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Review

The neuropsychiatry of neuroacanthocytosis syndromes

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ABSTRACT

The neuroacanthocytoses are a group of disorders characterised by peripheral blood acanthocytes, central nervous system as well as neuromuscular symptoms. These disorders uniformly result in pathology in the basal ganglia, which account for the characteristic motor symptoms such as chorea or dystonia, but may also account for the apparent elevated rates of major mental disorders in these syndromes. Elevated rates of dysexecutive syndromes, obsessive–compulsive disorder, depression and schizophrenia-like psychosis appear to occur in chorea-acanthocytosis, McLeod's syndrome, pantothenate kinase-associated neurodegeneration, and Huntington's disease-like 2. Disruptions to key frontostriatal loops secondary to pathology in the striatum and pallidum appear to predispose individuals to major neuropsychiatric syndromes; however, treatment can be instituted for a number of these manifestations, which lessens the overall burden of disease in neuroacanthocytosis patients and their families.

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1. Introduction

The term *neuroacanthocytosis* is an umbrella term used to describe a group of disorders that present with neurological and psychiatric manifestations, and *acanthocytes*, spiculated red blood cells (Table 1). The term *acanthocyte* was first used in 1950 to describe the spiky deformation of erythrocytes seen in Bassen–Kornzweig syndrome (Bassen and Kornzweig, 1950), a form of hypobetalipoproteinemia associated with peripheral neurological signs; between 1960 and 1970, Levine and Critchley described acanthocytosis associated with a choreiform disorder without hypobetalipoproteinemia (Levine–Critchley syndrome) in three families (Critchley et al., 1970, 1967; Levine et al., 1967, 1960). The term *neuroacanthocytosis* was later used as a supraordinate term to describe a range of disorders presenting with peripheral blood acanthocytosis and neurological disturbance (Sakai et al., 1985; Spitz et al., 1985). The

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Table 1
Neuroacanthocytosis syndromes.

Chorea-acanthocytosis[a]
McLeod syndrome[a]
Pantothenate kinase-associated neurodegeneration[a]
Huntington disease-like 2[a]
Familial acanthocytosis with paroxysmal exertion-induced dyskinesias
Bassen–Kornzweig syndrome
Hypobetalipoproteinemia

[a] Syndrome associated with neuropsychiatric illness.

neuroacanthocytoses (NA) can be divided into a number of groups:

1. Core NA syndromes involving degeneration of the basal ganglia and choreiform and other movement disorders
   a. Chorea-acanthocytosis (ChAc)
   b. McLeod syndrome (MLS)
2. Degenerative disorders where acanthocytosis is occasionally seen
   a. Panthothenate kinase-associated neurodegeneration (PKAN)
   b. Huntington disease-like 2 (HDL2)
3. Paroxysmal dyskinetic disorders
   a. Familial acanthocytosis with paroxysmal exertion-induced dyskinesias (FAPED)
4. Disorders with reduced blood lipoprotein levels associated with ataxia and peripheral sensory signs but no movement disorder
   a. Bassen–Kornzweig syndrome
   b. Hypobetalipoproteinemia

The NA syndromes that result in significant movement disturbance (from groups 1 to 3) invariably affect the basal ganglia. Chorea is the clinical neurological hallmark of these disorders, although dystonia, Parkinsonism and tic-like movement disorders may also present (Danek et al., 2005; Walker et al., 2007). Historically, clinicians have focussed on the progressive external motor manifestations of disease, but increasingly evidence suggests that these disorders can present with significant psychological and neurocognitive comorbidity (Walterfang et al., 2010). Psychiatric and cognitive impairments may be as disabling for patients with basal ganglia disorders as the motor disturbances, and may be the most problematic aspect of the patient's care for relatives and carers (Rosenblatt and Leroi, 2000).

The basal ganglia consist of the caudate nucleus and putamen (collectively known as the striatum), the globus pallidus, subthalamic nucleus, substantia nigra and the nucleus accumbens (Alheld et al., 1990). These subcortical grey matter nuclei are linked to cortical association areas by multiple loops that run through the basal ganglia and thalamus and then return to the cortex. There are 5 main cortico-striatal-cortical loops or circuits (motor, oculomotor, cognitive, associative and limbic) that each receive multiple cortical inputs which are then integrated, projected to a restricted thalamic region, and then to a single cortical region (Alexander et al., 1986). Much of the output of these loops projects to the prefrontal cortex (PFC), including motor, associative and limbic cortical regions. As these loops are not anatomically separate, cognitive, motor and emotional loops can interact in the striatum to modulate each others' output to the cortex (Kimura and Matsumoto, 1997). As a result, disorders that affect the basal ganglia as a structure tend not to discriminate between these circuits, and thus present with a combination of cognitive, motor and emotional disturbance. Neuropsychiatric disturbance appears to arise when the normal function of the striatum is disturbed (Walterfang et al., 2010). Within the striatum, the putamen is involved in simple motor behaviours of limited flexibility (such as habit learning and stimulus-response associations). The caudate is involved in goal-directed decision-making through its role in processing action-outcome contingencies, where behavioural choices are based on previously acquired knowledge, and the expected outcome and reward of the behaviour (Grahn et al., 2008). Disorders that affect the striatum are thus likely to lead to a combination of disturbances that characterises many of the neuroacanthocytosis syndromes: the co-development of movement disorder, cognitive impairment and neuropsychiatric illness.

This review aims to highlight the comorbid neuropsychiatric disorders that may be a presenting feature of the differing neuroacanthocytosis syndromes, and to relate the distinct neuropathology of these disorders to the neurobiology of psychiatric illness.

2. Chorea-acanthocytosis

Chorea-acanthocytosis (ChAc; MIM 200150) is an autosomal recessive disorder associated with mutations or deletions in the *VPS13A* gene on chromosome 9q, which codes for the membrane protein chorein (Rampoldi et al., 2001; Ueno et al., 2001). Chorein is strongly expressed in the brain (Dobson-Stone et al., 2002). Loss of chorein particularly affects the basal ganglia, especially the caudate nucleus and putamen, but also the ventrolateral substantia nigra and globus pallidus, with relative sparing of the cortex (Hardie et al., 1991). Onset of neurological disturbance in ChAc is usually between the third and fifth decades, commonly with limb and orobuccal chorea that may be indistinguishable from Huntington's disease (HD) (Danek et al., 2005), although some movement disturbance – particularly the frequent lip and tongue mutilation that occurs – has been described as a motor compulsion (Walker et al., 2006). The illness is progressive with no definitive treatment, and results in death in 5–10 years. Apart from chorea, other neurologic features may include dystonia, Parkinsonism and ocular-motor impairment (Walker et al., 2007). The frequent occurrence of mutilation of the tongue, lips and cheeks seen in ChAc is not generally a feature of HD however and can help to clinically distinguish the two disorders (Dobson-Stone et al., 2002; Walker et al., 2007). The diagnosis of ChAc is suspected with the detection of acanthocytes making up 5–50% of red blood cells on a fresh blood smear (Storch et al., 2005), although acanthocytes can be variable at different stages of the disease. Magnetic resonance imaging of the brain may show a combination of dramatic caudate atrophy and an increased T2 signal in the basal ganglia (Danek et al., 2005; Walker et al., 2007; Walterfang et al., in press). The standard diagnostic test is a Western blot test showing absent or diminished chorein on red blood cells (Dobson-Stone et al., 2004). A lipid profile and testing for Kell group antigens can help to differentiate it from the other neuroacanthocytosis syndromes such as abetalipoproteinemia and McLeod syndrome. Identification and sequencing of the *VPS13A* gene (Rampoldi et al., 2001; Ueno et al., 2001) can confirm the diagnosis of ChAc although this test is not generally commercially available (Dobson-Stone et al., 2004).

Clinically significant psychopathology, ranging from behavioural disturbance to frank psychiatric illness, has been reported to occur in up to 60% of ChAc patients (Danek et al., 2004; Hardie et al., 1991; Walterfang et al., 2008). Frank psychiatric illness may precede the onset of neurological disturbance in some cases by up to a decade (Sorrentino et al., 1999; Walterfang et al., 2008). Early reports of neuropsychiatric illness focussed on behavioural and cognitive change (apathy, disinhibition, poor judgement and planning), consistent with a dysexecutive syndrome, in more than half of patients (Hardie et al., 1991). Recent reports have described typical symptoms of obsessive–compulsive disorder (OCD) in ChAc patients, most particularly compulsive behaviours relating to checking, cleanliness, symmetry and hoarding (Bohlega et al., 2003; Bruneau et al., 2003; Habermeyer et al., 2006; Lossos

et al., 2005; Müller-Vahl et al., 2007; Robertson et al., 2008; Saiki et al., 2004; Walterfang et al., 2008). Compulsive over-eating has also been described (Ichiba et al., 2007; Rodrigues et al., 2009). Furthermore, the characteristic orobuccal mutilation has also been conceptualised along the OCD spectrum of illness (Walker et al., 2006). In a review of published cases of ChAc up to 2006 on whom behavioural data were available, 16 of 38 patients presented with psychiatric symptoms at the time of illness diagnosis. Of these patients, 50% presented initially with psychiatric symptoms. The group that presented initially with psychiatric illness had a mean interval between psychiatric and neurological presentation of more than ten years, with half of these patients presenting with OCD-like symptoms (Walterfang et al., 2008). Only a limited number of cases with treatment data have been described, although patients have generally responded to serotonergic medication (such as selective serotonin re-uptake inhibitors) (Habermeyer et al., 2006; Walterfang et al., 2008).

Schizophrenia-like psychosis has also been described in a number of ChAc patients (Bohlega et al., 2003; Bruneau et al., 2003; Ichiba et al., 2007; Müller-Vahl et al., 2007; Rodrigues et al., 2009; Takahashi et al., 1983; Yamada et al., 2009). As in patients with OCD, the majority of ChAc patients with psychosis developed psychotic symptoms months or years prior to the onset of frank neurological disturbance. Symptoms are typically in the form of auditory hallucinations and bizarre and/or persecutory delusions. Treatment has been described with a variety of typical and atypical antipsychotic agents (Bohlega et al., 2003; Bruneau et al., 2003; Yamada et al., 2009). Using high-potency agents in ChAc may be problematic, as both severe Parkinsonism (Müller-Vahl et al., 2007) and neuroleptic malignant syndrome (Yamada et al., 2009) have been described, and as such atypical and low-potency agents may be preferred. Other psychiatric illnesses have also been reported, including depression (Gold et al., 2006; Ichiba et al., 2007; Rodrigues et al., 2009), and déjà-vù experiences in the setting of temporal lobe epilepsy (Al-Asmi et al., 2005; Scheid et al., 2009).

Significant executive disturbance, usually presenting as impaired judgement, disinhibition, and impulsivity, appears to present in a majority of ChAc patients as the illness progresses (Hardie et al., 1991; Kartsounis and Hardie, 1996; Walterfang et al., 2008), and may be the initial presentation. Additionally, patients develop impairments in speed of processing and memory (Danek et al., 2001b), and ultimately develop a frank frontosubcortical dementia as the illness progresses (Hardie et al., 1991; Kartsounis and Hardie, 1996).

As the most striking neuronal loss in ChAc occurs in the striatum, the disruption of frontal-subcortical loops traversing the caudate nucleus and putamen is likely to underlie the psychiatric and behavioural syndromes that occur in ChAc. The apparent high rate of OCD in ChAc (Walterfang et al., 2008) suggests that the disruption of these frontal-subcortical loops plays a significant role in the genesis of OCD-like symptoms. The head of the caudate, which may be most severely affected in ChAc (Henkel et al., 2007), plays a key role in the lateral orbitofrontal loop (LOFL). The LOFL integrates information from the anterior cingulate, orbitofrontal and dorsolateral prefrontal cortices to determine behavioural and motor programmes and facilitating decision-making (Aouizerate et al., 2004; Chamberlain et al., 2005). The role of the striatum in this loop may be to integrate incentive-related signals from the limbic system with cognitive inputs from frontal cortex to determine whether and when a movement or behaviour should occur (Graybiel and Kimura, 1995). In OCD patients, impaired decision-making due to alterations to LOFL transmission may be a core illness component (Cavedini et al., 2006; Sachdev and Malhi, 2005). The pure motor compulsions seen in many ChAc cases, including the characteristic orobuccal mutilation, may result from direct caudate pathology, leading to a behavioural dysregulation of simple motor acts.

The origins of schizophrenia-like symptoms may be similar, as frontostriatal pathology may play a role in the origins of psychotic symptoms (Pantelis et al., 1992). Whilst the striatal loss in ChAc cannot be directly compared to the neurochemical and microstructural changes that are observed in schizophrenia (Pantelis et al., 1997; Robbins, 1990), loss of caudate neurons may disrupt crucial processing of striatal-limbic information (Parent and Hazrati, 1993) and lead to psychotic symptoms in some ChAc patients.

3. McLeod syndrome

McLeod syndrome (MLS, MIM 314850) is an X-linked multisystem disorder that results from mutations of the *XK* gene (Jung et al., 2001). Hematologically, MLS is characterized by absent Kx red blood cell (RBC) antigen, weak expression of Kell RBC antigens, peripheral blood acanthocytosis and elevated creatine kinase (CK) levels. MLS predominantly affects males, although there are manifesting female carriers. Illness onset is usually between the ages of 25 and 60; the mean age of onset of 40 years of age suggests that patients often present significantly later than ChAc patients (Danek et al., 2001a; Rampoldi et al., 2002).

XK and Kell are expressed in a range of tissues, including the brain, heart and muscle. Only a few neuropathological studies of confirmed MLS cases have been described; these report neuronal loss in the basal ganglia, most dramatic in the caudate and putamen, very similar to that seen in ChAc (Brin et al., 1993; Hardie et al., 1991; Rinne et al., 1994). This striatal cell loss is reflected by neuroimaging findings which, again like ChAc, often show marked caudate and putamen atrophy (Danek et al., 1994; Dotti et al., 2000; Jung et al., 2001; Miranda et al., 2007; Oechsner et al., 2001; Takashima et al., 1994; Zeman et al., 2005), reduced striatal D2 binding (Danek et al., 1994; Oechsner et al., 2001), and decreased striatal glucose uptake (Jung et al., 2001; Oechsner et al., 2001). One study showed hypometabolism not only of the basal ganglia but also of the frontal lobes suggesting that the cell loss in the striatum results in downstream alterations to frontal cortical activity, altering frontostriatal transmission (Dotti et al., 2000). One magnetic resonance spectroscopy study in MLS has suggested significant extra-striatal involvement: an examination of cortical regions in 5 affected MLS patients (4 with a psychiatric diagnosis) and 5 female carriers showed altered *n*-acetyl-aspartate to creatine/choline ratios in frontal and medial temporal cortex and thalamus in affected patients (Dydak et al., 2006). However, limited neuropathological studies suggest an absence of cortical neuronal loss (Rinne et al., 1994), suggesting that cortical changes may disrupt neuronal integrity and function without frank neuronal dropout.

More than 80% of MLS patients present with neuropsychiatric illness at some stage during their illness course (Danek et al., 2001a); much as in ChAc, the two most common illness presentations are of schizophrenia-like psychosis (SLP) and obsessive–compulsive disorder (OCD). Neuropsychiatric presentations often predate chorea and other neurological manifestations in MLS, which may occur later in the illness course (Danek et al., 2001a; Hewer et al., 2007). OCD-like syndromes have been reported by a number of authors (Miranda et al., 2007; Oechsner et al., 1996; Vazquez and Martinez, 2009; Zeman et al., 2005), and this may present as co-morbid with both psychosis (Oechsner et al., 1996) and major depression (Vazquez and Martinez, 2009).

Psychotic disorders have been reported at the same, if not a greater frequency in MLS than OCD, with cases of schizophrenia-like psychosis being reported where the typical thought disorder, persecutory delusions and auditory hallucinations that characterise schizophrenia preceded the onset of chorea by some years (Danek et al., 2001a; Jung and Haker, 2004; Miranda et al., 2007). As

with other basal ganglia disorders, there is a tendency to diagnose choreiform disorders after exposure to antipsychotic medication as tardive dyskinesia (TD), which potentially delays the diagnosis of MLS (particularly when neurological symptoms are presaged by psychosis), leading to the suggestion that patients with suspected TD are screened routinely for MLS (Jung and Haker, 2004). A number of other related psychotic disorders have been described, including schizoaffective disorder, bipolar disorder, and schizotypal personality disorder (Dydak et al., 2006; Jung et al., 2001). Schizophrenia-like psychosis in MLS has been reported to respond to both typical and atypical antipsychotics (Jung and Haker, 2004; Miranda et al., 2007).

The intimate relationship between the striatal pathology and both OCD and schizophrenia is best illustrated by the report of two MLS-affected brothers, one of whom presented with a psychotic illness and the other with typical OCD (Miranda et al., 2007). It may be that the striatal changes that occur in MLS may interact with other biological diatheses for both OCD and schizophrenia to result in these disorders in susceptible individuals, and may not be sufficient alone to cause major psychiatric illness; alternatively, given there is significant evidence of co-morbidity between schizophrenia and OCD (Bottas et al., 2005), it is also possible that a single pathological process may result in both disorders. Other more common psychiatric illnesses have also been reported in MLS, including depression and anxiety disorders (Jung et al., 2001). However, given the high base rate in the population for these disorders, at this stage there is no evidence that they represent more than a chance co-occurrence with MLS, or a non-specific response to dealing with a progressive neurodegenerative illness.

In common with other frontostriatal disorders, executive impairment is common in MLS, and often presents as behavioural disturbance characterised by poorly judged and/or impulsive behaviour (Danek et al., 2001a; Jung et al., 2001). Notably, impaired executive function has also been described in neurologically unaffected female carriers (Jung et al., 2001). One patient presented initially with a frontotemporal dementia (FTD)-like syndrome, with significant hoarding of car parts, tools and rubbish, increasing behavioural disorganisation and disinhibition with indifference, prior to the onset of chorea (Zeman et al., 2005), suggesting that MLS may be a consideration in patients diagnosed with FTD, particularly in the presence of striatal atrophy. The prevalence of significant dysexecutive syndromes in MLS patients, combined with the neuroimaging evidence suggesting hypofrontality in MLS (Dotti et al., 2000), reinforces the crucial role of frontostriatal circuits in modulating behaviour and the impact on this circuitry if one crucial node in the network is disrupted.

4. Pantothenate kinase-associated neurodegeneration

Pantothenate kinase-associated neurodegeneration (PKAN, MIM 234200) is a rare autosomal recessive disorder characterised by iron accumulation in the basal ganglia, due to mutations in the *PANK2* gene. It is alternatively described as neurodegeneration with brain iron accumulation 1 (NBIA1). *PANK2* encodes a pantothenate kinase, the key regulatory enzyme in coenzyme A synthesis (Zhou et al., 2001). Neuropathologically, this results in characteristic axonal spheroids, excessive iron-containing granules and accompanying neuronal loss and gliois, in the globus pallidus and substantia nigra. Diffuse cortical Lewy bodies have not uncommonly been described (Arawaka et al., 1998), and tau-related neuropathology (predominantly in subcortical nuclei) has also been described in PKAN (Zarranz et al., 2006). The neuroradiologic hallmark of the "eye of the tiger sign" is characterised by bilateral areas of hyperintensity within a region of hypointensity in the median globus pallidus on T2-weighted brain MRI, corresponding to increased iron deposition in these structures (Savoiardo et al., 1993). Two main phenotypes have been identified; classic PKAN manifests in the first decade with severe hyperkinetic movements and progresses rapidly with loss of ambulation within 15 years from onset. In atypical PKAN, the onset is in the second to third decade with a less severe movement disorder, slower progression, and maintenance of independent ambulation well after 15 years of disease (Hayflick et al., 2003). Other symptoms include dysarthria, dystonia, rigidity, and corticospinal signs.

Psychiatric signs, such as behavioural disturbances (Hayflick et al., 2003; Pellecchia et al., 2005), OCD (Nardocci et al., 1994; Nicholas et al., 2005; Pellecchia et al., 2005; Scarano et al., 2002), psychosis (Gouider-Khouja et al., 2000; Müller-Vahl et al., 2007; Öner et al., 2003), tic disorders (Pellecchia et al., 2005; Scarano et al., 2002) or depression (Morphy et al., 1989) are common, occurring in up to half of patients (Pellecchia et al., 2005; Thomas et al., 2003). Pellechia et al. described a series of 16 genetically confirmed patients, five of whom had OCD-like symptoms, with two of these patients having co-morbid vocal and motor tics (Pellecchia et al., 2005). Ten of these patients also had cognitive decline, although the exact pattern of impairment was not described. Notably, one further series described 2 out of 3 affected siblings presenting with a schizophrenia-like psychosis marked by indifference, hallucinations and delusions, with visual hallucinations being particularly prominent; both patients responded to neuroleptic treatment (Gouider-Khouja et al., 2000). Severe depression has also been described in most affected members of a large PKAN pedigree (Morphy et al., 1989). The most commonly reported psychiatric presentation appears to be OCD, at rates similar to those seen in ChAc, in adult patients. As in MLS, the divergence of presentations into OCD or schizophrenia-like psychosis is exemplified by a recent report of two adolescent siblings, in which a 14-year old girl showed compulsions and motor tics, but her 16-year old brother presented with a psychotic illness characterised by hallucinations, thought alienation, and persecutory and referential delusions (Sunwoo et al., 2009). This again illustrates how a presumably similar illness process can interact with covert neurobiological variables to determine disease outcome.

Cognitive decline is frequent, and almost universal, in PKAN (Dooling et al., 1974; Pellecchia et al., 2005; Sachin et al., 2009; Thomas et al., 2003). Cognitive function can vary from normal to markedly impaired, with earlier-onset patients being more severely affected (Freeman et al., 2007). The pattern of cognitive impairment often implicates executive function and attention (Marelli et al., 2005), and impairment may predate motor signs (Cooper et al., 2000). In younger patients, significant impairment is the norm, and there is often a discrepancy between performance and verbal IQ, with verbal functions being more preserved (Angelini et al., 1992). In atypical, late-onset patients, relative preservation of cognitive function has also been described (Nicholas et al., 2005), and it is possible that cognitive impairment may, in some atypical cases, precede motor impairment by some years (Cooper et al., 2000). A striking single case report detailing the pattern of cognitive decline in an adult patient revealed profound attentional and executive disturbance, memory impairment and visuospatial dysfunction, corresponding to hypometabolism in frontal, temporal and parietal regions (particularly on the left) and the caudate nucleus (Cooper et al., 2000).

5. Huntington disease-like 2

Huntington disease-like 2 (HDL2, OMIM 606438) is an autosomal dominant neurodegenerative condition with clinical features of chorea and cognitive decline, and shares many features in common with Huntington's disease (HD). HDL2 is due to a

CTG expansion in the junctophilin3 gene (*JPH3*) on chromosome 16q24.3 (Holmes et al., 2001; Margolis et al., 2001). JPH3 is a brain-specific protein from the junctophilin gene family, and may play a role in anchoring the endoplasmic reticulum to the plasma membrane, allowing calcium flux into the reticulum. The normal repeat number is 6–28; expansions of 40 or more are associated with disease, and as in HD, the HDL2 repeat length is correlated with age of disease onset (Margolis et al., 2004b). The mutation has been identified in patients of Black African ancestry (Holmes et al., 2001). HDL2 is estimated to account for up to 15% of patients with a Huntington's disease-like condition who do not carry the HD mutation (Margolis et al., 2004a), and it may present indistinguishably from ChAc (Walker et al., 2003b). Brain imaging reveals significant striatal and cortical atrophy, and neuropathologically patients demonstrate prominent neurodegeneration and gliosis in the caudate and putamen, with lesser degenerative changes in the substantia nigra and pallidum, and little in the way of changes in thalamus, hippocampus, amygdala, basal forebrain, cerebellum or cortex (Margolis et al., 2001; Rudnicki et al., 2008).

The pedigree described by Margolis et al. (2001) noted psychiatric symptoms including depression, anxiety and psychosis, in addition to more dysexecutive behaviours including apathy, perseveration and irritability, and eventually dementia (Margolis et al., 2001). All four cases described in a Brazilian series exhibited some psychiatric symptoms including depression (2), aggression (2) and hallucinations (1) (Rodrigues et al., 2008). In all four cases the psychiatric symptoms became apparent years after the onset of a movement disorder. Two of the five cases in the series described by Walker et al. (2003a) had depressive symptoms together with dementia, chorea and movement disorder. Neither of the two patients described in a French study exhibited psychiatric symptoms, though one was described as showing frontal behaviour (Stevanin et al., 2003). One of the three patients described in a South African pedigree with illness identified over three generations exhibited psychotic symptoms late in the illness having presented earlier with cognitive decline, aggression and movement disorder; one other patient presented with disinhibition and aggression, and all three ultimately developed dementia (Bardien et al., 2007).

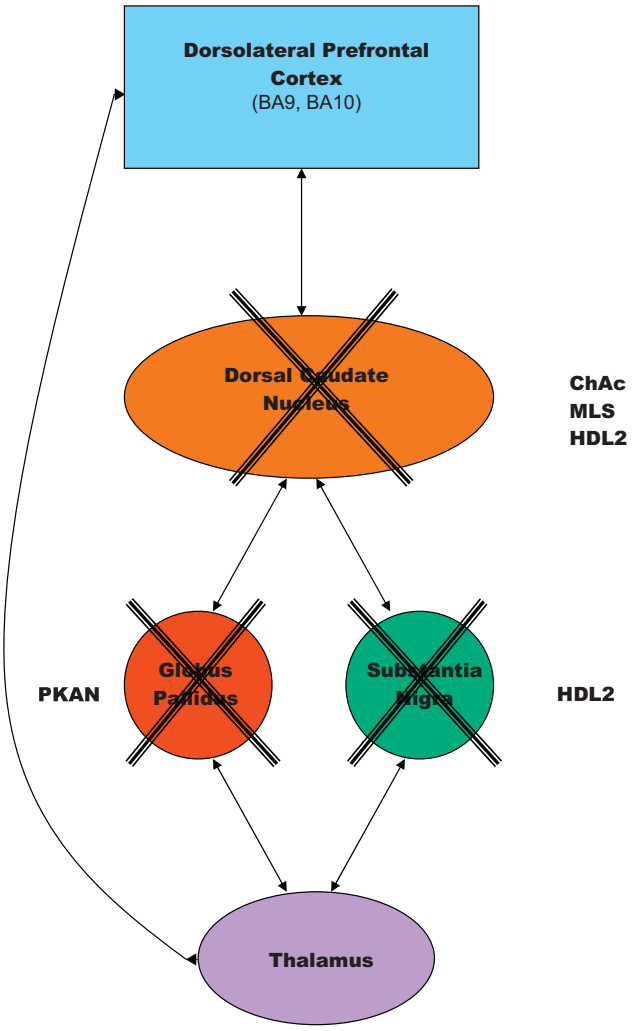


Fig. 1. Dorsolateral prefrontal cortex circuit. Pathological alterations to the head of the caudate nucleus result in altered transmission through dorsolateral prefrontal cortex, resulting in impaired flexibility, judgement and planning. Shaded lines indicate areas affected by differing neuroacanthocytosis disorders.

6. The origin of neuropsychiatric illness in neuroacanthocytosis

The neuroacanthocytosis syndromes appear to present with a higher rate of dysexecutive syndromes, OCD, depression and psychosis, and for the disorders with a richer literature of neuropsychiatric illness (such as ChAc and MLS), the rates of presentation of neuropsychiatric illness appear similar. Although the pathophysiological processes that underpin the neuropathology of these disorders varies, the commonality in psychiatric presentation can perhaps best be understood by a common site of impingement: the striatum, which is most clearly affected in ChAc, MLS and HDL2.

Three of the five main frontal-subcortical loops, which originate in the frontal lobe and project to the striatum, the globus pallidus and substantia nigra and then to specific thalamic nuclei and finally back to the frontal lobe, are known to result in significant behavioural disturbance when they are disrupted (Bonelli and Cummings, 2007). Disruption to the dorsolateral-prefrontal loop (Fig. 1), which projects from Brodmann's areas 9 and 10 of the frontal cortex to the dorsal head of the caudate nucleus, results in typical executive disturbance, characterised by impairment in planning, shifting behavioural set, reasoning, sustaining attention and mental flexibility (Tekin and Cummings, 2002). When the orbitofrontal loop (projecting from areas 10 and 11 (orbitofrontal) to the ventromedial caudate nucleus, Fig. 2) is disrupted, impaired behavioural inhibition, poor social judgement, and demonstration of utilisation behaviour usually result (Tekin and Cummings, 2002). Finally, when the anterior cingulate circuit (from cingulate cortex (Brodmann's area 24), projecting to the ventromedial caudate and putamen, Fig. 3) is disrupted, apathy, lack of drive and initiative, and reduced spontaneous speech and movement is the behavioural result (Tekin and Cummings, 2002). Furthermore, dysfunction of the orbitofrontal and anterior cingulate circuits have been strongly implicated in the pathophysiology of OCD, depression and psychosis (Cummings, 1993; Swerdlow and Koob, 1987).

The head of the caudate nucleus plays a key role in these latter two basal ganglia-thalamo-cortical loops where it integrates information from the anterior cingulate, orbitofrontal and dorsolateral prefrontal cortices to determine behavioural and motor programmes that occur to resolve conflict or facilitate decision-making (Aouizerate et al., 2004; Chamberlain et al., 2005). Disruptions within this loop may account for some of the broader behavioural and cognitive changes seen in neuroacanthocytosis such as apathy, disinhibition, poor judgement and planning. Additionally, the motor compulsions seen in many neuroacanthocytosis patients may result from direct caudate pathology, leading to behavioural dysregulation of motor acts, felt to be the basis for compulsions in primary OCD (Chamberlain et al., 2005). Depression may result

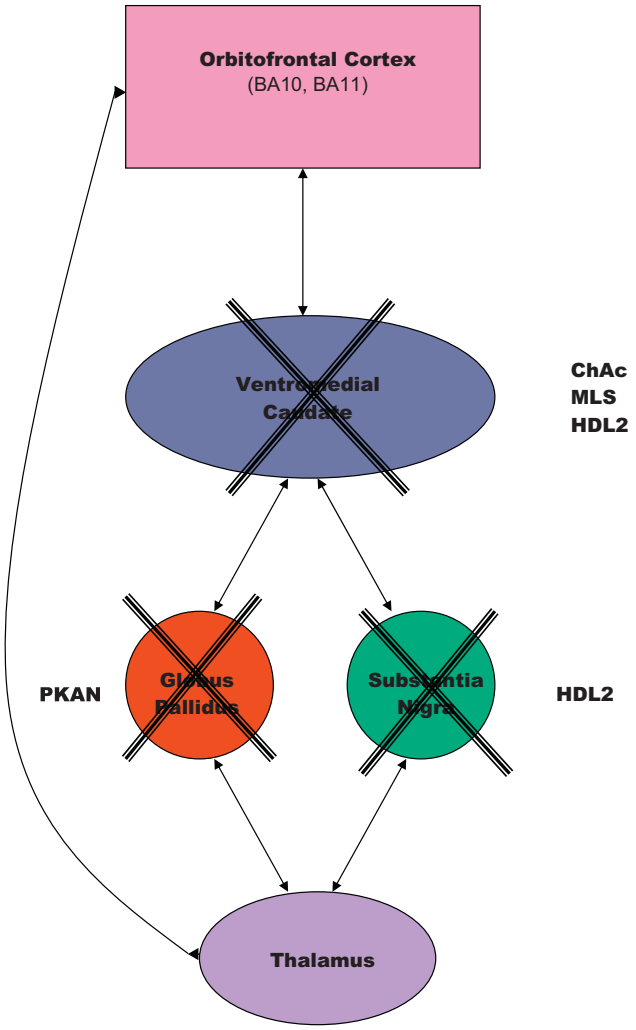


Fig. 2. Orbitofrontal loop. Pathological disruptions to ventromedial striatum results in altered transmission through orbitofrontal cortex, with patients presenting with disinhibition, poor judgement, and utilisation behaviour, in addition to compulsive behaviours. Shaded lines indicate areas affected by differing neuroacanthocytosis disorders.

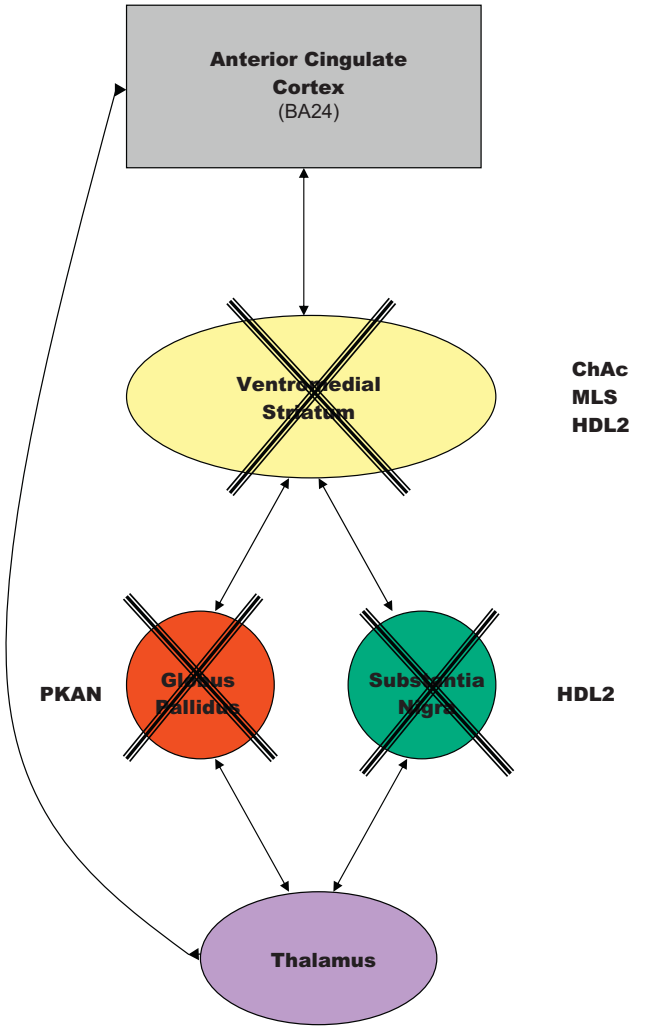


Fig. 3. Anteior cingulate circuit. Disruptions to ventromedial striatum result in impaired transmission through anterior cingulate cortex, producing apathy, lack of volition, and reduced spontaneous activity. Shaded lines indicate areas affected by differing neuroacanthocytosis disorders.

from underactivity of dopaminergic striatal neurons, resulting in an inability to inhibit corticothalamic activity by limbic pallidal input, thus resulting in an impairment of "modulation" of affective states (Swerdlow and Koob, 1987). Psychosis likewise may result from altered striatal dopaminergic activity that impacts upon striatal "filtering" of cognitive processes at the level of the nucleus accumbens, and thus impaired regulation of corticothalamic interactions (Swerdlow and Koob, 1987).

7. Management of psychiatric disturbance in neuroacanthocytosis

Management of psychiatric disturbance in neuroacanthocytosis syndromes is generally symptomatic, in that the treatments that are used for OCD, psychosis, mood disorders and other illnesses are the same as those used in primary psychiatric illness. When dealing with the neuroacanthocytoses, the clinician must be vigilant for the presence of psychiatric illness, as untreated major mental disorders can add considerably to functional impairment of the patient and carer burden. Recognition of covert illness is also crucial: depression, for example, may not be diagnosed particularly if the patient has difficulty in communicating, or if their debilitating neurological symptoms result in clinicians and carers labelling a depressive illness as "understandable". Difficulties with speech or communication may also mask psychotic illness. Additionally, differentiation of depressive illness from apathy and amotivation can often be difficult; evaluation of accompanying symptoms that may be indicative of neurovegetative disturbance, such as changes in appetite, sleep or agitation, may be helpful.

Depressive illnesses generally respond well to antidepressant treatment, including modern antidepresasants such as the selective serotonin re-uptake inhibitors (SSRIs), which have less of the anticholinergic and anti-histaminic properties of older antidepressants such as the tricyclic antidepressants (TCAs) – which may worsen cognitive impairment – and have a very wide therapeutic index. As in patients with a major depressive illness in the absence of a neurological condition, full remission is sometimes only effected with the addition of antipsychotic medication as an adjunctive treatment (Komossa et al., 2010); this may also have the beneficial effect of lessening chorea in some patients. Electro-convulsive therapy (ECT) has been reported as being effective for otherwise treatment-resistant illness (Kennedy et al., 2003).

The treatment of psychosis can be difficult in neuroacanthocytosis, as dopamine-blocking agents, the primary agents used to treat psychotic symptoms, do not readily discriminate between motor and non-motor aspects of the striatum. Small dose, high-potency

neuroleptics (usually those with a high dopamine D2-receptor affinity such as haloperidol and trifluoperazine) are useful in suppressing chorea and may also alleviate psychotic symptoms; however, when dosages need escalation to control psychosis, worsening dystonia and Parkinsonism may result in impaired gait and mobility, increasing the risk of falls, and neuroleptic-induced dyskinesias. As a result, use of newer agents with less D2 receptor blockade, in addition to 5HT2 receptor blockade, may be preferable (Fernandez and Friedman, 1999). "Atypical" antipsychotic medications such as clozapine, olanzapine, quetiapine and risperidone can often be used to provide adequate treatment of psychosis without significant worsening of motor symptoms. Theoretically, the unique receptor profile of aripiprazole – which acts as a D2 receptor partial agonist – may make it a useful treatment option in patients with psychosis. Caution needs to be exercised in patients with dementing disorders, as the anticholinergic effects of some medications (including clozapine and olanzapine, in addition to older first-generation medications including chlorpromazine and thioridazine) may negatively impact upon cognition. A number of these antipsychotics may also lower seizure threshold, meaning caution should be exercised in patients who have difficult-to-control seizures as part of their disorder.

Limited evidence exists on the treatment of compulsive disorders, although these symptoms have been reported to respond to serotonergic medications (Habermeyer et al., 2006; Robertson et al., 2008; Walterfang et al., 2008). Given that supra-maximal dosages and a lengthy duration of treatment is often required in treatment of OCD with serotonergic medication (Bloch et al., 2010), lengthy treatment with high-dose treatment is likely to be required in treating compulsive disorders in the neuroacanthocytosis syndromes.

The most recent treatment development in the neuroacanthocytoses is the use of deep-brain stimulation (DBS), with stimulation of the globus pallidus internus (GPi) reported as showing promise in both ChAc and MLS (Guehl et al., 2007; Ruiz et al., 2009) and the motor thalamus in ChAc (Burbaud et al., 2002a,b). However, none of the reports to date have reported whether psychiatric presentations were induced or altered by the use of DBS. Stimulation of the subthalamic nucleus has been reported to induce or worsen depression and impulsivity in patients treated with DBS for Parkinson's disease (Bronstein et al., 2010), and hypomania and suicidal ideation has been reported in patients treated with subthalamic stimulation for OCD (Mallet et al., 2008). Rates of suicide have been suggested to be elevated in DBS treatment for a range of disorders, including when GPi stimulation is used, suggesting that pre-treatment screening and post-treatment monitoring is mandatory to mitigate this (Appleby et al., 2007). Thus neuroacanthocytosis patients who are treated with GPi stimulation should be carefully monitored for their suicide risk prior and subsequent to treatment.

8. Conclusion

The neuroacanthocytosis syndromes present with an elevated rate of dysexecutive syndromes, OCD, depression and possibly psychosis, which may precede the frank motor and cognitive impairment that heralds significant physical decline in these patients. The origins of psychiatric illness in neuroacanthocytosis appear to result from the disruption of frontostriatal circuitry, in particular the lateral orbitofrontal loop. Recognition of commonly occurring major mental disorders in these patients is of great clinical importance, as symptomatic treatment is readily available and it may significantly reduce the burden of illness for patients and carers alike.

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