

REVIEW

Chorea and related disorders

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Chorea refers to irregular, flowing, non-stereotyped, random, involuntary movements that often possess a writhing quality referred to as choreoathetosis. When mild, chorea can be difficult to differentiate from restlessness. When chorea is proximal and of large amplitude, it is called ballism. Chorea is usually worsened by anxiety and stress and subsides during sleep. Most patients attempt to disguise chorea by incorporating it into a purposeful activity. Whereas ballism is most often encountered as hemiballism due to contralateral structural lesions of the subthalamic nucleus and/or its afferent or efferent projections, chorea may be the expression of a wide range of disorders, including metabolic, infectious, inflammatory, vascular, and neurodegenerative, as well as drug induced syndromes. In clinical practice, Sydenham's chorea is the most common form of childhood chorea, whereas Huntington's disease and drug induced chorea account for the majority of adult onset cases. The aim of this review is to provide an up to date discussion of this disorder, as well as a practical approach to its management.

Other inherited causes are also discussed in more detail later in this review. In secondary chorea, tardive syndromes are the most common causes, related to long term use of dopamine blocking agents. Choreiform movements can also result from structural brain lesions, mainly in the striatum, although most cases of secondary chorea do not demonstrate any specific structural lesions.

HEREDITARY CAUSES OF CHOREA**Huntington's disease**

Huntington's disease, the most common cause of chorea, is an autosomal dominant disorder caused by an expansion of an unstable trinucleotide repeat near the telomere of chromosome 4.^{1, 2} Each offspring of an affected family member has a 50% chance of having inherited the fully penetrant mutation. According to the first description of the disease by George Huntington in 1872, there are three marked peculiarities in this disease: (1) its hereditary nature; (2) a tendency for insanity and suicide; (3) manifestation as a grave disease only in adult life.³ However, Huntington failed to mention cognitive decline, which is now recognised as a cardinal feature of the disease.⁴

Epidemiology

Huntington's disease has a worldwide prevalence of 4–8 per 100 000 with no gender preponderance.⁵ Huntington's disease has the highest prevalence rate in the region of Lake Maracaibo in Venezuela, with approximately 2% of the population affected, and the Moray Firth region of Scotland.⁵ Huntington's disease is notably rare in Finland, Norway, and Japan but data for Eastern Asia and Africa are inadequate. It is believed that the mutation for Huntington's disease arose independently in multiple locations and does not represent a founder effect. New mutations are extraordinarily rare, accounting for a very small population of cases.

Genetics

Although the familial nature of Huntington's disease was recognised more than a century ago, the gene mutation and altered protein (huntingtin) was described only recently.⁶ Huntington's disease is a member of the growing family of neurodegenerative disorders associated with trinucleotide repeat expansion. The cytosine-adenosine-guanidine (CAG) triplet expansion in exon 1 encodes an enlarged polyglutamine tract in the huntingtin protein. In unaffected

Chorea is a manifestation of a number of diseases, both acquired and inherited. Although not completely understood, current evidence suggests that chorea results from the imbalance in the direct and indirect pathways in the basal ganglia circuitry. The disruption of the indirect pathway causes a loss of inhibition on the pallidum, allowing hyperkinetic movements to occur. In addition, enhanced activity of dopaminergic receptors and excessive dopaminergic activity are proposed mechanisms for the development of chorea at the level of the striatum. Based on current knowledge, it is possible to understand chorea and ballism as manifestations of a common pathophysiological chain of events so that classification of choreic syndromes are increasingly based on aetiology, while phenomenologically based distinctions between chorea and ballism are becoming less important. Chorea is characterised as primary when idiopathic or genetic in origin or secondary when related to infectious, immunological, or other medical causes (table 1). When chorea is proximal and of large amplitude, it is termed ballism. Athetosis refers to irregular, forceful, slow, writhing movements generally of the extremities, commonly with finger movements. These movements frequently overlap and coexist in the same patient. Huntington's disease is a choreic prototypic disorder of inherited origin.

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Abbreviations: DRPLA, dentatorubralpallidoluysian atrophy; KF rings, Kayser-Fleischer rings; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; SSRIs, selective serotonin reuptake inhibitors

Table 1 Classification of chorea (only common causes listed)

Primary chorea	Secondary chorea	Others
Huntington's disease	Sydenham's chorea	Metabolic disorders
Neuroacanthocytosis	Drug induced chorea	Vitamin deficiency: vitamin B1 and B12
Dentatorubralpallidolysian atrophy	Immune mediated chorea	Exposure to toxins
Benign hereditary chorea	Infectious chorea	Paraneoplastic syndromes
Wilson's disease	Vascular chorea	Postpump choreoathetosis
Pantothenate kinase associated neurodegeneration (PKAN or formerly Hallervorden-Spatz syndrome)	Hormonal disorders	
Paroxysmal choreoathetosis		
Senile chorea		

individuals, the repeat length ranges between 9 and 34 with a median normal chromosome length of 19. Expansion of a CAG repeat beyond the critical threshold of 36 repeats results in disease, and forms the basis of the polymerase chain reaction based genetic test. This expanded repeat is somewhat unstable and tends to increase in subsequent offspring, termed "anticipation". Expansion size is inversely related to age at onset, but the range in age at onset for a given repeat size is so large (with a 95% confidence interval of ± 18 years for any given repeat length) that repeat size is not a useful predictor for individuals.^{6,7} It is likely that other genetic or environmental factors have a significant role in determining age of onset. With the exception of juvenile onset cases, there has been poor correlation between phenotype and CAG repeat length. Because of meiotic instability with a tendency to increasing expansion size during spermatogenesis, juvenile onset cases with very large expansions usually have an affected father.⁸ Predictive genetic testing of asymptomatic at-risk relatives of affected patients is available and governed by international guidelines.⁹ However, the implications of Huntington's disease predictive testing are many and demand careful consideration.

Clinical features

Huntington's disease is a progressive disabling neurodegenerative disorder characterised by the triad of movement disorders, dementia, and behavioural disturbances. Illness may emerge at any time of life, with the highest occurrence

between 35 and 40 years of age. Although the involuntary choreiform movements are the hallmark of Huntington's disease, it is the mental alterations that often represent the most debilitating aspect of the disease and place the greatest burden on families of Huntington's disease patients. There is also a large variability in the clinical presentation and some of this variability is predictable; for example, the juvenile onset form may present with parkinsonism (the so-called Westphal variant), while late onset form may present with chorea alone.¹⁰

Chorea is the prototypical motor abnormality characteristic of Huntington's disease, accounting for 90% of affected patients. Chorea usually starts with slight movements of the fingers and toes and progresses to involve facial grimacing, eyelid elevations, and writhing limb movements. Motor impersistence is another important associated feature, whereby individuals are unable to maintain tongue protrusion or eyelid closure. Other motor manifestations are also common in Huntington's disease including eye movement abnormalities (slowing of saccades and increased latency of response), parakinesias, rigidity, myoclonus, and ataxia.¹¹ Dystonia tends to occur when the disease is advanced or is associated with the use of dopaminergic medications. While dysarthria is common, aphasia is rare. Dysphagia tends to be the most prominent in the terminal stage and aspiration is a common cause of death.

Cognitive impairment seems to be inevitable in all patients with Huntington's disease whether to a greater or lesser degree.^{12,13} Typically, the impairment begins as selective deficits involving psychomotor, executive, and visuospatial abilities and progresses to more global impairment, although higher cortical language tends to be spared.

Although Huntington focused on the tendency of insanity and suicide, a wide range of psychiatric and behavioural disturbances are recognised in Huntington's disease, with affective disorders among the most common, thought to be secondary to the disruption of the frontal-subcortical neural pathway.¹³ Depression occurs up to 50% of patients. The suicide rate in Huntington's disease is fivefold that of the general population.¹⁴ Psychosis is also common, usually with paranoid delusions. Hallucinations are rare. Apathy and aggressive behaviour are commonly reported by caregivers. Presently, it is unclear whether cognitive and psychiatric difficulties antedate other manifestations of Huntington's disease.^{12,15}

Differential diagnosis

A variety of hereditary and acquired neurological disorders may mimic Huntington's disease. Benign hereditary chorea is a clinically distinct condition from Huntington's disease. Although inherited in an autosomal dominant fashion like Huntington's disease, the symptoms are non-progressive with no alterations in cognitive or behavioural functions.

Box 1: Clinical features of Huntington's disease (modified from Poewe *et al*⁶⁴)

- Autosomal dominant disorder with 100% penetrance (CAG trinucleotide expansion on chromosome 4).
- Prevalence of 4–8 per 100 000 people.
- Age of onset: 40 years (5% juvenile onset at <20 years of age, 30% late onset at >50 years of age).
- Choreic movements and hypotonia.
- Personality and mood changes, psychosis, and dementia are common.
- Oculomotor abnormalities: slowing of saccades and increased response latency.
- Rigidity, hypokinesia, and dystonia are common in juvenile onset cases.
- No curative treatment; symptomatic treatment with dopamine agonists.
- Relentlessly progressive with mean duration of 17 years.

The onset is much earlier than Huntington's disease, usually before the age of 5 years. Other dominant disorders that may mimic Huntington's disease include dentatorubralpallidolucyan atrophy (DRPLA), which is a triplet repeat polyglutamine disorder with profound clinical heterogeneity. It is rarely reported in North America and Europe, but is more common than Huntington's disease in Japan. Symptoms vary and may include chorea, myoclonus, ataxia, epilepsy, and dementia. Although its pathology is reminiscent of Huntington's disease, the involvement of the dentate nucleus of the cerebellum differentiates the disorder. Spinocerebellar ataxia type 17 may also present with chorea, associated with prominent cerebellar ataxia. Patients with Huntington's disease-like 2 usually have clinical and pathological features indistinguishable from Huntington's disease. It is due to CTG expansion in junctophilin-3 and it is almost exclusively in African ethnicity. In a group of recessive disorders, the presence of sensorimotor neuropathy may suggest alternative diagnosis of neuroacanthocytosis. This is a genetically heterogeneous disorder and may be clinically indistinguishable from Huntington's disease. The diagnosis is supported by the presence of acanthocytes on a peripheral smear in the context of appropriate clinical presentation. Wilson's disease should be considered in all patients with movement disorders who are less than 40 years of age, although patients with Wilson's disease rarely exhibit chorea. Pantothenate kinase associated neurodegeneration, formerly known as Hallervorden-Spatz syndrome, is characterised by early onset dystonia, spasticity and dementia, although chorea is a less frequent manifestation. Other forms of hereditary conditions, such as McLeod's syndrome (X-linked) or mitochondrial disorders may also present with chorea.

Neuropathology

Grossly, the Huntington's disease brain shows significant atrophy of the head of caudate and putamen, and to a lesser extent, the cortex, globus pallidus, substantia nigra, subthalamic nucleus, and locus coeruleus.¹⁶ Microscopically, medium spiny neurons are the vulnerable population in Huntington's disease.¹⁷ Indirect projections to the external globus pallidus are the first to degenerate. In addition, intraneuronal inclusions have been reported in the nuclei and neurophil of striatal and cortical neurons and represent aggregates of the mutant huntingtin protein and ubiquitin.¹⁸

Treatment

Unfortunately, there are currently no effective therapies to slow the progression or delay the onset of Huntington's disease. An excitotoxic pattern of cell death resulting from mitochondrial dysfunction has been suggested as a contributing factor in Huntington's disease; intrastriatal injections in animals as well as systemic administration of mitochondrial toxins in animals and people can produce the symptoms and neuropathological lesions of Huntington's disease. Therefore, both symptoms and lesions may be partially blocked or reduced by *N*-methyl-D-aspartate receptor blockade or deafferentation of cortical glutamatergic inputs. Different agents are currently under investigations including coenzyme Q10, racemide hydrochloride, and riluzole.¹⁹

Current treatments in Huntington's disease are largely symptomatic, aimed at reducing the motor and psychological dysfunction of the individual patient. In general, treatment of chorea is not recommended unless it is causing disabling functional or social impairment. Olanzapine or risperidone, atypical antipsychotics, have been found to reduce chorea with less risk of the extrapyramidal side effects, compared to the typical agents. Other agents including riluzole, tetra-benzazine, and amantadine have been shown to improve

chorea.^{20, 21} Traditional neuroleptics such as haloperidol can improve chorea but are associated with increased risk of tardive dyskinesia, dystonia, difficulty swallowing, and gait disturbances, and should not be considered first line agents.

The selective serotonin reuptake inhibitors (SSRIs) have become the first line agents in the treatment of depression in Huntington's disease. Although there are no controlled trials of SSRIs in depressed patients with Huntington's disease, these agents seem to be well tolerated and effective. In addition, SSRIs may suppress chorea and reduce aggression in Huntington's disease.²² The dose should be started low and doubled every two weeks if necessary. A brief course of benzodiazepines may be useful for co-occurring anxiety. The new antipsychotic agents, such as clozapine, quetiapine, and olanzapine are often required to treat psychosis in Huntington's disease.²³ Valproic acid may be useful in the long term management of aggression and irritability.²⁴

Human fetal striatal grafts may survive transplantation and induce clinical benefits in patients with Huntington's disease.²⁵ Functional neuroimaging studies have shown increased metabolic activity and small improvements in motor, cognitive, and behavioural measures in some patients.²⁶ This treatment approach is still experimental and information about long term outcome is not yet available.

Neuroacanthocytosis

Clinical features

Neuroacanthocytosis is a rare, multisystem, degenerative disorder of unknown aetiology that is characterised by the presence of deformed erythrocytes with spicules known as acanthocytes and abnormal involuntary movements. The disorder seems to be particularly common in Japan and can be transmitted by autosomal recessive, dominant, or X-linked inheritance.²⁷ The mean age of onset is around 30 years and tends to be progressive, with death occurring within 15 years of diagnosis. Involuntary choreic and dystonic movements of the orofacial region, as well as tongue and lip biting are virtually diagnostic, although a full spectrum of movement disorders may be seen.²⁸ Other clinical features include chorea of the limbs (predominantly the legs) that can mimic Huntington's disease, axonal neuropathy (50% of cases), areflexia, and raised plasma creatine kinase level. Seizures are also common and can be a presenting feature. Psychiatric symptoms are typical and include apathy, depression, anxiety, and obsessive-compulsive syndrome. However, in contrast to Huntington's disease, mental deterioration is minimal.²⁹

Diagnosis and treatment

Diagnosis is usually made on the basis of family history, morphological analysis of erythrocytes, and a raised plasma

Box 2: Clinical features of neuroacanthocytosis

- A multisystem degenerative disorder of unknown aetiology.
- Variable mode of inheritance.
- Age of onset: approximately 30 years.
- Chorea as well as orofacial-lingual dystonia are prominent.
- Axonal neuropathy in 50% of cases.
- Presence of acanthocytes on peripheral blood smears.
- No curative treatment available; treatment is largely supportive.
- Relentlessly progressive (mean duration 15 years).

creatinase kinase level. The pathogenesis of acanthocyte formation is still unclear.²⁸ Magnetic resonance imaging (MRI) has shown degeneration of the caudate and more generalised cerebral atrophy. Increased signal on T2-weighted MRI in the caudate and putamen is a common feature. These findings are non-specific. The most consistent neuropathological finding is extensive loss of predominantly small and medium sized neurons and gliosis in the caudate, putamen, pallidum, and substantia nigra with relative sparing of the subthalamic nucleus and cerebral cortex.³⁰ Treatment is largely supportive.

Dentatorubralpallidolysian atrophy

DRPLA is a triplet repeat polyglutamine disorder with the gene defect localised to chromosome 12.³¹ Development of clinical phenotypes is associated with CAG repeat lengths exceeding 53.³² Atrophin-1 is a mutant protein and its function is not known. The condition is rarely reported in North America and Europe but it is more common in Japan.³³ It is inherited in an autosomal dominant fashion and clinical features include chorea, myoclonus, ataxia, epilepsy, and cognitive decline. Neuroimaging studies have revealed atrophy of the cerebellum, midbrain tegmentum, and cerebral hemispheres with ventricular dilatation. Pathologically, there is neuronal loss and gliosis in the dentate nucleus, red nucleus, globus pallidus, and subthalamic nucleus.³¹

Wilson's disease

Wilson's disease is an autosomal recessive disorder with a single disease locus residing on chromosome 13q14.3.³⁴ The gene appears to be fully penetrant, with all individuals homozygous for Wilson's disease developing some form of the disease and a 25% of their siblings developing the disease. Most aspects of clinical heterogeneity of hepatic versus neurological presentations do not seem to be determined by features of genetic heterogeneity. Although the exact pathophysiology in Wilson's disease remains unknown, the main defect is most likely to be a problem of protein complexing, resulting in impairment of copper excretion.³⁵

Clinical features

The most puzzling aspect of Wilson's disease is the marked variety in clinical presentation. The manifestations usually begin monosymptomatically or simultaneously with other clinical features with a tendency for asymmetric or focal deficits. Almost half of all patients with Wilson's disease first experience neurological problems in the second or third decade of life. Tremor is usually the initial symptom, which can be at rest, during action, or postural while chorea tends not to occur alone, rather as a combination with dystonia, rigidity, and dysarthria. The most characteristic pattern of tremor in Wilson's disease involves a coarse, irregular, to-and-fro movement elicited by action when the arms are held forward and flexed horizontally with a "wing beating" quality. Cerebellar findings are also common, resembling a common pattern of multiple sclerosis. Seizures, sometimes undifferentiated from paroxysmal movement disorders, have been described, although they are more common in juvenile cases. It is important to recognise that excess copper load can be severe even in patients with mild symptoms.

One of the most striking ophthalmological presentations in Wilson's disease is the presence of Kayser-Fleischer rings (KF rings). KF rings have a brownish or greenish tint and are generally found in the upper pole of the peripheral cornea. KF rings can be missed by direct ophthalmoscopic examination and a definitive analysis requires a careful slit lamp examination by an experienced ophthalmologist. With appropriate clinical history, the diagnosis of Wilson's disease,

especially the neurological form, can be made when a KF ring is present.

Recognition of subtle clinical features is the major challenge in clinical diagnosis of Wilson's disease. Variable physical signs and symptoms that can be intermittent pose another difficulty in early diagnosis. This diagnosis should always be considered in all patients with movement disorders of any type who are younger than 40 years old, as missing the opportunity for diagnosis when its signs and symptoms are mild is one of the greatest challenges in this treatable disorder.

Diagnosis and treatment

Although a diagnostic blood test of genetic abnormalities in Wilson's disease has recently become available, diagnosis still very much relies on appropriate clinical history and compatible clinical findings, along with blood tests involving copper metabolism for which the results can vary with disease stage. While serum ceruloplasmin is a simple and useful screening test, ceruloplasmin deficiency is not unique for Wilson's disease and can be found in other conditions such as nephrotic syndrome, protein-losing enteropathy, and sprue. Measurement of 24 hour urine copper excretion provides a more sensitive result, although the finding can be normal in asymptomatic patients or patients with hepatic Wilson's disease. Liver biopsy is the most sensitive and accurate test, yielding an increased hepatic copper content in almost all patients with Wilson's disease; however, this test is invasive and not widely available. MRI of the brain is usually abnormal in patients with neurological Wilson's disease, revealing increased signal intensity on T2-weighted images involving basal ganglia, midbrain, and pons. However, these abnormal findings can improve after successful treatment. Therefore, in typical newly diagnosed symptomatic patients, we should expect to see a reduced serum ceruloplasmin level (<300 mg/l), high 24 hour urinary copper excretion (>100 µg/day), a high hepatic copper content from biopsy (if performed), and the presence of KF ring in neurological cases.

As mentioned, Wilson's disease is treatable and there is a potentially curative treatment by liver transplantation. This disease, if diagnosed and treated early, can be associated with full recovery. On the other hand, if missed, the disease may result in irreversible neurological disabilities in affected individuals. Low copper or copper-free food, as in lactovegetarian diet, is seldom adequate without additional therapy. The role of zinc therapy in symptomatic Wilson's disease is unclear, although it is generally recommended in asymptomatic individuals. Penicillamine is probably the most potent copper chelating agent available and has been mostly used as the first line therapy for initial and long term management, although chronic treatment is associated with various side effects, mainly skin rash and discoloration. Penicillamine can trigger neurological deterioration after the start of therapy.

Benign hereditary chorea

Benign hereditary chorea or essential chorea is another disorder inherited in an autosomal dominant fashion and characterised by choreiform movements, but is distinct from Huntington's disease in several ways (table 2). In contrast to Huntington's disease, the onset of choreiform movements in benign hereditary chorea is in early childhood; severity of symptoms peaks in the second decade and the condition is non-progressive.^{36 37} Life expectancy is normal and some reports have suggested that the disease improves with age. The condition is not associated with other neurological deficits, although some authors believe that it is a heterogeneous syndrome that may have a variety of causes.³⁸ In addition, some families with this initial diagnosis prove to have other disorders when more thoroughly investigated.

Table 2 Distinguished features between Huntington's disease, benign hereditary chorea (BHC), dentatorubralpallidoluysian atrophy (DRPLA), and neuroacanthocytosis

Features	Huntington's disease	BHC	DRPLA	Neuroacanthocytosis
Onset	4th decade	Early childhood	<20 years, or >40 years	3rd decade
Genetics	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive, dominant, or X-linked
Natural history	Progressive, mean disease duration 17 years	Non-progressive, normal life expectancy	Progressive	Progressive, mean disease duration 15 years
Seizures	May be present	None	Present in juvenile type	Common
Dystonia	Later in disease course	None	Present	Present, esp. in orofacial region
Myoclonus	Later in disease course	None	Common in juvenile type	Present
Ataxia	Later in disease course	None	Common (100%)	May be present
Cognitive deficits	Invariably	None	Invariably	Minimal
Psychiatric symptoms	Common and prominent	None	Present	Present
Others	Motor impersistence, dysarthria	None	Mental retardation (100%)	Sensorimotor neuropathy, acanthocytes, raised creatine kinase

Nevertheless, benign hereditary chorea is considered to be a distinct disease of early onset, non-progressive, uncomplicated chorea with a mutation in TITF-1 gene on chromosome 14q.³⁷⁻³⁹

Others

There are other inherited neurological disorders that can present with prominent chorea. These conditions are rare and the details are not included in this review. Examples include paroxysmal choreoathetosis, familial chorea-ataxia-myoclonus syndrome, pantothenate kinase associated neurodegeneration (PKAN or Hallervorden-Spatz syndrome), intracerebral calcification with neuropsychiatric features, multisystem degeneration, olivopontocerebellar atrophy, and spinocerebellar degeneration (Sanger Brown type).⁴⁰

NON-HEREDITARY CAUSES OF CHOREA

Sydenham's chorea

Sydenham's chorea is a delayed complication of group Aβ haemolytic streptococcal infections and forms one of the major criteria of acute rheumatic fever.⁴¹ It is characterised by chorea, muscular weakness, and a number of neuropsychiatric symptoms. It is considered to be an autoantibody mediated disorder with the evidence suggesting that patients with Sydenham's chorea produce antibodies that cross react with streptococcal, caudate, and subthalamic nuclei.⁴² However, documented evidence of previous streptococcal infection is found in only 20%–30% of cases. The age of presentation is usually between 5 and 15 years with female

Box 3: Clinical features of Sydenham's chorea

- Preceding streptococcal group A infection.
- Age of onset: 5–15 years.
- Female predominant.
- Symmetrical chorea.
- Personality change can occur including obsessive-compulsive disorder and irritability.
- Self limiting course.
- Raised antistreptolysin titre.

preponderance. Chorea is usually generalised, consisting of finer and more rapid movements than those seen in Huntington's disease. It occurs at rest or with activity but remits during sleep. The condition is self limited within five to 16 weeks, but recurs in 20% of patients. It has a good prognosis for full recovery so treatment is not warranted in most cases. However, symptomatic treatment with neuroleptics, tetrabenazine,⁴³ or valproic acid can be considered in severe cases with generalised chorea. Previously affected females are at increased risk of developing chorea during pregnancy (chorea gravidarum) and during sex hormone therapy. Evidence of striatal dysfunction in Sydenham's chorea is supported by MRI revealing lesions in the caudate and putamen in some patients and reversible striatal hypermetabolism on brain single photon emission computed tomography during the acute illness.⁴⁴⁻⁴⁶

Other immune mediated chorea

Although central nervous system involvement in systemic lupus erythematosus (SLE) is common, occurring in 50% to 70% of cases, chorea has been reported in less than 2% of these patients.⁴⁷ It usually appears early in the course of the disease and is characteristically generalised. It is often difficult to recognise chorea as a manifestation of a systemic autoimmune disease because it can simulate Sydenham's and Huntington's chorea and not infrequently appears in childhood long before other manifestations of SLE or antiphospholipid syndrome have emerged.⁴⁸ The use of oestrogen-containing oral contraceptives or pregnancy may precipitate the appearance of chorea. In addition, chorea can occur not only in patients with well defined SLE, but also in patients with "probable" or "lupus-like" SLE and in patients with primary antiphospholipid antibody without clinical features of SLE.⁴⁹ The mechanism of action of these antiphospholipid antibodies remains obscure, although the concept of primary endothelial cell damage and impairment of production of endothelial cell products or damage to platelets have been proposed. Treatment of chorea in autoimmune disease has not been well established, although some reports suggested that steroid therapy can lead to resolution.

Less commonly, chorea can be associated with other autoimmune diseases including polyarteritis nodosa,

Behçet's disease, and isolated angiitis of the central nervous system.⁵⁰

Drug induced chorea

Drug induced chorea may be an acute phenomenon or the consequence of long term therapy. Multiple drugs including dopamine agonists, levodopa therapy, oral contraceptives, and anticonvulsants have been implicated in the acute chorea (box 4). Levodopa induces dyskinesias and, to a lesser extent, the dopamine agonists only induce chorea in patients with idiopathic Parkinson's disease or other parkinsonian disorders. Dopamine antagonists, on the other hand, seem to be capable of inducing dyskinesias in everyone exposed. However, the nature of the induced abnormal movements—chorea, dystonia, or others—as well as their incidence depends on additional factors including age, dose, potency, and duration of exposure (table 3). When drug induced chorea occurs, withdrawal of the offending agent is the treatment of choice. However, the movement disorder does not always remit with the discontinuation of the offending drug. When the onset of chorea is after exposure to dopamine antagonists, it is called tardive dyskinesia. Tardive dyskinesia is an involuntary, choreic movement disorder that typically affects the mouth and tongue causing random and stereotyped tongue protrusion and facial grimacing. Elderly females are the most susceptible, with an incidence of 20%–50% in patients being treated with neuroleptics. Other risk factors are duration of exposure, patients' age, and prior neurological deficits. In contrast, tardive dystonia develops more often in younger patients and presents with dystonic symptoms such as retrocollis and blepharospasm. The classic neuroleptics such as haloperidol, which possess high affinity for blocking D2 dopamine receptors, are most commonly implicated. Although the exact aetiology of delayed onset tardive dyskinesia is unclear, the most popular hypothesis is denervation hypersensitivity of blocked dopamine receptors. Tardive movements can also develop during the stable treatment or may be unmasked during attempts at dose reduction (withdrawal emergent). Once the offending medication has been withdrawn, the resolution of tardive movements can be a slow process (months to years) and is not assured. A dopamine depleting agent, such as reserpine or tetrabenazine can be considered in resistant cases. Vitamin E has been shown to hasten the resolution. When multiple medications are implicated, withdrawal of one medication at a time will allow the identification of the most offending agent. Discontinuation should begin with the most recent addition to the regimen. Although many medications have been tied to the induction of dyskinesia, very few medications other than neuroleptics produce permanent movement disorders.²⁹

Infectious chorea

Multiple infectious agents that affect the central nervous system have been associated with chorea. Chorea can occur in the setting of acute manifestation of bacterial meningitis, encephalitis, tuberculous meningitis, or aseptic meningitis. Movement disorders are also encountered in 2% to 3% of all patients with AIDS. In the setting of AIDS, hemichorea and hemiballismus are relatively common due to toxoplasmosis abscess; however, direct HIV invasion and injury to the basal ganglia resulting in chorea can occur.⁵¹ Less commonly, Lyme's disease has been reported to cause chorea.⁵²

Vascular chorea

Chorea is the most common movement disorder after stroke.⁵³ The subthalamic nucleus is the most common reported location of ischaemic or haemorrhagic damage in patients with poststroke chorea, especially when the chorea is severe and proximal (called hemiballismus).⁵⁴ Chorea can

Box 4: Drugs known to cause chorea (in addition to antipsychotic medications) (modified from Jain *et al*⁶³)

1. Anticonvulsant medications: common causative agents include:
 - Phenytoin.
 - Carbamazepine.
 - Valproate.
 - Gabapentin.
2. Central nervous system stimulants:
 - Amphetamines.
 - Cocaine.
 - Methylphenidate.
3. Benzodiazepines.
4. Oestrogens.
5. Lithium.
6. Levodopa.
7. Dopamine agonists.
8. COMT inhibitor in conjunction with levodopa.
9. Antihistamines: H1 and H2.
10. Others—for example, baclofen, cimetidine, aminophylline, etc.

also occur in polycythaemia vera, although it manifests in less than 1% of cases.⁵⁵ It remains unclear how polycythaemia can give rise to chorea. Several mechanisms have been proposed including transient ischaemia, reduced levels of catecholamines, or receptor upregulation.

Hormonal disorders

Hormonal disorders including hyperthyroidism, hypoparathyroidism with hypocalcaemia, pregnancy, and oral contraceptives have been implicated in the induction of dyskinesias. Two percent of patients with hyperthyroidism have chorea.⁵⁶ The movements are usually generalised and improve once treatment has been initiated. Hypocalcaemia with hypoparathyroidism can produce both generalised and focal dyskinesias.

Chorea gravidarum or chorea occurring during pregnancy is an increasingly rare disorder. Affected patients usually have the previous episodes of chorea associated with the use of oral contraceptives or history of rheumatic fever.⁵⁷ It is plausible that hormonal changes in pregnancy may require immunological cofactors from previous streptococcal infection to produce chorea. The movements usually remit after the delivery but may recur in the subsequent pregnancy.

Other causes of chorea

Metabolic alterations including hyperglycaemia and hypoglycaemia, hypernatraemia and hyponatraemia, hypomagnesaemia, hypocalcaemia, and hepatic or renal failure have been implicated in the development of various movement disorders including chorea. Correction of the metabolic abnormality leads to the resolution of the movement disorders. Postoperative encephalopathy with choreoathetosis or post-pump choreoathetosis is a recognised complication of childhood cardiac surgery.⁵⁸

Exposure to various toxins including alcohol, amphetamines, heroin, glue sniffing, thallium, and mercury can cause choreiform movements. The movements can be transient or permanent. Intoxication with carbon monoxide, methanol,

Table 3 Drug induced chorea (Modified from Poewe *et al*⁶⁴)

Features	Neuroleptic induced chorea	Levodopa induced chorea in Parkinson's disease
Age of onset	Elderly > young	Young > elderly
Sex	Female > male	Female = male
Prevalence	10% after month/years of treatment	50% after 3–5 years of treatment
Treatment	Discontinuation of neuroleptics or replacement by clozapine, tetrabenazine	Reduction of levodopa combined with the use of dopamine agonists

cyanide, or manganese produces bilateral necrosis of the pallidum, causing unconsciousness or parkinsonism. Involuntary movements can be a delayed sequel to acute high level exposure and disappear after a few months.⁵⁹ Chorea can also occur in the setting of paraneoplastic syndrome associated with small cell lung carcinoma, renal cell carcinoma, and lymphoma.⁶⁰

Diagnosis and management

Although there are extensive causes of chorea, careful history and a concomitant neurological and psychiatric review of systems will guide the individual workup. A detailed medical history is very important to rule out, in particular, prior streptococcal infections or rheumatic fever. As previously mentioned, a past history of rheumatic fever predisposes

Box 5: Recommended investigations in patients with chorea (careful history and physical examination will guide individual workup)

Start with careful history, including psychiatric, drug, and family history and physical examination, focusing in the distribution of chorea, evidence of motor imperistence, and frontal lobe dysfunction.

1. Complete blood count.
2. Electrolytes, calcium.
3. Magnesium.
4. Renal function tests.
5. Hepatic function tests.
6. Venereal Disease Research Laboratory test.
7. HIV antibody.
8. Thyroid function tests.
9. Erythrocyte sedimentation rate and antinuclear antibody titre: in cases with suspected autoimmune aetiology.
10. Antistreptolysin O titre: in cases with suspected streptococcal infection.
11. Lyme disease: in cases with recent travel history to endemic areas.
12. Toxoplasmosis titres: in immunosuppressed patients.
13. A copper study with serum ceruloplasmin and 24 hour urine copper: in cases with movement disorders under the age of 40, especially with a family history of neuropsychiatric symptoms or medical history of liver disease
14. MRI: in rule to intracranial structural lesion, especially in the setting of acute choreiform movements in older patients or younger patients with focal neurological signs.
15. Electroencephalography: when need to differentiate between paroxysmal movement disorders and seizures.

individuals to the development of a paroxysmal movement disorders under the influence of different agents. A family history of choreic or degenerative illness should be noted as well as a medication history of potential causative agents. Most of the time, the above history will narrow down the exhaustive differential list. Genetic testing, neuroimaging, and laboratory investigations will help us confirm the suspected diagnosis. Box 5 provides a list and when to consider individual tests. Despite the above careful workup in most patients, causes are unidentified in 6% of cases.³²

For primary chorea, dopaminergic antagonists such as neuroleptic medications are effective in treating chorea; however, their use is limited due to the side effects of mainly parkinsonism and tardive syndromes. Dopamine-depleting agents such as tetrabenazine, which inhibits the presynaptic dopamine release and blocks postsynaptic dopamine receptors, show favourable results compared with other medications used to treat chorea, especially in Huntington's disease, and have been reported to have synergistic effects when used in combination with the dopamine antagonist pimozide.^{20 61} For secondary chorea, the treatment objective should focus on the primary causative factor. If chorea is due to exogenous agent, the offending agent should be withdrawn. Infectious process should be treated accordingly. The drug used to treat primary chorea can be used to symptomatically treat secondary chorea.

SUMMARY

Chorea is a common finding in rare diseases as well as a rare manifestation of some common conditions. Although the exact pathophysiology of chorea is not well understood, most physiological and anatomical evidence suggests that disruption of the indirect pathway either structurally or neurochemically causes chorea.⁶² With such evidence, the concept of therapy can be potentially approached. Although not currently curative, most current therapies may alter the disease course, especially in Huntington's disease, or decrease the mortality and morbidity. Neurosurgical interventions may have a significant role in cases with medication resistant or progressively debilitating chorea. Keeping in mind the various ethical issues, additional longitudinal research is needed to further our understanding of this condition, which will lead to the effective treatment in the future.

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Cachexia in malaria and heart failure: therapeutic considerations in clinical practice

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Cachexia is an independent prognostic marker of survival in many chronic diseases including heart failure and malaria. Morbidity and mortality from malaria is high in most of the third world where it presents a very challenging public health problem. Malaria may present in the UK as fever in the returning traveller or as fever in overseas visitors. How and why cachexia develops in malaria in a manner similar to the cachexia of chronic heart failure and the treatment strategies that would alter outcomes in both diseases are discussed in this review.

also acts as a reservoir of infection. It may rarely be transmitted by blood transfusion, injection, or transplacentally. The clinical picture of *P falciparum* malaria typically includes fever, malaise, joint pains, anorexia, headache, nausea and vomiting, and cough and may progress to delirium, seizures, renal failure, coma, and death. This is because falciparum malaria is a complex disease that causes multiorgan dysfunction.² This is thought to occur through the excessive stimulation of inflammatory and immunological pathways mediated by pro-inflammatory cytokines.

The hallmark of malaria is haemolysis, which occurs when the red blood cells rupture to release schizonts. Rupture of schizonts liberates antigenic substances and toxins, which can cause widespread organ damage and failure. In falciparum malaria, red blood cells containing schizonts adhere to the lining of capillaries in brain, kidney, liver, lungs, and the gut. These vessels become congested and anoxia may develop within the organs. Repeated malaria attacks can result in long standing devitalisation that will ultimately lead to cachexia.

The interaction between malaria and cachexia is complex. Some workers have attempted to relate this interaction to socioeconomic factors and malnutrition, while others emphasise the importance of co-morbidity, and yet others stress the role of anaemia. The protective effect of intestinal helminths and chronicity is proposed to confound the malaria-cachexia interaction. Factors due to the frequency of parasite inoculation are also important. Malaria is a source of great morbidity and mortality. Immunity accrues slowly in survivors, over a period of years, and the immune response is not capable of protecting from reinfection. The most vulnerable are the individuals who lack adequate immunity: young children, pregnant women, and people with no previous exposure.³

Chronic malaria

There is no agreed definition for chronic malaria. In this review, we have used the term “chronic malaria” to mean three or more acute attacks of malaria within one year in an individual with low levels of parasitaemia but not symptoms of malaria between attacks. This is different from recurrent malaria in which there is complete elimination of parasitaemia between attacks.

Abbreviations: CHF, chronic heart failure; GPI, glycosylphosphatidylinositol; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IL, interleukin; MHCI, myosin heavy chain isoform; TNF, tumour necrosis factor; WHO, World Health Organisation

Cachexia is an important feature of many chronic disorders. It occurs in infectious diseases such as malaria and tuberculosis, and in many other chronic illnesses including heart failure, liver cirrhosis, chronic obstructive pulmonary disease, cystic fibrosis, chronic renal failure, and malignancy. It is important to specifically compare cachexia in malaria and heart failure because data from research in recent years suggests that the aetiology may be similar. This may have significant clinical considerations for the specialties that are involved in the management of patients with these conditions. This comparison may explore common themes that will enable us to selectively target cachexia irrespective of its cause and modify disease prognosis. This paper aims to review the evidence for cachexia in malaria and heart failure and to highlight common denominators in aetiology, clinical manifestation, or treatment.

METHODS

Papers reviewed were identified by searching Medline (1966 to January 2004), the Cochrane Database of Systematic Reviews, EMBASE, DARE, ACP Journal Club, Excerpta Medica, the Cochrane Controlled Trials Registry, and by reviewing the bibliography of relevant articles.

MALARIA

The protozoa that cause malaria are:

- *Plasmodium falciparum*.
- *Plasmodium malariae*.
- *Plasmodium vivax*.
- *Plasmodium ovale*.

Ninety five percent of deaths occurring in malaria worldwide are due to *Plasmodium falciparum*.¹ Malaria is transmitted by the bite of its insect vector, the anopheles mosquito, which

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Thus chronic malaria is a frequent feature of the indigenous population in endemic areas. It may well represent an adaptation by the host to survive repeated parasitic invasion or evolution by the parasite to exist successfully within the host.

Public health challenge

About 100 million people worldwide are subject to malaria infection annually, of whom 1% will die during the acute illness. About 90% of the worldwide malaria burden is borne by sub-Saharan Africa, and lately, the disease has reappeared in previously malaria-free areas as a result of epidemics, the decline in public health systems, and drug resistance.⁴ The World Health Organisation (WHO) report of 1997 states that about 40% of the world's population is at risk of malaria.⁵ This percentage at risk may increase if the disease continues to spread at the present rate. Specifically, about 25–30 million people from non-tropical countries will visit areas in which malaria is endemic yearly. Out of this number, about 10 000 to 30 000 will become infected.⁶

Molecular basis of the pathogenesis of falciparum malaria

It was the Italian physician Camillo Golgi who first hypothesised in 1886 that the cause of the febrile paroxysm in malaria was the release of a toxin of parasite origin.⁷ Maegraith in 1948 posited that the various pathological processes in malaria were the results of the induction of endogenous mediators of host origin.⁸ There is now evidence to suggest that host cells, acting under the influence of the parasite *P falciparum*, trigger the release of pro-inflammatory cytokines, which then provokes its onset. There are studies showing a close correlation between disease severity and circulating levels of tumour necrosis factor (TNF) in both children and adults.^{9,10} These cytokines can generate the inducible form of nitric oxide synthase and thus produce a continuous large supply of nitric oxide in tissues and cause cerebral symptoms, immune suppression, and weight loss.¹¹

CD4+ T-cells in malaria

CD4+ T-cells are thought to have a role in immunity to the blood stages of malaria, and cytokines associated with monocyte and T-cell activation have been implicated in the disease.¹² Similar cytokines are known to occur in the pathogenesis of cachexia in heart failure.

Glycosylphosphatidylinositol (GPI)

GPI produced by *P falciparum* is a parasite toxin inducing the production of TNF and interleukin (IL)-1 by host macrophages. This exerts its effect by the activation of a two component signalling pathway within the host cells.¹³ GPI causes TNF-mediated weight loss in mice.¹⁴

Overlap of symptomatology: algid malaria

Algid malaria is a shock-like syndrome. Most patients with severe falciparum malaria exhibit a raised cardiac index (>5 l/min/m²), which can be traced to pyrogen-mediated vasodilatation with low systemic vascular resistance and low or normal pulmonary arterial wedge pressures. The WHO report on falciparum malaria in 2000 states that the clinical picture produced in algid malaria is similar to Gram negative septicaemia.⁵ Endotoxaemia also occurs in patients with falciparum malaria.¹⁵ An agonal fall in cardiac index secondary to metabolic acidosis, hypoxaemia, and septicaemia may occur. This is similar to what is observed in the final stages of heart failure from non-cardiac causes, especially that associated with end stage renal disease and sepsis. Malaria may thus be viewed as a collection of overlapping syndromes acting through different organ systems with several mechanisms.¹⁶

Immunity to falciparum malaria

Plasmodium falciparum is one of the most virulent human pathogens. The factors that determine its virulence are poorly defined, although the adhesion of infected red blood cells to the vascular endothelium has been associated with some of the syndromes of severe disease. Immune responses cannot prevent repeated attacks of malaria. Specific immunity has been attributed either to the presence of cytotoxic lymphocytes that act against the parasite's liver stage of infection or to antibodies that react against blood stage antigens. Antigenic diversity, clonal antigenic variation and T-cell antagonism may contribute to the parasite's evasion of the protective and parasitocidal host responses. It is proposed that an understanding of immunity in the setting of malaria may be the link to understanding how cachexia develops in chronic heart failure (CHF) with a known similar cytokine profile.

Evidence for cachexia in malaria

The studies that provide the evidence for the occurrence of cachexia in chronic malaria are summarised in table 1. Various workers have studied the relationship between malarial immunity and nutritional status. In Tanzania, no correlation was found between malaria antibody titres and indices of malnutrition.¹⁷ In Kenya, a variant surface antigen specific IgG in chronic pregnancy associated malaria was found to protect against low birth weight.¹⁸ In Colombia, mean antibody titres to *P falciparum* were lower in malnourished children than in well nourished ones. *P vivax* antibody titres were higher in malnourished children.¹⁹ There is evidence from observational cohorts that malnutrition decreases the susceptibility to malaria and that this may be due to an interaction with host immunity.²⁰ There is also evidence that malnutrition worsens the prognosis in malaria.²¹ The level at which malnutrition ceases to become protective and becomes an adverse prognosticator is not clear. The host immunity described is related to "stunting" and "wasting" rather than malnutrition. Stunting has been shown to be protective in malaria. Thus, it has been proposed that the improved ability of malnourished children to produce certain cytokines in response to stimulation by specific malarial antigens may be the key.²² Tanner *et al* reported that malaria was the main contributory factor to growth retardation in children in a hyperendemic rural community of Tanzania.²³ Mbago *et al* determined that malaria was a significant predictor of weight for height measurements in underweight children living in holoendemic areas of urban Tanzania.²⁴ We have not found any studies that addressed directly the issue of the response of cachexia to treatment interventions in malaria and how this might affect prognosis. However, a small study by Van Den Broeck *et al* in 1993 found an association between nutritional status and mortality risk and extreme malnutrition in holoendemic areas of Zaire.²⁵

Similarly, there are no large studies involving long term endpoints on the effect of long term suppression of parasitaemia in chronic malaria in endemic areas and the relationship to cachexia and prognosis. Because manipulation of cachexia may modify chronic disease, it is important to design and conduct large intervention studies in chronic malaria to see whether manipulation of either endpoint will affect prognosis or other outcome measures when both endpoints occur together.

HEART FAILURE

"Heart failure is a fascinating cluster of syndromes, full of paradoxes, defies simple definition yet is common and deadly".²⁶ The 2001 guidelines issued by the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the

Table 1 Studies on weight loss in malaria

Author(s)	Year	Region/country	Parameters studied	Results
Tanner <i>et al</i> ²³	1987	Tanzania	Stunting/wasting	3%–20% wasting, 35%–71% stunting
Dominguez-Vazquez and Alzate-Sanchez ¹⁹	1990	Colombia	Malnutrition using the Gomez classification	49% mild, 14% moderate, 2% severe
Mbago and Namfua ²⁴	1991	Tanzania	Weight for height, weight for age, wasting underweight	Male sex, better; mother's age and education, better; immunisation status; number of children under 5
Kikafunda <i>et al</i> ²⁸	1998	Uganda	Mid-upper arm circumference Weight Supine length Stunting	21.6% low MUAC 24.1% underweight 23.8% short for age 6.9%
Genton <i>et al</i> ²²	1998	Papua New Guinea	Stunting/wasting, height for age score	21% stunted, 10% wasted, 5% both
Nacher <i>et al</i> ²⁰	2001	Thailand	Body mass index	8.9%–9.8%
Deen <i>et al</i> ²¹	2002	Gambia	Height for age score, stunting	51% stunted, 38% not stunted
Staalsoe <i>et al</i> ¹⁸	2004	Kenya	VSA specific IgG, resistance to PAM, birth weight, maternal anaemia	Chronic PAM and low or absent VSA specific IgG causes: low birth weight babies, maternal anaemia

MUAC, mid upper arm circumference; PAM, pregnancy associated malaria; VSA, variant surface antigen.

European Society of Cardiology states that heart failure is a syndrome containing certain key features typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling plus an objective evidence of cardiac dysfunction at rest. That a clinical response to treatment directed at heart failure should demonstrate some improvement in symptoms and/or signs.²⁷

Cachexia in CHF

Cachexia is an adverse prognosticator in heart failure.²⁸ There is considerable disagreement in the question of the percentage of heart failure patients who develop cachexia and how this should be defined and measured. Carr *et al* reported that up to 50% of patients with CHF suffered from some form of malnutrition.²⁹ Anker and Coats published that up to 15% of patients attending their CHF clinic developed cachexia during the clinical course of CHF.³⁰ Roubenoff *et al* observed that loss of more than 40% of lean body tissue would cause death.³¹ Several studies show that CHF is characterised by persistent immune activation in vivo. This is reflected in the increased levels of inflammatory cytokines TNF, IL-1 β , and IL-6; and chemokines monocyte chemoattractant protein-1 and IL-8 within the blood and the enhanced expression of various inflammatory mediators within the failing myocardium.

Competing theories

There are several theories for the causes of cachexia in CHF. Figure 1 shows the factors that are known to affect the development of cachexia in chronic diseases like CHF and the relationship between these factors. We point out, however, that it would be difficult to propose a specific hypothesis regarding molecular mechanisms of cachexia as the different mechanisms and pathways proposed have not been fully defined.

Physical inactivity and muscle atrophy

Widespread abnormalities of skeletal muscle bulk, function, and metabolism is a recognised consequence of CHF. Around 400 BC, a syndrome of "heart failure" in which the "shoulders, clavicles, chest and thighs melt away" was described by a scholar from the school of Hippocrates.³² William Withering in 1795 wrote of a patient with heart failure as someone "whose body was greatly emaciated".³³ There is recent evidence to support this.^{34 35} Physical inactivity

and deconditioning may play a part in the muscle atrophy seen in many chronic disease states, although in CHF this atrophy is significantly different from that observed in physical inactivity.

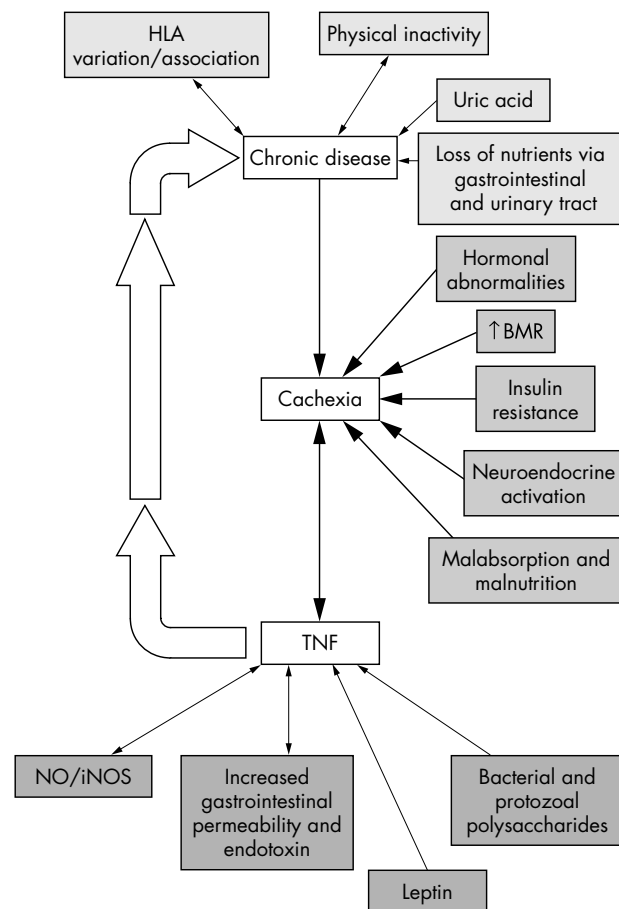


Figure 1 Interplay between chronic disorders and cachexia (BMR, basal metabolic rate; NO/iNOS, nitric oxide/inducible form of nitric oxide synthetase; TNF, tumour necrosis factor).

Muscle hypothesis

Coats *et al* postulated that haemodynamic alterations trigger the development of complex peripheral alterations which contribute to sympathetic excitation during exercise and symptom generation and degeneration.^{36 37} Regular exercise increases skeletal muscle bulk and improves survival in CHF.

Chronic low frequency electrical stimulation

A small clinical trial by Nuhr *et al* reported that four hours a day of chronic low frequency stimulation for 10 weeks improved exercise performance and significantly increased peak oxygen uptake.³⁸ These changes were associated with changes in the profiles of the enzymes citrate synthase and glyceraldehyde phosphate dehydrogenase, and the myosin heavy chain isoforms (MHCIs) were shifted in the slow direction. The increases in the MHCII slow isoform was at the expense of the MHCII/d/x fast isoform suggesting an increase in lean muscle mass and improvement in deconditioning due to CHF.³⁷

Neurohormonal hypothesis

Merrill *et al* reported an increased concentration of renin in the blood of patients with CHF.³⁹ Subsequently the mechanism for salt and water retention in CHF was described.⁴⁰ The concept that neuroendocrine activation is central to the pathogenesis and prognosis of heart failure is well established.^{41 42} Packer used the neurohormonal hypothesis to postulate that CHF progresses because activated endogenous neurohormonal systems are deleterious to the heart and cardiovascular system.⁴³ Thus catecholamines are now accepted to be raised in cachexia because of heart failure.⁴⁴

Cytokines in CHF

Levine *et al* observed that patients with severe CHF had raised circulating levels of TNF.⁴⁵ This was followed by reports of increased concentrations of TNF in patients with cardiac cachexia. The clinical significance of these observations is that TNF elevation in CHF is associated with marked activation of the renin-angiotensin system, cachexia, advanced disease, and an adverse prognosis.⁴⁶ It has also been observed that the TNF receptor family (F_{as}) transduces the apoptotic signal into cells. And there are reports of the occurrence of apoptosis with abnormal consequences in the human heart.⁴⁷ TNF is now thought to play a significant part in left ventricular remodelling.

Insulin resistance

Insulin resistance and the development of the metabolic syndrome have been implicated as a contributing cause of cachexia in CHF.⁴⁸ In infectious diseases, hyperinsulinaemia and insulin resistance are commonly associated with hypoglycaemia. In malaria, insulin resistance may also occur in association with hypoglycaemia.⁴⁹ It may be due to parasitaemia or treatment with quinine.

Dehydroepiandrosterone/cortisol ratio, growth hormone, and basal metabolic rate

The role of hormonal changes, dehydroepiandrosterone/cortisol ratio, growth hormone, and insulin-like growth factor as underlying the severe metabolic and endocrine abnormalities in these diseases was described by Anker *et al*.³⁹ An increase in basal metabolic rate is thought to be central to this.

Leptin

Leptin may also play a part in cachexia. Like cytokines, leptin serves as a peripheral messenger to convey signals to the brain. Expression of leptin is stimulated by glucocorticoids, endotoxins, and cytokines and its actions include inhibition of the hypothalmo-pituitary-adrenal axis. Indeed leptin exerts a direct, dose dependent inhibition of stimulated

cortisol secretion by normal human and rat adrenal cells *in vitro*.⁵⁰ Adipocytes are implicated in the cachexia seen in malaria.⁵¹ The evidence is not clear.⁵²

Malnutrition/malabsorption

Malnutrition and malabsorption are well known causes of cachexia in chronic diseases. Losses of nutrients through the gastrointestinal and urinary tracts are other mechanisms proposed as possible causes. In CHF increased right atrial pressure and tricuspid regurgitation is associated with whole body protein turnover and cachexia.^{53 54} What is not so clear is whether this is a cause or effect.

COMPARISON BETWEEN CACHEXIA IN CHF AND CACHEXIA IN MALARIA

The body of evidence discussed above shows that many immunological, physiological, and clinical features are

Table 2 Comparison between cachexia in CHF and cachexia in malaria

Chronic heart failure	Malaria
HLA association not known. Genotypes not known to ameliorate disease severity	Strong HLA association with disease severity. Also AS genotype associated with protection from disease
Associated with malnutrition	Associated with malnutrition
Skinfold thickness associated with prognosis	Decrease in skinfold thickness is an adverse prognosticator especially in severe disease
Respiratory distress and pulmonary oedema frequently present	Respiratory distress and pulmonary oedema when present is an ominous sign
Nitric oxide implicated in the pathogenesis	Nitric oxide has a central and deleterious role in cerebral malaria
Prostaglandins D ₂ , E ₂ production increased	Prostaglandins D ₂ , E ₂ production increased
Multiorgan failure a feature of the terminal stages of CHF	Multiorgan failure especially liver, kidney and bone marrow failure present
High blood levels of TNF present	High blood levels of TNF present. Inhibition of TNF levels beneficial
Increased production of IL-6, IL-1	Increased production of IL-6, IL-1, in cachexia associated with moderate disease Decreased production of anti-inflammatory cytokine IL-10, IL-12 in severe malaria
High serum uric acid is a marker of systemic inflammation	High serum uric acid associated with more severe disease
High blood levels of cholesterol beneficial	High blood levels of cholesterol associated with fewer and less severe malarial attacks
Increased gastrointestinal permeability associated with endotoxin levels	Increased gastrointestinal permeability associated with severe <i>P falciparum</i> infection
Bacterial lipopolysaccharide triggers release of proinflammatory cytokines	Plasmodial lipopolysaccharide triggers release of proinflammatory cytokines. GPI also known to induce TNF and IL-1 production by macrophages and TNF-mediated cachexia
Hypoinsulinaemia associated with insulin resistance and the onset of the metabolic syndrome	Hyperinsulinaemia associated with hypoglycaemia and anti-malarial treatment. Insulin resistance associated with chronicity
Growth hormone and insulin-like growth factor implicated in pathogenesis of disease	Growth hormone and somatostatin analogues modulate severity of disease

common to those with chronic malaria and CHF. Table 2 provides a list of the key features. How useful is this background knowledge? We recognise some of these features may not apply in routine clinical settings, because they are still experimental. We have nonetheless provided them because there are on-going efforts by researchers to make some of them the routine therapeutic considerations of the future.

CYTOKINES IN MALARIA

Malaria infected individuals produce large amounts of proinflammatory cytokines. This cytokine response is responsible for the high levels of fever that occur within a few days of the inoculation of non-immune individuals with *Plasmodium* spp.⁵⁵ The idea that cachexia in malaria is mediated by TNF was first mooted by Hotez *et al.*⁵⁶ Animal models have shown that weight loss in malaria is influenced by TNF. Blocking TNF in mice that received parasite specific T-cells prolongs survival.⁵⁷ In human studies the production of proinflammatory cytokines like IL-1, IL-6, and TNF have been shown to mediate the clinical progress of fever, anorexia, and weight loss.⁵⁸ TNF as noted in CHF above, acts by inducing the synthesis of IL-6, and by the induction of nitric oxide synthesis. Details of various studies of cytokines in malaria are summarised in table 3. TNF is down-regulated by IL-10 in children living in malaria holoendemic areas of Kenya and appears to inhibit the production of erythropoietin. Raised serum concentrations of TNF have been reported in malaria, and high concentrations correlate with increasing disease severity. IL-10 is also increased in malaria, and has been shown to down-regulate TNF. Severe anaemia has been associated with severe malaria in Ghanaian children with defective IL-10 production. Previously, it was shown that IL-10 gene knockout mice develop more severe disease and experienced higher mortality rates than normal mice, prompting the suggestion that children with *P. falciparum* infection who produce balanced levels of IL-10 to regulate excessive TNF are better able to control severe anaemia, and the observation that severe anaemia may be a further consequence of the

deranged immunology seen in malaria.⁵⁹ It has thus been proposed that the balance between IL-10 and TNF may modulate the severity of anaemia in malaria in children.⁶⁰

CYTOKINES IN CHF

TNF, IL-1 β , and IL-6 are known to have important pathogenic roles in CHF, and may contribute to cachexia associated with CHF.^{66 67}

COMPARISON OF PLASMA TNF IN CHF AND MALARIA

Figure 2 was derived from the data published by Kurtzhals *et al* and Cicoira *et al.*^{68 69} It shows plasma levels of TNF in a normal population, CHF patients, and malaria patients. They provide no direct comparison and should be interpreted with caution. The methodologies employed in assaying and analysing the samples are not the same, and the Kurtzhals group did not screen for chronic malaria. However, the trend is that TNF levels are highly raised in the acute event like malaria and increased to a lesser amount in CHF. Whether an acute event with highly raised TNF levels occurs before the onset of CHF is not yet known. Clearly more studies are needed to confirm absolute TNF and endotoxin levels in all stages of both diseases before postulating a common denominator.

GENETIC REGULATION OF TNF EXPRESSION

TNF- α related cachexia in malaria might be influenced by the genetic make-up of individuals and populations. TNF- α has two subtypes (TNF- α 1/TNF- α 2) and severe malaria is found significantly more frequently in heterozygotes.⁷⁰ Rates of TNF- α subtypes vary between populations and may influence susceptibility to severe malaria and cachexia.⁷¹

THERAPEUTIC AND PROGNOSTIC IMPLICATIONS

Cachexia complicating any chronic disease state is associated with an increased risk of death during the course of that disease. Anker *et al* have suggested that the loss of more than

Table 3 Summary of data on cytokines in malaria

Author(s)	Region/country	Cytokine studied	No of patients	Blood level
Allan <i>et al</i> ⁶¹	Gambia	TNF- α	34 children with cerebral malaria	56–91 pg/ml, 95% CI 41 to 154
			66 children with uncomplicated malaria	70–618 pg/ml, 95% CI 42 to 2033
Kurtzhals <i>et al</i> ⁶⁸	Ghana	IL-10	41 children with cerebral malaria	110–200 pg/ml (TNF) 640–1400 pg/ml (IL-10)
		TNF- α	26 children with uncomplicated malaria	80–140 pg/ml (TNF) 400–1200 (IL-10)
Singh <i>et al</i> ⁶²	India	TNF- α	15 adults with cerebral malaria 39 adults with uncomplicated malaria	915 pg/ml (falciparum) 280.6 pg/ml (vivax)
Migot-Nabias <i>et al</i> ⁶³	Gabon	IL-10	300 children with uncomplicated malaria	2.5 pg/ml range: 0–157.5
		TNF- α		2.4 pg/ml range: 0–161.7
		IFN- γ	186 children with uncomplicated malaria	0.3 pg/ml range: 0–60.5
Nussenblatt <i>et al</i> ⁶⁴	Cameroon	IL-10	273 children with uncomplicated malaria	63–426 pg/ml (range: 28–1380)
		TNF- α		5–25 pg/ml (range: 1–62)
Jason <i>et al</i> ⁶⁵	Malawi	IL-10	32 children with uncomplicated malaria	39 pg/ml range: 8–23000
		IL-6		387 pg/ml range: 9–124300
		TNF- α		<16 pg/ml range: <16–971
		IFN- γ		26 pg/ml range: <16–1280

CI, confidence interval; IFN- γ , interferon gamma.

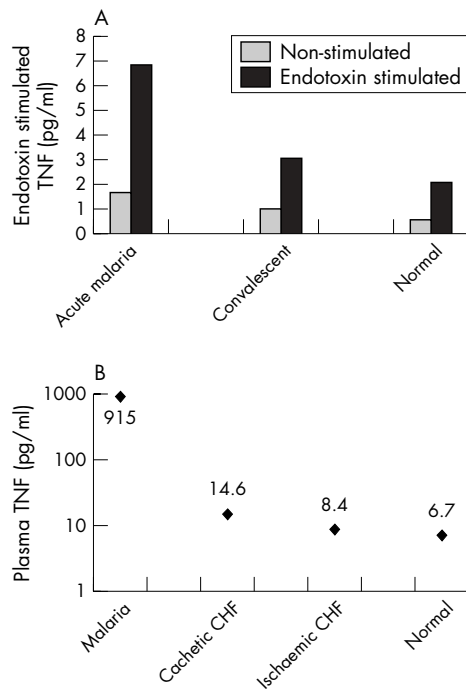


Figure 2 (A) In vitro endotoxin stimulated TNF production in falciparum malaria; (B) comparison of plasma TNF levels in malaria and CHF.

6% of the pre-morbid body weight or the presence of a body mass index <15 in an adult being treated for a chronic disease should prompt heightened therapeutic consideration.⁷² This may include:

- Nutritional support.
- Exercise training.⁷³
- Periodic weighing or a carefully documented weight history.
- Modification of lipid profile.
- Anticytokine therapy.
- Intravenous immunoglobulin.⁷⁴
- Administration of anti-inflammatory cytokines.
- More regular follow up.

Table 4 Novel intervention possibilities

Chronic heart failure	Malaria
Value of anti-TNF drugs not proven in clinical trials	Anti-TNF drugs may be useful in malaria
Intravenous immunoglobulin may modulate peripartum cardiomyopathy	Intravenous immunoglobulin useful in severe malaria
Statins modulate CHF without cachexia	Statins may modulate malaria without cachexia
ACE inhibitors useful in all stages of CHF	ACE inhibitors maybe useful in moderate to severe cachexia of malaria, although the evidence is not clear cut
Role of vitamin D unclear	Vitamin D may have beneficial immunomodulatory effects
Role of antioxidants controversial	Antioxidants low in severe disease
Role of polyclonal specific Fab fragment directed against human TNF unclear	Polyclonal specific Fab fragment directed against human TNF known to inhibit clinical manifestations of falciparum malaria

ACE, angiotensin converting enzyme.

SIMILARITIES AND POTENTIAL FOR NOVEL INTERVENTION

Table 4 lists the various points in the pathophysiology of these two diseases where it is theoretically possible for new intervention strategies to be applied.

Modification of lipid profile

Cytokines and endotoxin are known to stimulate triglycerides and cholesterol synthesis.⁷⁵ Dyslipidaemia is a feature of severe malaria.⁷⁶ Recent studies suggest that the inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase can interfere with the activation of anti-inflammatory pathways in the body causing down-regulation of cytokine and chemokine production. This enzyme is raised in CHF and in malaria.⁷⁷ Thus, there arises the question of whether the low blood levels of cholesterol seen in severe cachexia complicating chronic malaria should be viewed as an adverse prognostic marker and subject to the same therapeutic considerations as blood cholesterol levels in CHF.⁷⁸⁻⁷⁹ In CHF high and moderately raised levels of blood cholesterol would be treated with statins. Perhaps, the enhancement of the immunomodulatory effects of statins may see a novel role for HMG CoA reductase inhibitors in malaria. In contrast, cholesterol-rich serum lipoproteins are able to modulate the inflammatory immune response because they bind to, and detoxify, bacterial lipopolysaccharide whose production is increased in CHF and many chronic diseases.⁸⁰

Anticytokine drugs

There are many probable therapeutic interventions that may modify the profiles of cytokines in chronic disease states.⁸¹ A summary is given below:

- (1) Anti-inflammatory cytokines such as IL-10, IL-12, IL-18, and interferon suppress the inflammation and may play a part in therapeutic interventions.
- (2) The inhibition of cytokine synthesis using drugs such as glucocorticoids, cyclosporine A, Th₂ selective inhibitors, myphenolate, and tacrolimus may modify cachexia.
- (3) The administration of soluble cytokine receptors to mop up secreted cytokines.
- (4) The use of humanised blocking antibodies to cytokines or their receptors.
- (5) The use of drugs that block the signal transduction pathways activated by cytokines.⁸²

Serum levels of uric acid are high and correlate with systemic inflammation in severe malaria and CHF. Anticytokine therapy using agents like pentoxifylline may be another ground common to both diseases. Two large clinical trials using etanercept, a TNF receptor analogue that blocks the effect of TNF, the RENAISSANCE and RECOVER, were stopped early in 2001 because they failed to demonstrate a benefit in patients with CHF. However, the addition of pentoxifylline to standard antimalarial treatment is known to decrease the duration of coma and mortality in patients with *P falciparum* cerebral malaria as shown by Di Perri *et al.*⁸³ This better outcome was associated with a decrease in serum TNF levels. Addition of pentoxifylline to treatment with standard heart failure drugs in patients with dilated cardiomyopathy may be associated with a significant improvement in left ventricular ejection fraction and symptoms.⁸⁴

Intravenous immunoglobins

Recent evidence suggests that there may be a survival advantage in using intravenous immunoglobins in peripartum cardiomyopathy, CHF, and malaria.⁸⁵⁻⁸⁷ The approach may be

similar to the strategy in other chronic diseases like Kawasaki disease, dermatomyositis, and multiple sclerosis.

CONCLUSION

Many advances were made in our understanding of the pathogenesis of severe malaria and its sequelae in the second half of the last century. During the same period, notable advances were made in the management of CHF. Despite this, morbidity and mortality related to both diseases remain unacceptably high. The prognosis of patients with CHF remains poor, and malaria is re-emerging in areas once thought of as free from the disease. This may be because treatment in malaria is directed at the causative parasite and prevention of reinfection, while in CHF the empirical treatment of heart failure and lifestyle modification is the cornerstone of modern treatment. Our review of the literature suggests that there are significant similarities in the cachexia seen in CHF and that of malaria, especially as related to the effects of muscle mass and immunology. This challenges our understanding of recent techniques in modification of neurohormonal, cytokine, and lipid profiles and augmentation of lean muscle mass in CHF, and may present opportunities for novel therapeutic interventions.

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CORRECTION

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An error occurred in the paper “Chorea and related disorders” by Bhidayasiri and Truong published in the September issue (*Postgrad Med J* 2004;**80**:527–34). On page 528, “Box 1: Clinical features of Huntington’s disease”, the 8th bullet point should read “No curative treatment; symptomatic treatment with dopamine antagonists”.