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# Neuropsychiatry of movement disorders

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## **Neuropsychiatry of movement disorders**

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## **Summary**

Movement disorders include both psychiatric illnesses with neurologic features and neurologic illnesses with frequent psychiatric complications. During 1998, neuropsychiatric progress was made on several fronts, notably in parkinsonism and tic disorders. This remains an exciting area for research, with many unsolved, clinically important problems, but increasing neurobiologic knowledge and sophistication.

## **Introduction**

The term “movement disorders” is applied to a large and heterogeneous group of illnesses that affect the quality of volitional movement, produce unwanted excessive movements, or both. Phenomenologically, the abnormal movements include the parkinsonian syndrome, tremor, dystonia, chorea, myoclonus, hyperekplexia, and stereotypies. Many of these illnesses are often accompanied by disturbances of perception, memory, language, or mood. Additionally, several movement abnormalities have interested psychiatrists of their own right, including tic disorders, catatonia, the motor retardation of melancholic depression, odd movements as a feature of hysteria, and tardive movement disorders. During the past year, exciting new results have been reported in several of these areas.

## **Neuropsychiatry of parkinsonism**

### *Cognition in parkinsonian disorders*

A variety of cognitive deficits have been described in PD. The most well characterized are relatively subtle deficits that are usually attributed to dysfunction of frontal corticostriatal

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circuits [1]. These include difficulties with shifting, sequencing, or maintaining behavioral set in the face of interfering stimuli. It has not been clear if the “frontal” dysfunction in PD is due to loss of dopamine innervation of frontal cortex, or to loss of the normal basal ganglia output to frontal cortex (via thalamus), or to a combination [2]. A recent study comparing patients with early PD to patients with damage to the left or right frontal lobes demonstrated clear differences between the groups [\*3]. PD subjects showed an increased error rate as they performed successive trials, but not an increased time to switch between tasks. The authors suggested that intact dopamine neurotransmission is required to sustain cognitive and motor processes over prolonged time periods.

Another relatively common cognitive difficulty in PD is the development of dementia. It has been estimated that 10 - 20 % of patients with PD eventually become severely demented [4]. It is becoming increasingly clear, however, that dementia in PD is not due primarily to nigrostriatal dopamine loss, but is due instead to other mechanisms including coexistent Alzheimer’s disease, multi-system atrophy with loss of other subcortical nuclei, or diffuse Lewy body disease (DLBD) [5,6]. Churchyard and Lees [\*\*7] examined the brains of 27 patients diagnosed during life with PD and compared them with 11 control brains. None of the subjects met clinical diagnostic criteria for DLBD, the Lewy body variant of Alzheimer's disease, or senile dementia of the Lewy body type. Five PD patients, 2 with moderate dementia and 3 with severe dementia, met pathological criteria for DLBD. There was no difference between PD brains and controls in measures of neuronal density, neurofibrillary tangles, or neuritic plaques in the hippocampus or amygdala. There was an increased density of Lewy bodies in hippocampal region CA2 in severely demented PD brains, but no correlation with severity of dementia.

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However, increasing Lewy neurite densities in CA2 was related to worsening dementia as assessed by the mini-mental status exam and DSM-III criteria. The authors suggested that Parkinson's disease and dementia with Lewy bodies overlap both clinically and pathologically.

Another recent study used MRI volumetric analysis to investigate the relationship between hippocampal size and deficits on verbal, visual, or spatial memory or set-shifting ability in non-demented PD subjects [8]. The authors found an inverse relationship between performance on visual or verbal memory tasks and hippocampal volume. There was no relationship between performance on spatial working memory or set-shifting tasks and hippocampal volume. They concluded that memory deficits in PD are due to hippocampal atrophy. These results appear to differ with those of Churchyard and Lees [\*\*7] who reported no hippocampal atrophy in demented PD subjects. However, the volume loss as seen with MRI may not be due to change in neuronal density.

### *Mood disorders in PD*

One important complication of PD and its treatment is the development of mood fluctuations which parallel plasma levodopa levels. Maricle and colleagues have reported several studies of this phenomenon, confirming that this is most likely a direct cerebral effect of levodopa [9,10]. They have now shown that earlier in PD, patients show smaller fluctuations in mood [\*\*11]. This fits well with the hypothesis that mood fluctuations in advanced PD are similar in etiology (though probably different in functional neuroanatomy) to motor fluctuations.

A large minority of PD patients have persistent major depression. Unfortunately, there is little sound data on treatment; one review found no published study with adequate methodology

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[12]. Recent reports include a survey of neurologists from the Parkinson's Study Group regarding antidepressant treatment [\*13], and a study in which moclobemide was added to selegiline for treatment of depression in PD [\*14]. A retrospective study of ECT for depression in PD [\*15] confirmed that ECT is an effective antidepressant treatment in PD patients, though delirium was a frequent and serious side effect [16].

### *Psychosis in PD*

Psychosis is a frequent complication of PD and probably a substantial risk for nursing home placement and death [17,18]. However, 46 years after chlorpromazine, there is still no peer-reviewed, methodologically adequate trial of any antipsychotic in this population. Perhaps the best published study was the 1996 report on olzapine, but in that study raters were aware of treatment assignment [19]. Fortunately, we will not have to wait much longer. A presentation at the 1998 American Academy of Neurology meeting described a multicenter, double-blind, placebo-controlled study of clozapine in PD [\*\*20]. Also, several small case series suggested that initial enthusiasm about risperidone, olanzapine and quetiapine must be tempered by the fact that they can occasionally cause significant worsening of parkinsonism in this population [21,22,\*23,24,25,26,27,28]. More rigorous data are required before we can decide the merits of any of the newer antipsychotics in PD.

The neurobiology of psychosis in PD is still largely unknown, but a pilot study by Goetz and colleagues [\*29] confirms clinical evidence that levodopa-induced hallucinations are a long-term rather than immediate effect of levodopa. Two recent phenomenological studies [\*30,\*31] show that PD patients who develop psychosis early in their course may comprise a different

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group than patients who develop psychosis only in late PD, often accompanied by dementia or depression. However, the suggestion [\*29] that psychosis early in the course of parkinsonism requires a diagnosis other than idiopathic PD seems premature, pending (1) studies in which parkinsonian etiology is ascertained blind to presence of psychosis, and (2) firmer consensus on the nosology of diffuse Lewy body disease and parkinsonism with Alzheimer's disease. Auditory hallucinations are less common than visual hallucinations but clearly occur in PD patients [32].

### **Huntington's Disease**

One simple but clever study attempted to “determine why patients with Huntington disease (HD) are apparently unaware of their involuntary movements” [\*33]. The results support the view that patients have a form of anosognosia rather than dementia or psychologically motivated denial.

Two reports address the question of whether cognitive deficits can be identified in asymptomatic gene carriers for HD. Clinically unaffected carriers showed no significant cognitive deficits in one study [\*34]. In a larger study [\*\*35], logical and verbal memory test performance was worse in neurologically normal at-risk individuals who later were found to have abnormal versus normal number of CAG repeats in the huntingtin gene. Additionally, gene carriers with higher repeat numbers tended to do worse on several tests. These studies show that there are statistically significant, but clinically subtle, cognitive disturbances before development of abnormal neurological signs in HD. However, motor abnormalities below the neurological exam threshold may precede these cognitive abnormalities.

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### **Psychological symptoms in dystonia**

An interview study of 44 adult patients with cervical dystonia found frequent panic disorder, major depression, and OCD [\*36]. The 66% frequency of diagnosable psychiatric illness in this group implies that, contrary to suggestions in the literature [37], the presence of preexisting mental illness is unreliable as an indicator of atypical or “psychogenic” dystonia.

### **Pathophysiology of Tics**

The prevailing hypothesis of tic pathophysiology involves increased dopamine activity in basal ganglia circuits. This idea is variably supported by neurochemical, functional imaging, and clinical pharmacologic data [38]. Recent support comes from functional MRI findings of BOLD signal changes in basal ganglia and thalamus that correlated inversely with tic severity during attempts to suppress the tics [39]. One prediction of this hypothesis is that dopamine depletion should decrease or eliminate tics. However, a recent report of 4 individuals with tics beginning in childhood and Parkinson’s disease beginning in later adulthood found that tics neither decreased with onset of PD nor worsened with dopaminergic treatment [\*40]. This suggests that tics are not exclusively due to functional overactivity of the dopamine system, but must involve other systems as well.

Over the past several years, there has been increasing evidence for a post-infectious or immune-mediated mechanism in some individuals with tics or TS. It has long been known that neurologic illness, especially Sydenham (rheumatic) chorea, can follow group A beta-hemolytic streptococcal (GABHS) infections [41]. Less well-known is that obsessions, compulsions, inattentiveness, tics, and even mania can accompany Sydenham chorea [41,42]. Thus, it may not



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be surprising that some individuals develop obsessive-compulsive disorder (OCD), tics (including Tourette syndrome), or both in close temporal relationship to an antecedent GABHS infection. Post-infectious onset of tics or OCD has been an area of active research by several investigators [\*\*43]. Although tics associated with infections other than strep have been reported, including Lyme disease [44], the strep association appears to be the most convincing. A group at the NIMH has coined the term PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection) and has recently published a description of their first 50 patients [\*45]. They define PANDAS by abrupt childhood onset of OCD or tics, temporally related to GABHS infection, with neurologic signs (hyperactivity, choreiform movements, tics) during an exacerbation.

Support for PANDAS as a possible etiology of tics comes from several independent lines of evidence, as reviewed recently by Kurlan [\*\*43]. Two lines of evidence will be discussed here. One is the presence of antineuronal antibodies in subjects with TS. Singer et al. [\*\*46] found increased levels of antibodies against putamen in 41 children with TS compared to 39 age-matched controls. However, there was substantial overlap. In TS subjects, these antibodies were more common in those with serologic evidence of GABHS infection. There was no association between elevated antineuronal antibodies and age of tic onset, tic severity, sudden onset of tics, presence of OCD, or presence of ADHD.

The second line of evidence concerns the presence of markers associated with acute rheumatic fever in individuals without rheumatic fever, but with tics or OCD. One such marker is a B cell surface marker called D8/17. This marker had is present in 90 - 100% of subjects with rheumatic fever and virtually absent in controls [47]. In a study by Murphy et al. [48], patients

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with either TS or OCD, but without rheumatic fever, had an elevated average percentage of B cells expressing D8/17. All patients but only one control were considered D8/17 positive.

Another study investigated the frequency of D8/17 positive individuals among groups of 27 children with PANDAS, 9 children with Sydenham chorea, and 24 healthy controls [49]. They found that 85% of the PANDAS group, 89% of the Sydenham chorea group, and 17% of the control group were D8/17 positive. Thus, some individuals with tics or OCD appear to share a genetic marker with individuals who are susceptible to developing rheumatic fever. This lends support to the notion that in some predisposed individuals, tics or OCD may be a manifestation of post-streptococcal immune-mediated disease.

Although many studies have suggested an autosomal dominant inheritance of TS, attempts to identify a specific gene have been unsuccessful, as reviewed recently [\*50]. One approach has been to test candidate genes in neurotransmitter systems thought to be involved in TS. Previous studies have suggested that the dopamine receptor D2, D3, or D4 loci might be implicated in TS, but other studies have not confirmed those findings [\*50]. A recent report using single stranded conformational polymorphism analysis of the D1 receptor gene failed to demonstrate any mutations in subjects with TS [51].

### **Comorbidity in Tourette Syndrome**

Although TS is defined solely by tics, many TS patients find other symptoms more problematic, especially obsessions, compulsions, or impaired attention or learning. An important unanswered question is whether comorbid psychological symptoms define a clinically meaningful subgroup of TS.

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In a multicenter German family study of TS and OCD, obsessions and compulsions (OC symptoms) were more frequent in relatives of TS patients who themselves had OC symptoms [\*\*52]. However, OC symptoms in relatives were most likely caused by the same gene(s) as tics, as they were usually accompanied by tics (in male relatives). Also, if OC symptoms were present, their severity, including the diagnostic threshold for OCD, was irrelevant to heritability of either tics or OC symptoms. These findings support the concept that the presence or absence of OC symptoms may be a biologically meaningful clinical feature of TS. This study also reports several other clinically relevant findings, including the observation that five relatives had otherwise typical tic syndromes but definitely dated tic onset to after age 21.

Another report also supports the validity of subdividing TS by presence or absence of OC symptoms. A group from Harvard [\*\*53] examined 61 patients with TS, OCD, or both (TS-OCD) for various other psychiatric syndromes. The rates for most mood and anxiety disorders did not differ between the TS-only group and the OCD-only group. However, the 3 groups differed significantly in rates of bipolar disorder, social phobia, body dysmorphic disorder (BDD), trichotillomania, attention deficit hyperactivity disorder (ADHD), and substance abuse. To summarize, the TS+OCD group had the highest frequency of comorbidity, ADHD segregated with tics, and (surprisingly) BDD also seemed more closely related to TS. The authors conclude that TS+OCD has more substantial comorbidity than either diagnosis alone, and that this group is probably linked more closely to TS than to OCD.

In this study, three of 20 patients with both TS and OCD met criteria for bipolar disorder [\*\*53]. Given a population prevalence for bipolar disorder of <1%, the 15% prevalence here is remarkable. However, a study from Spain found that 12% of 90 consecutively examined patients

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with TS had either bipolar disorder or schizoaffective disorder, and an additional 21% had bipolar II disorder or cyclothymia [54]. The majority of these patients (80%) also had OCD, and many of them reported fewer tics during depressive episodes and more with manic episodes [54]. This surprising prevalence of manic illness in TS+OCD patients is probably not due to excessive symptom reporting in general, as this group reported less panic disorder or agoraphobia than the other groups [\*\*53]. Further studies of this difficult to treat subgroup are warranted.

### **Tardive movement disorders**

Molho et al [\*\*55] contrasted clinical features of torticollis patients with presumed tardive or primary etiologies. Contrary to clinical lore, several clinically useful distinctions were found. Another large report on tardive cervical dystonia also found frequent retrocollis [\*56]; although the disease was chronic, stopping neuroleptics could clearly help the dystonia.

A large prospective study on the incidence of tardive dyskinesia (TD) in the elderly found staggeringly high cumulative rates of 25% and 53% after 1 and 3 years of total antipsychotic treatment, respectively [\*\*57]. Surprisingly, a past history of electroconvulsive therapy treatment was a strong risk factor for later development of TD; whether this reflects diagnosis, severity of illness, or other symptomatic features remains to be shown. A meta-analysis of vitamin E treatment of TD concludes that a subgroup of patients shows statistically meaningful but clinically modest benefit without substantial side effect risk [58]. However, methodological flaws in several of the studies reviewed render these conclusions tentative. In a randomized study, fully informed consent regarding TD risk did not negatively affect antipsychotic compliance [59].

The availability of a direct genetic test for HD allowed a study of 12 patients with

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presumed senile chorea to conclude that six had Huntington's disease with a negative family history [60]; this has implications for prior studies of "spontaneous" dyskinesias in the elderly. On the other hand, the existence of abnormal movements in never-treated subjects with schizotypal personality disorder [61] or schizophrenia suggests that movement disorder may be an integral part of these illnesses [62]. However, in this study and in prior reports on untreated schizophrenia, the abnormal movements observed are often complex and are generally not the orofacial stereotypies with tongue protrusion which are typical of tardive dyskinesia.

### **Catatonia and neuroleptic malignant syndrome**

Two interesting reports on the genetics of periodic catatonia, an illness marked by relapsing and remitting catatonic episodes, involved 83 probands [63,64]. The authors found evidence for a single major gene effect with genetic anticipation and a 27% risk to first-degree relatives. There was a trend ( $p < 0.10$ ) for paternal transmission of illness to be associated with younger age of onset in the probands. These results are preliminary but may be consistent with a triple repeat mechanism.

A case-control of study neuroleptic malignant syndrome (NMS) confirmed previously reported risk factors for development of NMS, including parenteral administration of neuroleptics and catatonia, and also revealed risks for agitation, parkinsonism, akathisia, and neuroleptic dosing [\*65]. Another study [66] examined the relationship between catatonia, NMS, and low serum iron, an acute phase reactant which had previously been found in NMS [67]. Low serum iron was found in every instance of "malignant catatonia" (NMS-like without neuroleptic exposure), and these patients had a high risk of NMS upon exposure to neuroleptics. Some

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catatonic patients without malignant features also had low serum iron, but these patients did not tend to develop NMS. These interesting results may indicate a clinically meaningful subdivision of catatonia, and deserve confirmation in prospective studies.

## Conclusion

Important advances were reported in 1998 in the neuropsychiatry of movement disorders. We should soon see the long-awaited publication of adequate treatment studies of psychosis in Parkinson's disease. Also, increasing evidence supports the hypothesis that some cases of Tourette syndrome or OCD may be caused by autoimmune responses to streptococcal infections. However, at our current stage of knowledge, it remains appropriate to study TS using several different approaches, including genetic and neuroimaging studies. Exciting research opportunities remain in this field of medicine.

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