Inherited Ataxias: An Overview

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Introduction

The hereditary ataxias are a heterogeneous group of diseases. Most attempts at classification have been based on pathologic findings and are not always useful for the clinicians. Many of these disorders are multisystem degeneration in which the underlying biochemical or other defect is usually unknown. The pathophysiology is correspondingly poorly understood. Hereditary ataxia can be divided into the hereditary congenital ataxia, the ataxia linked with metabolic disorder, and early onset ataxia of unknown etiology (1) (Table 1). Primary care physicians should be aware of the differential diagnosis of hereditary ataxia when faced with ataxia of unknown etiology.

Table 1. Classification of Hereditary Ataxia

I. Congenital Cerebellar Ataxia

II. Ataxia associated with metabolic disorders
a. Intermittent ataxia syndromes
b. Progressive unremitting ataxia syndromes
c. Ataxia disorders associated with defective DNA repairs

III. Progressive ataxia disorders of unknown etiology.
a. Early - onset cerebellar ataxia (onset usually before age 20)
b. Late - onset cerebellar ataxia (onset usually after age 20)

Classification

The degenerative cerebellar and spinocerebellar disorders are a complex group of diseases, most of which are genetically determined. Tremendous confusion exists in classifying degenerative disorders causing ataxia, and there is no universally accepted system, these disorders can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset are autosomal recessive, and the later onset ones autosomal dominant (2). Most of these disorders are multisystem degenerations in which the underlying biochemical or other defect is usually unknown; the pathophysiology is correspondingly poorly understood. The differential diagnosis of ataxia is important since some of them are treatable if detected early. The discussion will concentrate on congenital cerebellar ataxia, ataxia associated with metabolic disorders and progressive ataxia of unknown etiology.

I. Congenital Cerebellar Ataxia

Non-progressive rare type of ataxia: Cerebellar dysfunction usually starts in infancy with abnormal motor development, and hypotonic. Other symptoms includes nystagmus, intention tremor, feeding problems, marked truncal ataxia, delay in ability to sit, and stand, and variable degree of mental retardation and spasticity (2). Classification of the congenital cerebellar syndromes are shown in Table 2. The inheritance pattern of the majority of these syndromes are of autosomal recessive, with a 25% recurrence risk to subsequent siblings.

Table 2: Congenital Cerebellar Ataxias

Congenital ataxia with mental retardation and spasticity (includes pontoneocerebellar hypoplasia)
Congenital ataxia + /- mental retardation (includes granule cell hypoplasia)
Congenital ataxia with mental retardation, episodic hypernea, and abnormal eye movements (Joubert's syndrome)
Congenital ataxia with partial aniridia and mental retardation (Gillespie's syndrome)
Dysequilibrium syndrome
X-linked recessive ataxia with mental retardation and spasticity (Paine's syndrome)

II. Ataxia Associated with Metabolic Disorders

Ataxia secondary to metabolic disorder may lead to either persistent progressive ataxia or to intermittent ataxia. The underlying pathophysiology is usually accumulation of neurotoxic substances such as ammonia. (Table 3).

Table 3: Ataxia Associated with Metabolic Disorders

INTERMITTENT ATAXIA SYNDROMES
With hyperammonia
Aminoacidurias
Disorders of pyruvate and lactate metabolism
Progressive Unremitting Ataxic Syndromes
Abeta-and hypobetalipoproteinemia
Isolated vitamin E deficiency
Hexosaminidase deficiency *
Cholestanolosis *
Leukodystrophies * (metachromatic, late-onset globoid cell, adrenoleukomyeloneuropathy)
Mitochondrial encephalomyopathies *
Wilson's disease
Ceroid lipofuscinosis*
Sialidosis
Sphingomyelin storage disorders*
Ataxia Disorders Associated with Defective DNA Repair
Ataxia - telangiectasia
Xeroderma pigmentosum
Cockayne's syndrome

* Ataxia may not be prominent feature.

A. Intermittent Ataxia Syndrome

The hyperammonemias are usually caused by deficiencies of urea cycle enzymes and are of autosomal recessive inheritance, with the exception of ornithine - Transcarbamylase deficiency, which is X-linked. The clinical manifestations include intermittent ataxia, dysarthria, vomiting, headache ptosis, involuntary movements, confusion seiuzures and mental retardation. These episodes are usually precipitated by intercurrent illness and high protein load (3).

Ornithine Transcarbamylase deficiency is the most common urea cycle enzyme deficiency; it is X-linked. Antenatal diagnosis is available for this deficiency and for some of the other hyperammonemias. Protein restriction is the treatment of choice in addition to intravenous fluid administration during acute episodes of neurologic dysfunction. Aminoacidurias usually have similar manifestations as that of the hyperammonemias. Inheritance is autosomal recessive and treatment consists of restricting the intake of branched chain amino acids through special diets (4). Pyruvate dehydrogenase disorders are heterogeneous and rare. When the level of enzyme activity is between 35 and 50% of normal a syndrome of intermittent ataxia and choreathetosis occur during febrile illness and mild cerebellar dysfunction between episodes (5). Severe lactic acidosis occurs when the activity of this enzyme is below 15% of normal (5). A ketogenic diet may slow progression of the disease.

B. Progressive Unremitting Ataxia Syndrome

A number of hereditary metabolic ataxia lead to progressive unremitting syndrome (Table 3). Most of them are autosomal recessive disorders. Abnormal function of apolipoprotein B, the carrier of lipid from the intestinal cells to plasma, lead to Abetalipoproteinemia. The most prominent features of this disease include ataxia, areflexia, loss of vibration and position sense, and pigmentary retinopathy. Symptoms of fat malabsorption are often mild and may be overlooked. Serum cholesterol level is low and serum vitamin E concentrations are low or undetectable from birth and this deficiency may be the cause of neurologic disorders. Onset of symptoms is usually in the second decade of life. Large doses of vitamin E results in improvement or stabilization of symptoms or may prevent the development of neurological symptoms. Retinopathy may be related to deficiency of both vitamins A & E (6).

Isolated cases of vitamin E deficiency with no evidence of hypolipidemia or generalized fat absorption can occur (6). This is caused by a specific defect of vitamin E absorption which is inherited as an autosomal recessive trait. Adequate vitamin E therapy usually halts the progression of neurologic symptoms. Other disorders associated with ataxia include adrenoleukomyeloneuropathy, the sphingomyelin lipidoses (combined with supranuclear gaze palsy and dementia), metachromatic leukodystrophy, galactosylceramide lipidoses (Krabbe's disease), and the hexominidase deficiencies (7). A rare autosomal recessive disorder in cholestanolosis is caused by defective bile salt metabolism. This disease is characterized by ataxia, dementia, spasticity, peripheral neuropathy, cataract, and xanthomas in the second decade of life. Neurological function usually improves with treatment with chenodeoxycholic acid (8). Mitochondrial myopathies consist of various phenotypes with late onset ataxic disorders associated with such features as deafness, dementia, ataxia, peripheral neuropathy and myoclonus (9). Ataxia is an important albeit pathognomic finding in the poorly glycosylated glycoprotein syndrome.

C. Ataxia Disorders Associated With DNA Repair

Ataxia - telangiectasia is the most common ataxic disorder associated with defective DNA repair. It is a multisystem, autosomal recessive disorder. It usually starts with recurrent sinopulmonary infections. Telangiectasis appear on the skin between 3 & 6 years. Ataxia is truncal and is progressive. Other symptoms include dysarthria, tremor, ophthalmologic and insulin resistance. Immunologic abnormalities include reduced level of secretary IgA serum IgE and abnormalities in cellular immunity. The cause of death is usually recurrent infections or malignant tumors. Helpful diagnostic clues are elevation of serum and fetoproteins (10).

A heterogenous disorder consisting of at least six genetically distinct autosomal recessive diseases is Xeroderma Pigmentosum. It is caused by reduced capacity to perform excision repair of DNA damaged by ultraviolet light and of some carcinoembryonic antigen. The disorders manifest mainly with skin photosensitivity, skin diseases malignancies and in three forms of the disease neurologic dysfunction occurs (11). In about half of the patients with neurologic disease, ataxia and hyporeflexia occur with mental retardation, deafness, involuntary movements and spasticity being more common.

III. Progressive Ataxia Disorders of Unknown Etiology

These can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset disorders are autosomal recessive, and the later onset ones autosomal dominant (2).

A. Early Onset Cerebellar Ataxia

Friedreich's ataxia (FA)

Friedreich's ataxia is the most common of the early onset ataxia. It is one of the best defined and most common forms of hereditary ataxias of unknown etiology(1,2). In some large case series it comprises about 50% of the hereditary ataxia (2,12). It is transmitted in an autosomal recessive manner, and usually appearing in childhood or in adolescence but rarely in old age (13). The disease usually progresses slowly without remission, affecting both the central and peripheral nervous system (13-14). The most frequent first symptom is ataxia of gait.

The epidemiology of Friedreich's ataxia is perplexing. The clinical features and diagnostic criteria were defined by the Quebec Cooperative Study of Friedreich's Ataxia (QCSFA) (15) and by Harding (1,2) (Table 4). Both authors regarded recessive inheritance, progressive ataxia of limbs and gait and lower limb areflexia as obligatory criteria. The onset, according to the QCSFA and Harding (2, 15), should never occur after the age of 20 years, and always before 25, according to Harding (2). A recent case was reported in the literature where symptoms started at a later stage (16). Dysarthria, decreased lower limb deep sensation and weakness, obligatory signs for the QCSFA, are not considered essential for an early diagnosis by Harding (2). The diagnosis is made essentially on clinical grounds, CT scan of the brain may show mild cerebellar atrophy.

The prevalence is known only for some populations (12, 17-20). The range is from 0.6 to 1.4/100,000 population. The incidence has been estimated to be approximately 1-2/100,000 (17, 21).

Friedreich's ataxia is characterized by degeneration of the spinocerebellar pathways, the dorsolateral columns, and the dentate nuclei (1). There are few changes in the cerebellar cortex itself (1). The cerebrospinal fluid is usually normal and the CT scan of the brain is either normal or shows mild cerebellar atrophy. The primary clinical signs include ataxia, most marked in the lower limbs and often accompanied by dysarthria; nystagmus is usually present in 70% along with skeletal-muscle weakness (22). Optic atrophy and retinal pigmentation is usually present. Pes cavus and scoliosis almost always develop (23). Death is usually sudden and may be secondary to cardiac arrythmias (22). Cardiac involvement is frequent occurring in some 50% to 90% of cases (24); most commonly concentric hypertrophic cardiomyopathy is found (24,25).

Multiple studies have shown that the small coronary arteries are abnormal in patients who have cardiac disease and Friedreich's ataxia (26,27). The functional significance of this has been chal-

Table 4: Friedreich's Ataxia : Diagnostic Criteria

Essential Criteria for Diagnosis: Present in More than 95% of Cases
Autosomal recessive inheritance
Age at onset of symptoms before 25 years
Progressive limb and gate ataxia
Absent knee and ankle jerks
Extensor plantar responses
Motor nerve conduction velocity > 40m/s in upper limbs
Small or undetectable sensory action potentials Additional Criteria, Not Essential for Diagnosis: Present in More than 65% of Cases
Dysarthria*
Pyramidal weakness of lower limbs
Absent reflexes in upper limbs*
Distal loss of joint position and vibration sense in lower limbs*
Scoliosis
Abnormal electrocardiogram
Other Features Present in 50% of cases or less
Nystagmus
Optic atrophy
Deafness
Distal weakness and wasting
Pes cavus
Diabetes

lenged by Hewer (26). Biller et al. (27) reported a prevalence of 1.5% of cerebral infarction in 131 patients. It occurred in half of the patients who developed atrial fibrillation or atrial flutter with underlying symptomatic cardiomyopathy (27). Speech disorder is common in FA (28).

Electrophysiological and pathological studies suggest that axon degeneration and secondary demyelination occur in peripheral sensory nerves (29).

Electrophysiological evaluation of FA patients usually includes determination of motor and sensory conduction velocities (MCV, SCV) and multimodal evoked potentials (30). The degeneration of peripheral sensory and somatosensory pathway is usually measured by using nerve conduction studies and somatosensory evoked potential (SEPs) and brain-stem auditory evoked potentials (BAEPs) and the blink reflex (30).

Biochemical alterations observed in this disease include a reduced insulin receptor activity which leads to an insulin resistance state and a reduced glucose tolerance in about 40% of patients (31). Several lipid abnormalities have been noted as well, including a striking reduction in linoleic acid (32), low cholesterol levels with a total cholesterol reduction in serum and in the LDL and HDL fractions are described (32).

The results of therapeutic trials in Friedreich's ataxia with a number of drugs, including choline chloride, lecithine, physostigmine, y-vinyl aminobutyric acid, 5-hydroxytrptophan, benserazide,and thyrotropin releasing hormone, have been inconsistent or unconfirmed in terms of producing functional neurologic improvement.(2)

Amantadine hydrochloride (AH) is known to stimulate dopamine release (33). The use of AH in FA and OPCA was recently tested (34). Both studies revealed an improvement in reaction time (RT) and movement time (MT).

So there is no treatment known to influence the slowly deteriorating disease course. In order to minimize disability and prolong ambulation, strengthening and stretching exercises and functional retraining including aerobic endurance exercise are recommended (35).

Early - Onset Cerebellar ataxia with Retained Tendon Reflexes

The other early onset ataxia are listed in Table (5) . They are usually rare, with the exception of early onset cerebellar ataxia with retained reflexes, which occurs at a frequency about one quarter of that of FA, and is often confused with it, but is genetically distinct. The main clinical difference is that the tendon reflexes are normal or brisk in the disorder(36). It is important to distinguish between these two disorders, since the prognosis is better in the former, with patients losing the ability to walk on average 13 years later than in FA. In addition, severe skeletal deformity, heart disease, and diabetes do not occur (37).

Cerebellar Ataxia with Hypogonadism

The association of progressive ataxia with hypogonadotrophic hypogonadism is rare (2). Neurological symptoms usually develop in the third decade and hypogonadism is obvious at puberty. Neurological syndromes include dysarthria, nystagmus, progressive limb and gait ataxia, mental retardation, dementia deafness, choreoathetosis, retinopathy and sensory loss.

Table 5: Early-Onset Ataxic Disorders of Unknown Etiology

Friedreich's ataxia
Early-onset cerebellar ataxia with
Hypogonadism
Myoclonus (idiopathic Ramsay Hunt syndrome, progressive myoclonic ataxia)
Pigmentary retinopathy
optic atrophy + or - mental retardation
cataract and mental retardation (Marinesco-Sjogren syndrome)
Deafness
Extrapyramidal features
X-linked recessive spinocerebellar ataxia

Table 6: Late-Onset Ataxic Disorders Of Unknown Etiology

Autosomal dominant cerebellar ataxia (ADCA) with
Ophthalmoplegia, dementia, optic atrophy, extrapyramidal features and amyotrophy may include
Machado- Joseph disease)
(ADCA type I)
ADCA with pigmentary retinopathy +/- Ophthalmoplegia and extrapyramidal features (ADCA type II)
Pure ADCA of later onset (after age 50) (ADCA type III)
Periodic ADCA
Other syndromes

Cerebellar Ataxia with myoclonus

The association of cerebellar ataxia and myoclonus, is often referred to as the Ramsay Hunt syndrome. This is a very heterogenous entity. Some of the identifiable causes include Baltic myoclonus, mitochondreal encephalomyopathy, and sialidosis (37). The rest of cases can be labelled as progressive myoclonic ataxia (37). Symptoms include the development of stimulus - sensitive myoclonus or generalized seizures at the end of the first decade of life. Ataxia and dysarthia develop a few years later with pyramidal signs in the limb. The myoclonic part of this syndrome may respond to clonazepan or valproate sodium with marked improvement in motor function.

B. Late Onset Cerebellar Ataxia

These disorders have proved the most difficult and controversial in terms of classification (Table 6). The pathological findings are heterogenous reflecting huge clinical variations in the dominant ataxia (2).

Autosomal Dominant Cerebellar Ataxia Type I (ADCA Type I).

The age of onset of symptoms in this syndrome ranges from 15 to 65 years but is most commonly in the third or fourth decade of life. Ataxia of gait is the most frequent presenting symptom; it usually involves the limbs and is invariably associated with dysarthria. Early onset usually predicts more progressive disability (38). Associated symptoms may include ophthalmoplegia, nystagmus, lid retraction and optic atrophy. Bulbar symptoms are common during the later stages of disorder and predispose the patient to respiratory infection. Other common symptoms include dementia, extrapyramidal signs, wasting and fasiculation of the face and tongue.

Autosomal dominant cerebellar ataxia Type II (ADCA Type II).

This is clinically and genetically different from ADCA type I. It is characterized in all families having retinopathy. The age at onset is earlier than that of ADCA type I, most commonly occurring between 15 and 35 (2,39).

Autosomal Dominant Cerebellar Ataxia Type III

This is relatively pure cerebellar syndrome in which dementia, ocular or extrapyramidal features do not occur and onset of symptoms are usually after the age of 50 years(3). Nystagmus and pyramidal signs in the limbs are quite common.

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