Cardio-cerebral diseases

Abstract

The connection between Cardio-vascular diseases (CVD) and CNS (Central nervous system) diseases is well known. Here we review most of the well-known and studied diseases connecting both systems to get a better view of that spectrum of diseases. When we discuss that kind of diseases, we mean that one organ is originally healthy and would function normally until it is affected by the other diseased system. Previously known, cardiovascular diseases usually cause CNS disorders by interrupted blood flow to the CNS, while the CNS disorders disrupt the cardiovascular autonomic functions leading to the excessive sympathetic discharge and catecholamines release. In our review article, we focus mainly on the brain disorders when CNS is mentioned, not the spinal cord disorders.

Keywords: cardiovascular, central nervous, autonomic, catecholamines

Abbreviations: AD, alzheimer dementia; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; NCS, neurocardiogenic syncope; POTS, postural tachycardia syndrome; MCA, middle cerebral artery; SUDEP, sudden unexplained death in epilepsy; TTS, Takotsubo cardiomyopathy; AED, anti-epileptic drugs; SAH, subarachnoid hemorrhage; NPE, neurogenic pulmonary edema

Introduction

Cardiovascular diseases are well known to cause different CNS diseases like stroke and syncope. The mechanism is known to be likely secondary to interrupted blood flow going to the brain. Embolic spread is a well-known pathway. On the other side, seizures (as an example of CNS disease) can be reflected on the cardiovascular system causing cardiomyopathy or cardiac arrhythmias for example. That is attributed to excess catecholamines discharge and autonomic dysfunction (Table 1).

Cardio-cerebral diseases

Stroke and TIA

Cardiac arrhythmias are well known causes for Cerebro-vascular strokes. Both persistent and paroxysmal AF increases the risk of first and recurrent stroke. Other cardiac arrhythmias are like bradycardia-tachycardia (sick sinus syndrome), spontaneous echo contrast is an independent echocardiographic risk factor for left atrial thrombus and its appendage and cardiac thrombo-embolic events. Atrial ectopic beats (AEBs) could be an independent risk factor. Frishman et al., reported significantly higher rates of cerebrovascular accidents among older subjects with slow heart rate (<60 bpm) or AV block. Congenital heart diseases could be potential sources for stroke. Potential mechanisms of stroke in patients with PFO with or without an ASA include paradoxical embolization. Left ventricular thrombus complicating acute myocardial infarction (AMI) results from turbulent blood flow and stasis related to a kinetic left ventricular wall segment or aneurysm. Heart failure Accounts for 9% of strokes. As a consequence of the activation of the sympathetic nervous system and of the renin-angiotensin-aldosterone system, there is a hypercoagulable state. Moreover, there is evidence of endothelial dysfunction in CHF patients, rheological alterations consistent with increased blood velocity, and malfunctioning of cerebral autoregulation. Valvular heart disease, Aortic and mitral valve diseases are associated with an increased stroke risk. Mitral valve prolapse and mitral annular calcification have also been associated with increased stroke risk in some studies.

Table 1

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Infective endocarditis

Complications (like stroke, mycotic aneurysm or intra-cranial abscess) result from dislodgment or fragmentation of cardiac vegetations leading to septic emboli spread to the brain. It can be complicated by Stroke including hemorrhagic, mycotic aneurysms, meningitis, and intra-cerebral abscesses.

Cognitive impairment

Stroke can complicate many cardiac procedures, including percutaneous coronary Intervention (PCI), coronary artery bypass operations, valvuloplasty, and catheter ablation for AF. AF is associated with an increased risk of stroke and with post-stroke dementia depending on the location of the stroke, cognitive impairment can be common. However, even having AF without a stroke may place a patient at increased risk for cognitive dysfunction. The mechanisms by which AF causes cognitive dysfunction in patients without a stroke are not well defined. One hypothesis posits that AF creates a hyper-coaguable state and that formation of microemboli leads to cognitive impairment. Chronic heart failure is linked to cognitive impairment, deficits in attention, learning ability and delay recall, working memory, executive function, and psychomotor speed. Several linking features such as hypoxia, amyloid-beta and oxidative stress have been proposed as a connecting point between AD (Alzheimer dementia) and CVD. The hypoxic events in the brain triggers increased amyloid-beta deposition and plaque formation in central neurons.

Syncope

Syncope is a transient loss of consciousness and is considered an example of interaction between the cardiovascular and nervous system. There are different cardiovascular causes for syncope. Vascular diseases include vertebral-basilar disease, subclavian steal, and bilateral carotid disease. Vasovagal syncope (Gower syndrome) is a drop in stroke volume and blood pressure will interrupt the cerebral blood flow leading to syncope. The pathophysiology is explained by disruption in cardiovascular regulation to such an extent that postural hypotension or tachycardia or bradycardia occurs. Centrally mediated (or "reflex") fall in systemic blood pressure is a condition that has been referred to as vasovagal (and later named as neurocardiogenic) syncope. That is referred to as neurally mediated hypotension, the fainting reflex or vaso-depressive syncope.

That autonomic disturbance could be idiopathic or secondary to diseases like Diabetes and Amyloidosis. The reflex syncope tend to exhibit abrupt falls in blood pressure that are often associated with a definitive prodrome. In contrast, the loss of consciousness in the orthostatic (or "dysautonomic") syncope tends to be slow and gradual. The reflex syncope occurs because of a sudden failure of the ANS to maintain adequate vascular tone during orthostatic stress, resulting in hypotension (frequently associated with bradycardia). The two most frequent types of reflex syncope are neurocardiogenic (vasovagal) syncope and carotid sinus syndrome. The other types of reflex syncope are often referred to as situational because they are often associated with specific activities or conditions. Neurocardiogenic syncope (NCS) can be quite varied in presentation. Postural tachycardia syndrome (POTS) could present with near syncope, lightheadedness, dizziness, cognitive impairment and visual disturbance. The hallmark of this group is a persistent tachycardia while upright, which can achieve rates of 160bpm or higher. The second type of POTS is referred to as the “β-hypersensitivity” or “central” form. In this form, there is believed to be an inadequate feedback process that arises from above the level of the baroreflex. Heart rates drop to 45 to 55bpm, with complete chronotropic incompetence. Recent studies completed by Verino et al. have demonstrated that many of these patients have high levels of antibodies to acetylcholine receptors in the autonomic ganglia, which suggests that the disorder is autoimmune in nature.

Cardiac causes into mechanical and electrical

Mechanical causes abruptly impede blood flow and lead to systemic hypo-perfusion and syncope.

i. Mechanical causes include (from common to less common)
   - Ischaemic heart disease
   - Non-ischaemic dilated cardiomyopathy
   - Aortic stenosis
   - Hypertrophic cardiomyopathy
   - Arrhythmogenic right ventricular cardiomyopathy
   - Cardiac tumors (atrial myxoma)
   - Cardiac tamponade
   - Severe pulmonary hypertension
   - Pulmonary embolus
   - Congenital heart disease

Electrical causes manifest in the form of arrhythmias. Primary electrophysiological disorders are more common in younger age. It includes inherited channelopathies, long QT syndrome, short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia. In patients with age below 40, most common causes of syncope are vasovagal syncope, less likely, hypertrophic cardiomyopathy. Above age of 40, mechanical causes like heart failure and aortic stenosis are more common. In addition to that, arrhythmias are more common causes like ventricular tachycardia and fibrillation. Both bradyarrhythmias and tachyarrhythmias can lead to syncope. Tachyarrhythmias include ventricular or supra-ventricular arrhythmias. Bradycardia due to sick sinus syndrome or advanced atrioventricular block is another common cause of syncope in patients with heart disease. Stokes-Adams attack is syncope (sometimes with seizure like activity) secondary to complete (third-degree) heart block is seen on the ECG during an attack with other ECG abnormalities such as tachy-brady syndrome might also be seen.

Seizures

Cardiac causes of seizures are missed by some physicians who prescribe unnecessary anti-epileptic drugs. Some patients with presumed and re-evaluated seizure disorders were treated with, but were unresponsive to, AED (anti-epileptic drugs) therapy. In these studies it was confirmed that vasovagal syncope may be accompanied by myoclonus, as well as carotid sinus hypersensitivity and primary arrhythmias such as bradycardia, caused by sinus node dysfunction and intermittent atrioventricular (AV) block, as well as ventricular (torsade de pointe) and, more rarely, supraventricular tachycardia.
Categorization of patients presenting with seizures due to cardiac causes and referred to a cardiologist should take age into consideration. The long QT syndrome (LQTS) is more considered in younger age, while in older patients, sinus node disease or intermittent high degree AV block should be looked for; in the highest age group coronary sinus syndrome should be investigated.33 Because fainting and seizures are common symptoms of LQTS, the disorder is often mistaken for epilepsy and treated with antiepileptic drugs (AEDs) while the underlying cardiac risk goes undetected.32 Channelopathy disorders as Inherited LQTS results from genetic mutations disrupting normal calcium and potassium ion channel regulation in the heart, resulting in a prolonged Q-T interval. Potassium channel defects in the brain, notably in the hippocampus, have been associated with epileptic seizures.34 Misdiagnosis of LQTS as epilepsy may explain many cases of sudden unexplained death in epilepsy (SUDEP). Because it is common for arrhythmias and subsequent seizures in LQTS patients to be triggered by exercise, excitement, notably, sudden noise, neurologists can screen for LQTS by asking whether seizures are precipitated by noise, he continued.33 Valvular heart diseases can be presented with syncpe and maybe convulsions as in Aortic stenosis.35 Mitral valve prolapse (MVP), often asymptomatic, occurs in 5-7% of the adult population, and therefore is commonly cited as a cause for many medical disorders, including epilepsy and stroke.36 Atrial Myxoma is the most common primary cardiac tumor can present with severe dizziness/syncpe which is experienced by approximately 20% of patients. Embolization to the central nervous system may result in transient ischemic attack, stroke, or seizure.17

Cerebro cardiac diseases

Cerebrogenic arrhythmia

In adults and children, most complex partial and generalized tonic-clonic seizures cause an increase in heart rate.36 Seizure-related asystole and bradycardia are much less common. In one retrospective analysis, only 5 out of 1244 patients who underwent video-EEG monitoring had ictal asystole.37 Electrical stimulation of the human insular cortex suggests that the right hemisphere may have greater sympathetic influence, while the left hemisphere may be associated with greater parasympathetic control.40 However, patients with refractory epilepsy appear to have a higher risk for seizure-related cardiac rhythm and conduction abnormalities.41 These abnormalities included atrial fibrillation, supraventricular tachycardia, bundle branch block, atrial premature depolarizations, ventricular premature depolarizations, ST-segment elevation, and asystole. Potentially serious abnormalities, including junctional escape rhythm, atrial fibrillation, ST-segment elevation, and asystole, were seen in 14% of individuals; both longer seizure duration and generalized tonic-clonic seizures were associated with an increased occurrence of EKG irregularities. Tigran et al.,42 reported that 40% of patients with refractory focal epilepsy had seizure-related ST-segment depression, suggesting that cardiac ischemia might occur during seizures. Experimental data suggest that ictal bradyarrhythmias can lead to complete heart block.43 Several studies have identified decreased heart rate variability among people with epilepsy, particularly when the epilepsy is refractory, which raises the concern that altered autonomic function might contribute to cardiac arrhythmias and SUDEP (sudden unexplained death in epilepsy).44 It is acknowledged that the presence of ECG changes, for example T wave inversion, ST segment elevation and a prolonged QT interval, in patients with intracranial pathology, such as subarachnoid haemorrhage, are a manifestation of massive catecholamine release and autonomic dysregulation resulting in ventricular wall motion abnormalities, vasospasm and subsequent cardiac contraction band necrosis.44 Inter-ictal cardiac changes on the EKG may vary and show only minor, non-significant changes.45 However, a recent preliminary study of 128 patients with severe refractory epilepsy and learning disability, revealed inter-ictal ECG abnormalities in approximately 60% of patients, including first degree atrio-ventricular block and poor R wave progression46 The laterality of cardiovascular presentations is of interest because of previous observations that in the human, right carotid amylobarbital infusion produces bradycardia, and left carotid infusion is accompanied by tachycardia.48 Additionally, an increased incidence of supraventricular tachycardia was reported in patients with right middle cerebral artery stroke.49 Some investigations in the human indicate that left caudal anterior insular stimulation during surgery for intractable epilepsy increases the frequency of bradycardia and depressor responses, whereas stimulation of a similar region of the right anterior insula is associated with heart rate and diastolic blood pressure elevation. That represents sympathetic predominance in right insula and parasympathetic predominance in left insula. Studies have indicated a significant role for the right insular cortex in cardiovascular decapsulation after stroke. Tokgozoglu et al.,50 showed that compared to age-gender matched controls total spectral energy was reduced after ischemic stroke as noted previously by others. However, this was particularly marked in patients with stroke involving the right middle cerebral artery (MCA), or the insular cortex. Sudden death was observed in 11%, but occurred more often after right MCA lesions. On the other hand, Li et al.,51 indicated that supraventricular arrhythmias were more frequently encountered after right insular infarction compared with strokes in other locations. Interestingly, ST abnormalities were more frequent after left insular involvement in comparison with controls or strokes in other locations. Sander showed that right hemisphere infarction reduced circadian blood pressure variability and increased nocturnal blood pressure compared to left hemisphere infarcts. Additionally, higher serum noradrenaline levels, longer QTC prolongation and more cardiac arrhythmias were observed after right hemisphere infarction.52 Electrocardiographic abnormalities and cardiac arrhythmias are commonly noted after acute stroke. Risk of malignant ventricular arrhythmias is increased after a stroke and is associated with sudden cardiac death. Experimental and clinical evidence suggests that insular cortex infarcts play a key role in autonomic dysregulation that lead to arrhythmias in the acute setting.53 Between 50 and 100% of patients experience cardiac rhythm disturbances during the acute phase of SAH. The majority of these abnormalities are benign, with sinus tachycardia, sinus bradycardia, and premature atrial and ventricular beats being the most common. Only 1-4% of patients experience a clinically significant arrhythmia, such as ventricular tachycardia or atrial tachyarrhythmias.54 Cardiovascular complications are common after traumatic brain injury and associated with increased morbidity and mortality.55 The spectrum of abnormalities includes hypertension, hypotension, ECG changes, cardiac arrhythmias, release of biomarkers of cardiac injury, and left ventricular (LV) dysfunction.56 The abnormalities are usually reversible. Neurogenic cardiac injury is related to brain injury-induced catecholamine and neuroinflammatory responses.57

Takotsubo Cardiomyopathy (TTS) is a transient cardiac syndrome that involves left ventricular apical akinesia and mimics acute coronary syndrome. It was first described in Japan in 1990 by Sato et al.58 Patients often present with chest pain, have ST-segment
elevation on electrocardiogram, and elevated cardiac enzyme levels consistent with a myocardial infarction TTS is linked to stroke and seizures.\textsuperscript{64,65} Subarachnoid hemorrhage (SAH) is the most common neurological disorder resulting in TCM.\textsuperscript{59,60} It can be either associated with or without epilepsy. Multiple mechanisms have been reported to be resulted in TCM post SAH. Previously coronary vasospasm has been reported as a cause of TCM by Yuki et al.,\textsuperscript{66} as a cause of stunned myocardium after SAH.\textsuperscript{62} Studies have reported increase in the levels of catecholamines post SAH. The increased levels of metanephrines have been found to be resulting in coronary vasospasm thereby inducing TCM.\textsuperscript{63} Neurogenic pulmonary edema (NPE), The most important cause of NPE is subarachnoid hemorrhage followed by cerebral trauma and epilepsy.\textsuperscript{64,65} Other less common causes may include cervical spine trauma, meningitis, multiple sclerosis, cerebellar hemorrhage, cerebral gas embolism, intracranial tumors\textsuperscript{5} and ventricular shunt dysfunction.\textsuperscript{64} It is postulated that NPE may be a consequence of two mechanisms, an excessive adrenergic discharge which leads to pulmonary vasoconstriction and a rapid increase in pulmonary capillary hydrostatic pressure, thus causing fluid leakage to the alveolar space. Such raise in hydrostatic pressure may damage or induce an inflammatory response to the endothelium and basement membrane, leading to protein leakage and promoting the alveolar exudate typically seen in NPE.\textsuperscript{64} Seizures, Plasma noradrenaline and adrenaline rise sharply within 30 minutes of the seizure and then decline rapidly. The noradrenaline response is attributed to generalized sympathetic neural activation, and the adrenaline response is due to adrenal activation. This sudden surge of catecholamine can cause TCM in patient with status epilepticus.\textsuperscript{57} Although Seizures may also trigger TCM, but it is rare for TCM to result in sudden unexpected death in epilepsy (SUDEP).\textsuperscript{59,60} It has been postulated that neurogenic coronary vasospasm may be implicated, and that, if recurrent, may eventually progress to perivascular and interstitial fibrosis.\textsuperscript{68} This may, in turn, predispose the heart to arrhythmogenesis, particularly in the setting of considerable autonomic imbalance during seizures.\textsuperscript{69} A study found significant elevation in Serum troponin-I following temporal lobe epilepsy and status epilepticus. That was more with patients with underlying cardiovascular risk factors.\textsuperscript{70} This is in accordance with the significant role of temporal lobe structures in the neural control of the heart, which has been described well in the past.\textsuperscript{71} The study findings could be a hint that patients with temporal seizure activity are at higher risk of cardiac complications including myocardial ischemia. Epileptic patients are more susceptible to sudden death than the general population, and more so are patients with refractory seizures. The most frequently recognized cause is cardiac arrhythmia occurring in consequence with seizures.\textsuperscript{72} Ischemic EKG changes following seizures have been documented in a substantial proportion of refractory epileptic patients\textsuperscript{62} However, a clinically defined, overt myocardial infarction (MI) is an extremely rare complication of epileptic events.\textsuperscript{73} Authors explain myocardial infarction complicating seizures due to a mismatch between oxygen supply and myocardial metabolic demand. This imbalance can be caused by increased muscular activity associated with convulsions or by massive catecholamine release from sympathetic nerve endings, causing a raise in heart rate, arterial blood pressure and myocardial contractility. Also the possibility that increased heart contractile activity could damage or rupture a preexisting plaque has been considered. Although it is rare, it is postulated that acute coronary artery disease is under-diagnosed and should be pursued especially in patients with epilepsy with underlying cardiovascular risk factors.\textsuperscript{74}

Link between both systems
Some diseases link both cardiovascular and CNS disorders. It is considered as mutual association and affection. Channelopathy was discussed above as an example of linking a cardiac arrhythmia to syncope and seizures, as an example of impairment in the ion transport channels in the heart and the brain. Congenital heart disease also occurs in syndromes of multiple congenital abnormalities, further predisposing these patients to seizures. Congenital heart diseases in autopsy series are associated with a 68% incidence of cerebral malformations. Seizures and congenital heart diseases are considered association in diseases like Down syndrome and tuberous sclerosis.\textsuperscript{55} A study found a link between Parkinson disease and idiopathic cardiomyopathy. Patients with idiopathic (dilated or hypertrophic) cardiomyopathy could have in the same time Parkinson’s disease and mitochondrial encephalomyopathies through underlying genetic mutations.\textsuperscript{75} Parkinson disease (PD) patients, 30-40% of them have orthostatic hypotension (OH). PD with OH patients has failure of both the parasympathetic and sympathetic components of the arterial baroreflex. OH in PD therefore seems to reflect a bad influence of cardiac and extra-cardiac noradrenergic denervation and baroreflex failure.\textsuperscript{76} As we mention PD, A cross-sectional study concluded that risk of heart failure is higher in PD patients.\textsuperscript{77} The etiology of the excess prevalence of heart failure in PD is unknown, but the disease process, autonomic nervous system dysfunction, antiparkinsonian medications, and concurrent co-morbidities may be contributing factors. The autonomic nervous system modulates cardiac function and is involved in the pathophysiology of heart failure.\textsuperscript{77} Multiple sclerosis (MS) patients were studied in one study and were found to have a higher prevalence of Cardio-vascular diseases (CVD), like myocardial infarction (MI), stroke and heart failure. That could be explained by the coexistence of several unmeasured, but shared CVDs risk factors. Common etiological factors in MS and CVDs, such as immune system dysfunction and inflammation, can to some extent explain our findings. Identification of several clinical risk factors for CVDs in patients with MS, such as high plasma levels of homocysteine, altered thrombogenic factors, endothelial dysfunction, cardiovascular autonomic dysfunction and lower arterial compliance may also support the findings of a higher risk of CVDs among the MS patients in that study.\textsuperscript{80} Migraine headaches patients have increased risk of cardiovascular diseases like MI and stroke, including hemorrhagic strokes.\textsuperscript{81,82} Migraine has long been considered a vascular headache and cerebral vasoconstrictive phenomena associated with migraine had been considered the cause of cerebrovascular ischemic events in migraineurs. Hypothesized mechanisms include the role of confounders such as pharmacologic agents used to treat migraine (nonsteroidal antiinflammatory drugs, triptans, and ergotamine) or anxiety and depression, prothrombotic factors, including prothrombin factor, factor V of Leiden, elevations in von Willebrand factor antigen and activity, decreased platelet hemoctasis time, clotting time and collagen-induced thrombus formation time MTHFR, and ACE D/I polymorphisms, cervical arterial dissection, and patent foramen ovale.\textsuperscript{83}

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Conflict of interest
The author declares no conflict of interest.
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