Movement disorders are a common expression of neurological diseases of varied etiology. The clinical recognition of the movement disorder is a vital first step, towards diagnosis and treatment. Therapeutic options are however, still far from satisfactory and so the search is on to understand the neurological basis and etiopathological mechanisms that underlie these diseases to effect better treatment strategies.

Neuroimmunology is a rapidly expanding field and fascinating new research shows that immune mediated mechanisms may have significant roles to play in a wide spectrum of movement disorders. Evidence now exists for active and chronic inflammation, presence of auto-antibodies, T-cell mediated processes and a wide variety of other immune mechanisms in certain movement disorders.

A discussion of the current spectrum of immune mediated movement disorders highlighting both the pathophysiology and clinical features is presented. Some of the disorders discussed may not be considered “true” movement disorders by purists in the strictest sense, as their origin lies outside the basal ganglia, but are included as they do indeed manifest clinically as “movement disorders” (Table 1).

The Spectrum of Post-Streptococcal Movement Disorders (Fig. 1)
In 1686 Thomas Sydenham described a disorder in children characterized by the sudden onset of rapid, involuntary and purposeless limb movements. This movement disorder “chorea”, was in fact the first extrapyramidal movement disorder to be described clinically.

In Sydenham’s chorea (SC), the symptoms may be bilateral or may manifest as hemichorea. Dysarthria and hypotonia are common accompaniments. The clinical severity can vary from a mild subtle movement disorder to a severely incapacitating illness.

Neuropsychiatric symptoms are frequently seen in these patients and this fact was recognized in even in the early days as a “choreic temperament” in the sufferers. Common symptoms include disruptive behavior, obsessive compulsive symptoms, emotional lability, distractibility, anxiety and depression.

Clinical observations and subsequent epidemiological studies confirmed the relationship between group A beta hemolytic streptococci, rheumatic fever and Sydenham’s chorea.
In the 1980s, there occurred a spate of outbreaks, first in the Rhode Island region of the United States, of a sudden onset movement and emotional disorder in children following streptococcal throat infections. However, quite unlike SC, the movement disorder consisted of motor tics (without any chorea) with prominent neuropsychiatric symptoms usually of an obsessive compulsive nature and was commoner in boys. These and further recognized cases were then grouped together under the new acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections).

Diagnostic criteria, which eloquently summarize the clinical features of PANDAS, have since then been put forward (Table 2).

<table>
<thead>
<tr>
<th>Table 1: Immune Mediated: Movement Disorder Syndromes / Diseases with Movement Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post–streptococcal autoimmune movement disorders:</strong></td>
</tr>
<tr>
<td>Sydenham’s Chorea</td>
</tr>
<tr>
<td>PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections)</td>
</tr>
<tr>
<td>Post-streptococcal ADEM with anti basal ganglia antibodies</td>
</tr>
<tr>
<td>Post-streptococcal myoclonus</td>
</tr>
<tr>
<td>Post-streptococcal dystonia</td>
</tr>
<tr>
<td>Post-streptococcal paroxysmal dystonic choreoathetosis</td>
</tr>
<tr>
<td>Autoimmune /connective tissue disease associated movement disorders</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Primary antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
</tr>
<tr>
<td>Polymyositis nodosa</td>
</tr>
<tr>
<td>Behcet’s disease</td>
</tr>
<tr>
<td>Isolated CNS angiitis</td>
</tr>
<tr>
<td>Churg Strauss syndrome</td>
</tr>
<tr>
<td>Paraneoplastic / idiopathic autoimmune associated movement disorders</td>
</tr>
<tr>
<td>Opsoclonus – myoclonus syndrome</td>
</tr>
<tr>
<td>Neuromyotonia</td>
</tr>
<tr>
<td>Stiff – person syndrome</td>
</tr>
<tr>
<td>Paraneoplastic chorea</td>
</tr>
<tr>
<td>Demyelinating disease associated movement disorders</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis.</td>
</tr>
<tr>
<td>Demyelinating neuropathies</td>
</tr>
<tr>
<td>Classic Idiopathic/degenerative syndromes: “immune mechanisms proposed”</td>
</tr>
<tr>
<td>Idiopathic tic disorder / Tourette syndrome</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Diagnostic criteria for PANDAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presence of OCD and / or tic disorder</td>
</tr>
<tr>
<td>2. Pediatric (childhood) onset.</td>
</tr>
<tr>
<td>3. Episodic course of symptoms severity, characterized by the abrupt onset or dramatic exacerbation of symptoms</td>
</tr>
<tr>
<td>4. Symptomatic exacerbation are temporally related to group A beta hemolytic streptococcal infection, usually occurring within four weeks of infection</td>
</tr>
<tr>
<td>6. The presence of neurological abnormalities include hyperactivity and choreiform movements (during clinical exacerbation)</td>
</tr>
</tbody>
</table>

In the 1980s, there occurred a spate of outbreaks, first in the Rhode Island region of the United States, of a sudden onset movement and emotional disorder in children following streptococcal throat infections. However, quite unlike SC, the movement disorder consisted of motor tics (without any chorea) with prominent neuropsychiatric symptoms usually of an obsessive compulsive nature and was commoner in boys. These and further recognized cases were then grouped together under the new acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections). Diagnostic criteria, which eloquently summarize the clinical features of PANDAS, have since then been put forward (Table 2).
PANDAS cases by definition have a relapsing remitting course requiring 2 or more exacerbations for the definite diagnosis. SC on the other hand is usually thought to be a benign self limiting disorder, though chronic persistence of chorea is well known. Diagnostic criteria notwithstanding, it is quite likely that both SC and PANDAS can vary from a monophasic self limiting illness to having a persistent relapsing remitting course over decades.

SC is well recognized in adults and recently an adult form of PANDAS satisfying all criteria except pediatric onset has also been reported.²

Other Post-Streptococcal Movement Disorders
In 2001 Dale et al reported 10 patients with an acute disseminated encephalomyelitis (ADEM) like illness which occurred after streptococcal infections³. Clinical features included dystonia in all the patients along with other variable features like encephalopathy and pyramidal tract signs.

What distinguished these patients from any other post-infective ADEM cases were the presence of unique antibasal ganglia antibodies (ABGA), demonstrable by ELISA, reactive against 3 dominant protein bands of 60, 67 and 80 kDa of the human basal ganglia.

Post streptococcal dystonia with isolated bilateral striatal necrosis, presenting with the phenotype of infantile bilateral striatal necrosis (IBSN) has also been described. Other post streptococcal movement disorders reported include acute myoclonus and paroxysmal dystonic choreoathetosis.

Pathophysiology of the Post Streptococcal Disorders
Over three centuries since the initial description, the pathophysiology of post streptococcal movement disorders still remains incompletely understood. There is no evidence to suggest that streptococcal organisms or bacterial toxins enter the brain so the immunological mechanism remains the only attractive hypothesis.

Husby et al were the first to demonstrate antineuronal antibodies in SC.⁴ These antibodies cross
reacted with caudate and subthalamic nucleus neurons and were shown to decrease in titer as clinical improvement in patients occurred. A more recent study by Church et al using Western immunoblotting technique with human basal ganglia as the autoantigen has shown antibodies reactive against basal ganglia universally (100%) in SC. The autoantigens have molecular weights of 40, 45 and 60 kDa and appear to be prominent in the basal ganglia. The exact identity of these antigens is unknown but Dale et al were able to find similar anti neuronal antibody findings their post streptococcal autoimmune dystonia patients.

They propose that these auto antigens are involved in all post-streptococcal movement disorder syndromes including SC, PANDAS, dystonia and others.

Neuro-Imaging in the Post-Streptococcal Syndromes
Conventional imaging is commonly normal in SC/ PANDAS though at times in ammatory change predominantly involving the basal ganglia have been described. Detailed volumetric analysis of basal ganglia has shown that the caudate nucleus and putamen may be specifically enlarged during the acute phase of SC and PANDAS. Majority of the neuroimaging findings are reversible but irreversible striatal changes suggesting permanent damage have also been described in SC.

The patients reported by Dale et al with post streptococcal dystonia had bilateral signal changes predominantly in the basal ganglia (80%) with ADEM like white matter changes.

Therapy in the Post-Streptococcal Syndromes
Current therapeutic strategies focus on immunomodulation to treat the illness and antibiotic prophylaxis to prevent exacerbating infections. Antibiotic prophylaxis is well accepted in rheumatic fever and SC. In PANDAS a recent uncontrolled study of antibiotic treatment in PANDAS showed considerable improvement in symptoms.

Standard therapy for symptoms in SC include sodium valproate or carbamazepine and clonazepam which are preferable to haloperidol which can cause unacceptable side effects Immunotherapy with plasma exchange and IVIg has been used successfully in severe unremitting SC.

Post-streptococcal syndromes occur only in a minority, of infected individuals and hence genetic predisposition must play a role in the etiopathogenesis. It also appears that across the spectrum of post-streptococcal syndromes the anti-neuronal antibodies are probably very similar. The question that arises then is - why do some patients present with SC, others with PANDAS and yet others with dystonia or myoclonus. At present we have no definite answers but it is possible that differing areas of the basal ganglia may be involved with varying severity or that host mechanisms may in uence the outcome.

Autoimmune Connective Tissue / Vasculitic Diseases Associated Movement Disorders (Table 3)
Postulated mechanisms to explain the movement disorder in these diseases include an immune mediated in ammatory vasculopathy resulting in ischemic damage to the basal ganglia or alternatively the binding of antibodies /immune complexes to basal ganglia proteins can result in a direct pathogenic effect. PET studies have shown an immune mediated excitatory effect with hypermetabolism noted in the striatum in SLE and PAPS patients with chorea and so favor the latter mechanism.

SLE
Around 4% of SLE patient’s exhibit choreoathetosis. Chorea may develop anytime in SLE, but tends to manifest during a lupus flare. Chorea is usually transient but may be recurrent or even permanent. Brain MRI is often abnormal but the lesions are not always correlative and many patients without
chorea show similar lesions. Some patients with SLE and chorea harbor antiphospholipid antibodies which may be involved in the pathogenesis.\textsuperscript{7}

Cases of SLE manifesting an akinetic rigid parkinsonian syndrome with improvement on immunosuppressive therapy, though extremely rare, is also reported.\textsuperscript{8}

**Primary antiphospholipid antibody syndrome (PAPS)**

Primary antiphospholipid antibody syndrome (PAPS) is characterized by a hypercoagulable state associated with APLA but without an underlying autoimmune disorder like SLE. Movement disorders are predominantly seen in female patients (14:1) with acute onset of generalized chorea, hemichorea, hemiballismus or dystonia especially during pregnancy or after starting oral contraceptive pills.

**Hashimoto’s Thyroiditis**

Hashimoto’s thyroiditis can cause an encephalopathy which is sometimes associated with prominent choroathetosis and myoclonus.\textsuperscript{9} Different classes of antithyroid antibodies have been recognized in this syndrome and symptoms may come up despite a euthyroid state suggesting that the movement disorder occurs due to an immune mechanism rather than hormonal dysregulation. MRI may be normal or show transient/permanent hyperintense T2 signal especially in the frontal/temporal lobes. Patients usually show dramatic response to steroid therapy.

**Other Autoimmune Disorders**

Chorea has also been reported as a rare complication of Behcet’s disease/polyarteritis nodosa isolated angitis of the central nervous system and the Churg Strauss syndrome.

**Paraneoplastic / Idiopathic Disorders Associated Movement Disorders**

(Table 4)

Paraneoplastic neurological syndromes are remote effects of tumors mediated by the immune system. Tumors express proteins some of which are isolated only to the nervous system triggering an autoimmune response against the tumor and consequently also the nervous system. To date numerous...
antibodies against this tumor expressed neuronal proteins (onconeural antigens) have been detected in the various neurological syndromes.

Not all the antibodies found so far have direct etiopathogenic roles, but the detection of a particular antibody strongly suggests the presence of an underlying tumor and so has great diagnostic value and should prompt a diligent search for the tumor.

Opsoclonus Myoclonus Syndrome (OMS)

Opsoclonus is an uncommon eye movement disorder characterized by involuntary, chaotic but conjugate saccadic eye movements. The abnormal eye movements occur multi directionally or horizontally (oculogyric crises) and are precipitated by change in fixation. The associated myoclonus occurs in the face and limbs or trunk and is typically exacerbated by muscle activation.

OMS can occur due to varied etiologies; toxic, metabolic, structural disorders paraneoplastic and idiopathic. The idiopathic and paraneoplastic syndromes are postulated to occur due to immune mediated mechanisms resulting in dysfunction of “omnipause” neurons in the brain stem responsible for maintaining gaze.

Approximately 2-3% of children with neuroblastoma develop OMS but on the other hand nearly 50% of children presenting with OMS have an underlying neuroblastoma.

Symptoms in children often respond dramatically to ACTH, steroids or IVIg. There is however, increasing recognition that this disorder is actually also a progressive encephalopathy resulting in a significant proportion of children suffering from psychomotor retardation and behavioural disorders, as a sequelae.\(^\text{10}\)

In the adult paraneoplastic OMS is associated chiefly with anti-Ri onconeural antibodies (breast and gynecological cancers).

Symptoms in adults may respond to immunotherapy (steroids, IVIg) but if the underlying tumor is not treated majority of patients have a poor outcome.\(^\text{11}\)

Neuromyotonia

Neuromyotonia (Isaacs’ syndrome) is a rare and heterogenous syndrome of disorders characterized by continuous motor unit activity of peripheral nerve origin. It manifests as various combinations of muscle stiffness, cramps, twitching, weakness and delayed muscle relaxations (pseudomyotonia). Examination may show hypertrophy of the involved muscles and undulating myokymia. The spontaneous activity continues during sleep and after proximal nerve block but is abolished by curare blockade of neuromuscular transmission suggesting peripheral nerve origin. Needle electromyography reveals myokymic discharges which consists of bursts of motor unit potentials appearing as doublets, triplets or multiplets with a high interburst frequency.

Although neuromyotonia may be seen associated with some inherited neuropathies most cases are acquired and often associated with autoimmune disorders like myasthenia gravis, thyrotoxicosis, systemic sclerosis and demyelinating neuropathies. The syndrome can also be paraneoplastic in association usually with thymoma but also with small cell lung carcinoma, Hodgkin’s lymphoma and plasmacytoma.\(^\text{12}\)

The immune hypothesis is proved by the finding of etiopathogenic antibodies directed against voltage gated potassium channels (VGKC) important in the regulation of normal cell excitability Morvan’s fibrillary chorea is a rare variant characterized by neuromyotonia, pruritis, hyperhidrosis, insomnia and delirium.

Clinical neuromyotonia often improves with diphenylhydantoin or carbamazepine and the syndrome may improve with immunotherapy with plasma exchanges, steroids or azathioprine IVIg has been
reported, on occasion, to have worsened the disorder

Stiff Person Syndrome
Stiff person syndrome includes a spectrum of disorders caused by muscle stiffness of central origin. These disorders are characterized by

1. Stiffness of muscles that is prominent in axial muscle and occasionally in limb muscles (with co-contraction of agonist and antagonist muscles)
2. Sudden episodic spasms
3. Absence of another disease that can cause similar symptoms
Variants of this syndrome include focal stiff-person syndrome, stiff-limb (leg) syndrome, jerking stiff-person syndrome and the syndrome of progressive encephalomyelitis with rigidity and myoclonus (PERM)\textsuperscript{13}

The diagnosis is predominantly clinical but is aided by the finding of electromyographic evidence of motor unit firing simultaneously in agonist and antagonist muscles of the proximal limb muscles / trunk despite attempted relaxation (which improves with diazepam).

The syndrome is often idiopathic and may be associated with autoimmune disorders like Insulin dependent diabetes mellitus (IDDM) (40%), Hashimoto’s thyroiditis, Grave’s disease, myasthenia gravis, vitiligo, pernicious anemia and others.

Up to 60% patients show evidence of antibodies to glutamic acid decarboxylase (GAD). GAD is the rate limiting enzyme for the synthesis of GABA – the brain’s main inhibitory neurotransmitter. GABA enhancing agents like benzodiazepines, valproate, baclofen, vigabatrin and gabapentine provide symptomatic relief. Immuno modulation with steroids, plasmapheresis or IVIg infusion can provide additional and long lasting benefit.

Paraneoplastic Chorea
Generalized or asymmetric chorea has been described as a paraneoplastic manifestation occasionally. In a recent report, chorea was the initial and most prominent symptom as a paraneoplastic manifestation in 11 patients.\textsuperscript{14} Majority of the cases were associated with small cell carcinoma of the lung and all patients showed the presence of the CRMP-5 anti-neuronal antibody.

Paraneoplastic Myelitis
Paraneoplastic myelitis is generally seen as a component of the encephalomyelitis syndrome seen with anti-Hu antibodies. Symptoms include motor weakness as a result of upper and lower motor neuron dysfunction. Movement disorders may be seen as a feature of this syndrome and include spinal myoclonus, segmental rigidity and muscle spasms.

Demyelinating Disease Associated Movement Disorders
Multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) are the prototypic in amnatory demyelinating disorders of the central nervous system. A variety of immunological mechanisms beyond the scope of this review underlie both disorders.

Multiple Sclerosis
Movement disorders, except for tremor, are in general uncommon in MS. Moreover the tremor of MS is usually cerebellar in nature due to involvement of cerebellar connections. The different types of tremor usually observed in MS are a cerebellar tremor with a dominant intention component, Holmes tremor with the addition of a rest and postural component and palatal tremor. Severe tremor may respond to deep brain stimulation in the Vim thalamus.
A few cases have been reported where a parkinsonian syndrome occurred as a symptom of relapsing remitting MS and improved with corticosteroid treatment.

ADEM
Though multifocal involvement of subcortical white matter predominates in ADEM, involvement of the deep grey matter including the thalamus and basal ganglia are for more likely to occur than in MS. Yet movement disorders are unusual and occasionally choreoathetosis and dystonia have been reported.

Demyelinating Neuropathy Associated Movement Disorders
Tremor associated with peripheral neuropathy though uncommon is well recognized since long. Immune mediated demyelinating neuropathies may at times manifest a neuropathic tremor which is usually symmetrical, confined to the upper limbs and unrelated to proprioceptive loss, weakness or fatigue. Disabling tremor if at all, is seen in the anti-MAG antibody positive IgM paraproteinemic neuropathy.

Classic Idiopathic/degenerative syndromes: “immune mechanisms proposed”

Idiopathic Tic Disorder / Tourette syndrome / OCD
Idiopathic tic disorder, Tourette syndrome (TS) and obsessive compulsive disorder (OCD) are considered to be different expressions of primary dysfunction of cortico- striatal circuits. The exact etio-pathology is as yet unknown but with the finding of immune mechanisms and response to immuno modulation in SC / PANDAS which share similar features, a search is on for the same in these idiopathic disorders.

Anti basal ganglia antibodies have been found in TS patients these antibodies were both novel as well as similar to those found in SC. The D8/17 marker which figures so prominently in SC / PANDAS is also over expressed in TS patients.

Idiopathic Parkinson’s Disease(PD)
The etio-pathogenic mechanisms that underlie neuronal death in idiopathic Parkinson’s disease are as yet unknown. Various proposed mechanisms include free radical-oxidative damage, mitochondrial dysfunction, and excitotoxic damage, genetic and immune or infective in ammyatory mechanisms.

The current theories for cell death mechanisms in PD mainly centers on induced apoptosis. Immune abnormalities however have been frequently reported in PD. Antibodies against dopaminergic neurons and sympathetic ganglion cells have been noted. Increased IgG immunity in the cerebrospinal uid to heat shock proteins has also been noted in some patients of PD. An elevated (gamma delta plus) T cell population has been found in PD patients and T helper cell analysis has revealed a decreased percentage of CD45RA+ naïve cells and an increased percentage of CD45RO+ memory T cells. The significance of these and other T cell changes have to be elucidated.

Conclusions
A body of evidence is building up in favour of underlying immune mechanisms in a wide variety of movement disorder syndromes. The link is still weak in the idiopathic neurodegenerative disorders like Parkinson’s disease and even in the post-streptococcal “auto-immune” syndromes SC and PANDAS and related disorders the final evidence is yet to be presented. However from a clinical perspective the timely recognition of immune mediated neurological syndromes is especially important since many of these disorders are eminently treatable with current available immunomodulation strategies.

References