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Neuroacanthocytosis

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Introduction

Neuroacanthocytosis refers to a group of inherited genetic disorders resulting in a combination of misshapen red blood cells (acanthocytes) and progressive neurological decline.[1] The neurological presentation can vary widely among diseases and can include shared characteristic features of movement disorders, neuropathy, psychiatric symptoms, neurocognitive degeneration, and seizures.[2] Specific diseases are many, including chorea-acanthocytosis (ChAc),[3] McLeod syndrome (MLS),[4] Huntington like-disease 2 (HDL2),[5] pantothenate kinase-associated neurodegeneration (PKAN, also known as Hallervorden Spatz disease),[6][7] HARP Syndrome (considered part of the PKAN spectrum consisting of hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration), abetalipoproteinemia (ABL),[8] hereditary hypobetalipoproteinemia (HHBL),[9] and aceruloplasminemia.[10][11] The two core conditions are chorea-acanthocytosis and McLeod Syndrome. Each neuroacanthocytosis disorder is extremely rare, with a prevalence of less than 1 to 3 per 1,000,000 individuals for PKAN or fewer than 100 cases ever reported in the case of ABL.

Etiology

Neuroacanthocytosis syndromes are caused by a variety of genetic mutations that are inherited in several different patterns, with the most common being autosomal recessive (see Tables 1 & 2). Other syndromes such as McLeod syndrome are inherited in an X-linked recessive pattern, whereas Huntington like-disease 2 and hereditary hypobetalipoproteinemia are inherited in autosomal dominant and codominant patterns, respectively. HDL2 directly results from trinucleotide expansions of JPH3 very similarly to Huntington disease with patients experiencing intergenerational disease anticipation based on the extent of genetic expansion. Many of these diseases vary in genetic penetrance and phenotypic manifestations.[3][4][5][6][8][9][10]

Epidemiology

Each neuroacanthocytosis syndrome is exceedingly rare (see Table 1). Several populations have been identified as having higher prevalence compared to the global population. Examples include HDL2 demonstrating increased reported cases among individuals of African heritage and PKAN occurring more often in small pockets in the Netherlands and the Dominican Republic.[5]

Pathophysiology

The pathophysiology of these syndromes is unique to each and can vary widely in phenotypic disease manifestation (see Table 2). The direct cellular mechanisms of several syndromes such as PKAN, aceruloplasminemia, and diseases of lipoproteins are understood and described in the current literature. These syndromes tend to have better outcomes either due to milder disease progression or treatment modalities that prevent significant mortality and morbidity.[6][8][9][10] Other diseases such as ChAc, MLS, and HDL2 are not well understood despite the identification of involved

genes.[3][4][5] These diseases tend to be much more chronically debilitating and are not uniformly responsive to attempted treatments that have been sparsely reported.

History and Physical

Nearly all patients affected by neuroacanthocytosis syndromes will experience the eventual onset of progressive abnormalities in movement (usually ataxia or hyperkinetic movements) with a neurocognitive decline and behavioral changes (see Table 3). Each specific disease, however, may present with symptoms and comorbidities unique to the disease. If the clinician possesses significant clinical suspicion of a neuroacanthocytosis syndrome, a thorough physical exam is required. This would include a complete physical and neurological examination, including reflexes, cranial nerves, gait, muscle strength, and mental status exams.

A clear history of progressive neurological, neuromuscular, or neuropsychiatric symptoms that are not consistent with other more common diseases plays an integral role in identifying these rare syndromes as possible diagnoses. The acquisition of prior records, family history, collateral history, and any prior genetic testing may prove instrumental in establishing accurate differential diagnoses and choosing clinically appropriate diagnostic modalities for further evaluation.

Evaluation

For many of these syndromes, the clinical symptoms will often prompt the use of additional diagnostic modalities that are instrumental in establishing a correct diagnosis (see Table 4). Such modalities include magnetic resonance imaging (MRI), or computed tomography (CT) scans to assess neurological involvement in the cerebral or spinal nervous tissues. Additionally, laboratory testing of serum samples may be useful in ruling out some diseases while providing confirmatory data for others, as in the case of the diseases of lipoproteins (ABL and HHBL) or aceruloplasminemia. For most neuroacanthocytosis syndromes, there are either no clear diagnostic criteria (e.g., ChAc, ABL, and HHBL) or genetic testing to identify diseases that may otherwise be indistinguishable from other syndromes (e.g., HDL2).

Treatment / Management

There is no cure or definitive treatment for several of the neuroacanthocytosis syndromes, such as ChAc and MLS (see Table 5).[12] With the exception of ABL, HHBL, and aceruloplasminemia, the goals of management generally are to:

1) Treat symptomatically

2) Slow the development of progressive symptoms

3) Evaluate for and prevent where possible serious causes of morbidity and mortality such as ophthalmic involvement, metabolic/hormonal imbalances, seizures, cardiac involvement, and status dystonicus.

Interprofessional treatment teams have been advocated as the ideal approach in caring for patients who likely have complex and significant symptoms that run the gamut of neurological to psychiatric to multiple organ systems.[12]

Consultation by medical specialists in neurology, psychiatry, neuropsychiatry, ophthalmology, or clinical genetics may be appropriate in identifying, evaluating, and managing patients diagnosed with neuroacanthocytosis syndromes (see Table 6).

Differential Diagnosis

The differential diagnoses for these rare syndromes are many and sometimes may be indistinguishable from other disease entities without the appropriate radiological, laboratory, or genetic workup (see Table 7).

Pertinent Studies and Ongoing Trials

Due to the extreme rarity of these syndromes, there have been no randomized control trials or experimental treatment studies assessing the efficacy of diagnostic or treatment modalities.[12][13][14] Information regarding diagnostic criteria and possible treatments have been largely developed from the aggregation of case reports and case series.[12]

Toxicity and Side Effect Management

There are several side effects to keep in mind for several specific syndromes and their associated management (see Table 5). For example, antiepileptic drugs (AEDs) such as carbamazepine and lamotrigine should be avoided in patients with ChAc due to the worsening of involuntary movements.[3] Conversely, long-term use of benzodiazepines should be avoided as an AED in patients with McLeod syndrome due to potential negative effects on the neuromuscular system. Additionally, dopamine antagonists or tetrabenazine should be avoided due to increased risk of extrapyramidal symptoms (EPS) in MLS patients.[4]

Another consideration for MLS patients is to avoid heterologous blood product transfusions due to an increased risk of adverse transfusion reactions. Case reports have suggested avoiding alpha-tocopherol and idebenone in treating the neuromuscular symptoms of patients with PKAN due to anecdotal evidence suggesting worsening of symptoms.[6] Finally, patients should avoid iron supplementation or other sources of exogenous iron due to the iron accumulation inherent in the disease.[10]

Prognosis

The prognosis for these syndromes is variable. Syndromes such as ChAc, MLS, typical PKAN, and HDL2 are known to be chronic and progressive, often resulting in complications of dysarthria such as malnutrition and aspiration pneumonia with eventual death (see Table 8). In some cases, complicating symptoms such as seizures, cardiac arrhythmias, cardiomyopathy, and status dystonicus may cause premature death. On the other hand, the mortality and progression of aceruloplasminemia, ABL, and HHBL are heavily influenced by appropriate management with chelating agents and fat-soluble vitamin supplementation (respectively) with patients enjoying a typical lifespan if managed appropriately.[8][9][10]

Complications

Many of the complications arising from neuroacanthocytosis syndromes derive from neuromuscular deficits or neurocognitive decline (see Table 3). Neuromuscular symptoms such as chorea, ataxia, myopathy, dystonia, loss of dorsal column, or spinocerebellar spinal tracts can result in gait disturbances and inability to participate in ADLs. Additional progressive cognitive deficits or personality changes (including increased impulsivity, aggression, or psychiatric symptoms) can further complicate care for patients diagnosed with a neuroacanthocytosis syndrome. Several complications can be life-threatening, including seizures, cardiac arrhythmias, cardiomyopathy, status dystonicus, and psychiatric comorbidities such as suicidality.

Ophthalmological complications such as retinal degeneration and retinopathy are commonly described in cases of PKAN, ABL, HHBL, and aceruloplasminemia. In the case of several metabolically driven diseases such as ABL, HHBL, and aceruloplasminemia, multiple organ systems can be involved resulting in anemia, diabetes mellitus, cardiomegaly, hepatosplenomegaly, and hypothyroidism.

Deterrence and Patient Education

Genetic counseling plays an important role in the management as well as appropriate evaluation and education for both the patient and involved family members. Consultation with a genetic counselor and clinical geneticist can provide important clinical information such as genotypic and phenotypic characteristics of the disease, possible disease progression, and the likelihood of disease occurring in relatives or offspring.[1]

Enhancing Healthcare Team Outcomes

Recent literature advocates interprofessional team-based care as the ideal approach in caring for patients diagnosed with neuroacanthocytosis syndromes due to the severity and chronic progression of symptoms as well as possible development of severe medical comorbidity.[12] Such a care team would likely consist of the patient's primary care clinician, neurologist, clinical geneticist (or genetic counselor), and several other therapeutic modalities (see Table 5). Providers may seek additional care in consultation with specialists in psychiatry, ophthalmology, and cardiology in diseases such as MLS, PKAN, and ABL/HHBL. The extreme rarity of these syndromes significantly limits evidence-based treatments. Patients with these syndromes may require involved and prolonged team-based care to improve symptoms and prevent the development of serious medical complications.

Continuing Education / Review Questions

- Access free multiple choice questions on this topic.
- Earn continuing education credits (CME/CE) on this topic.
- Comment on this article.

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Figures

Table 1: Epidemiology of Neuroacanthocytosis Syndromes

Syndrome	Prevalence
Chorea-acanthocytosis [2]	500-1000 cases worldwide
McLeod Syndrome [3]	Approximately 250 known cases, prevalence of ~1:10,000,000
Huntington like-disease 2 [4]	Worldwide prevalence is approximately 1% of individuals suspected of having Huntington Disease Most common HD phenocopy in patients of African ancestry with highest number of cases in South Africa
PKAN/Hallervorden Spatz Disease [5][6]	1-3:1,000,000 (small pockets in the Netherlands and Dominican Republic) HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration) falls within the phenotypic spectrum of PKAN
Abetalipoproteinemia/Hereditary Hypobetalipoproteinemia [7][8]	Fewer than 100 cases have been reported
Aceruloplasminemia [9][10]	One study in Japan estimated a prevalence of 1:2,000,000; no other prevalence data is available

Table 2: Genetics of Neuroacanthocytosis Syndromes

Syndrome	Inheritance Pattern	Genes	Cellular Mechanisms
Chorea-acanthocytosis [2]	Autosomal recessive	VPS13A	Function of chorein is unknown
McLeod Syndrome [3]	X-linked recessive	XK	XK protein is expressed in blood, brain, and muscle cells but appears to differ in function among cell types. Loss of XK function leads to abnormal RBC membrane shape due to loss of disulfide bonding with Kell glycoprotein. Neuronal and cardiac involvement is not well understood.
Huntington like-disease 2 [4]	Autosomal dominant	CTG expansion on JPH3	Unknown pathogenesis but may be due to: 1. Loss of function RNA sequestration 2. Gain of function toxicity
PKAN/Hallervorden Spatz Disease [5][6]	Autosomal recessive	PANK2	Deficient or absent pantothenate kinase 2 results in CoA depletion and accumulation of N-pantothenoyl-cysteine and pantetheine which may lead to direct cell toxicity or iron free radical damage
Abetalipoproteinemia [7]	Autosomal recessive	MTTP	Microsomal triglyceride transfer protein (MTTP) is an essential cofactor in lipoprotein function. When mutated, MTTP becomes an insoluble aggregate causing defective interaction with PDI or loses lipid transfer activity
Hereditary Hypobetalipoproteinemia [8]	Autosomal recessive	ApoB, PCSK9, MTP	ApoB is an apolipoprotein present in VLDL and chylomicrons that acts as a recognition signal for lipoprotein binding and subsequent cholesterol transfers to target tissues
Aceruloplasminemia [9]	Autosomal recessive	CP	Ceruloplasmin is a carrier protein for nearly all plasma copper and is expressed by hepatocytes, astrocytes, and visceral organs. Genetic mutations result in defective ceruloplasmin resulting in inappropriate intracellular copper processing

Table 1: Epidemiology of Neuroacanthocytosis Syndromes Table 2: Genetics of Neuroacanthocytosis Syndromes. Contributed by Joshua Feriante DO, MBA

Table 3: Clinical Manifestations of Neuroacanthocytosis Syndromes

Syndrome	Onset	Neuromuscular	Neurological	Neurocognitive	Additional Symptoms
Chorea-acanthocytosis [2]	Mean age: 30	Chorea, parkinsonian syndromes, oral dystonia, distal myopathy	Seizures (50% of cases), impaired upward gaze or saccades	Progressive behavioral changes resembling frontal lobe syndrome; apathy, depression, bradyphrenia, aggression, impulsivity	Dysarthria increases the risk of aspiration and nutritional loss Uncommonly cardiomyopathy
McLeod Syndrome [3]	Mean age: before 40	Sensorimotor axonopathy, neurogenic muscle atrophy, myopathy, absent DTRs	Progressive chorea with head drops, dystonia, gait abnormalities; seizures (40% of cases)	Cognitive deficits (50% of cases); psychiatric changes including personalities disorders, anxiety, depression, OCD, bipolar disorder, schizoaffective disorder (80% of cases)	Congestive or dilated cardiomyopathy; cardiac arrhythmias (e.g. atrial fibrillation); hepatosplenomegaly secondary to hemolysis (30% of cases); increased risk of aspiration and nutritional loss due to dysarthria
Huntington like-disease 2 [4]	Mean age: 41	Chorea affecting gait, speech, swallowing; oculomotor abnormalities; dystonia (late)	Progressive dementia; neuronal loss in striatum and cerebral cortex	Personality changes (e.g. apathy, irritability), depression	Retinal degeneration (2/3 of cases)
PKAN/Hallervorden Spatz Disease [5][6]	**Typical form**: 1st decade **Atypical form**: 2nd-3rd decade	**Typical:** extrapyramidal dysfunction (e.g. dystonia, spasticity, choreoathetosis); loss of ambulation (varies by type) **Atypical:** slower progression with eventual spasticity, hyperreflexia, and limited ambulation n with "freezing"; tremor syndrome	Extrapyramidal symptoms (e.g. dysarthria, dystonia); status dystonicus secondary to long bone fractures and osteopenia; rarely seizures; corticospinal tract involvement; dementia	**Typical:** Intellectual impairment (inversely correlated to age of onset) **Atypical:** personality changes (e.g. impulsivity, agitation, depression, emotional lability); verbal tics, obsessive-compulsive behavior, and psychotic symptoms	**Typical:** restricted visual fields due to retinopathy **Atypical:** multiple speech defects such as palilalia, tachylalia, tachylogia, and dysarthria Retinopathy (rare)
Abetalipoproteinemia/Hereditary Hypobetalipoproteinemia [7][8]	Presents at birth with failure to thrive, vomiting, and fat malabsorption	Spinocerebellar ataxia and myopathy; progressive loss of DTRs, vibratory sense, and proprioception; muscle weakness; dysarthria	Friedrich's-like ataxia in untreated individuals Evaluate for hyporeflexia, proprioception, loss, and muscle strength		Failure to thrive, severe diarrhea, vomiting, fat malabsorption, loss of night or color vision; atypical retinal pigmentation Acanthocytosis Multiorgan involvement rarely including cardiomegaly and hypothyroidism
Aceruloplasminemia [9][10]	Age 30 to >70	Ataxia, chorea, tremors; facial or neck dystonia, blepharospasm, grimacing	Parkinsonism (e.g. rigidity, akinesia)	Cognitive dysfunction (e.g. apathy, forgetfulness)	Iron-restricted microcyte (80%), Retinal degeneration (75%), Diabetes mellitus (70%)

Table 3: Clinical Manifestations of Neuroacanthocytosis Syndromes. Contributed by Joshua Feriante DO, MBA

Table 4: Diagnostic Testing for Neuroacanthocytosis Syndromes

Syndrome	Diagnostic Criteria	Imaging	Laboratory Findings	Electrophysiologic Tests	Genetic Testing
Chorea-acanthocytosis [2]	No clearly established diagnostic criteria	MR of brain: atrophy of caudate nuclei and putamen; dilated lateral ventricles	Elevated CK, occasionally elevated LDH, AST, ALT; decreased chorein on Western blot analysis (normal levels do not exclude diagnosis); muscle biopsy reveals neurogenic and myopathic atrophy ("Nemaline" rods)	Sensory axonopathy with reduced sensory action potentials	Sequence analysis or deletion/duplication analysis for VPS13A
McLeod Syndrome [3]	Clinical suspicion and XK mutation (in men) OR McLeod blood phenotype by chromosomal microarray analysis (CMA) OR Single/multigene panel (females)	CT & MR of brain: caudate nucleus and putamen CT: fatty degeneration of lower leg muscles	Absent Kx antigen Reduced Kell antigens Elevated serum CK Acanthocytosis and compensated hemolysis in nearly all males Occasionally elevated LDH, AST, ALT	ECG may show atrial fibrillation or tachyarrhythmia Electromyography may show neurogenic and myopathic changes Nerve conduction studies may show axonal damage	Single or multigene panel genetic testing based on clinical suspicion
Huntington like-disease 2 [4]	Clinically indistinguishable from Huntington disease and requires genetic testing	MR of brain: caudate and cerebral cortex atrophy sparing brain stem and cerebellum	Acanthocytosis on blood smear in a minority of reported cases		Detection of >40 CTG trinucleotide repeats in *JPH3*
PKAN/Hallervorden Spatz Disease [5]	Diagnosed clinically with identified early onset of: EPS dysfunction Loss of ambulation "Eye of the tiger" sign on T2-weighted brain MRI Molecular genetic testing establishes the diagnosis if unable to clinically diagnose	T2-weighted MRI of brain: "Eye of the tiger" (globus pallidus abnormality)	Acanthocytosis in some patients; low or absent pre-beta lipoprotein fraction		Sequence analysis or gene-targeted deletion/duplication analysis; single gene testing, multigene panel, or comprehensive genomic testing
Abetalipoproteinemia/Hereditary Hypobetalipoproteinemia [7][8]	No formal diagnostic criteria have been published	Hepatic imaging in context of transaminitis may show cirrhosis or hepatocellular carcinoma	Hypocholesterolemia; severely decreased plasma LDL-cholesterol, Apo B, triglycerides; acanthocytosis; transaminitis; prolonged INR; low fat-soluble vitamin concentrations (A, D, E, and K)		Molecular testing including single-gene testing or multigene panel to establish biallelic variants in MTTP and exclude differential diagnoses
Aceruloplasminemia [9][10]	Diagnosis is established in a program with clinical findings and molecular genetic testing showing biallelic pathogenic variants in *CP* gene	MR of brain: hypointensities in basal ganglia, striatum, thalamus, dentate nucleus suggesting iron deposition MRI abdominal: hepatic hypointensities	Iron-deficient microcytic anemia (~80 of cases); aceruloplasminemia, elevated serum ferritin, low serum iron, low serum copper with normal urinary copper		Molecular genetic testing showing biallelic pathogenic variants in *CP* gene

Table 4: Diagnostic Testing for Neuroacanthocytosis Syndromes. Contributed by Joshua Feriante DO, MBA

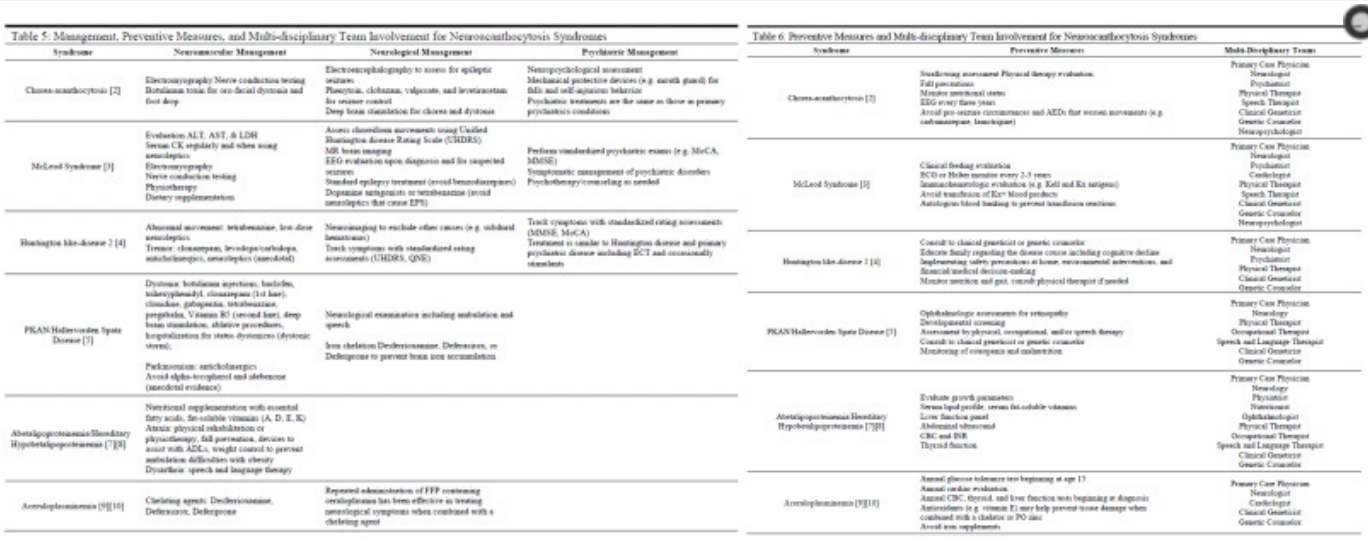

Table 5: Management, Preventive Measures, and Multi-disciplinary Team Involvement for Neuroacanthocytosis Syndromes

Syndrome	Neuromuscular Management	Neurological Management	Psychiatric Management
Chorea-acanthocytosis [2]	Electromyography Nerve conduction testing Botulinum toxin for oro-facial dystonia and foot drop	Electroencephalography to assess for epileptic seizures Phenytoin, clobazam, valproate, and levetiracetam for seizure control Deep brain stimulation for chorea and dystonia	Neuropsychological assessment Mechanical protective devices (e.g. mouth guard) for falls and self-injurious behavior Psychiatric treatments are the same as those in primary psychiatrics conditions
McLeod Syndrome [3]	Evaluation ALT, AST, & LDH Serum CK regularly and when using neuroleptics Electromyography Nerve conduction testing Physiotherapy Dietary supplementation	Assess choreiform movements using Unified Huntington disease Rating Scale (UHDRS) MR brain imaging EEG evaluation upon diagnosis and for suspected seizures Standard epilepsy treatment (avoid benzodiazepines) Dopamine antagonists or tetrabenazine (avoid neuroleptics that cause EPS)	Perform standardized psychiatric exams (e.g. MoCA, MMSE) Symptomatic management of psychiatric disorders Psychotherapy/counseling as needed
Huntington like-disease 2 [4]	Abnormal movement: tetrabenazine, low dose neuroleptics Tremor: clonazepam, levodopa/carbidopa, anticholinergics, neuroleptics (anecdotal)	Neuroimaging to exclude other causes (e.g. subdural hematomas) Track symptoms with standardized rating assessments (UHDRS, QNE)	Track symptoms with standardized rating assessments (MMSE, MoCA) Treatment is similar to Huntington disease and primary psychiatric disease including ECT and occasionally stimulants
PKAN/Hallervorden Spatz Disease [5]	Dystonia: botulinum injections, baclofen, trihexyphenidyl, clonazepam (1st line), clonidine, gabapentin, tetrabenazine, pergolides, Vitamin K5 (second line), deep brain stimulation, ablative procedures, hospitalization for status dystonicus (dystonic storm); Parkinsonism: anticholinergics Avoid alpha-tocopherol and idebenone (anecdotal evidence)	Neurological examination including nutrition and speech Iron chelation Desferrioxamine, Deferasirox, or Deferiprone to prevent brain iron accumulation	
Abetalipoproteinemia/Hereditary Hypobetalipoproteinemia [7][8]	Nutritional supplementation with essential fatty acids, fat-soluble vitamins (A, D, E, K) Ataxia: physical rehabilitation or physiotherapy, fall prevention, devices to assist with ADLs, weight control to prevent ambulation difficulties with obesity Dysarthria: speech and language therapy		
Aceruloplasminemia [9][10]	Chelating agents: Desferrioxamine, Deferasirox, Deferiprone	Repeated administration of FFP containing ceruloplasmin has been effective in treating neurological symptoms when combined with a chelating agent	

Table 6: Preventive Measures and Multi-disciplinary Team Involvement for Neuroacanthocytosis Syndromes

Syndrome	Preventive Measures	Multi-Disciplinary Team
Chorea-acanthocytosis [2]	Swallowing assessment Physical therapy evaluation Fall precautions Monitor nutritional status EEG every three years Avoid pro-seizure circumstances and AEDs that worsen movements (e.g. carbamazepine, lamotrigine)	Primary Care Physician Neurologist Psychiatrist Physical Therapist Speech Therapist Clinical Geneticist Genetic Counselor Neuropsychologist
McLeod Syndrome [3]	Clinical feeding evaluation ECG or Holter monitor every 2-3 years Immunohematologic evaluation (e.g. Kell and Kx antigens) Avoid transfusion of Kx+ blood products Autologous blood banking to prevent transfusion reactions	Primary Care Physician Neurologist Psychiatrist Cardiologist Physical Therapist Speech Therapist Clinical Geneticist Genetic Counselor Neuropsychologist
Huntington like-disease 2 [4]	Consult to clinical geneticist or genetic counselor Educate family regarding the disease course including cognitive decline Implementing safety precautions at home, environmental interventions, and financial/medical decision-making Monitor nutrition and gait, consult physical therapist if needed	Primary Care Physician Neurologist Psychiatrist Physical Therapist Clinical Geneticist Genetic Counselor
PKAN/Hallervorden Spatz Disease [5]	Ophthalmologic assessments for retinopathy Developmental screening Assessment by physical, occupational, and/or speech therapy Consult to clinical geneticist or genetic counselor Monitoring of osteopenia and malnutrition	Primary Care Physician Neurology Physical Therapist Occupational Therapist Speech and Language Therapist Clinical Geneticist Genetic Counselor
Abetalipoproteinemia Hereditary Hypobetalipoproteinemia [7][8]	Evaluate growth parameters Serum lipid profile, serum fat-soluble vitamins Liver function panel Abdominal ultrasound CBC and INR Thyroid function	Primary Care Physician Neurology Physician Nutritionist Ophthalmologist Physical Therapist Occupational Therapist Speech and Language Therapist Clinical Geneticist Genetic Counselor
Aceruloplasminemia [9][10]	Annual glucose tolerance test beginning at age 13 Annual cardiac evaluation Annual CBC, thyroid, and liver function tests beginning at diagnosis Antioxidants (e.g. vitamin E) may help prevent tissue damage when combined with a chelator or PO zinc Avoid iron supplements	Primary Care Physician Neurologist Cardiologist Clinical Geneticist Genetic Counselor

Table 5: Management, Preventive Measures, and Multi-disciplinary Team Involvement for Neuroacanthocytosis Syndromes Table 6: Preventive Measures and Multi-disciplinary Team Involvement for Neuroacanthocytosis Syndromes. Contributed by Joshua Feriante DO, MBA

Table 7: Differential Diagnoses for Neuroacanthocytosis Syndromes

Syndrome	Differential Diagnoses	
Chorea-acanthocytosis [2]	Huntington disease Wilson disease McLeod syndrome PKAN (including HARP syndrome) HDL2	Abetalipoproteinaemia & Hypobetaproteinaemia Lesch-Nyhan syndrome DRPLA Benign hereditary chorea Infantile neuroaxonal dystrophy
McLeod Syndrome [3]	Huntington disease Hypobetalipoproteinaemia Type 1 & 2 Abetalipoproteinaemia HDL3 or HDL2 PKAN (including HARP) Chorea-acanthocytosis DRPLA Wilson Disease	SCA3 SCA17 Aceruloplasminaemia X-linked dystonia-parkinsonism Neuroferritinopathy Lesch-Nyhan syndrome Benign hereditary chorea PLAN6-associated neurodegeneration
Huntington like-disease 2 [4]	Neuroferritinopathy Spinocerebellar Ataxia Type 2, 3, or 17 Familial Creutzfeldt-Jakob disease Neuronal ceroid-lipofuscinoses Primary familial brain calcification Mitochondrial disorders	Hereditary cerebellar ataxia Early-onset Alzheimer Disease Frontotemporal dementia Amyotrophic lateral sclerosis Parkinsonian conditions
PKAN/Hallervorden Spatz Disease [5][6]	Typical: Early-onset Parkinson disease Primary familial brain calcification Aceruloplasminaemia Neuroferritinopathy Steele-Richardson-Olszewski syndrome	Atypical: X-linked intellectual disability with Dandy-Walker Malformation Alpha-L fucosidosis Leigh syndrome Infantile neuroaxonal dystrophy
Abetalipoproteinaemia/Hereditary Hypobetalipoproteinemias [7][8]	McLeod syndrome	Friedreich ataxia
Aceruloplasminaemia [9][10]	Atypical PKAN Neuroferritinopathy Wilson Disease HFE-associated hereditary hemochromatosis	Huntington disease DRPLA Dystonia Hereditary spinocerebellar ataxias

Table 8: Prognoses of Neuroacanthocytosis Syndromes

Syndrome	Prognosis	Mortality	Cause of Death
Chorea-acanthocytosis [2]	Can cause disability within a few years; many bedridden or wheelchair-dependent by 3rd decade; facial dystonia can lead to mutism in a third of cases	Age of death: between 28-61 years	Dysarthria with increased risk of aspiration pneumonia and malnutrition, several cases of death from seizures or sudden unexplained death
McLeod Syndrome [3]	Chronically progressive with a third of patients presenting initially with chorea and then developing in nearly all patients; approximately half of patients develop neurocognitive deficits, seizures, and cardiac manifestations	Mean age of death: 53 years	Cardiac arrhythmias appear to be a major cause of death; other causes include sepsis, pneumonia, seizures, and suicide
Huntington like-disease 2 [4]	Chronically progressive with triad of abnormalities in movement, emotion, and cognition	Death within 10-20 years of diagnosis (trinucleotide expansion is inversely correlated with age of onset)	Similar to Huntington disease
PKAN/Hallervorden Spatz Disease [5][6]	Typical: chronically progressive with a relapsing and remitting pattern; loss of skills is permanent; increased rate of progression is correlated with early age of onset; most are wheelchair-bound as teenagers Atypical: progression is slower often presenting with speech disruption (e.g. palilalia, tachylalia/tachylogia, and dysarthria)	Typical life expectancy	Dysphagia, malnutrition, and aspiration pneumonia secondary to orofacial dystonia are common causes of premature death Status dystonicus is a rare cause of death
Abetalipoproteinaemia/Hereditary Hypobetalipoproteinemias [7][8]	Historically patients have died from severe neuromyopathy and respiratory failure, but life-long treatment with fat-soluble vitamins generally leads to good outcomes	Typical life expectancy	Severe neuromyopathy and respiratory failure if poorly managed
Aceruloplasminaemia [9][10]	Variable prognosis given heterogeneity of classic triad of retinal degeneration, diabetes, and neurological disease	Typical life expectancy	Complications of cardiac iron deposition and diabetes mellitus

Table 7: Differential Diagnoses for Neuroacanthocytosis Syndromes Table 8: Prognoses of Neuroacanthocytosis Syndromes. Contributed by Joshua Feriante DO, MBA

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