Review Article

Neurobehavioral Changes Associated with Rheumatic Fever and Rheumatic Heart Disease: A Narrative Review

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Abstract

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are autoimmune conditions triggered by Group A *Streptococcus* skin or throat infections. If ARF/RHD is undetected, misdiagnosed or antibiotic treatment is not provided early, patients may develop cardiac failure, leading to premature death. Although it is an easily preventable disease, ARF/RHD remains the most significant cause of heart disease-associated deaths in people under 25 years old, both in low- and middle-income countries and among First Nations in high-income countries. Up to 30% of the patients with ARF/RHD present with a neurobehavioral condition – Sydenham's chorea (SC). The clinical course of SC is mostly self-limiting and is characterized by the onset of involuntary choreiform movements and neuropsychiatric features such as obsessive-compulsive disorder, tics, depression and anxiety, psychosis, and attention-deficit hyperactivity disorder. While the precise mechanism as to why only a proportion of patients with ARF/RHD develop SC remains unknown, an impaired blood–brain barrier is considered to play a central role in its development. The most well-characterized neurobehavioral outcome is stroke which may occur in isolation or as part of systemic thromboembolism. Both infective endocarditis and mitral valve disease with or without aortic valve disease increase the embolic and ischemic stroke risk. ARF/RHD is known to significantly impact the quality of life with neuropsychiatric consequences. Another neurobehavioral syndrome which occurs in the absence of ARF/RHD is "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS). PANDAS has been categorized as a subset of pediatric acute-onset neuropsychiatric syndromes. However, establishing a diagnosis of PANDAS has been challenging. In this review, we discuss the current status of our understanding regarding the different manifestations of poststreptococcal neurobehavioral changes. Particular attention is given to ARF/RHD-associated SC, and we highlight the areas for further research to understand the association between poststreptococcal sequelae and neurobehavioral abnormalities.

Keywords: Acute rheumatic fever, Group A *Streptococcus*, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), poststreptococcal immune complications, rheumatic heart disease, Sydenham's chorea

Introduction

Globally it is estimated that streptococci cause more than 700 million infections. These infections can vary from superficial to deep tissue infections. A proportion of individuals affected with streptococcal infection could go on to develop poststreptococcal immune-mediated sequelae such as acute poststreptococcal glomerulonephritis (APSGN), acute rheumatic fever (ARF), and rheumatic heart disease (RHD).[1]

The aim of this narrative review is to describe the different neurobehavioral complications that are associated with poststreptococcal immune sequelae and in particular in those with ARF/RHD. Although ARF/RHD predominantly involves the heart and the circulatory system, a significant proportion of patients also have neurobehavioral symptoms as part of the clinical spectrum of this disease process. A comprehensive review of published research was conducted on PubMed

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using keywords by the multidisciplinary panel of co-authors. We extracted information from manuscripts published in English that are indexed in PubMed. The review highlights the current status of knowledge, the possible mechanisms involved in the development of these conditions, and the major gaps in knowledge where further research has to be focused. Furthermore, it also provided information on pathological processes and neurobehavioral changes considered to develop poststreptococcal infections.

ARF is an autoimmune pathology triggered by Group A streptococcal (GAS) throat or skin infection and if not diagnosed and treated in a timely manner leads to RHD followed by cardiac failure and death.[2,3] Those affected are mostly from low- and middle-income countries or socioeconomically disadvantaged populations, including the First Nations Peoples of Australia and New Zealand. ARF/RHD affects around 40 million people globally[4] and annually accounts for approximately 300,000–400,000 deaths.[5] ARF/RHD leads to irreversible cardiac damage culminating in congestive cardiac failure. Early diagnosis followed by appropriate treatment for ARF significantly reduces disease burden. The current diagnosis of ARF/RHD requires expert clinical interpretation of multiple symptoms and laboratory tests including echocardiography which are all part of the Revised Jones Criteria.[6] However, several of these criteria are associated with other conditions and can lead to misdiagnosis. Second, the lack of specific diagnostic laboratory markers for ARF, as opposed to GAS infection, further delays the confirmation of the diagnosis.

In addition, in up to 30% of patients presenting with ARF/RHD present with Sydenham's chorea (SC). SC is a neurobehavioral condition that is mostly self limiting and is characterized by the onset of involuntary choreiform movements and neuropsychiatric impairment. A longer-term neurobehavioral impact can occur in patients with ARF/RHD due to cardiac complications that lead to stroke. ARF/RHD is known to significantly impact on the quality of life (QOL) with neuropsychiatric consequences. Another syndrome considered to involve an autoimmune consequence of GAS infection that occurs in the absence of ARF/RHD is pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS). While cardiac complications associated with ARF/RHD and the pathological processes that lead to heart damage have been relatively well established, the pathological processes in ARF/RHD that lead to neurobehavioral changes characteristic of SC and the long-term neuropsychiatric of ARF/RHD are less well defined. Far less is known about the pathogenesis of PANDAS.

The Role of Group A Streptococci in the Pathogenesis of Acute Rheumatic Fever/Rheumatic Heart Disease

The bacterium, Group A *Streptococcus*, is typically found on the throat or skin and is responsible for a wide range of diseases which vary in clinical symptomatology and severity.[3,7] Although the pathogenesis of ARF/RHD and APSGN are completely different, GAS is the predominant etiologic agent that triggers both the autoimmune sequelae [Table 1]. Within GAS, a small set of "rheumatogenic" serotypes were long thought to be responsible for most cases of ARF/RHD.[8] These serotypes, or "M-types," were originally defined based on differential serological responses between different GAS M-type strains and M-type specific antisera. The differential response arises due to variation in the amino acid sequence of the surface-bound M-protein.[9] This variation also offered a possible mechanism to explain differing disease associations with different M-types, paving the way for studies assessing the role that M-type-specific M-protein-derived epitopes play in the immunopathogenesis of ARF/RHD.[10,11] The M-protein is the major virulence factor of GAS and contributes to pathogenesis by enabling the bacterium to evade or inhibit a range of host immune responses.[7,12,13] However, other virulence factors including cell wall-associated and secreted proteins of GAS may also contribute to the development of ARF/RHD and other poststreptococcal immune complications [Table 1].[14-24] Today differences in the M-protein are determined by nucleic acid sequencing of the corresponding emm gene, of which more than 250 have been identified.[25] This has challenged the concept of "rheumatogenic" emm types. In countries or regions where ARF/RHD currently remains endemic, recovery of the so-called "rheumatogenic" emm types is rare. A systematic review of this conducted by Crombrugghe spanning 70 years also found that 73 different emm types had been linked to ARF.[26] Recent global genomic population studies of GAS are now providing new insights into the molecular epidemiology and evolution of GAS. However, these genomic studies have provided little insight into the genetic factors or variants of GAS that may be important in the pathogenesis of ARF/RHD.

Streptococcus dysgalactiae subspecies *equisimilis* (SDSE; a group G *Streptococcus*) is closely related to GAS and shares many of the same virulence factors of GAS, including the M-protein. Often considered a commensal or opportunistic pathogen, SDSE is associated with a similar spectrum of disease and possesses a similar site of virulence factors, including the M-protein.[27,28] However, a role of SDSE in ARF/RHD is controversial. A possible association between SDSE and ARF/RHD was first posed by Haidan *et al*.[29] Following epidemiological studies in First Nation populations of Northern Australia. While rates of ARF/RHD are among the highest in the world in this population, recovery of GAS from the throat is rare. With advances in animal models of ARF/RHD described further below, experimental evidence for M-protein from SDSE-inducing responses akin to M-proteins of GAS or potentiating the responses initially induced by M-proteins of GAS in the same model are emerging.[30] Finally, evidence for ongoing recombination between SDSE and GAS has been presented by several groups.[31,32] If there are genes, genetic variants, or combination of genes that increase the "rheumatogenicity" of a particular isolate, it is plausible that they could be shared between GAS and SDSE.

Table 1: Group A streptococcal virulence factors implicated in the development of post-streptococcal immune sequelae

GAS virulence factors	Functions	Implication in the development of
Cell wall associated (surface bound) virulence factors		
M protein *Anchored adhesins*	Opsonophagocytosis inhibition, immunomodulation, pyroptotic cell death within macrophage, bacterial colonisation by epithelial adhesion	ARF, RHD, PANDAS
GAPDH/SDH/Plr/NAPlr *Anchorless adhesins*	Plasminogen, actin, myosin, lysozyme, and fibronectin bindings	APSGN
α-Enolase *Anchorless adhesins*	Plasminogen binding	ARF, PANDAS
Secreted virulence factors		
Extracellular DNase	Degradation of NETs to facilitate entrapped bacterial release, bacterial DNA auto-degradation to prevent recognition by host immune system	ARF, APSGN
Streptokinase	Plasminogen activation leading to fibrinolysis and bacterial dissemination, streptokinase-plasminogen complex formation and degradation of histone proteins	APSGN
Neuraminidase	Bacterial colonisation	APSGN
Cysteine protease (i.e., SpeB/zSpeB)	Host epithelial-barrier cleavage leading to bacterial invasion, inactivation of antimicrobial peptide, complement, and cytokine, plasminogen activation, T cell proliferation	APSGN
Superantigens, i.e., Spes (prophage-encoded: SpeA, SpeC, SpeH, SpeI, SpeK–M and SSA; chromosome-encoded: SpeG, SpeJ, SpeQ, SpeR and SmeZ)	T cell stimulation and proliferation leading to cytokine release	ARF, RHD
SIC	Inhibition of MAC of complement, inactivation of antimicrobial peptides	APSGN

ARF=Acute Rheumatic Fever; RHD=Rheumatic Heart Disease; PANDAS=Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; APSGN=Acute Post-streptococcal Glomerulonephritis; DNA=Deoxyribonucleic acid; DNase=Deoxyribonuclease; GAPDH=Glyceraldehyde-3-phosphate dehydrogenase; MAC=Membrane attack complex; NAPlr=Nephritis associated plasmin receptor; NETs=Neutrophil extracellular traps; Plr=Plasmin receptor; SDH=Streptococcal dehydrogenase; SIC=Streptococcal inhibitor of complement; SpeB=Streptococcal pyrogenic exotoxin B; Spes=Streptococcal pyrogenic exotoxins; zSpeB=Zymogen precursor of streptococcal pyrogenic exotoxin B

The poststreptococcal autoimmune responses that lead to ARF/RHD are multifactorial. It is known that antibodies and T-cells generated against GAS M-protein and N-acetyl-beta-D-glucosamine cross-react with host tissue proteins, a hallmark of ARF/RHD immunopathogenesis.[33,34] It has been demonstrated that monoclonal antibodies against these GAS antigens, derived from patients with ARF, cross-react *in vitro* with human cardiac myosin and valvular endothelium.[33] Antibodies and T-cells against recombinant GAS M5 have been shown in *ex vivo* experiments in animal models to facilitate the transmigration of activated T-cells across the endothelium of the heart valves.[35] These observations have added further evidence that cross-reactive antibodies generated against streptococcal proteins that bind to tissue proteins are a major mechanism involved in the immunoinflammatory process observed in ARF/RHD leading to carditis. There is also evidence that structural similarities between tissue proteins, such as laminin and vimentin, could be the basis of antibody-mediated damage to valve structures. T-cell clones derived from valvular lesions from patients react with myosin and valve-derived proteins,[36] and Th1/Th17 inflammatory response may also facilitate epitope spreading within the valvular tissue. This will further expose other tissue antigens such as vimentin and collagen, perpetuating and amplifying the inflammatory process.[34] There is also evidence that some streptococcal M-protein N-terminus domains bind the CB3 region of collagen type IV and initiate an autoantibody response to collagen establishing an inflammatory process leading to the spectrum of disease presentation observed in ARF/RHD.[37] However, these autoantibodies do not cross-react with streptococcal M-proteins.[38,39] Once the inflammatory changes are initiated in the valvular tissue, the hemodynamic stress associated with transvalvular pressure gradient across different valves perpetuates the disease process[40] that could explain the disparate pathology observed in the different valves.

Antibodies against GAS N-acetyl-beta-D-glucosamine are known to cross-react with neuronal cells in the basal ganglia, leading to the deposition of immune complexes causing excessive release of dopamine that forms the basis of the symptomatology observed in SC, a neurobehavioral abnormality that is observed in patients with ARF/RHD.[41,42] However, compared to the pathogenesis of carditis, there is a paucity of experimental data on the neurobehavioral changes, arthritis, erythema marginatum, and the development of subcutaneous nodules that are characteristic of ARF/RHD.

Clinical Presentations, Diagnosis, Treatment, and Prevention of Acute Rheumatic Fever/ Rheumatic Heart Disease

ARF manifests most often in children over 5 years of age and young adults where there is a pathological immunological reaction to Group A streptococcal infection.[2] Children with ARF develop a range of clinical features which occur a few weeks to months (in the case of SC) following an acute GAS infection. These clinical features include arthritis and arthralgia, chorea, carditis, skin lesions (erythema marginatum), and subcutaneous nodules. Associated features include fever and elevation in inflammatory blood markers.[43]

With no single diagnostic test, diagnosis rests upon a constellation of clinical and laboratory features called the Revised Jones Criteria which include clinical features described above along with measures of inflammation plus laboratory evidence of recent Group A streptococcal infection.[44] There have been a number of revisions to these criteria aiming to improve the sensitivity and specificity of the test. The current modification of the Jones Criteria includes different criteria for individuals from high-risk populations which are defined as populations where ARF is endemic with rates of ARF >30/100,000 per year in 5–15-year-olds. This stratification of risk adjusts the criteria based on prior probability of test positivity before assessment against the Jones Criteria. The revision also includes subclinical carditis as a major criterion defined on echocardiographic valvular changes and can lead to a definite diagnosis or probable or possible ARF.[45]

Accurate diagnosis is important because it allows the institution of secondary prevention but is challenging because of the complex criteria and testing required. An ARF calculator has been developed to assist clinicians in this assessment.[46] RHD is diagnosed by echocardiography and classified based on severity. Established RHD can be diagnosed when a cardiac murmur is discovered on routine examination or echocardiographic screening where the primary diagnosis of ARF has been missed.

Treatment of ARF includes nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis, antiepileptic drugs including valproate and carbamazepine, neuroleptics such as risperidone and possibly steroids for chorea if severe and bed rest, treatment of heart failure, and steroids for acute carditis. Severe RHD is managed with valve repair or if not possible valve replacement.

The most important interventions to reduce the morbidity and mortality associated with ARF/ RHD are to implement prevention strategies.[47] Primordial prevention targets activities to reduce risk factors and social determinants and include improving social-economic conditions and improving living conditions including housing and hygiene-related infrastructure. Primary prevention is aimed at early treatment of GAS infections of the throat and skin.[47] Secondary prevention is regular administration of antibiotics to prevent a recurrent episode of ARF and is recommended after a primary diagnosis of ARF. A recurrent episode of ARF poses a significant risk of RHD in an individual who did not develop RHD after the initial episode, and has a high risk of progression of mild heart disease to moderate or severe heart disease.[48]

The key functions of ARF/RHD programs are to promote primordial and primary prevention, to support early and accurate diagnosis, and to deliver secondary prophylaxis and to provide health care to children with a diagnosis or ARF/RHD. Secondary prophylaxis is best delivered with regular (usually every 28 days) delivery of intramuscular long-acting penicillin. The injections are painful for the child and delivery requires high degrees of organization from health services. It is difficult for health services to achieve high rates of delivery of secondary prophylaxis and poor compliance is often a function not of the individual but of the health service to support families, recall patients, and deliver injections.[49] The natural history for a child with ARF who is repeatedly exposed to GAS infections would be recurrent episodes of ARF and progression of heart involvement with each recurrence. The aim of RHD control programs is to prevent this progression of heart disease by reducing GAS infections and preventing recurrent episodes of ARF.

Although preventing GAS infection with vaccines is a rational approach, a safe and globally effective vaccine has been fraught with challenges.[50] Antistreptococcal vaccines have to not only overcome the vast genetic diversity and regional differences observed in GAS strains but more importantly the potential autoimmune consequences of using epitopes that may inadvertently cause complications which can lead to heart damage. Testing vaccine efficacy for an exclusively human infection in animal models is also problematic. Recent vaccine candidates currently on early trials have overcome these challenges and have reached early Phase 1 trials.[7]

Clinical Spectrum of Sydenham's Chorea

SC is the most common form of acquired chorea in pediatric populations,[51] with a preponderance in females.[52] Its highest incidence is in children aged 8–9 years.[53] The clinical course of SC has traditionally been noted to be self-limiting (lasting a number of weeks); however, symptoms have been known to persist and recur over the course of multiple years.[54] The condition is characterized by the onset of involuntary choreiform movements and can also be associated with other neuropsychiatric features such as obsessive-compulsive disorder (OCD), tics, depression and anxiety, psychosis, and attention-deficit hyperactivity disorder.[55] It has also been postulated that SC may give rise to lasting cognitive deficits[56,57] and issues with executive functioning.[58] It is pertinent to note that these clinical features of SC confer a high degree of functional impairment and disability upon affected individuals.[55]

According to a 2016 systematic review conducted by Punukollu *et al*., OCD symptoms have been observed at various stages of SC.[55] These symptoms have included obsessions with violence and contamination and compulsive checking and cleaning.[59] Mood disturbances and anxiety symptoms observed in SC have included depression, hypomania, and social phobia.[55] In small-scale studies, acute psychosis – characterized by auditory hallucinations and other schizophreniform symptoms – has been noted to have a temporal relationship with SC.[55] Furthermore, individuals with SC have demonstrated impaired performance in a variety of cognitive domains.[55] It has also been suggested that those who present with a history of SC are more likely to have poorer social and occupational outcomes as counterparts without a history of SC.[58,60]

Given the heterogeneity of potential SC symptoms, the clinical management of the condition is varied and falls into three main categories: (1) management of chorea and psychiatric symptoms, (2) immunomodulatory therapies, and (3) antibiotic therapy for acute GAS infection and secondary prophylaxis.[54] In terms of the symptomatic management of neuropsychiatric symptoms of SC, neuroleptics (such as haloperidol, risperidone, and olanzapine), anti-epileptics (such as valproic acid, carbamazepine, and levetiracetam), and steroids have been employed as "off-label" agents to dampen down what is thought to be autoimmune-mediated overactivity of the basal ganglia. There is limited randomized controlled trial-level evidence to support such interventions.[54] Antichoreic agents such as tetrabenazine, which are employed in Huntington's disease and exert anti-dopaminergic effects, have also been proposed as treatments for SC.[61] It is pertinent to note that nonpharmacological psychiatric treatments, such as cognitive behavioral therapy, have also been thought to have efficacy in treating some of the clinical manifestations of SC including OCD.[54] Furthermore, it is noteworthy that neuroimaging has little utility in informing the management of SC, given that magnetic resonance imaging (MRI) findings tend to be nonspecific, with hyperintensities on T2-weighted images seen in multiple regions including white matter, brain stem, and caudate nucleus.[62] Studies suggest that neuroimaging in SC is of questionable benefit.[63]

Mechanisms of Neurobehavioral Changes in Sydenham's Chorea

While there are several hypotheses, the pathogenesis for SC remains unknown and raises important questions as to why only a certain percentage of people who have ARF go on to develop SC. The pathogenesis of SC involves a complex interaction between the immune system and the brain, which leads to the characteristic symptoms of SC.[64,65] The prevailing hypothesis is that antibodies triggered by GAS antigens cross-react with neuronal proteins in the basal ganglia.[64,66-71] A specific epitope of streptococcal M-protein that cross-reacts with the basal ganglia[53] ultimately leads to motor, behavioral, and cognitive symptoms[65,72-75] demonstrated that serum from SC patients had immunoglobulin G antibodies that interacted with epitopes within the basal ganglia.[41] These antibodies from SC patients reacted with neuronal ganglioside, lysoganglioside, and N-acetyl-beta-D-glucosamine. Further studies demonstrated the cross-reactivity of antibodies from SC patients to other basal ganglia epitopes, including β-tubulin and dopamine receptors 1 (DR1) and 2 (DR2).[72,76,77]

Although antibodies against streptococcal antigens that cross-react with brain proteins are considered the cause of SC, the precise mechanism of how these antibodies enter the central nervous system (CNS) is unknown. A compromised blood–brain barrier (BBB) is a possible link. During systemic inflammation and infection such as ARF, many circulating soluble inflammatory mediators could influence BBB permeability.[78] Inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β can affect the integrity of the BBB by either degrading tight junction proteins, modifying their phosphorylation states, or affecting the turnover rate.[67] Following GAS infections, cytokines released after phagocytosis by activated microglia are also present in the CNS, which may also contribute to BBB breakdown.[67,79]

Recent studies in our laboratory (unpublished observation) using adoptive transfer of hyperimmune serum from GAS M5-injected rats confirmed the importance of a compromised BBB in the development of neurobehavioral changes associated with ARF. Adoptive transfer of antibodies against GAS rM5 to naïve rats resulted in cardiac abnormalities without neurobehavioral signs which only developed in rats with co-administered lipopolysaccharide (a known disruptor of the BBB). Hence, a compromised BBB [Figure 1] could be a key factor in allowing the access of cross-reactive antibodies into CNS, leading to the manifestations seen in SC.[80] Antibodies against GAS cross-react with dopamine receptor I, II and neural proteins tubulin and lysoganglioside in the basal ganglia.[41,42,72,77,81,82] These antibodies activate CaMKII and also bind to lysoganglioside or DR1 and DR2 on neuronal surface possibly leading to alterations in dopamine transmission (Developed by RAM Rafeek using BioRender.com) [Figure 1]. Research should therefore focus on understanding factors that have the potential to compromise the BBB in patients with ARF who go on to develop SC.

Possible Long-term Neurobehavioral Consequences of Acute Rheumatic Fever/ Rheumatic Heart Disease

The long-term neurobehavioral impacts of RHD are only beginning to emerge. The most well-characterized neurobehavioral outcome is stroke which may occur in isolation or as part of systemic thromboembolism. Both infective endocarditis and mitral valve disease with or without aortic valve disease increase the embolic and ischemic stroke risk.[83] Artificial valves are also a risk for stroke (embolic stroke due to thrombosis or infection). In addition, hemorrhagic stroke can be a complication of anticoagulation which is required following

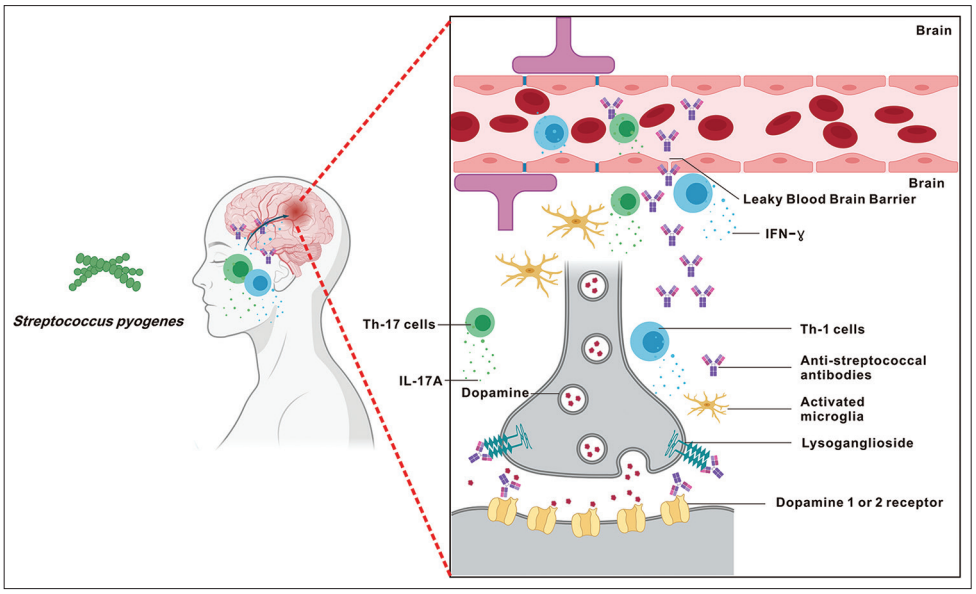

Figure 1: Proposed mechanisms involved in the pathogenesis of GAS induced neurobehavioral changes. GAS=Group A streptococcal

insertion of artificial valves. A global registry of 3,343 patients obtained from low- and middle-income countries reported that the prior stroke prevalence in RHD patients was between 3.8% and 14.5%.[84] The incidence of stroke over 2 years in RHD patients was between 1.0% and 2.4% that translated to a stroke incidence of 8.45 per 1,000 patient-years.[84] A data linkage study in the Northern Territory of Australia reported stroke outcomes to 10 years and observed 4% of patients experiencing a stroke which translated to a relatively low stroke rate of 0.58 per 100 person-years.[85] However, these incident stroke rates must be interpreted in the context of the all-cause mortality rate, which has been estimated between 28 and 52 per 100,000 persons among First Nations peoples older than 25 living in the Northern Territory of Australia.[86]

Other possible explanations for the uncertainty pertaining to the long-term neurobehavioral impacts of ARF/RHD is the presentation of ARF/RHD in youth, remote, and marginalized people making long-term neurological follow-up difficult to achieve.[85] Another possible explanation for the limited knowledge of long-term brain health is that empirical investigations combine ARF alongside other complications, resulting in sparse information specific to ARF/RHD. Indeed, SC is the ARF symptom most likely to recur.[45] Observed changes to children's executive function corroborate changes to prefrontal-striatal brain circuitry beyond the acute phase of ARF,[87] verified by our recent work in novel rat models of ARF/RHD.[88] Frontostriatal circuitry is susceptible to neuronal damage in other heart–brain axis pathologies,[89] raising the possibility that cardiac mechanisms in ARF/RHD accelerate the degeneration of vascular brain tissue already degraded by an initial autoimmune phase. This premise is supported by very recent evidence suggesting that ARF/RHD portends a two-fold higher risk mainly for vascular dementia, with evidence inconsistent for Alzheimer's disease and all-cause dementias.[90] Immunological biomarkers partly mediated the association between ARF/RHD and vascular dementia,[87] suggesting that a long-term immune response still plays a role in long-term neurobehavioral sequelae of ARF/RHD. Studies of long-term brain health are otherwise sparse, and there is a paucity of brain imaging data in ARF/RHD. Brain imaging with dynamic contrast-enhanced computed tomography and MRI would help identify BBB permeability in the acute phase and MRI to quantify cerebral small vessel disease in the long term. Nonetheless, parallel lines of evidence provide possible human models of ARF/RHD-brain health, derived from associations between comorbidities experienced in ARF/RHD such as heart failure and atrial fibrillation and dementia risk[91] as well as the cognitive impairments observed after traditional and transcatheter valve repair and replacement procedures.[92,93]

The impact of ARF/RHD on QOL is also pronounced in comparison to their age- and sex-matched counterparts.[94] Among the youth who receive positive echo screen for ARF/RHD, physical and mental QOL is diminished compared to prescreening levels.[95] The impact of RHD on QOL outcomes from surgical intervention is conflicting. Evidence from Namibia suggests that quality-adjusted life years improve with surgical intervention.[96] Conversely, a Ugandan study showed that only 60% of RHD patients receiving a valve replacement (mechanical and bioprosthetic) had optimal cardiac-specific QOL.[97] Fears relating to bleeding risk with warfarin, social concerns relating to having a valve replacement, and injection pain were identified as persisting factors that impinged on QOL.[97]

Other Neurobehavioral Pathology Associated with Streptococcal Infections

There are two clinically distinct groups of syndromes

that comprise the widely recognized neurological and neuropsychiatric sequelae of GAS infections.[55,98] The first of which, already described in this paper, is SC.[99] The second group, occurring in the absence of ARF and significant chorea at onset,[55] is termed "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS).[100] PANDAS has been categorized as a subset of pediatric acute-onset neuropsychiatric syndromes.[101] While SC is a well-characterized clinical entity,[54] PANDAS has been the subject of deliberation since its description in 1998 by Swedo *et al*.[102,103] PANDAS is defined by five clinical criteria: the presence of OCD or tic disorder, symptom onset prior to puberty, an acute onset and episodic course, temporal association with GAS infection, and association with neurological abnormalities.[101] Akin to SC, there is heterogeneity in the spectrum of clinical manifestations of PANDAS. Apart from OCD and tics, clinical characteristics may include separation anxiety, aggressive or hyperactive behavior, perceptual abnormalities, dysgraphia, issues with sleep, urinary symptoms, and issues with food intake akin to anorexia nervosa and avoidant/restrictive food intake disorder.[104,105]

Since its inception, PANDAS has been subject to a degree of speculation given the challenges in clinically establishing a temporal relationship between streptococcal infection and the onset of neuropsychiatric symptoms.[106] Such difficulties include the lack of clinical utility of a negative throat swab, whereby a swab containing a few colonies of the bacterium may not be detected as positive for GAS infection.[107] Further to this, there are challenges in demonstrating temporality using serological tests due to the persistence of elevated anti-GAS titers long after the emergence and cessation of neuropsychiatric symptoms.[107] There is also a lack of consensus on the measured level of antibodies required to distinguish individuals with infection.[107] Moreover, in a significant proportion of infections, antibody titers may become elevated to a level that remains lower than that of the threshold considered to be the upper limit of normal, making it difficult to identify true cases.[107] Adding to diagnostic challenges, neuroimaging in PANDAS tends to be normal; however, in some cases, there may be basal ganglia enlargement and T2 hyperintensities seen on MRI.[108]

Diagnostic challenges aside, the treatment of PANDAS can be categorized into three domains (as is the case with SC): (1) psychiatric and behavioral interventions,[109] (2) immunomodulatory therapies,[110] and (3) the treatment and prevention of GAS infection.[111,112] Three consensus papers authored by a consortium of clinicians and experts provide guidelines for treatment modalities falling into the aforementioned three domains.[109,110,112] Despite the presence of consensus guidelines, there is a paucity of high-level evidence demonstrating the efficacy of a number of these clinical approaches.[111] There is, however, a significant body of anecdotal evidence arising from case reports and series suggesting that intravenous immunoglobulin, therapeutic plasma exchange, antibiotics, NSAIDs, and corticosteroids may be effective in ameliorating symptoms of PANDAS or reducing flare duration.[111]

Clinical aspects considered, the PANDAS concept still gives rise to a degree of conjecture over two decades since it was first described. There remains room for refinement of diagnostic techniques, and, furthermore, current management strategies need to be subjected to more rigorous clinical trials. Importantly, the elucidation of the molecular mechanisms that underpin PANDAS would allow for better characterization of this entity and would lay the foundation for more targeted and effective diagnostic and management strategies.

Animal Models of Rheumatic Heart Disease and Associated Neurobehavioral Changes

Animal models are useful tools for understanding the pathogenesis of ARF/RHD and associated neurobehavioral complications. Since humans are the only hosts of GAS that develop poststreptococcal complications leading to ARF/RHD, finding a suitable animal model is problematic. In the past decades, many attempts were made to develop an animal model of ARF/RHD and neurobehavioral disorders associated with streptococcal infections. Numerous animals including cattle, goats, sheep, pigs, dogs, cats, rabbits, guinea pigs, rodents, and nonhuman primates have been used to investigate the pathophysiological mechanisms of ARF/RHD following injection streptococcal antigens.[113-117] However, none of the animals demonstrated the characteristic pathology of ARF/RHD. The Rat Autoimmune Valvulitis (RAV) Model developed by Quinn *et al.* is a promising laboratory model to investigate the pathogenesis of ARF/RHD.[118] Initially, this model was used to study the pathological mechanism of streptococcal-induced cardiac damage.[30,35,119-124] Following exposure to streptococcal antigens, characteristic functional, histological, and immunological changes were observed in RAV model. Furthermore, numerous experiments have also been conducted to develop an animal model of streptococcal-related neuropsychiatric disorders. Initial experiments were carried out by infusion of serum from patients with suspected streptococcal-related neuropsychiatric disorders directly into the striatum of rats. Although many rat studies succeeded in modeling these stereotypic behavioral changes,[125,126] other studies failed to do so.[127,128] Some studies have also attempted to model immunological, histological, and behavioral abnormalities in mice and rats following the injection of streptococcal proteins and serum from rats injected with streptococci.[76,129-132]

We recently extended our work on the RAV model to determine both cardiac and neurobehavioral changes associated with streptococcal infection.[88,98,133,134] Following injection of rats with streptococcal antigens, rats developed impairment in fine motor control, gait and balance, and obsessive-compulsive symptoms. Furthermore, serum from these rats showed elevated levels of cross-reactive antibodies against neuronal targets including dopamine receptors I and II, tubulin, and lysoganglioside$_{GM1}$.[88] Currently, this is the only animal model

fully characterized to investigate the early events which lead to cardiac and neurobehavioral changes associated with streptococcal infection. We find this model to be a valuable platform to assess vaccine safety, to develop rapid screening tests by identifying biomarkers, and to assess adjunct therapeutic agents.

Conclusion

Group A streptococcal infection is implicated in the pathogenesis of RF/RHD including SC. The diagnosis relies upon clinical and laboratory assessment. However, unlike SC in AFR/RHD, diagnosis of PANDAS is more problematic given the challenges in clinically establishing a relationship between streptococcal infection and the onset of neuropsychiatric symptoms. While neurobehavioral complications associated with SC and PANDAS have a wide clinical spectrum, the precise mechanisms leading to these conditions remain largely unclear. Prevention of both RF/RHD and PANDAS relies upon early recognition and management of psychiatric symptoms, preventive antibiotic regimens, and immunomodulatory therapy. The development of safe and efficacious vaccines against streptococcal infections has the possibility to significantly reduce the incidence of these complications. Moreover, the characterization of animal models that reflect the early events that lead to the disease pathogenesis may also provide insights into better treatment and screening procedures. Until a suitable and safe vaccine is available, early recognition remains the mainstay of management of these conditions.

Author contributions

Natkunam Ketheesan conceptualised the review and drafted the introduction. Individual sections were researched and drafted by the different co-authors. The section on the role of group A streptococci in the pathogenesis of ARF/RHD was drafted by David McMillan while Table 1 was collated by Mohammad Raguib Munif. The section on the clinical presentations, diagnosis, treatment and prevention of ARF/RHD was drafted by both Andrew White and Robert Norton. The sections on the clinical spectrum of Sydenham's Chorea and other neurobehavioral pathology associated with streptococcal infections was drafted by Sarangan Ketheesan. Adam Hamlin and Riya Thapa drafted the section on the mechanisms of neurobehavioral changes in Sydenham's Chorea. Phillip Tully compiled the section on the possible long-term neurobehavioral consequences of ARF/RHD. While Rukshan Ahamed Mohamed Rafeek designed the figure and drafted the section on animal models of rheumatic heart disease and associated neurobehavioral changes. All authors edited the manuscript and approved the final version to be published.

Ethical statement

Ethical statement is not applicable for this article.

Data availability statement

All data generated or analyzed during this study are included in this published article

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Conflicts of interest

Dr. Phillip Tully is an editorial board member of *Heart and Mind*. The article was subject to the journal's standard procedures, with peer review handled independently of Dr. Phillip Tully and the research groups. There are no conflicts of interest.

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