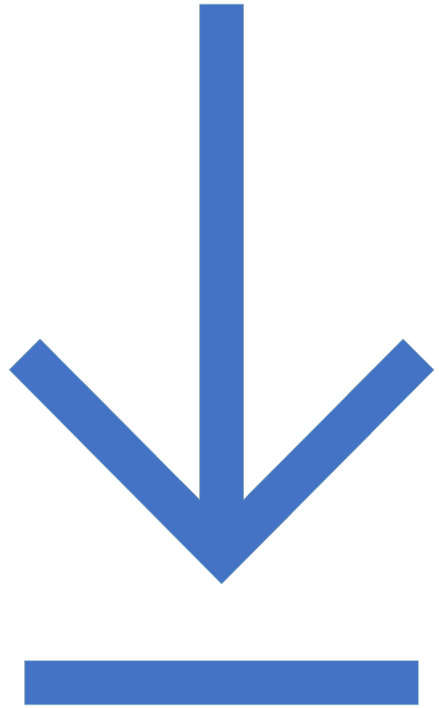
WHAT GOES UP MUST COME DOWN



SPEAKER: DR HELEN ZHANG
CHAIRPERSON: DR PHILIP LAM
HKSCCM GRAND ROUND
19TH JANUARY 2021

CLINICAL CASE

- 55/F
- Nonsmoker, nondrinker
- Past medical history
  - Hypertension
  - Limited scleroderma
  - Sjogren's syndrome
  - Renal tubular acidosis (Baseline creatinine 250)
  - Primary biliary cirrhosis, esophageal varices
  - Hypothyroidism
- Usual medications
  - amlodipine, propranolol, simvastatin
  - calcitriol, caltrate, slow K, $NaHCO_3$
  - ursodeoxycholic acid, vitamin K1
  - thyroxine

HISTORY & PHYSICAL EXAM

- Presented with 1 day history of reduced consciousness, 4 limbs weakness, no verbal response
- Physical exam
  - Vitals
    - Afebrile
    - BP 249/130 -> rechecked BP 170/90. Pulse 90bpm
    - SpO2 100% on room air
  - Small mouth opening, mild skin tightening over fingers, cyanotic fingers

HISTORY & PHYSICAL EXAM

- Neurological exam
  - GCS E4V2M3
  - Pupils equal and reactive to light
  - No eye deviation
  - Negative doll's eyes test
  - Preserved gag reflex
  - 4 limbs mildly spastic
  - Extensor plantar response
- HSDNM
- Abdomen soft
- Urine output 40ml/h

INVESTIGATIONS

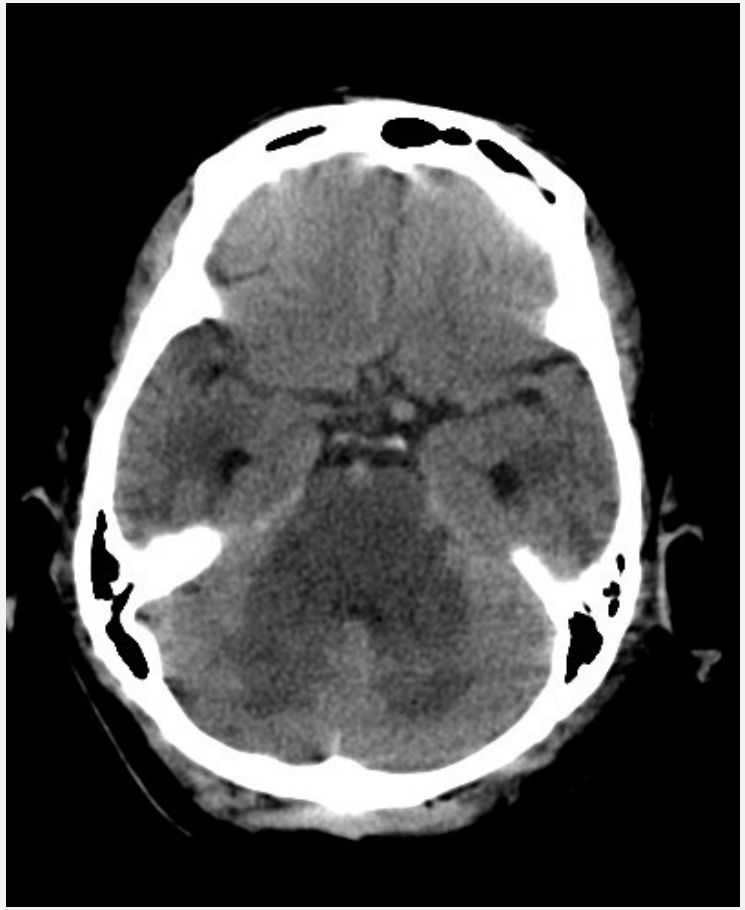
Bloods

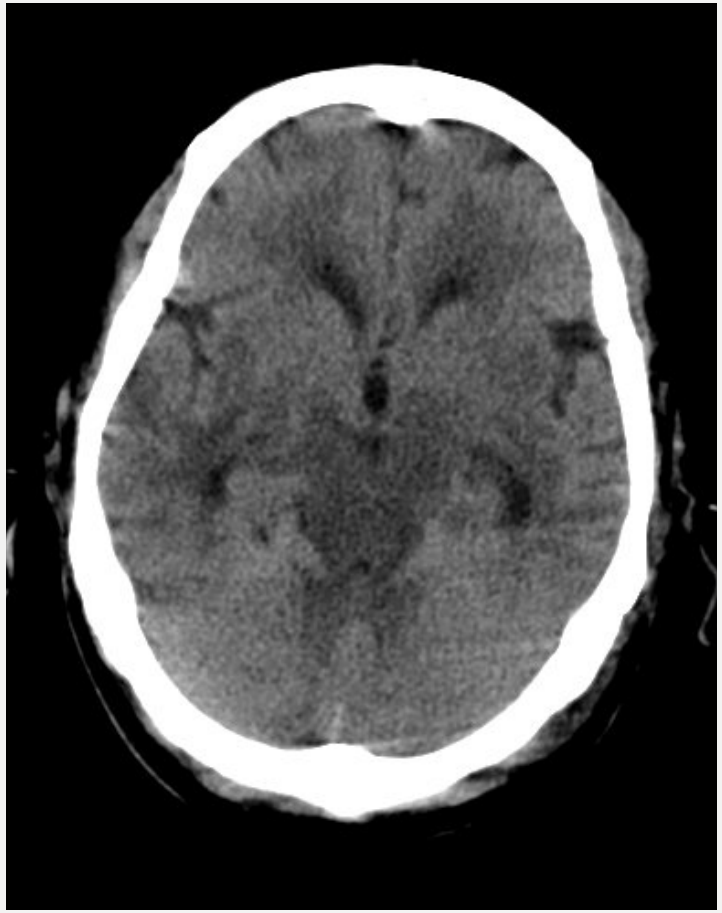
- Hb 13.8, WBC 10.2, Platelets 131
- Na 137, K 4.1, Urea 19, Creatinine 427 (Baseline 250)
- Bilirubin 17, ALP 224, ALT 20
- LDH 349 CK 214

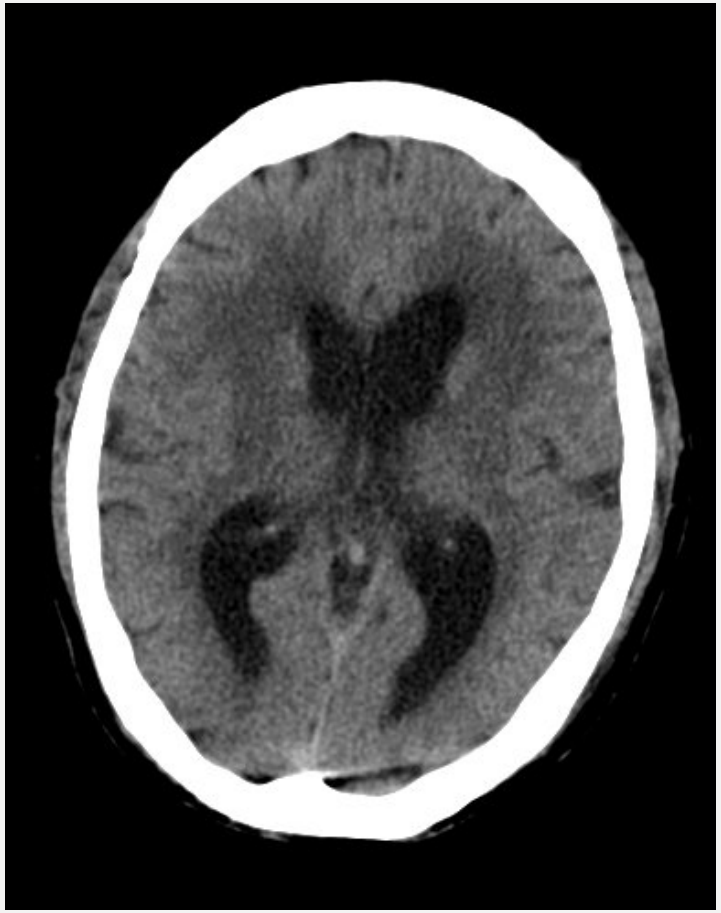
Urine multistix: moderate RBC

INVESTIGATIONS

CT brain plain







DIFFERENTIAL DIAGNOSES

- Posterior reversible encephalopathy syndrome
- Extensive brainstem/cerebellar infarction

CLINICAL PROGRESS – DAY 1

- Admitted to ICU
- Given labetalol infusion, amlodipine, propranolol to achieve target SBP 140mmHg
- GCS improved to E4V2M5

CLINICAL PROGRESS – DAY 1

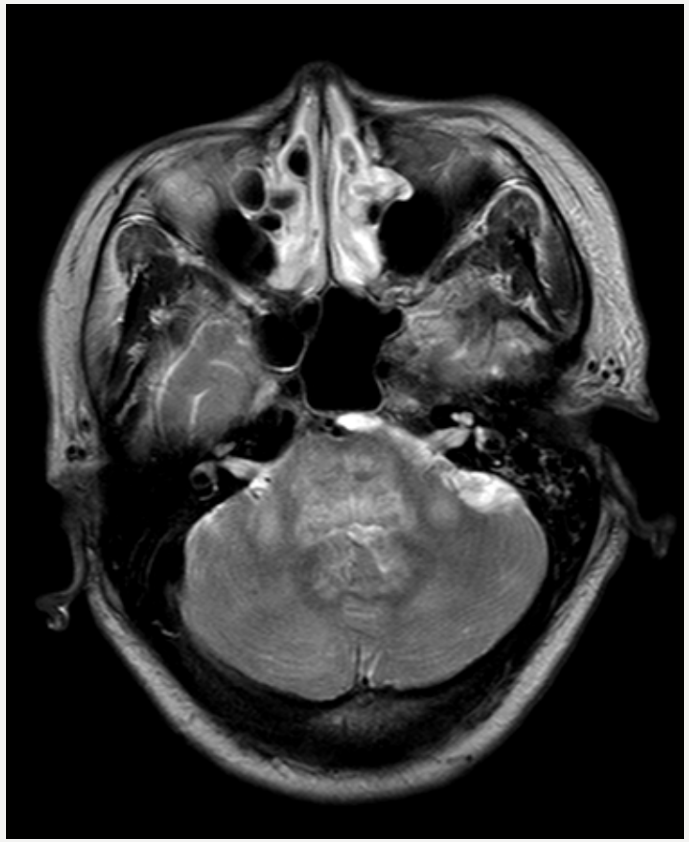
- Consulted neurosurgery for suspected hydrocephalus, replied:
  - Likely brainstem stroke with II and IV ventricle compressed by brainstem swelling
  - For conservative management and not for surgery because of poor prognosis
- Consulted neurology
  - Need urgent MRI/MRA brain to look for recent posterior circulation ischemic stroke involving brainstem and cerebellum VS PRES
  - Aspirin started empirically for possible brainstem ischemic stroke as suggested by neurologist

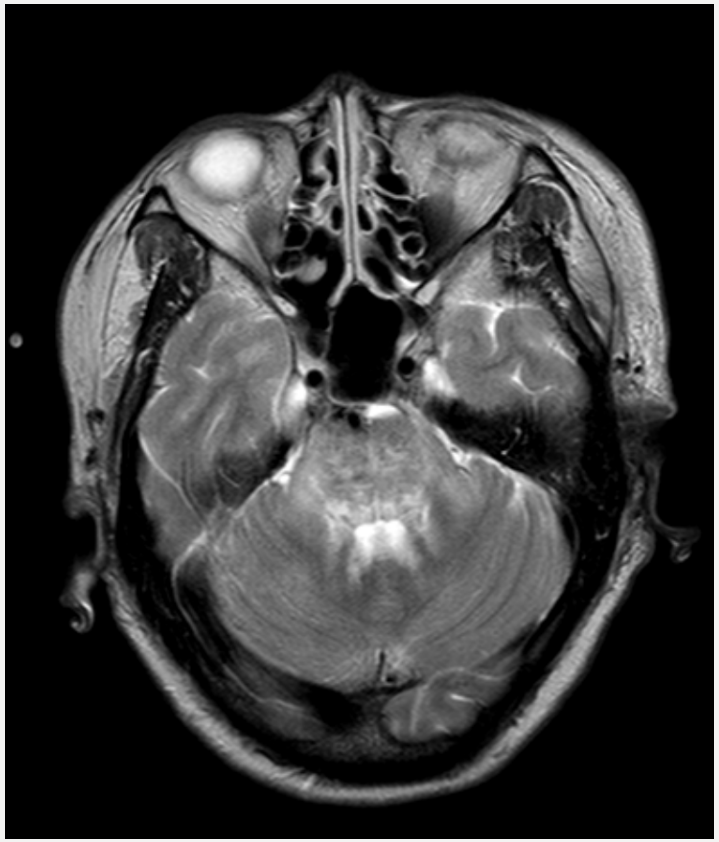
CLINICAL PROGRESS – DAY 2

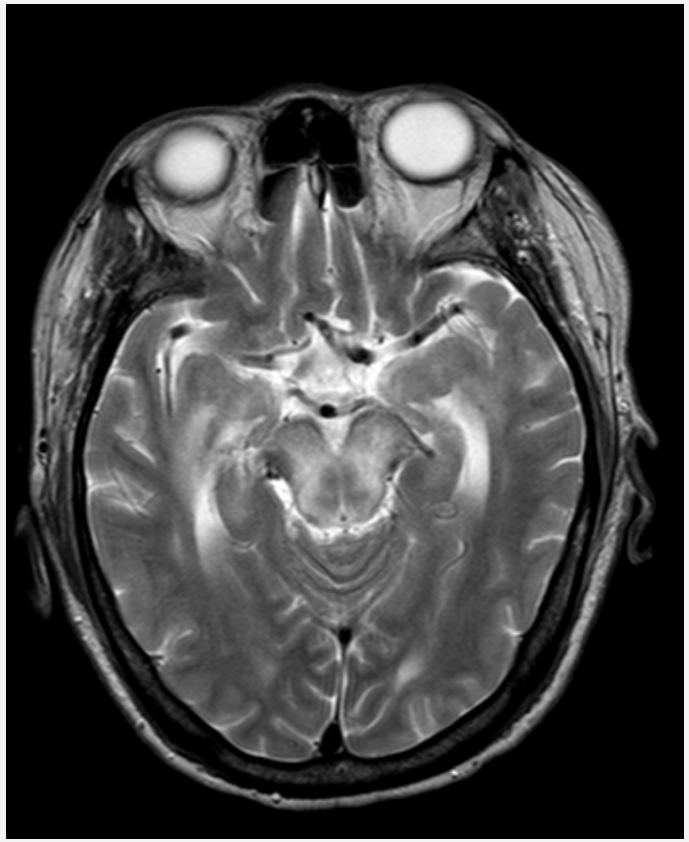
- Weaned off labetalol infusion
- Elective intubation for MRI

CLINICAL PROGRESS – DAY 2

MRI Brain T2W







CLINICAL PROGRESS – DAY 2

- Worsening of acute on chronic renal failure
  - Urine output 10-20ml/h
  - Urea 27.6 Creatinine 509
  - Lisinopril started for scleroderma renal crisis

CLINICAL PROGRESS – DAY 3

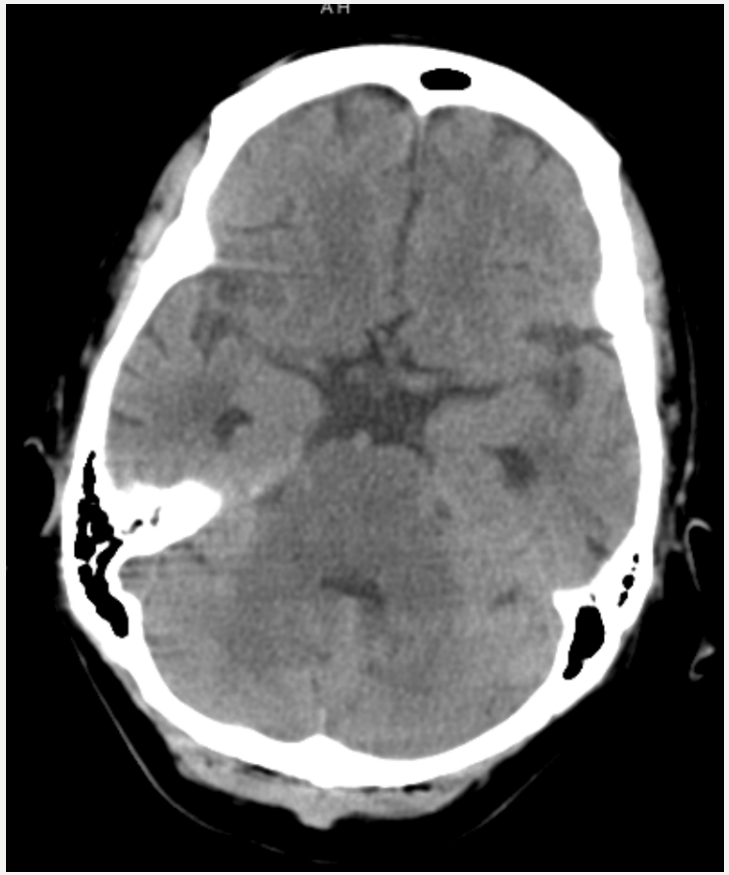
- Neurological
  - GCS 15/15
  - 4 limbs power 2/5
  - Extubated
- Renal
  - Urine output recovered, Urea/Creatinine plateaued
- Continued on oral lisinopril and amlodipine
- Aspirin stopped

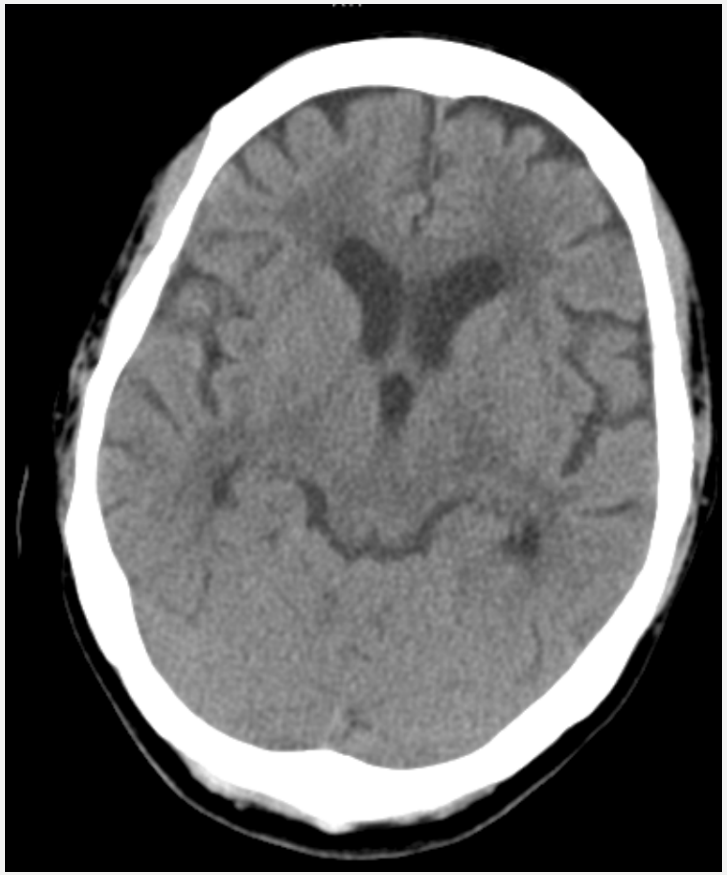
CLINICAL PROGRESS – DAY 4

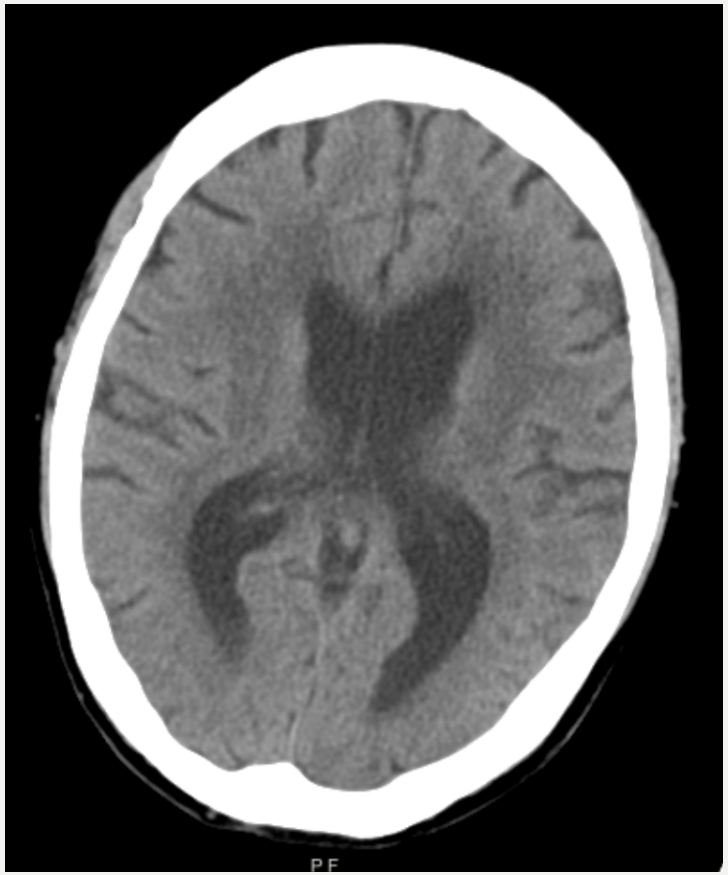
- GCS 15/15
- 4 limbs power returned 5/5

CLINICAL PROGRESS – DAY 4

Follow up CT brain plain







CLINICAL PROGRESS – DAY 5

- Lisinopril increased to 10mg BD
- RFT improved
  - Ur 26.5 ← 27.6
  - Cr 349 ← 509
- USG kidney: Bilateral renal parenchymal disease with cysts and medullary nephrocalcinosis. No signs of obstructive uropathy.
- Discharged to general ward

SUMMARY

Patient with scleroderma renal crisis who presented with PRES and acute kidney injury

DISCUSSION

SCLERODERMA / SYSTEMIC SCLEROSIS (SSC)

Background

- Complex systemic autoimmune disease

(1) Innate/adaptive immune system abnormalities leading to production of **autoantibodies and cell-mediated autoimmunity**

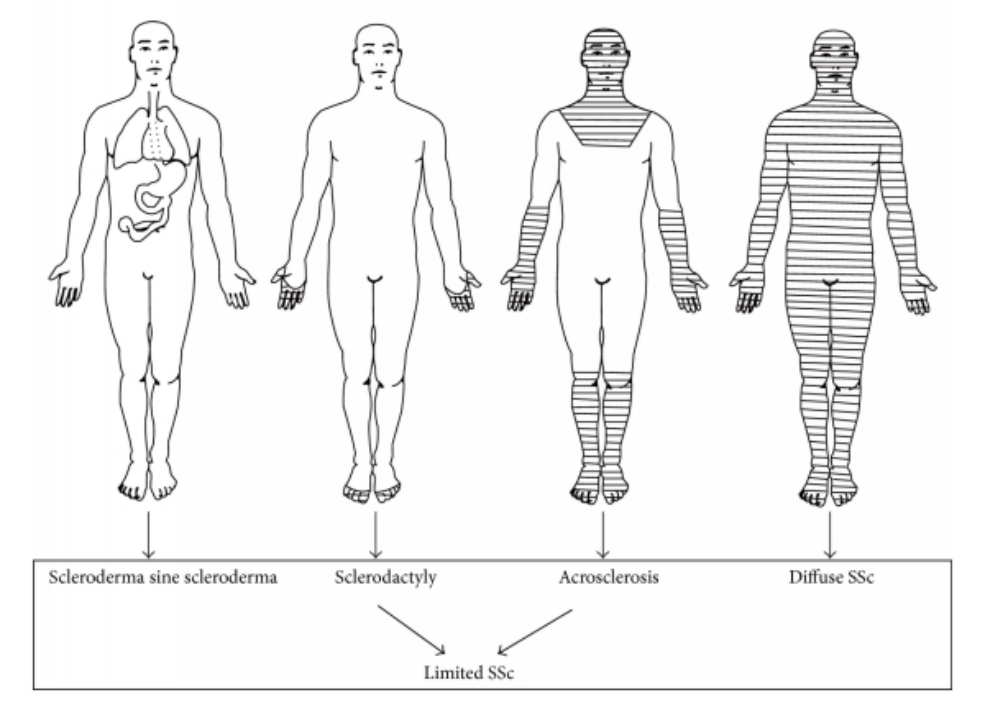
(2) Microvascular **endothelial cell vasculopathy**

(3) Fibroblast dysfunction generating excessive accumulation of **collagen** and other matrix components in skin and internal organs.

SCLERODERMA / SYSTEMIC SCLEROSIS (SSC)

Major disease subsets

- **Limited cutaneous systemic sclerosis**
  - Puffy fingers distal to the MCPJ -> skin sclerosis distal to the elbows and knees -> face and neck
  - CREST syndrome, pulmonary hypertension, biliary cirrhosis
- **Diffuse cutaneous systemic sclerosis**
  - Puffy hands and have skin thickening that extends proximally to the upper arms, thighs, and/or trunk
  - Rapid progression of skin thickening, lung fibrosis, renal crisis, cardiac involvement



POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

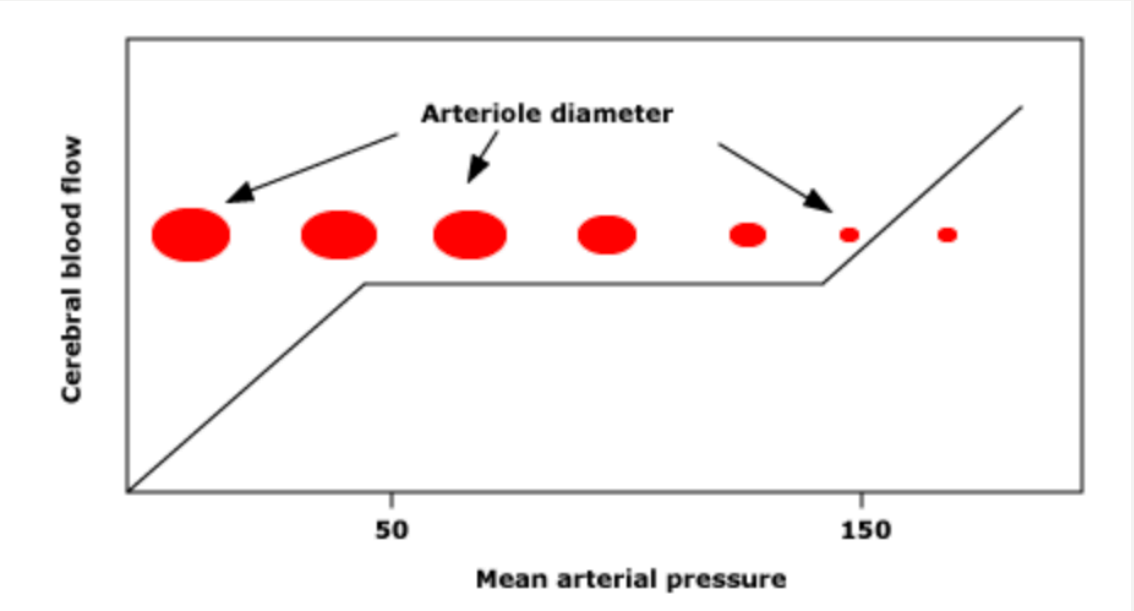
Clinical manifestations

- Evolve rapidly over hours to days ✓
- Hypertension ✓
- Altered consciousness ✓
- Visual disturbances
- Seizures
- Fundoscopy: often normal
- Brisk reflexes, extensor plantar response ✓
- Weakness and incoordination of the limbs ✓

PATHOPHYSIOLOGY

1) Autoregulatory failure and hypertension

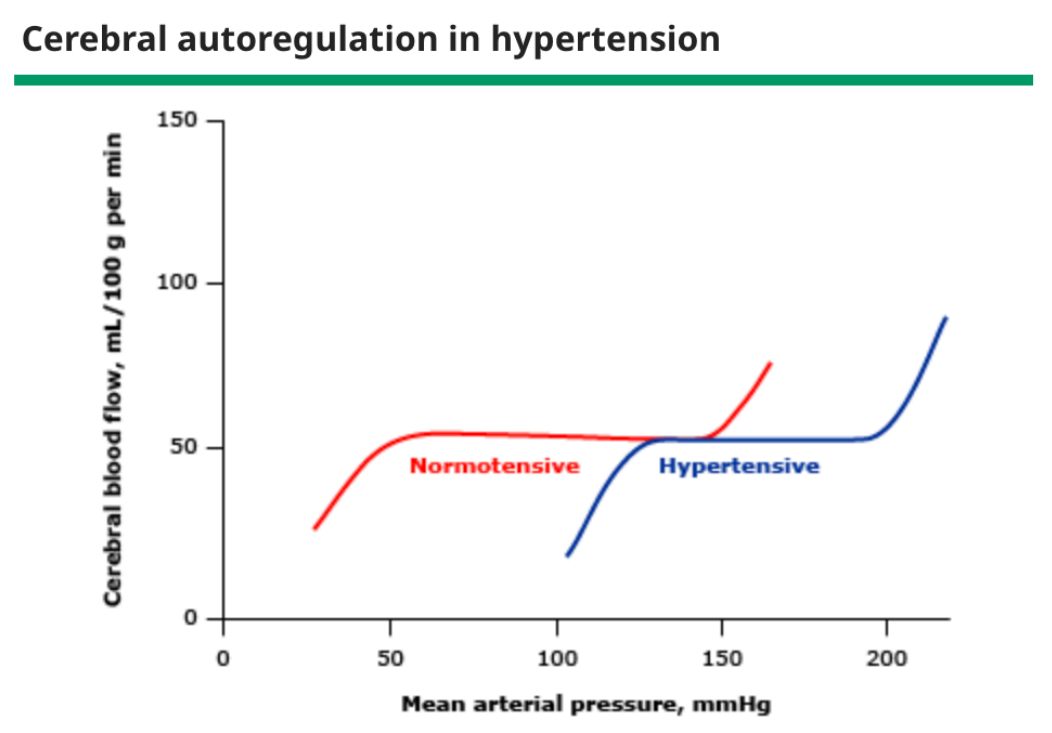
- Normal autoregulation maintains constant cerebral blood flow over a range of systemic BPs
- Exceed upper limit of cerebral autoregulation: ↑ BP -> ↑ CBF
- Brain hyperperfusion -> breakdown of the blood-brain barrier allowing extravasation of fluid and blood products into the brain parenchyma



PATHOPHYSIOLOGY

Autoregulatory failure and hypertension

- In chronic hypertension, adaptive vascular changes "reset" the range of autoregulation to higher systemic blood pressures
- Patients with PRES in the setting of longstanding HT may have markedly elevated BPs
- Patients without HT have less severe elevations or even normal BPs



PATHOPHYSIOLOGY

2) Cerebral ischemia

- Disordered cerebral autoregulation leads to reactive focal vasoconstriction -> local hypoperfusion, cytotoxic edema, and cerebral infarction
- Cerebral infarctions could result from compression of the microcirculation from the mass effect of vasogenic edema.

PATHOPHYSIOLOGY

Cerebral ischemia

For	Against
• Clinical and neuroradiographic findings are completely reversible in most patients. • Radionuclide studies have demonstrated perfusion deficits in some patients with PRES	• Limited pathologic studies have not revealed ischemia or infarction • Increased rather than decreased perfusion can also be seen on radionuclide imaging studies • Most patients do not have demonstrable vascular narrowing

PATHOPHYSIOLOGY

3) Endothelial dysfunction

- Cytotoxic therapies
- Preeclampsia
- Uraemia
- Sepsis
- Lupus nephritis
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura

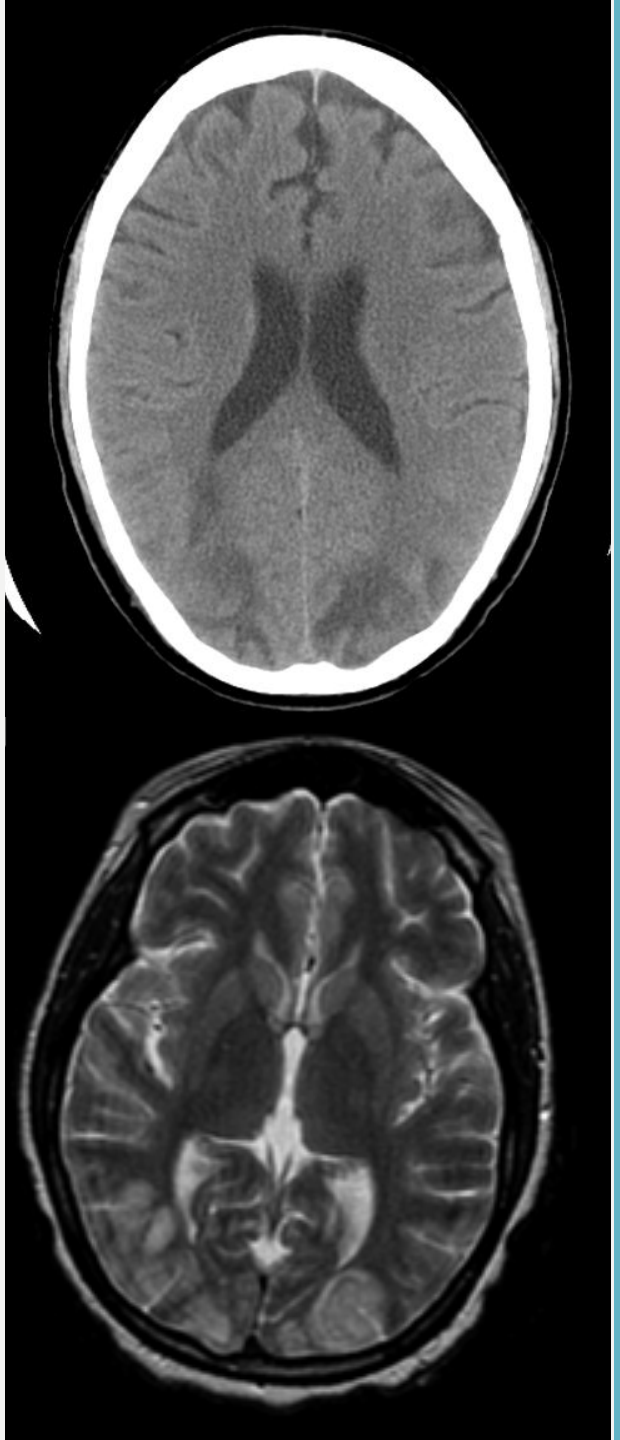
NEUROIMAGING

Locations:

- Subcortical white matter edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions
- May also involve cerebellum, brainstem, frontal lobes, temporal lobes, cortex and basal ganglia

What to look for in:

- CT: hypoattenuation
- MRI: increased signal on T2-weighted images



NEUROIMAGING

Distinguishing features:

- Distribution of abnormalities is usually not confined to a single vascular territory
- Relative sparing of the cortical gray matter in PRES

Prognostication:

- Extensive vasogenic edema, brain ischemia, and intracerebral hemorrhage have been associated with worse functional outcome

MANAGEMENT

- In patients with hypertensive emergency, lower the MAP by 10-15% in the first hour
- No more than 25% compared with baseline by the end of the first day of treatment
- IV agents:
  - Labetalol
  - Sodium nitroprusside
  - Nicardipine

PROGNOSIS

- Usually benign
- Seems to be fully reversible within a period of days to weeks, after removal of the inciting factor and control of the blood pressure
- Radiologic improvement lags behind clinical recovery.
- Death may result from progressive cerebral edema, intracerebral hemorrhage, or as a complication of the underlying condition

SCLERODERMA – A RISK FACTOR FOR PRES?

Prevalence of PRES in systemic sclerosis

- 9 cases of SSc-related PRES
- Including 3 cases of SRC-related PRES

Risk factors for PRES in scleroderma

- Endothelial dysfunction
  - Immunotherapy e.g. cyclosporine
  - Renal crisis → microangiopathic damage to the central nervous system
- Autoregulatory failure and hypertension
  - Renal crisis → malignant hypertension

SCLERODERMA RENAL CRISIS

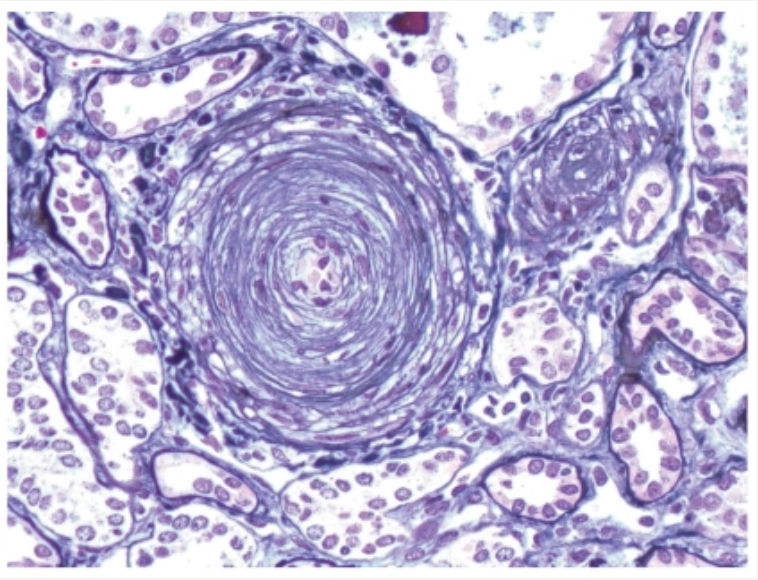
- Epidemiology
  - United States: 10% of patients with diffuse scleroderma, 2% of patients with limited disease
  - Europe: 5% of diffuse scleroderma, 2% of limited

- Risk factors
  - Diffuse skin involvement, palpable tendon friction rubs
  - Glucocorticoids use particularly in high doses (dose dependent effect)
  - anti-RNA polymerase III autoantibodies
  - New onset anaemia
  - New cardiac events

HISTOPATHOLOGY

Histopathology

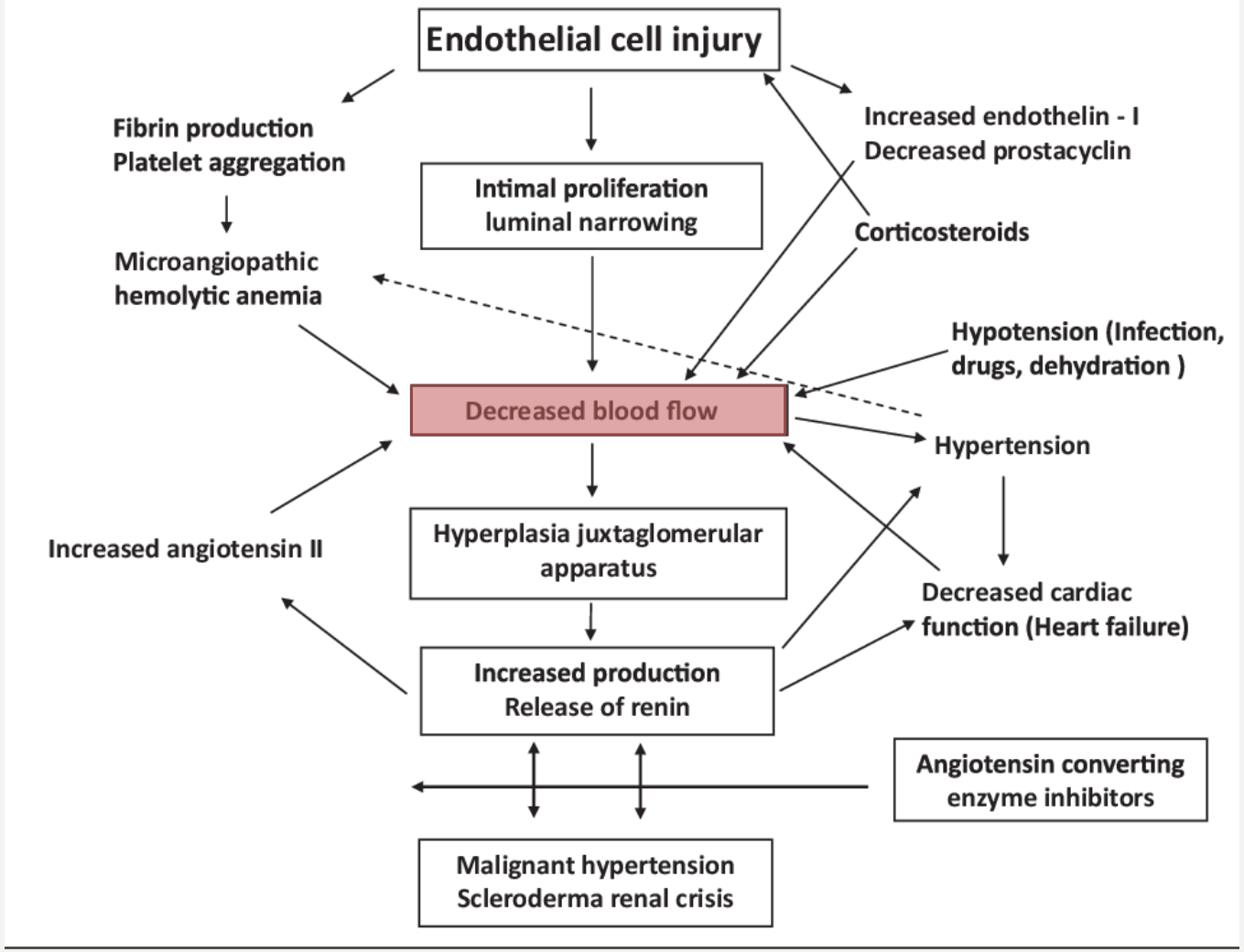
- Small arcuate and interlobular arteries and the glomeruli
- Intimal proliferation and thickening that leads to narrowing and obliteration of the vascular lumen, with concentric "onion-skin" hypertrophy
- Similar to SSc-associated vascular lesions found in other organs
- Similar to other thrombotic microangiopathy e.g. TTP/HUS -> kidney biopsy not definitive for diagnosis



Batal, Ibrahim & Domsic, Robyn & Medsger, Jr, Thomas & Bastacky, Sheldon. (2010). Scleroderma Renal Crisis: A Pathology Perspective. International journal of rheumatology. 2010. 543704. 10.1155/2010/543704.

PATHOPHYSIOLOGY

Impairment of arterial blood flow in the kidney



CLINICAL FEATURES

- Presents early
  - 3.2 years since onset of disease
  - 25% of cases, the diagnosis of scleroderma is made at the time of SRC presentation
- **Rapidly progressive renal failure**
- **Accelerated hypertension**
  - 90% have BP levels greater than 150/90 mmHg, 30% have DBP >120 mmHg
  - 10% have normal BP (but raised compared to their baseline)

Clinical manifestations of scleroderma renal crisis

Neurologic
Hypertensive encephalopathy
Cerebral hemorrhage
Headache/Altered mental status
Seizures

Renal
Acute kidney injury
Electrolyte abnormalities
Hematuria/Proteinuria
Decreased urine output

Gastrointestinal
Esophageal dysfunction
Elevated liver enzymes

Ophthalmologic
Hypertensive retinopathy
Altered vision

Cardiovascular
Congestive heart failure
Hypertension
Pericardial effusion
Pericarditis
Arrhythmias

Systemic
Thrombocytopenia
Microangiopathic hemolytic anemia
Fatigue
Weight loss

Pulmonary
Rapidly progressive dyspnea
Pulmonary edema
Pulmonary hemorrhage

Musculoskeletal
Skin thickening/Sclerodactyly
Swollen hands and lower extremities
Carpal tunnel syndrome
Tendon friction rubs
Polyarthritis
Raynaud's phenomenon

Diagnostic Criteria for Scleroderma Renal Crisis

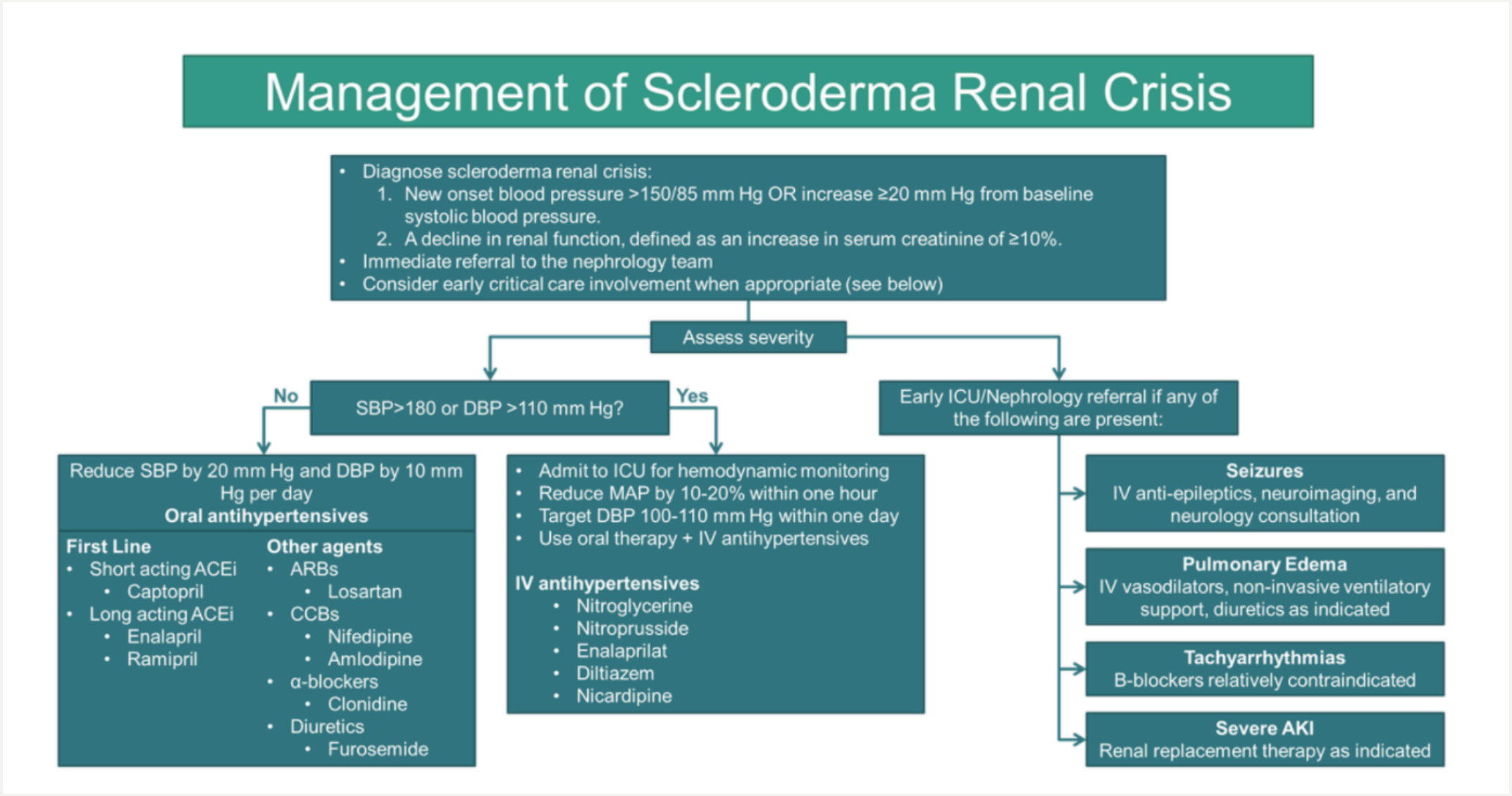
Diagnostic Criteria:

1. New onset blood pressure >150/85 mm Hg OR increase ≥20 mm Hg from usual systolic blood pressure.
2. A decline in renal function, defined as an increase in serum creatinine of ≥10 %

Supportive features:

- Microangiopathic hemolytic anemia
- Findings consistent with accelerated hypertension on retinal examination
- Microscopic hematuria on urine dipstick and/or red blood cells on urine microscopy
- Oliguria or anuria
- Flash pulmonary edema
- Renal biopsy with typical features of SRC including onion skin proliferation within the walls of intrarenal arteries and arterioles, fibrinoid necrosis, glomerular shrinkage

Lynch BM, Stern EP, Ong V, Harber M, Burns A, Denton CP. UK Scleroderma Study Group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp Rheumatol. 2016 Sep-Oct;34 Suppl 100(5):106-109. Epub 2016 Sep 29. PMID: 27749244.



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MANAGEMENT

ACEi

- Captopril
  - Permit rapid dose titration due to rapid onset and short duration of action
  - Start 6.25 to 12.5 mg -> + 12.5 to 25 mg Q4-8H until target BP
  - May be initial transient rise in serum creatinine
  - Low dose long acting ACEi is continued indefinitely even if not needed for BP control

Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med. 1990 Sep 1;113(5):352-7. doi: 10.7326/0003-4819-113-5-352. PMID: 2382917.

MANAGEMENT

ACEi

- Pharmacodynamics: inhibition of the renin-angiotensin system, reduce the degradation of bradykinin, vasodilation of the renal vessels
- Significantly higher rate of recovery of renal function
  - Steen et al. 1990:
    - Among patients who survived dialysis for more than 3 months, 11 of 20 patients who continued ACEi therapy were able to discontinue dialysis after 3-15 months VS 0 of 15 patients who were not treated with ACEi (55% VS 0%)
    - Continued improvement in renal function for up to 18 months in patients treated with ACE inhibitors

	Type of study	Size (n)	Patients on ACEI n (%)	Outcome/conclusions
Therapeutic				
Steen VD, Ann Intern Med 1990	Prospective	108	55 (51)	1-year survival 15% without ACEI vs 76% with ACEI ($p < 0.001$).
Steen VD, Ann Intern Med 2000	Prospective	145	145 (100)	No dialysis or temporarily dialysis in 61% of patients.
Penn H, QJM 2007	Retrospective	110	108 (98)	Dialysis in 64% of patients, 23% temporarily; 5-year survival 59%.
Teixeira L, Ann Rheum Dis 2008	Retrospective	50	50 (100)	Dialysis in 56% of patients, 16% temporarily; 1-year survival 78%, 5-year survival 69%.
Guillevin L, Rheumatology 2012	Retrospective	91	83 (91)	Dialysis in 53.8% of patients, 13% temporarily; 1-year survival 70.9%, 5-year survival 60%.

MANAGEMENT

If blood pressure control remains suboptimal at maximum tolerated doses of ACEi, add:

- Calcium channel blockers as 2nd line
- Diuretics and alpha-blockers as 3rd line treatment
- Beta blockers?

Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med. 1990 Sep 1;113(5):352-7. doi: 10.7326/0003-4819-113-5-352. PMID: 2382917.

MANAGEMENT

- Beta blockers in scleroderma?
  - Theoretical risk of worsening Raynaud's phenomenon
    - Pathophysiology: unopposed stimulation of vascular alpha-adrenoreceptors, ↓ cardiac output and blood pressure, ↑ reflex sympathetic vasoconstriction
  - Prevalence of Raynaud's phenomenon in patient's receiving β-blockers: 14.7%
    - 2012 meta-analysis, 13 studies (1012 patients,1971 to 1984)
  - No evidence that beta blockers worsen symptoms in patients with Raynaud's phenomenon
    - 1992 RCT: propranolol, metoprolol and pindolol → no adverse effect detected on baseline finger skin perfusion and recovery after cold-induced vasoconstriction

- Mohokum M, Hartmann P, Schlattmann P. The Association of Raynaud Syndrome With β-Blockers: A Meta-Analysis. Angiology. 2012;63(7):535-540. doi:10.1177/0003319711432861
- Franssen, C., Wollersheim, H., de Haan, A. and Thien, T. (1992), The Influence of Different Beta-Blocking Drugs on the Peripheral Circulation in Raynaud's Phenomenon and in Hypertension. The Journal of Clinical Pharmacology, 32: 652-659.

PROGNOSIS

- 5-year mortality rate of about 50–70%
- 20-50% of patients require renal replacement therapy
  - Half of these patients will eventually recover sufficient renal function to discontinue dialysis
- Survival on dialysis in patients with SRC is worse than in other forms of ESRD
  - 2002 study from the United States Renal Data System: two-year survival is 49% in SSc VS 64% in all other patients
- Improvement in renal function can continue for up to 18 months → postpone decisions on kidney transplantation

Abbott KC, Trespalacios FC, Welch PG, Agodoa LY. Scleroderma at end stage renal disease in the United States: patient characteristics and survival. J Nephrol. 2002 May-Jun;15(3):236-40. PMID: 12113593.

TAKE HOME MESSAGES

- Differentiate PRES vs brainstem stroke
- In any patient presenting with hypertensive emergency and AKI, scleroderma should be considered
- SRC & PRES treatment focuses on aggressive BP control