Neuropsychiatric Correlates and Treatment of Lenticulostriatal Diseases: A Review of the Literature and Overview of Research Opportunities in Huntington's, Wilson's, and Fahr's Diseases

A Report of the ANPA Committee on Research

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This report reviews clinical neuropsychiatric findings and opportunities for research in Huntington's, Wilson's, and Fahr's diseases. Consistent, systematic methodology is lacking among neuropsychiatric studies in these lenticulostriatal diseases. Systematic cross-sectional and longitudinal assessments are needed to ascertain the prevalence of psychiatric disorders as a function of disease course. Preliminary synthesis of existing data suggests the following heuristic relationships in these diseases: depression with parkinsonian states; personality changes with caudate or putamen disease; psychosis, impulsivity, and sexual disorders with caudate disease; dementia and mania with caudate and pallidal diseases; and compulsions with pallidal disease. Correlation of neuropsychiatric findings with disease stage, clinical signs, and radiologic, metabolic, physiologic, and pathologic markers of disease will add to our understanding of these conditions.

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The basal ganglia lenticulostriatal system is integral to processing cortical and limbic information. This system is composed of circuits communicating between the lenticular nucleus (putamen and globus pallidus) and the striatum (caudate nucleus and putamen). The lenticulostriatal system receives information from multiple limbic structures including the amygdala, cingulate gyrus, and nucleus accumbens.[1] Projections to the thalamus and frontal lobe make the basal ganglia lenticulostriatal system of great importance in understanding behavior.[2]

The lenticulostriatal system is connected to the frontal cortex through five functionally segregated circuits implicated in motor, cognitive, and psychiatric manifestations of basal ganglia diseases.[3,4] Three of these circuits—the dorsal prefrontal, orbitofrontal, and anterior cingulate—are implicated in primary psychiatric illnesses including depression, obsessive-compulsive disorder, and schizophrenia. Moreover, neurologic diseases involving these circuits carry an unusual proclivity for neuropsychiatric[5] and behavioral[6] disorders. Conse-

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quently, the basal ganglia lenticulostriatal system is one of the most important brain systems in neuropsychiatry.

This report reviews neuropsychiatric findings in major basal ganglia diseases with principal lenticulostriatal pathology. We focus on three representative diseases that primarily produce principal structural pathologic changes in the striatum and lenticular nucleus: Huntington's disease, Wilson's disease, and Fahr's disease. Our goal is to provide an overview of relevant neuropsychiatric findings of clinical interest in these illnesses and highlight directions for future research. Other basal ganglia diseases lacking principal pathology in these structures (Parkinson's disease), predominantly affecting other structures (dentatorubropallidoluysian atrophy), or with etiologies coincidentally affecting the lenticulostriatal complex (basal ganglia infarcts, carbon monoxide poisoning) are not considered here. Instead, we have limited our consideration to Huntington's disease (affecting principally the caudate), Wilson's disease (affecting principally the putamen), and Fahr's disease (affecting principally the globus pallidus).

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a dominantly inherited CAG trinucleotide repeat disease affecting the IT15 gene at 4p16.3.[7,8] HD prevalence approximates 4.1–7.5 per 100,000 but varies in different parts of the world.[9] An expanded IT15 CAG repeat (37 or more repeats) is 100% specific and 98.8% sensitive for HD.[10,11] Longer repeat length is correlated with earlier ages of onset and death.[10,12] Age at onset is variable, but HD typically presents between ages 35 and 50.[13] Genetic anticipation is associated with paternal transmission of the gene. Average life expectancy after HD onset is 15 years, although some patients survive up to 40 years.[13]

Expanded CAG sequences are translated into expanded polyglutamine repeats in the protein huntingtin, the gene product.[14] Although the function of huntingtin is not known, its effects may be amplified by this polyglutamine expansion,[15] possibly through interactions with other proteins.[16–18] Pathogenic mechanisms in HD may involve glutamatergic excitotoxicity, free-radical generation, oxidative metabolism defects, and apoptosis.[19,20] Caspase 3 (apopain), important in apoptosis, cleaves huntingtin in a CAG length–dependent manner.[21]

The pathology of HD is well known. It principally involves the loss of striatal medium spiny GABAergic neurons, especially in the caudate nucleus, although neuronal loss also can be observed in the globus pallidus, reticular portion of the substantia nigra, ventral anterior nucleus of the thalamus, cerebral cortex, cerebellar dentate nucleus, brainstem, and spinal cord.[22] Striatal atrophy becomes apparent on computed tomography (CT) and magnetic resonance imaging (MRI) during HD progression.[23] Reduced striatal D_1 and D_2 dopamine receptor binding occurs in HD and is more severe in rigid HD.[24] Frontal white matter atrophy occurs later in the illness.[25]

Clinical features vary, but they generally include movement disorders (usually chorea, sometimes myoclonus, dystonia, or parkinsonism), dementia, and psychiatric disorders (principally mood disorders). Childhood-onset HD usually presents with rigidity rather than chorea, cerebellar signs, and rapid cognitive decline. As the disease progresses, patients become demented, mute, achoreic, and often parkinsonian. Whether CAG repeat length influences disease progression[26,27] or neuropsychiatric presentation remains controversial.

Presymptomatic genetic testing for HD by means of a blood sample for determining an expanded CAG repeat sequence is available; there are attendant ethical considerations. Most subjects receiving test results seem to cope well over the short term when the findings are disclosed in the context of education and counseling,[28,29] although significant exceptions have occurred.[30] Clinical guidelines for presymptomatic testing have been developed,[31] and the psychological consequences of this testing have been reviewed.[32] Pre- and post-test counseling is an important element of presymptomatic testing.

Neurological Features

Involuntary movement disorders in HD can be followed by use of the Quantified Neurologic Examination[33] and the Unified Huntington's Disease Rating Scale.[34] Loss of lateral striatopallidal projections correlates with chorea, whereas loss of medial striatopallidal projections correlates with akinetic-rigid presentations.[35] Medial pallidal γ-aminobutyric acid (GABA) concentrations increase as the chorea progresses.[36] Disturbances of voluntary eye movements also occur (e.g., abnormal saccadic and pursuit eye movements). In contrast to the waning of chorea late in the illness, these disturbances progress throughout the illness[13,37] and correlate with functional disability.[38]

Neuropsychiatric Features

HD is dominated by abnormal involuntary movements, dementia, and psychiatric disorders. Psychiatric features are the presenting manifestation of HD in 24% to 79% of cases and occur at some point during the illness in 35% to 79%,[39] although these estimates were determined by using a wide variety of methods. Irritability,

apathy, and mood disorders are the most common psychiatric disorders.[9] Ranen has recently reviewed clinical aspects of psychiatric disorders in HD.[40]

Dementia: Initial manifestations of dementia include impairments in cognitive speed, mental flexibility, concentration, executive function, new verbal learning, and the reverse serial sevens task of the Mini-Mental State Examination.[41–43] Memory retrieval is affected more than storage, and patients may respond to cueing.[44,45] The dementia progresses to become more global, impairing visuospatial ability and judgment.[46] Dementia has been related to caudate GABA and glutamate depletions.[47] Attempts to relate other psychiatric manifestations to cognitive changes have usually shown little correlation.[48] Aphasia and agnosia are absent in HD dementia.[49]

Personality Changes: Personality changes may present prodromally and may occur to some extent in all patients as the disease progresses.[48] Personality changes were found in 72% of 110 patients with HD in one recent prevalence survey.[50] Apathy and aggression are greater in HD than in Alzheimer's disease.[51] Aggression, irritability, and apathy did not correlate with each other in one study.[51] Personality changes may relate to reduced ventrobasal striatal glucose metabolism and orbitofrontal dysregulation.[4,52]

Apathy occurs in nearly half of patients,[51] and in a small sample of patients it became more prominent over the course of HD.[53]

Among the more troubling conditions are irritability and disinhibited aggression. Irritability occurs in about half of patients,[51,54] is severe in about one-third,[9] may be directed against specific individuals, and is associated with premorbid irritable traits.[51] Subjects at risk for HD have higher ratings of anger and hostility than control subjects on measures of present mood.[55]

Elevated aggression scale scores were found in 59% of patients with HD.[51] Although aggression most commonly occurs early in the course of HD,[56] one-third of patients with advanced HD in nursing homes exhibited aggression that correlated with the severity of their functional impairment.[57] Violent behavior in patients with HD may at times assume the form of assault, arson, and homicide.[58,59]

Psychoses: Symptomatic schizophrenia has been observed in up to 9% of patients with HD.[9,50] Psychotic symptoms can occur in up to 25% of patients with HD and can include multiple forms of hallucinations and delusions.[13,39,60] Rates of psychosis vary by setting and sample selection factors.[60] Psychotic symptoms are more common in early-onset HD.[9] Psychosis in HD has been correlated with medial caudate pathology[61] and reduced anterior hemispheric metabolism.[52]

Mood Disorders: Mood disorders occur in about 40% of patients with HD.[9,50] Bipolar disorders occur in approximately 10%.[9] Depression often precedes the onset of the movement disorder.[9] The pattern of depressive symptoms in HD resembles idiopathic major depression, and psychotic features tend to be mood congruent.[62] Depression did not correlate with apathy or irritability but did correlate with reduced orbitofrontal glucose metabolism in a fluorodeoxyglucose positron emission tomography (PET) study of HD.[63] Depression may relate to dorsomedial caudate pathology.[13,64]

Suicide rates in HD are as high as 12.7%,[65] which is more common than in stroke or Parkinson's disease with depression.[48] Suicide risk is especially of concern in older patients with HD.[65] In a retrospective case-controlled study, risk for suicide in patients with HD was chiefly determined by childlessness.[66] Family history of suicide, single marital status, living alone, depression, and contact with others afflicted with HD contributed weakly to suicide risk.

Anxiety Disorders: An early study reported that anxiety occurred in nearly 12% of 102 patients with HD and was the most common prodromal symptom.[56] Anxiety occurs early in the course of HD and was associated with longer survival in one study.[67] Although panic disorder, generalized anxiety, and obsessive-compulsive disorder (OCD) have been observed in patients with HD, the prevalences of these anxiety disorders have not yet been determined. Obsessions often involve cleanliness and checking as in primary OCD, and certain families with HD may carry a predisposition toward OCD.[68] Mixed anxiety and depression has been associated with akinetic-rigid HD.[56]

Impulse Control and Sexual Disorders: Intermittent explosive disorder was found in 31% of 186 patients with HD.[13] Sexual disinhibition, hypersexuality, and paraphilias have been described,[54,58,69] although most patients eventually develop sexual apathy or impotence.[13] Hypersexuality occurred in 12% of men and 7% of women in one study.[58] By DSM-III-R criteria, 82% of 39 patients with HD had sexual disorders, with the most frequent being hypoactive sexual disorder.[70]

Treatment

Several strategies aimed at reducing the underlying pathological effects of excitotoxic amino acids have been suggested.[71] Blinded controlled trials of baclofen[72] and

idebenone[73] did not evidence any slowing of HD progression. D-alpha-tocopherol 3,000 IU per day improved neurological symptoms early in the course of HD.[74] Treatment with coenzyme Q10 reduced elevated cortical lactate concentrations in patients with HD, although clinical correlates were not studied.[75] Ciliary neurotrophic factor demonstrated a protective effect against quinolinic acid–induced striatal degeneration in a monkey model of HD.[76]

Movement disorder treatment attempts have yielded mixed results. Optimal reduction of chorea with haloperidol was obtained at doses of 1.5–10 mg/day (2–5 ng/ml), whereas higher doses rarely produced additional benefit.[77] Under double-blind placebo-controlled conditions, apomorphine actually improved chorea and motor impersistence,[78] clozapine variably improved chorea but worsened functional capacity,[79] and piracetam worsened chorea.[80] Cannabidiol failed to alter chorea in a randomized double-blind placebo-controlled crossover study.[81] Milacemide, a glycine prodrug, affected neither chorea nor cognition under double-blind placebo-controlled conditions.[82]

Neuropsychiatric treatment data are limited by a paucity of controlled trials.[62] There are no specific treatments for the cognitive disorder of HD. Fluoxetine failed to improve cognition, functional capacity, or neurological status in a randomized double-blind placebo-controlled study in nondepressed patients with HD, although there was a slight improvement in agitation and in need for routine.[83] Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, worsened memory and exacerbated psychiatric symptoms in a double-blind placebo-controlled study involving patients with HD.[84] Sertraline was effective in 2 consecutive cases against irritability and violent behavior.[85] Propranolol is reported to relieve aggression associated with frustration and impatience in HD.[86] Anecdotal evidence also supports the utility of buspirone in aggression.[87,88]

Psychotic features may be either responsive or refractory to neuroleptic treatment.[53] There is some evidence that clozapine may be particularly efficacious in psychosis[89,90] and that delusions may be more responsive to neuroleptics than hallucinations,[62] but more data are needed. Although mood stabilizers in HD require study, lithium rarely has been considered to be effective in treating bipolar disorders associated with HD.[62]

Major depression in HD is thought to be undertreated,[91,92] presumably due to underrecognition. Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are regarded as first-line treatments for depression,[53,62,93] and patients with HD seem to respond to antidepressant treatment in a manner similar to patients with primary depression, although appropriate studies are lacking.[53] Monoamine oxidase inhibitors may be useful for patients not responding to first-line agents.[94] Augmentation of fluoxetine with deprenyl led to beneficial mood, motor, and behavioral effects in 1 patient.[95] Delusional depression predicted the most favorable response to ECT among 5 depressed patients with HD.[96]

There is some evidence that medroxyprogesterone and leuprolide may be useful in reducing sexual disinhibition in HD.[97] Although there are several descriptions of family therapy in HD, controlled outcome data are lacking.[98]

Opportunities for Further HD Research

1. *Effects of CAG repeat length.* The effect of HD gene CAG repeat length on disease progression and neuropsychiatric symptoms requires clarification.
2. *Heritability of neuropsychiatric phenomena.* Definition of the heritability of neuropsychiatric phenomena (such as OCD) in kindreds with HD may distinguish those at risk and improve our understanding of these phenomena.
3. *Prevalence of psychiatric disorders.* Determination of the prevalence of anxiety disorders by use of standardized diagnostic criteria is needed. Replication of prevalences of psychiatric disorders across different clinical settings is needed to determine the generalizability of earlier studies, as well as the effects of ascertainment and sample biases in previous studies.
4. *Correlates of psychiatric disorders over disease course.* Elucidation of neuropathological correlates of psychiatric disorders and their evolutionary time courses in relation to HD progression would facilitate our understanding of the basal ganglia circuitry mediating these conditions.
5. *Functional imaging correlates of psychiatric disorders.* Additional correlation of functional imaging data with particular psychiatric sequelae would be useful, as would further characterization of the differences among subjects with HD and depression, HD without depression, and primary depression without HD.
6. *Neuroprotective agents.* Controlled treatment trials of the effects of neuroprotective agents against HD progression, employing larger sample sizes, are indicated. Such trials may allow detection of subtle protective effects not evident in previous studies.
7. *Pharmacologic interventions.* Controlled treatment trials of neuropharmacologic and psychopharmacologic interventions in HD are needed. This is especially true of the cognitive disorder, which cur-

rently lacks any specific treatment. Appropriate controls would include patients with progressive dementing illnesses, medically ill patients with depression or anxiety, and patients with primary psychiatric disorders.

8. *Treatment-refractory conditions.* Novel approaches to treating neuropsychiatric conditions refractory to conventional treatments are needed.
9. *Psychotherapy and genetic testing.* Issues relating to psychotherapy and the psychological effects of genetic testing require further detailed study.
10. *Family therapy.* The efficacy of family therapy interventions requires further assessment. Caregiver burden should be a particular focus of concern.

WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

Wilson's disease (WD) is an inherited disorder of copper metabolism leading to abnormal copper deposition in the liver, brain, and other organs. Mutations of the gene ATP7B on chromosome 13q14 band 14.1–21.1[99] disrupt coding for a copper-containing P-type adenosine triphosphatase that alters apoceruloplasmin function, a copper-transporting protein. The absence of biliary ceruloplasmin in WD apparently prevents biliary excretion of copper.[100] Subsequent copper accumulation with its pro-oxidant effects may lead to cellular demise, including mitochondrial DNA mutations.[101]

More than 40 mutations of the ATP7B gene are known.[102] Some mutations are associated with ethnicity, WD severity, age at onset, or presentation.[103] Mutations leading to severe gene dysfunction produce an aggressive disease course (early-onset WD with severe liver manifestations), whereas mutations leading to milder gene dysfunction produce a less aggressive disease course (late-onset neurological and subclinical liver manifestations).[104]

The worldwide incidence of WD approximates 12–30 per million,[103,105] with higher prevalences in Japan linked to consanguinity.[106] Mean age at onset ranges from 5 to 35 years of age (mean age 17), but onset and initial manifestations sometimes vary between families. Generally, a rule of thirds applies to the manifestations, with approximately one-third each presenting with predominantly hepatic, neurological, or psychiatric symptomatology. Although neurological and psychiatric features constitute the most common manifestations, WD can affect a wide range of organs throughout the body. An important extrahepatic manifestation is copper deposition at the corneal limbus, the Kayser-Fleischer ring (KF ring), which correlates with WD severity.[107] Treatment-related reductions in KF rings correlate with improvements in MRI scan quantitative scores in WD.[108] Treatment may prolong survival beyond 20 years. In the absence of treatment, patients may die within 5 years after developing WD manifestations, and patients with neurologic features may die within 6 months.

On MRI, increased signal on T_2-weighted images due to copper deposition is usually present in the putamen or other structures.[109,110] T_1 signal is generally reduced, but signal can be increased in the globus pallidus in patients with portal-systemic encephalopathy due to liver necrosis in WD.[111,112] Several recent studies have examined the distribution of MRI findings in WD.[112–114] The putamen and pons were most frequently affected (80%–90% of patients) in two studies.[112,113] In one study, there was a predilection for abnormal signal in the anterior rim of the putamen and the ventral nuclear mass of the thalamus, although the sample size ($N = 25$) was too small to indicate any correlation with clinical findings.[113] The dorsal and central regions were the most commonly involved pontine areas.[112] In another study, parkinsonian signs correlated with striatal and pontocerebellar abnormalities, whereas cerebellar signs correlated with dentatothalamic tract abnormalities.[114] Cortical and subcortical abnormalities tended to occur predominantly within the frontal lobe.[112] The predilection for copper deposition in particular brain regions is poorly understood. On CT, the most common findings are ventricular dilatation, basal ganglia hyperdensities, and atrophy of cerebral cortex, brainstem, or cerebellum.[115] Basal ganglia MRI T_2 hypointensity and CT hypodensity are consistent with cavitations found in more aggressive WD.

Reduced glucose metabolism in cerebellum, striatum, cerebral cortex, and thalamus may be seen on PET in WD.[116] Reduced striatal glucose metabolism was correlated with neurological sign severity, and striatal glucose metabolism and D_2 receptor binding improved with clinical improvement in response to chelation therapy.[117] On MR spectroscopy, pallidal *N*-acetylaspartate was reduced in WD patients compared with control subjects, and WD patients with portosystemic shunting had lower pallidal *myo*-inositol than WD patients without shunting.[118] In patients with neurologic WD, reduced D_2 binding on single-photon emission computed tomography (SPECT) correlated with the overall severity of neurological deficits but not with specific neurological signs.[119]

Laboratory diagnosis of WD is made by identifying abnormal ceruloplasmin and high urinary copper levels and is confirmed by hepatic biopsy disclosing copper. Ceruloplasmin is reduced in 95% of WD cases, but it can also be normal or elevated. Serum copper levels are not

of diagnostic value. Neuroimaging is supportive but not diagnostic, and the clinical neurological exam is more diagnostically sensitive than CT.[120] Western blot analysis of ceruloplasmin can distinguish WD homozygosity, heterozygosity, and other non-WD hypoceruloplasmic conditions.[100] Presymptomatic molecular genetic testing using DNA linkage analysis (restriction fragment length polymorphisms and polymerase chain reaction–based analysis) is useful in studying siblings.[121]

Neurological Features

A wide range of oculomotor, cerebellar, speech, movement, pyramidal, autonomic, and seizure disorders have been described in WD. Prevalences of some neurological signs have been established in small samples. Dysdiadochokinesia and dysarthria occur most commonly.[122] Initial presenting neurological features include mild tremor, speech problems, and micrographia.[123] Features at 10-year follow-up have also been determined.[124] Dystonia and chorea seem to occur most commonly in childhood-onset and in endstage WD.[103] Whereas 6% of patients with WD manifest seizures, more than 60% remit with WD treatment.[125] Visual and sensory systems are curiously spared despite high copper concentrations in sensory cortex.[103] The prevalence of KF rings in neurologic WD approximates 50%, in contrast to less than 10% in hepatic WD.[122]

Neuropsychiatric Features

Clinical suspicion is critical in diagnosing WD. The diagnosis was missed in two-thirds of neurologic WD initial presentations, producing a 13-month delay in diagnosis.[126] Across studies, up to one-fifth of patients with WD present initially with psychiatric features in isolation, one-third present with predominating psychiatric features, and two-thirds of patients with WD eventually develop psychiatric features. The exact lifetime prevalence of psychiatric disorders is not known but is estimated to range between 30% and 100%.[127–129] Half of patients may undergo psychiatric hospitalization before WD is recognized. Psychiatric manifestations may precede neurological signs in the early stages of WD.[127] Incongruous behavior, irritability, depression, and cognitive impairment were the most common psychiatric symptoms among 129 patients with WD.[130] It is thought that psychiatric disturbances secondary to liver dysfunction are rare in isolated hepatic WD, but systematic study is needed. Selection factors, sample sizes, and diagnostic approaches vary across studies, and other variables are not universally taken into account. As an example of selection factors that can vary, one study involving 24 patients with neurological manifestations disclosed a high rate of personality changes (71%).[123] Findings in patients lacking neurological manifestations may be different.

Cognitive Disorders: Cognitive impairment is generally mild,[131] occurring in less than 25% of patients.[122,128,132] Cognitive impairment worsens with increasing disease duration[133] and neurological manifestations.[124] Some apparent cognitive deficits may be due to reduced motor speed rather than reduced information processing speed.[134] Hence, exact rates of true cognitive impairment in neurological and other symptomatic presentations of WD remain unclear.

Personality Changes: The life-prevalence of persistent personality change ranges between 46% and 71%,[123,132] typically manifesting as irritability or aggression.[122,127,129,132,135,136] Personality syndromes have been correlated with dyskinesia, dysarthria, and lesions of the putamen and pallidum.[137] Sociopathic features correlate with dysarthria.[135] Irritability and incongruous behavior are associated with brainstem signs and dystonia but not with tremor.[128]

Psychoses: Schizophreniform disorders, catatonia, and hallucinations are no more common in WD than in the general populction,[122,128] but psychosis and catatonia occurred somewhat more commonly (8% each) in neurological WD.[123]

Mood Disorders: Essentially nothing is known about mania or its prevalence in WD. Major depression occurred in 27% in a prospective study of 45 subjects with WD.[122] Mild depression has been correlated with cognitive impairment, parkinsonian rigidity, bradykinesia, and third-ventricle dilatation[137] as well as unspecified gait disorders.[135] Whether depression is a psychological reaction to WD or is due to biologic compromise is unresolved. Application of diagnostic criteria will be needed in future studies to distinguish adjustment disorders from mood disorders in WD. Suicidal behavior occurs in 4% to 16% of patients with WD across studies.[122,127]

Other Psychiatric Disorders: As with mania, essentially nothing is known about anxiety disorders, substance abuse, or other psychiatric disorders in WD.

Treatment

Clinical improvement in WD with treatment is generally limited to the first 5 years of symptoms and the first 2 years of WD treatment.[127,130] Early recognition and treatment are therefore essential. Treatments include cupriuretic copper chelators (penicillamine and trientine) and

copper-depleting agents (zinc and thiomolybdate). Specific indications for these various agents remain controversial. There are some outcome data regarding these drugs, but these data usually refer to neurological outcome, whereas psychiatric outcome is more anecdotally described.

Of 137 patients with neurologic WD undergoing chelation, 42% became asymptomatic, 26% improved neurologically, 17% were disabled, and 15% died; of the entire sample, 22% suffered neurological exacerbations.[138] Glucose metabolism and dopamine receptor binding on PET correlated with improved motor function after 1 year of treatment in a single patient with WD.[139] Auditory and somatosensory evoked potentials have detected neurological improvement with treatment[140–142] but did not correlate well with psychiatric improvement.[124] Psychiatric symptoms resolved more often in patients without dysarthria, incongruous behavior, and hepatic symptoms.[130] Incongruous behavior and cognitive impairment improved more than irritability and depression during WD treatment.[130] Memory, Performance IQ, Full Scale IQ, and psychosis have each responded to treatment.[127,130,143–145] Other manifestations resolving with WD treatment have included amnestic disorder, dementia, hypersexuality, aggression, hyperactivity, and disinhibition.

D-penicillamine treatment has been correlated with improvements in T_2 abnormalities on MRI, dopamine receptor binding on SPECT[146] and PET,[139,146] and glucose metabolism.[139] Neurological exacerbations can occur with penicillamine therapy and may lead to further neurological disability, seizures, movement disorders, and neuropsychiatric disturbances including psychosis.[147] These exacerbations may be irreversible and can occur even in previously asymptomatic patients.[148]

Tetrathiomolybdate has been suggested as the initial treatment for neurologic WD, although more data are needed.[149] Good to excellent recoveries have been obtained in most patients reported.[150] In psychiatric WD treated with this agent, symptomatic exacerbations did not occur and most patients had made a good recovery at 1-year follow-up.[149]

Zinc has been considered to act too slowly to be used as the initial treatment for neurological WD.[123] Although neurologic exacerbations can occur,[151] dramatic improvements in the neurological exam and nearly complete resolution of increased T_2 signal in the putamen, thalamus, and brainstem on MRI were demonstrated in a patient undergoing zinc treatment.[152] Simultaneous administration of chelators and zinc does not increase the effectiveness of treatment.[153]

Both transient[154] and irreversible[155] neurological exacerbations have been observed with trientine. Dimercaprol, a chelator, was the earliest treatment for WD, but it requires frequent, painful injections and is rarely used. Potassium disulfide, ascorbic acid, and vitamin E are, as yet, of unproven value. Whereas deionized or distilled water may be useful in communities with high copper levels in drinking water,[123] a low-copper diet is ineffective.[156] Pregnant patients with WD should be treated with zinc, which actually protects against some forms of birth defects[157] as well as WD-related fetal demise. Penicillamine is teratogenic and can produce hydrocephalus, cerebral palsy, craniofacial defects, and other stigmata in the developing fetus, although normal pregnancies and births have been reported.

Secondary manifestations of hepatic WD can reverse with WD treatment, and liver transplantation is not always necessary in severe hepatic disease.[158,159] Liver transplantation indications and outcome have been reviewed elsewhere.[160–162] Neurological signs may improve as early as 4 weeks after transplantation.[162]

Controlled trials of psychotropic treatment, psychotherapy, and family therapy have not been carried out in WD.[163] It is anecdotally reported that patients with WD are predisposed to extrapyramidal side effects from antipsychotics.[164] A case of neuroleptic malignant syndrome in WD that responded to bromocriptine and dantrolene has been reported.[144] Whether this predisposition to extrapyramidal syndromes also applies to treatment with SSRIs is not known. ECT for delusional depression in a patient with WD led to a 3-minute motor seizure followed by a switch to mania.[165] Further ECT treatment was interrupted by orthopedic surgery after a fall related to manic behavior. The authors pondered whether this case suggests greater sensitivity to ECT due to intracerebral copper deposition. Beyond these rare anecdotes, little is known about treating psychiatric conditions in WD.

Opportunities for Further WD Research

1. *Role of copper deposition.* Basic research may help establish the pathogenic role of copper and the basis for localized copper deposition in specific brain structures, clarifying how certain structures (e.g., sensory cortex) endure substantial copper deposition yet still maintain functional integrity.
2. *Early neuropsychiatric signs.* Confirmation of the earliest neuropsychiatric manifestations is needed because early detection is critical to successful treatment, and early WD is frequently missed. This is especially important in patients lacking neurological signs, since these patients have been less well studied.

3. *Assessment instruments for WD.* The relative sensitivities of the neurologic exam, mental status exam, CT, MRI, and physiologic tests for diagnosing and following WD require further evaluation.
4. *Prevalences of neuropsychiatric disorders.* The prevalences of neuropsychiatric manifestations need replication across a variety of settings to reduce sample biases. Prevalences should be determined while controlling for severity and clinical features. In particular, the prevalence of neuropsychiatric manifestations in patients with hepatic WD should be carefully and systematically evaluated, since data are lacking.
5. *Pattern and course of psychiatric disorders.* The pattern and course of certain psychiatric disorders should be consistently characterized by using uniform diagnostic criteria and sensitive quantitative rating scales. Specific questions that might be addressed follow:
   a. What is the nature of cognitive impairment in WD? Specifically, how much is due to motor slowing? What are its clinical, anatomical, and physiological correlates? Which features respond to treatment?
   b. What are the prevalence rates of various depressive diagnoses in WD? What are the characteristic features of depressive illness in WD? Do these features differ from those of depression in other illnesses? What are the most reliable correlates of depression (since a number of correlates have been linked to depression)?
   c. Do mania, anxiety disorders, or substance abuse occur? If so, what are their prevalences, symptomatologies, courses, correlates, and responses to treatment?
   d. Are certain neuropsychiatric features correlated with certain mutations? Do neuropsychiatric disorders cluster in certain kindreds with WD?
6. *Correlates of neuropsychiatric disorders over disease course.* The progression of neuropsychiatric manifestations and their clinical, radiologic, neuropathologic, metabolic, and neurotransmitter correlates over the course of WD require further characterization. Moreover, the impact of individual manifestations on overall outcome and family function should be studied.
7. *Copper chelating and depleting agents.* Treatment studies are needed to define the effectiveness of specific copper chelating and depleting agents on individual neuropsychiatric manifestations, including the relative rates of neuropsychiatric exacerbations with each drug.
8. *Pharmacologic interventions.* The efficacy and risks of neuropharmacologic and psychopharmacologic interventions for WD and correlates of good and poor outcome with these interventions remain to be determined.
9. *Psychotherapy and family therapy.* Psychotherapy and family therapy issues need definition in WD.

FAHR'S DISEASE

Fahr's disease (FD) refers to idiopathic calcification of the basal ganglia. This condition has been known since the middle 1800s. The more general term *Fahr's syndrome* has been applied variably throughout the literature to indicate either FD or cases of secondary basal ganglia calcification. For the purpose of clarity, we will use the term *basal ganglia calcification* or *BGC* when referring to BGC in general (including idiopathic FD and secondary calcification), and *FD* when referring specifically to idiopathic BGC.

Lowenthal set forth pathological criteria defining FD, including characteristic pallidal calcification evident on CT and on macroscopic pathological exam.[166] Although clinical manifestations vary, clinical definitions have been devised. One definition requires bilateral calcifications with neuropsychiatric and extrapyramidal disorders attended by normal calcium and phosphorus metabolism.[167] Another stipulates seizures, rigidity, and dementia with characteristic calcification of the basal ganglia.[168]

Clinical findings are important because radiologists may view BGC as an incidental finding.[169] Incidental discovery of BGC before age 50 merits diagnostic investigation.[170] The course of FD is progressive.[171] In adult-onset FD, calcium deposition generally begins in the third decade of life, with neurological deterioration two decades later,[172] but BGC can also occur in pediatric populations.

The frequency of BGC apparent on CT in radiologic studies approximates 0.93% of 29,484 scans,[173–179] but the prevalence of neurological findings in BGC can vary from 0%[175] to 20%.[178] The radiologic prevalence of calcification is higher in children (15%) than in adults,[180] indicating that BGC is a frequent nonspecific response in a variety of pediatric neurological disorders.

Although calcifications can involve other structures as well, the globus pallidus is most commonly involved.[181,182] The lateral pallidum tended to be more affected than the medial pallidum in one study.[183] Defective iron transport and free radical production may damage tissue, initiating calcification.[168] The mineral and biochemical content as well as the histopathological correlates of calcifications have been defined.[166,184–186]

Mineral composition varies by anatomic site and proximity to vasculature.[187]

Despite variable calcification distributions and severities, clinical findings in FD are remarkably constant, including seizures of all types, EEG abnormalities, and movement, cognitive, and psychiatric disorders.[166] BGC is associated with a wide variety of conditions. Besides idiopathic FD, endocrinologic disorders are leading etiologies of BGC. The frequencies of calcifications have been determined in various endocrinologic disorders,[188,189] and the relationship of endocrine dysfunction to BGC has been assessed.[174–176,178,181,184,190] These associations are detailed elsewhere.[173]

CT has greater diagnostic specificity for BGC, whereas MRI correlates better with functional impairment.[172,191,192] Reduced blood flow to calcified regions correlates with clinical signs.[193] Calcification in primary hypoparathyroidism is more diffuse than in other etiologies of calcification,[194] whereas post-thyroidectomy hypoparathyroidism calcifications are more focal.[179] The EEG displays various abnormalities in FD and BGC, showing no characteristic pattern.[195]

Familial BGC is associated with a diversity of modes of inheritance, chromosomal aberrations, and clinical manifestations.[166,172,196–215] Cases of BGC associated with Down's syndrome, trisomy 5, mitochondrial encephalopathies, and other conditions may have pediatric presentations.

Other neuropsychiatric conditions have been found among the many causes of BGC, including CNS lupus,[216,217] tuberous sclerosis,[218] early-onset Alzheimer's disease,[198] motor neuron disease,[219] myotonic muscular dystrophy,[220] and others. Mitochondrial encephalopathies are yet another cause.[221–228] Of 11 cases of mitochondrial encephalopathies, 5 had BGC.[226] Neurobrucellosis is linked to BGC, occurring in 13.8% of brucellosis patients with neuropsychiatric symptoms.[229] BGC in AIDS may occur in patients with abnormal calcium metabolism.[230] Anticonvulsants have also been associated with BGC.[178] Microencephaly, pigmentary macular degeneration, progeria, and abnormal calcium metabolism are variably associated with infantile and juvenile BGC.

Neurological Features

About half of patients with BGC have neurological features.[178,179,182] Headache, vertigo, movement disorders, paresis, strokelike events (including episodes resembling transient ischemic attacks), seizures, and syncope represent the most common manifestations of BGC.[179] The frequency of strokelike episodes in clinical populations may indicate that unrecognized mitochondrial encephalopathies are a leading cause of BGC, but research is needed to establish this observation. Other specific neurological features include paresis, spasticity, gait disorder, speech impairment, coma, dementia, parkinsonism, chorea, tremor, dystonia, myoclonus, and orthostatic hypotension.[171,179,231–234] Seizures occurred in 22% and extrapyramidal movement disorders in 56% in a literature review of 213 cases.[179] Konig analyzed the frequency of neurological features in patients initially presenting with BGC, as well as on follow-up.[179] Again, movement disorders were the most common feature, and these and seizures became more common over time. These figures need replication across larger samples. Seizures correlated best with isolated pallidal calcifications in one series.[182] In a Bavarian door-to-door study with CT follow-up, 1 of 17 subjects with parkinsonism (5.9%) had BGC.[235] Infantile BGC is rare and heterogeneous in etiology but can be associated with infantile spasms, a burst-suppression pattern on EEG, microcephaly, blindness, early death, hyperammonemia, reduced hepatic ornithine transcarbamylase activity, and consanguinity.[236] Aicardi-Goutieres syndrome, an autosomal recessive disorder with BGC, is characterized by increased CSF alpha interferon and lymphocytosis, with encephalopathy manifesting shortly after birth and causing developmental arrest.[237]

Neuropsychiatric Features

A problem with the literature is that most studies involve patients with BGC of various etiologies, including FD. Consequently the data are limited for pure FD, although neuropsychiatric manifestations do not appear to vary by BGC etiology.[179] About 40% of patients with BGC present initially with psychiatric features.[179] Cognitive, psychotic, and mood disorders are common.

Symptomatic features may change over time.[234,238] More extensive calcification and subarachnoid space dilatation correlate with the presence of psychiatric manifestations,[178,179,181] but calcific distribution and etiology do not.[179] Konig analyzed the frequency of psychiatric disorders in patients with BGC on both initial presentation and follow-up.[179] Mood disorders were the most common, and these, intellectual impairment, and compulsions became more common over time. These figures need replication across larger samples. Dementia, chronic cognitive disorders, paranoia, hallucinations, substance abuse, and personality changes were found as manifestations.[179]

Cognitive Disorders: FD may present as a progressive subcortical dementia in the sixth decade of life.[239] Delirium, apathy,[240] and amnesia[234] also occur. Earlier presentation as a psychosis may progress to dementia with cortical features.[238] Follow-up on patients within 2 years

after CT identification of BGC revealed impairments in motor speed, executive function, visuospatial skills, and selected memory functions when compared with matched control subjects.[182] The neuropathology of FD dementia may include frontotemporal atrophy, cortical neurofibrillary tangles, and neuronal loss in the nucleus basalis of Meynert, but senile plaques are lacking.[241] It is not clear whether this neuropathologic description applies to FD in general or only to the Japanese BGC "diffuse neurofibrillary tangles with calcification."[242] Other neuropathological features include calcareous deposits, white matter demyelination, and fibrous gliosis. Nearly all of 35 subjects with BGC showed intellectual impairment on long-term follow-up, and nearly one-third of patients had dementia or chronic cognitive disorders.[179]

Psychoses: Paranoid and psychotic features often present between the ages of 20 and 40 in FD.[239,243] Symptoms include auditory hallucinations (sometimes musical), complex visual hallucinations, perceptual distortions, paranoid delusions or nondelusional trends, and fugue states.[206,207,234,238,244] Ideas of reference or influence and catatonia also have been observed. A statistical association between psychosis and BGC is disputed,[169] with some finding[239,245] and others contesting[179,246,247] an association. Nevertheless, schizophreniform psychosis was associated with BGC extending over four generations in one family.[206,207] Moreover, review of 23 cases in the literature indicates two patterns of psychotic presentation in FD, including early onset (mean age 30.7 years) with minimal movement disorder and late onset (mean age 49.4 years) attended by dementia and movement disorder.[243]

Mood Disorders: Mood disorders include mania and depression and are the most common behavioral changes in BGC, initially present in one-fifth, eventually occurring in about two-thirds, and occurring more commonly than in neuropsychiatric control subjects.[179,247] Of 58 patients, mania eventually occurred in up to 31%.[167,179,182] Perhaps up to one-half of patients develop depression at some point over the illness course. One study found DSM-III depressive disorders in 37%,[179] and another found DSM-III-R minor depressive symptomatology in 16.7%.[182]

Anxiety and Other Disorders: Up to one-third of patients with BGC meet DSM-III-R criteria for obsessive-compulsive disorder.[179,182] Exact rates of other anxiety disorders in FD remain to be determined. Correlates of anxiety in FD require definition. Substance abuse and personality alterations occur in 8%,[179] similar to rates in the general population. Other disorders have not been reported.

Treatment

Although treatment of underlying etiologies (such as hypoparathyroidism[248,249] or mitochondrial encephalopathy[250]) has led to neuropsychiatric improvement, there are no specific treatments to limit calcification progression to our knowledge, except for a theoretically appealing yet unconfirmed report of improvement using chelators (xydifon, penicillamine, deferoxamine) with antioxidants and calcium antagonists.[251]

There are no systematically conducted controlled psychotropic treatment studies in FD. Patients with secondary BGC may also have heart, renal, or other system diseases that influence the use of psychotropics. Patients may or may not respond to conventional treatments. BGC-related parkinsonism often responds to levodopa,[252–254] but some patients fail to respond to either levodopa or treatment of associated hypoparathyroidism.[255]

Psychosis responds variably to treatment and is sometimes unresponsive.[206,243] Four of 7 patients were found to be particularly susceptible to extrapyramidal side effects.[206] Consequently, patients may be predisposed to neuroleptic malignant syndrome, which, in 1 case, was refractory to bromocriptine but responsive to dantroline.[238] Some cases of psychosis have proven refractory to haloperidol but have responded instead to lithium.[256] In a series of 5 cases of FD with mood disorders, 3 of 4 patients with depression responded to antidepressant treatments including imipramine and ECT; chronic mania in the fifth patient did not respond to lithium, haloperidol, or carbamazepine.[167] ECT is probably best avoided, given BGC seizure risk and the variable presence of increased intracranial pressure in some patients.

Opportunities For Further FD Research

1. *Calcium deposition*. Basic research may help establish the basis for localized deposition of calcium in the brain.
2. *Mitochondrial disease*. The frequency of occult mitochondrial encephalopathy with lactacidosis and strokelike episodes presenting as FD requires investigation.
3. *Relationships of FD and BGC*. Clarification of the relationships, if any, between FD and BGC is needed.
4. *Heritability of neuropsychiatric disorders in familial FD*. Definition of the heritability of neuropsychiatric phenomena in kindreds with familial FD may be instructive. Are certain neuropsychiatric features correlated with certain mutations? Do neu-

ropsychiatric disorders cluster in certain kindreds with FD?

5. *Prevalences of psychiatric disorders.* Further determination and replication of the prevalences of psychiatric disorders in FD, using standardized diagnostic criteria and controlling for FD severity and clinical features, are needed.
6. *Imaging correlates of neuropsychiatric disorders.* Structural and functional correlates of neuropsychiatric disorders in FD would assist our understanding of the basal ganglia circuitry involved in mediating these conditions.
7. *Longitudinal assessment of neuropsychiatric disorders.* Longitudinal assessment is needed of the evolution and progression of individual neuropsychiatric manifestations over the course of FD, and their clinical, radiologic, metabolic, and neurotransmitter correlates over the disease course require characterization.
8. *Neuroprotective agents.* Controlled treatment trials of the effects of neuroprotective agents on FD progression and neuropsychiatric manifestations are needed.
9. *Pharmacologic interventions.* The efficacy and risks of neuropharmacologic and psychopharmacologic interventions in FD and correlates of good and poor outcome with these interventions remain to be defined.
10. *Treatment-refractory conditions.* Novel approaches are needed in treating conditions such as psychosis that are refractory to conventional treatments.
11. *Psychotherapy.* Psychotherapy issues in FD remain to be elucidated.

SUMMARY: LENTICULOSTRIATAL DISEASES

HD, WD, and FD are very different disorders, although each is dominated by mood and movement disorders. Preliminary observations identify phenomenologically different profiles of behavioral disturbances, suggesting that the form of neuropsychiatric features elicited may depend heavily on which component of the lenticulostriatal system is damaged. Although further work is needed, similarities and differences between HD, WD, and FD suggest the importance of caudatopallidal circuits in cognition and mania (in HD and FD), perhaps related to thalamic disinhibition.[234] Personality changes have been documented principally in striatal diseases (HD and WD), whereas depression is equally prominent in HD, WD, and FD.

Regrettably, the current state of the literature makes it difficult to compare neuropsychiatric sequelae in different lenticulostriatal diseases (LSDs). Studies have employed varying diagnostic criteria and different assessment instruments in different stages of these illnesses. It seems necessary to determine neuropsychiatric prevalences at individual stages of these progressive illnesses, denoting the extent and neuroanatomic distribution of the pathology, before definite comparative conclusions about the differential roles of the caudate, putamen, and internal and external pallidal segments can be drawn across LSDs. Correlation of neuropsychiatric features with radiologic, metabolic, and pharmacologic measures has the potential to increase our understanding of the function of these structures in neuropsychiatric illnesses.

Opportunities For Further Research in Lenticulostriatal Diseases

The following tentative conclusions drawn from the extant data provide testable heuristic hypotheses, provided that appropriate methodology is applied:

1. HD is particularly associated with chorea, dementia, personality changes, psychosis, mania, depression, suicidality, impulse dyscontrol, and sexual disorders.
2. WD is especially associated with dysdiadochokinesia, dysarthria, bradykinesia, tremor, cognitive impairment, personality changes, and depression.
3. In FD, extrapyramidal disorders, seizures, dementia, mania, depression, and compulsions are particularly common.
4. Across LSDs, parkinsonian features may correlate with medial striatal and lateral pallidal disease, whereas hyperkinesias and mania may correlate with lateral striatal and medial pallidal disease.
5. Dementia and mania in LSDs may be associated with caudate and pallidal disease rather than putaminal pathology.
6. Personality changes other than irritability in LSDs may be associated with striatal disease.
7. Irritability may be prominent in LSDs and may correlate with striatal pathology, especially in HD and WD.
8. Psychosis, suicidality, impulse dyscontrol, and sexual disorders may be associated with caudate disease, especially in HD.
9. Depressive disorders in LSDs may correlate with parkinsonian features, especially in HD and WD.
10. Mania and compulsions may be especially associated with pallidal disease, as in FD.

If these tentative conclusions are confirmed, further attention to the questions of which specific regions of

lenticulostriatal structures are pathologically involved, what additional pathology is present, and the clinical and physiologic correlates of these syndromes may clarify the functional significance of these structures. Following neuropsychiatric features over the longitudinal course of these illnesses also can add to this understanding, as well as lead to better prediction of outcome in these diseases. Treatments aimed at limiting disease progression and studies of efficacy and risks of both neuropharmacologic and psychopharmacologic treatments in LSDs are needed. Methodological difficulties involved in carrying out such research include small sample sizes, variable symptomatic presentations, and neurological confounds of psychiatric rating scale items, among others. Adequate and standardized observations such as these will be best carried out through collaborative ventures.

Collaborative Research Opportunities

The Committee on Research of the American Neuropsychiatric Association (ANPA) has a dedicated interest in fostering collaborative research endeavors in neuropsychiatric disorders. If you are interested in collaborative research in these disorders, contact the Committee on Research through this journal or through ANPA, Suite 550, 700 Ackerman Road, Columbus, OH 43202.

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