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MOVEMENT DISORDERS (M OKUN, SECTION EDITOR)

Diagnosis and Treatment of Chorea Syndromes

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Abstract Chorea is a common movement disorder which can be caused by a large variety of diseases including neurodegenerative diseases, metabolic diseases, and autoimmune diseases, or can be secondary to structural changes. The basal ganglia seem to be mainly involved in the pathophysiology indicating the vulnerability of this region. The diagnosis can be challenging, especially if chorea occurs during the treatment of neuropsychiatric conditions, and in these cases, it is difficult to distinguish between medication side effects (i.e., tardive dyskinesia) and the development of a neurodegenerative disease. Most therapeutic approaches are predominantly symptomatic, with a focus on multidisciplinary care for many patients. Nevertheless, some underlying diseases can be successfully treated and must not be missed. In this review, we summarize recent new developments in the differential diagnosis of chorea syndromes and suggest a pathway for a successful diagnosis of chorea in infancy, childhood, and adulthood for daily practice.

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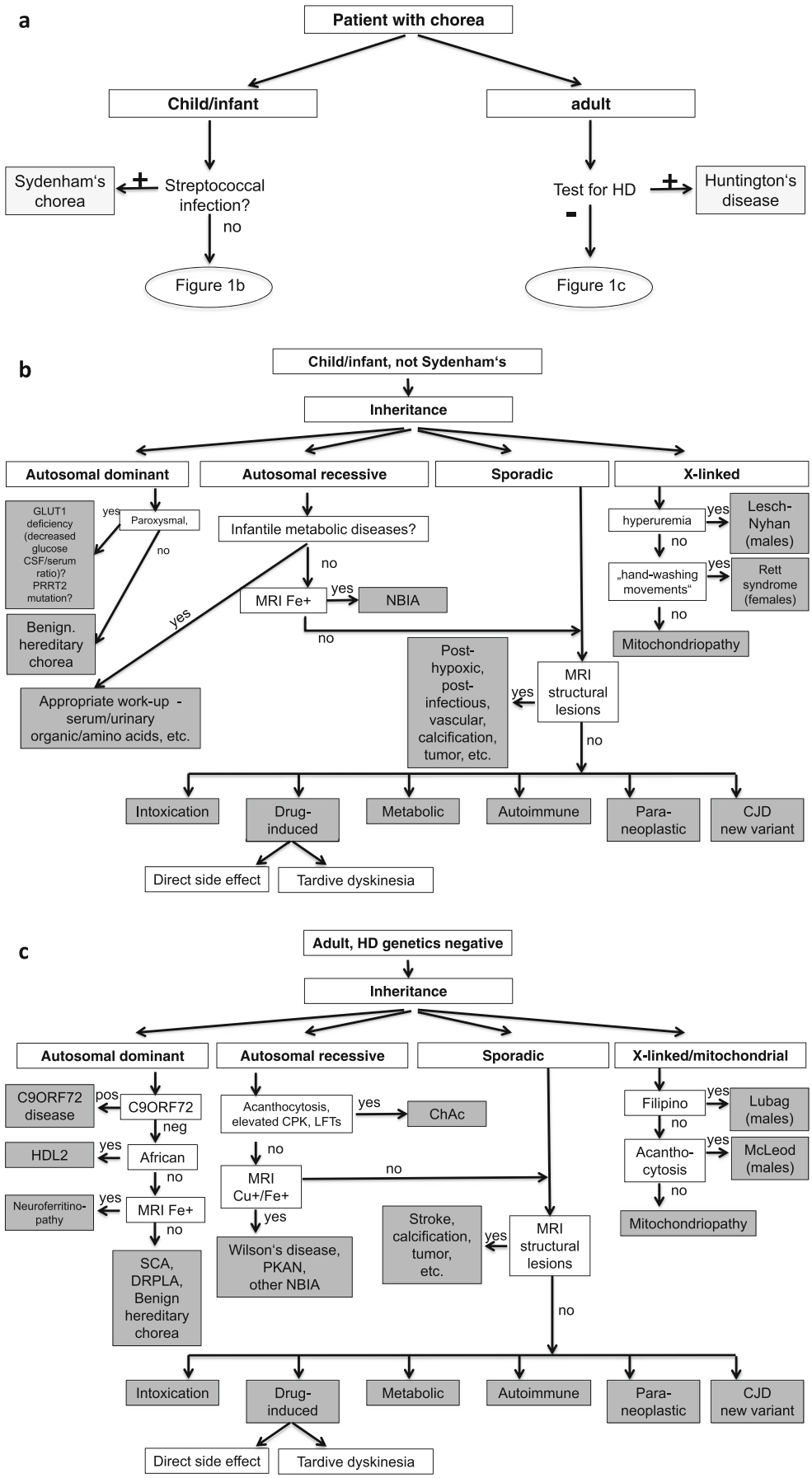
Introduction

Chorea refers to involuntary movements of limbs, trunk, neck, or face that rapidly flit from region to region in an irregular, flowing, nonstereotyped pattern. This hyperkinetic movement disorder may be generated by a large number of causes, including genetic, pharmacologic, metabolic, and structural. The work-up of the patient with chorea can be extensive and, in some cases, unrewarding. Here, we focus upon recent developments in the genetic etiologies of chorea, followed by causes of sporadic chorea. Treatment, after identifying reversible causes, remains, for the most part, symptomatic.

The First Approach

When diagnosing a patient with chorea or mixed involuntary movements, it may be helpful to distinguish initially between onset in adulthood or prior to the age of 16 (Fig. 1). The most common cause of chorea in children is Sydenham's chorea, while in adults, it is Huntington's disease (HD); thus, the first approach is to exclude these disorders, depending upon the age of the patient (Fig. 1). If this initial testing is negative, we suggest further diagnostic approaches (Fig. 1b, c).

Family history should be carefully evaluated, even if it suggests an unrelated disorder. We suggest asking about any neuropsychiatric disorder in the family history. If present, the pattern of inheritance should provide a guide to possible diagnoses (Fig. 1b, c). The absence of a family history does not exclude a genetic cause. This may be due to adoption, nonpaternity, nondisclosure of illness, parental death before disease manifestation, mis- or nondiagnosis, or decreased penetrance in a parent. Due to


a
Patient with chorea
Child/infant
adult
Sydenham's chorea
+
Streptococcal infection?
no
Figure 1b
Test for HD
+
Huntington's disease
-
Figure 1c
b
Child/infant, not Sydenham's
Inheritance
Autosomal dominant
Autosomal recessive
Sporadic
X-linked
GLUT1 deficiency (decreased glucose CSF/serum ratio)? PRRT2 mutation?
yes
Paroxysmal,
no
Benign. hereditary chorea
Infantile metabolic diseases?
no
MRI Fe+
yes
NBIA
no
yes
Appropriate work-up - serum/urinary organic/amino acids, etc.
Post-hypoxic, post-infectious, vascular, calcification, tumor, etc.
yes
MRI structural lesions
no
hyperuremia
yes
Lesch-Nyhan (males)
no
„hand-washing movements"
yes
Rett syndrome (females)
no
Mitochondriopathy
Intoxication
Drug-induced
Metabolic
Autoimmune
Para-neoplastic
CJD new variant
Direct side effect
Tardive dyskinesia
c
Adult, HD genetics negative
Inheritance
Autosomal dominant
Autosomal recessive
Sporadic
X-linked/mitochondrial
C9ORF72 disease
pos
C9ORF72
neg
HDL2
yes
African
no
Neuroferritino-pathy
yes
MRI Fe+
no
SCA, DRPLA, Benign hereditary chorea
Acanthocytosis, elevated CPK, LFTs
yes
ChAc
no
MRI Cu+/Fe+
yes
Wilson's disease, PKAN, other NBIA
no
Stroke, calcification, tumor, etc.
yes
MRI structural lesions
no
Filipino
yes
Lubag (males)
no
Acantho-cytosis
yes
McLeod (males)
no
Mitochondriopathy
Intoxication
Drug-induced
Metabolic
Autoimmune
Para-neoplastic
CJD new variant
Direct side effect
Tardive dyskinesia

◀ **Fig. 1** **a** The initial approach to the patient with chorea. **b** A diagnostic approach to children/infants with chorea after negative testing for Sydenham's chorea. **c** A diagnostic approach to adults with chorea after negative testing for Huntington's disease

smaller sibships in many Western countries, autosomal recessive inheritance is often missed.

Childhood-Onset Chorea Syndromes

Sydenham's Chorea

A relatively common cause of chorea in childhood is Sydenham's chorea, due to the cross-reaction of antistreptococcal antibodies with basal ganglia neurons, involving the epitopes intracellular tubulin and extracellular lysoganglioside [1, 2]. Cases are usually self-limited if the streptococcal infection is thoroughly treated, although in some cases, the movements can be quite violent and bizarre.

Autosomal Dominant Chorea

The only autosomal dominant chorea syndrome with childhood onset is benign hereditary chorea. Glucose transporter 1 (GLUT1) deficiency and *PRRT2* mutations can cause a childhood-onset paroxysmal disorder, which can be choreic in nature.

Benign Hereditary Chorea

Benign hereditary chorea may develop in childhood and is not typically associated with cognitive impairment or other significant neurologic abnormalities apart from mild ataxia. However, in a recent case series of 28 patients in 13 families, Gras and colleagues reported learning difficulties in 20/28 patients [3]. One family was reported with developmental delay and short stature in some mutation carriers [3]. Mutations may be found in the gene for thyroid transcription factor 1 (*TITF-1*; *NKX2.1*) [4] or other genes [5]. The chorea may respond to levodopa [6] or, conversely, to tetrabenazine. Mutations in *TITF-1* may also cause a severe multisystem disorder with congenital hypothyroidism, hypotonia, and pulmonary problems, in addition to chorea [7].

GLUT1 Deficiency

This pediatric disorder accounts for an increasing spectrum of neurologic deficits, including chorea, mental retardation, epilepsy, and dystonia (DYT18) [8–11]. The movement disorder is typically seen following prolonged exertion but may also be present at rest. Mutations of *SLC2A1* affect the glucose transporter 1, which transports glucose into the brain. The diagnosis is suggested by a decreased ratio of cerebrospinal fluid to serum glucose. It is important to recognize these patients since many of them remarkably improve with a ketogenic diet [12].

PRRT2 Mutations

Paroxysmal chorea or dystonia can be part of the spectrum of episodic neurologic disease due to mutations of *PRRT2* [13•, 14–16]. In addition, ataxia, hemiplegic migraine, infantile convulsions, and other manifestations can be seen [17, 18]. Episodes are typically frequent and brief and can be precipitated by exercise, movements, talking, yawning, or hyperventilation. Abnormalities of synaptic vesicle function and neurotransmitter release are postulated to be the underlying cause.

Autosomal Recessive Chorea

Several childhood-onset metabolic disorders can cause movement abnormalities, typically as part of a complex neurologic presentation. Dystonia tends to be more prominent with younger onset. The evaluation is directed by the associated neurologic and nonneurologic features and may involve measurement of organic and amino acids in blood and urine, assay of lymphocytic enzymes, and/or genetic testing.

Phenylketonuria

Phenylketonuria is one of the most common inborn metabolic diseases with an incidence of 1:8000 newborns. If not treated, the child will ultimately develop severe mental retardation, epilepsy, and sometimes chorea. It is caused by a loss-of-function mutation in the phenylalanine hydroxylase gene. All newborns are screened using the neonatal heel prick or the Guthrie test. The treatment is a strict diet with reduced phenylalanine thereby enabling normal development.

Glutaric acidemia Type I

Glutaric acidemia type 1 is caused by mutations within the enzyme glutaryl-CoA-dehydrogenase causing diminished metabolism of lysine and tryptophan, leading to increased production of glutaric acid and 3-hydroxyglutaric acid in the urine. Symptoms are precipitated by a catabolic crisis, for example fever, diarrhea, or other infections. The children show different movement disorders including chorea [19]. Most patients do not develop mental retardation or dementia. After the age of 5, these crises disappear. Ideally, the diagnosis is made prior to the first crisis; thus, newborns are screened for the disease in many countries. Treatment is the administration of carnitine as well as a diet with reduced lysine. The typical MRI finding is of dilation of the Sylvian fissures and lesions of the putamen.

Methylglutaconic Aciduria Type III

Methylglutaconic aciduria type III (Costeff syndrome) is an organoaciduria with atrophy of the optic nerve, chorea-athetosis, and increased urinary secretion of 3-methylglutaconic acid. Most, if not all, patients are Iraqi-Jewish. Chorea-athetosis is seen within the first 10 years of life, typically appearing after the decrease of vision [19].

Other Pediatric Inherited Metabolic Disorders

Chorea can occasionally occur in various aminoacidopathies. These include propionic acidemia due to propionic-coenzyme A carboxylase deficiency and succinic semialdehyde dehydrogenase deficiency. Atypical, mild forms of nonketotic hyperglycinemia can cause chorea and encephalopathy in childhood or adulthood, often precipitated by febrile illness [20] or medication [21].

Other occasional causes of chorea, either during childhood or adulthood, include Niemann-Pick type C [22], chronic GM2 [23], and late-onset GM1 gangliosidoses, neuronal intranuclear inclusion disease, and metachromatic leukodystrophy.

Neurodegeneration with Brain Iron Accumulation

Abnormal brain iron accumulation in the basal ganglia is seen in an increasing number of disorders. Some of these may present with chorea as one of the initial symptoms [24]. The diagnostic MRI shows the "eye-of-the-tiger" or other characteristic forms of iron accumulation in the brain. Most of the neurodegenerations with brain iron accumulation (NBIAs) are autosomal recessively inherited—only neuroferritinopathy is autosomal dominant (see below).

Aceruloplasminemia is due to mutations of the gene for ceruloplasmin [25]. Retinal degeneration and diabetes mellitus appear in early adulthood, followed by ataxia, orofacial dystonia, parkinsonism, chorea, and cognitive impairment [26•, 27••].

X-linked Chorea

Lesch-Nyhan Syndrome Lesch-Nyhan syndrome presents in boys at 3 to 6 months with psychomotor retardation and hypotonia, subsequently developing self-mutilation with biting of the hands and lips, spasticity, dystonia, and choreoathetosis. This disorder is caused by mutation of hypoxanthine phosphoribosyltransferase, resulting in the accumulation of uric acid.

Rett Syndrome Rett syndrome (cereboatrophic hyperammonemia) is an X-chromosomal-dominant developmental disorder with disease onset between 6 to 18 months of age. It almost exclusively affects females; hemizygosity is normally embryonic lethal. Stereotypic "hand-washing" movements are characteristic.

Mitochondrial Causes of Chorea A broad spectrum of neurologic abnormalities can be seen in Leigh's syndrome, including acute encephalopathy, psychomotor retardation, hypotonia, spasticity, myopathy, dysarthria, seizures, and dystonia [28]. Neuroimaging typically demonstrates lesions in the thalamus or caudate/putamen. An overlap with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) [29] and other mitochondrial disorders [30, 31] may occur. Onset is in early childhood, but may occasionally be in adulthood [28].

Adult-Onset Chorea Syndromes

The most common cause of chorea in adulthood is HD; thus, we suggest performing genetic testing for HD prior to any further diagnostic testing. In the following sections, we describe potential differential diagnoses (Fig. 1c).

Autosomal Dominant Chorea

HD remains the most common inherited cause of chorea. Prior to the identification of the causative gene, the diagnosis was based upon the clinical picture and a supportive family history and should be genetically confirmed.

Huntington's Disease

HD is caused by inheritance of an expanded trinucleotide repeat (>39) within the Huntingtin (htt) gene on chromosome 4p16.3. The longer the CAG repeats the earlier disease onset. The precise dysfunction responsible for neurodegeneration remains unknown. The normal range of repeats is between 6 and 26; in the range of 27 to 35 repeats, the expansion is unstable and is liable to expand in subsequent generations. There are apparent cases of clinical HD in subjects with repeats within this range but most are unaffected carriers [32, 33]. Subjects with expansions in the premutation range 35 to 39 may pass on a pathologically expanded allele to their offspring and may be clinically affected themselves, usually at much older ages, and sometimes with a relatively mild phenotype.

Brain pathology shows a generalized brain atrophy with predominance in the basal ganglia, in particular the tail and body of the caudate rather than the head of the caudate nucleus (for review, see [34]).

Neuropsychiatric symptoms often precede the development of the movement disorder. These may include personality changes, irritability, social withdrawal, obsessive-compulsive disorder,

psychosis, and depression. These symptoms should be aggressively treated because suicide is not uncommon.

Non-HD Syndromes

Approximately 1 % of patients with a clinical suspicion of HD have a non-HD Huntingtonian syndrome [35]. Of these, the most common form is the newly identified C9ORF72 disease [36••]. This is followed by SCA type 17 (1.1 %), Huntington's disease-like 2 (0.7 %), Friedreich's ataxia (0.35 %), and inherited prion disease (0.24 %) [35].

C9ORF72 Disease

C9ORF72 was initially identified as the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [37, 38]. Mutations are intronic hexanucleotide repeat expansions [37, 38]. *C9ORF72* repeat expansions appear to also be the most common genetic cause of non-HD syndromes [36••], with a prevalence of 1.95 % of all huntingtin-negative cases. The clinical spectrum currently known for these *C9ORF72*-positive cases is limited, comprising only ten reported individuals. Of these, 3/10 had chorea—6/10 showed rigidity, executive dysfunction, or impaired memory. Future studies are warranted to describe this syndrome in more detail and to determine whether *C9ORF72* disease is really a Huntingtonian syndrome.

Spinocerebellar Ataxias

Movement disorders can sometimes be seen in the autosomal dominant spinocerebellar ataxias (SCAs) [39], which are caused by trinucleotide repeat expansions or conventional mutations of a variety of genes [40]. The size of the expansions correlates with the phenotype and the appearance of noncerebellar symptoms and inversely correlates with the age of onset [41]. SCA3 (Machado-Joseph disease), the most common SCA in most populations, can present with parkinsonism, dystonia, and chorea. Patients with SCA1 [42, 43] and SCA2 [44] may occasionally present with or develop chorea. SCA17 may show parkinsonism, dystonia, and chorea [45, 46], in addition to the typical phenotype of ataxia, dementia, and hyperreflexia. Chorea and myoclonus can be seen in dentatorubropallidoluysian atrophy (DRPLA), usually in addition to ataxia and dementia. DRPLA is more common in Japanese populations, but appears occasionally in Caucasian [47, 48] and African-American [49] families.

Huntington's Disease-Like 2

Huntington's disease-like 2 (HDL2) has been reported to date only in families of African ancestry [46, 50]. HDL2 is due to a CTG/CAG trinucleotide repeat expansion within junctophilin-3 (JPH3) on chromosome 16q24.3 [50]. Affected individuals have repeat expansions of 41 to 58 triplets. Acanthocytosis is reported in about 10 % of cases [51].

Symptoms very similar to those of HD develop in young-mid adulthood, with an age of onset inversely related to size of the trinucleotide repeat expansion [52]. Dystonia and parkinsonism appear to be more prominent than in HD and are unrelated to repeat size [53]. As in HD, early signs may be personality change and psychiatric symptoms.

Huntington's Disease-Like 1

Huntington's disease-like 1 is a familial prion disease carrying octapeptide repeat insertions of different length in the PRNP gene [35]. Initially, it was described in a family with autosomal dominant personality change, dementia, and chorea; however, the phenotype can vary within the same family (for review, see [35, 54]).

Neuroferritinopathy

Neuroferritinopathy is the only autosomal dominant NBIA disorder identified to date [55]. It is caused by mutations in the gene for the light chain of ferritin. Onset is at age 40 to 55 years and can include a variety of movement disorders, including chorea, dystonia, and parkinsonism [56, 57], and occasionally cognitive impairment.

Idiopathic Basal Ganglia Calcification

Idiopathic basal ganglia calcification or "Fahr's disease" refers to a heterogeneous group of disorders with autosomal dominant inheritance defined by the radiologic finding of calcium deposition in the basal ganglia and other regions, often including the deep cerebellar nuclei. Diagnosis is made by radiological presence of basal ganglia calcification (BGC) and exclusion of other causes such as phosphocalcic metabolic disorders, mitochondriopathies, and numerous congenital syndromes (for review, see [58]). Patients may exhibit neurological and/or psychiatric symptoms. Dystonia, parkinsonism, chorea, ataxia, cognitive impairment, and behavioral changes may be seen. Recently, several genes were identified causing idiopathic basal ganglia calcification (iBGC), namely SLC20A2, PDGFRB, and PDGFB; however, these account only for a portion of all iBGC patients [59•].

Association with Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Chorea may be seen in patients with mutations of TDP-43, normally associated with familial amyotrophic lateral sclerosis (ALS) [60] and with familial [61] or sporadic ALS [62]. Patients with behavioral-variant frontotemporal dementia (of

unknown genotype and pathology) may also develop chorea [63]. This report was published prior to discovery of *C9ORF72*; thus, these cases might be due to C9ORF72 disease.

Autosomal Recessive Chorea

Wilson's Disease

Even though chorea is only occasionally seen in Wilson's disease [35], it is essential to exclude this treatable disorder by ophthalmological slit-lamp examination, serum ceruloplasmin, and 24-h copper excretion.

Autosomal Recessive Ataxias

Friedreich's ataxia (FA) accounts for approximately 0.35 % of HD phenocopies [35]. FA is the most common inherited autosomal recessive ataxia, usually characterized by onset during childhood and clinical appearance with progressive ataxia, areflexia, and dysarthria. FA is caused by homozygous GAA repeat expansion (>66 up to 1300) within the Frataxin gene. One fourth of patients have an atypical appearance with normal or increased deep tendon reflexes. Rarely, chorea can be seen and may even be a presenting symptom prior to the development of other features.

Ataxia-telangiectasia and ataxia with oculomotor apraxia types 1 and 2 typically present with ataxia during infancy and childhood and may present with or develop chorea. Ataxia-telangiectasia has been reported to present in adulthood [64]. Serum levels of α-fetoprotein, albumin, and cholesterol may be abnormal and may help guide the diagnosis.

Chorea-Acanthocytosis

Chorea-acanthocytosis (ChAc) typically presents in young-mid adulthood with lingual-buccal dystonia, often pronounced with eating. Lip- and tongue-biting, chorea, and occasionally parkinsonism can be seen [65]. Sometimes, these symptoms are preceded by tics, behavioral changes, psychiatric disease, or subtle cognitive dysfunction. Other symptoms include seizures, peripheral (motor) neuropathy with areflexia, and muscle atrophy. Elevated creatine kinase and liver enzymes are common and should not be attributed to seizures. Detection of acanthocytosis may be enhanced by use of a standard protocol [66], but a negative result does not exclude the diagnosis.

ChAc is caused by loss-of-function mutations of *VPS13A* which codes for chorein [67]. Absence of chorein in erythrocytes on Western blot confirms the diagnosis [68] and is available on a research basis (https://www.euro-hd.net/edit/na/network/docs/na-blood-sampling-instructions.pdf). The disorder, originally known as "Levine-Critchley syndrome," has been confirmed to be ChAc, at least in Critchley's original Kentucky family [69].

Recent new data suggest the disturbance of the Lyn kinase pathway in patient erythrocytes [70, 71]. Mice carrying up-regulated Lyn develop blood cell acanthocytosis [72]. Furthermore, we recently described chorein as an upstream regulator of cortical actin depolymerization in erythrocytes and thrombocytes through the PI3K-RAC-PAK pathway [73, 74]. Whether this holds true for neurons is as yet unknown.

X-linked Choreas

McLeod Syndrome

McLeod neuroacanthocytosis syndrome (MLS) is similar in presentation to autosomal recessive ChAc, with the additional involvement of other organ systems, in particular cardiac muscle [65]. It is seen typically in middle-aged males [75]. MLS is diagnosed by decreased expression of Kell and Kx antigens on erythrocytes, known as the "McLeod phenotype," caused by mutation of the XK gene. Even though genetic testing is available, the diagnosis is typically made at blood banks, using the requisite panel of anti-Kx and anti-Kell antibodies. (A report of "Kell negative" is not adequate.) Important for management is the cardiac involvement, which is seen in two thirds of patients and may be a significant source of morbidity and mortality [75].

As in ChAc, blood cell acanthocytosis is typical, but not invariable. Patients should bank their own blood in case of need for transfusion, to avoid the production of anti-Kell antibodies and subsequent transfusion reactions. Abnormalities of cation transport may underlie at least some of the erythrocyte manifestations [76].

Sporadic Chorea Syndromes

Many conditions can cause chorea syndromes. It is often helpful to identify key elements as medical history (side effects, tardive syndrome), localizing neurological features (structural lesions vs. multifocal disease) and time course of the disease (acute onset vs. chronic onset, fluctuations) (discussed in more detail in [77]).

Metabolic Disorders

Hemichorea can be seen acutely in patients with nonketotic hyperglycemia as well as hypoglycemia. MRI demonstrates hyperintensity of the contralateral putamen [78, 79]. It is not known why only one side might be affected, but some patients can have bilateral changes. Correction of the metabolic abnormality is normally curative, but rarely chorea may persist for

months after resolution of the hyperglycemia [80], possibly due to permanent vascular changes in the striatum.

Screening for thyroid disease and vitamin B12 deficiency should be performed in evaluating any new movement disorder [81, 82] as both can be successfully treated. Disturbances of calcium metabolism, related to parathyroid disorders, should also be considered, especially in paroxysmal movement disorders.

Chorea may occasionally appear during pregnancy (*chorea gravidarum*). This occurs more often in women with a history of Sydenham's chorea or another autoimmune disorder and may be due to be a sensitization of dopamine receptors by estrogens.

Infectious and Post-infectious

The most prevalent post-infectious form of chorea is Sydenham's chorea, discussed above. In adulthood, a subacute cognitive and motor deterioration over months is suggestive of Creutzfeldt-Jakob disease, and in particular, the new variant [83, 84]. Chorea can also be seen with HIV infection, either as a direct effect of HIV encephalopathy or as the result of a secondary mass lesion [85, 86], and rarely syphilis [87]. In children, striatal necrosis may occur as a complication of encephalitis from various infectious agents, typically viral, or mycoplasma.

Autoimmune Disorders

The basal ganglia may be vulnerable in many systemic autoimmune disorders, including systemic lupus erythematosus [88, 89], Sjögren's syndrome [90], and antiphospholipid antibody syndrome [91]. In polycythemia vera, chorea may be due either to autoantibodies or, as currently appears more likely, to hyperviscosity [92]. The presentation can be remarkably asymmetric [93]. Celiac disease has been associated with various possible neurologic conditions, including chorea, which may respond to a gluten-free diet [94]. Nonparaneoplastic anti-LGI1 antibodies may cause chorea, which may be asymmetric [95].

Paraneoplastic Disorders

Recognition of paraneoplastic neurologic syndromes is expanding as new autoantibodies are being identified. Thus, it is critical to exclude cancer in any patient with a subacute or acute presentation of chorea (or neuropsychiatric syndrome). Renal, small cell lung, breast, Hodgkin's, and non-Hodgkin's lymphomas have been reported as causative, due to antibodies against CRMP-5/CV2 [96], Hu [97], LGI1, Yo [98], GAD65, and CASPR2. Anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies can cause chorea, in addition to the classical syndrome of encephalopathy and bizarre stereotyped involuntary movements [99, 100].

Treatment

Childhood

Adequate antibiotic therapy is mandatory in Sydenham's chorea, including prophylactic monthly penicillin therapy for up to 5 years. Involuntary movements sometimes require therapy with neuroleptics or valproic acid. Immunomodulatory treatment options such steroids, plasmapheresis, or intravenous immunoglobulins may be required [101].

Strict diets can reduce the symptoms in some metabolic disorders, such as the ketogenic disease in GLUT1 deficiency. Other examples include phenylketonuria and glutaric acidemia type 1, in which carnitine is administered in addition to a lysine-reduced diet. If these are done prior to disease onset, or at least early during the disease, disease onset can be postponed. This is facilitated by newborn screening programs.

Adulthood

Recognition and diagnosis of antibody-mediated chorea syndromes is important. If these are not due to malignancy, they normally respond well to steroid therapy or treatment with immunoglobulins. This holds especially true for limbic encephalopathies. Even in the case of paraneoplastic origin, patients may profit from steroid therapy, if this is administered in the early stages. Removal of the original tumor is the overall aim, thereby eradicating the ectopic source of the antigen.

Symptomatic Treatment

In neurodegenerative disease, therapeutic approaches are directed at reducing symptoms. Goals should be to improve function, which may or may not involve reducing the involuntary movements. It is often of greater importance to the patient and caregivers to address other symptoms, particularly psychiatric and behavioral in the neurodegenerative conditions. Ideally, this includes a multidisciplinary team approach to address psychological, nutritional, communicative, motor, and psychiatric issues in a cohesive, goal-oriented manner.

Treatment of Hyperkinesia

Indications for the treatment of chorea include interference with work activities, physical injury, loss of balance, social stigma, or sleep disturbance. This is normally achieved by decreasing dopamine neurotransmission either through postsynaptic blockade, ideally with atypical neuroleptics, or with presynaptic depletion, using tetrabenazine or reserpine. There exist controversies about recommendations and respective levels of evidence [102, 103••]. The decision regarding which antihyperkinetic drug to use first differs depending on

additional symptoms. If patients suffer from neuropsychiatric symptoms besides chorea such as depression, psychosis, aggression, or compulsive behavior, we would suggest to start with antipsychotic drugs (off-label) such as tiapride, olanzapine, and quetiapine [103••]. In patients without neuropsychiatric symptoms, tetrabenazine is suggested as the first-line therapy [102, 103••]. Amantadine and riluzole may be helpful, although the evidence is controversial [102, 103••].

It is of note that the natural course of some diseases may change from chorea to parkinsonism; therefore, the need for treatment of chorea should be continually reconsidered and adjusted. Additionally, care should be taken to monitor for the side effects of depression, parkinsonism, and akathisia. Anticonvulsants may be tried, particularly levetiracetam, valproic acid, and carbamazepine. The mechanism of action of these agents in chorea is unclear.

A small number of reported cases, mainly HD, have undergone surgical therapies, specifically deep brain stimulation (DBS) or ablative procedures, with mixed outcomes [104, 105]. The customary target is the internal segment of the globus pallidus (GPi); however, the subthalamic nucleus and the motor thalamic nuclei have also been targeted. Risks and benefits of these procedures in disorders with progressive neurodegeneration should be carefully weighed; however, this may be an appropriate option for nonprogressive disorders [106]. Neural cell transplantation for HD has shown some limited benefits, and may still be promising, but has not been as dramatically therapeutic as was initially hoped [107, 108].

Deep brain stimulation has been reported to ameliorate chorea in patients suffering from chorea-acanthocytosis. Bilateral DBS of the GPi can effectively reduce the severity of the hyperkinetic movements without effects upon parkinsonism [109•].

Other Symptomatic Treatments

Depression should be treated with SSRIs,SNRIs, or mirtazapine. This last may have the useful side effect of weight gain. Caution should be used with the tricyclic antidepressants, which might worsen neuropsychiatric symptoms due to anticholinergic action and additionally might worsen chorea.

Obsessive-compulsive symptoms might benefit from escitalopram or atypical neuroleptics such as quetiapine. Aggression or psychosis may be treated by haloperidol or atypical neuroleptics. Cholinesterase inhibitors seem to have no effects on cognitive dysfunction in HD [110].

Disease-Modifying Treatment Options

No substance has yet been shown to modify the disease course in HD, including vitamin E, idebenone, baclofen, lamotrigine, creatine, coenzyme Q10, remacemide, ethyl-eicosapentaenoic acid, and riluzole [111]. Latrepirdine and pridopidine showed no significant effects [112–114]. Coenzyme Q10 and creatinine are currently being investigated in phase III trials.

Weight loss is commonly seen in HD, and body mass index (BMI) inversely correlates with disease progression [115]. High numbers of CAG repeats correlate with weight loss but the latter is independent of chorea [116] and seem to be independent of caloric intake [117]. Hypercaloric nutrition is thus advised as soon as the BMI falls markedly.

Conclusions

Even though chorea syndromes are often manifestations of neurodegenerative disorders without a specific therapy, it is important not to miss the few treatable or reversible etiologies. A thorough work-up includes a detailed family, medical, and medication history; neurologic and medical examinations; a range of laboratory tests; and neuroimaging. Despite extensive testing, a significant proportion of patients remain still undiagnosed.

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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