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REVIEW ARTICLE

Update on Failure of Cerebral Autoregulation and Clinical Application

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ABSTRACT

Cerebral autoregulation controls cerebral blood flow(CPF)in response to changes and fluctuation in blood pressure through strict dynamic adjustment of arterial calibre, but the impact of autoregulatory mechanism on local vascular responses and microvascular perfusion remains not fully understood and remain a subject of research, regulation of cerebral blood flow is a key and essential protective and compensatory mechanism for a healthy brain function and rely on interplay of complex vascular control mechanism, Cerebral autoregulation can be evaluated either a static or dynamic phenomenon, there is a lot of body of evidence to show the role of dynamic autoregulation, the clinical data on static autoregulation is limited, in this minireview we will concentrate on the not uncommon and commonly undiagnosed clinical syndromes due to failure of cerebral autoregulation cerebral such as reversable cerebral vasoconstrictor syndrome(RCVS) and posterior reversable encephalopathy Syndrome(PRES)

Introduction

Cerebral autoregulation is the automatic ability of cerebral blood vessels to keep and maintain stable and sufficient cerebral blood flow (CFB) despite changes and fluctuation of blood pressure ensuring a sufficient supply of oxygen and micronutrients. To maintain sound brain function by either vasoconstriction or vasodilation to manage cerebrovascular resistance and maintain efficient blood flow and cerebral perfusion pressure (CPP).[1,2,3]

Cerebral perfusion pressure ranged between the minimum below which Cerebral blood flow(CBF) drops and upper limit when maximum cerebral blood flow, before autoregulation fails (dysregulation) leading to hyper perfusion injury to the brain, cerebral autoregulation needs a bundle of sound brain tissue which includes endothelial function, myogenic tone via constriction or dilation of the vascular smooth muscles, intact cerebral nerve supply to cerebra vessels and efficient metabolic through changes in the partial pressure of CO2 and Hydrogen (H).[4]

Dysregulation of autoregulation can be acquired or iatrogenic like inhaled anaesthetics like isoflurane and desflurane which have depressive effect on autoregulation, on the other hand propofol does not affect autoregulation and considered the drug of choice in patients with high intracerebral pressure.[5]

In this minireview we are going to discuss dysregulation of cerebral autoregulation which often not diagnosed in a timely manner specially in low-income country where the resources like MRI are not available all of the time as the diagnosis is mainly radiologically and needs expert neuroradiologist to draw the attention of the clinician to the diagnosis.

Failure of cerebral autoregulation can lead to vast number of brain syndromes which included stroke, subarachnoid haemorrhage, dementia and cognitive impairment, sepsis -associated brain dysfunction, cerebral Autosomal dominant Arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), heart failure causing brain dysfunction.

In this minireview we going to discuss the difficult to diagnose brain syndrome due to failure of cerebral autoregulation based on the recent publications of Reversable cerebral vasoconstrictor syndrome, posterior reversable encephalopathy and Vasculitis of the central nervous system for the last five years including case reports with typical and a typical clinical manifestation.

Reversable Cerebral vasoconstriction Syndrome (RCVS)

This syndrome is rare and often undiagnosed by the clinician until diagnosed by the neuroradiologist, it is characterised by a thunderclap headache, the headache usually peaks in one minute and described as the worst headaches in his life and usually remain for 5 minutes or less.

RCVS is characterised by recurrent headache over few weeks, although headache peaks in less than a minute and often stay for five minutes before the severity of the headache reduced, before recuring again. This is usually explained by the patient as it is very explosive and sudden, associated manifestation includes visual symptoms like diplopia, field defect, scotoma, confusion, seizures (mainly generalised), and less commonly focal seizure, before the discovery of RCVS, such patients were diagnosed as primary angiitis of the central nervous system (PACNS) and were exposed to the risk of invasive brain biopsy and treatment with long term steroid and cyclophosphamide and antiseizure medications.

RCVS is now considered as a syndrome of cerebrovascular dysregulation triggered by eclampsia, increased sympathetic drive, illicit drugs like cocaine, amphetamine, and licit drugs like cannabis, other triggers of RCVS are pre-eclampsia, pheochromocytoma, paraganglioma, carotid dissection, thrombotic thrombocytopenia purpura (TTP), haemolytic uraemic syndrome (HUS, antiphospholipid syndrome, and rare genetic disease like adult-onset Leigh syndrome.

The incidence of RCVS is increasing worldwide due to increased use of Vascular and imaging (MRI, MRA). Although the exact pathophysiology is not well understood, the consensus suggests and even confirm that transient failure of cerebral vascular autoregulation leads to multi-focal vasoconstriction and dilation which are pathognomonic neuroradiological sign in confirming the diagnosis of CRVS due to endothelial dysfunction, sympathetic over stimulation and oxidative stress leading to impairment of blood-brain barrier.

RCVS is common in females and the ratio of females to male ranged between 2-1 up to 10-1. The Massachusetts general hospital Research group implemented RCVS2 score for the diagnosis of RCVS with a maximum score of 10 (range from 2-10).

RCVS2 score includes the following:

- Female sex
- An identified trigger factor
- Involvement of intracranial carotid artery
- Presence of convex subarachnoid Haemorrhage
- Thunderclap headache (TCH)

TCH alone engenders a score of 5. Score of 5 or higher has a sensitivity of 90% and specificity of 99% for the diagnosis, recurrent TCH is very common in CRVS and excludes any other fatal condition including aneurysmal subarachnoid Haemorrhage.

The nature of TCH can guide the diagnosis, when it is recurrent, the pretest probability as shown in RCVS2 score is almost 100%. When TCH is single, the differential diagnosis is cervical artery dissection, pituitary apoplexy, aneurysmal subarachnoid haemorrhage, cortical vein thrombosis, meningoencephalitis, Cerebral angiitis of the central nervous system.

Diagnosing recurrent TCH will obviate and preclude the need to any invasive investigation like lumbar puncture or brain biopsy, most patients with recurrent TCH will develop convexity subarachnoid haemorrhage in the first two weeks, initial noncontracted CT can be normal, but it can show nonaneursymal convexity subarachnoid haemorrhage, lobar haemorrhage, ischemic stroke in the watershed areas or vascular narrowing in CTA after 3-5 days, and it can exclude aneurysmal subarachnoid haemorrhage.

MRI similar to CTA can be normal in the first three days, but it may show Vasogenic Oedema in T2/flair imaging, and hyperintensity of vessels (dot sign) can be seen in 25% of patients, dot sign correlate with impaired blood flow and development of ischemic stroke and posterior reversible leukoencephalopathy(PRES), of note, the dote sign occurs in other serous clinical problems like status epilepticus, leptomeningeal carcinomatosis, and meningoencephalitis.[6,7,8,9]

MRA with contrast and without contrast using time -of -flight can diagnose cervical artery dissection which can complicate RCVS.

Although digital subtraction angiography is the gold stander to diagnose RCVS, it is not advisable to expose the patient to invasive testing as the harm outweigh the benefit in diagnosing RCVS and it is much safer to accept some diagnostic uncertainty and repeat non-invasive tests like MRA or CTA in few days especially if the TCH is recurrent and the imaging showed convexity non aneurysmal subarachnoid Haemorrhage.[10,11,12,13]

Digital subtraction Angio is indicated only if the patient deteriorates and aneurysmal subarachnoid haemorrhage could not be excluded, the same applies to lumbar puncture as based on the international headache society criteria, CSF leukocyte less than 10-15 and protein less than 80 mg/DL with no xanthochromia and elevated erythrocytes are consistent with the diagnosis of RCVS.[14]

Management of RCVS is guided by observational data and expert opinion which includes early recognition of the syndrome, and ruling out other serous clinical problems like cortical vein thrombosis, intracerebral bleed, intraventricular haemorrhage, acute subdural haemorrhage, cerebral infarct, colloid cyst of the third ventricle, haemorrhagic aneurismal subarachnoid haemorrhage, dissection of the cervical vessels, meningoencephalitis, head trauma, pituitary apoplexy, primary angiitis of central nervous system, all these patients should be considered as having RCVS till proved otherwise.

When secondary cause of RCVS had been established, first line is to treat the secondary cause, for examples vasoconstrictor medication should be ceased, patients with eclampsia and preeclampsia, should be induced.

Depending on comorbidities and complication, additional treatment may be started. Patients with TCH without ischemic stroke, oral calcium channel blockers should be started, patients with convexity non aneurysmal subarachnoid haemorrhage will benefit from intravenous calcium channel blockers, the rational for using calcium channel blockers are to counteract the influx of calcium in vascular smooth muscle cells and improve the outcome by reducing the vasospasm which caused neurologic deficits.

Patients with comorbidity should be monitored in high dependency area for hypotension which could cause ischemic stroke in watershed areas. Some studies have shown that short course of steroid had beneficial effect in relieving the vasospasm in some patients with convexity subarachnoid haemorrhage (SAH) due to its anti-inflammatory effect.

Magnesium sulphate had shown promising effect in patients with RCVS triggered by eclampsia and pre-eclampsia. In summary, RCVS can be a primary disorder or secondary to vasoactive drugs or states of high blood pressure causing vasospasm in cerebral vessels, causing TCH, decreased level of consciousness, vistal symptoms or seizures, treating the TCH with analgesic will reverse the disease if high blood pressure and vasospasm is due to pain, RCVS due to secondary causes should be treated with elimination of the triggers.

Recurrent TCH is diagnostic of RCVS using RSVS 2 score, RCVS is a benign and self-limited disease which usually improve in three months' time,8% of patients will develop progressive symptoms and complication like ischemic stroke, cytotoxic oedema, PRES or SAH, diagnosing RCVS in a timely manner and treating the secondary triggers are curative.Posterior reversable encephalopathy syndrome (PRES) is a clinic radiological syndrome characterised by acute. To subacute clinical symptoms which includes headache, the occurrence of thunderclap headache in a patient with PRES should prompt urgent evaluation for an overlapping or alternative diagnosis, headache usually dull, diffuse, and gradual on onset,

Other manifestations include visual disturbance (diplopia, field defect, scotoma, cortical blindness, temporary blindness, blurring of vision, visual hallucination, visual neglect) seizures, encephalopathy.

Increasing use of tyrosine kinase inhibitors, immunotherapy, anti D19 chimeric antigen receptor T-cell therapy in addition to the recent advance in neuroimaging specially MRI spectroscopy (MRS) have expanded the spectrum of PRES presentations,

The pathophysiology of PRES is a disease due to endothelial dysfunction and disruption of blood0brain barrier, MRI findings in patients with PRES are very characteristic which include vasogenic oedema involving the parietooccipital region due to failure of cerebral autoregulation and endothelial dysfunction in addition to relative decrease sympathetic supply to the occipital lobe,

The upper limit of cerebral blood flow autoregulation is roughly 150-165 mmHG which usually seen in patients with chronic hypertension, beyond this limit, increasing blood pressure causes increased blood flow and dilation of the arterioles and endothelial dysfunction, vasogenic oedema and hypoperfusion injury, PRES is triggered by significant systemic diseases which include bone marrow transplant, solid organ transplant, Graft Versus Host Disease, cytotoxic therapy, specifically Cytarabine, cisplatin, bevacizumab and gemcitabine, cyclosporine, tacrolimus, autoimmune diseases like polyarteritis nodosa, SLE, polyangiitis with granulomatosis, pre-eclampsia, sepsis and septic shock.

Other causes are Thrombotic Cytopenia, Haemolytic uraemic syndrome, cryoglobulinemia, massive blood transfusion, chronic kidney disease and porphyria, hypomagnesemia, hypercalcaemia, hypocholesteraemia, intravenous immunoglobulin, tumour necrosis factor, Guillain-Barre syndrome.

MRI findings are very characteristic which includes:

- T1: hypointense in affected regions which could be
  - Parito -occipital
  - Superior frontal sulcal
  - Holohemispheric
  - T1+GD: patch variable enhancement
- T2: hyperintense in affected regions
- DWI: increased signal in the affected regions
- GRE (gradient echo MRI) Hypointense signal in the affected regions due to haemorrhage
- SWI (susceptibility weighted image) microhaemorrhage in up to 55%

Recently another variant of PRES was recognised which unlike the classical form of PRES which involve the posterior part of the brain, central variant of PRES is characterised by involving the central brain structures which includes the spinal cord, basal ganglia, brain stem, thalamus and spares the classic parieto-occipital region.

Management of PRES

Manging the triggering factor is crucial, in addition to treating acute hypertension, blood pressure should not be reduced by more than 25% of the initial blood pressure in the first 6 hours, careful blood pressure management in monitored bed with intravenous labetalol or nimodipine, or nicardipine, with aim of blood pressure 130-150 systolic and 80-100 mmhg diastolic, there is no indication for antiseizure prophylaxis but patient should be treated with a broad spectrum anticonvulsant should they developed seizure.

There should be a low threshold to investigate patient with confusion with EEG to rule out non-convulsive status epilepticus(19), although corticosteroid improve vasogenic oedema, there is no role for steroid in treating PRES, if PRES is attributed to immunosuppressive or immunotherapy, reduction of the dose or substitution of medication is recommended, other differential diagnosis should be ruled out which are mainly intracranial bleed, hypoglycaemia, aneurismal subarachnoid haemorrhage, subdural haemorrhage, cerebral venous sinus thrombosis, posterior circulation stroke, haemorrhagic stroke, basilar artery thrombosis, autoimmune encephalitis, non-convulsive status epilepticus, metabolic encephalopathy.

Prognosis of PRES is favourable if diagnosed early and treated, symptoms of PRES could be irreversible if syndrome was not diagnosed early, or delay of treatment or if the patient has massive vasogenic oedema or if the patient has a variant of central PRES which involve the brainstem and thalamus, which could evolve into life threatening complication like transforaminal cerebellar herniation and death.

In summary posterior cerebral reversible encephalopathy is a radio neurovascular syndrome characterised by vasogenic oedema in parietooccipital region of the brain due to failure of cerebral autoregulation, usually it is monophasic and not recurrent unlike RCVS which is recurrent benign self-limiting disease caused by loss of cerebral autoregulation, although vasoconstriction of cerebral vessels are reversable, symptoms might not be reversable if treatment was delayed, ruling out other serious conditions are mandatory and treatment of secondary causes are the corner stone of treatment with careful and monitoring blood pressure with aim to decrease high blood pressure but no more than 25% in the first 6 hours.

Both RVCS and PRES are caused by dysregulation of autoregulation and MRA and CTA show beaded arteries with a sausage-like shape, there is overlap between the two disorders as RCVS can trigger PRES and vice versa, thunderclap headache is common in RCVS but can occur in PRES.

Vasogenic oedema is common in PRES due to loss of integrity of blood brain barrier and can progress to cytotoxic oedema, but it can occur in RCVS if patient has intense vasoconstriction leading to ischemia and hyper perfusion injury causing haemorrhage.

Classic posterior vasogenic oedema is commoner in PRES and bleeding is more common in RCVS. RCVS is self-limiting in 90% of patients, and not monophasic.

PRES is a serious disease and needs to be diagnosed and treated very early to avoid serious complications. Primary angiitis of central nervous system (PACNS) is a rare type of cerebral vasculitis which can affect the brain and spinal cord with no involvement of other organs or other systemic blood vessels, there is a notable association with herpes Zoster and amyloid angiopathy,main manifestations are multifocal infarctions in patients with no risk factors for stroke, headache, cognitive impairment, seizures, ataxia, psychiatric disorder, visual disturbance, myelopathy, personality changes, rapid decline and loss of independency, CSF is abnormal in more than 95% of cases in the form of pleocytosis and high protein but normal sugar.[15,16]

CTA and MRA usually show alternating constriction and dilation, both are irreversible, high resolution vessel wall imaging (HRV-MRI) has emerged as a supplementary diagnostic tool, followed by brain biopsy to exclude vasculitis, other important investigations include echocardiography, hyper coagulopathy work up, blood culture, vasculitis and autoimmune panel to exclude secondary vasculitis.

Once diagnosis has been confirmed, it is recommended to start treatment with steroid and cyclophosphamide, response rate is over 70%, patient with resistant PACNS should be treated with Rituximab.

Maintenance therapy with Azathioprine or mycophenolate should continue for12- 18 months, patients diagnosed and treated early can be cured with no relapse, 20-30% of patient might experience relapse, poor prognostic factors are shorter interval between relapses, severe cognitive impairment, intolerance to medication, increased load of the disease in the brain due to delayed diagnosis.

In conclusion PRES and RCVS share many similar clinical and radiological features and not uncommonly overlap, Both are caused by dysregulation of cerebral autoregulation and endothelial dysfunction, both has convexal nonanurismal subarachnoid haemorrhage and dynamic segmental cerebral vasoconstriction that could reverse in few weeks, RCVS2 score facilitated robust early diagnosis, PRES has a monophasic course unlike CRVS which recur of time.

conclusion

Both have similar clinical features like thunderclap headache, confusion, visual symptoms, neurologic deficits and seizures, CRVS is a self-limiting disease in 90% of cases unlike PRES which can cause serious complication including permanent neurological deficits, coma and death if not diagnosed and treated in a timely manner, patients presented with thunderclap headache should have an urgent workup to rule out other serious diseases like aneurysmal subarachnoid haemorrhage, pituitary apoplexy, pseudotumor cerbri, cortical venous sinus thrombosis, cervical artery dissection, illicit and licit drugs and Posterior reversable vasoconstrictor syndrome and posterior reversable leukoencephalopathy meningoencephalitis.[16,17,18,19,20]

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