Chorea
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Abstract
Chorea is an involuntary movement disorder characterised by flowing and rhythmic in nature. Hyperkinetic movement disorders such as myoclonus may be mistaken for chorea. Pathogenesis of chorea is complex and results from dysfunction of network between motor nucleus of thalamus and subcortical nuclei including globus pallidus interna. There are genetic and non genetic causes of chorea. Huntington’s disease is most common genetic cause of chorea. Clinical manifestations of Huntington’s disease are mainly neurological and psychiatric. Recently non neurological clinical manifestations of this disease have been described. Genetic test for Huntington’s disease is available which may be done for diagnosis and detection of family members at risk of developing disease. Other genetic causes of chorea are neuroacanthocytosis and Wilson’s disease. Treatment of genetic causes of chore is usually symptomatic with exception of Wilson’s disease. Sydenham’s chorea is a neurological manifestation of acute rheumatic fever and most important cause of chorea seen in paediatric population. Treatment includes penicillin prophylaxis and drugs such as sodium valproate and carbamazepine. Diagnosis of chorea is mainly clinical. Family history is very important in diagnosis of genetic causes of chorea. In other patients a detailed work up is required before a final diagnosis is made. Hematological and blood chemistry investigations are helpful in diagnosis of some of the patients. Neuro imaging may also be useful mainly in Huntington’s disease patients. Metabolic disorders and drugs are very important causes of non genetic chorea. Early diagnosis is important because majority of the patients respond to the treatment.

Introduction
The word “Chorea” is derived from Greek word meaning dance. It is characterised by involuntary rhythmic movement which is random and brief. Chorea may involve face, tongue, neck, trunk, upper extremities and lower extremities. Very severe chorea with predominant proximal distribution is labelled as ballismus. Unilateral chorea is called hemichorea and if associated with ballismus it is called choreoballistic movement. Description of chorea has been available in literature since 14th century when epidemic dancing mania was described. Thomas Sydenham described post infectious chorea for the first time.

Chorea can be hereditary or acquired. Most common form of hereditary chorea is Huntington’s disease. Most common causes of non genetic chorea are autoimmune, infectious, vascular, drug and metabolic.

Pathogenesis
Chorea originates from dysfunction of a neuronal network between motor cortex and basal ganglia which includes subcortical nuclei like globus pallidus interna (GPI) and externa (GPe), caudate nuclei, subthalamus and thalamus. There are inhibitory GABAergic projections from GPI to motor nucleus of thalamus. Dysfunction of these inhibitory inputs leads to hyperkinetic choreiform movements. However this model is not so straightforward. In Parkinson’s disease patient’s pallidotomy leads to abolition of chorea raising a question mark over this model.

Clinical Symptoms
Movements in chorea may be simple or complex. Sometimes they are superimposed with voluntary actions leading to a bizarre character. It may be mistaken for myoclonus but a flowing nature of chorea is most characteristic. Another difference is speed of movement which is more in case of myoclonus in comparison with chorea. Hypotonia is a consistent feature and knee jerks may be pendular. “Hung-up” reflex may be seen due to a combination of choreic movement with reflex.

Many clinical methods have been described to elicit chorea, like milkmaid’s grip (while squeezing examiner’s fingers irregular contractions of hand muscles), piano sign (when arms are extended repeated hand spooning and pronation), tongue movement (worm like movement on protrusion) and handwriting (to demonstrate motor impersistence).

Causes of Chorea
Chorea may result from genetic or nongenetic causes (Table 1). Most common genetic cause is Huntington’s disease. Non genetic causes of chorea include metabolic, infectious disorders and stroke.

Huntington’s Disease (HD)
Hereditary form of chorea was first described by Walters in 1842. However first detailed description and genetic mode of transmission was described by George Huntington in 1872. Since Huntington was first to give a detailed description of this...
disorder it is known as Huntington’s disease (HD). Huntington described three peculiarities of this disorder; hereditary character, suicidal tendency and adult onset. Prevalence rate of HD is 3 to 7 per 100,000 population in North America and Europe and annual incidence is between 2 to 7 per million.1

Huntington’s disease symptom may start any time between 1 to 80 years of age. But usual age of onset is in fourth decade of life in most of the families.6 Onset of symptoms mainly depends upon number of CAG repeats. Earlier onset in subsequent generation is known as anticipation, which is a hallmark of all trinucleotide repeat disorders. Before the symptom onset there is a presymptomatic phase which is characterised by personality and cognitive changes. Early and late onset HD patients have more parkinsonian features than chorea and they progress faster. Clinical features may start with neurological or psychiatric features alone or simultaneously. In patients presenting with psychiatric features anxiety, anger and irritability are most common symptoms. They may be wrongly diagnosed as psychiatric patients till they have motor manifestations. Other psychiatric manifestations may be in form of irritability, aggressive behaviour, depression, anxiety and suicidal tendency. Impulsive behaviour may lead to criminal activities. Impaired cognition in form of speech difficulty and poor executive function are most characteristic. Dementia is quite common in HD patients but is more frequent in Juvenile HD. In some patients motor impersistence may be the only initial manifestation. Other psychiatric manifestations may be in form of irritability, aggressive behaviour, depression, anxiety and suicidal tendency. Impulsive behaviour may lead to criminal activities. Impaired cognition in form of speech difficulty and poor executive function are most characteristic. Dementia is quite common in HD patients but is more frequent in Juvenile HD. In some patients motor impersistence may be the only initial manifestation. Neurological features may be in form of chorea, dystonia or gait abnormality. Gradually chorea is replaced by rigidity and bradykinesia. In some patients upper motor neuron signs in form of spasticity and hyper-reflexia may be seen. Different types of eye movements have been described in HD. Slow saccade is most consistent abnormality seen. Up gaze restriction and frequent blinking are other characteristic ocular features.7 Progression of disease is usually slow but can be rapid in juvenile and late onset cases. Neuropathology studies have revealed that striatal medium neurons are most vulnerable and interneurons are generally spared.4 Nuclear and cytoplasmic inclusions containing huntingtin and polyglutamate have been reported.5 Cause of death may be a complication of psychiatric symptoms leading to suicide or because of poor nutrition or aspiration pneumonia.

Non neurological manifestations of HD have been widely reported in the literature (Table 2). Major non neurological features include weight loss, muscle atrophy, testicular atrophy and heart failure. Huntington’s disease may not always present with typical history of chorea, psychiatric and cognitive impairment. Different variations have been reported in the literature.

### Juvenile Huntington’s Disease

Juvenile form of HD is having onset before 20 years of age. Major clinical features are bradykinesia, rigidity and dementia. Progression is rapid in comparison to HD patients.

### Huntington’s Disease without Chorea

Some cases of HD have been reported where cognitive dysfunction and dementia are the major manifestation and chorea is minimal or absent.

### Huntington’s Disease without Dementia

Chorea without dementia or psychiatric symptoms has been reported in some families. On pathology there has been predominant involvement of basal ganglia with sparing of cortex.

Huntington disease like 2 (HDL2): It is caused by Junctophilin -3 mutation and exclusively reported from African community. Clinical features are similar to HD patients.

### Genetics and Huntingtin Protein

Huntington’s disease gene has been located on short arm of chromosome 4. This gene is responsible for CAG repeats.

Huntingtin protein is mostly found in mammals in brain and is involved in transcriptional process.10 It has also been found in other tissues like testes, liver, heart and lung. In normal individuals less than 36 CAG repeats are seen in Huntington protein. But in mutant huntingtin protein number of repeats are more than 39. Mutant huntingtin protein is toxic in nature and leads to impaired transcriptional process leading to apoptosis. More repeats are associated with early onset of symptoms, known as anticipation. Genetic test in family members of HD patients can predict the disease in advance and is an important tool for diagnosis in preclinical stage. Certain group of individuals having suicidal thoughts should be excluded from this test. Worldwide only 5-10% such individuals go for this test because of fear and anxiety.11 Major reason of anxiety is losing job and medical insurance. Recently some European countries have banned disclosure clause for genetic test in health insurance. This step is needed by other countries also to motivate people for getting genetic test done.

Neuroacanthocytosis: Similar to HD neuroacanthocytosis also starts in younger or middle age individuals. Characteristic features include chorea, self-mutilation, peripheral neuropathy and dystonia. Gait in neuroacanthocytosis is very typical and some authors have labelled this as rubber man syndrome. Demonstration of acanthocytes on peripheral blood smear examination is crucial for the diagnosis. Neuropathological studies have demonstrated atrophy and gliosis of caudate nuclei and putamen without involvement of other part of brain. McLeod neuroacanthocytosis syndrome is a multisystem disorder characterised by central nervous system (CNS), neuromuscular, and hematologic manifestations in males. McLeod blood group phenotype results from abnormal expression of Kell surface antigens on the erythrocyte.

Benign hereditary chorea (BHC): Benign hereditary chorea is also known as essential chorea. It is inherited in an autosomal dominant pattern and starts in first decade of life with a peak in second decade. Characteristic features include chorea and ataxia. BHC is non progressive and sometimes improves with age. Mutation in thyroid transcription factor -1(TITF-1) on chromosome 14q is diagnostic.
### Wilson’s Disease

Wilson’s disease is characterised by autosomal recessive inheritance and mutation in chromosome 13q14.3. Clinical features include tremor, dystonia, chorea and Kayser-Fleischer rings (KF rings). In neurological cases diagnosis is made by serum ceruloplasmin level (<300 mg/l), 24 hour urinary copper excretion (>100 mg/day) and presence of KF ring. Treatment includes chelating agent such as penicillamine and zinc.

### Paroxysmal Chorea

Paroxysmal chorea may manifest in two different ways; paroxysmal kinesogenic choreoathetosis (PKC) or paroxysmal dystonic choreoathetosis (PDC). Symptoms start in first decade of life and episodes start with exercise or physical activity. Majority of the patients respond to antiepileptic drugs.

### Sydenham’s Chorea

Sydenham’s chorea (SC) is one of the neurological manifestations of acute rheumatic fever. It usually starts in first decade of life and is more common in girls. Manifestation of chorea in acute rheumatic fever is late and occurs in 10-30% of patients usually in absence of other symptoms. Acute carditis is seen in 40-80% patients and arthritis in 10-30% patients of Sydenham’s chorea. In a study of 50 patients with rheumatic fever; arthritis was more common in patients without chorea (84%) than patients with chorea (31%). Predominantly head and upper limbs are involved. Typically chorea appears after 4-5 weeks of streptococcal infection when other manifestations of rheumatic fever are not seen. Twenty percent patients may have asymmetrical onset of chorea and may present as hemi chorea. Rarely chorea may be very severe leading to chorea paralytics. Hypotonia is a common feature. Other motor findings like tics are very common. Association with migraine, papilloedema, seizure and central retinal artery occlusion has also been seen. Patients may have psychiatric manifestations like hyperactivity, irritability and learning disorders. In Sydenham’s chorea individual muscle contractions are longer (>100 msec) than HD patients (50-100 msec). Activities of daily living, motor function and behavioural disorders can be measured by Universidade Federal de Minas Gerais Sydenham chorea Rating Scale. It has 27 items each having 0 (no symptom or disability) to 4 (severe symptom, sign or disability) score. Most likely pathogenesis is molecular mimicry between central nervous system and streptococcal antigen. Diagnosis is mainly presumptive and clinical. Anti-basal ganglia antibodies, antistreptolysin-O titre, throat culture and erythrocyte sedimentation ratio helps in diagnosis. Neuroimaging may be helpful in some patients. In a study of Sydenham’s chorea patients 3 out of 19 had alteration in caudate nucleus on Magnetic resonance imaging (MRI). Other causes of chorea such as Wilson’s disease, drugs, systemic lupus erythematosus and benign hereditary chorea should be ruled out. In majority of the patients penicillin prophylaxis is recommended.

### Chorea Gravidarum

Chorea occurring during pregnancy is known as chorea gravidarum. Many such patients have previous history of Sydenham’s chorea also. Other conditions such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APLS), Syphilis and encephalitis have been associated with chorea gravidarum. There have been association with use of oral contraceptive pills (OCP) also. Patients should also be investigated for collagen disorders and management includes stoppage of oral contraceptive pills. Clinical symptoms usually develop in first trimester and majority of the patients have remission after delivery.

*Drugs causing chorea:* There are many drugs which may cause chorea (Table 3). Drug induced chorea may be seen during acute phase of treatment or may appear after some time. Antiparkinsonian and anti epileptic drugs are most important causes of chorea. Levodopa induced chorea is most common cause of chorea in adults. Treatment includes withdrawal of the offending drug. It may take days to months before patient is free from symptoms. In difficult cases drugs like tetrabenazine has been tried.

*Metabolic chorea:* Hyperthyroidism, hypoglycaemia, chronic acquired hepatolenticular degeneration and renal failure may manifest as chorea. Transitory chorea may be seen in hyperosmolar hyperglycaemia and hyponatremia. Majority of the patients recover after correction of underlying metabolic abnormality.

*Vascular chorea:* Another important cause of chorea in middle age group and elderly is stroke. But chorea is usually unilateral in this setting. Most common site of insult is subcortical; predominantly in basal ganglion, caudate, thalamus, and subthalamic nucleus. Chorea is also seen in approximately 1% patients of polycythemia vera. Pathophysiology includes chronic hyperviscosity leading to hypoxia and ischemia of basal ganglia region. Patients may require repeated venesection.

*Infective causes:* Most common infectious causes of chorea are human immunodeficiency virus and opportunistic infections associated with it. Lymphoma, toxoplasma, progressive multifocal leukoencephalopathy and tuberculosis are most common. Rarely tuberculosis and neurocysticercosis may involve caudate nucleus and may lead to chorea in immunocompetent persons.

### Senile Chorea

Sporadic chorea with onset after 50 years of age is termed as senile chorea. Its exact pathogenesis is not clear. Causes of senile chorea include drugs, stroke, metabolic and genetic.
correlated with caudate atrophy and inter caudate atrophy on progression and neuroimaging in selected patients. Caudate atrophy is a consistent finding in HD patients on neuroimaging. Progression of disease can be monitored by using unified Huntington disease rating scale. Many experimental drugs like creatine, minocycline and lithium have been tried. Different genetic animal models (mouse, drosophila and caenorhabditis elegans) have been used for development of drugs which may be quite effective.

**Treatment**

Chorea does not require treatment if it is mild. But many times patients and their family members seek treatment because of cosmetic reasons. Most of the drug studies have been done on Huntington’s disease patients. Neuroleptic drugs were first to be used but they carry significant extrapyramidal side effects in form of parkinsonian features, so they are least preferred. Nongenetic causes of chorea which are secondary to infection, metabolic disorders and drugs respond to the treatment of underlying cause. Sydenham’s chorea is usually treated by sodium valproate in a dosage starting from 250 mg/day and gradually increasing to 250 mg three times a day. A maximum dosage of 1500 mg/day has also been tried. Other alternatives are carbamazepine, haloperidol, risperidone and pimozide. Steroids have also been tried but its use remains controversial.

Treatment of HD is mainly symptomatic. For chorea most potent drug is Tetrabenazine which has been found to be quite effective. Behavioural symptoms may be treated with antidepressants and anxiolytics. For psychotic symptoms atypical neuroleptics are preferred. Surgical treatments like pallidotomy and deep brain stimulation have been tried. Progression of disease can be monitored by using unified Huntington disease rating scale. Many experimental drugs like creatine, minocycline and lithium have been tried. Different genetic animal models (mouse, drosophila and caenorhabditis elegans) have been used for development of drugs which may be effective in preclinical stage and may prevent further progression of the disease. YAC 72 and YAC 128 is the most common mouse model used.

Supportive treatments like physical, speech and occupational therapy with adequate nutrition is very important. Patients should be counselled for disability benefits and life planning. Care givers should also be counselled regarding physical and emotional need of the patient.

**Conclusion**

Chorea is an important movement disorder seen in adult and paediatric neurology. Huntington’s disease is most common genetic causes of chorea, whereas Sydenham’s chorea is usually seen in paediatric population, especially in Indian subcontinent. Metabolic disorders like hyperthyroidism, Wilson’s disease and hyperglycaemia are important reversible causes. Many infectious and vascular disorders may also lead to chorea. Treatment is usually symptomatic. More research is needed to understand the pathogenesis of chorea.

**References**


