Communication • DOI: 10.2478/v10134-010-0016-9 • Translational Neuroscience • 1(2) •2010 •115–123

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REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

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Abstract

Reversible posterior leukoencephalopathy syndrome (RPLS) is characterized by subacute onset of headache, decreased alertness, vomiting, seizures, visuoperceptual disturbances, together with bilateral white matter lesions in posterior brain regions on brain imaging. The most frequently associated conditions related to RPLS are arterial hypertension and the use of immunosuppressive or cytotoxic treatment. T2-, Fluid Attenuation Inversion Recovery (FLAIR), and Apparent Diffusion Coefficient (ADC)- weighted magnetic resonance imaging (MRI) reveal hyperintensities in parietooccipital white matter but grey matter and other regions including frontal and temporal lobes, brainstem, cerebellum, basal ganglia, or even spinal cord may also be involved. According to ADC findings, the underlying pathophysiologic mechanism is probably one of vasogenic (rather than cytotoxic) oedema. These MRI findings help in differentiating RPLS from ischaemic events and other diseases resembling RPLS. Failure of cerebral autoregulation, endothelial dysfunction, disrupted blood-brain barrier, vasospasm, and direct toxic drug effects may all play a role in the pathophysiology of RPLS. Treatment consists of discontinuation of the causal drug, treatment of high blood pressure, and antiepileptic therapy. Clinical recovery and regression of radiological abnormalities are typically seen after early treatment. However, delay in diagnosis and treatment can result in irreversible brain damage, often in association with complicating cerebral infarction or haemorrhage.

Keywords

Drug-induced • Hypertensive • White matter • Cyclosporine • MRI • Brain • Immunosuppression

Received 19 May 2010
accepted 15 June 2010

Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) was first described by Hinchey et al in 1996 who reported 15 patients with a wide variety of diseases presenting with headache, decreased alertness, vomiting, seizures, and visuoperceptual disturbances [1]. Of these 15 patients, 7 had previously received immunosuppressive treatment, 1 was on interferon treatment, 3 had eclampsia, and 4 suffered from acute hypertensive encephalopathy related to renal disease. In 12 of these patients, arterial hypertension was noted. Brain imaging showed bilateral extensive white matter abnormalities suggestive of oedema in the posterior cerebral regions. In all 15 patients, neurological abnormalities resolved after antihypertensive treatment and withdrawal or dose reduction of immunosuppressive therapy. Prior to this initial description, several patients with similar clinical findings and radiological abnormalities had been described (e.g. associated with malign hypertension, eclampsia, or cyclosporine use) [2-4]. Most RPLS patients are adults. However, RPLS can also occur in children and is the most common abnormality leading to seizures in children with leukaemia[5].

Most of the literature concerning RPLS is based on reports of single or multiple cases rather than consecutive series of at-risk populations. To the best of our knowledge no reliable estimates of incidence of RPLS are available. Furthermore, the condition may be underdiagnosed: the clinical syndrome of RPLS is often incomplete, magnetic resonancy imaging (MRI) is not always performed, and symptoms may be reversible (e.g. after correction of hypertension, change or withdrawal of immunosuppressive or cytotoxic treatment) even when the diagnosis of RPLS was overlooked. It is generally considered a relatively uncommon disorder. The two most frequently associated conditions related to RPLS are arterial hypertension and the use of immunosuppressive or cytotoxic treatment. The distinction between drug-related RPLS and hypertension-induced RPLS may be difficult since elevated blood pressure often complicates RPLS associated with immunosuppressive and cytotoxic treatment.

In principle, RPLS should be distinguished from more diffuse toxic leukoencephalopathies that lack any posterior predilection and by definition affect periventricular white matter and the centrum semiovale relatively evenly [6] (see below).

Post-mortem studies of RPLS reveal relatively aspecific changes, such as oedema, reactive astrocytosis, neuronal loss, demyelination, ischaemic infarction, and haemorrhage.

Risk factors

Drugs associated with RPLS are often - but not limited to - immunosuppressive and cytotoxic agents (Table 1).

The exact offending drug is sometimes difficult to identify since oncological patients undergoing chemotherapy or transplant patients on immunosuppressive medication typically receive multiple drugs that could contribute to the development of RPLS. The RPLS risk associated with specific drugs is hard to quantify since most of the literature consists of case reports rather than prevalence studies in at-risk populations. RPLS symptom onset is often related to the introduction of new drugs, dose increase, or increased blood pressure but can also occur in patients on stable doses of

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Table 1. Non-exhaustive list of drugs that have been associated with RPLS

Relatively frequently reported associations	Less frequently reported associations	Rare case reports
Cyclosporine	L-asparaginase	Erythropoietin
Methotrexate	Interferon alpha	Granulocyte-colony stimulating factor
Tacrolimus	Cytarabine	Adriamycin
Paclitaxel	Sunitinib	Antiretroviral therapy (indinavir)
Platinums (cisplatinum, oxaliplatinum)	Vincristine	TNF-alpha inhibitors
Bevacizumab	Gemcitabine	
Immune globulin therapy	Alkylating agents (cyclophosphamide, ifosfamide)	

chronically used drugs [7]. Drug levels above the therapeutic range may play a role in the development of RPLS although in most of the reports drug levels were within the therapeutic range [8-9]. Some drugs can indirectly lead to RPLS because they affect the pharmacodynamics of immunosuppressant agents. For instance, introduction of omeprazole in a patient chronically treated with methotrexate can lead to RPLS. Drugs that inhibit the cytochrome P450 system, such as steroids, can increase cyclosporine levels. The drug administration route influences the risk and severity of RPLS. For instance, intrathecally administered methotrexate and cytarabine are associated with a higher risk than intravenous administration and intravenous administration of cyclosporine leads to a higher risk than oral administration [10]. These distinctions however are not absolute and long-term oral methotrexate therapy, for instance, can also give rise to RPLS [7]. The risk of developing RPLS also appears to be higher if chemotherapy is combined with cranial radiation [11].

Hypertension seems to play an important role in the pathophysiology of RPLS since blood pressure is elevated in the vast majority of reported cases. However, RPLS can occur in the absence of elevated blood-pressure readings. Elevated blood pressure is a frequent adverse effect of many of the immunosuppressive and cytotoxic drugs described in RPLS. Cases with RPLS primarily related to drugs often present with only moderate hypertension. If, however, malignant hypertension is the principal cause, other organs apart from the brain are often also affected leading to renal failure, papilloedema, retinal oedema and retinal haemorrhages (Figure 1).

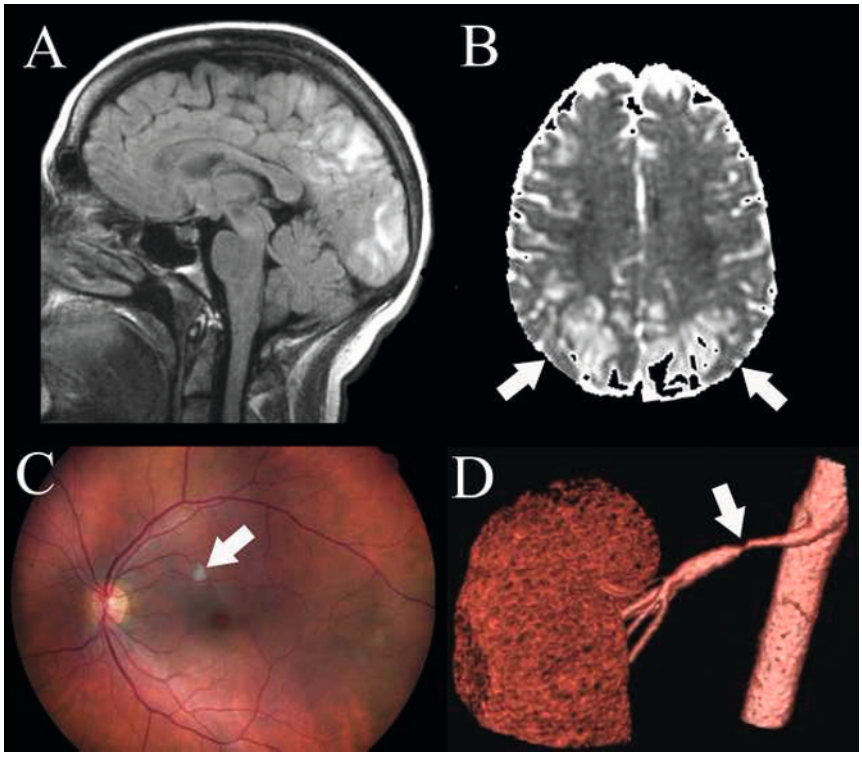

Figure 1. A. B. Brain MRI showing subcortical and cortical hyperintense signal predominant in posterior regions on FLAIR- (A) and ADC-weighted (B) imaging (vasogenic oedema). Arrows: ADC hyperintense lesion. C. Eye fundus examination showed hypertensive-related retinal exudates (indicated by arrow). D. CT angiography revealed high grade stenosis of the right renal artery (indicated by arrow), responsible for hypertension, with post-stenotic dilatation.

Electrolyte imbalance, sepsis, fever, and renal failure may predispose to RPLS through damage of the blood-brain barrier (BBB) leading to vasogenic oedema at blood pressure levels that usually would be well tolerated [12-13]. Hypocholesterolaemia has also been described as a possible risk factors for RPLS [14-16]. Cyclosporine, one of the most frequently reported drugs associated with RPLS, is highly lipophilic. Fifty to 60% is bound to lipoproteins, especially low density lipoprotein (LDL). Cyclosporine enters the cells through transmembrane diffusion or can be transported into the cell by LDL particles binding to the LDL receptor. Low cholesterol levels increase the concentration of cyclosporine in LDL particles and the density of LDL receptors on the cell membranes, thereby augmenting cyclosporine uptake. In the brain, the LDL receptor is expressed primarily by astrocytes and by

arachnoid cells. Under normal conditions the BBB transport of cyclosporine is restricted but a direct toxic effect of cyclosporine on the endothelium or coexisting hypertension may increase BBB permeability for cyclosporine. Hypomagnesaemia is also a risk factor for RPLS [17]. Hypomagnesaemia can occur as a side effect of cyclosporine treatment because cyclosporine causes intracellular migration and renal wasting of magnesium [18].

Tumor lysis syndrome, most commonly associated with Burkitt or other high-grade lymphoma and leukaemia, is another risk factor for RPLS [19-20]. Massive lysis of malignant cells can occur spontaneously or after antineoplastic treatment. It can lead to release of intracellular potassium, phosphorus and uric acid as well as many other cellular components into the blood stream leading to vascular endothelial damage.

Risk factors for RPLS in children are similar to those described in adults and include, among others, arterial hypertension, with or without associated renal involvement (e.g. haemolytic uremic syndrome, nephrotic syndrome, glomerulonephritis), steroids, immunosuppressive and chemotherapy (for bone marrow transplantation, kidney transplant, systemic lupus erythematosus, acute lymphoblactic leukaemia, and other cancers), Henoch-Schönlein purpura, thrombotic thrombocytopenic purpura (TTP), sickle cell disease, Wegener's granulomatosis, and haematopoietic stem cell transplantation [21-28]. In young children the physiological myelination process is incomplete making them particularly susceptible to permanent leukotoxic effects of radiation therapy.

Clinical features

The common clinical features of RPLS include headache, often resistant to simple analgesia, decreased alertness, vomiting, seizures, and visuoperceptual disturbances. Disease onset is generally subacute but thunderclap headache has been reported as the initial symptom in some cases of RPLS [29-32]. Agitation, confusion, and restlessness may alternate with apathy.

Seizures often precede the other manifestations [33-34]. Generalized tonicoclonic seizures may be preceded by visual auras, consistent with occipital onset of partial epileptic discharges [33-34]. A wide variety of visual abnormalities may occur, including visual field defect, blurred vision, visual neglect, visual hallucinations, cortical blindness, visual agnosia, denial of blindness (Anton's syndrome), simultanagnosia (with or without other components of the Balint syndrome), or alexia without agraphia. Homonymous hemi- or quadrantanopsia (in case of asymmetric involvement of the occipital lobe) and altitudinal visual field (in case of strictly supra- or infracalcarine lesions) defects are frequent. Since brain lesions are typically located posterior to the lateral geniculate body, pupillary reflexes are preserved and fundus examination is normal. Plantar responses may be in extension and deep tendon reflexes are often brisk. If brain lesions extend beyond parieto-occipital regions (e.g. frontal or temporal zones, brainstem, cerebellum, spinal cord), additional symptoms may be present depending on the regions involved.

Imaging

Brain imaging is essential to the diagnosis of RPLS. Lesions most typically affect occipital and posterior parietal white matter (Figure 2A,B).

Watershed areas between middle and posterior cerebral artery are frequently involved (Figure 2A). Brain abnormalities in RPLS can be seen on Computerized Tomography (CT) as bilateral hypodense areas (oedema). CT is also sensitive for the detection of haemorrhagic complications (Figure 3A-C).

MRI has the ability to show smaller focal abnormalities at an earlier stage (Figure 3D-E).

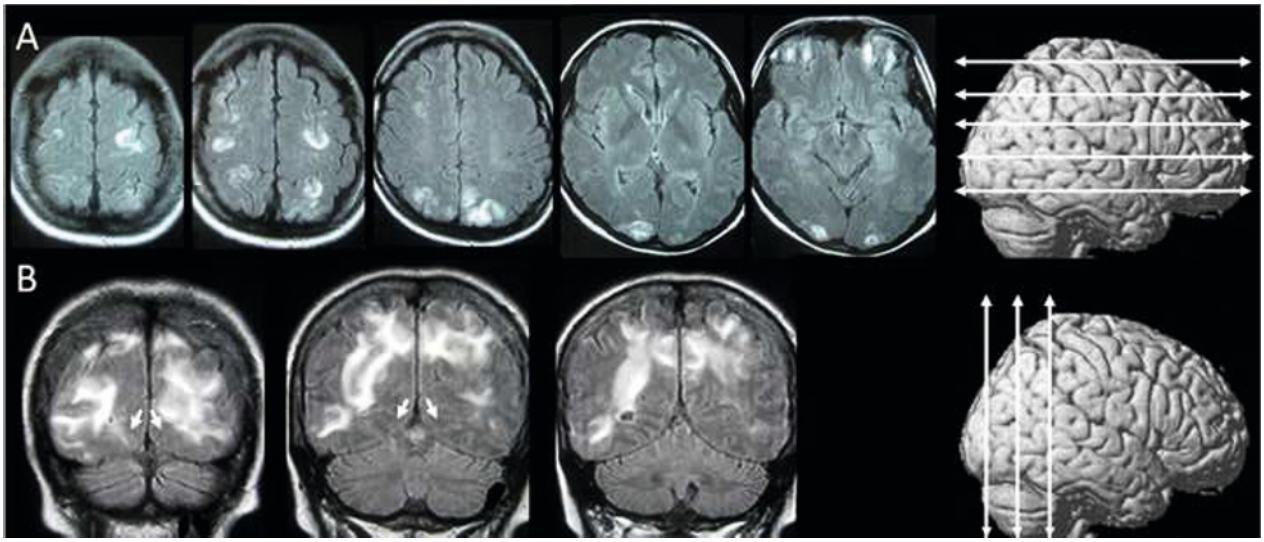

Figure 2. A. Axial FLAIR sequences showing subcortical and cortical multifocal hyperintensities in the bilateral frontal, parietal, and occipital regions in a 24-year-old woman with RPLS associated with hypertension and eclampsia. B. Posterior-located, mainly subcortical, hyperintense lesions on coronal FLAIR imaging with an asymmetrical distribution (right hemisphere more involved than the left one) in a 67-year-old patient with RPLS associated with immune globulin therapy and hypertension. Arrows point to the calcarine sulcus (striate cortex) which is relatively spared. The side view of the brain gives an approximate indication of the level at which the axial and coronal sections are taken.

On Fluid Attenuated Inversion Recovery (FLAIR) sequences (Figure 3E), brain abnormalities are often more easily seen than on conventional T2-weighted sequences, especially in brain structures adjacent to cerebrospinal fluid (e.g. cerebral cortex). MRI signal characteristics in RPLS are indicative of vasogenic oedema: iso- to hyperintense on Diffusion Weighted Imaging (DWI) sequences, hyperintense on Apparent Diffusion Coefficient (ADC), T2, and FLAIR sequences and hypointense on T1-weighted imaging (Figure 3D-F). This differs from cytotoxic oedema, which is visible as ADC hypointensities, similarly to what can be seen in acute infarction. Lesions are usually bilateral and asymmetrical but can be strictly unilateral. Despite its name, RPLS affects frontal (Figure 2A) and temporal lobes in up to 90% of cases. Brainstem and cerebellum (Figure 4) may also be affected as well as corpus callosum, basal ganglia, thalamus, and, exceptionally, spinal cord.

In addition to white matter, cortical grey matter is involved in up to 94% of cases (Figure 5) [35-37].

The radiological extent of brain abnormalities is not strictly correlated with clinical symptoms. Mass effect is unusual in RPLS but may cause obstructive hydrocephalus if the brainstem is involved [38]. Contrast-enhancement is exceptional but may occur at the earliest stage [39]. In case of persistent offense of BBB (such as with TTP), the contrast-enhancement phase may be prolonged. Occurrence of acute cerebral haemorrhage and ischaemia may also prolong the period of contrast-enhancement [39].

In the absence of complications and with early treatment (i.e. by discontinuing offending drugs and treating elevated blood pressure), radiological abnormalities are typically reversible. Longitudinal MRI reveals permanent lesions in up to 26% of patients but these are usually restricted in size (Figure 3G-I). Presence of ischaemia, haemorrhage, gadolinium enhancement, and extensive oedema are associated with poorer outcome [40]. In brain areas with massive oedema, elevated tissue perfusion pressure may lead to decreased cerebral blood flow, impairment of microcirculation, and infarction.

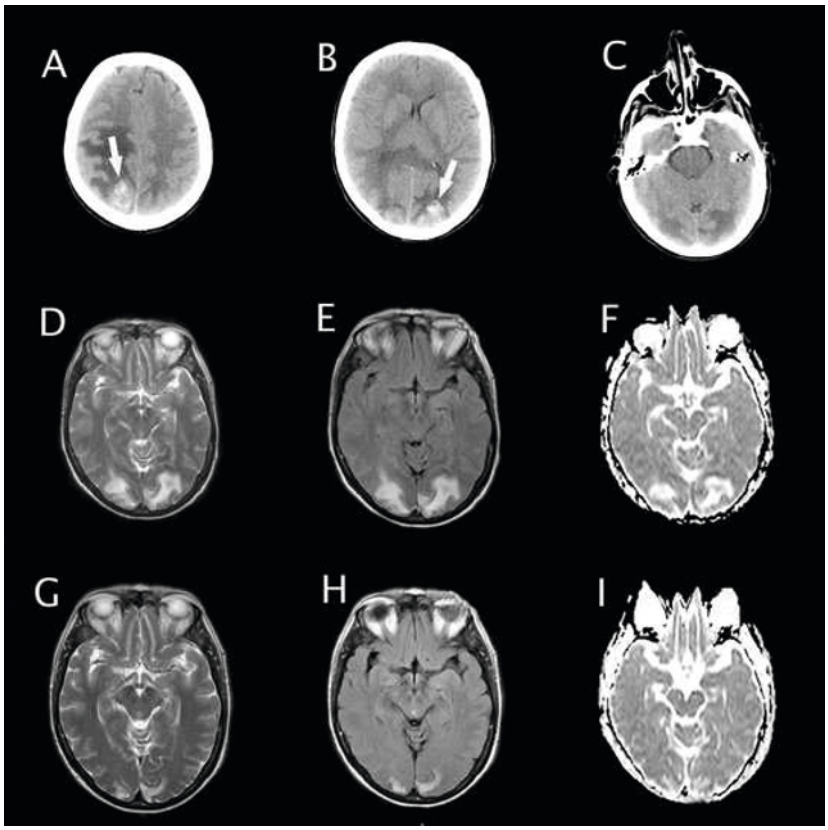

Figure 3. Imaging results in a 47-year old woman with RPLS. A-C. CT scan. White matter hypodensity in the right fronto-parieto-occipital and the left parieto-occipital lobe, together with a right parietal and left parieto-occipital haemorrhage. D-F. MRI performed on the same day. Increased white matter signal on T2 (D), FLAIR (E) and ADC (F) sequences with the same distribution as white matter hypodensity on CT. G-I. MRI 3 months later. Partial resolution of the MRI lesions.

If RPLS is complicated by ischaemia, affected regions show increased DWI signal and pseudonormalized or decreased signal on ADC sequences, concordant with cytotoxic oedema, surrounded by areas of vasogenic oedema with iso- to hyperintense DWI signal and hyperintense ADC signal [41- 43].

Cerebral micro- or macrohaemorrhages have also been described as a complication of RPLS (Figure 3). Brain haemorrhage is more often described in hypertension-induced RPLS [39,44,45]. Gradient Recalled Echo (GRE) T2 weighted MRI is a sensitive technique for detecting this complication.

Multifocal areas of arterial narrowing, consistent with vasospasms, can be seen angiographically in some RPLS cases, most often at the level of large cerebral blood vessels and their second-order branches [46-52].

Magnetic resonance spectroscopy (MRS) during the acute phase of RPLS may reveal high choline and creatine peaks and normal or mildly decreased N-acetyl aspartate (NAA)/creatine [53,54]. The rise in choline and creatine may possibly reflect microglial activation, e.g. due to immunosuppressive therapy and radiation or disruption of the BBB. An increase of lactate may be indicative of ischemia and predictive of a less favourable outcome.

Other laboratory findings

Cerebrospinal Fluid (CSF) analysis is usually normal, although slightly elevated total protein has been described. Electroencephalographic (EEG) findings are not specific, with (diffuse or focal) slowing and epileptic discharges as most commonly reported abnormalities.

Differential diagnosis

Some elements of RPLS may resemble what is seen in ischaemic stroke, central nervous system (CNS) vasculitis, venous sinus thrombosis, encephalitis, autoimmune diseases, progressive multifocal leukoencephalopathy (PML), pontine and extrapontine myelinolysis, anoxic and hypoglycemic encephalopathy, Wernicke encephalopathy, CNS lymphoma, protracted seizures, and diffuse toxic leukoencephalopathy,. Other conditions that may resemble RPLS clinically or radiologically are listed in Table 2.

The distinction between ischaemia and RPLS has important therapeutic implications: reducing blood pressure minimizes vasogenic oedema in RPLS but may be deleterious in the case of stroke. Symptom onset due to bilateral posterior cerebral artery infarction (most often caused by embolism to the rostral basilar artery - 'top of the basilar' syndrome) is usually acute. Lesion distribution differs between the two diseases: involvement of striate or paramedian occipital cortex, thalamus, or midbrain is much more frequent in ischaemia than in RPLS which relatively spares striate cortex (Figure 2B). Brain lesions in RPLS are often not restricted to one vascular territory and have a predilection for watershed areas between middle and posterior cerebral artery. Signal intensities on DWI and ADC sequences can also help one to differentiate between RPLS and ischemia, as outlined above (Figure 3F). In patients with cerebral venous sinus thrombosis (CVST), bilateral oedema, ischaemia and/or haemorrhage in posterior brain regions can be found on brain imaging. CVST patients may present with headache, nausea, vomiting, seizures and decreased alertness, symptoms that are also found in RPLS. The differential diagnosis is particularly important during the first days postpartum, which is associated with an increased risk of CVST as well as eclampsia-associated RPLS. In most cases of CVST, headache precedes the development of other neurological deficits for days or even weeks. Typically the obstruction of the venous sinuses can be visualized by means of MR or CT angiography and the intravenous

Table 2. Conditions that may resemble RPLS clinically and radiologically in addition to those described in the main text.

Hypertensive encephalopathy
(Pre-)eclampsia
Renal diseases
Thrombotic thrombocytopenic purpura
Haemolytic uremic syndrome
Hepatorenal syndrome
Dialysis disequilibrium syndrome
Haematological diseases
Sickle cell disease
Stem cell re-infusion
Post-transplantation lymphoproliferative disorder
Metabolic disorders
Hypercalcaemia
Acute intermittent porphyria
Mitochondrial encephalopathy
Acquired Immunodeficiency syndrome
Tetanus
Systemic autoimmune diseases
Systemic lupus erythematosus
Systemic sclerosis
Wegener's granulomatosis
Polyarteritis nodosa
Demyelinating diseases
Vascular white matter lesions due to microangiopathy
Radiation leukoencephalopathy

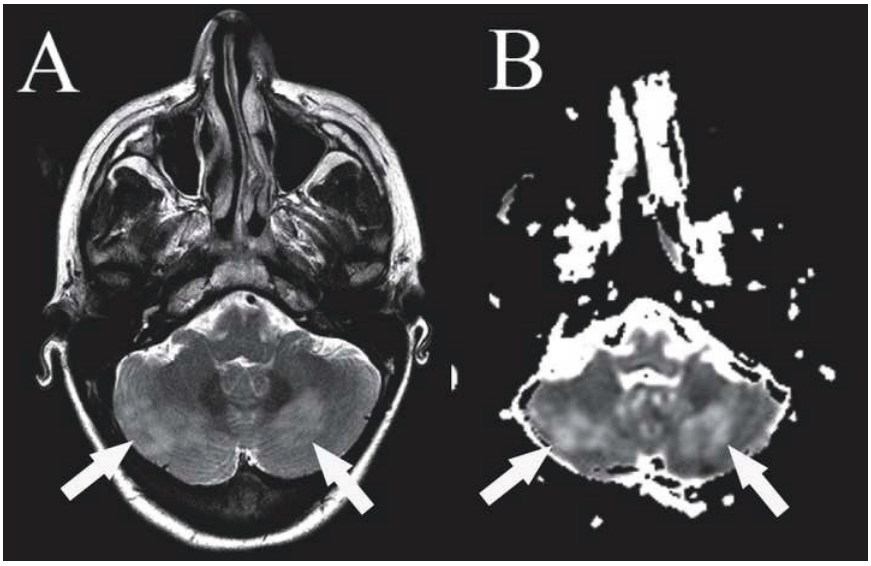

Figure 4. Cerebellar involvement in a case of hypertension-induced RPLS. A. Axial T2- weighted B. ADC imaging showing cerebellar hyperintense signal in a patient with typical hypertension-induced RPLS.

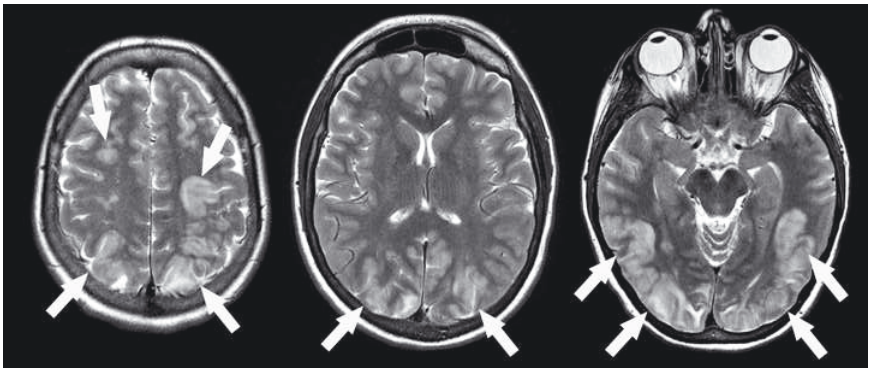

Figure 5. Cortical, multifocal involvement. Axial T2-weighted imaging in a patient with hypertension-induced RPLS.

thrombus can sometimes be detected on T1-weighted or FLAIR MRI sequences. Intracranial haemorrhage is more common in CVST than in RPLS [55].

CNS vasculitis may be associated with encephalopathy, visual loss, or seizures, similarly to RPLS. The distinction between RPLS and CNS vasculitis is especially important in patients with underlying rheumatologic or autoimmune disorders: CNS vasculitis requires immunosuppressive therapy whereas management of RPLS requires withdrawal or reduction of immunotherapy. CNS vasculitis lacks the typical posterior distribution of brain lesions. Segmental vasoconstriction on angiography is much more frequent in vasculitis than in RPLS. If it is present in RPLS, it principally affects large arteries of the circle of Willis and its second-order branches while vasculitis may also affect more distal branches depending on the type of vasculitis [46-52].

PML is a subacute demyelinating brain disease caused by the JC virus (which can be detected in CSF or urine), most often in patients with chronic immunodeficiency state (e.g. AIDS, immunosuppressive therapy). Clinical features of PML often include visual field defects, confusion, dementia, and coma. MRI shows multifocal, mostly asymmetrical, hyperintense white matter signal on T2 and FLAIR sequences. Lesions are often located in the parietooccipital region, and may cross the corpus callosum. In contrast to RPLS, PML often leads to death in the months following symptom onset.

Central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) are characterized by a subacute onset of clinical signs including seizures, altered mental status, pseudobulbar palsy, and quadriplegia, and the presence of white matter lesions on brain imaging, most often in a context of profound current or recent metabolic dysregulation. On MRI, there is no posterior predominance of brain abnormalities, and pontine lesions are far more frequent than in RPLS [56-58].

Partial and generalised status epilepticus can lead to increased T2 signal changes resembling those described in RPLS [59]. These seizure-related alterations, however, are typically mainly localised cortically but may extend subcortically, and are usually seen in the maximally discharging regions as documented by electroencephalography (EEG), single photon emission computerized tomography (SPECT) or positron emission tomography (PET). Transient restricted diffusion on MRI may be seen in these areas, especially if imaging is performed during or immediately after seizures. Although seizures are often seen in RPLS, status epilepticus is rare.

T1- and T2-weighted MRI images in anoxic or hypoglycemic encephalopathy may resemble those seen in RPLS. However, under such conditions, restricted diffusion is usually seen with high DWI-signal intensities and decreased ADC values.

The non-specific clinical presentation of RPLS with encephalopathy, headache and seizure may mimic a (para)infectious encephalitis. Encephalitis associated with opportunistic infections may be suspected in immunocompromised patients or in patients receiving immunosuppressive or cytotoxic drugs. The lack of CSF pleocytosis and the absence of gadolinium enhancement on MRI would favour RPLS over encephalitis.

CNS lymphoma may present with rapidly progressive clinical features similar to RPLS. In case of CNS lymphoma T1- and T2-weighted MRI images shows most often one or multiple homogeneous isointense/hypointense lesions with mild surrounding oedema, together with possible restricted diffusion in the lesion. In contrast to RPLS, strong and homogenous gadolinium enhancement is typical. Ring-enhancing lesions with central necrosis are often seen in immunocompromised patients (e.g. AIDS) with CNS lymphoma. CNS lymphoma frequently affects the deep grey nuclei, the periventricular zones, the corpus callosum, and often extends along ependymal surfaces.

In diffuse toxic leukoencephalopathy [6] MRI changes are by definition more evenly distributed over the cerebral white matter, starting with periventricular white matter and the centrum semiovale and strictly sparing cortex [61]. This contrasts with RPLS which mainly affects subcortical white matter extending into cortex and has a posterior predilection. Myelinated pathways may be prominently affected in diffuse toxic leukoencephalopathy. Clinical features range from inattention, forgetfulness, and changes in personality to dementia, coma, and death. Visual disturbances are less frequent than in RPLS. Some of the risk factors, namely antineoplastic or immunosuppressive drugs, overlap with those of RPLS but risk factors for diffuse toxic leukoencephalopathy also include environmental toxins (arsenic, carbon tetrachloride, carbon monoxide), illicit drugs (toluene, cocaine, heroin, psilocybin, amphetamine), and antimicrobial agents (metronidazole, amphotericin B, hexachlorophene) [6]. Acute diffuse toxic leukoencephalopathy is more frequently associated with reduced ADC than RPLS [61]. Both conditions can be reversible and the exact pathophysiological differences between the two entities are unclear. Possibly, oligodendroglial and myelin sheath damage is more prominent in diffuse toxic leukoencephalopathy while vascular endothelial damage and vasogenic oedema may play a relatively more important role in the origin of RPLS.

Pathophysiology

The exact pathophysiology of RPLS is incompletely understood and probably multifactorial. As hypertension frequently coexists with drug-related RPLS and given the striking clinical and radiological similarities between drug-related and hypertension-induced RPLS, the underlying pathophysiological mechanisms probably overlap.

Cerebrovascular autoregulation (by inducing vasoconstriction or vasodilatation) serves to keep cerebral blood flow constant when mean arterial blood pressure (MAP) remains between 60-120 mmHg, thereby protecting the brain from acute blood pressure changes [61,62].

Cerebral vasoconstriction, mediated by sympathetic innervation, protects the brain from acute increases in blood pressure. Carotid arteries are better supplied with sympathetic adrenergic innervation than the vertebrobasilar artery system [63]. If increased blood pressure exceeds the vascular autoregulatory capacity, cerebral arterioles start to dilate. Capillary permeability and BBB dysfunction will result

in plasma leakage into the extracellular space, producing vasogenic oedema. The cortex is more tightly packed and organized than the white matter and may therefore be more resistant to the development of oedema.

Many studies show evidence of endothelial cell dysfunction in RPLS, with release of endothelial cell surface molecules and subendothelial cell matrix components [64,65]. In eclampsia, brain oedema is associated with the presence of abnormal red blood cell morphology (schistocytes, acanthocytes, and anisocytosis) and elevated lactate dehydrogenase (LDH) levels suggesting shear injury to circulating red blood cells due to endothelial damage [13].

In addition to arteriolar dilatation and vasogenic oedema, hypertension may also cause severe vasoconstriction leading to cytotoxic oedema and ischaemia. The mechanism by which RPLS may lead to ischaemia in the absence of radiological vasospasm, is unclear. In areas of massive vasogenic oedema, increased tissue pressure may impair microcirculation leading to brain ischaemia.

Calcineurin inhibition affects sympathetic outflow. The pathophysiology of drug-related RPLS in the absence of hypertension may be related to a direct toxic effect on vascular endothelium leading to vasogenic oedema similar to that seen in hypertensive-induced RPLS.

Treatment

RPLS treatment needs to be started as soon as possible, as delay may result in permanent brain damage. In drug-related RPLS, treatment consists of withdrawal or dose reduction of the offending drug, blood pressure regulation, and antiepileptic treatment in patients who develop seizures. Since multiple drugs are often used in oncological patients under cytotoxic treatment or in transplant patients receiving immunosuppressant therapy, the exact causal drug associated with RPLS is often difficult to identify. Therefore, time of onset of clinical symptoms and/or increased blood pressure has to be correlated with the moment of introduction (or dose increase) of drugs. If possible, this drug has to be discontinued. Dose reduction can be an option if there is no alternative treatment available. An important decision is whether or not to withhold the potential inciting agent in future treatment. If no alternative treatment is available, continued use of the drug can be tried by decreasing drug dose and by managing other possible risk factors (e.g. hypertension, hypocholesterolaemia, hypomagnesaemia, steroid use, metabolic abnormalities).

If arterial hypertension is present, systemic blood pressure must be reduced but not too agressively. Agressive lowering of blood pressure may cause worsening of end organ function and cerebral infarction may occur. Intravenous antihypertensive therapy (including labetolol, calcium channel blockers, and nitroprusside) is generally preferred. Angiotensin converting enzyme (ACE) inhibitors should be avoided in patients with possible underlying renal artery stenosis. Antihypertensive treatment options in pregnancy include hydralazine, labetalol, and methyldopa [66,67]. Atenolol and ACE-inhibitors are contraindicated during pregnancy. Epileptic seizures should be treated with anticonvulsant medication. Intravenous loading of antiepileptic drugs is often required, especially if multiple seizures occur or in case of status epilepticus. Some antiepileptic agents (e.g. phenytoin) may interfere with ongoing chemotherapy through enzyme induction. Long-term antiepileptic treatment is usually not required as seizures disappear together with the improvement of other clinical and radiological abnormalities.

Prognosis

Early diagnosis and treatment of RPLS is of the essence. Most patients show complete recovery within weeks following appropriate treatment. Delay in diagnosis and treatment, however, can result in irreversible brain damage, coma, or even death, often in association with cerebral infarction or haemorrhage. Clinicians must be aware of the potential complication of intracranial haemorrhage, particularly in patients with thrombocytopenia or other clotting abnormalities induced by co-morbidity or medication. Certain MRI characteristics seem to be of prognostic value. More extensive T2 signal abnormalities were seen in patients with poor outcome. High DWI signal and pseudonormalized or reduced ADC values are associated with cerebral infarction and may represent the earliest sign of irreversibility.

Future directions

The arsenal of cytotoxic and immunosuppressive drugs at the disposition of oncologists and transplantation medicine is rapidly increasing. Even drugs that belong to a same class, such as the tyrosine kinase inhibitors, may differ in their risk of drug-induced leukoencephalopathy. More reliable estimates of the incidence of this potentially life-threatening neurological complication, e.g. based on consecutive series of at-risk populations [68], would be of clinical use for each of these drugs. Apart from the association between a given drug and clinically significant leukoencephalopathy, a multivariate approach may also reveal risk modifiers that may differ between the offending drugs and ways to reduce this risk so that potentially lifesaving drugs can be continued or re-started.

Acknowledgments

RV is a senior clinical investigator of the Research Foundation Flanders (FWO).

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