

## Original Article

# Reversible Posterior Leukoencephalopathy Syndrome: A Review with Two Illustrative Cases

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## ABSTRACT

**Objective:** To shed more light on the newly recognized neurological disorder, reversible posterior leukoencephalopathy syndrome (RPLS).

**Setting:** Medical Department, Al-Adan Hospital, Kuwait.

**Materials and Methods:** In two patients who were hospitalized for acute illness, we had noted a syndrome of altered mental functioning, seizures and motor signs with findings indicating predominantly posterior leukoencephalopathy on neuroimaging studies. The findings on neuroimaging studies were characteristic of subcortical edema without infarction and reversible.

To elucidate this syndrome, we searched the literature for the differential diagnoses of reversible radiological shadows on neuroimaging of the brain (CT scan and MRI).

**Results:** Hinchey and colleagues reported the syndrome of RPLS for the first time in 1996. Thereafter, the syndrome was reported with increasing frequency both in pediatric and adult populations.

In this study, we report two cases of RPLS due to acute hypertensive encephalopathy. The patients were treated with antihypertensive medications and the neurological deficits abated completely within two weeks.

**Conclusion:** Essentially the diagnosis of RPLS is retrospective; significant reversal of neuroradiological abnormalities coupled with complete clinical recovery suggests the diagnosis. Clinicians must be aware of this syndrome as its recognition obviates unnecessary diagnostic procedures. Moreover, the syndrome is reversible with prompt treatment and has a good outcome.

KEYWORDS: cerebral edema, hypertension, immunosuppressive therapy, leukoencephalopathy

## INTRODUCTION

Reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome and reversible posterior cerebral edema, is a newly recognized neurological disorder<sup>[1]</sup>.

Hinchey *et al* in 1996 used this phrase for the first time and in a retrospective study noted white matter edema on neuroimaging studies in the posterior temporo-parieto-occipital regions in a variety of conditions including severe hypertension, and they proposed the acronym RPLS to emphasize its location and relatively reversible nature<sup>[2]</sup>.

The syndrome may occur in a host of clinical situations (Tables 1 and 2) such as hypertensive encephalopathy<sup>[2-6]</sup>, toxemia of pregnancy<sup>[7,8]</sup>, chemotherapy<sup>[9-11]</sup>, immunoglobulin therapy<sup>[12,13]</sup>, thrombotic thrombocytopenic purpura<sup>[14]</sup>, acute intermittent porphyria<sup>[15]</sup>, following organ transplantation<sup>[16,17]</sup>, collagen vascular disease such as systemic lupus erythematosus, polyarteritis nodosa, Behcet's disease and acquired immunodeficiency syndrome<sup>[18]</sup>.

As many clinicians and radiologists are not aware of this newly recognized neurological disorder, we decided to shed more light on its etiopathogenesis, clinical features, differential diagnoses, investigations, treatment and outcome.

## MATERIALS AND METHODS

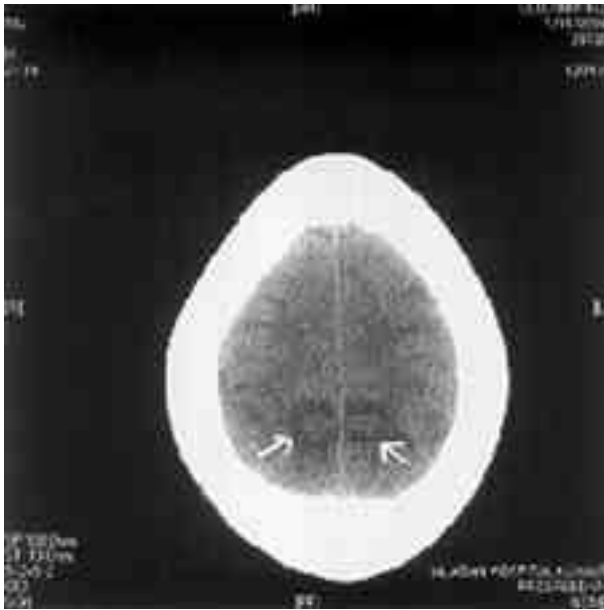
In two patients who were hospitalized for acute illness, we noted a syndrome of altered mental functioning, seizures and motor signs with findings indicating predominantly posterior leukoencephalopathy on neuroimaging studies. The appearance on neuroimaging was characteristic of subcortical edema without infarction and was reversible (Figs. 1 and 2).

To elucidate this syndrome, we searched the literature for the differential diagnoses of reversible radiological shadows on neuroimaging of the brain (CT scan and MRI).

The syndrome of RPLS was included in the differential diagnoses of such reversible shadows. As there was little data available on this syndrome, we searched the literature again under the title

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**Fig. 1:** Non-contrast Cranial CT scan; **1a:** Bilateral symmetrical posterior parieto-occipital white matter hypodensities (arrows) on presentation. The patient presented with an acute onset of confusion, coma, multiple witnessed seizures, severe hypertension (blood pressure of 300/120 mmHg) and motor signs.

RPLS for more detailed information on the syndrome. There was scant data available in the textbooks, and therefore, our search was done mostly in journals of all specialties and on the Internet.

## RESULTS

Hinchey and colleagues, in 1996, reported the syndrome of RPLS for the first time. Thereafter, the syndrome was reported with increasing frequency both in pediatric and adult populations.

In our study, we reported two cases of RPLS secondary to acute hypertensive encephalopathy (one in a 27-year-old male patient associated with renal disease due to focal segmental glomerulosclerosis as proved by renal biopsy, and the other in a 61-year-old male patient due to poor drug compliance with antihypertensive medications). The clinical findings included severe hypertension (blood pressure of 300/120 mmHg) confusion, coma, multiple witnessed generalized tonic-clonic seizures and motor signs in the first patient, and severe hypertension (blood pressure of 250/130 mmHg) headache, vomiting, cortical blindness and motor signs in the second patient. The reported motor signs included generalized weakness of pyramidal nature grade III-IV, hypertonia, generalized brisk deep tendon jerks, bilateral extensor plantar response in both patients; the first patient also had bilateral sustained ankle clonus. Fundus examination and pupillary responses were normal in both patients apart from grade II hypertensive changes in the second patient. The results of laboratory tests in the first patient showed



**1b:** Resolving hypodensities after 10 days (The neurological deficits disappeared completely in thirteen days).

Hb of 10.3 g/dl of normocytic normochromic type, blood urea of 16.9 mmol/l, S. creatinine of 386 umol/l, S. albumin of 19 g/l, T. protein of 4.8 g/l, T. cholesterol of 7.2 mmol/l, 24-hour urinary protein of 3.6 g with normal blood sugar, S. electrolytes, S. calcium and magnesium. Renal biopsy was subsequently done and showed focal segmental glomerulosclerosis. Serologic tests for vasculitis, HIV 1/2, syphilis, echinococcosis, toxoplasmosis, blood film for malaria and blood cultures were negative. The results of laboratory tests in the second patient showed blood urea of 8.6 mmol/l, S. creatinine of 165 umol/l with normal Hb, S. electrolytes, S. calcium, magnesium, lipid profile and blood sugar. CT and MRI studies showed extensive bilateral white matter abnormalities suggestive of edema in the posterior regions of cerebral hemispheres (Figs. 1a and 2a). The patients were treated with antihypertensive medications and the neurological deficits resolved completely within two weeks (thirteen days in the first patient and four days in the second one). Follow-up scanning showed resolution of abnormalities at ten days in the first patient and two months in the second one (Figs. 1b and 2b).

We have observed reluctance on the part of physicians to consider the possibility of hypertensive encephalopathy without demonstrable evidence of end-organ damage attributable to elevated blood pressure such as schistocytes on blood film, evidence of retinal edema, papilledema or left ventricular hypertrophy on ECG.

In view of the range of blood pressure values associated with this clinical syndrome and the evidence for factors predisposing to selective



Fig. 2: T2-weighted axial MRI sections; 2a: Bilateral symmetrical hyperdensities (arrows) in the occipito-parietal lobes. The patient presented with sudden onset of severe headache, vomiting, confusion, cortical blindness, severe hypertension (blood pressure of 250/130mmHg), and motor signs.



2b: Resolving hyperdensities after two months (The neurological deficits ceased completely in four days).

vulnerability of the cerebral circulation with even modest acute elevation of blood pressure, this position should no longer be tenable.

## DISCUSSION

### Etiopathogenesis:

The causes of this syndrome are diverse. However, hypertensive encephalopathy, toxemia of pregnancy and uremic encephalopathy are the most common causes of RPLS<sup>[19]</sup>. The exact etiopathogenesis of the condition is not known. It may result from a rapid rise in blood pressure that overcomes the brain's normal autoregulation of cerebral blood flow. This disturbance of homeostasis produces dilatation of cerebral arterioles with opening up of endothelial tight junctions and leakage of plasma into the extracellular space producing cerebral edema<sup>[4,5]</sup>. Clinical and radiological parameters indicate that the occipito-parietal vasculatures are the most vulnerable<sup>[2]</sup>. The vulnerability of posterior circulation to the cerebral hemisphere may be explained by a paucity of autonomic innervations as compared to the anterior circulation. The resulting edema is usually vasogenic and reversible but may become cytotoxic in some patients<sup>[20]</sup>. The frequent association of the syndrome with precipitating factors not usually responsible for blood pressure elevation and the occasional occurrence of this syndrome in patients with only modest elevation of blood pressure suggest that some additional factor(s), either local or systemic, may be responsible for predisposing

the cerebral circulation to the effects of acute elevation in blood pressure. Dysfunction of particular subtypes of endothelial cells has also been hypothesized to result in vasospasm, blood-brain barrier breakdown and loss of fluid from the intravascular compartment, all of which are seen in this syndrome. However, mechanism(s) leading to the endothelial cell dysfunction in this syndrome are at present unclear<sup>[21]</sup>.

The pathophysiology of immunosuppression on the development of RPLS in the absence of hypertension is not clear but is probably related to either a primary or secondary breakdown of the blood-brain barrier<sup>[2]</sup>. Eichler *et al* reported that widespread metabolic abnormalities consisting of increased choline and creatine levels and mildly reduced N-acetylaspartate occurred in the regions with both normal and abnormal MRI appearances. They suggested that proton MR spectroscopic imaging might be helpful for the diagnosis and investigations of the underlying pathophysiology of RPLS<sup>[22]</sup>.

### Clinical Features:

The syndrome characteristically begins with a subacute prodromal period of altered alertness and activity. Lethargy and somnolence are often the first signs noted, with slowing of mental functions and confusion as the syndrome progresses. Increasing headache and visual blurring may occur during this period and frequently brings the patient to

**Table 1: Causes of RPLS****Common causes:**

- ◆ Hypertensive encephalopathy
- ◆ Eclampsia
- ◆ Immunosuppressive agents and cytotoxic drugs
- ◆ Renal failure with hypertension

**Other reported causes:**

- ◆ Collagen vascular disease
  - Systemic lupus erythematosus (SLE)
  - Polyarteritis nodosa
  - Behcet's disease
- ◆ Thrombotic thrombocytopenic purpura
- ◆ Acute intermittent porphyria
- ◆ Following organ transplantation
- ◆ Acquired immunodeficiency syndrome

medical attention. This prodromal period is important to recognize as it provides an opportunity to minimize morbidity by initiating early treatment and may help to differentiate this syndrome from other disorders. However, the syndrome can also become manifest by acute seizures without an obvious prodrome. A 1996 study of 15 patients in Europe and the United States with this syndrome listed the most common clinical features as headache, altered alertness and behavior, seizures and abnormalities of visual perception<sup>[2]</sup>. A review of 52 cases of RPLS in the pediatric population confirmed these four signs and symptoms as being the most common<sup>[23]</sup>. In the latter study, 76% of the cases had at least three of the four listed signs and symptoms, although their severity varied considerably among cases. Alteration in alertness ranged from drowsiness and diminished spontaneity to stupor. Abnormalities of visual perception ranging from blurred vision to frank cortical blindness are almost always detectable; some patients with cortical blindness have also denial of blindness (Anton's syndrome)<sup>[2]</sup>.

Fundus examination (especially in eclampsia and patients with renal failure) and pupillary reflexes are often normal<sup>[18]</sup>.

Deep tendon reflexes are frequently brisk and the plantar reflex may be extensor. A few patients may have weakness and incoordination of the limbs<sup>[1,3]</sup>. The clinical features usually disappear after appropriate treatment is started and the majority of the patients recover completely<sup>[18]</sup>. The clinical features are summarized in Table 3.

**Investigations:**

CSF examination is usually normal; however, it may show mild elevation in protein. Metabolic abnormalities in RPLS may include hypomagnesaemia, hypocholesterolemia; both of which are present in 50% of patients with RPLS secondary to cyclosporine A<sup>[9]</sup>. Aluminum overload and elevated

**Table 2: Immunosuppressive agents and drugs causing RPLS**

- ◆ Cyclosporine A
- ◆ Interferon alpha
- ◆ Intravenous immunoglobulins
- ◆ Erythropoietin
- ◆ Cisplatin
- ◆ Tacrolimus (FK506)
- ◆ Cytarabine

drug levels are present in 50% of patients with RPLS secondary to cyclosporine A<sup>[9]</sup>.

**Radiological Findings:**

The findings on neuroimaging studies in RPLS include non-enhancing white matter abnormalities that appear as areas of low attenuation on CT scan and appear hypo-intense on T<sub>1</sub>-weighted MRI and hyper-intense on T<sub>2</sub>-weighted MRI (Figs. 1a and 2a). These abnormalities partially or completely resolve on follow-up scanning, thereby suggesting subcortical edema without infarction (Figs. 1b and 2b).

The lesions are mainly seen in posterior regions of the cerebral hemispheres<sup>[6,20,24]</sup>. In patients with extensive involvement, other structures such as brainstem, basal ganglia and frontal lobes can also be affected. The imaging abnormalities are often symmetrical; however asymmetric involvement is not unusual. At times, the grey matter is also extensively affected<sup>[1,2,7]</sup>.

The lesions of RPLS are best visualized with MRI studies. However, Hinchey *et al* consider that MRI is not essential for the diagnosis of RPLS; CT scans can also be used satisfactorily for these patients<sup>[2]</sup>.

**Differential Diagnosis:**

The differential diagnosis of RPLS includes various acute neurological conditions such as stroke, cerebral venous thrombosis, encephalitis and demyelinating disorders<sup>[18]</sup>. Radiological distinction from top-of-the basilar syndrome with bilateral posterior cerebral artery infarction with cytotoxic edema is evident by sparing of the cortical and paramedian occipital structures as well as resolution of the lesions on follow-up imaging. Diagnosis can be easily recognized with MRI imaging. Acute infarction usually demonstrates hyper-intensity on Echo-planar diffusion weighted imaging (DWI) and T<sub>2</sub>-weighted imaging with reduced apparent diffusion coefficient (ADC) levels. As opposed to those findings, there is hypo- or iso-intensity on DWI, hyper-intensity on fluid attenuated inversion recovery imaging (FLAIR) and T<sub>2</sub>-weighted imaging, and markedly elevated

**Table 3:** Clinical features of RPLS**Acute to subacute onset**

## Neurological symptoms

- Headache
- Altered mental status / confusion / drowsiness

## Visual disturbances

- Hemianopia
- Visual neglect
- Cortical blindness or Anton's syndrome (denial of blindness, confabulation)

## Seizures

- Often precede the other symptoms
- Usually generalized, tonic-clonic in nature
- May be preceded by visual aura or hallucinations
- Single seizure infrequent, usually multiple

## Systemic Signs

- Usually acute rise in blood pressure
- Hypertension may be mild, moderate or severe depending on the patient's usual BP

ADC levels with RPLS<sup>[25]</sup>. The differential diagnosis is summarized in Table 4.

If the history of an acute seizure or uncontrolled blood pressure is not obtained or is an under-emphasized aspect of the clinical presentation and not mentioned to the radiologist, an incorrect diagnosis of gliomatosis cerebri, progressive multifocal leukoencephalopathy, demyelinating disease or infection may be offered on the basis of neuroimaging. Such incorrect diagnoses may result in invasive biopsies or inappropriate therapies<sup>[26]</sup>. So, it is recommended that when high signal intensity is seen on MRI and there is history of seizures or high blood pressure, a follow-up scan in a period of 1-2 weeks will most often document reversibility of vasogenic edema and avoid expensive or potentially invasive work-up for other primary cerebral disease<sup>[27]</sup>.

**Treatment:**

The recognition of the syndrome is critical as delay in the diagnosis or treatment can result in permanent neurological deficits while prompt early control of blood pressure or withdrawal of causative drugs can reverse the syndrome<sup>[28,29]</sup>.

- A 10-20% reduction in mean arterial pressure is usually sufficient to terminate the dysfunctional process
- Discontinue or reduce the dose of offending drugs (e.g. cytotoxic agents)
- Treat hypomagnesemia
- Treat seizures with anti-convulsants

**Prognosis:**

After prompt treatment, most patients recover completely within hours (12-24 hours) to days. Imaging findings may persist for weeks. If the

**Table 4:** Differential diagnoses of RPLS

## Vascular

- ◆ Infarction especially "Top-of-the-Basilar syndrome" with bilateral posterior cerebral artery ischemia
- ◆ Hemorrhage
- ◆ Venous thrombosis

## Infection

- ◆ Encephalitis, meningitis

## Inflammatory/autoimmune Vasculitis

- ◆ Especially SLE

syndrome is not treated promptly, it can lead to posterior circulation infarction or hemorrhage<sup>[30]</sup>.

The extent of combined T<sub>2</sub> and DWI signal abnormalities correlate with the patient outcome. High DWI signal intensity and pseudo normalized ADC values are associated with cerebral infarction and may represent the earliest signs of non-reversibility as severe vasogenic edema progresses to cytotoxic edema<sup>[31]</sup>.

Patients do not require chronic anti-epileptic treatment once imaging abnormalities have resolved<sup>[4,32]</sup>.

**CONCLUSION**

Early diagnosis of this syndrome is of utmost importance as it is generally considered to be reversible and readily treated by controlling the patient's blood pressure. It is also important to distinguish this syndrome from conditions, which require specific treatment such as immunosuppressive therapy or anticoagulation, and from conditions in which aggressive lowering of blood pressure may be harmful as in acute ischemic stroke. The potential reversibility of the syndrome, the risk of permanent neurological dysfunction, if left untreated, and the potential for diagnostic confusion with other serious disorders affecting the CNS mandate that a high index of clinical suspicion be maintained in patients presenting with neurological symptoms associated with acute elevation of blood pressure. Such patients should be evaluated and treated on an emergency basis.

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