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NEUROLOGY OF SYSTEMIC DISEASES (J. BILLER, SECTION EDITOR)

Neurological Manifestations of Myocarditis

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Abstract

Purpose of Review The present review discusses the neurological complications associated with myocarditis of different etiologies.

Recent Findings Myocarditis can be idiopathic or caused by different conditions, including toxins, infections, or inflammatory diseases. Clinical findings are variable and range from mild self-limited shortness of breath or chest pain to hemodynamic instability which may result in cardiogenic shock and death. Several neurologic manifestations can be seen in association with myocarditis. Tissue remodeling, fibrosis, and myocyte dysfunction can result in heart failure and arrhythmias leading to intracardiac thrombus formation and cardioembolism. In addition, peripheral neuropathies, status epilepticus, or myasthenia gravis have been reported in association with specific types of myocarditis.

Summary Multiple studies suggest the increasing risk of neurologic complications in patients with myocarditis. Neurologists should maintain a high suspicion of myocarditis in cases presenting with both cardiovascular and neurological dysfunction without a clear etiology.

Keywords Myocarditis · Stroke · Heart failure · Anticoagulation · Cognitive decline · SARS-CoV-2

Abbreviations

CNS	Central nervous system
AM	Acute myocarditis
HF	Heart failure
TLR	Toll-like receptors
EMB	Endomyocardial biopsy
ECMO	Extracorporeal membrane oxygenation
DCM	Dilated cardiomyopathy
TTS	Takotsubo syndrome
ICI	Immune checkpoint inhibitors
HES (idiopathic)	Hypereosinophilic syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Introduction

Myocarditis encompasses a broad spectrum of disorders characterized by cardiac dysfunction secondary to myocardial inflammation. This is in contrast with other mechanisms of cardiac injury, such as ischemic heart disease or genetic cardiomyopathies, where inflammation is considered reactive or secondary to primary insult [1]. The presentation of acute myocarditis (AM) is heterogeneous and ranges from asymptomatic, with occasional arrhythmia or impaired systolic LV function on cardiac screening, to mild disease presenting with unexplained fatigue, fever, dyspnea, palpitations, or atypical chest pain, to severe life-threatening arrhythmias or cardiogenic shock in the absence of coronary artery disease or other known causes of heart failure (HF) [2••]. Preceding flu-like symptoms, respiratory manifestations, or gastrointestinal illness can be seen in up to 80% of AM cases. Complications associated with AM include acute HF or cardiogenic shock, which can represent the initial symptom in up to 26% of the patients [3]. AM can also evolve into an irreversible chronic phase characterized by tissue remodeling, fibrosis, and myocyte damage which lead to dilated cardiomyopathy (DCM) or chronic HF [4]. Myocarditis is considered an important cause of HF-related death or sudden death in young individuals [5, 6]. However,

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it should be mentioned that, owing the variable presentation and course, its epidemiology is not completely known.

Most common causes of myocarditis are infectious, autoimmune, toxic, and idiopathic (Table 1) [1, 7, 8]. The diagnosis is established by the histopathological findings in endomyocardial biopsy (EMB) as defined by the *Dallas criteria*. Typical cases are characterized by an infiltrate of mononuclear cells associated with myocyte degeneration and necrosis which is non-ischemic in origin [9]. Immunohistochemically, myocarditis is characterized by the presence of ≥ 14 leucocytes/mm^2, including up to 4 monocytes/mm^2, and ≥ 7 cells/mm^2 of CD3$^+$ T lymphocytes [10]. The inflammatory response leads to cytoskeletal disruption and development of interstitial edema and focal necrosis resulting in myocyte dysfunction or death, and predisposing to the development of unstable tachyarrhythmias or left ventricular (LV) dysfunction [11]. The characteristics of intracellular infiltrate can be used to classify the type of myocarditis. The most common forms are the lymphocytic, eosinophilic, giant-cell myocarditis, and granulomatous [12••]. This article provides a review of the pathogenesis, causes, evaluation, and presentation of myocarditis with special emphasis on its associated neurologic manifestations.

Pathogenesis

Myocarditis is typically classified based on the infiltrating cell as eosinophilic, lymphocytic, giant cells, or granulomatous. The presence of a *lymphocytic* infiltrate suggests that the myocarditis is caused by infections, mainly viruses, drugs, radiation, or immune-mediated mechanisms as can occur in the context of systemic inflammatory disorders [13]. Polymerase chain reaction studies from children and adults with AM and DCM have demonstrated that different viruses, such as parvovirus B19, enteroviruses, adenoviruses, or coxsackievirus B, commonly infect the myocardium of these patients. In addition, genomes of viruses have been isolated in the later stages of DCM [14]. These findings support the notion that certain viruses can be cardiotropic and play a role in the transition from AM to DCM, although the exact mechanisms involved in this process are not well understood [15, 16]. Based on data obtained in preclinical models, a direct invasion of the myocardium by viral pathogens leads to the activation of pattern recognition receptors such as toll-like receptors (TLR), especially TLR3 and TLR4, which stimulate both innate and acquired immune responses resulting in the activation of macrophages, neutrophils, and dendritic cells. In addition, there is an increased

Table 1 Etiology of myocarditis

Infectious

1. Bacterial: *Staphylococcus aureus*, *Streptococcus* (group A or G), *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Salmonella enteritidis*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*
2. DNA viruses: *Adenoviridae*, *Herpesviruses* (*human herpes virus six*, *Cytomegalovirus*, *Epstein-Barr*, *varicella zoster*), *Parvovirus B19*
3. RNA viruses: *Enteroviruses* (*Coxsackievirus*, *Poliovirus*), *Flaviviridae*, *Orthomyxovirus* (*influenza A*, *B*), *human immunodeficiency virus*
4. Spirochetal: *Leptospira*, *Borrelia burgdorferi*, *Treponema pallidum*
5. Parasite: *Trichinella spiralis*, *Echinococcus granulosus*, *Taenia solium*
6. Fungal: *Aspergillus*, *Actinomyces*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucormycosis*, *Nocardia*, *Sporothrix*
7. Protozoa: *Trypanosoma cruzi*, *Toxoplasma gondii*, *Plasmodium falciparum*, *Leishmania*

Non-infectious immune-mediated

1. Systemic and autoimmune disorders: Eosinophilic granulomatosis with polyangiitis, mucocutaneous lymph node syndrome, systemic sclerosis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, rheumatic heart disease, hypereosinophilic syndrome, inflammatory bowel disease, rheumatoid arthritis, Sicca syndrome, systemic lupus erythematosus, aortic arch syndrome
2. Drugs: Penicillin, cefaclor, colchicine, furosemide, thiazide diuretics, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, methyldopa, phenylbutazone, amitriptyline
3. Autoantigens: Giant-cell myocarditis and lymphocytic myocarditis

Non-infectious toxic

1. Drugs: Penicillin, cefaclor, colchicine, furosemide, thiazide diuretics, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, methyldopa, phenylbutazone, amitriptyline
2. Toxins: Ethanol, anthracyclines, arsenic, carbon monoxide or carbon tetrachloride, catecholamines, cocaine, heavy metals (copper, mercury, lead)
3. Hypersensitivity: Cephalosporins, clozapine, diuretics, lithium, sulfonamides, tetanus toxoid, tetracycline; bites (insects, scorpion, snake wasp or black widow spider venom)
4. Hormones: Phaeochromocytoma, vitamins (beri-beri)
5. Physical agents: Radiation, electric shock

Adapted from references [1, 7], and [8]

expression of cytokines IL-6, IL-1, or TNF-α. It is likely that the ultimate goal of this initial immune response is to clear the virus [17, 18]. However, it has been observed that this early inflammation can also overcome tolerance mechanisms and progress to chronic myocarditis and DCM [17]. The persistence of viral replication in the myocardium can also lead to progressive impairment of the LV ejection fraction and a worse prognosis [19].

The pathogenesis of *eosinophilic myocarditis* has been linked to delayed hypersensitivity reactions to drugs, allergens, inflammatory illnesses, proliferative disorders, or infections (parasites) [20]. Patients typically have elevated serum levels of eosinophil granule proteins, mainly major basic protein (MBP) and eosinophil cationic protein (ECP). In autopsy studies, MBP and ECP accumulate in the endocardium and in cardiac thrombi. In addition, in patients with chronic myocarditis, these proteins can be seen in necrotic myocardiocytes and lead to HF or DCM [21, 22]. Mechanistically, MBP facilitates platelet adhesion and eosinophil extracellular trap formation which in turn enhance platelet activation and thrombosis [23].

Giant-cell myocarditis (GCM) and *granulomatous myocarditis* are rare cases of myocarditis. GCM, in particular, has an idiopathic origin and a progressive course that often results in HF and death [24]. EMB usually reveals a mixture of myocardial necrosis associated with macrophages and multi-nucleated giant cells. In animal models, GCM is associated with a dysregulation of Th1 subtype of T lymphocytes, cells known to be involved primarily in cell-mediated immunity and in the upregulation of chemokine receptors which can lead to end-stage cardiomyopathy [25, 26]. *Granulomatous myocarditis*, in comparison, can be seen in patients with *cardiac sarcoidosis* (CS). This condition is characterized by well-organized noncaseating granulomas, absence of significant myocardial necrosis, and a considerable amount of tissue eosinophilia and fibrosis [27, 28]. Compared to patients with GCM, patients with CS have higher survival rates and are more likely to develop atrioventricular block [28].

Evaluation

Laboratory studies show elevated levels of inflammation markers (C-reactive protein and erythrocyte sedimentation rate) and myocardial necrosis (high-sensitivity troponins, creatinine kinase-MB). Electrocardiographic (EKG) abnormalities, particularly ST segment elevation, are commonly encountered [3]. Echocardiography findings are non-specific and may include increased cardiac wall thickness or wall motion abnormalities. Left ventricular dysfunction with an EF of $\leq 50\%$ is a strong predictor of in-hospital complications compared with patients with preserved EF [29]. EMB is rarely performed given its invasive nature and low sensitivity. However, it can be indicated for cases of acute cardiomyopathy and when the identification of the pathogen could change the medical management and clinical course [30]. More recently, cardiac magnetic resonance imaging (CMRI) with gadolinium enhancement has become increasingly utilized for the detection of myocardial inflammation [31] and to aid in the diagnosis of patients presenting clinically with cardiac symptoms, elevated troponins, and a negative coronary angiogram [32]. It should be noted, however, that CMRI does not differentiate between etiologies of myocarditis.

Neurological Complications Associated with Myocarditis

The interplay between the cardiovascular and nervous systems has been increasingly recognized [33•]. The neural control of the heart involves the sympathetic and parasympathetic systems, along with specific neuroanatomical areas of the brain, including highly interconnected cortices (anterior cingulate cortex and anterior insula), forebrain structures (amygdala and hippocampus), and certain brainstem areas (periaqueductal gray matter, parabrachial nucleus, and ventrolateral medulla) [34, 35]. Thus, patients with central or peripheral nervous system disorders can experience myocardial dysfunction and present with signs of myocardial inflammation. Conversely, patients with primary myocarditis can experience neurologic complications resulting from a variety of mechanisms, such as (1) cardioembolism due to intracardiac thrombi formation or tachyarrhythmia, (2) heart failure associated thrombotic events, hemodynamic instability, or chronic hypoperfusion, (3) immune-mediated mechanisms and epitope mimicry, or (4) complications related to certain drugs and radiation. In the next section, we discuss different neurologic disorders reported in association with myocarditis.

Idiopathic Hypereosinophilic Syndrome Idiopathic hypereosinophilic syndrome (HES) encompasses a group of disorders characterized by marked hypereosinophilia with evidence of organ involvement. Previously, the diagnostic criteria [36] required ≥ 1500 eosinophils/μL and blood hypereosinophilia lasting for at least 6 months. However, these criteria are no longer necessary if marked eosinophilic infiltration associated with organ dysfunction is identified [37]. The presentation of HES is pleomorphic and the reported prevalence of associated cardiovascular and neurological complications ranges between 20 and 58% [37].

Cardiac manifestations include early necrosis with subsequent thrombosis and fibrosis. Diffuse cardiac eosinophil infiltration, also known as eosinophilic endomyocardial

fibrosis or *Loeffler endocarditis* [38], is associated with acute HF, arrhythmias, and intracardiac thrombosis leading to embolism [39]. Neurologic complications seen in association with HES include embolic stroke, encephalopathy, and peripheral neuropathies. HES-associated encephalopathy is characterized by ataxia, behavioral changes, including confusion and memory loss, and findings suggestive of upper motor neuron dysfunction [40]. Eosinophilic meningitis, peripheral neuropathies, including symmetric or asymmetric sensory polyneuropathy and mononeuritis multiplex, seizures, and intracranial hemorrhage have also been described in association with this condition [39].

Sarcoid Sarcoid is a systemic inflammatory disease characterized by the formation of noncaseating granulomas. This condition can affect virtually any organ. Nervous system involvement can manifest with a variety of neurologic and psychiatric signs and symptoms resulting from cranial neuropathies, peripheral neuropathies, myopathies, hydrocephalus, papilledema, meningitis, encephalitis, myelopathy, and radiculopathy. Cardiac involvement in sarcoidosis is associated with increased mortality [41, 42]. Different complications can be observed in these patients, such as HF, DCM, and atrioventricular (AV) conduction disease [42, 43]. Cardiac structural changes in CS can lead to blood stasis or cardiac wall hypokinesia with the subsequent risk of intracardiac thrombosis and cerebral or systemic infarction. Cardiac thrombi, however, can also develop indirectly due to the strong inflammatory response and cytokine release from the sarcoid granuloma (mainly, IFN-gamma and IL-12) [44, 45]. In fact, data obtained in preclinical models have shown that proinflammatory cytokines, such as IFN-gamma, IL-2, IL-12, and TNF, are associated with cerebral ischemia. Conversely, anti-inflammatory cytokines, such as IL-4, IL-5, IL-10, and IL-13, seem to be protective [46]. The major causes of death in CS are ventricular tachyarrhythmias and fulminant congestive HF [47].

Other Systemic Inflammatory Diseases Myocarditis and neurologic disorders can occur in patients with systemic inflammatory diseases. Several pathogenic mechanisms contribute to the development of neurologic manifestations, including inflammatory and non-inflammatory vasculopathy, inflammation within the brain parenchyma, and autoimmunity. Also, some of these disorders can be associated with antiphospholipid antibodies and other conditions which increase the risk of arterial and venous thrombotic events. The neurologic manifestations seen in classic systemic inflammatory disorders are summarized in Table 2. The prevalence of coexisting myocarditis and neurologic involvement in these conditions is unknown. However, there have been cases of myocarditis due to systemic lupus erythematosus associated with myasthenia gravis [48] or presenting with status epilepticus [49]. Posterior reversible encephalopathy syndrome has also been reported in association with myocarditis in patients with severe leptospirosis [50], and with fulminant myocarditis in patients requiring use of ECMO [51].

Neuromuscular Disorders Myasthenia gravis (MG) is an autoimmune disorder resulting from the production of antibodies that recognize the neuromuscular acetylcholine receptor (AChR) in skeletal muscles. Patients with MG typically present with muscle fatigability and weakness [52]. Cases of myositis and/or myocarditis in MG patients have been reported, though the prevalence of these conditions is only 0.9 to 2.3% [53, 54]. A recent meta-analysis including thirty-five patients with MG-associated myocarditis showed that the prognosis of these patients is usually poor. Factors associated with poor outcome include lack of specific signs and symptoms attributable to myocarditis, fulminant progression, and development of life-threatening arrhythmia or HF [55••].

Immune checkpoint inhibitors (ICI) are immunotherapeutic agents that are increasingly utilized for the treatment of malignant tumors [56, 57]. Inflammatory diseases, including myocarditis, polymyositis, and dermatomyositis, have been observed in patients receiving treatment with ICI. These ICI-related inflammatory complications have a low incidence (< 1%) but are associated with poor prognosis [53]. Mechanistically, it has been hypothesized that ICI-related inflammatory complications are secondary to epitope-sharing between muscle and tumor cells with muscle cells becoming the target of activated T lymphocytes [58]. Alternative mechanisms include loss of peripheral tolerance, epitope-spreading, direct muscle toxicity, and flare-up of pre-existing autoimmune disorders [59]. Cases of simultaneous ICI-related MG and myocarditis have also been reported [57, 60].

Neurocardiovascular Disorders Associated with SARS-CoV-2 Coronavirus-19 (COVID-19) syndrome is caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 can affect different organs and has been associated with a variety of clinical manifestations (Table 3). From the neurologic standpoint, patients can experience Guillain-Barré syndrome, acute transverse myelitis, acute encephalitis, seizures, and stroke. From the cardiac standpoint, they can experience cardiogenic shock, acute heat failure, arrhythmias, myocardial infarction, or myocarditis [61]. There are few reports of concomitant transverse myelitis and myo-pericarditis [62] or postinfectious Bell's palsy and acute myocarditis [63]. Direct viral infection, procoagulability resulting in thrombotic and thromboembolic complications, and overproduction of cytokines leading to increased risk of vascular hyperpermeability and

Table 2 Neurologic manifestations of systemic inflammatory diseases associated with myocarditis

Condition	Neurologic complications
Systemic lupus erythematous	Stroke and transient ischemic attack Cerebral venous sinus thrombosis Posterior reversible encephalopathy syndrome Delirium Headache Meningitis/meningoencephalitis Demyelinating syndrome Chorea Seizure disorders Transverse myelitis Dysautonomia Myasthenia gravis Peripheral neuropathy Sensorineural hearing loss Cranial neuropathy
Rheumatoid arthritis	Stroke and transient ischemic attack Myelopathy Vasculitis Rheumatoid nodules within the central nervous system Meningitis Peripheral neuropathy Autonomic neuropathy Myopathy/myositis
Sjögren syndrome	Stroke and transient ischemic attack Cerebral venous sinus thrombosis Posterior reversible encephalopathy syndrome Headache Meningitis/meningoencephalitis Neuromyelitis optica spectrum disorder Multiple sclerosis-like syndrome Amyotrophic lateral sclerosis-like syndrome Seizure disorders Transverse myelitis Dysautonomia Peripheral neuropathy Cranial neuropathy
Granulomatosis with polyangiitis	Stroke and transient ischemic attack Posterior reversible encephalopathy syndrome Isolated parenchymal mass lesions Headache Meningitis Seizure disorders Transverse myelitis Peripheral neuropathy Sensorineural hearing loss Cranial neuropathy
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Stroke and transient ischemic attack Posterior reversible encephalopathy syndrome Headache Meningitis Spinal cord involvement Peripheral neuropathy Dysautonomia
Behçet syndrome	Stroke and transient ischemic attack Cerebral venous sinus thrombosis Parenchymal involvement Meningitis Myelitis Headache Peripheral neuropathy

Table 3 Manifestations described in patients with acute infection and post-acute sequelae of SARS-CoV-2

Organ	Acute SARS-CoV-2 infection	Post-acute sequelae of SARS-CoV-2
Neurologic	Stroke Encephalopathy and delirium Anosmia Ageusia Guillain-Barré syndrome Transverse myelitis Encephalitis Seizures	Fatigue Myalgia Headache Dysautonomia Cognitive impairment Anxiety/Depression Post-traumatic stress disorder Sleep disturbances
Cardiovascular	Arrhythmia Myocarditis Kawasaki-like syndrome Acute myocardial infarct Heart failure	Chest pain Palpitations Myocardial fibrosis and scarring Arrhythmias Autonomic dysfunction
Pulmonary	Pneumonia Hypoxemic respiratory failure Acute respiratory distress syndrome	Hypoxia Dyspnea Decreased exercise capacity Restrictive pulmonary capacity Fibrotic changes and ground-glass opacities
Other	Coagulopathy/thrombotic events Livedo reticularis Urticaria, purpura Diarrhea Acute liver injury Acute kidney injury/hematuria/proteinuria Sepsis and septic shock	Hair loss Alteration of gut microbiome Reduced estimated glomerular filtration rate Newly diagnosed diabetes mellitus Worsening control of existing diabetes mellitus Subacute thyroiditis Bone demineralization

hemodynamic instability have been implicated with end-organ damage, multiorgan failure, and death [64]. Those who survive the acute infection may experience persistent deficits. The manifestations of these so-called long haulers or patients with post-acute sequelae of SARS-Cov-2 are summarized in Table 3.

Stroke and hypoxia have been implicated in the development of cognitive impairment in patients with SARS-CoV-2 infection [65]. In addition, there is mounting evidence supporting the notion that persistent inflammation beyond the acute infection can play an active role in long haulers. In a small cohort of college athletes, 15% of them had CMRI findings consistent with myocarditis. Also, in another small study, it was observed that up to 60% of the patients with diagnosis of COVID-19 can have findings suggestive of myocardial inflammation 2 months after the acute infection. Mechanistically, inflammation has been associated with cardiac fibrosis and scarring leading to re-entrant arrhythmias with the consequent risk of thromboembolism [66••, 67]. Interestingly, in a small cohort of twenty-four patients with COVID-19, IL-6 levels correlated with the severity of the neurologic sequelae and SARS-CoV-2 titers [68]. In addition, in another small study including twenty-nine patients who recovered from COVID-19, cognitive performance, measured by a battery of neuropsychological tests, correlated with post-infection blood inflammatory levels [69]. It should be noted that associations do not prove causation and that most of the studies done in this area suffer from methodological limitations, including small sample size, short follow-up, and presence of confounding factors. However, evidence obtained in animal models demonstrate that an active bidirectional communication exists between inflammatory and neurodegenerative processes. To this end, the hallmarks of Alzheimer's disease, amyloid beta, and phosphorylated tau attract and activate glial cells which release proinflammatory mediators [70]. Conversely, persistent systemic inflammation leads to blood–brain barrier dysfunction which facilitates the infiltration of peripheral immune cells into the brain. The final pathway is characterized by CNS inflammation, which results in oxidative stress and increased accumulation of amyloid beta and phosphorylated tau in the brain parenchyma [70, 71]. These observations support the notion that patients who recover from the acute SARS-CoV-2 infection can experience persistent inflammation which can, directly or indirectly (for example, via myocarditis-associated cardioembolism), lead to cognitive impairment [72, 73].

Recently, concerns were raised regarding myocarditis as a potential complication post-mRNA COVID-19 vaccination [74, 75••, 76]. The incidence and pathophysiology of post-mRNA vaccine myocarditis have not been completely elucidated, but it is thought to be related to hypersensitivity [74]. An individual data meta-analysis of sixty-nine patients from twenty-five qualifying case reports and case series showed

that post-mRNA vaccination myocarditis is predominately seen in young males (median age 21 years) after second dose of vaccine. To date, however, COVID-19 vaccines have not been associated with cognitive impairment.

Takotsubo Cardiomyopathy Takotsubo cardiomyopathy (TTS), also known as stress cardiomyopathy or broken heart syndrome, is a non-ischemic reversible cardiomyopathy leading to transient akinesia/hypokinesia of the myocardium in response to severe stress or emotions. Classically, the pathogenesis of TTS has been associated with an excessive sympathetic stimulation resulting in catecholamine-induced myocardial toxicity which is characterized by a decreased number of contracting units, myofiber and endothelial dysfunction, and multi-vessel epicardial spasm [77, 78]. Thus, TTS is not considered a classic myocarditis. Yet, myocardial macrophage infiltration and systemic cytokine activation have been observed in patients with TTS. Also, these findings were recapitulated in the rodent model of TTS. Thus, it has been suggested that immune-mediated mechanisms could play a role in the pathogenesis and recovery of this condition [79, 80]. TTS has been associated with multiple neurological disorders, including hemorrhagic (subarachnoid or intracerebral) and ischemic stroke, epilepsy, encephalitis, posterior reversible encephalopathy syndrome, and traumatic brain injury [77, 81]. In addition, TTS has been reported as the first presentation of multiple sclerosis [82]. On echocardiography, patients present with left ventricular apical ballooning due to akinesis of hypokinesis with preserved hypercontractile basal segments in the absence of significant coronary artery disease. At the histological level, TTS is characterized by contraction band necrosis. Arrhythmias or acute HF can also complicate TTS, both being conditions that can lead to thrombus formation with the consequent risk of cerebral or systemic embolism.

Myocarditis and Stroke AM can lead to the development of arrhythmias, cardiomyopathy, or sudden cardiac death [83]. Over a mean follow-up period of 3 years, non-ischemic DCM can develop in up to 50% of patients with AM [83]. DCM and HF carry elevated rates of morbidity and mortality from associated arrhythmias and increased risk of thrombosis which can lead to venous and arterial thromboembolism [84, 85]. The rate of stroke in patients with myocarditis-associated HF is not well described. However, in a population-based cohort study, the age- and sex-adjusted risk of ischemic stroke in the first month after the diagnosis of HF due to unselected etiologies increased approximately six times (HR 5.79, 95% CI 2.15–15.62). At 1–6 months after diagnosis, however, the age- and sex-adjusted HR for stroke decreased to 3.50 (95% CI 1.96–6.25) and this became comparable to that seen in the control group after 6 years (HR 0.83, 95% CI 0.53–1.29) [86]. In another large cohort of participants with HF, the stroke rate ratio for intracerebral hemorrhage was elevated to 2.13 (95% CI 1.53–2.97) and 3.52 for subarachnoid hemorrhage (95% CI 1.54–8.08) in the first 30 days post HF diagnosis. However, these estimates decreased over time (time range, 1 month to 30 years follow-up) to 1.4- to 1.8-fold for intracerebral hemorrhage and to 1.1- to 1.7-fold for subarachnoid hemorrhage, compared to the age- and sex-matched control group in the cohort [87••]. The risk of thromboembolism after myocarditis-associated HF has been confirmed in preclinical models. In the mouse model of viral myocarditis, for example, HF increases the risk for cardiac thrombus formation compared to those with viral myocarditis but without HF [88]. Autopsy studies done in patients with ischemic heart disease have also shown a higher incidence of chronic myocarditis leading to fibrosis and adiposis of the myocardium and development of in situ cardiac thrombosis [89].

EMB studies done in individuals with known atrial fibrillation (AF) revealed evidence of myocardial inflammation of the left atrium wall in up to 66% of patients [90, 91]. The pathogenesis of thrombus formation in classic AF has been linked to Virchow's triad. In the heart, this is represented by endocardial denudation and fibroelastic infiltration, flow stagnation in the atrium during fibrillating events or atrioventricular asynchrony, and upregulation of markers of inflammation and platelet activation [92, 93]. It is possible that similar pathogenic mechanisms occur in myocarditis, though the evidence in this case is less robust. AF accounts for ≥ 15% of all strokes in the USA and is associated with increased stroke severity and significant disability, especially for patients ≥ 85 years [94]. From the clinical standpoint, the CHA_2DS_2-VASc score constitutes a risk stratification tool used for the prediction of stroke and thromboembolic events. CHA_2DS_2-VASc stands for congestive heart failure, high blood pressure, age, diabetes, previous stroke, transient ischemic attack or thromboembolism, vascular disease, and female sex [95]. One point is assigned to each condition, except for age greater than 75 years and history of stroke, transient ischemic attack, or thromboembolism which receive 2 points. The use of oral anticoagulation, particularly oral direct thrombin and factor Xa inhibitors, is recommended for reducing stroke/VTE risk in patients with elevated CHA_2DS_2-VASc score (≥ 2 in men and ≥ 3 in women). Warfarin, however, remains the agent of choice for patients with valvular AF and mechanical heart valves [96].

Myocarditis and Cognitive Impairment As previously described, HF and cardiac arrhythmias can be a sequela of myocarditis. Based on observational data, it has been estimated that 4.3% of people aged 65–70 have HF and this is projected to increase to 8.5% through year 2030 [97]. Previous studies have shown that cognitive impairment is particularly prevalent among patients with HF [98, 99]. In a

population-based sample including individuals ≥ 75 years, the 5-year relative risk of developing cognitive decline was increased 1.8 times in individuals with HF (95% CI, 1.02–3.27) relative to those without such history [100]. Also, in another study including adults ≥ 63 years with HF, it was observed that individuals with EF ≤ 30% had significantly impaired verbal delayed recall and recognition compared to age-matched adults with HF and EF ≥ 30% [101]. The association between HF and cognitive decline has been confirmed in multiple cohorts. Different mechanisms may play an active role in this association. Patients with HF have abnormal cardiac output and cerebrovascular reactivity which are determinants of cerebral perfusion [102]. In addition, low cardiac output and cerebral microvascular dysfunction are associated with cognitive impairment and dementia [103]. Interestingly, neuroanatomical areas implicated in cognition, such as the frontal cortex and parahippocampal gyrus, seem to be particularly vulnerable in patients with HF [104, 105]. Thus, it has been proposed that the chronic hypoperfusion of areas involved in cognitive function may explain the cognitive decline observed in patients with HF. MR studies have also shown that patients with HF have an increased prevalence of cortical and subcortical ischemic lesions and a significant burden of white matter hyperintensities, findings consistent with cerebrovascular injury and blood–brain barrier dysfunction. Furthermore, emerging evidence indicates that microvascular dysfunction, hypoperfusion, and blood–brain barrier dysregulation may accelerate the accumulation of cerebral beta-amyloid which is a hallmark of neurodegenerative processes such as Alzheimer's disease [106••].

Patients with myocarditis are also at a higher risk of experiencing AF and other arrhythmias. In a population-based study including 3045 community-dwelling adults ages ≥ 65, AF was associated with all-cause dementia (OR 1.38; 95% CI 1.10–1.73) and possible or probable Alzheimer's disease (OR 1.50, 95% CI 1.16–1.94) after adjustment for confounders [107]. In addition, in a meta-analysis including forty-three studies, AF was associated with dementia (OR 1.6; 95% CI 1.3–2.1) and the composite of cognitive impairment or dementia (OR 1.5; 95% CI 1.4–1.8) and these associations were independent of history of stroke. Interestingly, AF was associated with both vascular and Alzheimer's dementia [108]. Stroke and silent or covert cerebral infarction appear to be the primary drivers of AF-associated cognitive decline [109, 110]. In addition, AF is associated with decrease cardiac output resulting in hypoperfusion, which can be particularly deleterious for the hippocampus and other neuroanatomical areas involved in learning and memory. Therefore, it has been proposed that hypoperfusion could contribute to cognitive impairment through the accumulation of toxic products, ischemic demyelination, and upregulation of inflammatory-mediated neurodegenerative processes.

The epidemiology of cognitive decline in patients with myocarditis-associated HF and AF, in particular, has not been reported. However, based on current knowledge, it is likely that patients with chronic HF and AF have an elevated prevalence of cognitive impairment, independent of whether these cardiac conditions are secondary to myocarditis or other processes.

Treatment of Myocarditis

The treatment of myocarditis has been published elsewhere [14]. In general, myocarditis and the neurologic manifestations associated with it have a variable prognosis which is influenced by the etiology. For the most part, myocarditis is a self-limited condition. Mild cases typically respond well to conservative treatment and have a good prognosis for recovery. Treatment is geared toward the specific pathogen (antibiotics) or immunosuppressive treatment for immune-mediated diseases [12••]. Severe myocarditis with hemodynamic compromise is uncommon. In these cases, inotropic agents, antiarrhythmic support, and temporary use of venoarterial ECMO may be required [111]. It should be mentioned that approximately 11% of the patients on ECMO experience neurological complications. Seizures and ischemic stroke are seen in 4.1% of the cases and intracerebral hemorrhage in 3.6%. Risk factors for neurological complications include end-organ hypoperfusion requiring the use of vasopressors and presence of acute kidney injury, myocardial stunning, infections, or pulmonary failure [112, 113]. Refractory cases of myocarditis may require left ventricular assist device implantation or cardiac transplant [12••].

Conclusions

Myocarditis comprises a group of diseases characterized by cardiac inflammation. Patients with AM may experience different neurological complications, including stroke, encephalopathy, and peripheral neuropathy. Myocarditis patients with residual chronic AF and HF, in addition, may be at higher risk of developing cerebrovascular injury and cognitive decline. Additional studies are necessary to understand the long-term effects of myocarditis on the nervous system and the pathogenic mechanisms that take place in such association.

Declarations

Conflict of Interest Gabriela Trifan and Fernando D. Testai each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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