Movement Disorders
CLINICAL PRACTICE

REVIEW

Movement Disorders and Hematologic Diseases

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Abstract: Background: Movement disorders can be associated with or caused by hematological abnormalities. The objective of this review is to highlight features that will aid in the clinician's recognition and treatment of these disorders.

Methods: MESH terms relevant to movement disorders and hematologic diseases were searched to identify conditions included in this narrative, educational review.

Results: Several conditions were identified, and they were organized by hematologic categories to include red blood cell abnormalities, white blood cell abnormalities, disorders of clotting and bleeding, hematologic malignancies, and others.

Conclusions: This review will increase providers' understanding of disorders that include movement disorders and hematologic abnormalities. Basic hematologic laboratories can aid in assessment of these disorders, to include complete blood count/hemogram and peripheral blood smear. Recognition is key, especially in the setting of underlying malignancy, vitamin deficiency, or other disorder in which treatment is available.

The overlap between movement disorders and hematology may be greater than other organ systems due to the close relationship of the hematologic system to the nervous system. Many of the diseases discussed in this review are rare and are distinguished by their underlying hematological abnormalities or multisystem involvement. Genetics play a large role in many of these conditions although acquired, autoimmune, and ischemic disorders are also prominent themes. Some common movement disorders have hematologic manifestations, such as Parkinson's disease and restless leg syndrome, but are addressed only in short in this review.

This narrative review focuses on primary neurologic or hematologic disorders with both movement disorders and hematologic manifestations, which are summarized in Table 1. The disorders are organized based on hematologic process. Some disorders may fit into multiple categories, so they were included in the category associated with the most common or distinctive hematologic manifestation. At the end, there is a brief discussion of lysosomal storage and metal metabolism disorders which have both hematologic and movement disorders features; they are included in a separate section since they are not considered "primary" neurologic or hematologic disorders. Each disorder is described with regards to clinical manifestations, pathophysiology, genetics if applicable and treatment. This review will increase providers' understanding of these disorders and provide framework for identifying conditions based on distinguishing neurologic or hematologic characteristics. Movement disorders specialists may not readily identify these disorders due to their rarity. Additionally, hematologic associations with common disorders and medication complications are addressed, which are pertinent to movement disorders providers and patients. Tables 2 and 3 provide a summary of neurologic conditions by hematologic process and recommendations for hematologic testing, respectively, which can be used as a practical reference for clinicians.

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TABLE 1 *Disorders with movement abnormalities and hematologic involvement*

Disorder	Etiology	Hematologic manifestations	Movement disorder & neurologic manifestations
Disorders of red blood cells			
Abetalipoproteinemia	*MTP* gene mutation	Acanthocytes, coagulopathy (due to vitamin K deficiency)	Ataxia, vibratory and proprioception loss, hyporeflexia, myopathy, ophthalmologic problems (neurologic symptoms are similar to vitamin E deficiency)
Huntington disease like-2	*JPH3* trinucleotide repeat expansion	Acanthocytes	Chorea, dystonia, myoclonus, parkinsonism, neuropsychiatric disorder
Infantile tremor syndrome	Possibly nutritional deficiency	Anemia	Self-limiting episode of neuromotor regression, course body tremors and hypotonia
Neuroacanthocytosis	*VPS13A* mutation (chorea-acanthocytosis); X-linked XK mutation (Mcleod syndrome)	Acanthocytes, hepatosplenomegaly	Chorea, dystonia, psychiatric and cognitive dysfunction, myopathy, seizures
X-linked sideroblastic anemia and ataxia	X-linked mutation in *ABCB7* gene	Ringed sideroblasts, iron inclusions in mature RBCs, microcytic and hypochromic anemia	Early-onset ataxia, tremor, pyramidal signs
Paroxysmal exertion-induced dyskinesia	Sporadic or genetic (eg GLUT-1 deficiency)	Hemolytic anemia, macrocytic anemia, echinocytes	Lower limb dystonia and choreoathetiotic movements precipitated by exercise, ataxia, epilepsy
Paroxysmal nocturnal hemoglobinuria	*PIGA* mutation	Chronic anemia; episodes of hemolytic anemia with systemic stress	Episodes of smooth muscle dystonia including abdominal or back pain, esophageal spasm, and erectile dysfunction
Parkinson's disease	Idiopathic	Anemia	Bradykinesia, rigidity, postural instability, resting tremor
Restless leg syndrome	Idiopathic; sometimes caused be iron deficiency anemia	Iron deficiency anemia, low ferritin and TIBC	Uncontrollable urge to move legs, associated with uncomfortable sensation
Vitamin B12 deficiency	Acquired, multiple causes	Megaloblastic anemia; rare hemolysis and pancytopenia	Ataxia, myelopathy, dorsal column dysfunction, neuropathy, cognitive impairment
Vitamin E deficiency	Acquired, multiple causes	Hemolytic anemia	Ataxia, weakness, hyporeflexia, cranial neuropathies, cognitive impairment, retinitis pigmentosa
Disorders of white blood cells			
Chediak-Higashi Syndrome	*LYST* or *CHS1* mutation	Neutropenia, anemia, thrombocytopenia, giant inclusion bodies (granules) in leukocytes, fulminant hemophagocytic syndrome	Neurodevelopmental delay, neuropathy, spasticity, dystonia, parkinsonism, ataxia, epilepsy
Clozapine-induced leukopenia	Chronic clozapine use	Agranulocytosis	N/A
Ataxia-telangiectasia	*ATM* mutation	Lymphopenia, low Ig levels, increased risk for leukemia/lymphoma	Ataxia, oculomotor apraxia, chorea, cognitive impairment, parkinsonism, dystonia, pyramidal signs
Copper deficiency	Acquired, multiple causes	Leukopenia, anemia; cytoplasmic vacuolization within precursor cells	Spastic-ataxic gait, myelopathy, neuropathy, motor neuron disease

(Continues)

TABLE 1 *Continued*

Disorder	Etiology	Hematologic manifestations	Movement disorder & neurologic manifestations
Disorders of bleeding and clotting			
Antiphospholipid syndrome	Autoimmune	Thrombocytopenia, bone marrow necrosis, thrombotic microangiopathic syndromes	Chorea, dystonia, and other movement disorders; often associated with thrombo-occlusive event
Hemolytic uremic syndrome	Toxic/peri-infectious	Thrombocytopenia, thrombotic microangiopathy	Ataxia, dystonia, encephalopathy, diplopia, weakness
Polycythemia vera	*JAK2* mutation	Polycythemia, thrombosis due to hyperviscosity	Chorea and other hyperkinetic movements
Sickle cell disease	Mutation in beta-globulin subunit in hemoglobin-beta gene	Sickle shape RBC, chronic anemia, episodes of acute vaso-occlusive and hemolytic crises	Periodic leg movements of sleep, acute stroke syndromes, chorea
Hematologic malignancies			
Ataxia-pancytopenia syndrome	*SAMD9L/SAMD9* mutation	Cytopenias, anemia, immunodeficiency, hypoplastic bone marrow, myelodysplasia	Ataxia, nystagmus, hyperreflexia, abnormal gait, cognitive impairment; MIRAGE syndrome is more severe phenotype
Leukopenia and lymphoma	Varies, often idiopathic	Varies depending on the type of malignancy	Rare ataxia, parkinsonism, encephalopathy, and hyperkinetic movements
Paraproteinemias	Autoimmune or idiopathic	Monoclonal gammopathy	Ataxia, tremor, peripheral neuropathy, cranial neuropathies
Storage disorders or disorders of metal metabolism			
Gaucher disease	*GBA* mutation	Anemia, thrombocytopenia, hepatosplenomegaly, increased risk for hematologic malignancies	Parkinsonism, slow horizonal saccades, severe neurodegeneration subtype (type 2)
Neimann-Pick disease type C	*NPC1* or *NPC2* mutation	Anemia	Vertical supranuclear gaze palsy, parkinsonism, ataxia, gelastic cataplexy, psychiatric disorder
Hypermanganesemia with dystonia	*SLC30A10* or *SCL39A14* mutation	Polycythemia	Dystonia, parkinsonism
Hematochromatosis	*C282Y* or other gene mutation	Elevated serum ferritin, iron and TIBC	Rare parkinsonism, chorea, myoclonus, ataxia, dystonia, tremor
Neurodegeneration with brain iron accumulation	Multiple gene mutations	-Neuroferrinitinopathy: low ferritin -Aceruloplasminemia: low ceruloplasmin, microcytic anemia, elevated ferritin -PKAN: acanthocytes -HARP: acanthocytes -FHAN: PAS-positive granular inclusions in bone marrow biopsy	Dystonia, dysarthria, spasticity, parkinsonism, neuropsychiatric problems, optic atrophy or retinal degeneration
Wilson's disease	*ATP7B* mutation	Thrombocytopenia, leukopenia, rare hemolytic anemia	Tremor, dystonia, parkinsonism, dysarthria, orofacial dyskinesias, ataxia, pyramidal signs, seizures, neuropsychiatric symptoms

TABLE 2 *Neurologic disorders associated with specific hematologic processes*

Hematologic process	Neurologic disorder
Anemia	Infantile tremor syndrome
	Paroxysmal exertion-induced dyskinesia
	Paroxysmal nocturnal hemoglobinuria
	Parkinson's disease
	Restless leg syndrome
	Vitamin B12 deficiency
	Chediak-Higashi syndrome
	Copper deficiency
	Hemolytic uremic syndrome
	Sickle cell disease
	Ataxia-pancytopenia syndrome
	Gaucher disease
	Neimann-Pick disease type C
	Aceruloplasminemia
Hemolysis	Paroxysmal exertion-induced dyskinesia
	Paroxysmal nocturnal hemoglobinuria
	Vitamin E deficiency
	Hemolytic uremic syndrome
	Sickle cell disease
	Wilson's disease
Abnormal RBC morphology	Abetalipoproteinemia (acanthocytes)
	HDL-2 (acanthocytes)
	Neuroacanthocytosis (acanthocytes)
	Paroxysmal exertion-induced dyskinesia (echinocytes)
	PKAN (acanthocytes)
	HARP (acanthocytes)
Polycythemia	Polycythemia vera
	Hypermanganesemia with dystonia
Leukopenia	Chediak-Higashi syndrome
	Ataxia-telangectasia
	Copper deficiency
	Ataxia-pancytopenia syndrome
	Wilson's disease
Thrombocytopenia	Chediak-Higashi syndrome
	Antiphospholipid syndrome
	Hemolytic uremic syndrome
	Ataxia-pancytopenia syndrome
	Gaucher disease
	Wilson's disease
Thrombosis	Antiphospholipid syndrome
	Hemolytic uremic syndrome
	Polycythemia vera
	Sickle cell disease
Immunoglobulin abnormalities	Ataxia-telangectasia
	Ataxia-pancytopenia syndrome
	Paraproteinemias

Search Strategy

The following MESH terms were used to identify relevant conditions and papers: "parkinsonian disorders," "ataxia," "dystonia," "myoclonus," "tremor," "chorea," "tics" or "movement disorders" in combination one of the terms: "anemia," "hemoglobin," "red blood cell," "leukopenia," "leukocytosis," "blood platelet disorders," "blood coagulation disorders," "lymphoproliferative disorders" or "myeloproliferative disorders." Articles were selected relevant to the focus of this review.

Disorders of Red Blood Cells

Anemia and abnormalities of red blood cell (RBC) morphology are associated with movement disorders. Abnormal RBC morphology can be identified via peripheral blood smear and include acanthocytes and echinocytes. Acanthocytes are RBCs with spiked cell membrane due to thorny projections, and they can be seen in conditions such as abetalipoproteinemia, Huntington's disease like-2, and neuro-acanthocytosis. Echinocytes contain small projections and are seen in paroxysmal exertion-induced dyskinesia. The most common RBC disorder is anemia, which is characterized by a reduction in the proportion of RBCs and is assessed by blood hemoglobin and hematocrit levels.

Abetalipoproteinemia

Abetalipoproteinemia (ABL) is a rare, autosomal recessive disorder that belongs to a group of disorders termed hypobetalipoproteinemias. It is caused by mutations in the microsomal triglyceride transfer protein (MTP)-encoding gene which is responsible for trafficking lipids and lipid-soluble nutrients within the gastrointestinal tract. This disorder is characterized by low or absent levels of cholesterol, low-density lipoproteins (LDL), and very-low-density lipoproteins (VLDL).[1]

Most patients present in infancy with steatorrhea and fat malabsorption leading to failure to thrive. Decreasing fat intake can lead to symptom resolution, however long-term deficiency of fat-soluble vitamins, especially vitamin E, leads to long-term neurologic sequelae if untreated. Demyelination of spinocerebellar and posterior column axons can lead to ataxia, proprioception and vibratory sensory loss, and hyporeflexia.[2] Myopathy, myositis, weakness, neuropathy, and ophthalmologic complications, including retinitis pigmentosa, have also been reported.[1,2] The neurological manifestations typically manifest in the second decade if the diagnosis is not made in childhood. Death from cardiomyopathy has been reported in a few cases.[1]

Acanthocytosis is the hallmark hematologic abnormality in ABL, with acanthocytes making up approximately 50% of all circulating RBCs.[1] Elevated prothrombin time and INR has been reported due to a deficiency of vitamin K but bleeding rarely occurs.[2] Treatment of ABL is focused on dietary modification including reduction in fat intake and oral vitamin supplementation; early initiation is associated with better neurological outcomes.[1,2]

Huntington Disease Like-2

Huntington's disease like-2 (HDL-2) is an autosomal dominant disorder that manifests in the third or fourth decade.[3] All patients with HDL-2 identified thus far have had African ancestry. Clinical features include chorea, dystonia, myoclonus, parkinsonism, psychiatric abnormalities and cognitive deficits. Parkinsonism and dystonia occur more frequently than in Huntington's disease (HD), and eye movements are normal or only mildly

TABLE 3 *Hematologic tests which may be helpful based on presenting movement disorder. (Note this is not a comprehensive list, and it is focused on identifying abnormalities using common tests that may help with initial diagnostic work-up)*

Movement disorder	Recommended hematologic tests
Mixed movement disorder (includes some combination of chorea, ataxia, parkinsonism, tremor and/or dystonia)	- Peripheral blood smear (acanthocytes, giant inclusions in leukocytes, schistocytes) - Prothrombin time (PT) and International normalization ratio (INR) - Platelet count - Leukocyte count with differential - Hemoglobin, hematocrit, mean corpuscular volume - Immunoglobulin levels - Ferritin, iron, total iron binding capacity - Ceruloplasmin - Bilirubin, lactate dehydrogenase (LDH), haptoglobin and transaminase enzymes (screen for hemolytic process)
Chorea	- Hemoglobin, mean corpuscular volume, hematocrit, leukocytes and platelets - Peripheral blood smear (sickle cells)
Ataxia	- Hemoglobin, mean corpuscular volume, hematocrit, leukocytes and platelets - Peripheral blood smear (RBC morphology if anemic) - Vitamin E, B12 and copper levels - Serum protein electrophoresis - Immunoglobulin levels
Parkinsonism	- Hemoglobin, mean corpuscular volume, hematocrit, leukocytes and platelets
Dystonia	- Hemoglobin, mean corpuscular volume, hematocrit, leukocytes and platelets - Peripheral blood smear (schistocytes or fragmented cells, echinocytes) - Bilirubin, lactate dehydrogenase (LDH), haptoglobin and transaminase enzymes (screen for hemolytic process)
Tremor (age <2)	- Hemoglobin, mean corpuscular volume - Peripheral blood smear (RBC morphology) - Vitamin B12, magnesium, calcium, zinc levels
Restless leg syndrome or periodic leg movements of sleep	- Hemoglobin, mean corpuscular volume - Peripheral blood smear (sickle cells) - Ferritin, iron, total iron binding capacity

hypometric. Behavioral or psychiatric manifestations can be the presenting symptom.[3,4] Ten percent of patients have acanthocytes, however the etiology of this is unknown. HDL-2 is caused by a CTG/CAG trinucleotide repeat expansion located within the *junctophilin 3 (JPH3)* gene, with expansions over 41 repeats causing disease. The age of onset is inversely related to the number of repeats, similar to HD, but anticipation has not been demonstrated; and imaging findings are similar to HD.[3,4] Junctophilin-3 appears to be involved in calcium regulation and junctional membrane structures. The pathogenesis of HDL-2 is unclear; it may be related to mRNA inclusions in the cytoplasm as well as loss of the function of the junctophilin-3 protein.[5] Treatment is symptomatic.

Infantile Tremor Syndrome

Most of the literature describing infantile tremor syndrome (ITS) comes from the Indian subcontinent where it accounts for 0.2%–2% of pediatric hospital admissions, though cases have been described worldwide.[6] ITS affects pediatric patients between 2 to 24 months of age and is more common in boys and families with low socioeconomic status.[7,8]

Clinically, ITS is a self-limiting condition with subacute onset of mental status and psychomotor changes, pigmentary changes, pallor and tremor in a "plump-looking child". There is typically a "pre-tremor phase" characterized by neuromotor regression, pallor and sometimes tremulous voice or crying. This is followed by a "tremor phase" characterized by coarse, rhythmic, tremulous movements in the body including head, trunk and extremities. Hypotonia is common, though rigidity has also been described. Skin and hair changes can occur. Mild to moderate anemia is almost always present, however RBC morphology is variable with most common being dimorphic and macrocytic. Bone marrow is predominantly normoblastic, with megaloblastic findings only described in a minority of patients. Leukocytosis may be related to concurrent infection. Nutritional deficiencies and hepatosplenomegaly have also been reported.[6–8] Though this condition is self-limiting, some patients may have long-term mild cognitive sequelae.[9]

The etiopathogenesis of ITS is unknown. Undernutrition may have a role and deficiencies in vitamin B12, magnesium, calcium and zinc have been reported, though findings are inconsistent. The role of infectious, toxic, and metabolic factors has also been speculated.[6] Treatment includes nutritional supplementation and supportive measures. Propranolol and anticonvulsants can be used to treat tremor.[7]

Neuroacanthocytosis

The two "core" neuroacanthocytosis syndromes are chorea-acanthocytosis and McLeod syndrome. They are both degenerative disorders characterized by acanthocytes and hyperkinetic movement disorders. Chorea-acanthocytosis (ChAc) is caused by autosomal recessive mutation in the gene for chorein, *VPS13A*, however the function of this protein is not well understood. It is possible that changes in autophagy, membrane structure, and cytoskeletal abnormalities can occur, and interaction of chorein with membrane proteins may account for formation of acanthocytes.[10] Clinically, ChAc is characterized by hyperkinetic

movements including chorea and dystonia; facial movements are fairly typical including grimacing, tongue protrusion, lip biting, dysarthria and dysphagia. These can be accompanied by psychiatric manifestations, cognitive decline, seizures, neuropathy, and muscle weakness.[11–13] CK is elevated in a majority of patients, and the disease typically progresses slowly over 10–20 years before death.[12] Treatment is symptomatic.

McLeod Syndrome (MLS) is an X-linked disorder caused by a mutation in the *XK* gene which codes for Kell antigen on RBCs. MLS is a multisystem disorder that affects men in middle age. It is less common than ChAc, and tends to be less severe with greater phenotypic variability.[14] The most common psychiatric manifestations are schizophrenia-like-psychosis and obsessive–compulsive disorder, but others have been reported.[13] Movement abnormalities reported include chorea, dystonia, and parkinsonism. Feeding dystonia can be seen in this disorder, however the tongue and lip biting with mutilation seen in ChAc is rare in MLS. Cognitive impairment, neuropathy, seizures and myopathy with CK elevation can occur. Acanthocytosis is common but not universal, similar to ChAc.[14] Of note, patients are encouraged to bank their own blood due to the possibility of development of anti-Kell antibodies after an initial transfusion leading to transfusion reaction on subsequent transfusions.[11,12]

X-linked Sideroblastic Anemia and Ataxia

Sideroblastic anemia can be acquired or inherited and is characterized by ringed sideroblasts, which are erythroid precursor cells found in bone marrow that have a pathologically increased iron levels in the mitochondria.[15] Iron inclusions, called "Pappenheimer bodies", can be seen in more mature erythrocytes. Sideroblastic anemia with ataxia is X-linked and due to a mutation of adenosine triphosphate (ATP)-binding cassette (ABC) transporter (*ABCB7*) protein. These transmembrane proteins transport substrates across cell membranes, including Fe-S clusters.[16] Patients usually have moderate hypochromic and microcytic anemia.[17]

Only four unrelated families have been reported to date with X-linked sideroblastic anemia and ataxia (XLSA/A). The characteristic movement disorder of XLSA/A is primarily cerebellar. Boys have early-onset ataxia with delayed walking, dysmetria, and dysdiadochokinesia. Other signs can include mild intention tremor, dysarthria, upper motor neuron signs in the legs, and strabismus. Treatment is supportive.[18–20]

Paroxysmal Exertion-Induced Dyskinesia

Paroxysmal exertion-induced dyskinesia (PEG), also known as paroxysmal exercise-induced dyskinesia, is a rare clinical syndrome characterized by lower limb dystonia and choreoathetotic movements, typically precipitated by walking or running, along with other manifestations including epilepsy, ataxia, migraine and hemolytic anemia. Onset varies from infancy to early adulthood.[21] Though many cases are sporadic, PEG has recently been associated with *SLC2A1* gene mutation (also known as DYT18) causing glucose transporter type 1 (GLUT-1) deficiency.[22–24] Other mutations have also been described including in *GCH1* gene (also associated with dopamine responsive dystonia),[25] early-onset genetic forms of PD, and others.[21] If GLUT-1 deficiency is identified, then a ketogenic diet should be initiated. Otherwise symptomatic treatment is considered including chemodenervation, levodopa, clonazepam or antiepileptics.[21]

Hemolytic anemia can be associated with PEG, and severity can vary. In a family with GLUT-1 deficiency due to *SLC2A1* mutation, 2 out of 4 affected individuals had acute hemolytic anemia at birth which required blood transfusion, and developed mild chronic anemia thereafter. All family members had scleral icterus, splenomegaly, macrocytic anemia, and blood smear revealing echinocytes (RBCs with thorny projections, burr cells). The mechanism for hemolytic anemia in PEG is unknown, but it may be related to changes in cation permeability which may lead to swelling and osmotic damage to RBCs.[24]

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder caused by mutation in the X-linked phosphatidylinositol glycan class A (*PIGA*) gene, which results in changes to protein expression in hematopoetic stem cells and leads to a lack of complement regulatory proteins (CD55 and CD59) on the RBC cell surface, making RBCs vulnerable to complement-mediated intravascular hemolysis. As a result, there is free hemoglobin in the plasma, which scavenges nitric oxide (NO), leading to clinical symptoms of smooth muscle dystonia, erectile dysfunction, and vasoconstriction from NO depletion.[26] Smooth muscle dystonia manifests as episodes of abdominal pain, back pain, esophageal spasm dysphagia and erectile dysfunction.[27]

Onset of PNH is usually in young adulthood. Patients suffer from chronic anemia and fatigue, and there is acute worsening of smooth muscle dystonia and hemolytic anemia during times of stress (eg, infection, surgery, alcohol intake). Thrombosis is common and can account for significant morbidity and mortality when it results in acute organ damage (eg renal failure, pulmonary embolism, myocardial infarction, cerebral venous thrombosis). Other complications include bone marrow failure, aplastic anemia, and recurrent infections.[26,27] Diagnosis is usually done by flow cytometry.[28] Treatment with eculizumab, a monoclonal complement inhibitor, is highly effective.[29]

Parkinson's Disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders worldwide and has been recognized as a multisystem disorder with non-motor and systemic features. One feature of PD may include anemia, which has been described in patients with PD,[30] and is associated with increased risk of developing future PD in healthy subjects as shown in large

epidemiologic case-control[31] and cohort[32,33] studies. However this relationship is controversial and a recent large longitudinal cohort study found that low hemoglobin was associated with reduced risk of developing PD, which may suggest a protective effect of anemia.[34] RBCs of PD patients demonstrate abnormal morphology and show evidence of eryptosis, a kind of programmed cell death.[35]

The mechanism of anemia in PD in not known. It may be related to iron deficiency as low iron, ferritin and TIBC have been associated with PD severity,[30] but interestingly iron supplementation does not modify PD risk.[32] It has also been proposed that bone marrow function may be impaired in prodromal PD, possibly through mechanisms of chronic neuroinflammation or oxidative stress, which may be involved in pathogenesis of PD.[33] Vitamin B12 deficiency is another possible mechanism since this is common in older adults and B vitamin deficiencies are particularly common in PD patients treated with duodenal levodopa infusion.[36] Dopaminergic drugs have been implicated in causing rare drug-induced immune hemolytic anemia including levodopa[37,38] and dopamine agonists cabergoline[39] and apomorphine.[40] Mechanism of this rare reaction may be related to antibody cross-reactivity of RBC antigens, or possibly direct interaction of the drug with cell structures.[40]

Restless Leg Syndrome

Restless leg syndrome (RLS) is present in up to 31% of individuals with iron deficiency anemia[41] and is associated with low ferritin. Low brain iron has been demonstrated in neuropathologic,[42] CSF,[43] and imaging[44,45] studies in those with RLS. Iron is a cofactor for monoamine synthesis, and in the substantia nigra it is a cofactor for tyrosine hydroxylase, the rate limiting enzyme of L-DOPA synthesis.[46] Iron deficiency causes an upregulation of tyrosine hydroxylase, increase in extracellular dopamine, and decrease in D1 and D2 receptors and dopamine transporters in the striatum, thus resulting in a hyperdopaminergic state in RLS patients. However, there may be a relative hypodopaminergic state at night in RLS which explains why dopaminergic therapy alleviates symptoms in patients with a hyperdopaminergic disorder.[47]

All patients with RLS should be screened for iron deficiency,[48] which is a microcytic anemia characterized by low mean corpuscular volume (<80 fl). Iron studies will show low total iron, low ferritin (<10 microgram/liter), and low total iron binding capacity (<16%). For iron deficiency anemia, oral ferrous sulfate, vitamin C or intravenous iron therapy can be used.[49] Several classes of medications can be used for symptomatic relief of RLS symptoms.

Vitamin Deficiencies

Vitamin B12 is a cofactor in multiple important conversions including methylmalonic acid to succinyl coenzyme A, homocysteine to methionine, and 5-methyltetrahydrofolate to tetrahydrofolate. These are important for DNA synthesis, RBC production, and neurologic function. It is absorbed with intrinsic factor in the terminal ileum, and is obtained through ingestion of fish, meat, dairy, and fortified products. Vitamin B12 deficiency is more common in older individuals, and causes can include dietary insufficiency (eg strict vegan diet), pernicious anemia, and long-term use of acid-suppressing medicines.[50] Clinically, vitamin B12 deficiency can affect multiple systems. Bone marrow suppression occurs, but megaloblastic anemia, when the bone marrow is filled with large RBCs which are unable to mature, is most common. Hemolysis and pancytopenia can also occur. In addition to developing symptoms associated with anemia, patients can develop neurologic sequelae including cognitive impairment, neuropathy and myelopathy, namely subacute combined degeneration which effects posterior and lateral columns.[51] Subacute gait ataxia can develop, which is usually secondary to sensory and myelopathic changes,[52] and rare chorea has been reported.[53] Of note, multiple B-vitamin deficiencies can often present simultaneously, particularly in the setting of poor nutritional status, so other neurologic and systemic abnormalities may also be seen (eg, ataxia, ocular changes and encephalopathy, as seen with comorbid thiamine deficiency). Treatment is B12 supplementation, either orally or via injection if severe.[50]

Vitamin E deficiency can be related to insufficient dietary intake, but it is more commonly due to problems with dietary fat absorption or metabolism. Etiologies include genetic disorders (eg, mutation in tocopherol transfer protein), malabsorption syndromes, cystic fibrosis due to failure to secrete pancreatic enzymes which help absorb fat-soluble vitamins, or ABL (see "Abetalipoproteinemia" section). Vitamin E has antioxidant, immunomodulation and antiplatelet effects.[54] Vitamin E deficiency is associated with hemolytic anemia, particularly in premature infants,[55] and excessive vitamin E can be associated with coagulopathy and bleeding, particularly in conjunction with vitamin K deficiency (eg induced by warfarin).[56] Neurological features of vitamin E deficiency include ataxia, weakness, hyporeflexia, cranial neuropathies, cognitive impairment, vision changes, and retinitis pigmentosa.[57,58]

Disorders of White Blood Cells

Many of the disorders discussed below are characterized by a low level of white blood cells (WBC), known as leukopenia, or dysfunctional leukocytes. Immunodeficiency is a common consequence of WBC disorders. Some of the conditions have other hematologic aberrations as well (eg anemia, thrombocytopenia), but they are included in this section because the WBC abnormality is prominent.

Chediak-Higashi Syndrome

This is an autosomal recessive condition caused by mutation in lysosomal trafficking regulator (*LYST*) or Chediak-Higashi syndrome (*CHS1*) genes, which are responsible for lysosomal trafficking and transport of cytoplastic granules. This results in

accumulation of enlarged vesicles and dysfunctional lysosomes. Lymphocytes containing these large granules are not able to perform antibody-dependent, cell-mediated cytolysis. There are also abnormalities in neutrophils, which leads to impaired bactericidal activity, and natural killer cells. Diagnosis of Chediak-Higashi syndrome (CHS) is made by identifying these granulocytes in peripheral blood or bone marrow.[59]

Clinically, CHS is characterized by immunodeficiency with recurrent severe infections beginning in infancy, easy bleeding, and partial oculo-cutaneous albinism. Neurological involvement varies, but can include neurodevelopmental delay, cerebellar dysfunction, peripheral neuropathy, spasticity, dystonia, parkinsonism (typically early-onset, levodopa-responsive parkinsonism[60,61]), epilepsy, and cognitive impairment.[61,62]

The disease can progress into an "accelerated phase" at any age, in which there is progression of fever, lymphadenopathy, anemia, neutropenia, thrombocytopenia, and neurological abnormalities, and prognosis is generally poor. This phase is driven by hemophagocytic lymphocytosis which causes multi-organ inflammation; it is caused by inappropriate stimulation of macrophages in the bone marrow. It is unclear how this accelerated phase is triggered.[59,63] Treatment with allogenic hematopoietic stem cell transplantation is associated with favorable outcomes.[64]

Clozapine-Induced Leukopenia

Due to its pharmacologic advantage, clozapine is a good option for patients with extrapyramidal disorders and psychosis, especially in Parkinson's Disease. Clozapine has weaker affinity for D2 receptors, and instead blocks serotonin receptors (particularly 5-HT 2A/2C) and other chemicals receptors, therefore it carries lower risk of extrapyramidal side effects compared to standard neuroleptic medication. The main factor limiting its use is the risk of potentially fatal agranulocytosis, thus its use requires frequent blood count monitoring which can be cumbersome for patients and clinicians must place patients in a national registry.[65] During post-marketing study of 11,555 patients, incidence of agranulocytosis was 0.8% at year one and 0.91% at 1.5 years, and out of 73 patients who developed agranulocytosis, two patients died from infectious complications.[66] Most cases occur early, within the first 6 months of starting treatment.[67] Transient neutrophilia, neutropenia, esosinophilia, thrombocytosis and thrombocytopenia have also been reported in laboratory testing, but these were usually transient and not clinically significant.[68] The pathophysiologic mechanism for clozapine-induced agranulocytosis is unknown, but it is possible that this is an immune-mediated process that affects polymorphonuclear leukocytes; risk factors for this reaction may include female gender, advanced age and genetic factors.[66,67]

Ataxia-Telangiectasia

Ataxia-telangectectasia (A-T) is an autosomal recessive disorder characterized by neurodegeneration and immunodeficiency. It is caused by mutation in the *ATM* gene, which is involved in cell cycle progression, DNA repair and apoptosis. Two-thirds of A-T patients have immune abnormalities, the most common of which is low levels of immunoglobulins; others include failure to make antibodies, lymphopenia especially affecting T-cells, reduced proportion of naïve B and T cells, and reduced antigen receptor function. Less commonly, patients can develop elevated IgM in combination with IgG or IgA deficiency, which can lead to mis-diagnosis of hyper-IgM syndrome.[69]

Disease-onset is typically in childhood. Multi-system involvement includes immunodeficiency that manifests as recurrent sinopulmonary infections, endocrinopathies, oculocutaneous telangiectasias (dilated blood vessels near the surface of skin or mucous membranes), radiosensitivity, and high risk for developing cancer predominantly leukemia and lymphoma. There is also increased risk for developing autoimmune and inflammatory disease (eg immune thrombocytopenia, vitiligo), likely secondary to immunodeficiency as opposed to aberrant DNA repair.[69] Classic neurologic presentation includes progressive ataxia, oculomotor apraxia, chorea, and cognitive dysfunction. Other findings have also been reported including dystonia, parkinsonism, myoclonus, tremor, and pyramidal signs, suggesting that there may be a wide phenotypic spectrum of neurologic involvement.[70] Serum alpha fetoprotein is often elevated, but definitive diagnosis is made by genetic testing. Treatment is symptomatic and supportive; infection prevention and reducing carcinogenic exposure (eg excessive sunlight) are important.[69,71]

Copper Deficiency

Copper is involved with cellular transport and serves as a cofactor for enzymes that perform vital functions including hemoglobin synthesis, iron oxidation, neurotransmitter synthesis, cellular respiration, pigment formation, antioxidant functions, and connective tissue formation. Copper deficiency can be hereditary or acquired; causes can include malnutrition, zinc-induced copper deficiency often related to denture adhesives (zinc reduces copper release into plasma from enterocytes), reduced absorption (eg associated with gastric bypass surgery, celiac disease), or genetic conditions (eg Menkes disease of congenital copper malabsorption).[72]

Hematologic features include anemia and leukopenia; the latter can include both neutropenia and lymphopenia. Copper-deficiency anemia can be microcytic, normocytic, or macrocytic. Thrombocytopenia is less common. Hematologic findings can mimic myelodysplastic syndrome, and bone marrow morphology can share similar features including dysplastic erythroid precursors and ringed sideroblasts. Cytoplasmic vacuolization within erythroid and myeloid precursors are unique to copper deficiency, and can help distinguish between these two conditions.[72] Neurologic involvement often takes the form of progressive spastic-ataxic gait due to myelopathy which is very similar to subacute combined degeneration.[73,74] Other neurologic features include myeloneuropathy, optic neuropathy, and motor neuron disease.

Treatment includes oral or intravenous copper replacement depending on severityand. Usually hematologic abnormalities are quickly reversible with copper repletion, however neurologic recovery is variable.[72]

Disorders of Bleeding and Clotting

The following disorders are characterized by coagulopathy or thrombosis. They are all primary hematologic disorders, which are sometimes associated with movement disorder complications.

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder that results in venous and/or arterial thrombosis in the presence of antibodies which include anticardiolipin, lupus anticoagulant, and anti-β2 glycoprotein antibodies. Pathogenic role of these antibodies is unclear. Thrombocytopenia is found in 22%–42% of APS patients, and other hematologic manifestations can include bone marrow necrosis and other thrombotic microangiopathic syndromes (eg thrombotic thrombocytopenia purpura; hemolytic uremic syndrome; hemolysis, elevated liver enzymes, low platelet syndrome). APS can occur in systemic lupus erythematosus patients with autoimmune hemolytic anemia and identify a subgroup of patients with higher risk of thrombosis.[75]

Neurological abnormalities in APS most frequently include ischemic stroke, migraine, seizures, cognitive decline, transverse myelitis, and neuro-ophthalmologic involvement.[76] Chorea is the most common movement disorder seen in patients with APS, affecting approximately 1%–5% of patients, mostly women, and the severity is mild to moderate.[77,78] Chorea can be bilateral or unilateral, involve the head, upper and/or lower extremities, or manifest in oromandibular region.[78] Less common movement disorders in APS are ballism, dystonia, myoclonus, tics, and parkinsonism. Chorea and other movement disorders secondary to APS are typically associated with a thrombo-occlusive vasculopathy, cerebral infarctions, and white matter changes on MRI.[76] Long-term anticoagulation is the standard of care for APS, although rituximab, intravenous immunoglobulin and plasma exchange have been used in refractory cases.[79,80]

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is characterized by clinical triad of thrombocytopenia, anemia and acute kidney injury. It is classically associated with enterocolitis from Shiga toxin-producing *Escherichia coli* infection, and it is most common in children.[81] Shiga toxin binds to endothelial and renal tubular cells and causes ribosomal inactivation which leads to cell death. It also induces a systemic proinflammatory and prothrombotic state and activates the complement system. Atypical HUS is complement-medicated and accounts for 5% to 10% of cases; it is thought to be caused by a genetic abnormality in complement genes.[82]

HUS typically presents in a young child with a prodrome of diarrheal illness, which progresses to severe bloody diarrhea, abdominal cramping, nausea and vomiting. Thrombocytopenia and acute kidney injury evolve within 1 to 2 weeks of symptom onset. Extrarenal manifestations are thought to be a result of multisystem thrombotic microangiopathy, with neurologic involvement seen in 3% to 26% of cases. Other factors such as cytokine release, hypertension and hyponatremia may also contribute.[81] Neurologic symptoms can include seizure, encephalopathy, diplopia, dizziness, weakness, vision changes, decerebrate posturing, ataxia and dystonia.[83,84] Neurologic involvement tends to portend worse prognosis.[81,83] Management of HUS is primarily supportive; plasma exchange is sometimes performed in patients with neurologic involvement. For atypical HUS, eculizumab, a complement inhibitor, may be helpful.[81]

Polycythemia Vera

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by increased morphologically normal erythrocytes, leukocytes, platelets, and their progenitor cells. Erythrocytosis is the hallmark of this disorder, with elevated hematocrit and hemoglobin being the main cause of complications in patients with PV. Patients with PV have higher incidence of inflammatory disorders, microvascular disease, thrombocytosis, and hemorrhage, with some patients progressing to leukemia.[85] PV is due to mutations in the *janus kinase 2* (*JAK2*) gene; its mechanism for disease is unclear. Thrombosis is the most common complication of PV and is thought to be due to increased blood viscosity leading to reduced cerebral blood flow.[85,86] In patients with chorea, decreased blood flow is thought to disrupt normal function in the basal ganglia.[87]

Neurologic abnormalities such as stroke, headache, visual disturbances, and vertigo, are very common in PV, occurring in approximately 50%–80% of patients.[85] Chorea is a rare complication in PV (0.5%) and tends to be more frequent in women.[88] The chorea is acute-onset, can be bilateral or unilateral, affecting the extremities or the face, and usually precedes exacerbation of hematologic abnormalities and can wax and wane with worsening hematocrit.[86,88,89] Treatment includes phlebotomy and antiplatelet therapy (to prevent thrombosis); hydroxyurea and chemotherapy agents are sometimes used.[85]

Sickle Cell Disease

Sickle cell disease (SCD) comprises several inherited disorders caused by mutations in the beta-globulin subunit causing the formation of Hemoglobin S. When Hemoglobin S is deoxygenated it changes structure, forming the typical sickle shape RBC. These sickle cells are rigid and cause ischemia through blockage of the microvasculature, which causes the clinical manifestations. As the cells are destroyed or removed from circulation by macrophages, there is resulting oxidative stress and inflammation from release of free heme molecules, as well as hemolytic anemia.[90] The most

common neurologic manifestation associated with SCD is ischemic stroke, however movement disorders are also described. Reports in children and adults with SCD have shown increased rate of periodic limb movements in sleep (PLMS), which is related to severity of hematologic abnormalities of SCD.[91–93] The exact mechanism of PLMS is unknown, however it may be related to abnormal brain iron metabolism, similar to RLS.[91] There have also been reports of chorea in a patient with SCD, in the context of hypertransfusion therapy and one in a patient with fever and behavioral abnormalities.[94,95]

Hematologic Malignancies

Ataxia-Pancytopenia Syndrome

Germline mutations in *SAMD9* and *SAMD9L* genes located on chromosome 7 are associated with clinical spectrum of disorders including myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital phenotypes and enteropathy (MIRAGE syndrome); ataxia-pancytopenia syndrome; and myelodysplasia and leukemia syndrome. Under normal circumstances, both genes are involved with cell proliferation and function as tumor suppressors in some cancers. Mutations are thought to result in a gain-of-function, and inheritance is autosomal dominant.[96]

SAMD9L is associated with ataxia-pancytopenia syndrome (ATXPC). Hematologic manifestations vary and can be intermittent; there are usually cytopenias in all lineages. Anemia and macrocytosis, immunodeficiency, hypoplastic bone marrow, leukemia, and myelodysplasia have been reported.[97] Neurologic features of ATXPC include cerebellar ataxia (with accompanying cerebellar atrophy on imaging), nystagmus, hyperreflexia, and gait changes. Attention deficit hyperactivity and mild cognitive impairment can also occur.[98] Age of onset ranges from infancy to adulthood. The *SAMD9* mutation is associated with a more severe phenotype and complex multi-organ disorder MIRAGE syndrome.[96,97] Onset typically occurs in infancy and death occurs fairly quickly. Treatment is largely supportive; the role of hematopoetic stem cell transplant is unclear.[99]

Leukemia and Lymphoma

Lymphomas and paraproteinemias are more likely to be associated with movement disorders compared to other hematological malignancies, such as leukemia. Primary central nervous system lymphomas (PCNSL) comprise a small population of all intracranial malignancies.[100] Movement disorders as a presenting sign of PCNSL are quite rare, but there have been reports of chorea,[101,102] dystonia,[101] including torticollis,[103] and parkinsonism[104–110] at presentation. There have also been reports of paroxysmal kinesigenic dyskinesia and non-paroxysmal dyskinesia, related to PCNSL tumor involvement of the thalamus[111] and systemic lymphoma involvement of the spinal cord[112] respectively. Treatment for PCNSL can also be associated with movement disorders. Leukoencephalopathy, a complication of PCNSL treatment, has manifested as lower body parkinsonism, characterized by gait difficulty with postural instability, freezing, and poor response to levodopa.[113] Paraneoplastic disorders, which occur in less than 1% of lymphoma patients, are most common with Hodgkin lymphoma.[114] Paraneoplastic chorea, dystonia, and ataxia have all been observed, with antibodies to DNER, mGluR, and others reported.[115–121]

The neurological presentation of leukemia is usually related to leptomeningeal metastases or intracranial hemorrhage, rather than basal ganglia pathology. Paraneoplastic movement disorders secondary to GlyR neuronal surface antibodies have been reported in association with chronic lymphocytic leukemia.[121] Treatment may cause movement disorders in leukemic patients including rare reports of hemiataxia[122] and chorea,[122,123] among other neurological symptoms in children treated with intrathecal methotrexate for acute lymphoblastic leukemia.[122] Parkinsonism has been associated with cyclosporine treatment.[124]

Paraproteinemias

The paraproteinemias are a heterogenous group of disorders characterized by secretion of monoclonal immunoglobulin by the bone marrow; they include multiple myeloma, Waldenstrom macroglobulinemia, immunoglobulin light chain amyloidosis, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) and monoclonal gammopathy of undetermined significance.[114] Paraneoplastic ataxia, with CASPR2, GABA, or GFAP antibodies, has been reported in patients with multiple myeloma.[121] Waldenstrom macroglobulinemia can manifest as a cerebellar syndrome when infiltration of the central nervous system occurs, called "Bing-Neel" syndrome. Presenting symptoms of Bing-Neel include gait ataxia, dizziness or cranial neuropathy and CSF will show lymphocytic pleocytosis, elevated protein levels, and IgM kappa or lambda restriction.[125]

Storage Disorders of Disorders of Metal Metabolism

The following are metabolic and multisystem disorders characterized by both hematologic derangements and movement disorders. They include lysosomal storage disorders (ie Gaucher disease, Neimann-Pick disease) and disorders of metal metabolism (ie Wilson's disease, hemochromatosis, and neurodegeneration with brain iron accumulation). These disorders are well described in the literature, so we will focus this discussion on reviewing the hematologic and movement disorders manifestations.

Lysosomal Storage Disorders

Gaucher disease (GD) is an autosomal recessive disease due to deficiency in glucocerebrosidase enzyme, leading to

accumulation of glucocerebrosidase in cells. The most common hematologic findings are anemia, thrombocytopenia and hepatosplenomegaly. Etiology of anemia and thrombocytopenia may be multifactorial. There is also an increased risk of developing multiple myeloma and B-cell lymphoma, which may be due to chronic inflammation from sphingolipid accumulation in macrophages.[126] Type 1 GD, which is the most common, is associated with parkinsonism and hematologic abnormalities. Type 2 GD is severe and characterized by rapid neurodegeneration and early death in infancy. Type 3 GD is a chronic form in which slow horizontal saccades is characteristic.[127] GBA mutation, which causes GD, is also the most common genetic risk factor for PD, and tends to cause early-onset parkinsonism with akinetic rigid syndrome that responds well to levodopa. Nonmotor features including cognitive decline, hallucinations, and rapid eye movement behavior disorder are more common in patients with GBA-associated PD, and they tend to have faster progression. Atypical phenotypes have also been described including corticobasal syndrome[128] and multiple systems atrophy.[129]

Neimann-Pick disease type C (NPC) is an autosomal recessive disorder caused by mutations in the *NPC1* or *NPC2* genes, which lead to dysfunction in sphingomyelinase resulting in a buildup of sphingomyelin within cell membranes.[130] Hematologic features can include anemia, thrombocytopenia, and hepatosplenomegaly.[131] Onset can be in childhood or adulthood, and neurologic manifestations include ataxia, vertical supranuclear ophthalmoplegia, dysarthria, parkinsonism, cognitive impairment, gelastic cataplexy, seizures and psychiatric disorder.[132,133]

Disorders of Metal Metabolism

Disorders of manganese metabolism result in manganese toxicity; they include hypermanganesemia with dystonia due to *SLC30A10* or *SCL39A14* mutations. *SLC30A10* is characterized by dystonia, polycythemia and chronic liver disease; *SCL39A14* lacks liver involvement and polycythemia and leads to rapidly progressive dystonia with variable parkinsonism and other neurologic signs. Early-onset lower extremity dystonia with "cock walk" gait may be suggestive of inherited hypermanganesemia.[134] Both disorders have characteristic T1 hyperintensities in basal ganglia, white matter, cerebellum and brainstem with relative sparing of the ventral pons.[135]

Hemochromatosis is a genetic condition characterized by reduction in concentration or activity of iron regulatory hormone hepcidin, leading to accumulation of iron in body tissues, particularly liver, pancreas and heart. Multiple genes have been implicated, the most common of which is homozygous mutation in *C282Y*.[136] Hematologic abnormalities include elevated serum ferritin, iron, and transferrin iron saturation; of which ferritin correlates best with total body iron stores. Mainstay of treatment is phlebotomy with close monitoring of hemoglobin since there is risk for anemia; iron chelation is a second-line option.[137] Movement disorders are rare but can include parkinsonism, chorea, myoclonus, ataxia, dystonia and tremor. Brain imaging usually reveals signal change in basal ganglia which suggests iron accumulation.[138–140]

Neurodegeneration with brain iron accumulation (NBIA) refers to a heterogenous group of inherited neurodegenerative disorders with characteristic abnormal accumulation of iron in the basal ganglia. Clinical manifestations can include dystonia, dysarthria, spasticity, parkinsonism, neuropsychiatric problems, and optic atrophy or retinal degeneration.[141] Hematologic manifestations vary depending on the specific condition. Neuroferritinopathy tends to have low serum ferritin; and aceruloplasminemia is associated with low (or undetectable) serum ceruloplasmin and copper, microcytic hypochromatic anemia, and elevated ferritin. In panthothenate kinase-associated neurodegeneration (PKAN), the most common genetic form of NBIA, acanthocytes can been seen on peripheral blood smear. Acanthocytes are also seen in hypobetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP) syndrome, which is part of PKAN-spectrum disorder since it is caused by different mutations in the PANK2 gene.[142] Fatty acid hydroxylase-associated neurodegeneration (FHAN) can have PAS-positive granular inclusions in bone marrow biopsy.[143]

Wilson's disease is an autosomal recessive disorder caused by mutation in the *ATP7B* gene, which leads to impaired copper release from the liver and reduced binding of copper to ceruloplasmin. This leads to copper accumulation in the liver, brain, cornea and other organs.[144] Neurologic features can vary and may include tremor (often described as an irregular, jerky, wing-beating tremor), dystonia, parkinsonism, dysarthria, orofacial dyskinesias including risus sardonicus, ataxia, pyramidal signs, seizures, and neuropsychiatric symptoms.[144] Low serum copper and ceruloplasmin, and elevated urine copper are characteristic, and hematologic problems are common. In a retrospective cohort of 54 Wilson's patients, 52% had thrombocytopenia, 30% had leukopenia, and one had severe intermittent hemolytic episodes as the initial complaint. Six patients with cytopenias had blood counts improve to normal after splenectomy. D-penicillamine, a long-term copper chelation therapy, can cause thrombocytopenia and leukopenia.[145]

Conclusions

Associations between the hematological system and movements disorders occur more frequently than overlap in other organ systems. Many of the disorders are on the rare side and have a host of genetic and non-genetic etiologies. Recognition is key in the event that an underlying malignancy, vitamin deficiency or specified treatment is available. Additional research is needed in some of the rare disorders. For example, in infantile tremor syndrome, gaining an understanding of the relationship of the disorder to socioeconomic status could lead to a potential prevention.

The collection of disorders presented in this review were chosen based on the literature search and writing team consensus. Several of the acquired conditions, including medication/toxin

induced disorders, autoimmune disorders, and lesional movement disorders were excluded as being outside the scope of this review. This includes such disorders as superficial siderosis, secondary dystonias, celiac disease, and neuroleptic malignant syndrome. The reader is referred to the extensive existing literature on these disorders.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of First Draft, B. Review and Critique.

R.A.P.: 3A, 3B

D.A.H.: 3B

S.E.: 3B

M.B.: 3A, 3B

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