THE NORTHERN HOSPITAL

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical - radiographic condition of heterogenic causation , that occurs secondary to the inability of posterior circulation to autoregulate in response to acute changes in blood pressure.

Hyperperfusion results in disruption of the blood brain barrier which then results in vasogenic oedema, but not infarction, most commonly in the parieto-occipital regions of the brain.

PRES is really a group of *heterogeneous* etiologies that are grouped together because of similar findings on **neuroimaging studies.**

MRI is the best neuroimaging technique for the diagnosis of PRES.

PRES is typically a reversible condition once the cause is removed. However, a small number of patients with severe manifestations of PRES, such as coma and/or status epilepticus, may suffer permanent neurological impairment or even death.

Prompt recognition and treatment is important in preventing the permanent damage that can occur in this otherwise typically reversible condition.

Since PRES is often unsuspected by clinicians, recognition of the characteristic imaging findings by radiologists is one key to diagnosing this syndrome.

Most cases resolve within 1 - 2 weeks of controlling the blood pressure and treating the underlying cause.

Terminology:

Posterior reversible encephalopathy syndrome (PRES) is or has also been known by many other names including:

- Reversible posterior leukoencephalopathy syndrome (RPLS)
- Hyperperfusion encephalopathy
- Brain capillary leak syndrome
- Reversible posterior cerebral edema syndrome

- Reversible occipital parietal encephalopathy

It is a subset of what has historically been termed "**hypertensive encephalopathy**"

None of these names is completely satisfactory however as the syndrome:

- Is not always reversible - permanent neurological deficit, even mortality is possible in some cases.

- Is often not confined to either the white matter or the posterior regions of the brain.

PRES should not be confused with *chronic hypertensive encephalopathy*, also known as hypertensive microangiopathy, which results in micro-haemorrhages in the basal ganglia, pons and cerebellum.

History

Although described in various specific case reports for some time, it was first synthesised as a single named syndrome in a 1996 case series. [1]

This described a clinical syndrome of insidious onset of headache, confusion or decreased level of consciousness, visual changes, and seizures, which was associated with characteristic neuroimaging findings of posterior cerebral white matter edema.

Recognition of PRES is increasing with the increasing availability of magnetic resonance imaging scanning.

Epidemiology

PRES is increasingly recognized and reported in case reports and case series; however, the true incidence of PRES is not currently known.

Patients in all age groups appear susceptible; reported cases exist in patients as young as two years and as old as 90 years, although most cases occur in young to middle-aged adults, with the mean age ranging across case series from 39 to 47 years.

PRES is more common in women, even when patients with eclampsia are excluded.

Many patients with PRES have comorbidities, which may be severe conditions, such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension.

Pathophysiology

The pathogenesis of PRES remains unclear, but it appears to be related to two factors:

1. Disordered cerebral autoregulation:

- Normal autoregulation maintains constant cerebral blood flow over a range of systemic blood pressure, by means of arteriolar constriction and dilatation.

  As the upper limit of cerebral autoregulation is exceeded, arterioles dilate and cerebral blood flow increases in a pressure-passive manner with rises in systemic blood pressure.

  The resulting brain hyperperfusion, particularly in arterial border zones, may lead to breakdown of the blood brain barrier allowing extravasation of fluid and blood products into the brain parenchyma.

  The **rate** of blood pressure elevation is also likely to be important. In chronic hypertension, adaptive vascular changes "reset" the range of autoregulation to higher systemic blood pressures. As a result, patients with PRES in the setting of longstanding hypertension may have markedly elevated blood pressures, while less severe elevations, even normal blood pressures, are associated with PRES in other settings.

  Children appear particularly vulnerable to PRES at lower blood pressures than adults.

2. Endothelial dysfunction:

   - Endothelial dysfunction has also been implicated in the pathophysiology of PRES, especially in cases associated with preeclampsia or cytotoxic drug therapies.

     The latter may have direct toxicity on vascular endothelium, leading to capillary leakage, and blood-brain barrier disruption and axonal swelling, which may then trigger vasogenic edema. RRES associated with these therapies may occur in *normotensive* individuals and with nontoxic levels of these drugs.

     In preeclampsia, markers of endothelial cell dysfunction (lactate dehydrogenase, abnormal red blood cell morphology) typically arise prior to the clinical syndrome and correlate better with the extent of cerebral edema than do blood pressure changes.

Because of the heterogeneous nature of this disorder, it may be that different mechanisms are etiologically important in different clinical situations.

Anatomic Distribution:

The combination of acute hypertension and endothelial damage results in hydrostatic edema, a specific form of vasogenic edema characterized by the forced leakage of serum

through capillary walls and into the brain interstitium, which, if severe enough, will be radiographically evident.

Unregulated vascular injury to blood-brain barrier endothelium leads to edema, protein extravasation, and fibrinoid necrosis.

The cortex, structurally more tightly packed than the white matter, resists accumulation of edema, hence predilection of abnormalities to be seen in the white matter.

The primary involvement of posterior brain regions is not well understood.

One possibility involves the *regional heterogeneity* of the sympathetic innervation of the intracranial arterioles, which has been shown to protect the brain from marked increases in blood pressure. A histochemical study revealed a greater concentration of adrenergic nerves around pial and intracerebral vessels in the anterior circulation than posteriorly. This observation may explain why the hyperperfusion and edema is mainly seen in the posterior circulation in PRES.

Causes:

PRES is really a group of *heterogeneous* etiologies that are grouped together because of similar findings on **neuroimaging studies.**

It has been described in a number of medical conditions, with hypertensive encephalopathy, eclampsia, and the use of cytotoxic and immunosuppressant drugs being the most common.

Causes include:

1. Acute severe hypertension:

    - In other words, a hypertensive encephalopathy. The neurologic syndrome in hypertensive encephalopathy in general is now believed to be caused by vasogenic edema from a breakthrough of autoregulation.

      The percent elevation of blood pressure over baseline, as well as the severity of the hypertension, are important. Therefore, while approximately 75% of patients have moderate to severe hypertension at presentation, RRES may also occur in normotensive patients.

      Although RPLS is described in malignant hypertension alone, it appears to be more common in patients with comorbid conditions, such as systemic lupus erythematosus cryoglobulinemia, or hemolytic uremic syndrome and renal failure.

2. Pregnancy related:

    - Eclampsia/preeclampsia:

- ♥ Most investigators now believe that hypertensive encephalopathy and preeclampsia share similar mechanisms.

- The post-partum period:

  - ♥ In many patients, the syndrome occurs during the puerperium rather than during pregnancy

3. Drug related causes.

   Most commonly:

   - Cytotoxic drugs

     - ♥ Cyclosporine is one of the more common cytotoxic therapies associated with PRES.

   - Immunosuppressant drugs

4. Autoimmune disease

Complications

Permanent neurological injury or death may occur due to:

1. Cerebral haemorrhage

2. Cerebral infarction

3. Complications of status seizure activity.

4. Severe cerebral edema.

Clinical features

The combination of suggestive clinical manifestations and radiological criteria establishes the diagnosis of PRES.

In doubtful cases, the clinical and radiological improvement that occurs once appropriate treatment is given confirms the diagnosis.

Nevertheless, there are no consensual guidelines to validate diagnosis of PRES.

PRES is typically a reversible condition once the cause is removed.

However, a small number of patients with severe manifestations of PRES, such as coma and/or status epilepticus, may suffer permanent neurological impairment or even death.

The clinical features of PRES include:

1. Hypertension:

    - Hypertension is frequent but not invariable, (as described above).

      The hypertensive crisis may precede the neurologic syndrome by 24 hours or longer.

2. Headache:

    - The headache is typically constant, non-localized, moderate to severe, and unresponsive to simple analgesics.

3. Visual disturbances:

    These may include:

    - Hemianopia
    - Visual neglect
    - Auras
    - Visual hallucinations
    - Cortical blindness

4. Neurological:

    CNS

    Altered consciousness, this can include:

    - Mild somnolence
    - Agitation
    - Confusion
    - Stupor or coma in severe cases.

    Peripheral nervous system:

    - The deep tendon reflexes are frequently brisk
    - Babinski signs often present.

- A few patients may have weakness and incoordination of the limbs
- Other focal neurologic deficits are rare.

5. Seizures:

   Seizures are often the presenting manifestation.

   - They are usually generalized tonic clonic
   - They may begin focally
   - They are often recurrent. Status epilepticus has been reported
   - Preceding visual loss or visual hallucinations suggest an occipital lobe origin in some patients.

Investigations

Blood tests

1. FBE
2. CRP
3. U&Es/ glucose
4. LFTs

CT Scan

CT scan findings are often **normal** or **nonspecific.**

White matter hypodensities in a typical topographic distribution may *suggest* PRES.

MRI

MRI is the best neuroimaging technique for the diagnosis of PRES.

MRA should also be done to rule out primary vascular pathology.

There are no *specific* diagnostic criteria for PRES, but three main radiological patterns of pathology are recognized:

1. Parieto-occipital dominance:

   - This is the most common form by far, approximately 95% of cases. [2]

Most commonly there is vasogenic white matter oedema within the occipital and parietal regions perhaps relating to the posterior cerebral artery supply.

The oedema is usually symmetrical.

The edema can vary in severity from mild to extensive.

Although abnormalities primarily affect the subcortical white matter, the cortex and basal ganglia may also less commonly be involved.

Despite being termed posterior, PRES can occasionally be found in a non-posterior distribution, including:

2. Superior frontal sulcus:

    - Patchy edema predominates in the frontal lobes along the superior frontal sulci.

      The parietal and occipital lobes are *variably* involved.

3. Holohemispheric at watershed zones:

    - A swath of confluent vasogenic edema extends through the frontal, parietal, and occipital lobes. Involvement of the temporal lobes is less marked.

      This topography matches the watershed zone between the anterior and posterior cerebral arteries, on the one hand, and the middle cerebral artery, on the other.

Radiologic improvement lags behind clinical recovery.

With treatment, **resolution** of MRI findings on neuroimaging within days to weeks is expected.

Differential diagnoses: [2]

General MRI **imaging** differential considerations include:

- Posterior circulation stroke
- Progressive multifocal leukoencephalopathy (PML)
- Severe hypoglycaemia
- Gliomatosis cerebri

- Sagittal sinus thrombosis
- Hypoxic-ischaemic encephalopathy

Managenmt

PRES should be promptly recognized, since it is *usually* reversible.

Clinicians should have a high index of suspicion in the appropriate settings e.g. pregnancy, cytotoxic therapy, hypertensive patients.

After clinical stabilization a confirmatory brain MRI/ MRA should be done.

Because of the heterogeneous clinical settings in which RRES occurs and because clinical reports are limited to case reports and small series, treatment recommendations are currently somewhat limited.

Treatment involves:

1. Attend to any immediate ABC issues:
    - Severe cases may require intubation and mechanical ventilation.
2. Seizures:
    - Seizures are treated along usual lines.

      Except in the setting of eclampsia, most patients with RRES and seizures are treated with **benzodiazepines** and **phenytoin.**

      Other antiepileptic drugs may also be just as effective and may be preferred, depending on the patient's other comorbid medical conditions and prescribed drugs.
    - In the setting of **eclampsia, magnesium sulphate** is used and is more effective than phenytoin.
3. Blood pressure control: [3]

   Malignant hypertension:
    - Hypertension is a feature in the majority of RRES patients, regardless of aetiology.

      With blood pressure lowering, patients will often improve dramatically.

Except in cases of malignant hypertension, patients with RRES often present with only moderate levels of hypertension but in the majority of cases, however, this still represents a significant increase above baseline levels.

The initial aim of treatment in malignant hypertension is to lower the diastolic pressure to about **100 to 105 mmHg.**

This goal should be achieved within 2-6 hours, with the maximum initial fall in BP not exceeding 25 percent of the presenting value.

More aggressive blood pressure lowering than this is generally unnecessary and may reduce the blood pressure below the autoregulatory range, possibly leading to ischemic events such as stroke or coronary disease.

Patients with lower levels of hypertension:

- For patients with *lower levels of hypertension*, lowering blood pressure is also recommended to treat RRES, but no specific guidelines are suggested as discussed for malignant hypertension above.

  Using clinical symptoms and any prior knowledge of baseline blood pressure as a guide, careful, incremental downward titration in 10 - 25 % increments of the mean arterial blood pressure seems a reasonable approach.

Drug Options:

The best option is probably:

- IV labetalol

Nitroprusside and GTN are also effective, with the caveat that there is a theoretical concern that these may paradoxically increase intracranial pressure through vasodilatation.

Oral antihypertensive agents have a slower onset of action and are not usually effective in consistently lowering the blood pressure to an appropriate range in hypertensive crises to prevent and treat PRES.

4. Drug induced:

   - If the cause is suspected to be a drug, such as a cytotoxic agent or an immunosuppressant, these should be ceased.

5. Eclampsia/ severe pre-eclampsia:

- Caesarean section delivery.

6. Supportive:

   - Other supportive measures such as dialysis are used as clinically indicated.

7. Steroids:

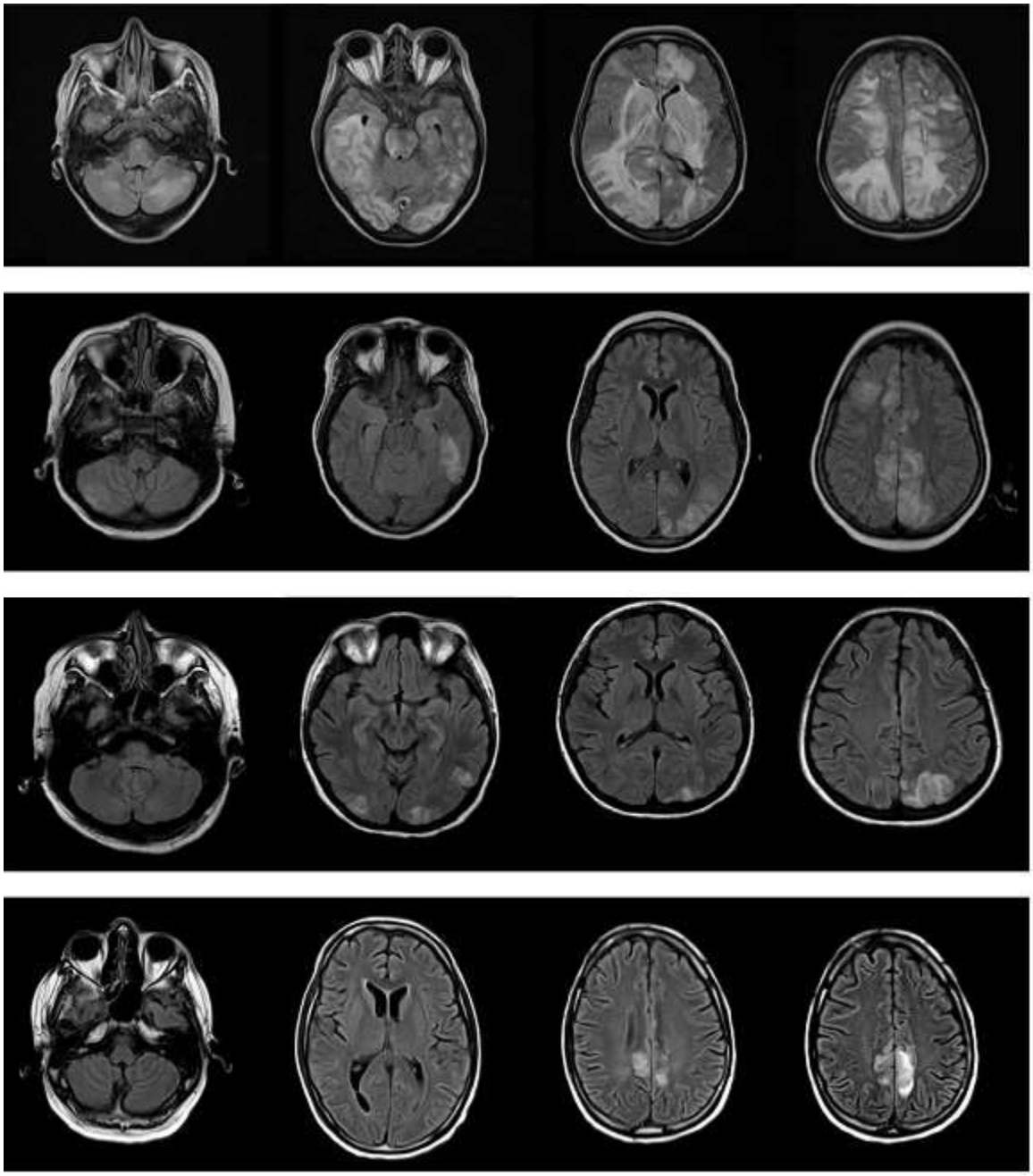
   - Steroids are **not** currently routinely recommended due to concerns over worsening hypertension and fluid overload, and electrolyte disturbances.

In many cases, RRES seems to be fully reversible within a period of days to weeks, after removal of the causative pathology, control of the blood pressure and supportive measures as required.

In some cases however there can be significant morbidity, with neurological impairment, and in some cases death.

Appendix 1:

MRI Patterns of PRES:



Top Row: *Holohemispheric watershed pattern.*

Second Row: *Superior frontal sulcus pattern.*

Third Row: *The dominant parietal-occipital pattern.*

Bottom Row: *Partial expression of the three primary patterns.*

References

1. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. NEJM 1996; 334:494.

2. B. Di Muzio, F. Gaillard, Posterior Reversible Encephalopathy Syndrome, Radiopedia Website, Accessed April 2016.

   - http://radiopaedia.org/

3. Terry A Neill et al. Reversible posterior leukoencephalopathy syndrome, in Up to Date Website, 29 April 2015.

4 S. Legriel, F. Pico, and E. Azoulay. Understanding Posterior Reversible Encephalopathy Syndrome. J.L. Vincent (ed.), Annual Update in Intensive Care and Emergency Medicine 2011. DOI 10.1007/978-3-642-18081-1.

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