Posterior leukoencephalopathy syndrome

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Abstract

Posterior leukoencephalopathy syndrome is a newly recognised brain disorder that predominantly affects the cerebral white matter. Oedematous lesions particularly involve the posterior parietal and occipital lobes, and may spread to basal ganglia, brain stem, and cerebellum. This rapidly evolving neurological condition is clinically characterised by headache, nausea and vomiting, seizures, visual disturbances, altered sensorium, and occasionally focal neurological deficit. Posterior leukoencephalopathy syndrome is often associated with an abrupt increase in blood pressure and is usually seen in patients with eclampsia, renal disease, and hypertensive encephalopathy. It is also seen in the patients treated with cytotoxic and immunosuppressive drugs such as cyclosporin, tacrolimus, and interferon alfa. The lesions of posterior leukoencephalopathy are best visualised with magnetic resonance (MR) imaging. T2 weighted MR images, at the height of symptoms, characteristically show diffuse hyperintensity selectively involving the parieto-occipital white matter. Occasionally the lesions also involve the grey matter. Computed tomography can also be used satisfactorily to detect hypodense lesions of posterior leukoencephalopathy. Early recognition of this condition is of paramount importance because prompt control of blood pressure or withdrawal of immunosuppressive agents will cause reversal of the syndrome. Delay in the diagnosis and treatment can result in permanent damage to affected brain tissues.

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Posterior leukoencephalopathy is a newly recognised neurological disorder. It is characterised predominantly by white matter oedema affecting the occipital and posterior parietal lobes of the brain (figs 1 and 2). Hinchey *et al* used this term for the first time[1] and described 15 patients who were already suffering from a wide variety of medical illnesses. Of these, seven were receiving immunosuppressive treatment after organ transplantation or as treatment for aplastic anaemia, and one was receiving interferon for treatment of a melanoma; three had eclampsia, and four had acute hypertensive encephalopathy associated with renal disease. In this series, 12 patients had abrupt increases in blood pressure, and eight had some impairment of renal function. In all 15 patients, the neurological abnormalities resolved within two weeks. The patients were treated either with antihypertensive drugs or by withdrawal of immunosuppressive agents. Later it was recognised that if treatment is delayed, there is a risk of permanent brain injury.[2] In this article I review the many reports on this subject that have appeared in the recent past and highlight the importance of the syndrome in day to day clinical practice.

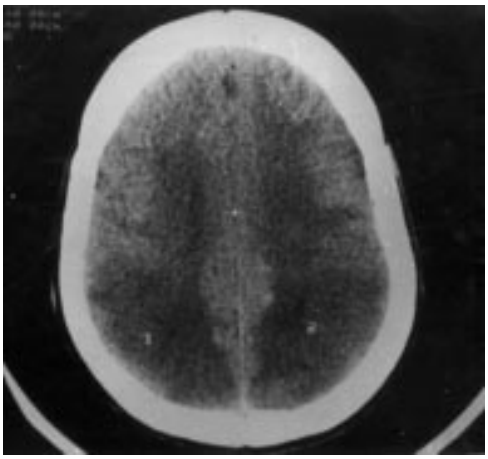

Figure 1 Cranial computed tomography showing bilateral and symmetrical hypodensities involving white and grey matter of posterior parietal and occipital regions of brain. Hypodensity extends well beyond the territory supplied by posterior cerebral arteries.

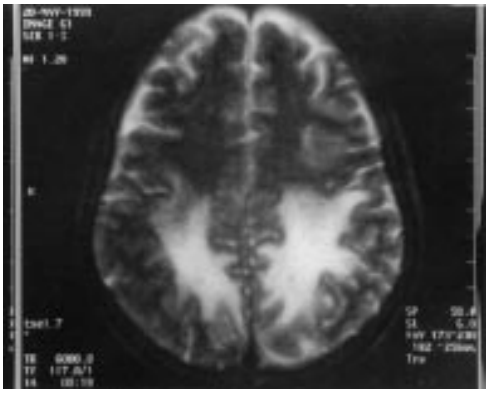

Figure 2 T2 weighted magnetic resonance image showing white matter signal abnormalities in parieto-occipital regions.

Imaging features

Neuroimaging, at the height of symptoms, shows diffuse oedema predominantly of white matter, selectively involving the parieto-occipital regions of the brain (figs 1 and 2). In patients with extensive involvement other structures such as brain stem, cerebellum, basal ganglia, and frontal lobes can also be affected. The imaging abnormalities are often symmetrical; however, asymmetrical involvement is not unusual. At times the grey matter is

also extensively affected.[1 3 4] The lesions of posterior leukoencephalopathy are best visualised with magnetic resonance (MR) imaging, which is able to show even small lesions. In a conventional MR study the lesions are usually isointense to hypointense on T1 weighted images, and hyperintense on T2 weighted images[5] (fig 2). Lesions shown on MR are better demonstrated on fluid attenuated inversion recovery (FLAIR) imaging. In this technique, with nulling of the ventricular and subarachnoid cerebrospinal fluid (CSF) signal, the parenchymal oedematous lesions (especially those in the cerebral cortex) show up better than on conventional T2 weighted images.[3]

Echo-planar diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps are new MR techniques whereby images are obtained that are sensitive to the microscopic random motion (diffusion) of water molecules. These techniques help in differentiating posterior leukoencephalopathy syndrome from ischaemic events such as "top of basilar syndrome" which produces bilateral occipital infarctions. In acutely infarcted areas of the brain, depletion of high energy phosphates leads to cessation of Na/K-ATPase activity; water becomes trapped intracellularly, and its motion is restricted. The decreased water diffusion is characterised by marked hyperintensity on DWI and hypointensity on ADC maps. Conversely, in posterior leukoencephalopathy syndrome the regions of vasogenic oedema are visualised as a hypointense or isointense signals on DWI and as markedly increased signals on ADC maps compared with normal brain tissue.[4]

Although MR studies yield a higher resolution image, Hinchey *et al* consider that MR is not essential for the diagnosis of posterior leukoencephalopathy.[1] Computed tomography (CT) can also be used satisfactorily in these patients. In all 15 patients of their series,[1] the first imaging study done was CT, and in all of these the radiological features of white matter disease were apparent on the CT scans. An important characteristic of posterior leukoencephalopathy was reversibility of the imaging abnormalities. In Hinchey's series,[1] in all 15 patients who were followed up with repeat CT or MRI scans, there was significant improvement or complete resolution of white matter abnormalities. Subsequently, similar observations were made by several other investigators as well.[3 4] If appropriate management (such as initiation of antihypertensive treatment or discontinuation of immunosuppressive drugs) is delayed there is a great risk of permanent neurological damage because of ensuing cerebral infarction or haemorrhages.[2 5]

Clinical features

The common clinical features of posterior leukoencephalopathy are headache, altered sensorium, confusional states, seizures, vomiting, and visual disturbances. Seizures generally precede the other manifestations. The seizures are usually of generalised tonic-clonic type and may be preceded by visual auras and visual hallucinations, consistent with occipital lobe seizures. Most patients experience multiple seizures, single seizure being infrequent. Following a seizure patients usually have prolonged alterations in alertness and activity. Temporary restlessness and agitation may alternate with lethargy. In a few patients stupor and coma may develop. The patients are often confused, spontaneity is decreased, and motor responses are slowed. There may be abnormalities of vision such as hemianopia, visual neglect, and cortical blindness. Some patients with cortical blindness also have denial of blindness (Anton's syndrome).[1] Fundus examination (especially in eclamptic patients and patients with renal failure) and pupillary responses are often normal. The deep tendon reflexes are frequently brisk and plantars may be extensor. A few patients may have weakness and incoordination of the limbs.[1 3 4]

The posterior leukoencephalopathy syndrome has been described both in paediatric and adult age groups. Antunes *et al* recently reported it in a two year old child with Down's syndrome who presented only with a severe oculogyric crisis.[6] Two months before, the child had had an allogeneic bone marrow transplant. A greater risk for females developing this syndrome has also been noted.[4] The onset and course of disease is generally acute or subacute; clinical features usually disappear after appropriate treatment is started, and the majority of the patients recover completely.

Differential diagnosis

The differential diagnosis of posterior leukoencephalopathy syndrome includes various acute neurological conditions such as stroke, cerebral venous thrombosis, encephalitis, and demyelinating disorders (box 1, table 1). In patients with an acute focal neurological deficit, the syndrome of posterior leukoencephalopathy may be difficult to distinguish from simultaneous bilateral posterior cerebral artery territory infarction caused by "top of basilar" embolism. It is of paramount importance to distinguish

Box 1: Causes of altered sensorium or seizures in pregnancy and the puerperium

- Eclampsia
- Vascular
  - Cerebral infarction
  - Intracerebral haemorrhage
  - Hypertensive encephalopathy
  - Cerebral venous thrombosis
- Metabolic encephalopathies
  - Porphyria
  - Hepatic encephalopathy
  - Hyponatraemia
- Infective
  - Viral encephalitis
  - Cerebral malaria
  - Bacterial meningitis
- Demyelinating
  - Postinfective encephalomyelitis
  - Collagen vascular disease (such as systemic lupus erythematosus)
- Pituitary apoplexy

Table 1 Common differential diagnoses of posterior leukoencephalopathy syndrome

	Posterior leukoencephalopathy	*Cerebral venous thrombosis*	*Top of basilar syndrome*
Predisposing factors	Eclampsia, renal failure, cytotoxic and immuno-suppresive agents, hypertension	Pregnancy, puerperium, dehydration	Risk factors for stroke, cardiac disorders
Onset and progression	Acute, evolves in days	Acute, evolves in days	Sudden, evolves in hours
Clinical features	Seizures precede all other manifestations, visual aura, cortical blindness, confusion, headache, rarely focal deficit	Headaches, seizures, stupor or coma, focal neurological deficits (monoporesis or hemiparesis), papilloedema, evidence of venous thrombosis elsewhere, infrequently hypertensive	Cortical blindness, hemianopia, confusional state, brain stem signs, cerebral signs, rarely seizures
Imaging features	Predominantly white matter oedema in bilateral occipital and posterior parietal regions, usually spares paramedian brain parenchyma	Haemorrhagic and ischaemic infarcts, small ventricles, "cord sign" caused by hyperdense thrombosed vein, evidence of major venous sinus thrombosis on MRI	Infarcts of bilateral paracalcarine cortex, thalamus, inferior medial temporal lobe, and brain stem
Prognosis	Completely resolves after rapid control of BP and removal of offending drug	Intensive management is needed; mortality high in severe cases	No recovery or only partial eventual recovery

BP, blood pressure; MRI, magnetic resonance imaging.

between these conditions because, in the case of ischaemic stroke, most treatment guidelines recommend that mild to moderate hypertension should not be treated[7]; in contrast, treatment of hypertension in patients with posterior leukoencephalopathy is essential in order to reverse the the pathological process before it progresses to cause permanent brain injury. The calcarine and paramedian occipital lobe structures are usually spared in posterior leukoencephalopathy syndrome (fig 1). This feature often distinguishes posterior leukoencephalopathy from bilateral infarctions of the occipital lobes secondary to top of basilar syndrome (fig 3).[1] In patients with top of basilar syndrome there are often accompanying thalamic and midbrain infarcts. In patients of posterior leukoencephalopathy, seizures (frequently new onset, secondarily generalised occipital lobe seizures) almost always occur in the course of the illness. In some patients seizure is the sole clinical manifestation of posterior leukoencephalopathy. However, reliable diagnosis may need newer MR techniques such as echo-planar DWI and ADC maps.

Box 2: Causes of posterior leukoencephalopathy

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

Other reported causes
- Collagen vascular disorders
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
  - Behçet's syndrome
- Thrombotic-thrombocytopenic purpura
- Acquired immunodeficiency syndrome
- Acute intermittent porphyria
- Following organ transplantation

Aetiopathogenesis

Known causes of the posterior leukoencephalopathy syndrome are summarised in box 2. The exact aetiopathogenesis of the condition is not known precisely. It may result from a rapid rise in blood pressure that overcomes the brain's normal autoregulation of cerebral blood flow. This disturbance of autoregulation produces dilatation of cerebral arterioles with opening up of endothelial tight junctions and leakage of plasma and red cells into the extracellular space, producing cerebral oedema.[8 9] The cerebral white matter is composed of myelinated fibre tracts in a cellular matrix of glial cells, arterioles, and capillaries that makes this structure more susceptible to accumulation of fluid in the extracellular spaces (vasogenic oedema).[1] Adrenergic sympathetic innervation of cerebral vessels is an important component in the physiological mechanism of cerebral blood flow autoregulation. The vessels of the carotid system are better supplied with sympathetic adrenergic innervation than those of the vertebro-basilar system. This inherent deficiency of adrenergic innervation may result in loss of vasoconstrictor properties of cerebral blood vessels, mainly in the posterior cerebral areas.[10]

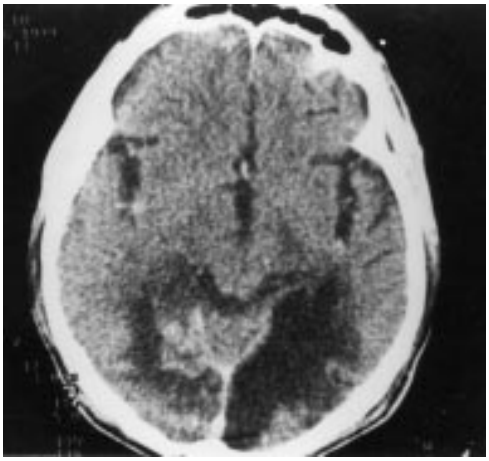

Figure 3 Cranial computed tomography (CT) showing bilateral infarction of occipital lobes. CT picture consistent with "top of basilar syndrome." In contrast to posterior leukoencephalopathy, there is marked involvement of the paramedian visual cortex.

According to another hypothesis, patients with posterior leukoencephalopathy develop vasospasm secondary to sudden and severe rises in blood pressure and ischaemia of brain tissue.[8 9] Ischaemic damage to brain tissue first produces cytotoxic oedema and then extracellular oedema. In a study by Naidu *et al*,[11] using single photon emission computed tomography (SPECT) and transcranial Doppler sonography, perfusional deficits were demonstrated in

Box 3: Immunosuppressive agents and drugs causing posterior leukoencephalopathy syndrome
- Cyclosporin A
- Interferon alfa
- Intravenous immunoglobulins
- Erythropoietin
- Cisplatin
- Tacrolimus
- Cytarabine

watershed areas of the brain. Angiographic and SPECT studies during the symptomatic period of posterior leukoencephalopathy further revealed segmental narrowing of the posterior cerebral arteries (consistent with vasospasm), possibly resulting in ischaemia of the corresponding cortical areas.[12] However, the reversibility of imaging abnormalities with immediate treatment is not consistent with the hypothesis of vasospasm and cerebral ischaemia.

The pathophysiology of posterior leukoencephalopathy in patients with immunosuppressive and cytotoxic drugs (box 3) is also obscure.[3 4 13–30] In relation to cyclosporin, Truwit *et al* have suggested that an acute toxic insult of undetermined origin produced by these pharmacological agents results in axonal swelling and increased water content in the white matter.[21] Alternatively, it has been proposed that vascular spasm secondary to raised endothelin concentrations might produce reversible ischaemia.[15 22] The immunosuppressive and cytotoxic drugs can also produce damage to the blood–brain barrier because of direct toxic effects on the vascular endothelium.

Although hypertensive encephalopathy is the most common cause of posterior leukoencephalopathy, cases have occurred in the absence of severe hypertension.[1 3 4] Only one of the 15 patients reported by Hinchey *et al* had a diastolic blood pressure greater than 130 mm Hg.[1] Other investigators also observed that neurological deterioration was preceded by only mild to moderate increases in blood pressure[4]; however, all the patients described had severe metabolic abnormalities (such as ischaemic bowel disease, sepsis, leucocytosis, hyponatraemia, proteinuria, and fever). These workers[4] suggested that metabolic abnormalities disturbed the integrity of the distal brain vasculature or interfered with sympathetic activity, leading to oedema formation with otherwise tolerable increases in systemic blood pressure. Renal dysfunction also appears to predispose the brain to posterior leukoencephalopathy, possibly because of chronic uraemia or fluid overload.

Another important group of persons likely to develop posterior leukoencephalopathy syndrome are women with toxaemia of pregnancy. Most investigators believe that hypertensive encephalopathy and eclampsia share similar pathophysiological mechanisms.[8 11] In many such patients the reversible posterior leukoencephalopathy syndrome occurred during the puerperium rather than during pregnancy, as illustrated by the case history in box 4. The fluid accumulation often observed during this period possibly accentuates the tendency for brain oedema to develop, and the syndrome is also seen in patients with renal failure.[21 27 28] Raps *et al* suggested that the presence of the imaging picture of posterior leukoencephalopathy could be considered an indicator of postpartum eclampsia, even when other characteristic features of eclampsia (for example, proteinuria, pedal oedema, hypertension) are not present.[29]

Treatment

The posterior leukoencephalopathy syndrome needs to be recognised promptly. The syndrome is usually reversible after controlling the blood pressure. Offending immunosuppressive agents should either be discontinued or the dose should be reduced. Delay in initiating the appropriate treatment may result in permanent damage to the brain. Patients experiencing seizures become seizure free after resolution of imaging abnormalities and do not require chronic antiepileptic treatment.[3 4]

Box 4: Illustrative case history

A 22 year old primaparous woman was delivered of a normal female child at full term in a local nursing home. Approximately four hours after delivery the patient developed a severe diffuse bursting headache associated with vomiting. Simultaneously visual problems developed and after a few hours she was unable to see at all. On the next day she had a single episode of generalised tonic-clonic convulsions, after which she became confused and was transferred for further care. Her blood pressure was 190/104 mm Hg, she was afebrile, there was no pedal oedema, and fundus examination was normal. She was drowsy and confused and had cortical blindness. The deep tendon reflexes were brisk and both planters were extensor. The rest of the neurological and systemic examination was normal. Her haematological and blood biochemical tests, including serum electrolytes and urinalysis, were normal. ECG, *x* ray chest, and cerebrospinal fluid examination were also normal. Electroencephalography showed intermittent generalised delta activity. Contrast enhanced cranial CT was done 24 hours after the seizure. This showed hypodensities in the white and grey matter of both posterior parietal and occipital lobes (fig 4). Antihypertensive treatment was immediately begun in the form of enalapril (5 mg twice a day) along with phenytoin sodium (300 mg/day). On 12th day after delivery the patient was discharged with a blood pressure of 140/86 mm Hg, markedly improved vision, and seizure free. Repeat CT seven days after the discharge was normal.

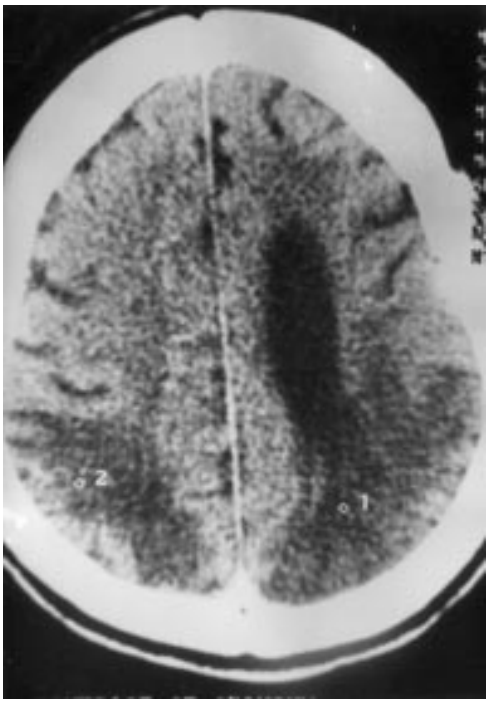

Figure 4 Cranial computed tomography showing bilateral posterior leukoencephalopathy in the patient described in box 4.

Box 5: Summary points

- Posterior leukoencephalopathy can complicate a wide variety of medical disorders.
- Hypertensive encephalopathy, renal failure, eclampsia, and administration of immunosuppressive and cytotoxic agents are the common causes.
- An acute rise in blood pressure and/or metabolic abnormalities usually produce the syndrome.
- Imaging studies reveal bilateral oedema predominantly in the white matter in the posterior parietal and occipital lobes of the brain.
- Clinical features include headache, vomiting, altered sensorium, disturbances of vision (cortical blindness), seizures, and rarely focal deficits.
- Prompt reduction of blood pressure or withdrawal of immunosuppressive agents leads rapid reversal of the syndrome.
- If treatment is delayed, permanent damage to affected areas of the brain is likely.

Conclusions

Knowledge of posterior leukoencephalopathy syndrome is of great significance in everyday clinical practice. The diagnosis is suggested by posterior cerebral white matter abnormalities seen on T2 weighted MR imaging, and by the presence of headache, altered mental status, seizures, and disturbances of vision. Clinicians must be aware of this syndrome, as its recognition obviates unnecessary diagnostic procedures. Moreover, the syndrome is reversible by prompt lowering of raised blood pressure, and by stopping the administration of offending immunosuppressive and cytotoxic agents (box 5).

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