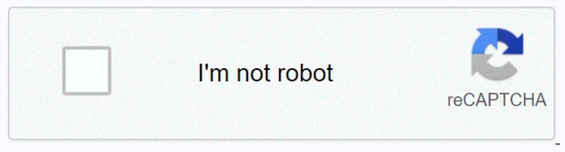

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Accelerated hypertension pdf

As many as 1% of patients with essential hypertension develop malignant hypertension, but the reason why some patients develop malignant hypertension while others are not unknown. The characteristic vascular lesion is fibrinoid necrosis of the arteries and small arteries, which causes the clinical manifestations of end-body damage. Red blood cells are damaged as they flow through vessels blocked by fibrin deposition, resulting in microangiopathic hemolytic anemia. In a retrospective study that evaluated hospital admissions data from the nationwide inpatient test for malignant hypertension, hypertensive encephalopathy, and significant hypertension, Polgreen et al found an increasing tendency for malignant hypertension and hypertensive encephalopathy from 2000 to 2011, with a dramatic increase after 2007. [4] However, there was no corresponding dramatic increase in morbidity for both conditions, which investigators believed could be the result of coding changes in 2007. Mortality decreased significantly for patients with malignant hypertension, but not for patients with hypertensive encephalopathy. [4] Another pathological process is dilation of cerebral arteries after a breakthrough in the normal autoregulation of cerebral blood flow. Under normal conditions, cerebral blood flow is kept constant by cerebral vasoconstriction in response to increases in BP. In patients without hypertension, the flow is kept constant above an average pressure of 60-120 mm Hg. In patients with hypertension, flow is constant above an average pressure of 110-180 mm Hg due to arteriolar thickening. When BP is raised above the upper limit of auto regulation, shells spill. This results in hyperperfusion and cerebral edema, which causes the clinical manifestations of hypertensive encephalopathy. Other causes of malignant hypertension include any form of secondary hypertension; complications of pregnancy, ie, preeclampsia and eclampsia; use of cocaine, monoamine oxidase inhibitors (MAOIs) or oral contraceptives and withdrawal of alcohol, beta blockers or alpha stimulants, such as clonidine. Kidney artery stenosis, pheochromotomy (most pheochromocytomes can be localized using computed tomography [CT] of the adrenal glands), aortic coarctation, and hyperaldosteronism are also secondary causes of hypertension. In addition, both hyperthyroidism and hypothyroidism can cause hypertension. The following conditions should also be considered when diagnosis: ischemic or hemorrhagic stroke, intracranial mass, head injury, epilepsy or postictal condition, connective tissue disease (especially lupus with cerebral vasculitis), overdose or withdrawal, cocaine or amphetamine ingestion, acute anxiety, and thrombotic thrombocytope purpura. [5, 6] Since malignant hypertension-induced thrombotic microangiopathy may mimic the thrombocytope purpura, there is a possibility that plasma exchange rather than antihypertensive agents may given to patients. In a literature review, Khanal et al reported factors more likely to be present in malignant hypertension-induced thrombotic microangiopathy are (1) a previous hypertension history, (2) high average arterial pressure, (3) significant renal impairment, but relatively modest thrombocytopenia and (4) lack of severe ADAMTS-13 reficiency (activity < 10%) diagnosis. [6] For more information, see Hypertension. Malignant hypertension is defined as marked high blood pressure (diastolic BP often >140mmHg) with retinal haemorrhages, exudates or papilloedema with or without signs of target organ damage, typically acute and progressive kidney damage with proteinuria and hemoturia ('malignant nephroclerosis'). From: Clinical Biochemistry: Metabolic and Clinical Aspects (Third Edition), 2014Donald G. Far, in Hypertension (Second Edition), 2005Malignant hypertension constitutes a syndrome of severe increases of average arterial pressure (MAP) often to or above 140 mm Hg, manifested clinically by retinal bleeding, exudates and papdeillema. The term malignant hypertension was previously reserved for those patients who exhibited advanced funduscopic changes, including papilledema, while the term accelerated hypertension was used when the syndrome was observed without papilledema. The distinction between accelerated and malignant hypertension has been underlined, because the short- and long-term prognosis are independent of the presence or absence of papilledema, and both pathogenesis and clinical treatment of accelerated and malignant hypertension are the same.7,8 In addition, the presence of papilledema may be difficult to detect by funduscopic examination and subject to observer interpretation.9Vascular injury is thought to relate to both the duration and severity of the elevated MAP. Untreated or inadequately treated essential hypertension represents the most common predecessor of malignant hypertension and has been observed to be more common among smokers.10 With improved hypertension control efforts, progression to the malignant stage of hypertension is seen less commonly. Secondary etiologies of hypertension are more common among patients who progress to accelerated or malignant hypertension. Theodore L. Goodfriend, Kristin M. Lyerly, in Pathophysiology of Kidney Disease and Hypertension, 2009Malignant hypertension is defined as a rapidly increasing pressure (also called accelerated hypertension) with severe, sudden damage to the brain, eyes, and kidneys. Several histological manifestations of inflammation and necrosis characterize malignant hypertension and differentiate it from nonmalignant hypertension:1.Fibrinoid necrosis of arterioles occurs. Fibrinoid is a term given to an eosin-dyeing substance, fi brin, that is extruded into the blood vessel wall under the extreme pressure of malignant hypertension (Fig. 15-4).2.In malignant hypertension, glomeruli can areas with thrombosis and necrosis areas. The bleeding of the kidney parenchyma cause the spotted, red, flea-bitten appearance of the surface.3.The arterial and arterial lesions result in a significant narrowing of all vascular lumina, with ischemia and infarctions distal to the abnormal vessels. The question of cause and effect is part of all discussions of kidney pathology in hypertension, whether benign or malignant. Diseases of the kidney arteries can cause hypertension either by impairing sodium excretion, by stimulating renin release, or both. On the other hand, hypertension itself damages the kidney vessels, so there is a vicious circle. In malignant hypertension, the vascular damage is acute, and renin release is a very important part of the pressure increase. In benign, essential hypertension, vascular damage is chronic, and its main pressure-raising influence is sodium retention. Aleksander Prejbisz, Andrzej Januszewicz, in Encyclopedia of Endocrine Diseases (Second Edition), 2019Malignant hypertension (MHT), also known as accelerated-malignant hypertension or malignant stage hypertension is clinically defined as high blood pressure associated with bilateral retinal flame haemorrhages, exudates or swabs, with or without papal pellets. It is the most severe form of hypertension. It has also been proposed to replace the term malignant hypertension with hypertensive crisis with retinopathy. Since the presence of retinopathy may allow other target bodies to be included, making the description of this type of hypertensive emergency more accurate (Kaplan and Victor, 2015; Mancia et al., 2013; van den Born et al., 2011; Januszewicz et al., 2016). MHT is associated with failure of blood pressure autoregulation and develops when the average arterial pressure (diastolic blood pressure + 1/3 of the difference between systolic and diastolic blood pressure) reaches a critical level of 150 mmHg, as reported in experimental animals. Fibrinoid necrosis appears in the artery walls, which may be caused by vasoactive factor (s) or may be an unspecific consequence of very high BP (Kaplan and Victor, 2015; Januszewicz et al., 2016). Possible pathophysiological mechanisms for the development of MHT have been proposed. These include: rapidly increasing blood pressure, pressure diuresis and natriuresis, severe kidney vasoconstriction and ischemia. In addition, there is activation of the renin-angiotensin-aldosterone system, microangiopathy, hemolytic anemia and development of retinopathy in MHT. The vascular lesions of MHT consist of fibrinoid necrosis and myointimal proliferation (Januszewicz et al., 2016). Various symptoms and complications can accompany MHT, the most typical being microangiopathic lesions or kidney failure. In some patients, the present manifestation may be an acute oliguric kidney failure. In patients with MHT many functions of renal dysfunction, including microalbuminuria, proteinuria, may also be present. About half patients with MHT may have hypokalemia, reflecting secondary aldosteronism from increased renin secretion caused by intrarennal ischemia. Hyponatremia is also common (Kaplan and Victor, 2015; Januszewicz et al., 2016). Since MHT is a hypertensive emergency, patients with MHT should receive immediate antihypertensive treatment, under ongoing supervision, preferably in an intensive care setting, due to a high risk of kidney failure, stroke, myocardial infarction and heart failure (Januszewicz et al., 2016). The 2013 Guidelines on Hypertension from the European Society of Hypertension (ESH) and ESC recommend treatment based on agents that can be administered by intravenous infusion and titrated after response, lower blood pressure gradually, avoid sudden decreases in BP and excessive hypotension (Mancia et al., 2013). William J. Lawton, ... Gerald F. DiBona, in comprehensive clinical nephrology (fourth edition), 2010Accelerated hypertension is severe diastolic hypertension (usually >120 mm Hg) in the presence of Class III retinopathy (arteriolosclerotic changes of arteriolar narrowing and nicking plus hypertensive changes of flame-shaped bleeding and soft exudates).29 In the past, malignant hypertension referred to severe diastolic hypertension and Grade IV retinopathy (Grade III plus papilledema). Because the prognosis for untreated severe hypertension with grade III or IV retinopathy is so poor, there is little clinical justification for using the two concepts separately. Recently, accelerated hypertension with hypertensive retinopathy is defined as a hypertensive urgency if treatment is needed to reduce BP within hours, while hypertensive emergencies are clinical conditions where severe hypertension must be lowered within minutes. Emergencies include acute dissection of the aorta, acute left ventricular failure, intracerebral bleeding, and crises caused by pheochromocytom, substance abuse, and eclampsia (see Chapter 36). Catherine L. Kelleher, Stuart L. Linas, in Clinical Critical Care Medicine, 2006Malignant hypertension is characterized by significantly elevated pressure with hypertensive neuroretinopathy. Funduscopic examination reveals acute vasculitis manifested by flame-shaped bleeding, cotton wool stains, or papilledema. Other findings include nephropathy, encephalopathy, microangiopathic hemolytic anemia, and cardiac anemia. Without treatment, malignant hypertension results in a greater than 90% 1-year mortality. In the classic series of Kincaid-Smith (1980), deaths from untreated malignant hypertension are due to kidney failure (19%), congestive heart failure (13%), kidney failure plus congestive heart failure (48%), stroke (20%), and myocardial infarction (1%). The primary objective is to reduce BP while keeping target bodies at risk. The autoreregisting range of cerebral blood flow increases in chronic hypertension, but the lower limit remains approximately 25% below dormant average arterial pressure (MAP) in with both normotension and chronic hypertension. Symptoms of low cerebral blood flow include nausea, yawning, hyperventilation, clamminess, and syncope. After the initial reduction of BP by 20% within the first hour, BP is further reduced over the next 2 to 6 hours to the 160/110 mm Hg range, as long as there is no evidence of changes in cerebral perfusion. Nitroprusside is the most useful intravenous agent for hypertensive crises. As malignant hypertension is associated with intravascular degradation of volume, nitroprus side should be started at low doses and titrated slowly (0.25 μg/kg/min or less with titrering every 3 to 5 minutes). Alternatives to nitroprusside include labetalol, phenoldopam, and nicardipine. Rebound hypertension can occur if parental treatment is completed early. Oral treatment is started after pressure has been stabilized on parenteral treatment. Parenteral therapy is then slowly removed and oral therapy titrated to maintain BP control. Kidney failure is common with malignant hypertension and can exacerbate hypertension (Fig. 32.5). Fibrinoid necrosis develops in afferent arteries, and proliferative endarteritis develops in interlobular arteries. As a result, the vessel lumen becomes narrowed, resulting in decreased kidney blood flow. The arteriolopathy of malignant hypertension results in fixed anatomical lesions, so that when BP is initially lowered creatinine can increase. Kidney function begins to improve after several weeks of treatment in most patients and can continue to improve for up to 26 months. Of patients in need of dialysis, 50% regain sufficient function to interrupt dialysis. Recovery of kidney function is more likely when the combined length of both kidneys is 20.2 cm or more and less likely when the kidney length is 14.2 cm or less. If kidney failure is secondary to malignant hypertension, adequate BP control can reverse kidney failure. However, when malignant hypertension is secondary to underlying kidney disease (e.g. glomerulonephritis), the primary kidney disease can cause progress to end-stage kidney disease (ESRD) regardless of BP control. In the past, nitroprusside has been the preferred remedy for treating hypertension and kidney failure. The metabolism of nitroprusside results in the production of cyanide, which is absorbed by red blood cells and conjugated to thiocyanate in the liver. Cyanide toxicity occurs in patients with anemia or liver disease, while thiocyanate toxicity is seen in the environment of kidney disease. Thiocyanate levels should be monitored and treatment duration should be kept less than 72 hours when possible. Alternatively, both phenoldopam and labetalol have no toxic metabolites and can protect kidney function. Clodagh M. Loughrey, Ian S. Young, in Clinical Biochemistry: Metabolic and Clinical Aspects (Third Edition), 2014Malignant Hypertension is defined as marked high blood pressure (diastolic often > 140 mmHg) with retinal bleeding, exudates or papilloedema with without any signs of damage to the target organ, typically acute and progressive kidney damage with proteinuria and hematuria ('malignant nephrosis'). Its management is a medical emergency and should precede investigations to determine if there is an underlying cause. Neurological signs in malignant hypertension may be due to intracerebral or subarachnoid hemorrhage or lactate infarction or hypertensive encephalopathy. The latter is associated with insidious onset and non-lateralizing symptoms, such as headache, vomiting, restlessness, confusion. It can be confirmed radiologically on the basis of MRI, which shows the edema of the white matter in occipito-parietal regions, referred to as 'reversible posterior leucoencephalopathy'. (The distinction is important because hypertensive encephalopathy requires aggressive reduction of blood pressure, which is not normally indicated for bleeding or infarction.) Robert G. Carroll PhD, in Elsevier's Integrated Physiology, 2007Fluid movement at each capillary bed depends on the balance of fluid pressure and osmotic pressure (Fig. 11-7 and Tables 11-1). Glomerular capillary blood pressure reflects resistance to flow on afferent and efferent arterioles. Preglomerular (primarily afferent arteriole) constriction decreases the flow of blood in glomerular capillaries and decreases glomerular capillary blood pressure. Postglomerular (primarily efferent arteriole) constriction decreases the flow of blood out of glomerulus and increases glomerular capillary pressure. Glomerular capillary blood pressure reflects the opposite influence of afferent and efferent arteriolar resistance (see Fig. 11-7). Afferent arteriolar constriction increases vascular resistance and decreases glomerular capillary pressure. Activation of renal sympathetic nerves laces preferably afferent arteriole. Efferent arteriolar constriction increases vascular resistance and increases glomerular capillary pressure. The efferent arteriolar smooth muscle is particularly sensitive to the vasoconstrictor effect of angiotensin II.Peritubular capillary blood pressure reflects the influence of preperitubular vessel constriction. Afferent arteriolar constriction slows kidney blood flow and decreases peritubular capillary pressure. Efferent arteriolar constriction decreases kidney blood flow and decreases peritubular capillary pressure. Peritubular capillary blood pressure represents the combined influence of afferent and efferent arteriolar constriction (Fig. 11-8). Plasma oncastic pressure is due to the presence of albumin and other large molecular proteins that cannot freely cross the capillary wall. On glomerulus, an ultrafiltrate of plasma enters Bowman's capsule, but albumin remains in glomerular capillaries. Therefore, glomerular filtration causes an increase in oncotic blood pressure of blood leaving glomerular capillaries. The increase in oncotic pressure in the glomerular capillaries may reduce net filtration in glomerulus. For example, in hypotensive shock, there is a reduced rate of renal blood flow. In this case, GFR is reduced due to the combined reduction in glomerular capillary hydrostatic pressure and the low flow-induced increase in glomerular capillary oncotic pressure. Conversely, if glomerular blood flow (per minute) is high, volume filtered (per milliliter of blood) decreases, dampening the normal increase in plasma oncotic pressure and increasing GFR. If the glomerular barrier is damaged so that the glomerular capillaries become permeable to albumin, the normal reabsorptive oncotic force is diminished and the GFR increases. The oncastic pressure in Bowman's capsule is usually 0 because the ultrafiltered in Bowman's capsule does not contain much albumin. The interstitial fluid oncastic pressure is low around peritubular capillaries due to the small amount of albumin that is present in the interstitial fluid. The filtration coefficient reflects the limitation of the movement of particles in the ultrafiltrate (Figures 11-9). The negatively charged basement membrane prevents filtration of negatively charged proteins and represents the main obstacle to filtration. In addition, capillary endothelial pores and podocyte (Bowman's capsule epithelium) pores and fibers in the basement membrane limit movement based on molecular weight. The filtration coefficient is variable and changes in some disease states. A decreased pore size is caused by contraction of endothelial cells. Endothelial contraction can be caused by angiotensin II, norepinephrine, prostaglandins, and bradykinin. Diseases that cause a thickening of the basement membrane also reduce filtration. Malignant hypertension is characterized by a progressive increase in blood pressure over a short period of time. Plasma angiotensin II levels increase in concert with the increase in blood pressure. Angiotensin is not the cause of hypertension, but rather angiotensin II constriction of the efferent arteriole helps preserve glomerular filtration and kidney function during this disease process. A loss of the negative charges on the basement membrane, such as by the glycosylation of basement membrane proteins or by antigen-antibody reactions, allows some proteins to pass into the urine (proteinuria). Two common causes of proteinuria are diabetes and streptococcal infection. About 7 days after a streptococcoc infection, the kidneys exhibit glomerulonephrosis. The increase in urine volume and protein excretion in the urine is caused by destruction of glomerular basement membranes of antibodies generated in response to the infection. In summary, fluid movement across the capillary is based on the combination of hydrostatic and oncical pressure. Filtration occurs on glomerular capillaries due to the high capillary pressure and normal oncical pressure. Therefore, 20% of the plasma entering the kidneys is filtered. Reabsorption occurs in peritubular capillaries due to capillary pressure and higher plasma oncotic pressure. For this reason, 80% to 99.5% of ultrafiltrate formed in glomerulus is reabsorbed. In Pocket Companion to Brenner and Principal's The Kidney (Eighth Edition), 2011Where malignant hypertension has long been recognized for leading to rapid loss of kidney function, the role of less severe hypertension in progressive kidney damage is not so clearly defined. Epidemiological data on patients on dialysis suggest a significant role for hypertension, as hypertensive nephroidrosis is the second most common cause of end-stage kidney failure, second only to diabetes. Among patients with a diagnosis of hypertensive nephroclosis, however, only 6% had a history of malignant hypertension, a finding that strongly suggests a causal role for less severe hypertension in the development of end-stage kidney failure. In addition, large epidemiological screening studies have found blood pressure (BP), specifically diastolic BP, to be a predictor of end-stage kidney disease in the general population. Remarkably, in some studies the association with increased kidney risk is already evident with systolic and diastolic pressure well within normotensive range. Although hypertension is very common, the development of kidney failure is a rare occurrence. This suggests the effect of BP on long-term kidney function depends on the concomitant presence of either a specific susceptibility to hypertensive kidney damage or the presence of other kidney risk factors (or a combination thereof). Several predictors of renal impairment have been identified in hypertensive populations, including racial factors, decreased glucose tolerance, increased uric acid levels, and elevated serum creatinine. In patients with chronic kidney disease (CKD), hypertension is common, and its prevalence increases with worsening kidney function. Hypertension is consistently associated with a poor kidney result in CKD. In diabetics, the development of hypertension is closely related to the transition from normoalbuminuria to microalbuminuria, with subsequent progression to overt proteinuria, and with progressive loss of kidney function. Likewise, in nondiabetic kidney disease, hypertension is associated with a poor long-term kidney result across a spectrum of kidney disease. Eduardo Pimenta, ... Suzanne Oparil, in Cardiac Intensive Care (Second Edition), 2010Iology of malignant or accelerated hypertension is unknown, but many conditions are related to hypertensive emergencies and urgency (Tables 28-2). The degree of BP elevation does not correlate closely with the severity of deterioration of the end-body, and it is uncertain whether malignant or accelerated hypertension is an unspecific consequence of very high BP or triggered by a specific constellation of neurohumoral factors and cytokines.14-17The primary abnormality in patients with hypertensive emergencies is the weakened autoulator regulatory capacity (i.e. blood vessels to play or constrict to maintain normal perfusion, especially in brain and kidney beds). An initial sudden increase in vascular resistance in response to excess production of catecholamines, angiotensin II, vasopressin, aldosterone, thromboxane and/or endothelin or deficient production of endogenous vasodilates – such as nitric oxide and prostacycline – appears to trigger increased vasoreactivity and resulting hypertensive emergencies (Fig. 28-1).17Autoregulatory function is compromised, results in end-body ischemia, which triggers the release of additional vasoactive substances, initiating a vicious circle of further vasoconstriction, myointimal proliferation, and end-organ ischemia.18 Preclinical studies have provided evidence that activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathophysiology of severe leading hypertension, to hyperstenive crisis. Animals that are double transgenic for human renin and angiotensogen genes develop severe hypertension plus inflammatory vasculopathy similar to that seen in severe human hypertension.19 Angiotensin II has direct cytotoxic effects on the vascular wall through the activation of expression of genes for pro-inflammatory cytokines and the transcription factor nuclear factor κB (NF-κB).20,21 RAAS also induces ex-inflammatory cytokines and the transcription factor nuclear factor κB (NF-κB).20,21 RAAS also induces ex-inflammatory cytokines depression of proinflamating cytokines and vascular cell annuity molecules, which can contribute to vascular damage and damage to the target organ.17 Arteriolar fibrinoid necrosis ensues precipitating endothelial bloodplate and fibrin deposition and thrombox release. Some studies have also reported a link between genetic polymorphisms in components of RAAS and hypertensive crisis. For example, the DD and ID genotypes of the angiotensin-converting enzyme (ACE) gene are more frequent in patients with malignant hypertension or hypertensive crisis.22,23Malignant or accelerated hypertension is more common among patients with secondary hypertension, especially hypertension secondary to kidney artery or renal parenchymal disease, than among significant hypertensive patients. However, significant hypertension is the most common underlying cause of malignant or accelerated hypertension due to its greater prevalence. Based on postmortem analysis, Kincaid-Smith found that of 124 cases of malignant hypertension, 44% occurred in the setting of primary hypertension; 13% had chronic glomerulone fritis; 9% had polyarteritis nodosa; and 6% had unilateral renal artery stenosis.24 In a study of 123 patients with no signs of primary renal maligna disease, referring to a tertiary care center for the assessment of severe hypertension with Grade III or IV retinopathy, Davis and associates found that 43% of white patients and 7% of black patients had renal artery stenosis documented by renal arteriography.25 Of the 242 patients with malignant hypertension identified by Lip and associates, 97 (40%) had secondary most commonly related to renal paral disease. 25 patients (10%) had pregnancy-induced hypertension.26 Aldosterone excess has also been detected in patients with hypertensive crisis. Labinson and colleagues reported eight patients with a clinical diagnosis of primary aldosteronism, whose trajectory was complicated by hypertensive emergencies.27 All of these responded well to laparoscopic adrenalectomy or medical treatment with aldosterone receptor blockers. Therefore, any patient who has experienced malignant or accelerated hypertension should undergo evaluation for secondary hypertension. Sashank Prasad, in Liu, Volpe, and Galetta's Neuro-Ophtrhagology (Third Edition), 2019A reversible posterior leukoencephalopathy syndrome (RPLS) is characterized by transient headaches, seizures, hemianopi or cerebral blindness, visual neglect, and mental status changes.272,273 In some cases, gray matter is involved, and the term posterior reversible encephalopathy syndrome (PRES) has been used in such cases.274-276 The pathological results of RPLS are attributed to capillary leakage from endhelotial dysfunction.277 Neuroimaging in this syndrome typically shows extensive bilateral white matter edema and lesions that is hypodese on CT and high signal on T2-weighted and FLAIR MRI (Fig. 8.35).278 On diffusion-weighted MRI scan, the lesions are usually isointense because the oath is vasogenic rather than cytoxic. The lesions may be diffuse, but they dominate in the posterior parts of hemispheres, which are thought to be more vulnerable due to impaired vascular sympathetic innervation in these areas.279Causes of RPLS usually fall into two groups. In the first group, consisting of malignant hypertension and eclampsia, the common function is elevation in blood pressure. The second group includes immunosuppressive agents cyclosporine and tacrolimus,280 and blood pressure is abnormal in only some of these cases. Both the clinical symptoms and radiographic abnormalities in RPLS usually resolve within days to weeks of treatment of hypertension or lowering of the dose or cessation of the illicit drug. The mechanism of malignant hypertension and eclampsia is likely faulty autoregulation of the brain vasculature caused by sudden increases in blood pressure.272 Resulting vasodilation and vasoconstriction cause breakdown of the blood-brain barrier with fluid transudation and petechiae bleeding. Malignant hypertension with reversible leukoencephalopathy typically occurs in patients with a history of renal insufficiency.281Reversible leukoencephalopathy in preeclampsia has been reported as the cause of temporary cerebral blindness.282,283 RPL During pregnancy typically develops before birth, but has been reported up to 9 days after birth.284Cyclosporin produces the reversible posterior leukoencephalopathy typically at toxic levels.285,286 Aggravating factors appear to be cranial irradiation , hypomagnesemire, high-dose steroids, hypertension, and uremia.286 The mechanism of this complication is unclear, but it may reflect either direct neurotoxicity or a vasculopathy.272 Tacrolimus is similar to cyclosporine in its effect and toxic side effects. Similar brain blindness and lesions of white matter have been observed.287,288 observed.287,288