Ataxias: Pathogenesis, Types, Causes and Treatment

Ataksiler: Patogenez, Tipleri, Nedenleri ve Tedavisi

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Abstract

Ataxia refers to incoordination in voluntary movements and abnormal postural control. There are many different statements concerning the definition, scope and terminology of ataxia. Different clinical findings, exposure to different neurological structures and several causes play a role in the formation of each ataxia type. In most cases, there is no cure for ataxia and a supportive treatment is necessary to control the symptoms. Ataxia usually results from a damage to the cerebellum and its connections such as the vestibular, proprioceptive and visual systems. Clinically, ataxias can be subdivided into cerebellar, vestibular, sensory, frontal, optic, visual, mixed ataxia and ataxic-hemiparesis. Etiologically, ataxias may be divided into hereditary ataxias, sporadic degenerative ataxias and acquired ataxias. Genetic forms of ataxia must be distinguished from the acquired ataxias including chronic alcohol use, cerebrovascular disorders, various toxic agents, immune-mediated inflammation, vitamin deficiencies, and chronic central nervous system infections. After the treatment of identified acquired causes, since ataxia is usually resistant to medical treatments, the management is supportive but may involve physical, occupational, and speech therapy.

Keywords: Ataxia, Causes, Pathogenesis, Types of Ataxia, Treatment

Öz

Ataksi istemli hareketlerde inkoordinasyon ve anormal postüral kontrol anlamına gelir. Ataksinin tanımına, kapsamına ve terminolojisine ilişkin birçok farklı ifade vardır. Farklı klinik bulgular, farklı nörolojik yapıların etkilenmesi ve birçok neden her bir ataksi tipinin ortaya çıkmasında rol oynar. Olguların çoğunda ataksinin tedavisi yoktur ve semptomları kontrol etmek için destek tedavisi gereklidir. Ataksi sıklıkla serebellum ve vestibüler, proprioseptif ve görsel sistemler gibi sistemlerle bağlantılarının hasarından kaynaklanır. Ataksiler klinik olarak serebellar, vestibüler, duyusal, frontal, optik, görsel, mikst tip ataksi ve ataksik – hemiparezi şeklinde alt gruplara ayrılabilir. Ataksiler etyolojik olarak herediter ataksiler, sporadik dejeneratif ataksiler ve edinilmiş ataksiler olarak gruplanabilir. Ataksilerin genetik formları mutlaka kronik alkol kullanımı, serebrovasküler hastalıklar, çeşitli toksik ajanlar, immun – aracılıklı inflamasyon, vitamin eksiklikleri ve kronik santral sinir sistemi enfeksiyonlarını içeren edinilmiş ataksilerden ayırt edilmelidir. Ataksi sıklıkla medikal tedavilere dirençli olduğu için, saptanan edinilmiş nedenlerin tedavisinden sonraki tedavi destek tedavisidir fakat fiziksel, mesleki ve konuşma terapilerini içerebilir.

Anahtar Kelimeler: Ataksi, Ataksi Tipleri, Nedenleri, Patogenez, Tedavi

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Introduction

The word ataxia is derived from Greek roots ("a-" a negative prefix and "taxia" to put in order), that means "without order." In a medical sense, it refers to lack of coordination and insufficient postural control. It is a non-specific clinical manifestation implying dysfunction of the cerebellum and/or its connections such as the proprioceptive, visual, vestibular systems and interconnections of these systems. Several different possible causes exist for these patterns of neurological dysfunction (1, 2). In this review, the neuroanatomic basis, types, causes, and treatment of ataxia are discussed in the light of the literature.

The articles and abstracts for this review were found by searching in Medline/Pubmed. A Medline literature search was conducted with the terms "ataxia and pathogenesis", "types of ataxia" , "cerebellar ataxia", "vestibular ataxia", "causes of ataxia", and "treatment of ataxia". Additional articles were obtained from the reference lists of retrieved articles. All journal articles reviewed were written in English.

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Pathogenesis

Ataxia describes a lack of muscle coordination during voluntary movements and inadequate postural control. Ataxia usually results from a damage to the cerebellum and its connections. The cerebellum plays a major role in establishing balance and coordination. Based on the information from the vestibular, visual, somatosensory systems and cerebral cortex, the cerebellum establishes postural control, coordinated and balanced movement by making the appropriate adjustments. The vestibulocerebellum accomplishes eye movements and balance through vestibuloocular, vestibulospinal and reticulospinal tracts by modulating the information in the vestibular and the reticular nuclei. The spinocerebellum receives proprioceptive sensory inputs from the periphery, and regulates body and limb movements, and contributes to locomotion, balance and tonus. The cerebrocerebellum is interconnected with the cerebral cortex, and it is involved in planning movements and evaluating sensory information for action, enabling fine, coordinated distal movement. On the other hand, the cerebrocerebellum participates not only in motor control, but also in emotion and cognition. So, the cerebellum is involved in maintenance of balance and posture, control of eye movements, planning and execution of coordinated limb movements, adjustments of motor performance, learning new motor tasks,

cognitive functions and neuroimmunomodulation. The lesion on the cerebellum and/or its connections causes ataxia, abnormal eye movements, dysmetria, dyssynergia, dysarthria, tremor, hypotonia, prolonged reaction time, and cognitive impairment called as "dysmetria of thought" (2-5).

Types of Ataxia

Ataxia can result from damage to the cerebellum, proprioceptive, vestibular and visual systems, and/or any interconnections of these systems. Although there is no consensus on classification of ataxias in literature, based on involvement of system, types of ataxias are classified as below:

1. Cerebellar ataxia
2. Vestibular ataxia
3. Sensory ataxia
4. Frontal ataxia
5. Ataxic-hemiparesis
6. Optic ataxia
7. Visual ataxia
8. Mixed ataxia

Cerebellar Ataxia

The term cerebellar ataxia is used to indicate ataxia due to dysfunction of the cerebellum. Cerebellar dysfunctions are characterized by ataxia, hypotonia, asynergy, dysmetria, dyschronometria, nystagmus, dysdiadochokinesia, tremor, and cognitive dysfunction. How and where these abnormalities manifest themselves depends on which cerebellar structures, such as vestibulocerebellum, spinocerebellum or cerebrocerebellum, have been damaged (Table 1) (6).

Table 1. Signs and lesion localization in cerebellar disorders

Cerebellar lesion	Signs
Archicerebellum Posterior (flocculo-nodular lobe)	Eye movement disorders, nystagmus, vestibulo-ocular reflex (VOR) dysfunction, postural and gait dysfunction
Paleocerebellum Midline (vermis)	Truncal and gait ataxia
Neocerebellum Hemispheres	Limb ataxia: dysmetria, dysdiadochokinesis, intention tremor, dysarthria, hypotonia

Dysfunction of the vestibulocerebellum (flocculonodular lobe) is characterized by vertigo, imbalance and abnormal eye movements. This presents itself with postural instability in order to gain a wider base. Therefore, instability is worsened when standing with the feet together, regardless of whether the eyes are open or closed. Some eye movement abnormalities such as gaze-evoked nystagmus, rebound nystagmus, ocular dysmetria, inability to suppress the vestibulo-ocular reflex and abnormalities of optokinetic nystagmus are also noticed (7). Dysfunction of the spinocerebellum (vermis and paravermis) presents itself with a wide-based "drunken sailor" gait called as truncal ataxia, characterized by uncertain starts and stops, lateral deviations, and unequal steps, and gait ataxia (8). Dysfunction of the cerebrocerebellum presents as disturbances in carrying out voluntary, planned movements by the extremities. These include: intentional tremor, writing abnormalities, dysarthria, dysmetria, abnormality in alternating movements, loss of the check reflex, and hypotonia. Intention tremor is a kinetic tremor characterized by a broad, course, and low frequency (below 5 Hz) tremor. The amplitude of an intention tremor increases as an extremity approaches the endpoint of deliberate and visually guided movement. Intention tremor is the result of dysfunction of the lateral zone of the cerebellum, and superior cerebellar peduncle. Intention tremors can also be seen as a result of damage to the brainstem or thalamus. Depending on the location of cerebellar damage, these tremors can be either unilateral or bilateral. Kinetic and postural tremors or titubations also occur in cerebellar diseases. There are also writing abnormalities in cerebellar ataxia characterized by large, unequal letters, and irregular underlining. Cerebellar dysarthria is characterized by slurred, monotonous or scanning speech. Dysmetria is inability to judge distances or ranges of movement, as undershooting (hypometria), or overshooting (hypermetria), the required distance or range to reach a target. Decomposition of alternating movements known as asynergia or dyssynergia refers to errors in the sequence and speed of the component parts of a movement. Dysdiadochokinesia can involve rapid switching from pronation to supination of the forearm. Bradyteleokinesia describes terminal slowing while reaching the target. The rebound phenomenon is also sometimes seen in patients with cerebellar ataxia. Hypotonia and hyporeflexia, pendular tendon reflexes are also seen in acute cerebellar lesion (2,6,8).

Vestibular Ataxia

Vestibular ataxia develops as a result of vestibular dysfunction. Its clinical aspect depens on the speed with which lesion develops, the extend of the lesion such as unilateral or bilateral, and the degree of vestibular compensation. Vestibular dysfunction due to acute-onset unilateral lesion is characterized by prominent vertigo, nausea, vomiting, blurred vision and nystagmus. In slow-onset, chronic bilateral cases of vestibular dysfunction, these manifestations may be absent, and dysequilibrium may be the sole presentation (6). Vestibular ataxia produces prominent difficulties with gait and balance reactions in sitting and

standing. The sudden onset of vertigo may be associated with an inability to walk or even to stand. The patient tends to stagger when walking, has a broad base support and may lean backwards or towards the side of the lesion. Head and trunk motion and subsequently arm motion are often decreased because of vertigo (9). Balance in vestibular ataxia is disrupted when performing a head or eye movement. Ataxia may be triggered by asking them to rotate the head from side to side while walking. The ability to balance on one foot or walk in tandem with the eyes open or closed may also be impaired (10). In addition, patients with vestibular dysfunction depend heavily on visual information, so closing the eyes accentuates the gait disorder. Since the vestibular ataxia is gravity-dependent, incoordination of limb movements cannot be demonstrated when the patient is examined lying down but becomes apparent when the patient attempts to stand or walk. Extremity ataxia is by no means observed in vestibular ataxia (11).

Vestibular dysfunction also includes spontaneous or positional nystagmus, robotic gait, ataxia with head movement, and difficulty in balancing on one foot or on a complaint surface with the eyes closed. Nystagmus is frequently present in unilateral peripheral vestibular lesion, typically unidirectional, and mostly pronounced on gaze away from the side of vestibular involvement. The head-shaking nystagmus is also a useful finding to identify patients having unilateral vestibular hypofunction. The head-thrust test is positive for peripheral vestibular disorders. Dix-Hallpike test is important, particularly when evaluating paroxysmal positional vertigo. Central vestibular disorders also lead to deficits in the conjugation of eye movements, saccadic pursuit and horizontal optokinetic abnormalities, central spontaneous or positional nystagmus, failure of fixation suppression, slowing of the nystagmus fast phases, a slowing down of the nystagmus slow phases, perverted nystagmus, vertical optokinetic abnormalities, and retraction nystagmus (Table 2). On the other hand, deep tendon reflexes are considered normal, and Romberg test is also negative in vestibular disorders (12).

Vestibular ataxia can develop due to central vestibular lesions such as medullar stroke (Wallenberg's syndrome), migraine, and multiple sclerosis; and peripheral vestibular diseases such as Meniere's disease, benign paroxysmal positional vertigo, or vestibular neuronitis (1).

Sensory Ataxia

The term sensory ataxia indicates ataxia due to loss of proprioception, the loss of sensitivity to the positions of joint and body parts. This is generally caused by dysfunction of the posterior columns of the spinal cord. In some cases, the cause of sensory ataxia may be dysfunction of the cerebellum, thalamus, parietal lobes, and sensory peripheral nerves (1,13).

Sensory ataxia presents itself with an unsteady "stomping" gait with heavy heel strikes, as well as a postural instability that is usually worsened when the lack of proprioceptive input cannot be compensated for visual input. In patients with sensory ataxia, they usually complain of loss of balance in the dark. When their eyes are closed, instability is worsened markedly, producing wide oscillations and possibly a fall (positive Romberg's test). Worsening of the finger-pointing test with the eyes closed is another feature of sensory ataxia. Also, when the patient is standing with arms and hands extended toward the physician, if the eyes are closed, the patient's finger will tend to "fall down" and then be restored to the horizontal extended position by sudden muscular contractions, it is called ataxic hand (2,3). Sensory ataxia is distinguished from cerebellar ataxia by the presence of near-normal coordination, and marked worsening of coordination when the eyes are closed. On the other hand, sensory ataxia also lacks the associated features of cerebellar ataxia such as pendular reflexes, cerebellar dysarthria, nystagmus and abnormal pursuit/saccadic eye movements (14).

Table 2. Differential diagnosis of central and peripheral vestibular disorders

	Central	**Peripheral**
Nausea	None/mild	Severe
Movement illusion	Less prominent	More prominent
Worse with head movement	No	Yes
Nystagmus	Changes direction in different gaze positions	Unidirectional in all gazes
Suppression with OF	No or minimal	Yes
Neurologic signs	Common	Rare
Imbalance	Severe	Mild to moderate
Oscillopsia	Severe	Mild
Head thrust test	(-)	(+)
Localization	Medulla, pons, cerebellum	Labyrinth, vestibular nerve
Recovery	Months or longer	Days to weeks

OF: optic fixation

Frontal Ataxia

Frontal ataxia is also called as gait apraxia, and is observed in frontal lobe lesions such as tumors, abscesses, cerebrovascular disorders and normal pressure hydrocephalus. Patients with frontal ataxia have a difficulty in erect position. A wide stance base, increased body sway and falls, the loss of

control of truncal motion, locomotor disability with gait ignition failure, start hesitation, shuffling, small steps, and freezing are also encountered in frontal ataxia. Even with the use of support, a patient tends to lean towards hyperextension. Typically, the patients with frontal ataxia tend to slide their foot along the floor instead of lifting and placing normally. This has been called a “glue-footed" or "magnetic" gait. Patient's legs are in scissors-cross position during walking and there is incoordination between the legs and trunk. Frontal ataxia is generally accompanied by dementia, urinary incontinence, and frontal release signs such as grasp, snout, palmomental and glabellar responses (1,15).

Typically, normal pressure hydrocephalus is characterized by frontal gait disturbance, dementia and/or urinary incontinence, and ventricular enlargement. Broad-based, short-step, magnetic gait with start hesitation and increased instability on turning, which is often called as apraxic/ataxic gait, are the cardinal signs of normal pressure hydrocephalus. The cerebrospinal fluid tap test is a major diagnostic measure because of the simplicity and less invasiveness. The programmable valves at shunt surgeries are used in the treatment of normal pressure hydrocephalus (16).

In differential diagnosis of frontal ataxia; the slowness of walking, lack of upper limb ataxia, dysarthria or nystagmus distinguishes the wide stance base from cerebellar ataxia. A lively facial expression, normal voluntary movements of the upper limbs, upper motor neuron signs, and the absence of a rest tremor distinguish from Parkinson's disease (17).

Ataxic-hemiparesis

Ataxic-hemiparesis is a well-known clinical syndrome involving homolateral ataxia with accompanying corticospinal tract impairment. Typically, ataxia is a much more bothersome symptom than the weakness in the affected arm or leg. The face is not usually involved. Since the fronto-ponto-cerebellar fibers may originate from the frontal cortex, including the precentral gyrus, probably near the cortico-spinal tract, damage at this location may cause ataxic- hemiparesis. Although ataxic- hemiparesis is mainly caused by the pontine or internal capsule/corona radiata lesions, it also occurs in the midbrain, diencephalic-mesencephalic junction, thalamus, parietal lobe, and the precentral gyrus lesions. Ischemic infarct is the most frequent cause of the syndrome, but hemorrhagic, neoplastic and demyelinating disorders have also been reported (18,19).

Optic Ataxia

Optic ataxia usually follows damage to the posterior parietal cortex, and is the inability to conduct meaningful movements or movements on command in the absence of paralysis or other sensory and cerebellar impairments. Optic ataxia occurs when the patient has a deficit in reaching under visual guidance that can not be explained by cerebellar, motor, somatosensory, visual field defects or acuity deficits. Patients with optic ataxia produce inaccurate reaching movements towards a target or object in space, this is especially true with their contralesional hand. Grasping of objects is also impaired in cases with optic ataxia. The lesion also impairs the ability to accurately shape the hand according to the objects configuration, and therefore produces a severe deficit in grasping or manipulating tools (20).

Optic ataxia is a common symptom in Balint's syndrome. This syndrome includes the clinical symptom triad of simultanagnosia, ocular apraxia and optic ataxia. These symptoms, visual disorientation or simultanagnosia; ocular apraxia, which is a deficit of visual scanning; or optic ataxia, an impairment of pointing and reaching under visual guidance, are rare and can be quite debilitating as they impact visuospatial skills, visual scanning and attentional mechanisms. Bilateral border zone infarction in the occipitoparietal region is the most frequent cause of the complete Balint’s syndrome (20,21).

Visual Ataxia

Visual ataxia is unsteadiness due to visual disturbances. Human being is very dependent on vision for balance and gait. Foveal vision appears to be the most important for this function, but peripheral vision also contributes to balance. The central area of the visual field as compared with the peripheral retina dominates postural control. Visual acuity causes a linearly increasing postural instability. Abnormalities in visual acuity or visual field defects increase body sway, disturbances of equilibrium, and predispose the person to fall down. Hemianopia increases lateral oscillations in patients in the standing position and the projection of the body's centre of gravity shifts towards the hemianopia. People adjusting to new bifocals may feel unsteady or even fall down. Vision may also be affected by abnormalities of eye movements. Limitation of eye movements, particularly downward movement, diplopia or ossilopsia can cause ataxia and falls. On the other hand, multisensory disequilibrium occurs with deficits in multiple sensory systems such as visual, vestibular, and proprioceptive (22,23).

Mixed Ataxia

Mixed ataxia occurs when the symptoms of two or more types of ataxia such as the occurence of symptoms of sensory and cerebellar ataxia, are

observed together. All types of ataxia can have overlapping causes, and therefore can coexist. In some neurologic diseases, mixed ataxia may be observed frequently. For instance, cerebellar, vestibular and sensory ataxia may be observed together in multiple sclerosis, whereas in cases of spino-cerebellar ataxias, cerebellar and sensory ataxia may be seen together. Frontal, vestibular and cerebellar ataxia can also be coexisted in some degenerative neurologic disorders such as multiple system atrophy. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) is also a mixed ataxia syndrome (24).

Causes of Ataxia

As summarized in Table 3, the age of onset, the course of illness and the degree of permanence of ataxia must be considered in the diagnosis of ataxic disorders.

Table 3. Selected ataxias according to the course of illness and age of onset

1. Congenital nonprogressive ataxias	
• Ataxic cerebral palsy	infancy
• Congenital inherited ataxias	infancy
2. Acute-onset ataxias	
• Cerebellar hemorrhage	usually adult
• Cerebellar infarction	usually adult
• Migraine	children / young adult
• Toxin and drugs	any
3. Subacut-onset ataxias	
• Disseminated encephalomyelitis	children / adult
• Post viral/vaccinal cerebellitis	children
• Paraneoplastic cerebellar degeneration	adult
• Multiple sclerosis	young adult
• Posterior fossa tumors	any
• Hydrocephalus	any
• Miller-Fisher syndrome	children / young adult
4. Chronic progressive ataxias	
Inherited ataxias	
• Autosomal recessive (Friedreich's ataxia)	usually before the age of 15
• Autosomal dominant (36 types)	usually over the age of 20
• Idiopathic degenerative ataxias	adult / old
• Craniocervical junction disorders	adult
• Paraneoplastic cerebellar degeneration	adult
• Alcoholic cerebellar degeneration	adult
• Vitamin E deficiency	any
• Hypothyroidism	any
• Primary progressive multiple sclerosis	young adult
• Hydrocephalus	any
5. Episodic ataxias	
• Transient ischemic attacks	adult
• Multiple sclerosis	young adult
• Autosomal dominant periodic ataxias (7 types)	before the age of 20
• Inherited metabolic ataxias	usually infancy
• Toxins and drugs	any
• Foramen magnum compression	old

Congenital nonprogressive ataxia occurs early in life, is truly nonprogressive, i.e. the symptoms are not worsened gradually. Motor development is usually delayed in these cases, and the associated mental retardation is common. They are the results of prenatal or perinatal trauma, arrested hydrocephalus, and other genetic and nongenetic disorders of the cerebellum. Acute onset ataxia is usually due to cerebellar hemorrhage and cerebellar infarction. Diagnosis should be made as a matter of urgency by CT or MRI. Viral or postinfectious cerebellitis causes a subacute onset gait and limb ataxia, dysarthria, and pyrexia developing over hours or days in children or young adults. Paraneoplastic cerebellar syndromes related to neuroblastoma in children, and lung or overian carcinoma in adults are also characterized by subacute ataxia, dysarthria, nystagmus, opsoclonus, and myoclonus. Other causes of subacute ataxia include hydrocephalus, foramen magnum compression, posterior fossa tumors, abscess, multiple sclerosis, toxins and drugs. The Miller-Fisher syndrome also includes subacute ataxia, ophthalmoplegia, and areflexia. The anti-GQ1b IgG antibody titer is most commonly elevated in Miller-Fisher syndrome (21).

Chronic progressive ataxias are generally associated with inherited degenerative disorders. On the other hand, chronic alcoholism, some of drugs and toxic agents, chronic rubella panencephalitis, Creutzfeldt-Jacob disease, severe vitamin E deficiency, primary progressive multiple sclerosis, hypothyroidism, paraneoplastic cerebellar degeneration are also presented as ataxia with chronic progressive course. Chronic alcoholism is one of the most common causes of cerebellar degeneration in adults (25).

Episodic ataxias can be usually caused by drug ingestion, transient vertebrobasilar ischemic attacks, multiple sclerosis, foramen magnum compression, colloid cyst, inherited periodic ataxias, and metabolic disorders such as mitochondrial encephalopathies, aminoacidurias, and Leigh's syndrome. The spells of ataxia in metabolic disorders may be precipitated by infection or diet, and may also be associated with lethargy, vomiting and seizures. Blood ammonia, pyruvate, lactate and amino acids are screening tests for metabolic disorders (Table 4) (26).

Cerebellar ataxia can be hereditary or non-hereditary. Non-hereditary cerebellar ataxia is known as sporadic cerebellar ataxia. The genetic forms of ataxia are diagnosed by family history, physical examination, neuroimaging, and molecular genetic testing. There are four ways of inheriting this genetic disease; a) Autosomal dominant inheritance: A faulty gene is inherited from only one parent.

Table 4. Common causes of ataxia

1.	Vascular	Ischemic and hemorrhagic stroke, migraine, frontal gait disorder of the elderly
2.	Inflammatory/infectious	Multiple sclerosis, sarcoidosis, systemic lupus erythematosus, Behçet's disease, Susac syndrome, cerebellitis, intracranial complications of suppurative otitis, HIV, Creutzfeld t-Jacob disease, progressive multifocal leucoencephalopathy, brainstem encephalitis, Guillain-Barre syndrome, Miller-Fisher syndrome, autoimmune ataxia with anti-GAD antibodies, lyme disease
3.	Neoplastic	Primary or secondary posterior fossa tumors, paraneoplastic cerebellar degeneration
4.	Craniocervical junction disorders	Chiari malformation,basilar impression,syringobulbia
5.	Hereditary	Autosomal recessive (Friedreich ataxia), dominant (36 types of spinocerebellar ataxias, 7 types of episodic ataxias), sporadic
6.	Metabolic	Wernicke's encephalopathy, vitamin E and B12 deficiency, diabetes mellitus, hypothyroidism, hypoparathyroidism, Wilson's Disease, inherited metabolic ataxias
7.	Toxic	Alcohol, drugs, radiation poisoning, toxins
8.	Degenerative	Progressive supranuclear palsy, multiple system atrophy, normal pressure hydrocephalus
9.	Trauma	Brain contusion, post-concussion syndrome
10.	Psychogenic	Chronic anxiety, panic disorder, phobic postural vertigo, psychogenic gait disorder
11.	Multisensory disturbance	neuropathy, myelopathy, visual loss

Autosomal dominant cerebellar ataxias are also known as spinocerebellar ataxias (SCAs). SCA1 was the first dominant ataxia discovered and SCA36 was discovered in 2011. b) Autosomal recessive inheritance: Parents are carriers. The most common recessive ataxia is Friedreich's ataxia. c) Mitochondrial ataxias: These types of ataxias are usually passed to all children by females. d) X-linked: In this case, only males are affected, while females act as carriers. The most common X-linked form of ataxia is Fragile X tremor ataxia syndrome (25,27).

Hereditary episodic ataxia (EA) is an autosomal dominant disorder characterized by sporadic spells of ataxia with or without myokymia. There are seven types of inherited episodic ataxias that have been recognised so far. There are two common types of episodic ataxia syndrome, called EA1 and EA2. Ataxia can be provoked by stress, startle, or heavy exercise. Some patients with episodic ataxia have progressive cerebellar degenerative disorders, familial hemiplegic migraine, spinocerebellar ataxia, or familial vestibulopathy consisting of episodic vertigo and migraine headache (26,28).

Treatment

The management of ataxia involves a regular review with a multidisciplinary team, which may include neurologists, rehabilitation physicians and therapists. After the correction of identified acquired causes, management is supportive but may include physical, occupational, and speech therapy. Ataxias due to underlying causes such as stroke, multiple sclerosis, hypothyroidism, vitamin E and B12 deficiencies, Wilson's disease, infections and some tumours or exposure to a toxic drug or chemical may be treated. Some cases with ataxia such as hereditary ataxias do not have any specific treatments (29). But the progression of ataxia in some patients has been slowed down by amantadine. On the other hand, it is reported that, in case series, riluzole has several mechanisms of action in patients with degenerative cerebellar ataxia. Riluzole activates calcium-dependent potassium channels, causing inhibition of deep cerebellar nuclei and decreasing cerebellar hyperexcitabililty. The use of riluzole (100 mg/day) received level B recommendations from the European Federation of Neurological Societies (30). Physical therapy applied to increase the strength of muscles plays an important role in the management of ataxia (29).

The patients diagnosed with ataxia due to vitamin E deficiency should be given vitamin E supplements (800 mg daily). This leads to cessation of progression of neurological symptoms and mild improvement in certain patients, especially in the early stages of the disease (31). Wilson's disease is an autosomal recessive inherited disorder of copper metabolism, resulting in accumulation of copper in many organs. The leading neurologic symptoms in Wilson's disease are ataxia, dysathria, and extrapyramidal signs. Symptoms may be fully reversible on treatment with zinc or with copper chelators (32). Ataxia with CoQ10 deficiency observed in children as well as in adults is an apparently autosomal recessive condition with heterogeneous clinical presentations. Patients with

this disorder improve with CoQ10 supplementation in early stage (33). In Friedreich's ataxia, there are damages due to oxidative stress and an accumulation of iron in the mitochondria. Due to these findings, there has been much interest in testing the effect of antioxidants (eg, idebenone), vitamin E and iron chelators (e.g., deferiprone) and drugs that have the potential to increase frataxin levels (34). Gluten ataxia has been recently defined as a sporadic cerebellar ataxia syndrome associated with the presence of antigliadin or endomysium or transglutaminase antibodies, and has been shown in a one-year controlled trial to be responsive to a gluten-free diet (35).

Symptomatic treatment also revolves around managing the co-existing conditions such as muscle cramps, stiffness, tremor, spasticity, dysphagia as well as depression, anxiety, sleep disorders, bowel, bladder, and sexual dysfunction, etc. Baclofen, tizanidine or botulinum toxin are medications for muscle stiffness, spasticity, cramps and pain. On the other hand, in patients with episodic ataxia type 2, symptomatic relief may be obtained by treating with acetazolamide and aminopyridines, and by avoiding triggers such as stress, alcohol and caffeine (26,28). Oscillopsia and abnormal eye movements may be treated using medications such as gabapentin. Depression may be treated using antidepressant medications as well as cognitive behavioral therapy. GABAergic agents such as clonazepam, beta-blockers such as propranolol, or primidone may reduce the prominence of some cerebellar tremors (29). Surgical ablation or deep brain stimulation of the ventral intermediate nucleus of the thalamus may be effective in reducing cerebellar tremor, however, they often do not significantly lessen ataxia, although a few cases have been reported with benefit (25).

Conclusions

Ataxia resulting from damage to the cerebellum and its connections, is described as incoordination and balance dysfunction in movements, and abnormal postural control. Clinically, ataxias can be subdivided into cerebellar, vestibular, sensory, frontal, optic, visual, mixed ataxia and ataxic-hemiparesis. Etiologically, ataxias are being divided into hereditary, sporadic degenerative, and acquired ataxias. Genetic forms of ataxia must be distinguished from the acquired ataxias. After the treatment of identified acquired causes, since ataxia is usually resistant to medical treatments, the management is supportive.

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