Review Article

Diagnosis and Management of acute Neurological disorders in Pregnancy and Postpartum

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Introduction

For physicians attending an emergency call from department of Obstetrics, pre-eclampsia and eclampsia are often the default diagnoses in pregnant and postpartum women who present with acute neurological symptoms of Headache, Acute neurological deficit and or Seizures. However, there are other conditions that overlap with eclampsia and with each other in terms of their presentations.

Pre-eclampsia is defined as the new onset of hypertension and proteinuria after 20 weeks in a previously normotensive woman. Eclampsia is defined as pre-eclampsia and a generalised seizure in the absence of other conditions that could cause seizures.

Acute neurological symptoms in pregnant and post-partum women could be caused by 1. Exacerbation of a pre-existing neurological condition. 2. The initial presentation of a non-pregnancy-related problem or 3. A new acute-onset neurological problem that is either unique to or occurs with increased frequency during or just after pregnancy.

Here we focus on diagnosis of the later patient group, which most commonly includes Pre-eclampsia and eclampsia. However there are a range of conditions that overlap with eclampsia and with each other in terms of their presentations, including cerebral venous sinus thrombosis (CVT), reversible cerebral vasoconstriction syndrome (RCVS; also referred to as postpartum angiopathy and Call-Fleming syndrome) which can develop during puerperium in the absence of hypertension or other features of pre-eclampsia. Pre-eclampsia, eclampsia, and RCVS can all be complicated by posterior reversible encephalopathy syndrome (PRES). PRES is not a primary diagnosis, but a clinical and imaging syndrome caused by vascular abnormalities that are present in preeclampsia and eclampsia, RCVS, and other conditions.

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The continuum between potential causes of some neurological problems that can arise in pregnancy must be recognized, and we need to understand that various diagnoses can arise independently or simultaneously, and are not mutually exclusive. Additionally, whereas eclampsia is specific to pregnancy, PRES, RCVS, and CVT occur in non-pregnant individuals too.

CEREBRAL VENOUS SINUS THROMBOSIS

About 75 percent of the adult patients are women. More than 75% of cases of CVT are post partum. The frequency of peripartum and postpartum sinus thrombosis is about 12 cases per 100,000 deliveries. Occlusion of the cerebral veins can cause localized edema of the brain and venous infarction.

Normally, the cerebrospinal fluid is transported from the cerebral ventricles through the subarachnoid spaces at the base and surface of the brain to the arachnoid villi, where it is absorbed and drained into the superior sagittal sinus. Thrombosis of the sinuses leads to increased venous pressure, impaired absorption of cerebrospinal fluid, and consequently, increased intracranial pressure.

Risk factors include - caesarean section, dehydration, traumatic delivery, anemia, raised

Table 1 : DIFFERENTIATING FEATURES OF THESE ACUTE NEUROLOGICAL DISORDERS:

Feature	PRES	RCVS	CVT	Eclampsia
Mode of onset	Rapid (hours), usually post partum	Abrupt, usually post partum	Third trimester or post-partum, symptoms often progress over days	Antepartum, intrapartum, or post partum (10–50%)
Key findings	Symptoms (eg, stupor, visual loss and visual hallucinations) usually accompany seizures; headache dull and throbbing, not thunderclap	Thunderclap headache, multiple episodes; seizures occur but are less common than in PRES; transient focal deficits (could become permanent in cases with intracerebral haemorrhage or infarction)	Headache nearly universal at onset, generally progressive and diffuse, thunderclap in small minority; seizures occur in roughly 40% of patients; focal signs might develop later	Seizures, frequent visual symptoms, abdominal pain, hyper-reflexia, hypertension, and proteinuria

PRES*-Posterior reversible encephalopathy syndrome
RVS**-Reversible cerebral vasoconstriction syndrome
CVT*** - Cerebral venous sinus thrombosis

homocysteine concentrations, and low CSF pressure due to dural puncture from a neuraxial anesthesia.

The clinical presentation is highly variable. The most frequent but least specific symptom of sinus thrombosis is severe headache present in more than 90 percent of patients. Usually increases gradually over a couple of days but can also start in a split second. Seizures occur in about 40% of patients. Seizures are limited and focal in 50 percent of these patients but may generalize to a life-threatening status- epilepticus.

Cortical lesions on both sides of the superior sagittal sinus: unilateral hemispheric symptoms such as hemiparesis or aphasia, followed within days by symptoms from the other hemisphere

Thrombosis of the deep venous system — the straight sinus and its branches: causes centrally located, often bilateral thalamic lesions, with behavioral symptoms such as delirium, amnesia, and mutism.

Infectious cavernous sinus thrombosis: headache, fever, and eye symptoms such as periorbital edema, proptosis, chemosis, and paralysis of eye movements due to involvement of the oculomotor, abducent, or trochlear nerves. Large unilateral infarcts or hemorrhages compress the diencephalon and brain stem, patients may become comatose.

The most sensitive examination technique is MRI in combination with magnetic resonance venography. T1-weighted and T2 -weighted MRI will show a hyper intense signal from the thrombosed sinuses. The combination of an abnormal signal in a sinus and a corresponding absence of flow on magnetic resonance venography confirms the diagnosis of thrombosis. If the diagnosis is still uncertain

Feature	PRES	RCVS	CVT	Eclampsia
Evolution over time	If blood pressure is controlled, symptoms resolve within days to wee	Dynamic process over time; generally, headaches common during first week, intracerebral haemorrhage during second week, and ischaemic complications during third week	Evolves over several days, non-arterial territorial infarcts and haemorrhages might develop	Can evolve (from pre-eclampsia) gradually or abruptly
CSF findings	Usually normal, might have slightly raised protein	Often normal (unless complicated by subarachnoid haemorrhage), but 50% of patients have slight pleocytosis and protein increases	Opening pressure raised in about 80% of patients; roughly 35–50% will have slightly raised protein or cell counts	Usually normal unless complicated by haemorrhage
Imaging aspects	CT positive in about 50% of patients; MRI shows prominent T2-weighted and FLAIR abnormalities nearly always in parieto-occipital lobes, but can involve other brain regions; intracerebral haemorrhage about 15% of patient	CT usually normal (if no subarachnoid haemorrhage); 20% show localised convexal subarachnoid haemorrhage on MRI; CT angiogram and magnetic resonance angiogram usually show typical string-of-beads constriction of cerebral arteries; digital subtraction angiogram is more sensitive; might have associated cervical arterial dissection; initial arteriogram might be negative	CT often negative; MRI might show non-arterial territorial infarcts; haemorrhage common; MRV shows intraluminal clot flow voids; although MRV is preferred, CT venogram is also sensitive	Same as for PRES, some patients have coincident acute ischaemic stroke or intracerebral haemorrhage

after MRI or CT venography has been performed cerebral angiography may be indicated.

The priority of treatment in the acute phase is to stabilize the patient's condition and to prevent or reverse cerebral herniation. This may require the administration of intravenous mannitol, surgical removal of the hemorrhagic infarct, or decompressive hemicraniectomy.

Anticoagulation: The most obvious treatment option is anticoagulation with heparin to arrest the thrombotic process.

In patients who have symptoms of chronic intracranial hypertension only, the first priority is to rule out a space-occupying process and to investigate whether sinus thrombosis is indeed the cause. If there are no contraindications, a lumbar puncture is then performed to measure the cerebrospinal fluid pressure. This is also the start of treatment, the objective of which is to lower the intracranial pressure, to relieve headache, and to reduce papilledema.

Oral acetazolamide (500 to 1000 mg daily): May reduce the intracranial pressure. Often, if effective and tolerated, this agent must be continued for weeks to months, as demonstrated among patients with idiopathic intracranial hypertension.

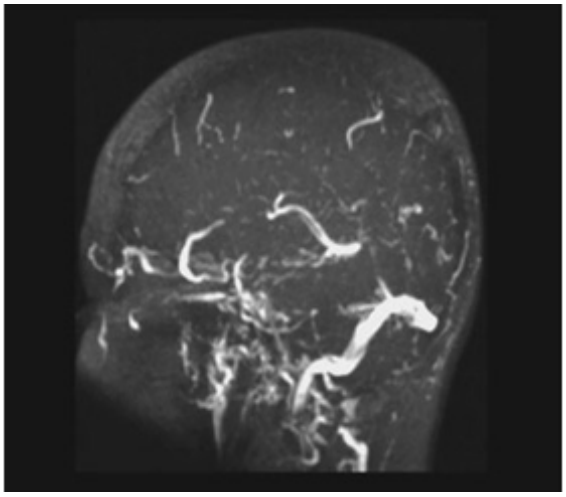


Figure 1, a magnetic resonance venogram obtained without the administration of contrast material reveals the absence of a signal in the superior sagittal sinus (upper arrows) and a normal flow signal in the transverse and sigmoid sinuses (lower arrow) as well as in a number of veins

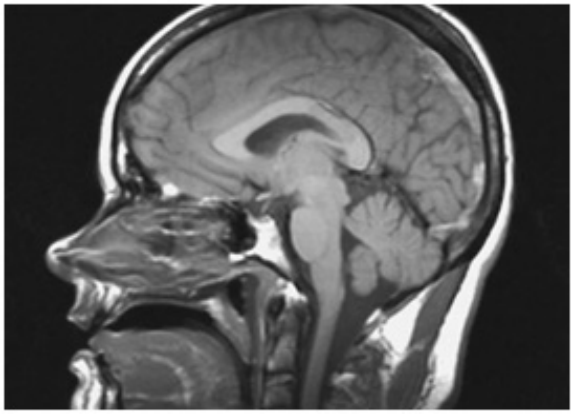


Figure 2 a T1-weighted MRI scan obtained with the spin–echo technique provides a sagittal view of a hyperintense signal in the thrombosed superior sagittal sinus (arrows).

If repeated lumbar punctures and treatment with acetazolamide do not control the intracranial pressure within about two weeks, surgical drainage of the cerebrospinal fluid is indicated, usually by a lumboperitoneal shunt. If the visual fields deteriorate, fenestration of the optic-nerve sheet should be considered.

REVERSIBLE CEREBRAL VASOCONSTRIC TION SYNDROME

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, with or without other acute neurological symptoms, and diffuse segmental constriction of cerebral arteries that resolves spontaneously within 3 months. Manifestations are attributed to a transient disturbance of the regulation of cerebral arterial tone. Thunderclap headache—severe pain peaking in seconds—is usually the first symptom and typically recurs for 1–2 weeks. Ischaemic and haemorrhagic stroke are the major complications of the syndrome. In 2007, Calabrese and colleagues proposed the name RCVS

RCVS has been reported in people aged from 10 to76 years, but occurrence peaks at around 42 years and the syndrome is more common in women than in men. More than half the cases occur post partum.

Clinical manifestations typically follow an acute and self-limiting course without new symptoms after 1 month. Headache is the main symptom and often remains the only manifestation of RCVS. Onset is acute with thunderclap headache—extreme head pain peaking in less than 1 min, mimicking that of a ruptured aneurysm

Typical headache is bilateral (although it can be unilateral), with posterior onset followed by diffuse pain. Nausea, vomiting, photophobia, and phonophobia frequently occur. By contrast with the headaches associated with ruptured aneurysms, the severe pain of RCVS is short lived (usually lasting 1–3 h).

A single attack is possible, but usually patients have a mean of four attacks, during 1–4 week all noteworthy headaches are generally gone 3 weeks after onset.

Associated neck pain should prompt investigations for cervical artery dissection.

Focal deficits, which can be transient or persistent, and seizures have been reported in 8–43% and 1–17%, respectively. Transient focal deficits are present in slightly more than 10% of patients, last from 1 min to 4 h, and are most frequently visual, but sensory, dysphasic, or motor deficits can also

occur. Persistent deficits, including hemiplegia, aphasia, hemianopia, or cortical blindness, suggest a stroke.

A third of patients have surges in blood pressure during acute headaches because of the pain, the syndrome itself, or an associated disorder.

Laboratory investigations:

The results of blood counts, measurements of ESR and concentrations of serum electrolytes, and liver and renal function tests are usually normal in patients with RCVS.

Tests for angiitis, including measurements of rheumatoid factor, antinuclear and antineutrophil cytoplasmic antibodies, and tests for Lyme disease are generally negative.

Urinary concentrations of vanillylmandelic acid and 5-hydroxy indoleacetic acid should be measured to exclude a diagnosis of phaeochromocytoma.

Serum and urine toxicology screens should be done to check for drug use.

Slight abnormalities of CSF are reported an excess of white blood cells (5–35 per µL), red blood cells with or without visible subarachnoid blood on an MRI scan. Increased protein concentrations of as much as 100 mg/dL. If the white blood cell count exceeds 10 cells per µL or the protein concentration exceeds 80 mg/dL, or if both measures are exceeded, analysis of CSF should be repeated after a few weeks to ensure that concentrations have returned to normal.

Neuroimaging:

Brain scans of many patients with RCVS look healthy despite the presence of diffuse vasoconstriction on concomitant cerebral angiograms.

Lesions include -

Convexity subarachnoid haemorrhage: Convexity subarachnoid haemorrhages are nonaneurysmal, usually mild, unilateral or bilateral, and manifest as a hyperintense signal on fluid-attenuated inversion recovery (FLAIR) MRI and a hypointense signal on T2*-weighted MRI in a few sulcal spaces near the convexity. Convexity subarachnoid haemorrhage is usually diagnosed within the first week of headache onset, sometimes after an initial normal MRI.

Focal intracerebral haemorrhage: Parenchymal haemorrhages are of variable volume, more frequently single than multiple and lobar than deep, and more often associated with another type of stroke. They occur early in the course of RCVS and are revealed mostly by a persisting focal deficit concomitant with thunderclap headache.

Cerebral infarction: Infarctions occur mainly in arterial watershed regions of the cerebral hemispheres, often between the posterior circulation and the carotid territories. Most patients with infarctions present with a focal deficit (transient or persistent). Ischaemic strokes usually occur later than do haemorrhagic strokes in the course of RCVS.

Reversible brain edema: Edema is an early manifestation of RCVS and is usually diagnosed within a few days of clinical onset. It is more frequently associated with at least one variety of strokes than isolated. Edema is better seen on MRI than on CT scans, with symmetrical FLAIR hyperintensities showing a distribution similar to that of posterior reversible encephalopathy syndrome. Edema usually totally reverses within 1 month of clinical onset, much earlier than does vasoconstriction.

Cerebral angiography

To diagnose RCVS, direct (transfemoral) or indirect (CT or magnetic resonance) cerebral angiography is needed to show segmental narrowing and dilatation (string of beads) of one or more arteries. Narrowing of arteries is not fixed; a repeat angiogram after a few days might show resolution of some vessels, with eventual new constrictions often affecting more proximal vessels. Furthermore, the patient's first angiogram, irrespective of type, might be normal if it is done early—i.e., within a week of clinical onset—even in the presence of haemorrhage or brain edema.

Diagnostic criteria for reversible cerebral

vasoconstriction syndrome

I. Acute and severe headache (often thunderclap) with or without focal deficits or seizures

II. Uniphasic course without new symptoms more than 1 month after clinical onset

III. Segmental vasoconstriction of cerebral arteries shown by indirect (e.g., magnetic resonance or CT) or direct catheter angiography

IV. No evidence of aneurysmal subarachnoid haemorrhage

V. Normal or near-normal CSF (protein concentrations <100 mg/dL, <15 white blood cells per μL)

VI. Complete or substantial normalization of arteries shown by follow-up indirect or direct angiography within 12 weeks of clinical onset

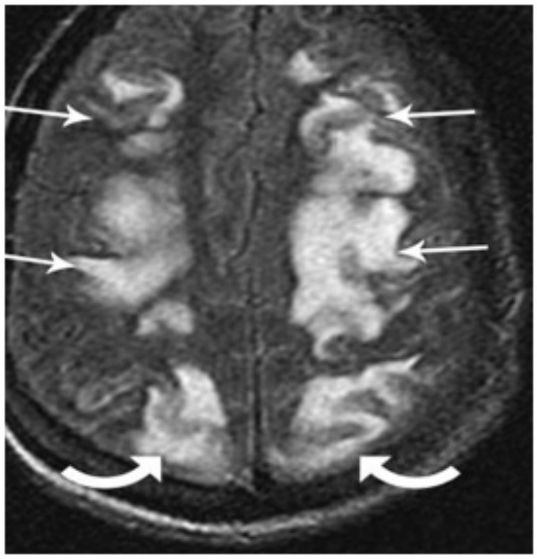
Management:

Primarily based on the identification and elimination of any precipitating or aggravating factors. Patients should be told to rest and advised to avoid physical exertion, Valsalva manoeuvres, and other headache triggers for a few days to a few weeks, depending on initial severity. Any vasoactive drugs should be stopped and avoided even after disease resolution. Treatment should include analgesics, antiepileptic drugs, monitoring of blood pressure. Clinicians should treat hypertension according to the guidelines for patients with acute stroke, but should keep in mind that hypotension in the setting of cerebral vasoconstriction is potentially more dangerous.

Nimodipine, verapamil, and magnesium sulphate have been used to relieve arterial narrowing. Nimodipine was given orally at the dose used for the prevention of vasospasm in aneurysmal subarachnoid haemorrhage (60 mg/4rth hourly). Duration of treatment ranged from 4 to 12 weeks.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

PRES is characterized by variable associations of seizure activity, consciousness impairment, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs. The cerebral imaging abnormalities are often symmetric and predominate in the posterior white matter. The main abnormality is cerebral vasogenic edema, the pathogenesis of which is still under debate. PRES is typically reversible once the cause is removed.



Axial MR images (fluid-attenuated inversion recovery) demonstrate extensive vasogenic edema in the frontal lobes (arrows), parietal region (curved arrows), occipital lobes (open arrows), and temporal lobes (arrowheads), bilaterally, consistent with PRES.

PRES has been reported in patients aged 4 to 90 years, although most cases occur in young to middle-aged adults, the mean age ranging from 39 to 47 years. There is a marked female predominance.

PRES is a clinicoradiological entity. The combination of suggestive clinical manifestations and radiological criteria establishes the diagnosis of PRES.

The typical features of PRES consist of consciousness impairment, seizure activity, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs. Consciousness impairment may range in severity from confusion, somnolence, and lethargy to encephalopathy or coma.

Acute hypertension is not usually described among the main signs of PRES. However, hypertension has been reported in most studies, in 67 %to 80 % of patients. Acute hypertensive emergency was not significantly associated with the intensity of the clinical or radiological manifestations of PRES. Therefore, high mean blood pressure is often observed in PRES but its level is not correlated to the severity of PRES.

The four radiological patterns of PRES – a.Holohemispheric watershed pattern (23 %) b.Superior frontal sulcus pattern (27 %) c.Dominant parietal-occipital pattern (22 %) d.Partial or asymmetric expression of the primary patterns (28 %)

MRI: Cerebral MRI is the key investigation for the diagnosis of PRES. Fluid-attenuated inversion recovery (FLAIR) sequences have been shown to improve the diagnosis of PRES and the detection of subcortical and cortical lesions in PRES.

Complications:

Cerebral ischemia: Cerebral infarction is among the early signs of non-reversible damage associated with adverse outcomes. In this setting, every effort must be taken to exclude RCVS.

Cerebral hemorrhage: Cerebral hemorrhage is uncommon in PRES. Cerebral hemorrhage may be more common among patients with allogeneic bone marrow transplantation or anticoagulant treatment.

Cerebral herniation: Posterior edema, particularly when located in the cerebellum and brainstem, may cause transtentorial cerebral herniation.

Conditions Most Commonly Associated With PRES:

Preeclampsia/Eclampsia: Pre-eclampsia/ eclampsia was present in 7 % to 20 % of patients with PRES.

Toxic Agents: Exposure to toxic agents is the most common condition associated with PRES, exposure to cancer chemotherapy and/or immunosuppressive therapy.

Hypertension: Hypertension is the second most common condition associated with PRES, being present in 6% to 72 % of cases.

Infection/Sepsis/Septic Shock: Infections have been reported in 8 % to 24 % of cases. The most common situation was PRES onset within 2 weeks after a Gram-positive bloodstream infection, often with hypertension at diagnosis.

Autoimmune Disease: Autoimmune disease has been encountered in 8 % to 10 % of cases.

Management: The need for upper airway protection should be evaluated continuously in patients with marked consciousness impairment or seizure activity. Patients with persistent seizure activity at ICU admission should be given intravenous benzodiazepines.

Antihypertensives: The aim is not to normalize the blood pressure but rather to decrease the Mean Arterial Pressure (MAP) by 20–25 % within the first 2 hours and to bring the blood pressure down to 160/100 mmHg within the first 6 hours correction of the underlying cause of PRES.

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