Movement disorders and psychiatry

Five new things

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Summary

In this article we report recent interesting diagnostic and therapeutic advances in a diverse range of movement disorders with associated psychiatric comorbidity. Areas discussed include social cognition in Huntington disease, neuroimaging of functional movement disorders, treatment of psychosis in Parkinson disease, new advances in autoimmune disease, and management of Tourette syndrome.

Most of the well-known movement disorders (Parkinson disease, Huntington disease, Tourette syndrome, and primary dystonia) are associated with major psychiatric comorbidities. These can have considerable implications for patient and caregiver stress, compliance with medications, and prognosis. It is challenging to find ways to prevent and treat these co-existent psychiatric disorders, especially because many pharmacologic agents conventionally used to treat them can have deleterious effects on motor function.

Psychogenic movement disorders, which typically present to neurologists but are traditionally treated by psychiatrists, can also present a major diagnostic and therapeutic challenge. Furthermore, a wide constellation of psychiatric and movement disorders with an immune-mediated etiology can present acutely in previously healthy adults and children, and these disorders have been the focus of intense research over the last decade.

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Recent advances in molecular medicine, genetics, and functional neuroimaging have enhanced our understanding of the neurobiological underpinnings of many of these disorders. Such findings will help inform new approaches to diagnosis and hopefully facilitate the development of more-effective targeted interventions. In this review we describe areas in which progress has been made in the understanding of the etiopathogenesis of these neuropsychiatric disorders. In addition, we discuss some promising new treatment strategies and highlight potential avenues for future research.

Functional neuroimaging of psychogenic dystonia

Prior to the advent of clinical neurophysiology and functional neuroimaging techniques, little was known about the pathophysiologic mechanisms underlying the clinical manifestations of psychogenic movement disorders (PMDs). Consequently, throughout much of the 20th century they have been regarded as the province of psychiatry rather than neurology. Recently, there has been a shift in thinking away from an exclusively psychodynamic model and renewed interest in determining neurobiological mechanisms associated with PMD.¹ Imaging studies using fMRI are now providing evidence of dysfunctional neural networks in PMDs such as dystonia.

A number of these studies have suggested that there is impairment in connectivity between limbic and motor areas involved in motor execution, as well as dysregulation of “top-down” control from higher-order frontal brain areas. Dysfunction in the generation of motor intention and motor conceptualization has also been implicated. In general, these imaging studies of PMDs indicate that there are abnormalities outside the core motor network, including the prefrontal cortex and anterior cingulate cortex.²

In a recent small but well-designed study, PET imaging was used to study the pathophysiology of psychogenic dystonia.³ The authors compared patients with psychogenic dystonia ($n = 6$) to patients with genetically confirmed DYT1 dystonia ($n = 5$) and healthy controls ($n = 6$), and demonstrated anatomically distinct patterns of cerebral blood flow in psychogenic and organic dystonia. Organic dystonia was associated with significantly greater regional blood flow in the primary motor cortex and thalamus compared to controls, with a reduction in the cerebellum. In contrast, psychogenic dystonia was associated with greater blood flow in the cerebellum and basal ganglia, with decreases in the primary motor cortex. The prefrontal cortex was implicated in both types of dystonia.

Caution is needed when analyzing and interpreting these studies, as it can be difficult to discern the difference between causative abnormalities and changes that are simply a result of the abnormal movement or compensatory mechanisms. Nevertheless, new imaging techniques have the potential to help with the diagnosis of PMDs and to yield highly informative results regarding their incompletely understood mechanisms and causes. As more data are collected to further refine the neuroanatomical networks underlying PMDs, it is also possible that we can develop novel treatment approaches to these disorders, such as modulating network dynamics by therapeutic transcranial magnetic stimulation or transcranial direct current stimulation.³

Social cognition in Huntington disease

Huntington disease (HD) is a relentlessly progressive autosomally dominant inherited neurodegenerative disorder for which only symptomatic treatment is available. The spectrum of psychiatric symptoms and behavioral disturbances associated with HD is broad and includes depression, anxiety, apathy, irritability, mood swings, impaired judgment, loss of empathy, aggression, obsessive-compulsive disorder, delusions, and paranoia. These can lead to difficulties and ultimately a breakdown in interpersonal relationships and are a major source of both patient and caregiver distress. There is a growing body of literature exploring social cognition in HD, with the hope that it may help us to understand and possibly predict the behavioral disturbances that are so common in these patients.⁴ Social cognition encompasses several subdomains, including the ability to recognize emotions from facial expressions, voice, or body posture, as well as “theory of mind” (ToM). ToM is the ability to attribute mental states to

Supplemental Data

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other people in terms of their beliefs, desires, intentions, and emotions.⁵ Several studies exploring emotional processing abilities in HD have demonstrated that both patients manifesting disease and premanifest gene carriers have difficulties decoding facial expressions and inferring complex mental states from photographs of peoples' eyes.⁶ Many patients have demonstrated disproportionate impairments in recognizing angry facial expressions and disgust, which in neuroimaging studies correlated with damage to the ventral putamen and atrophy of the anterior insula. Anger and disgust impairments have also been observed in non-HD patients with disorders of aggression,⁷ and it has been suggested that these emotional recognition deficits in patients with HD may also modulate some of their aggressive behavior, although the exact mechanism of this is unclear. Two recent studies have demonstrated that performance on emotion recognition tasks may be predictive of impending phenocconversion in HD.^{8,9} If these findings are replicated in future studies, it will be clinically important to assess emotional processing abilities in premanifest HD gene carriers because the results may have diagnostic utility.

The data so far provide sufficient reason to investigate the field further but leave many questions unanswered. The confounding effect of other variables such as mood and executive function on social cognition is difficult to dissect, especially because there can be shared neuroanatomical substrates between these domains. Most importantly, there is a need for larger well-designed studies with more homogenous HD cohorts to help refine the neuroanatomical networks underlying deficits in social cognition, which in turn could lead to more-objective diagnostic tests for impairments as well as new rehabilitation strategies or pharmaceutical therapies.

Treatment of Tourette syndrome

Tourette syndrome is a complex disorder with onset in childhood that is characterized by multiple fluctuating motor and phonic tics lasting for more than 1 year. It is frequently accompanied by a wide range of psychiatric comorbidities, including obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and depression.¹⁰ While many of the psychiatric comorbidities in Tourette syndrome are likely inherited (in separate but closely related genes to those that cause the tics), others may be reactive and caused by difficulties at school and with peer interactions. Many patients report that psychiatric symptoms associated with Tourette syndrome are more debilitating than the motor tics and can have a profoundly negative effect on quality of life. Despite being originally described in the late 19th century, the neurobiology of the condition has not yet been fully elucidated. Alteration of basal ganglia function within the corticostriatal-thalamocortical circuitry and involvement of the dopaminergic nigrostriatal pathway have been suggested by various imaging and postmortem studies as well as response to therapy.¹¹ However, these studies are limited by small numbers and heterogeneous patient populations.

There is a paucity of evidence-based data regarding the efficacy of different medications in the treatment of Tourette syndrome. Centrally acting α_2 adrenergic agonists such as clonidine are usually used as first-line treatment for tics in mild Tourette syndrome and can help improve comorbid ADHD. The most commonly prescribed drugs for moderate to severe tics are dopamine antagonists, such as typical (e.g., haloperidol, pimozide) and atypical

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(e.g., risperidone, aripiprazole) antipsychotics. Given the high frequency of coexistent OCD and tics, current guidelines recommend the addition of a serotonin reuptake inhibitor and behavioral therapy when a partial response occurs.

If patients have severe tics that prove refractory to conventional pharmacologic treatment and behavioral therapies, several studies over the last decade have suggested that tics can be improved by deep brain stimulation (DBS). Furthermore, DBS can also help to ameliorate psychiatric comorbidities such as OCD, aggression, impulsivity, depression, and anxiety. The optimum location for DBS has yet to be established, and at least 8 different targets have been reported to date, with thalamic stimulation being the most common. In 1999, the first patient with Tourette syndrome underwent thalamic DBS, and since then more than 100 patients have had similar procedures with varying degrees of success.¹² More data reporting long-term outcomes are needed to help refine the optimal selection of patients (age and clinical presentation) and to choose the most effective brain targets and stimulating parameters. While DBS remains an experimental therapy for patients with Tourette syndrome, it is a possible option for those with intractable disease but should preferably be performed as part of a controlled research trial.

Treatment of psychosis in Parkinson disease

Hallucinations are a common neuropsychiatric feature of Parkinson disease (PD) with a high incidence and prevalence over time, affecting more than 70% of patients in a 20-year follow-up period.¹³ Longitudinal studies of dementia in PD have shown that early hallucinations are associated with progression to cognitive impairment, while hallucinations in the setting of preexisting dementia can result in a more rapid cognitive decline. There is a well-established relationship between hallucinations and dementia in PD, and together they are an important risk for nursing home placement and mortality.

Pharmacologic approaches to managing psychosis in PD can be disappointing. Some patients have an improvement in hallucinations following a reduction of dopaminergic medication, although with this comes the risk of worsening their motor features. While quetiapine is often used in clinical practice, double-blind placebo-controlled trials have demonstrated safety but not efficacy. Clozapine has been shown to be effective at treating PD psychosis, but it is infrequently used due to the need for intensive hematologic monitoring to avoid the potentially serious side effect of agranulocytosis. A recent study demonstrated that pimavanserin, a selective serotonin 5-HT_{2A} inverse agonist, may be able to address this unmet need. In a 6-week double-blind study, 199 patients with PD psychosis were randomly assigned to receive pimavanserin 40 mg once daily or placebo. Patients were assessed at baseline and at days 15, 29, and 43 using the PD-adapted scale for positive symptoms, which is a 9-item scale rating symptoms like delusions and hallucinations. Patients treated with pimavanserin had clinically significant improvements on this scale and tolerated the medication well without experiencing sedation or worsening motor function.¹⁴ This novel compound is a promising new way to treat psychosis in PD.

Autoimmune movement and psychiatric disorders

A great advance in clinical neuroscience in the last 10 years has been the identification of specific autoantibodies to cell surface neuronal antigens that can cause a spectrum of neurologic diseases responsive to immunotherapy. Their identification has enabled the novel mechanism-level unification of aspects of diverse disorders, including those of movement, epilepsy, and cognition and

those with psychiatric symptoms, particularly psychosis. The historical intracellular antibody-associated paraneoplastic disorders with poor response to immunotherapies, first described in the 1960s, have conventionally been limited to the phenotypes of opsoclonus-myoclonus, encephalomyelitis, retinopathies, and cerebellar degenerations, and are probably resistant to treatment because of severe inflammation and cellular loss.¹⁵ In contrast, the novel cell-surface antibody (measured by cell-based assay) disorders have a broad range of neuropsychiatric phenotypes, are pathologically characterized by little inflammation, and clinically have a good response to immunotherapy.

The archetypal and most prevalent disorder is NMDA receptor (NMDAR) antibody encephalitis. The unifying discovery of autoantibodies targeting the NMDAR was made in 2007 and was initially limited to a group of young women with ovarian teratoma who presented with a prodromal psychosis followed by encephalopathy, seizures, dysautonomia, coma, and strikingly rhythmic movement disorder, often with dystonia. There have now been more than 600 reported cases of patients with NMDAR antibodies worldwide, mostly in young people of either sex, and most of these individuals had no underlying tumor.¹⁶ There may also be limited forms of encephalitis associated with this antibody, including isolated psychosis and early schizophrenia¹⁷ and seizures. Hyperkinetic movements associated with pediatric encephalitis lethargica with NMDAR antibodies, often with associated chorea and dystonia, have been described. There is growing evidence for the pathogenicity of the antibodies, which block NMDAR currents in vitro and in vivo, but as yet there are no proven mechanisms that explain the neurobiological basis of the distinctive movements and psychosis seen in this disorder. One hypothesis is that the marked rhythmic movements in NMDAR encephalitis are due to the release of brainstem central pattern generators from tonic inhibition. These generators are responsible for the rhythmic movements seen in suckling and feeding, for example.¹⁸ The psychosis may be due to NMDAR hypofunction and ensuing disconnectivity between brain regions, which is one of the strongest models for psychosis in schizophrenia, a condition strongly associated with NMDAR dysfunction.

In addition to NMDAR antibody encephalitis, other conditions associated with autoantibodies to neuronal cell surface channels and associated proteins are being described. Those associated with significant movement disorders and psychiatric symptoms include cases with autoantibodies to the voltage-gated potassium channel complex-related protein, leucine-rich glioma-inactivated 1 (LGI1), glycine receptors, and, more recently, D2 dopamine receptors. LGI1 antibodies are associated with faciobrachial dystonic seizures, brief tonic spasms of the ipsilateral face and arm that can occur up to 100 times a day. The seizures do not respond to conventional antiepileptic drugs but respond dramatically to corticosteroids and other immunotherapies. The severe stiff person variant, progressive encephalomyelitis with rigidity and myoclonus, has recently been linked to glycine receptor autoantibodies. A recent report described patients from a cohort of pediatric encephalitis lethargica with D2 receptor antibodies and a wide range of movement disorders and psychiatric symptoms, termed “basal ganglia encephalitis,” including dystonia, parkinsonism, chorea, motor tics, psychosis, and emotional lability.¹⁹

The challenge for the future is in novel autoantibody and syndrome discovery (for instance in systemic lupus erythematosus) and in the design of randomized controlled trials to

Movement disorders and psychiatry: Five new things

- Recent functional neuroimaging studies suggest that dysfunctional neural networks in psychogenic movement disorders (like functional dystonia) are different from those seen in organic disease.
- Huntington disease is associated with impairments in social cognition from an early stage, which may account for the emergence of behavioral disorders.
- DBS therapy is a possible treatment option for patients with refractory Tourette syndrome but remains unproven.
- A new drug, pimavanserin, has been shown to be effective at treating psychosis in PD in a new trial.
- Movement disorders with an autoimmune etiology are important to recognize and treat, as immune therapy can shorten disease duration and improve outcomes.

demonstrate pathogenicity of associated antibodies and efficacy and safety of treatments and their optimal dosing.

One “take home” message from these disorders is to have a high index of suspicion and test for the antibodies in cases of subacute encephalopathy associated with neuropsychiatric symptoms, in particular psychosis and hyperkinetic movement disorders. Another is that NMDAR encephalitis is mainly a disorder of the young, LGI1 encephalopathy is mainly a disease of the older patient, and the other recently described autoantibodies are relatively rare in their occurrence.

DISCUSSION

Despite their high prevalence, there is still a lack of efficacious, well-tolerated therapies to treat psychiatric manifestations of movement disorders. However, as our understanding of the pathogenesis of these conditions advances further, so too will our ability to design rational treatments to alleviate the heavy personal, social, and economic cost of these conditions.

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