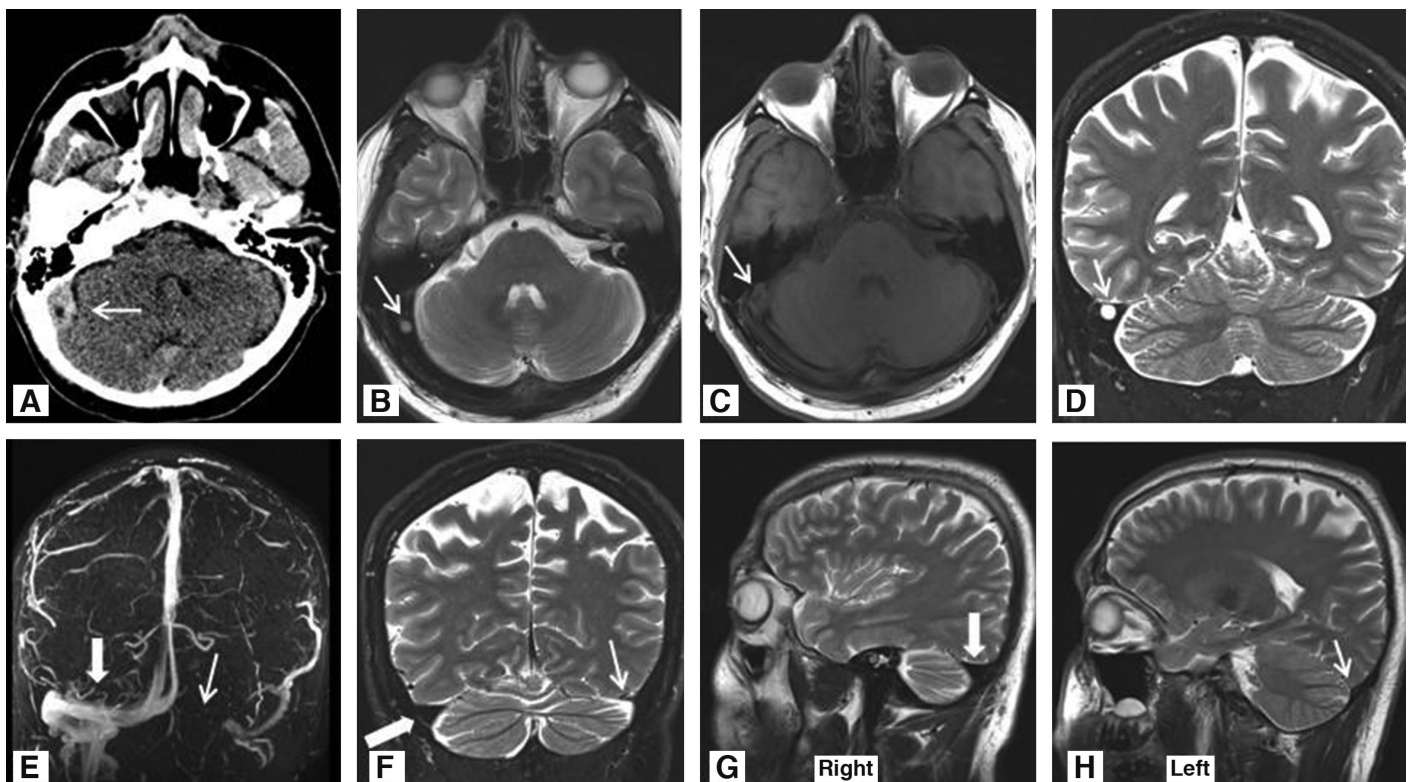


Figure 8. Images of a 37-year-old male patient admitted with headache. (A) Arachnoid granulation in the right transverse sinus in unenhanced axial CT examination; (B) axial T2, (C) axial T1 and (D) coronal T2 examinations revealed open right transverse sinus and hyperintensity consistent with arachnoid granulation in the sinus; (E) venography, (F) coronal T2 and (G, H) sagittal T2 images demonstrating open right transverse sinus (thick arrow) and atresia of the left transverse sinus (thin arrow). Note: Two separate reasons that could lead to mistakes coexisted in the same patient by coincidence. Arachnoid granulation in the right transverse sinus and atresia on the left side

after VST was observed as 2-4%. In a study of 145 cases, recurrence was observed in 3% of patients 6 years after discontinuation of anticoagulation (42).

Endovascular treatment has been tried in patients with severe VST with no improvement despite systemic heparin therapy or in patients with contraindication for anticoagulation.

Endovascular approaches include pharmacologic thrombolysis, balloon angioplasty, mechanical thrombectomy, and penumbra aspiration (43). In addition to the lack of agreed indications for endovascular thrombolytic therapy, there is no significant evidence of efficacy or superiority over other treatments except case series.

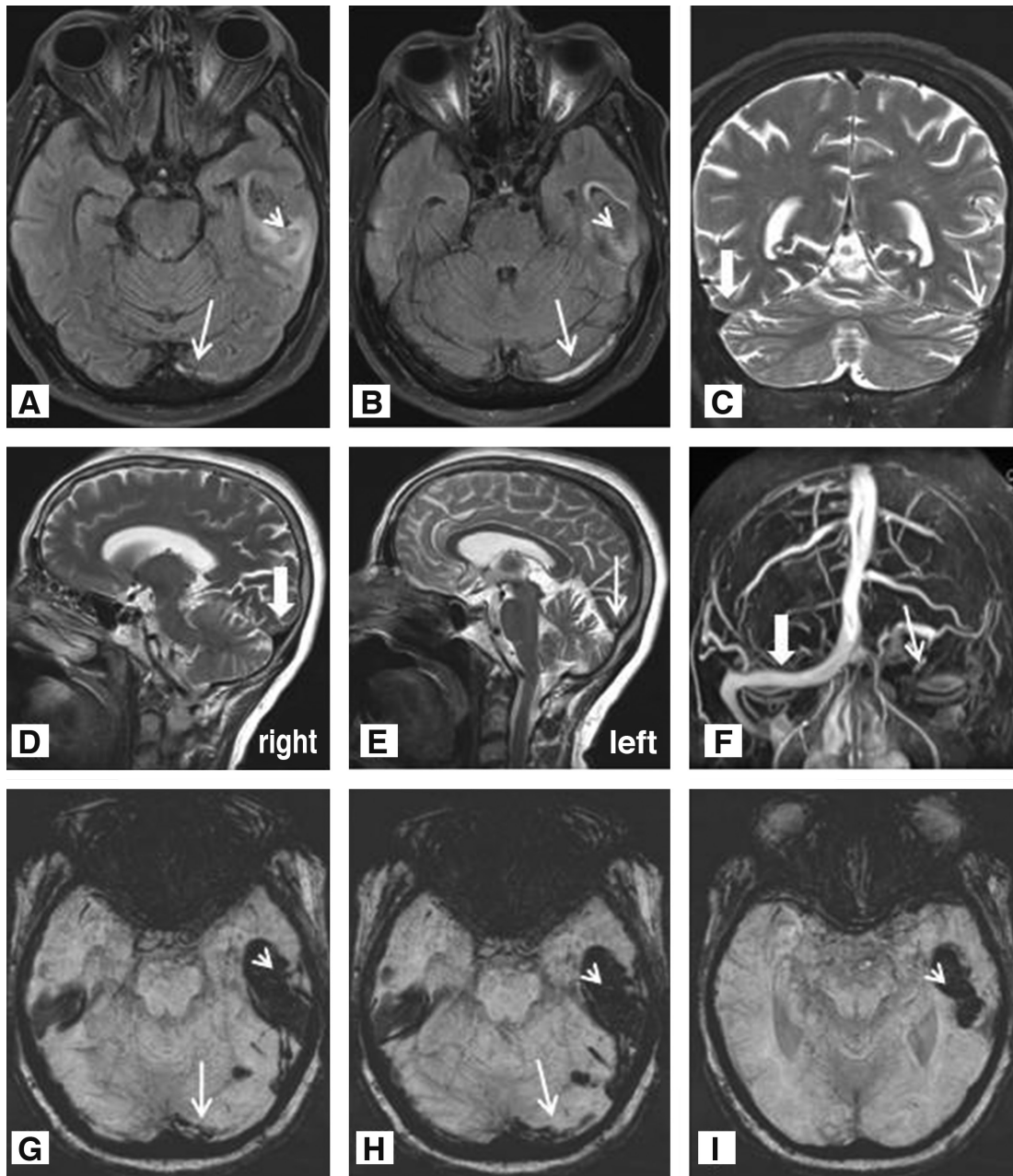


Figure 9. Hyperintensity (thin arrow) consistent with thrombus along the left transverse sinus trace and hyperintensity (arrowhead) consistent with left temporal parenchymal hemorrhage in axial fluid-attenuated inversion recovery images (A, B); coronal T2 (C) and sagittal T2 images demonstrating presence of both transverse sinuses, open right transverse sinus (thick arrow) and hyperintensity (thin arrow) (D, E) consistent with thrombus in the left transverse sinus; no flow in the left transverse sinus on venography (F); hypointensity consistent with venous sinus thrombosis in the left transverse sinus and hypointensity consistent with parenchymal hemorrhage in the left temporal region on axial susceptibility-weighted imaging sequence (G, H, I). Note: In this case, the diagnosis of venous sinus thrombosis and absence of atresia were confirmed with conventional axial, coronal and sagittal examinations rather than venography.

Prognosis

The increased knowledge on VST in recent years, easier diagnosis, better radiologic imaging, and rapid initiation of effective treatment has a positive impact on prognosis. The majority of patients may respond well to anticoagulant therapy. Compared with arterial ischemic strokes, the prognosis is better and mortality is lower in venous ischemic strokes. The mortality rate was reported as 4.3% in the International Study on Cerebral Vein and Dural Sinus Thrombosis (8). In a large multicenter study, transtentorial herniation due to unilateral hemorrhagic

lesions or diffuse edema due to bilateral lesions was shown to have important roles in mortality (44). The most important predictors of mortality are epileptic seizures within the first 30 days, impaired consciousness, a Glasgow Coma Scale score below 9, and hemorrhages, especially on the right side and posterior fossa lesions (44).

Ethics

Peer-review: Externally and internally peer-reviewed.

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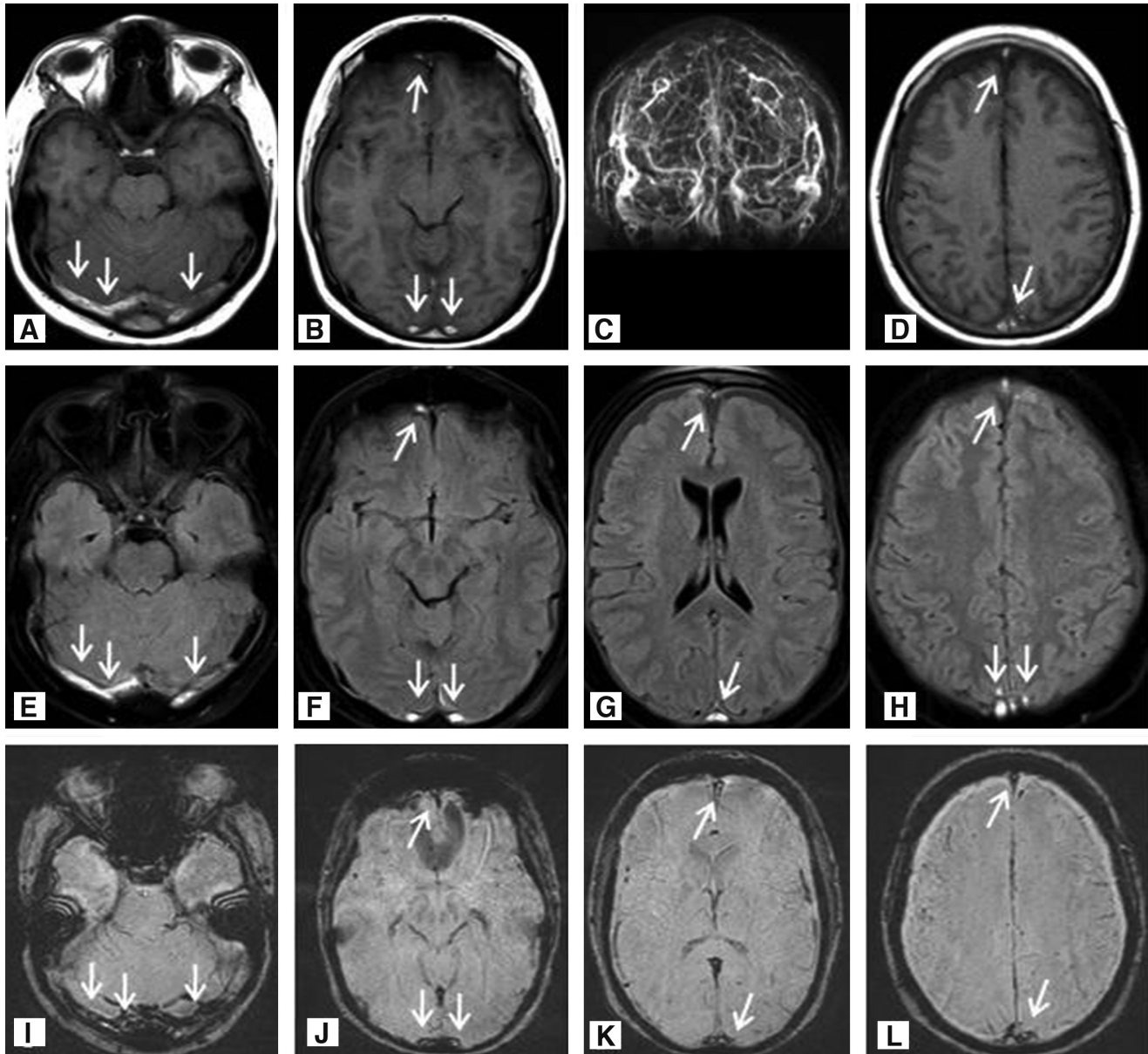


Figure 10. On axial magnetic resonance imaging slices from same regions in an 18-year-old male patient diagnosed with acute lymphoblastic leukemia (A, B, D) hyperintensity in anterior and posterior superior sagittal sinuses, both transverse sinuses in T1 images; (C) filling defects consistent with bilateral thrombosis in all sinuses in venography; (E, F, G, H) hyperintensity consistent with thrombosis in the same areas in fluid-attenuated inversion recovery examination; (I, J, K, L) hypointensity consistent with thrombosis in the same area on susceptibility-weighted imaging sequence

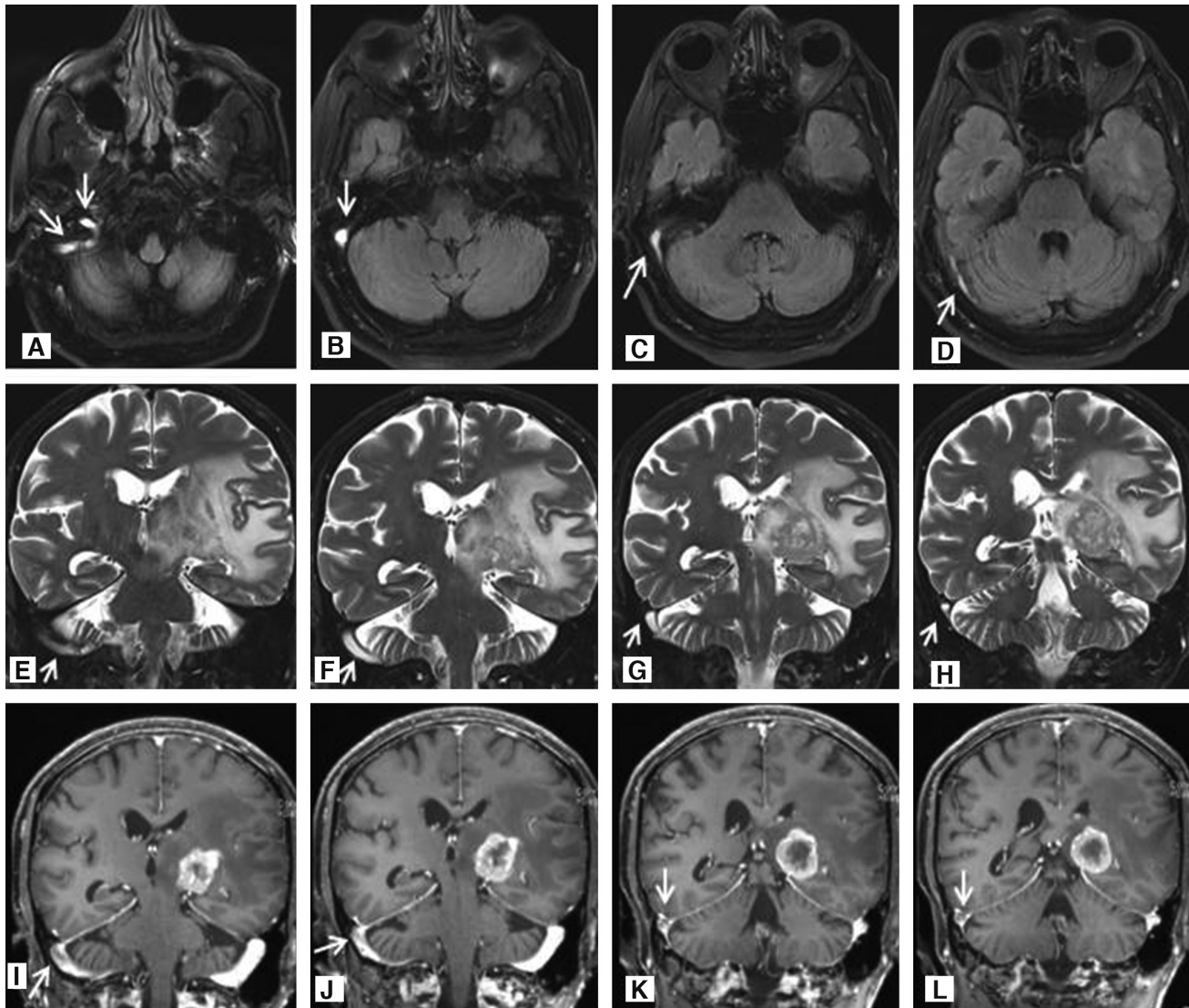


Figure 11. Cranial magnetic resonance imaging examination of a 57-year-old male patient diagnosed as having lung cancer and brain metastases. Hyperintensity consistent with thrombosis in the right transverse and sigmoid sinuses on axial fluid-attenuated inversion recovery slices (A, B, C, D); hyperintensity consistent with thrombosis in the right transverse and sigmoid sinuses in addition to the metastasis and edema appearance in the left thalamic and parietal region in coronal T2 images (E, F, G, H); contrast filling defect consistent with thrombosis in the right transverse and sigmoid sinuses in addition to the appearance of contrast-enhancing metastasis in the thalamus in contrast-enhanced coronal T1 examinations (I, J, K, L).

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