Autoimmune Basal Ganglia Disorders

Russell C. Dale, PhD and Fabienne Brilot, PhD

Abstract
The basal ganglia are deep nuclei in the brain that include the caudate, putamen, globus pallidus, and substantia nigra. Pathological processes involving the basal ganglia often result in disorders of movement and behavior. A number of different autoimmune disorders predominantly involve the basal ganglia and can result in movement and psychiatric disorders. The classic basal ganglia autoimmune disorder is Sydenham chorea, a poststreptococcal neuropsychiatric disorder. Resurgence in the interest in Sydenham chorea is the result of the descriptions of other poststreptococcal neuropsychiatric disorders including tics and obsessive-compulsive disorder, broadly termed pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Encephalitic processes affecting the basal ganglia are also described including the syndromes basal ganglia encephalitis, encephalitis lethargica, and bilateral striatal necrosis. Last, systemic autoimmune disorders such as systemic lupus erythematosus and antiphospholipid syndrome can result in chorea or parkinsonism. Using paradigms learned from other autoantibody associated disorders, the authors discuss the autoantibody hypothesis and the role of systemic inflammation in autoimmune basal ganglia disorders. Identification of these entities is important as the clinician has an increasing therapeutic repertoire to modulate or suppress the aberrant immune system.

Keywords
autoantibody, sydenham chorea, dystonia-parkinsonism, tics, dopamine, basal ganglia, poststreptococcal

Received May 16, 2012. Received revised May 18, 2012. Accepted for publication May 18, 2012.

Basal Ganglia Neuroanatomy and Neurocircuitry
The basal ganglia are a group of nuclei in the deep gray matter of the brain that include the striatum (caudate and putamen), the globus pallidus, the subthalamus, and the substantia nigra. Understanding of the basal ganglia was partially derived from the study of lesions or disorders that affect the basal ganglia such as tumors, stroke, and neurodegeneration. These studies demonstrated that pathological processes affecting the basal ganglia often result in hypokinetic or hyperkinetic movement disorders. In addition, there is a high rate of comorbid psychiatric and behavioral disorders in basal ganglia disorders, including attention deficit disorder and obsessive-compulsive disorder.

Rather than the basal ganglia nuclei acting in isolation, it is clear that the basal ganglia should be more accurately considered part of a circuit involving the cortex and thalamus, known as cortico-striato-thalamic circuits or “loops.” The basal ganglia are involved in inhibition of competing motor messages from the cerebral cortex and cerebellum. Failure of this inhibition can be associated with altered movement and behavior.

Basal Ganglia Neuropharmacology and Neurochemistry
Further understanding of the basal ganglia has come from the study of the dominant neurons in the nuclei. Dopaminergic neurons dominate in the substantia nigra, and gamma-aminobutyric acid and acetylcholine are common neurotransmitters in the medium spiny neurons and interneurones of the striatum. Relative predilection of medium spiny neurons to hypoxic or metabolic stress has been proposed as one explanation of why the basal ganglia is vulnerable in hypoxic injury and conditions such as organic acidurias and mitochondrial disease. Likewise, cholinergic interneurones appear to be relatively resistant to hypoxic and metabolic stress and may explain therapeutic benefit of anticholinergics in some patients with dystonia. However, most investigation of the basal ganglia neurochemistry has surrounded the role of dopamine. Indeed dopamine replacement remains the best treatment of Parkinson disease and dopa-responsive dystonia, and dopamine receptor blockade is still the most effective treatment of many patients with tics and chorea.

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What Is an Autoimmune Basal Ganglia Disorder?

Based on the preceding introduction, the definition of “autoimmune basal ganglia” disorder therefore includes clinical syndromes that are autoimmune or immune mediated that predominantly or solely affect the basal ganglia and typically present with movement and neuropsychiatric disease. Although movement disorders are a typical and common phenomenon in N-methyl-D-aspartate (NMDA) receptor encephalitis, the encephalitis appears to be part of a cortical and subcortical process (in stages) and there is a dedicated review on this topic in this edition. Likewise, the movement disorder of opsoclonus myoclonus ataxia syndrome does not appear to dominantly affect the basal ganglia (although may partially) and is not therefore discussed here.

Instead we focus on diseases in which the clinical, radiological, and pharmacological evidence generally points to dominant basal ganglia involvement and are now reviewed in detail and in Table 1.

Autoimmune Initiation and Autoaggressive Disease

Autoimmunity is a normal physiological process. Autoantibodies against self-antigens are present in normal individuals under resting circumstances, and there are multiple “checkpoints” involved in “immune tolerance” that prevent the expansion of self-reactive lymphocytes. Loss of this tolerance is complex, and when the autoimmune process is detrimental and results in disease, this is called “autoaggressive” disease. The loss of this tolerance may be spontaneous, or may be triggered by an infectious illness or a tumor (paraneoplastic). Most autoimmune diseases are complex and multifactorial with likely genetic and environmental factors. As most of the environmental “triggers” are present outside of the central nervous system, such as streptococcal infection in the pharynx or tumors in the abdomen, the initiating autoimmune process is considered to start outside of the brain.

How immune cells and proteins enter the central nervous system and cross the blood brain barrier is an important and poorly understood issue in neuroimmunology and neuroscience, and could include the following processes:

- Although resting lymphocytes cannot cross the blood brain barrier, activated lymphocytes can cross the intact blood brain barrier. Therefore, activated lymphocytes that target self-antigens can cross the blood brain barrier and expand in the cerebrospinal fluid or brain parenchyma if the self-antigen is encountered.
- Proteins such as antibody have very low access into the brain and cerebrospinal fluid. Indeed, in normal individuals, the cerebrospinal fluid total Immunoglobulin G is 1/500 that of serum total Immunoglobulin G. However, if the blood brain barrier is breached or compromised, as occurs in systemic inflammation, then antibody access to the brain parenchyma and cerebrospinal fluid can increase substantially.
- Finally, it is increasingly evident that the blood brain barrier, rather than being a passive “barrier,” is in fact dynamic and involved in active transfer of molecules and proteins across the endothelium into the brain parenchyma. The brain endothelium has a large number of transporters and receptors on the endothelium lumen. These transporters and receptors are increasingly used to improve drug delivery across the blood brain barrier.

Sydenham Chorea

History

First described by Thomas Sydenham in the 17th century, Sydenham chorea remains one of the most enigmatic of all

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**Table 1. Summary of Autoimmune Movement Disorder Syndromes, Evidence for Autoantibody-Mediated Disorder, and Benefit From Immune Therapy**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Movement disorder</th>
<th>Other features</th>
<th>Evidence of an autoantibody-mediated process</th>
<th>Benefit of immune therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sydenham chorea</td>
<td>Chorea</td>
<td>OCD, ADD, depression, carditis</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>PANDAS</td>
<td>Tics</td>
<td>OCD, ADD</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>NMDAR encephalitis</td>
<td>Stereotypy, orofacial dyskinesia, chorea, dystonia, rigidity</td>
<td>Psychosis, agitation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Basal ganglia encephalitis</td>
<td>Dystonia, parkinsonism, chorea</td>
<td>Emotional lability, ADD, psychosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lupus and antiphospholipid syndrome</td>
<td>Chorea, parkinsonism</td>
<td>Migraine, Emotional lability, thromboses, carditis</td>
<td>+/−</td>
<td>+/−</td>
</tr>
</tbody>
</table>

Abbreviations: ADD, attention deficit disorder; OCD, obsessive-compulsive disorder; PANDAS, pediatric autoimmune neuropsychiatric disorders associated; NMDA, N-methyl-D-aspartate.

Level of evidence for autoantibody: ++, clear evidence of a specific antibody with pathogenic properties; +, accumulating evidence of a specific antibody, but no definitive pathogenic proof; +/−, inconsistent evidence of a specific antibody. Level of evidence for benefit of immune therapy: ++, general agreement that immune therapy is beneficial and improves outcome, but no controlled trials; + some evidence of benefit of immune therapy, but limited to case studies and small series.

Dale and Brilot
acquired neurological syndromes and is the prototypic autoimmune movement disorder. In early descriptions, Sydenham chorea was often confused with hysteria, indeed the term St Vitus dance was originally used to describe epidemics of hysteria. Indeed, even now, the diagnosis can be delayed, and initial adventitious movements, grimacing, and clumsiness with altered behavior can be mistaken for difficult behavior or psychogenic disease. However, it became clear that Sydenham chorea was a component of rheumatic fever, and therefore a poststreptococcal autoimmune central nervous system phenomenon.

**Clinical Syndrome**

Sydenham chorea can occur as part of rheumatic fever, or in isolation. Rheumatic carditis is found in a proportion of Sydenham chorea sufferers, although the carditis incidence varies according to season and geographical region. The neurological phenomenon is highly characteristic when fully formed, and the movement disorder is pure chorea. The movement disorder is typically bilateral but may be unilateral in a minority of patients (hemichorea). Characteristic signs other than chorea include reduced tone and motor impersistence, and the milkmaid sign and the trombone tongue are frequently found. Rarely, the syndrome can be so severe that there is profound hypotonia and apparent “paralysis” termed “chorea paralytica.” Dysarthria is common with slurred speech, and detailed analysis of eye movements can demonstrate altered saccades. The majority of patients will have associated behavioral change. Although Sydenham chorea has become known as a theoretical model of obsessive-compulsive disorder, the more typical acute behavioral changes are of emotional lability, distractibility, and anger. Detailed neuropsychiatric phenotyping has demonstrated that attention deficit disorder, obsessive compulsive behavior, and depression are overexpressed in children with Sydenham chorea compared to those with rheumatic fever and controls. Sydenham chorea is frequently termed a “neuropsychiatric disorder,” as is true for many “basal ganglia disorders.” In contrast to NMDA-receptor encephalitis, there is very rarely memory loss, aphasia, seizures, and the EEG is normal. Sydenham chorea is therefore a predominant subcortical disease rather than cortical or diffuse process.

**Pathophysiology**

Sydenham chorea is more common in Aboriginal populations of Australia, and indigenous populations of South America, Asia and Africa. Although it is true that low socio-economic class and overcrowding is a risk factor it is also possible that there is a genetic predisposition that has yet to be determined. A family history of Sydenham chorea is described in ~14% of Sydenham chorea patients, and a family history of rheumatic fever is described in 26% to 36% of Sydenham chorea patients. Many autoimmune disorders demonstrate associations with certain human leukocyte antigen genotypes, and although small human leukocyte antigen studies in Sydenham chorea were not revealing, recent studies suggest that human leukocyte antigen markers may be involved in Sydenham chorea vulnerability.

**Investigation and Neuroimaging**

Given the fact Sydenham chorea is often seen in rheumatic fever, streptococcal serology or throat swab is often done to demonstrate evidence of group A or other rheumatic streptococci. Although Sydenham chorea can occur many months after streptococcal infection, negative streptococcal investigation should prompt consideration of alternative diagnoses such as systemic lupus erythematosus, antiphospholipid syndrome, or vasculopathy (particularly if unilateral). Heart examination and echocardiogram is mandatory and may demonstrate asymptomatic carditis.

MRI brain is frequently performed to exclude important differentials but should be normal in Sydenham chorea. There are occasional reports of inflammatory changes in the basal ganglia, but this would be atypical and would be more suggestive of basal ganglia encephalitis or other inflammatory disorders, discussed below. Volumetric study of the basal ganglia shows enlargement of the basal ganglia, although the enlargement is subtle and not clinically useful in individual patients. Single photon emission computed tomography scans, which can demonstrate changes in glucose metabolism have shown either hyper or hypo-metabolism in the basal ganglia, possibly related to the acute or subacute nature of the disease at the time of scanning.

In general neuroimaging does not significantly contribute to the diagnosis and is often done to exclude other pathologies.
Applying It has been shown that 2 years it is that penicillin prophylaxis 35-37 14,34 Where does the autoimmune process originate? It seems these finding lead to the hypothesis that although the movement disorder typically Sue Swedo explored the psychiatric and behavioral is there an important intrathecal component of the auto- From a pathophysiological basis, there are therefore therapies are most efficacious, although plasma exchange it is also unclear which of the immune therapies reduce the permanent burden of persistent neurop- chorea patients that there will be residual chorea in 50% 2 years improve to some degree, Cardoso showed in 50 Sydenham chorea had higher titres of serum Immunoglobulin G binding to the cell surface of live neurons compared with controls using a quantitative fluorescence-activated cell sorting method. It is likely that patients with Sydenham chorea harbor antibodies that bind to neuronal surface proteins that can mediate disease. Other evidence of potential pathogenicity of Sydenham chorea Immunoglobulin G comes from data showing that Immunoglobulin G results in altered neuronal calcium signaling, and alterations in cyclic AMP, one of the central signaling pathways.29,32

Therapeutics Including Immune Therapy and Outcome
Historical teaching suggests that Sydenham chorea is a benign disorder with a good outcome in the majority. However, that is not always the case. Although it is true that most patients will improve to some degree, Cardoso showed in 50 Sydenham chorea patients that there will be residual chorea in 50% 2 years after onset.33 Although the movement disorder typically improves, many patients can be left with ongoing psychiatric or behavioral alteration.14,34 It has been shown that obsessive-compulsive disorder, attention-deficit/hyperactivity disorder and depression are more common in children with Sydenham chorea, but it is unclear whether these disorders are typically persistent or permanent. Therefore, it is increasingly clear that Sydenham chorea should no longer be considered “benign,” and we believe that clinicians should be more proac- tive and aggressive with therapy. Relapse may occur in a minority of patients and is often associated with use of the oral contraceptive pill (oestrogen) or pregnancy.34 It has been established for some time that penicillin prophylaxis is necessary to protect the heart in rheumatic fever, and penicillin prophylaxis is recommended until the age of 21 years in patients with rheumatic fever and Sydenham chorea. There is evidence that immune therapies with intravenous immunoglobulin, plasma exchange, or corticoster- oids can shorten the duration of Sydenham chorea.35-37 However, there is no study to demonstrate whether these therapies reduce the permanent burden of persistent neuropsychiatric morbidity. This is an important issue that requires further attention. It is also unclear which of the immune therapies are most efficacious, although plasma exchange and intravenous immunoglobulin were more effective at shortening the duration of the illness than corticosteroids in one study.36 From a pathophysiological basis, there are still many unknowns that could influence therapeutic decision making, such as the following:

- Where does the autoimmune process originate? It seems most likely that the autoimmune process originates in the peripheral immune system as the initiating or provoking infection (group A Streptococcus) infects the nasopharynx. Therefore, autoreactive lymphocytes and antibodies are likely to involve the lymphatic system and peripheral blood, at least in the initial phases. If this is the case, then therapies that modulate the peripheral immune response should be effective, such as intravenous immunoglobulin, plasma exchange and steroid.
- Is there an important intrathecal component of the auto- immune process? If there is a considerable intrathecal autoimmune process, then therapeutic treatments should include treatments that can cross the blood brain barrier or cause an immune suppression that includes autoreactive lymphocytes in the brain. These therapies may include rituximab or cyclophosphamide, although most clinicians would consider these drugs too potent for a disorder such as Sydenham chorea. However the investiga- tion and examination of cerebrospinal fluid in Sydenham chorea shows no pleocytosis. Therefore, at this time, the evidence to date suggests that there is little intrathecal immune reactivity, and therefore therapies that modulate the peripheral immune system may be adequate. These important issues and the function of the blood brain barrier in autoimmune basal ganglia disor- ders, and autoimmune brain disease in general, require attention and investigation.

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcus (PANDAS)

History
The possibility that Streptococcus or other infections can trig- ger autoimmune basal ganglia disease resulting in phenotypes other than chorea has been considered for many years, but really gained significant momentum only in the 1990s. A clinical outbreak of streptococcal infections was associated with an apparent increase in tic disorders in Rhode Island, United States.38 Sue Swedo explored the psychiatric and behavioral manifestations of Sydenham chorea and described the increased prevalence of obsessive-compulsive behaviors in Sydenham chorea.16 These finding lead to the hypothesis that streptococcal infection could precipitate other “basal ganglia” phenotypes, specifically tic disorders and obsessive- compulsive disorder. In 1998, clinical criteria for PANDAS were described based on 50 children with tics and obsessive compulsive disorder whose course was temporally related to streptococcal infections.39
Clinical Syndrome

The criteria, although useful, have been problematic because there is currently a lack of a biomarker to confidently diagnose PANDAS. The clinical criteria proposed in 1998 are as follows:39

- Presence of obsessive compulsive disorder and/or tics
- Pediatric onset (prepubertal)
- Episodic course with abrupt onset and dramatic exacerbations
- Association with group A streptococcal infection
- Association with neurological abnormalities such as adventitious movements, motoric hyperactivity, or choreiform movements

Part of the challenge with the PANDAS hypothesis has been the ease with which it is possible to falsely associate the natural waxing and waning course of Tourette syndrome with streptococcal infection, which is very common in school-age children. Indeed, a random streptococcal serology test will likely yield a positive result in 20% to 40% of school age children, and a throat swab may show Streptococcus pyogenes in a significant minority of school-age children. Despite these limitations, there does appear to be a small subgroup of children with tics or obsessive-compulsive disorder who have an unusual course defined by dramatic infection-precipitated deteriorations, then often complete remissions (sawtooth course)—such a course is atypical of Tourette syndrome or obsessive compulsive disorder, but characteristic of PANDAS.40 In addition, advocates of the PANDAS hypothesis have noted other common neuropsychiatric changes in these children, including “baby-like” behavior, enuresis, and deterioration in dexterity and memory, symptoms that are atypical of Tourette and obsessive compulsive disorder.39 A recent study reported that the features most suggestive of PANDAS compared to non-PANDAS were dramatic onset of neuropsychiatric symptoms, complete remissions, remission of symptoms associated with antibiotic therapy, history of tonsillectomies or adenoidectomies, evidence of group A streptococcal infection, and clumsiness.41 Despite the critics and problems with the diagnostic criteria, the hypothesis remains appealing, and may prove to be true for a small subgroup of children with neuropsychiatric disease.

Pathophysiology

The name PANDAS infers that there is an autoimmune, or more correctly, an autoaggressive disease. This would suggest there is a specific and directed autoreactive response of the acquired immune system against the brain. Most attention has focused on autoantibodies. For an autoantibody hypothesis to be true in a specific neuropsychiatric syndrome, the proposed autoantibody would need to be biologically plausible. As stated above most pathogenic antibodies bind to cell surface antigens such as receptors or synaptic proteins. To identify such antibodies, cell-based approaches using live cells are necessary but these approaches have generally not been done in PANDAS. Most antibody investigation has used immunofluorescence binding to animal brain, or western blotting using homogenates of human basal ganglia or rodent brain, and the results have been inconsistent.46-48 Some reports have found antibodies against brain antigens in PANDAS patients, whereas other studies found no difference to controls.46-48 Using live neurone-like cells, Brilot was unable to demonstrate cell surface antibody in PANDAS patients compared with controls, in contrast to Sydenham chorea patients who had increased cell surface antibody binding as discussed above.33 However, using other approaches, Kirvan has shown that PANDAS patients, like Sydenham chorea patients, have antibodies to lysoganglioside GM1, and this Immunoglobulin G can alter cell signaling.49 In summary, the autoantibody data in PANDAS to date are conflicting. It is possible that a defining autoantibody still exists, but has yet to be found.

Although the autoantibody hypothesis is still uncertain in PANDAS, it is conceivable that the immune system could still influence the brain in PANDAS patients and be responsible for clinical fluctuations. Although there is no definitive evidence of a specific autoimmune process in PANDAS and Tourette syndrome, there is accumulating evidence of other immune aberrations that may influence disease expression and clinical fluctuations.46,50,51

The B lymphocyte marker D8/17 received a lot of attention in the past, and it was hoped that this marker could define genetic vulnerability to poststreptococcal autoimmune complications such as rheumatic fever, Sydenham chorea, and PANDAS. This antibody was derived from an individual with rheumatic fever, and binds to a B cell surface protein of unknown etiology (termed D8/17). Although D8/17 binding is overexpressed in most studies of rheumatic fever and Sydenham chorea,52 studies exploring D8/17 in PANDAS and Tourette syndrome have been inconclusive or inconsistent suggesting this is not likely to be a useful marker in children with neuropsychiatric disease.53,54

Although streptococcus has been a central participant in the PANDAS hypothesis, there is emerging evidence that some patients with dramatic infection-associated neuropsychiatric deteriorations are not the result of streptococcal infection, but other infectious insults. However, given the problems with the clinical definitions for PANDAS as described above, this further emphasizes the need for reliable biomarkers to be able to substantially help clinicians and scientists in this area.

Neuroimaging

The MRI of children with PANDAS is normal, and this investigation is unnecessary in a clinical setting. However, MRI has shed some insight into pathophysiology, including demonstration of minor basal ganglia enlargement or “swelling” during the acute phases of PANDAS that normalizes on convalescence.42 The enlargement is only 10% to 15% and is not useful in a clinical setting, but points toward the basal ganglia being involved in PANDAS pathogenesis.
**Therapeutics Including Immune Therapy and Outcome**

There are relatively little outcome data in PANDAS patients, which is disappointing, as it is of great importance to understand what actually happens to these children. Do PANDAS patients have a more benign, severe, or similar outcome to patients with “idiopathic” obsessive compulsive disorder or Tourette syndrome? Does the autoimmune process cause permanent or irreversible alteration to the brain of children with PANDAS, or is the disease completely reversible? These central issues are still unresolved and are important in determining how aggressive clinicians should be regarding treatment.

Given the apparent role of streptococcal infection, penicillin prophylaxis has been tried in PANDAS patients. However, it should be noted that very large cohorts were required in the initial rheumatic fever and Sydenham chorea trials to demonstrate efficacy. The trials in PANDAS have been relatively small and troubled by compliance. Therefore, the inconsistent results are probably not surprising, although one study showed encouraging results. At this time, it is difficult to provide scientific evidence to support the use of penicillin prophylaxis in PANDAS, although the authors of this review have used this approach in children who have clear and recurrent streptococcal associated deteriorations, with modest success. Many families describe a clear and rapid improvement of the neuropsychiatric symptoms with acute antibiotic usage, and prompt use of a short course of antibiotics in some patients with PANDAS can be adequate to promptly relieve the neuropsychiatric symptoms back to normality or near normality.

If PANDAS is an autoimmune disorder, then immune therapy with steroid, intravenous immunoglobulin or plasma exchange could theoretically be of value. The landmark article by Perlmutter et al treated PANDAS patients with intravenous immunoglobulin, plasma exchange, and placebo (n = 29 in the 3 treatment groups) and found the intravenous immunoglobulin and plasma exchange patients to have better short-term outcomes. However, the trial methodology and size could be criticized and suggest that this study should be considered a pilot or preliminary study rather than definitive study. A separate study treating unselected patients with tic disorders did not produce benefit with intravenous immunoglobulin. Therefore, it is difficult to strongly recommend the usage of immune therapies in PANDAS patients at this time, unless the clinical syndrome is severe, very impairing, or unresponsive to conventional neuropsychiatric approaches.

**Other Clinical Central Nervous System Syndromes Associated With Streptococcal Infections**

The spectrum of clinical disease associated with streptococcal infection is broader than chorea, tics, obsessive compulsive disorder, and other emotional disorders. There are reports of other poststreptococcal movement disorders including Parkinsonism, dystonia, and paroxysmal dyskinesia. One unusual patient with Sydenham chorea evolved into transient Parkinsonism presumably secondary to autoimmune basal ganglia disease. In addition, there are other neuropsychiatric syndromes that have been associated with streptococcal infection including anorexia nervosa. If the PANDAS hypothesis holds up, it is probably not surprising that the clinical spectrum is significantly broader than chorea alone. Again, only improved understanding of the pathogenic autoimmune or immunological process will help us better appreciate the clinical spectrum. However, as streptococcal infection is so common, it is possible that some of these descriptions are incidental rather than causal.

**Movement Disorders in Encephalitis Syndromes**

**N-Methyl-d-Aspartate Receptor Encephalitis: History**

Movement disorders have been described in association with encephalitis syndromes for many years and have been given a variety of names including basal ganglia or striatal encephalitis, encephalitis lethargica, and immune choreaencephalopathy syndrome.

**Clinical Syndrome**

In 2007, autoantibodies against the NR1 subunit of the NMDA receptor were found in patients with an unusual encephalitis, subsequently termed NMDA receptor encephalitis. A chapter is dedicated to NMDA receptor encephalitis in this journal, but it will be discussed in brief from a movement disorder perspective. Although initially described as a paraneoplastic syndrome in young adult females with ovarian teratoma, it is now recognized that NMDA receptor encephalitis affects young children and is typically idiopathic or postinfectious rather than paraneoplastic in children. One of the hallmarks of NMDA receptor encephalitis is a movement disorder and is present in 85% of children with this disorder. Indeed, these children in the past were called dyskinetic encephalitis lethargica, immune chorea encephalopathy syndrome, and acute encephalopathy with bursts of abnormal movements. The movement disorder can occur near the beginning of the clinical syndrome or more commonly occur latently after the initial psychiatric alteration or seizures. The psychiatric phenomenology is often remarkable and includes agitation, psychosis, and altered personality. The movement disorder phenomenology is often recognizable and includes agitation, psychosis, and altered personality. The movement disorder phenomenology is often remarkable and includes agitation, psychosis, and altered personality. The movement disorder phenomenology is often remarkable and includes agitation, psychosis, and altered personality.
**Therapeutics Including Immune Therapy and Outcome**

The movement disorder of NMDA receptor encephalitis should be treated with immune therapy. Symptomatic therapy of the movement disorders is difficult and often the patient needs to be sedated using benzodiazepines, chloral hydrate, and clonidine. Drugs that modify receptors such as dopamine receptor blockers may be associated with dystonic complications or neuroleptic malignant syndrome, and should be used with caution. It is clear that many children with NMDA receptor encephalitis can make a good and complete outcome, and children who had this condition before the NMDA receptor antibody biomarker sometimes made a good recovery even without treatment. Now, however, there is also new evidence that about 30% of children will be left with residual disability, particularly cognitive and psychiatric disability. Indeed, the emerging risk factors for worse outcome are younger age, lack of an ovarian teratoma, and a relapsing course. As there is now impressive evidence that NMDA receptor encephalitis is an autoimmune encephalopathy, and a poor outcome is possible, it is generally recommended to treat all children with high-dose intravenous steroid and intravenous immunoglobulin. Second-line therapies with cyclophosphamide, mycophenolate mofetil, and rituximab can be used if the course is resistant or relapsing.

**Basal Ganglia Encephalitis**

**Historical**

An encephalitis with dominant involvement of the basal ganglia has been described for centuries and given a variety of names. It is impossible to determine whether all of these syndromes have the same pathophysiology. However, the following names have been used that probably describe similar or related inflammatory diseases with predominant involvement of the basal ganglia including basal ganglia or striatal encephalitis, encephalitis lethargica, and infantile striatal necrosis. Encephalitis lethargica is an entity first described in the early 20th century, and the disorder has been associated with the work of Constantin von Economo. Von Economo and others described an apparent epidemic of encephalitis with dominant movement and psychiatric disorders. Encephalitis lethargica could be separated into 3 main forms: an akinetic parkinsonian form, an ophthalmoplegic form, and a hyperkinetic form. The clinical and pathological features appeared to suggest the encephalitis predominantly involved the basal ganglia, substantia nigra, and brainstem, although cortical regions were also involved. Although classically associated with the 1918 H1N1 influenza epidemic, the epidemiology and clinical descriptions at the time questioned the direct role of influenza. Furthermore, genetic studies of permafrost frozen encephalitis lethargica brains from the 1920s failed to detect the genome of H1N1 influenza in brain, and these studies conclude that encephalitis lethargica was not the result of direct invasion of the brain by influenza. The exact cause of encephalitis lethargica is therefore unknown although influenza and other infections may have had contributory roles.

Infantile bilateral striatal necrosis is a radiological and clinical syndrome that probably has multiple causes including metabolic, genetic and inflammatory processes. When occurring as a monophasic postinfectious inflammatory disorder, infantile bilateral striatal necrosis is the term typically used in younger children when there is radiological evidence of basal ganglia damage as demonstrated by MRI T1 weighted hypodensity and diffusion restriction followed by sclerosis or atrophy of the basal ganglia on convalescent scanning. We describe basal ganglia encephalitis and infantile bilateral striatal necrosis together, as these disorders may be part of the same clinical entity.

**Clinical Syndrome**

The discovery of the NMDA receptor antibody biomarker has been able to define subgroups of patients with encephalitis complicated by movement disorders. NMDA receptor antibodies, which define NMDA receptor encephalitis tend to have dyskinetic movements as described above, plus cognitive changes, aphasia, memory loss, psychiatric features, seizures, and dysautonomia. However, it is clear that many patients with encephalitis and movement disorders are negative for NMDA receptor antibodies. These patients often have Parkinsonism, dystonia or chorea plus psychiatric features, but they do not have significant seizures or aphasia. The clinical syndrome localizes to the basal ganglia, and neuroimaging abnormalities, when present, also localize to the basal ganglia and brainstem (described below).

**Neuroimaging**

Patients with basal ganglia encephalitis may have MRI T2 hyperintense lesions that strongly localize to the basal ganglia regions and sometimes the substantia nigra. Typically T1 sequences are normal, and diffusion weighted imaging is often normal. There may occasionally be contrast enhancement. When there is T1 weighted hypodensity or diffusion restriction of the basal ganglia or when there is convalescent basal ganglia atrophy, the term striatal necrosis is sometimes employed as these features suggest a more destructive process involving the basal ganglia.

**Pathophysiology**

Patients with NMDA receptor encephalitis often have cerebrospinal fluid pleocytosis; however, patients with basal ganglia encephalitis and infantile bilateral striatal necrosis typically do not have cerebrospinal fluid pleocytosis (personal communication). In basal ganglia encephalitis, the cerebrospinal fluid neopterin can be elevated, and mirrored or intrathecal oligoclonal bands are sometimes present. Patients with infantile bilateral striatal necrosis and basal ganglia encephalitis may have autoantibodies against human basal ganglia antigens;
However, these studies used western blotting, a method that reveals intracellular antigens and alters protein conformation.\(^5\),\(^7\) Therefore, although these patients have antibodies against brain proteins, studies using cell-based assays or live neurones are required to further explore the autoantibody hypothesis.

**Therapeutics Including Immune Therapy and Outcome**

There have been no clinical trials, but case reports and small uncontrolled case series report the potential benefit of immune therapy. Steroids and intravenous immunoglobulin have generally been used with some reported benefit.\(^5\),\(^7\) However, as for many neuroimmunological conditions, early detection and treatment improve outcomes. In cases where there is radiological basal ganglia damage, the potential for a good outcome is reduced.\(^7\) The outcome appears to be variable, and some patients make a complete recovery even without immune therapy.\(^5\) However, neurological disability is common and includes dystonia, psychiatric problems, and cognitive dysfunction.\(^6\) Some patients with basal ganglia lesions on MRI have complete resolution of the lesions, whereas others have evidence of basal ganglia sclerosis or atrophy.\(^7\)

**Movement Disorders in Infectious Encephalitis**

Movement disorders can sometimes complicate specific infectious encephalitides that can involve the basal ganglia such as *Mycoplasma pneumoniae*, varicella zoster, Epstein-Barr virus, and enterovirus.\(^7\),\(^8\) One of the most classic encephalitides associated with movement disorder worldwide is Japanese B encephalitis that is associated often with a severe dystonia-Parkinsonism and thalamic or substantia nigra lesions.\(^9\) These encephalitides are thought to be the result of direct microorganism invasion of the brain parenchyma, although autoimmunity mechanisms may be operating particularly in postmycoplasma encephalitis.\(^7\)

However, there is a latent complication of Herpes simplex encephalitis that requires further specific consideration. Herpes simplex type 1 and 2 can cause a severe and destructive encephalitis in young and old people, has predilection for the temporal lobes, and can cause necrosis of brain tissue with consequent poor outcome. However, in a minority of patients, after apparent partial improvements from the initial encephalitic phases, some patients relapse and evolve a movement disorder, typically chorea.\(^8\),\(^9\) Reports usually suggest that this is a latent complication and that this complication may respond to immune therapy. It is possible that this latent chorea may be an autoimmune process, and a further example for viral induced autoimmunity.\(^9\)

**Movement Disorders as Complications of Systemic Autoimmune Disorders: Background**

The entities described above are all inflammatory processes apparently isolated to the central nervous system. However, movement disorders can occur as an autoimmune process in systemic autoimmune disorders such as systemic lupus erythematosus and antiphospholipid syndrome.

Systemic lupus erythematosus is a multiorgan autoimmune disorder with a broad array of associated autoantibodies including antinuclear antibodies and anti-double-stranded DNA antibodies. Systemic lupus erythematosus commonly affects the brain, with headache, depression, psychiatric manifestations, and seizures being most common.\(^8\) About 20% of systemic lupus erythematosus patients will present in childhood.

Antiphospholipid syndrome is an autoimmune haematological disorder that is rare in childhood resulting in recurrent thromboses (venous typically) and recurrent miscarriage, plus nonhematological problems such as carditis and rash. Migraine is a common brain complication of antiphospholipid syndrome. A diagnosis of antiphospholipid syndrome is supported by the presence of persistently elevated anticardiolipin IgG, the presence of lupus anticoagulant, and anti-beta2-glycoprotein 1 antibodies. The Sapporo diagnostic criteria for antiphospholipid syndrome necessitate the presence of one or more thromboses; however, it is recognized that patients with antiphospholipid syndrome can present with brain manifestations without pro-thrombotic complications.\(^8\) It is common for both systemic lupus erythematosus and antiphospholipid syndrome to coexist in the same patient.

**Clinical Syndrome**

Both systemic lupus erythematosus and antiphospholipid syndrome can be complicated by movement disorders, and chorea is an uncommon but important presenting feature of systemic lupus erythematosus and antiphospholipid syndrome in adolescents.\(^8\) Indeed, the majority of patients with systemic lupus erythematosus chorea also have antiphospholipid antibodies, and antiphospholipid antibodies may be important in pathophysiology of lupus chorea.\(^8\) Other than chorea, Parkinsonism is well described in systemic lupus erythematosus and dystonia is occasionally described in both systemic lupus erythematosus and antiphospholipid syndrome.\(^8\),\(^9\)

Psychiatric manifestations are a common accompaniment of movement disorders in systemic lupus erythematosus and antiphospholipid syndrome, and migraine is common in antiphospholipid syndrome.\(^8\),\(^9\) Usually patients with movement disorders in systemic lupus erythematosus and antiphospholipid syndrome do not have seizures or memory loss, and the syndromes are usually strongly referable to the basal ganglia, rather than a disseminated or diffuse process.

**Neuroimaging**

The MRI in patients with systemic lupus erythematosus and antiphospholipid syndrome is often uninformative or normal. Subtle white matter lesions may occur in both conditions, but the lesions rarely involve the basal ganglia, and it is difficult to know whether these lesions have relevance to movement disorder evolution.\(^8\) Often the MRI is normal or shows subtle
There are a number of neurological and cardiac manifestations associated with systemic lupus erythematosus and antiphospholipid syndrome. Patients with lupus Parkinsonism appear to have a bilateral basal ganglia syndrome, but it seems unlikely that any of these antibodies is directly and specifically pathogenic to basal ganglia structures. However, the investigation of movement disorders associated with systemic lupus erythematosus and antiphospholipid syndrome is surprisingly limited. Investigators have found a broad array of serum autoantibodies associated with lupus chorea, but it seems unlikely that any of these antibodies is directly and specifically pathogenic to basal ganglia structures. One study has shown autoantibodies binding to dopaminergic neurons in a patient with lupus Parkinsonism. Using the paradigms described above, Dale et al demonstrated that patients with systemic lupus erythematosus and antiphospholipid syndrome movement disorders have elevated Immunoglobulin G binding to the cell surface of neurone-like cells, demonstrating a proof of principle that these patients have antibodies that may bind to important cell surface proteins of dopaminergic neurons. There are a number of neurological and cardiac similarities between rheumatic fever and Systemic lupus erythematosus, and it is possible that these entities share common pathophysiological pathways. Further biomarkers are required to better understand these patients and aid treatment.

Concluding Remarks and Future Directions
There is increasing interest in immune-mediated brain disorders including autoimmune basal ganglia disease. Over the past 5 years, there have been significant improvements in our understanding of autoimmune brain disorders with the discovery of new and specific antibody biomarkers. It is likely there are novel antibody biomarkers that have yet to be discovered. Improved understanding of autoimmune brain disorders is important as immune therapy may reduce or minimize long-term impairments.

Acknowledgments
The authors would like to acknowledge the following funding bodies: National Health and Medical Research Council, University of Sydney, Multiple Sclerosis Research Australia, the Tourette Syndrome Association, the Petre Foundation, and the Star Scientific Foundation.

Author Contributions
RCD and FB planned and researched the article, edited subsequent drafts, and approved the final version. RCD wrote the first draft of the article.
Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Disclosure/Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: RCD and FB have received funding from the following sources: National Health and Medical Research Council, University of Sydney, Multiple Sclerosis Research Australia, the Tourette Syndrome Association, the Petre Foundation, and the Star Scientific Foundation.

Ethical Approval

This review article did not require specific ethics approval.

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