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Ataxia: Neurological Condition with Intertwining Multifactorial Mechanisms

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Abstract

Ataxia is a neurological disorder describes poor muscle control that causes clumsy voluntary movements, characterized by a lack of muscle coordination, leading to difficulties with voluntary movements such as walking, speaking, and controlling fine motor skills. It is usually results from malfunction of the "cerebellum", located at the back of the brain beneath the occipital lobes, which fine tunes motor activity or movement via the flocculonodular lobe. Ataxia, is a physical finding, not a disease. The symptoms of ataxia can vary depending on the underlying cause and the specific areas of the brain affected. Common symptoms include unsteady gait, difficulty with balance, slurred speech, tremors, difficulty swallowing, and impaired fine motor skills.

In this review article we discuss the diverse disease types that lead to sporadic ataxia with adult onset. Medical imaging modalities comprise computed tomography (CT) scanners and magnetic resonance imaging (MRI), the most frequently performed imaging investigation in patients with ataxia, with clinical findings might reflect progressive disease changes such as cerebellar degeneration and other brain structures in people with ataxia. Recent advances in genetics have significantly contributed to our understanding of ataxia, particularly in identifying causative genes and uncovering underlying molecular mechanisms.

Keywords: *Ataxia; Epidemiology; Molecular Mechanisms; Medical Interventions*

Abbreviations

CA: Cerebellar Ataxia; TRD: Tandem Repeat Disorder; STR: Short Tandem Repeat; SCA: Spinocerebellar Ataxia; DRPLA: Dentatorubral-Pallidoluysian Atrophy; FRDA: Friedreich's Ataxia; CANVAS: Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome; AD: Autosomal Dominant; AR: Autosomal Recessive; MJD: Machado-Joseph Disease; AVED: Ataxia with Isolated Vitamin E Deficiency; α-TTP or TTPA: A-Tocopherol Transfer Protein; ALS: Amyotrophic Lateral Sclerosis; SARA: Scale for the Assessment and Rating of Ataxia; NGS: Next-Generation Sequencing; IMCA: Immune-Mediated Cerebellar Ataxias; Ab: Antibody; PCD: Paraneoplastic Cerebellar Degeneration; ICARS: International Co-Operative Ataxia Rating Scale; BVH: Bilateral Vestibular Hypofunctionpathy; DVA: Dynamic Visual Acuity; A-T: Ataxia-Telangiectasia; ATM: Ataxia-Telangiectasia Mutated; DSB: Double-Strand Break; HR: Homologous Recombination; AH: Ataxic Hemiparesis; AVED: Ataxia with Vitamin E Deficiency; IOSCA: Infantile-Onset Spinocerebellar Ataxia; IgA: Immunoglobulin A; TG2: Tissue Transglutaminase; DRPLA: Dentatorubral-Pallidoluysian Atrophy; CANVAS: Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome; SNAP: Sensory Nerve Action Potentials; VVOR: Vestibulo-Ocular Reflex; MRI: Magnetic Resonance Imagining; AOA1&2: Ataxia with Oculomotor Apraxia Types 1&2; AFP: Alpha-Fetoprotein; ER: Endoplasmic Reticulum; PFTs: Posterior Fossa Tumors; SCA: Spinocerebellar Ataxia;

MS: Multiple Sclerosis; ADR: Adverse Drug Reaction; Anti-GAD: Anti-Glutamic Acid Decarboxylase; CT: Computerized Tomography; FA: Friedreich's Ataxia; FXN: Frataxin; GABA: Gamma Aminobutyric Acid; EAs: Episodic Ataxias; ITB: Intrathecal Baclofen Therapy; SARA: Assessment and Rating of Ataxia; ARSACS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; FDA: Food and Drug Administration; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; ASOs: Antisense Oligonucleotides; ALS: Amyotrophic Lateral Sclerosis; VR: Virtual Reality

Background and Etiology

Apraxia, a lesion in the cerebrum, affects complex [29], skilled movements that may result from stroke, traumatic brain injury or degenerative dementias including Alzheimer's disease and corticobasal ganglionic degeneration (CBD). This disease affects the area of the brain that processes information and brain structures that control movement. Ataxia is a manifestation due to lesions in the cerebellar hemisphere and produces limb (appendicular) ataxia [3]. On the other hand, aphasia is trouble speaking or understanding other people saying [28], the major key differences are summarized in table 1.

Condition	Major criteria
Ataxia [3]	• Symptoms that causes problems with coordinating muscle movements, affecting all actions [regardless of whether they are new or familiar]. • The brain does not have any problem with processing or describing the tasks.
Apraxia [29]	• Condition that affects brain, making it hard for the affected person to do or describe actions already know how to do because of associated processing problems.
Aphasia [28]	• Condition in which there is a loss of ability to express or interpret spoken or written language, either partially or completely due to impairment of language controlling circuits.

Table 1: *Divergence of major neurological conditions.*

Clinical manifestations of ataxia can vary depending on the underlying cause, the specific areas of the nervous system affected and the progression of the condition. However, there are common clinical features and symptoms associated with ataxia. Sensory ataxia caused by polyneuropathy, parkinsonism, subcortical vascular encephalopathy, and dementia is among the most common neurological causes [1]. Some typical manifestations including but not limited to gait and balance difficulties because ataxia often affects the coordination of leg movements, resulting in an unsteady and uncoordinated gait. Individuals with ataxia may exhibit a wide-based, staggering walk, with an unsteady sway and difficulty maintaining balance. They may also have problems with turning or changing direction [2]. Neurological causes are more common than non-neurological causes.

Cerebellar impairment focus on the central concept of ataxia, which is often summarized as incoordination [3]. Cerebellar ataxias (CAs) are a heterogeneous group of neurological disorders characterized by impaired coordination of limb and eye movement and dysarthria. The primary pathology in CAs is progressive cerebellar atrophy.

Etiological factors are diverse involving many factors contributing to the disease state. Movement is produced by the coordinated action of several cortical and subcortical brain structures such as the spinal cord, brainstem, cerebral cortex, cerebellum and basal ganglia, which collectively fine-tune voluntary and involuntary movements [4]. Disease states, including Parkinson's, Huntington's, normal pressure hydrocephalus can alter the neurocognitive functions to the point that walking can become a difficult task. The weakness of the hip and lower extremity muscles commonly cause gait disturbances. Cerebral palsy, muscular dystrophy, Charcot Marie Tooth disease, ataxia-telangiectasia, spinal muscular atrophy, peroneal neuropathy and microvascular white-matter disease all cause significant gait disabilities.

Electrolyte Imbalance, and electrolyte disorders, including hyponatremia, hypokalemia and hypomagnesemia can cause gait disorders. Hyponatremia, being one of the most common can lead to severe neurological symptoms affecting gait [5]. Electrolyte balance is crucial to maintaining proper musculoskeletal function, which contributes directly to normal gait.

Cerebellar ataxias caused by tandem repeat expansions as after the discovery of the first trinucleotide repeat expansions in fragile X syndrome and spinobulbar muscular atrophy in 1991 [6,7] the era of identifying tandem repeat disorders (TRDs) has begun. Most TRDs in humans are caused by the expansion of short tandem repeats (STRs) (also known as microsatellite DNA), which consist of 1 - 6 bp repetitive DNA elements. Polyglutamine diseases, caused by the expansion of trinucleotide CAG repeat, account for the majority of TRDs [8]. Among dominantly inherited CAs, CAG repeat expansions were firstly described in SCA1 in 1993, and subsequently in dentatorubral-pallidoluysian atrophy (DRPLA), SCA3, SCA2, SCA6, SCA7, SCA12, and SCA17 [9].

Recently, there are at least 16 known repeat expansion ataxias. Pathogenic expansions are localized in coding or/and non-coding DNA sequences and comprise repeated motifs from 3 to 6 bp. The most recent discovery was a biallelic intronic AAGGG repeat expansion in Friedreich's ataxia (FRDA) gene in cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) in 2019 [10].

Other factor associated with common deficiencies in some vitamins that contribute to gait imbalances include folate, vitamin B12, vitamin E, and copper deficiencies [11]. The deficiency of these vitamins has been shown to cause neurological dysfunctions, which impede proper gait. Vitamin B12 deficiency, which causes subacute combined degeneration of the spinal cord, can lead to numbness and paresthesia, which ultimately affect gait.

Epidemiology of ataxia

Ataxia is a neurological disorder characterized by the loss of coordination of voluntary movements. It can affect various body parts, including the limbs, trunk, speech muscles, and eye movements. Ataxia can be caused by a wide range of factors, including genetic mutations, acquired conditions, trauma, infections, toxins, and certain medications [12,15]. The epidemiology of ataxia varies depending on the underlying cause:

1. Hereditary ataxias: There are several types of hereditary ataxias, including spinocerebellar ataxias (SCAs) and Friedreich's ataxia. These conditions are caused by genetic mutations and tend to run in families. The prevalence of hereditary ataxias varies depending on the specific subtype and population studied. For example, SCA3, also known as Machado-Joseph disease, is one of the most common types and is more prevalent in certain populations, such as those of Portuguese descent. Estimates of the prevalence of hereditary ataxias range from 0.5 to 5 cases per 100,000 individuals.
2. Acquired ataxias: Acquired ataxias can result from various factors, including trauma, infections, stroke, tumors, multiple sclerosis, vitamin deficiencies (e.g. vitamin E deficiency), autoimmune disorders, and certain medications. The epidemiology of acquired ataxias depends on the underlying cause [16]. For instance, post-stroke ataxia occurs in a subset of individuals who have experienced a stroke, and the prevalence varies depending on the population and the specific study. Similarly, ataxia associated with multiple sclerosis occurs in a proportion of individuals with this condition.
3. Idiopathic late-onset cerebellar ataxia (ILOCA): ILOCA refers to cases of ataxia with an unknown cause that typically manifest in adulthood. The prevalence of ILOCA is not well-established due to the lack of consistent diagnostic criteria and varying definitions used in research studies.

It is important to note that the epidemiology of ataxia can be challenging to determine accurately due to variations in diagnostic criteria, underreporting of cases, and the heterogeneity of the condition. Additionally, advancements in genetic testing have led to improved identification of specific subtypes, resulting in changes in reported prevalence rates.

Spinocerebellar ataxia type 3 (SCA3) disease was the most common dominant ataxia, followed by SCA2 and SCA6 as indicated in table 2 [22].

Type	Country	Prevelance
SCA 3		
	Brazil	69 - 92% of SCA families
	Portugal	58 - 74%
	China	48 - 49%
	Netherlands	44%
	Germany	42%
	Japan	28 - 63%
	USA and Canada	21 - 24%
	France	20%
	Mexico	12%
	Australia	12%
	India	5 - 14%
	South Africa	4%
	Italy	1%
SCA2		
	Mexico	43% of families with SCA
	Korea	31%
	India, Italy, and Spain	15 - 27%
	Japan	5%
SCA6		
	Germany, the Netherlands, the United Kingdom, Taiwan, Australia, the USA and Japan	10 - 30% of families with SCA
Friedreich ataxia (FRDA)		
	Caucasians	1 in 20000: 1 in 50000
	Spain	1 in 21000
	Finland,	1 in 750000
	Russians	1 in 330000

Table 2: *Epidemiology of differential spinocerebellar ataxia.*

The SCA3/MJD mutation may have resulted from two separate incidents, the first in Asia and the second in the Portuguese community; however, Portuguese emigration is blamed for the mutation's global spread. This information may help to explain why SCA3/MJD is so prevalent in Portugal (58 - 74% of families with SCA), especially on the Azores Islands, where Flores island has the greatest prevalence (1 in 239 individuals) ATXN3 is the name of the SCA3-related gene. The cause of the disease and the origin of the mutated protein known as ataxin-3 is a prolonged and abnormal and this defective allele is most commonly found in individuals of Portuguese-Azorean descent [34].

SCA2 was found in the province of Holguin in Cuba, where people of Spanish descent were thought to be affected at a frequency of 40 cases per 100,000 people. SCA2 makes up between 10 and 25% of autosomal dominant (AD) familial cases in people from different regions [22]. SCA6 is the third most common SCA worldwide [35].

While the autosomal recessive (AR) HCA prevalence range was 0.0 - 7.2/105, the average being 3.3/105. Friedreich ataxia (FRDA) was the most frequent AR-HCA with mean onset of 15.5 ± 8 years, followed by ataxia with oculomotor apraxia or ataxia-telangiectasia [37]. Friedreich ataxia primarily affects Caucasians, uncommon in African groups, and is extremely uncommon in the Far East.

According to the tables surveyed in the review article of Pierre Vankan in Special Issue: 150 Years of Friedreich Ataxia Research Volume 126, Issues 1 that illustrated the cases distribution very well. While ataxia-telangiectasia have prevalence of 1 in 40,000 or in 300,000, and the frequency of ATM allele heterozygosity represents 1.4-2% of the population which is considered as extremely rare.

Symptoms and manifestations of ataxia

Ataxia with isolated vitamin E deficiency (AVED) is a rare autosomal recessive disorder characterized by neurological symptoms due to vitamin E deficiency. It typically manifests in childhood or adolescence but can also present in adulthood. AVED is caused by mutations in the gene responsible for the alpha-tocopherol transfer protein (TTP), which is involved in the transport and distribution of vitamin E in the body [38]. Pioneer work in 1995 identified a homozygous pathogenic frame shift mutation in the TTPA gene c.706del (p.(His236fs)) in the TTPA gene encoding hepatic α-tocopherol transfer protein (α-TTP) and have been termed AVED [39]. This mutation resulted in loss of activity of the α-TTP [39]. The symptoms of AVED primarily affect the neurological system and can vary in severity from mild to severe. The hallmark symptom is progressive ataxia, which involves the loss of coordination and balance.

Other common symptoms are discussed below.

Ataxic dysarthria: Ataxic dysarthria is an acquired neurological and sensorimotor speech deficit: Impaired control of the muscles involved in speech, leading to slurred or unclear speech [40,41].

Speech and swallowing problems are common in any individuals with ataxia experience dysarthria which is characterized by poor articulation of phonemes, and by slurred or slow speech [42]. It is unrelated to problems with understanding language (that is, dysphasia or aphasia). There are many potential causes of dysarthria. They include toxic, metabolic, degenerative diseases, traumatic brain injury, or thrombotic or embolic stroke.

Loss of proprioception: Difficulty sensing the position of body parts, leading to unsteady movements and difficulties with tasks that require fine motor control. Degenerative diseases include parkinsonism, amyotrophic lateral sclerosis (ALS), multiple sclerosis Huntington's disease, Niemann-Pick disease, and Friedreich's ataxia [43]. Toxic and metabolic conditions include: Wilson's disease, hypoxic encephalopathy such as in drowning, and central pontine myelinolysis [42].

Some forms of ataxia may involve tremors, which are rhythmic, involuntary movements of the limbs, head, or other parts of the body. These tremors can be postural (occurring when holding a position) or action-induced (occurring during voluntary movements) [44].

Loss of reflexes: Absence or reduced reflexes, such as the knee jerk reflex. Muscle weakness: Weakness in the limbs, which can contribute to difficulties with movement and coordination. Loss of sensation: Some individuals may experience a decreased ability to feel touch, temperature, or pain.

Nystagmus: Involuntary rapid eye movements, rhythmic and repetitive movement of the eye usually may be vertical, horizontal, or circular, which can affect visual stability [55].

Celiac disease (gluten ataxia): It's important to note that the severity and progression of symptoms can vary widely among individuals with ataxia, even among those with the same underlying cause. Additionally, other non-motor symptoms, such as cognitive impairments, mood changes, or autonomic dysfunction, may be present depending on the specific type of ataxia and associated comorbidities.

In addition, speech problems with slurred and slow form, difficult in initiation process and problems controlling volume, rhythm as well as pitch of the voice. Speech is assessed by specialists during normal conversation, and given a score from 1 to 6 according to the severity of the case. Any words are difficult to understand, only single words are understandable speech unintelligible/anarthria [13]. Anarthria is speechlessness due to a severe loss of neuromuscular control over the speech musculature [organ's muscles involved in speech]. Anarthric patients are motivated to speak but are unable to do so. Some patients with anarthria can induce some oral movements but they usually produce undifferentiated vocalizations when attempting to speak [49].

Dysphagia, or difficulty swallowing, can occur in various types of ataxia. The presence and severity of dysphagia can vary depending on the specific underlying cause and the stage of the ataxia [50]. Here are some key points regarding dysphagia in ataxia:

1. Coordination and muscle control: Ataxia affects the coordination and control of muscles, including those involved in swallowing. The impairment of coordination can disrupt the normal swallowing process, leading to dysphagia.
2. Aspiration risk: Dysphagia in ataxia can increase the risk of aspiration, which is the entry of food, liquid, or saliva into the airway. This can potentially lead to respiratory issues, such as pneumonia or recurrent chest infections.
3. Symptoms: Dysphagia in ataxia can present with various symptoms, including:
    a. Difficulty initiating swallowing
    b. Sensation of food or liquid getting stuck in the throat or chest
    c. Choking or coughing during or after swallowing
    d. Recurrent chest infections
    e. Weight loss and malnutrition due to reduced food intake.

Diagnosis and clinical evaluation of ataxia

The diagnosis of ataxia requires a clinical examination, which is a vital tool. The first step in the diagnosis of ataxia, is clinical evaluation, which entails a thorough medical history and physical examination of the patient. According to the study, the doctor will evaluate the patient's coordination, balance, gait, and speech during the clinical examination. Additionally, they will look for other symptoms like tremors, muscle weakness, and vision issues. It may also be taken into account if there is a family history of ataxia or other related disorders with specific assessment rating as indicated in table 3.

Genetic testing

Genetic testing is a crucial method for diagnosing ataxia as many types of ataxia are caused by genetic mutations. Genetic testing can detect the particular gene mutations linked to ataxia, which can assist in identifying the root cause of the condition and in guiding treatment decisions. In their 2014 paper, Sandford and Burmeister provide an overview of the genetic basis of hereditary ataxias and the various genetic tests that can be used to diagnose them. They discuss the use of molecular genetic testing, which can identify mutations in specific genes associated with ataxia, including the spinocerebellar ataxias (SCAs) and Friedreich ataxia. They also mention the use of next-generation sequencing (NGS) technologies, the genetic testing method that is commonly used for ataxia, targeted next-generation sequencing is a useful tool for identifying gene mutations associated with ataxia. The study notes that targeted next-generation sequencing can be particularly useful for diagnosing ataxia in cases where the clinical features of the condition are atypical or where the diagnosis is uncertain. which have greatly increased the efficiency and accuracy of genetic testing for ataxia. The authors emphasize the importance of

1- **Gait** In this examination, patient is asked to: 1)- Walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) 2)- To walk in tandem (heels to toes) without support.	5- **Finger chase** Proband takes a comfortable seat, supporting their feet and trunk if necessary. The examiner sits in front of patient and makes five quick, rapid movements in a frontal plane at a distance that is roughly half of the subject's reach. Moves have an amplitude of 30 cm and occur once every two seconds.
2- **Stance** Proband is asked to stand: 1)- In natural position 2)- With feet together in parallel (big toes touching each other) 3)- In tandem (both feet on one line, no space between heel and toe).	6- **Nose - Finger test** Proband takes a comfortable seat, supporting their feet and trunk if necessary. The proband is instructed to repeatedly point with his index finger, which is about 90% of the way from his nose to the examiner's finger in front of him. Moderate pace is used for all movements.
3- **Setting** Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front	7- **Fast alternating hand movement** Proband settles back, feet and trunk supported if necessary. The proband is instructed to complete 10 cycles of rapid and accurate pronation and supination of the hand on the thigh repetitions. Within seven seconds, the examiner does the action at approximately 10 cycles.
4- **Speech disturbance** Speech is assessed during normal conversation.	8- **Heel-Shin slide** Proband is lying on the examination bed with his or her legs hidden. The proband is instructed to lift one leg, point the heel of it in the direction of the other knee, descend up the shin to the ankle, and then place the leg back on the examination table. Three times are used to complete the task. Slide-down movements must be made in less than one second.

Table 3: *Scale for the assessment and rating of ataxia (SARA) [13].*

genetic testing in the diagnosis of hereditary ataxias, as it can provide crucial information for genetic counseling and management of the condition. They note that genetic testing can also be useful for early diagnosis and identification of at-risk family members and highlight the need for continued research in this area to improve diagnostic accuracy and develop new treatments for ataxia [56].

Immune-mediated cerebellar ataxias - blood tests for ataxia

Immune-mediated pathophysiological mechanisms frequently affect the cerebellum, leading to progressive ataxia characterized by dysmetria in both motor and cognitive domains [57]. The identification of autoantibodies targeting cerebellar neurons led to a break-

through in immune-mediated cerebellar ataxias (IMCAs). First, the discovery of anti-Yo antibody (Ab), an autoantibody described in a patient with ovarian cancer, demonstrated the immune nature of the insult resulting in paraneoplastic cerebellar degeneration (PCD) [58]. IMCAs icomprise diverse etiologies. This suggests that the cerebellum can be the target of many types of autoimmune responses with different pathophysiological mechanisms. IMCAs of certain etiologies respond well to immunotherapy at least in the early stage, while the cerebellar reserve is preserved [59].

Pathophysiology of ataxia

Ataxia refers to a group of neurological disorders due to an interference in the sensory transmission to the cerebellum caused by a lesion. It can affect various parts of the body, including the limbs, trunk, head and eyes. An interruption in cortical signals from the cerebellum causes cerebellar ataxia. Spinocerebellar ataxias are a result of both of the above mentioned pathologies. The pathophysiology of ataxia can vary depending on the underlying cause. Some common causes of ataxia include genetic disorders, acquired conditions, toxins, infections, and trauma. Ataxia can be caused by damage to the cerebellum, proprioceptive, vestibular, and visual systems, as well as their interconnections. So, some others uncommon types are described.

Here, we provided a general overview of the pathophysiological mechanisms reported to be involved in ataxia according to the affected area (Table 4).

Affected Area	Cerebellar	Sensory	Vestibular
Differences	A complex motor disturbance that affects movement planning and execution and reduces movement accuracy and coordination. The quantification of ataxic signs is commonly accomplished through visual examination of motor tasks performed by the patient and assignment of scores to specific items comprising the international co-operative ataxia rating scale [ICARS]. The current study looked into an experimental procedure for objectively characterizing specific aspects of motor disturbances in ataxia [15].	Sensory ataxia can be caused by a loss of sensory input from the spinocerebellar tracts to the cerebellum. Any impairment in the proprioceptive pathway can result in a sensory loss [for example, Friedreich ataxia caused due to vitamin E deficiency, acquired sensory ataxias associated with ataxic polyneuropathies [e.g., paraneoplastic sensory neuropathy], Sjögren syndrome, diabetes mellitus, vitamin B6 toxicity, Miller Fisher syndrome] [3].	Due to dysfunction of the vestibular end organ and/or vestibular nerve, a rare but disabling condition with bilateral reduced or absent vestibular function occurs. Some bilateral vestibular hypofunctionpathy [often experiencing ataxia and visual instability] patients may focus primarily on their visual instability, while others may focus on their postural instability, and these patients may have very different perspectives on their disability. The vestibular system combines five different neuro-epithelia that can mechanotransduce head movements over a wide range of frequencies as well as over various types and directions [16].

Indication	Cerebellar ataxia is present with both open and closed eyes. There are two distinct cerebellar syndromes: • Vermis [or midline] is responsible for defects in static coordination as well as significant abnormalities in posture and gait. • Hemispheric syndrome, causes kinetic ataxia with ipsilateral extremity coordination problems during skilled motor activity [15].	Sensory ataxia is associated with gait disturbance. Additionally, individuals who have sensory ataxia will exhibit a positive Romberg sign. Due to associated motor weakness, Individuals may walk with a high-stepping gait or a feet-slapping gait [sound induced sensory feedback assists their moving process]. Pseudoathetosis [With eyes closed, random finger movements can be seen when hands being outstretched] can also occur in upper limb sensory neuropathy [3].	The most common symptoms of BVH are imbalance [vestibular ataxia], decreased dynamic visual acuity [DVA], and oscillopsia during head and body movements due to gaze instability [17].

Table 4: *Type of Ataxia according to affected area.*

As Ataxia refers to a group of neurological disorders due to an interference in the sensory transmission to the cerebellum caused by a lesion. It can affect various parts of the body, including the limbs, trunk, head, and eyes. An interruption in cortical signals from the cerebellum causes cerebellar ataxia. Spinocerebellar ataxias are a result of both of the above mentioned pathologies. The pathophysiology of ataxia can vary depending on the underlying cause. Some common causes of ataxia include genetic disorders, acquired conditions, toxins, infections, and trauma. The basic mechanism producing ataxia is not yet fully known, although studies highlighted some major findings regarding the attributing factors as summarized in figure 1 and mechanistic pathways in figure 2.

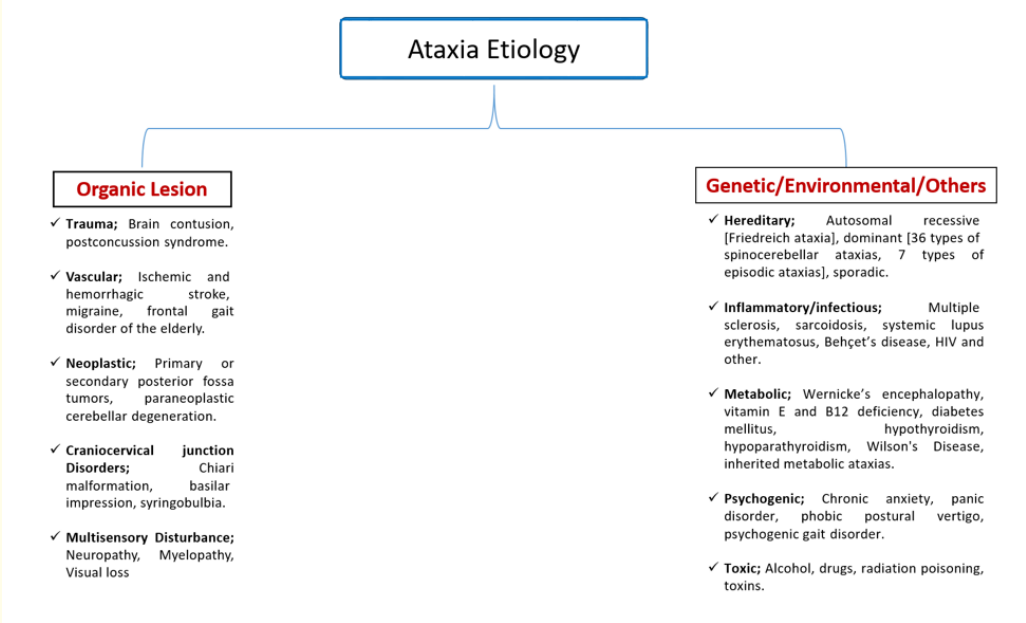

Figure 1: *A comprehensive analysis of diverse causative factors of ataxia [14].*

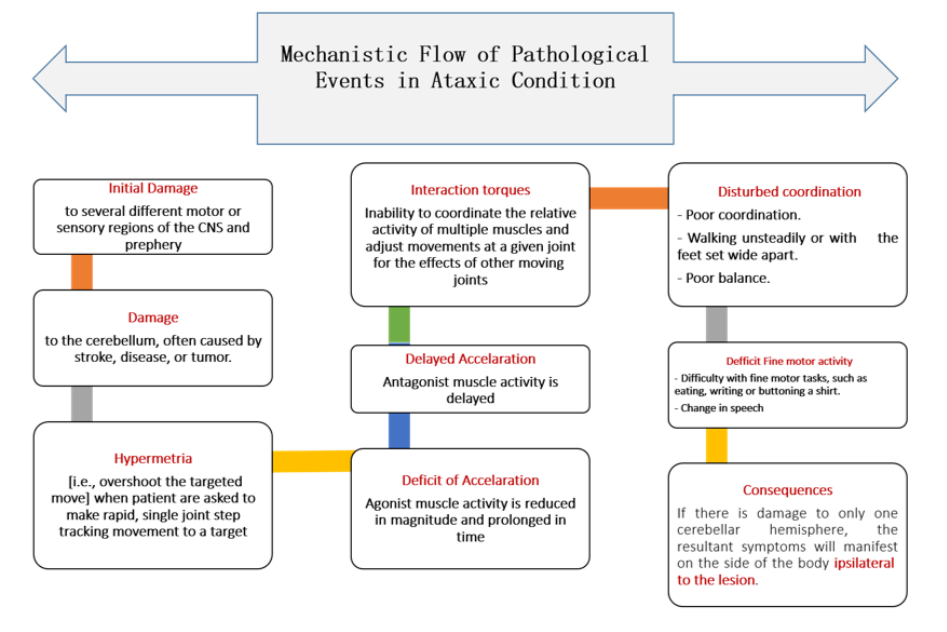

Figure 2: *Mechanistic overview of ataxia [13].*

Type-specific molecular pathogenesis

Ataxia-telangiectasia (A-T), also known as Louis-Bar syndrome, is an autosomal recessive, complex, multisystem disorder characterized by progressive neurologic impairment, cerebellar ataxia, variable immunodeficiency with susceptibility to sinopulmonary infections, impaired organ maturation, x-ray hypersensitivity, ocular and cutaneous telangiectasia, and a predisposition to malignancy. The disease is heterogeneous. The responsible gene (ATM gene) has been mapped to band 11q22-23 [61]. ATM serine/threonine kinase or Ataxia-telangiectasia mutated is a serine/threonine protein kinase that is recruited and activated by DNA double-strand breaks. It phosphorylates several key proteins that initiate activation of the DNA damage checkpoint, leading to cell cycle arrest, DNA repair or apoptosis. Ataxia-telangiectasia mutated (ATM) modulates cellular metabolism. ATM acts as an upstream signaling kinase [60], involved directly or indirectly in several aspects of DNA double-strand break (DSB) repair, including homologous recombination (HR), non-homologous end-joining, and cell-cycle regulation. DNA damage activates ATM to phosphorylate multiple downstream proteins regulate cell cycle arrest, DNA repair, and apoptosis pathways. Desferrioxamine has been shown to increase genomic stability of ataxia-telangiectasia cells and, therefore, may present a promising tool in ataxia-telangiectasia treatment [62].

In case of Ataxia telangiectasia that usually appear in childhood the child would appear a little wobbly, which means tending to move unsteadily from side to side. Spider veins in the whites of the eyes, the ears, or elsewhere on the face. Spider veins are swollen, red, purple or blue vessels that twist and turn, they are easily visible through skin. This is caused due to weak vein walls and also weakness in one-way valves found inside veins that let blood flow through and prevent it from flowing backwards but due to ataxia, the walls of these veins become stretched and lose their elasticity, causing the valves to weaken and unable to function properly which leads to accumulation and backwards flow of the blood in veins, which become swollen and enlarged. The exact mechanism of how the walls of the veins stretch and why the valves in veins are weakened is still not fully understood [51,52].

Ataxic-hemiparesis

Ataxic hemiparesis [AH] defines by the presence of both a pyramidal tract syndrome and a homolateral ataxic syndrome. Fisher and Cole [1965] elaborated on the core symptoms of AH as weakness and pyramidal signs on one side combined with ipsilateral cerebellar-like ataxia. Following reports, however, have expanded the clinical spectrum of AH to include cases with persistent hemisensory deficits as well as additional symptoms such as dysarthria or facial paresis. AH was initially thought to be a lacunar syndrome associated with lacunar infarctions. Recent reports, however, suggest that AH is not significantly associated with these infarctions, and a large number of studies have shown that lacunar infarction, as well as cardioembolic and large-artery atherosclerosis, can cause AH. AH has also been linked to hemorrhagic strokes, tumors, head trauma, infection, and demyelinating diseases. The most commonly reported lesion sites in AH are the pons, corona radiata, thalamus, and internal capsule; however, cortical lesions have also been observed in some AH patients. Specific AH symptoms are thought to result from damage to corticospinal and cerebellar pathways [efferent or afferent], while variations in symptomology reflect the size and precise location of the infarct lesion, regardless of the precipitating insult. Optimal treatment strategies are naturally dependent on treating the underlying etiology, and to date, anticoagulant and antiplatelet drug therapies have been used. The prognosis for AH after an ischemic stroke is generally favorable [25].

Infantile-onset spinocerebellar ataxia

Infantile-onset spinocerebellar ataxia (IOSCA) is a hereditary neurological disorder with early and severe involvement of both the peripheral and central nervous systems. It has only been described in Finnish families. Slowly progressive clinical symptoms appear usually between the ages of 10 and 24 months in previously healthy infants. The first symptoms are usually clumsiness and loss of the ability to walk. Ataxia, athetosis, and muscle hypotonia with loss of deep tendon reflexes, ophthalmoplegia with only convergence persisting, and hearing loss can be discovered on clinical examination. A polyneuropathy with profound decrease in sensory nerve conduction velocities and progressive loss of myelinated fibers in sural nerve biopsies may develop by adolescence. Involvement of the vestibular organ can markedly disturb the balance and may be present at the onset of symptoms.

IOSCA is a severe, progressive neurodegenerative disorder characterized by normal development until the age of one year, followed by the onset of ataxia, muscle hypotonia, loss of deep tendon reflexes, and athetosis. By the age of seven, ophthalmoplegia and sensorineural deafness have developed. Affected individuals are profoundly deaf and no longer ambulatory by adolescence, with sensory axonal neuropathy, optic atrophy, autonomic nervous system dysfunction, and hypergonadotropic hypogonadism in females becoming evident. Epilepsy can progress to a serious and often fatal encephalopathy: myoclonic jerks or focal clonic seizures, followed by epilepsia partialis continua and loss of consciousness [27].

Gluten ataxia

In people with certain genetic predispositions to the disease, gluten consumption can cause gluten ataxia, an immune-mediated condition. In the differential diagnosis of all patients with idiopathic sporadic ataxia, it should be taken into account. Ataxia can be improved and its progression stopped with early diagnosis and treatment using a gluten-free diet. Antigliadin antibodies are accessible and sensitive indicators of gluten ataxia. IgA deposits against TG2 are demonstrated to be additional trustworthy and possibly more specific markers of the full spectrum of gluten sensitivity in the small bowel and at extraintestinal sites. They might also be able to explain how its pathogenesis [28].

Dentatorubral-pallidoluysian atrophy or Naito-Oyanagi disease

Myoclonus, epileptic seizures, cerebellar ataxia, choreoathetotic movements, character change, and mental retardation or dementia are all symptoms of dentatorubral-pallidoluysian atrophy [DRPLA], also known as Naito-Oyanagi disease. Individual patients' key clinical features are determined by their age of onset. The dentate nucleus is the most severely affected pathologically, followed by the pallidum.

The DRPLA gene has recently been assigned to the short arm of chromosome 12, and the underlying abnormality has been identified as an expansion of a CAG repeat within its coding region [7 - 34 in normals and 53 - 88 in DRPLA]. The gene product is known as atrophin-1, and its function is unknown. DRPLA is the most unstable of the CAG repeat diseases in terms of the number of CAG repeats, which expands significantly across generations. Furthermore, DRPLA has an ethnic preference for Asian populations, particularly Japanese [21].

Cerebellar ataxia, neuropathy, vestibular areflexia syndrome [CANVAS] with chronic cough and preserved muscle stretch reflexes

CANVAS is a rare, late-onset ataxia characterized by bilateral vestibular, cerebellar, and somatosensory impairment. For clinically definite CANVAS, the following stage diagnostic criteria have recently been proposed: abnormal visually enhanced vestibulo-ocular reflex [VVOR], cerebellar atrophy on MRI primarily involving vermian lobules VI, VIIa, and VII, neurophysiological evidence of a sensory neuronopathy, and exclusion of genetic ataxias that can be gene tested. Several descendant generation cases reported, implying that CANVAS is an autosomal recessive [AR] disorder. In CANVAS, the somatic sensory deficit contributes to a significant level of disability. Neurophysiological studies have revealed an almost constant absence of sensory nerve action potentials [SNAP] and somatosensory evoked potentials in upper and lower limb nerves. A severe dorsal root ganglionopathy with secondary degeneration of central and peripheral sensory axons is the pathological background. Despite the fact that these electrophysiological and pathological features should be linked to generalized areflexia, intact muscle stretch reflexes have been observed in a significant proportion of CANVAS patients [30].

Ataxia with oculomotor apraxia types 1 and 2

AOA1 is distinguished by the onset of cerebellar ataxia in childhood, followed by oculomotor apraxia and severe primary motor peripheral axonal motor neuropathy. The first symptom is progressive gait imbalance, which is followed by dysarthria, upper-limb dysmetria, and mild intention tremor. Oculomotor apraxia progresses to external ophthalmoplegia a few years after the onset of ataxia. Around seven to ten years after onset, all affected individuals develop generalized areflexia, followed by peripheral neuropathy and quadriplegia, with loss of ambulation. Hands and feet are atrophic and short. Chorea and upper-limb dystonia are common conditions. Some people's intelligence remains normal, while others have varying degrees of cognitive impairment [31].

Axonal sensorimotor neuropathy, oculomotor apraxia, cerebellar atrophy, and an elevated level of alpha-fetoprotein in the blood are all symptoms of ataxia with oculomotor apraxia type 2 [AOA2]. AOA2 typically begins between the ages of three and 30 years after initial normal development [AFP] [32].

Ataxia-induced by other factors and diseases

Alcohol abuse

Chronic alcohol consumption has social and medical consequences. One of the most sensitive parts of alcohol consumption is the mature or developing cerebellum. Alcohol has either acute and transient or chronic and long-term effects on the nervous system. Alcohol's acute and transient effects are associated with impaired posture, ataxic gait, and scanning speech, which are referred to collectively as alcoholic cerebellar ataxia or ethanol-induced cerebellar ataxia. The majority of patients report a lack of coordination in their lower extremities, in contrast to the relative sparing of their upper limbs, indicating a preferential dysfunction of the vermis. Chronic alcoholism causes cerebellar atrophy, particularly in the anterior superior vermis above the primary fissure. Two potential mechanisms for this etiology have been depicted. One possibility underscored the role of nutritional deficits as a cause of cerebellar atrophy, hence the term "nutritional cerebellar degeneration". The second mechanism emphasized ethanol's direct effects on neurons and glia via multiple pathways that converge on oxidative stress and endoplasmic reticulum [ER] stress in the cortex's cellular components [18].

Stroke

Even when limb ataxia is not overtly present, impaired trunk control is common in stroke patients. Ataxia impairs trunk control, resulting in balance or gait dysfunction, an increased risk of falling, and a loss of independence in daily activities. According to studies, the

balance status is related to the length of hospitalization. Trunk control in the early stages of stroke predicts overall daily activities function at 6 months. Standing balance is related to functional state change during acute rehabilitation. Sitting balance is also strongly related to daily activities function. As a result, appropriate trunk control is critical to motor function and daily activities. A thorough assessment of not only muscle strength but also trunk and limb control is required for a thorough evaluation of stroke patients [14].

Brain tumor

Ataxia is the most common and disabling group of motor clinical signs in children with posterior fossa tumors [PFTs] before and after an intervention. Indeed, 58% to 90% of children with PFTs have this sign, which frequently describes balance or gait impairment, tremors, speech disturbance, or incoordination. Balance and coordination issues can interfere with daily activities, return to school, and participation with peers, so it is critical to gain a better understanding of these issues. Ataxia frequently persists after surgery. Despite its reported high prevalence, ataxia is less well understood. According to recent research, 70% of children with PFTs have long-term post-operative balance problems, implying ataxia but it is unclear what prognostic factors if any, exist preoperatively to determine this risk of the outcome [16].

Brain degeneration

Spinocerebellar ataxia [SCA] is a group of conditions defined by degenerative changes to many parts of the central nervous system, including the cerebellum, brain stem, and spinal cord, caused by mutations in human genes. If a parent has SCA, each of their children has a 50% chance of inheriting the mutated gene [19].

Multiple sclerosis

Coordination issues are common in MS and are caused primarily by pathology within the cerebellum or impairment in cerebellar connections, including proprioceptive afferent inputs. Patients with MS may present with either acute cerebellar dysfunction associated with an acute relapse or chronic cerebellar dysfunction associated with progressive disease. Cerebellar pathology can cause limb, gait, and truncal ataxia, as well as other cerebellar symptoms such as gaze-evoked nystagmus, dysarthria, and tremor. Ataxia occurs in approximately 80% of patients with established MS, with symptoms being more prevalent in those with progressive disease. Tremor in MS is thought to be caused primarily by cerebellar and/or thalamic disease. Tremors can affect the limbs, trunk, vocal cords, and head [titubation]. Although rest and rubral tremors are uncommon, intention and postural tremors are the most common. Although severely disabling, severe tremor is a relatively uncommon side effect of MS, occurring in 3% of patients in one study [21].

Drug-induced cerebellar ataxia

Acute ataxia is most commonly associated with intravenous drug administration or high benzodiazepine doses as an adverse drug reaction [ADR]. When a stroke is suspected as an alternative cause in such a scenario, the drug should be discontinued and a brain CT or MRI should be performed. However, drug-induced ataxia typically occurs within days to weeks of the introduction of a new drug or a dose increase. Other causes of subacute ataxia include para-infectious cerebellitis, paraneoplastic cerebellar degeneration, and anti-glutamic acid decarboxylase [anti-GAD]-associated cerebellar ataxia, to name a few. After years of using lithium, phenytoin, or valproate, ataxia can be developed. Degenerative or genetic diseases are other causes of chronic ataxia. When a patient exhibits slowly progressive ataxia, the effect of withdrawing a suspected causative drug can be awaited before further diagnostic testing is performed. The possibility of ataxia being an ADR of the drug should be considered, and other possible causes of ataxia should be investigated further if cessation does not result in an improvement in symptoms. In some cases, drug-drug interactions cause ataxia. This is most common with drugs that influence the pharmacokinetics of the other drug. If a drug-drug interaction is suspected, a pharmacologist should be consulted. It is also possible for a patient to use multiple drugs, each of which can cause cerebellar ataxia. When this occurs, the drug most likely to be the culprit should be stopped [if possible], and the physician should assess the effect on the symptoms. When two or more drugs that can cause ataxia

are prescribed together, the patient should be instructed to keep track of any possible ataxic symptoms, and the prescribing physician should keep a close eye on this ADR [20].

Genetic disorder

There are several genetic disorders associated with ataxia. These disorders are typically classified as hereditary ataxias, as they are caused by genetic mutations that are inherited from parents. Here are some examples of genetic disorders that can lead to ataxia.

Spinocerebellar ataxias (SCAs): Spinocerebellar ataxias are a group of genetic disorders characterized by progressive ataxia and degeneration of the cerebellum and its connections. There are multiple subtypes of SCAs, each caused by a specific genetic mutation. The symptoms and age of onset can vary depending on the subtype. Some examples include SCA1, SCA2, SCA3 (also known as Machado-Joseph disease), SCA6, and SCA7 [22].

Friedreich's ataxia: Friedreich's ataxia is an inherited disorder that affects some of the body's nerves. It is caused by a gene defect that is inherited from both parents by a mutation in the FXN gene which carries the genetic code for the production of a protein called frataxin mapped on chromosome 9. This mutation leads to a deficiency of frataxin, a protein involved in mitochondrial function. Frataxin is found in the energy-producing parts of the cell called mitochondria. In FA, an abnormal pattern in the DNA sequence of the protein (called a triplet repeat) appears hundreds or more times, which greatly disrupts the normal production of frataxin [63] Friedreich's ataxia typically manifests in childhood or adolescence and is characterized by progressive ataxia, muscle weakness, and other neurological symptoms. Nerve fibers in your spinal cord and peripheral nerves degenerate, becoming thinner. (Peripheral nerves carry information from the brain to the body and from the body back to the brain and signal the muscles to generate movement). For example, cone-rod retinal dystrophy in conjunction with familial ataxia may indicate spinocerebellar ataxia [SCA]; Native American ancestry or the presence of epilepsy may indicate SCA10. Hereditary ataxias are classified according to their mode of inheritance [autosomal dominant, autosomal recessive, X-linked, and mitochondrial], the gene in which causative mutations occur, or the chromosomal locus [22].

The most common symptoms include sideward curvature of the spine, or scoliosis: Typical signs include a visibly curved spine, one shoulder being higher than the other, which often requires surgical intervention. The prevalence of scoliosis is high among Friedreich's ataxia patients, ranging from 63% to 100%. Other skeletal deformities may occur such as high arching feet, club feet, deformities of the toes, and foot inversions, which means feet turning inward. Skeletal deformities are triggered by neuromuscular problems [54].

Another sign is Loss of touch sensation which is one of the most common symptoms of Friedreich's ataxia, this could be confirmed only in laboratory testing. First, positional sense or the awareness of the body in space would be impaired, then perception of pain, temperature and light touches may be affected later on [53].

Furthermore, Friedreich's ataxia patients may suffer from hearing disorders: which can progress to deafness in some cases [53]. Weakened heart muscle: heart abnormalities affect about 3/4 of people with Friedreich's ataxia, although, the severity varies extensively from a person to another. One of the most common FA-related heart problems is Hypertrophic cardiomyopathy, where the muscles of the heart become enlarged and weakened, which limits the pumping ability of the heart and prevents blood from reaching distal regions, which may lead to heart failure in later stages. Myocardial fibrosis also can occur. Heart rhythm abnormalities are also common such as tachycardia, which is a fast heart rate, and heart block, which is slow heart rate. Some other symptoms usually accompany heart problems such as extreme fatigue, chest pain and shortness of breath [53].

Diabetes in Friedreich's ataxia has been presumed to occur due to defects in insulin action or decreased insulin secretion from β islet cells in the pancreas. However, it is likely that both mechanisms contribute to pathogenesis. Dysfunction of β cells is a precondition for glucose intolerance. The molecular pathways of this disorder are pointing toward mitochondrial dysfunction and apoptosis, and endoplasmic

reticulum stress. The prevalence of diabetes in FA patients varies from 6% to 19%, with nearly 49% patients found to have impaired glucose tolerance in a recent study [53,54].

Medical interventions and treatment of ataxia

It is important to note that treatment outcomes can vary depending on the underlying cause and the individual's overall health. Therefore, a comprehensive evaluation by a healthcare professional specialized in neurology or movement disorders is crucial to determine the most appropriate treatment plan for someone with ataxia.

The treatment of ataxia depends on the underlying cause and the specific symptoms experienced by the individual [45]. Table 5 illustrates some common approaches used in the treatment of ataxia.

Treatment modality	Clinical relevance
Symptomatic treatment [46,47]	Medications can be prescribed to manage specific symptoms associated with ataxia, such as tremors, muscle stiffness, and spasms. These may include muscle relaxants, anticonvulsants, or medications targeting specific neurotransmitters.
Physical therapy [48]	Physical therapy plays a crucial role in managing ataxia. It focuses on improving coordination, balance and muscle strength through exercises and specialized techniques. Physical therapists may also use assistive devices such as canes or walkers to aid mobility.
Occupational therapy [64]	Occupational therapy aims to enhance the individual's ability to perform daily activities, such as dressing, eating, and grooming. Therapists may recommend adaptive techniques or devices to compensate for coordination difficulties.
Speech therapy [70]	Ataxia can affect speech and swallowing functions. Speech therapy can help improve articulation, speech clarity, and swallowing abilities through targeted exercises and techniques.
Assistive devices [69]	Depending on the severity of ataxia, individuals may benefit from using assistive devices such as braces, orthotics, or mobility aids to improve stability and prevent falls.
Genetic counseling [71]	In cases where ataxia is caused by a genetic disorder, genetic counseling may be recommended. Genetic counselors can provide information about the condition, inheritance patterns, and family planning options.
Supportive care [72]	Ataxia can have a significant impact on an individual's quality of life. Supportive care involves providing emotional support, counseling, and resources to help individuals cope with the challenges associated with ataxia. Support groups can also be valuable in connecting individuals with others facing similar experiences.

Table 5: *Potential management option/ strategy for ataxia.*

Here we provide an overview on some important strategies for managing ataxia condition.

Symptomatic treatment/pharmacological interventions

Perlman provides an update on the current pharmacological treatments for ataxia [65]. The author notes that while there is no cure for most forms of ataxia, medications can help manage symptoms and improve quality of life for affected individuals. One commonly

used medication for ataxia is the GABA agonist baclofen, which can reduce spasticity and improve gait stability in some patients. Other medications that may be used to manage ataxia symptoms include anticonvulsants such as carbamazepine and valproic acid, which can reduce tremor and improve balance in some patients. Additionally, some patients may benefit from dopamine agonists such as levodopa or pramipexole, which can improve motor function in certain forms of ataxia. The author also discusses emerging therapies for the treatment of ataxia, such as gene therapy and stem cell therapy. While these therapies are still in the experimental stages, they hold promise for the future treatment of ataxia.

Overall, the paper by Perlman provides a comprehensive overview of the current pharmacological treatments for ataxia, and highlights the need for continued research to develop more effective therapies for this condition. It is important to note that the choice of medication and dosage depends on the underlying cause of ataxia, and treatment should be individualized based on the specific needs of each patient [65].

There are several medications that can be used to help manage the symptoms of ataxia. These medications may include clonazepam, arimoclomol, acetazolamide, zonisamide and baclofen. Acetazolamide is a carbonic anhydrase inhibitor that is used in the treatment of epilepsy, congestive heart failure, and glaucoma [74]. Earlier study revealed that acetazolamide was effective in mitigating and preventing episodic ataxia symptoms [73].

Fampridine and acetazolamide are two medications that have been used in the treatment of episodic ataxia, a rare neurological disorder characterized by recurrent episodes of ataxia. However, it's important to note that the effectiveness of these medications can vary depending on the individual and the specific subtype of episodic ataxia [75].

The author declared that acetazolamide, a carbonic anhydrase inhibitor commonly used to treat glaucoma and seizures, has been found to be effective in treating Episodic ataxias (EAs) in some patients. Acetazolamide is thought to work by increasing the pH of cerebrospinal fluid, which can reduce neuronal hyperexcitability and improve cerebellar function. However, the author notes that the response to acetazolamide can vary among patients, and that the optimal dosage and duration of treatment are not well established. Overall, the paper by Kotagal highlights the potential role of acetazolamide in the treatment of ataxia, particularly in patients with EA2. However, the author emphasizes there is a strong need of a precise quantification of the effectiveness of acetazolamide and fampridine in patients with genetically confirmed EA2 by a new specifically designed trial [66].

On the other hand, the research by Berntsson., *et al*. (2017) focuses on the experiences of patients with cerebellar ataxia who were treated with intrathecal baclofen (ITB) therapy, which involves the administration of the muscle relaxant baclofen directly into the spinal fluid. The authors note that ITB therapy has been used to manage spasticity and other symptoms in patients with ataxia, but its effectiveness in improving gait and overall function has been inconsistent. However, the authors report that some patients in their study reported positive experiences with ITB therapy, including improvements in balance, gait, and overall quality of life. The authors note that ITB therapy is not without risks, and can cause side effects such as drowsiness, dizziness, and muscle weakness. The authors also report that some patients in their study experienced complications with the ITB pump or catheter, which required surgical intervention to correct. Overall, the study by Berntsson., *et al*. suggests that ITB therapy, including the use of baclofen, may be a possible treatment option for some patients with ataxia. However, the authors caution that the benefits and risks of ITB therapy should be carefully weighed on a case-by-case basis, and that further research is needed to better understand the effectiveness and safety of this treatment approach in ataxia [67].

Physical therapy

In the research by Milne., *et al*. (2020), the authors describe a randomized controlled trial of an outpatient and supported home-based physiotherapy program for people with hereditary cerebellar ataxia. The study aims to evaluate the effectiveness of physical therapy in improving motor function, balance, and quality of life in individuals with ataxia. The authors note that physical therapy is a commonly

used treatment approach for ataxia, as it can help to improve motor coordination, balance, and gait. The therapy typically involves exercises that focus on improving posture, trunk control, and limb coordination, as well as balance and gait training. In the study by Milne., *et al*. participants will receive a tailored physiotherapy program that includes supervised sessions in an outpatient setting, as well as home-based exercises with support from a physiotherapist. The authors will assess the effectiveness of the program using a range of outcome measures, including the scale for the assessment and rating of Ataxia (SARA), the 10-Meter Walk Test, and the Short Form-36 Health Survey. The authors note that the results of the study could have important implications for the management of ataxia, as physical therapy is a non-pharmacological and non-invasive treatment option that can improve functional outcomes and quality of life in affected individuals. The authors also highlight the need for further research to identify the most effective and appropriate physical therapy approaches for different forms of ataxia [68].

Speech therapy

In the research by Vogel., *et al*. (2019), the authors investigate the effectiveness of speech therapy in improving dysarthria (a speech disorder) in individuals with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), a rare genetic form of ataxia characterized by cerebellar ataxia, spasticity, and peripheral neuropathy. The study was a rater-blinded, controlled pilot study, in which participants with ARSACS were randomly assigned to either a speech therapy group or a no-treatment control group. The speech therapy group received 10 sessions of individualized speech therapy, which focused on improving articulation, phonation, and prosody. The control group did not receive any treatment during the study period. The authors report that participants in the speech therapy group showed significant improvements in their dysarthria, as measured by a standardized rating scale, compared to the control group. The authors note that the improvements in dysarthria persisted at a 3-month follow-up assessment. The authors suggest that speech therapy may be a promising treatment option for individuals with ataxia-related dysarthria, and that further research is needed to better understand the underlying mechanisms of the therapy and to identify the most effective treatment approaches for different forms of ataxia. Overall, the research by Vogel., *et al*. highlights the potential benefit of speech therapy in improving dysarthria in individuals with ataxia, and underscores the importance of addressing communication difficulties in the management of this condition [82].

Nutrition-based therapy in spinocerebellar ataxia

There are many factors that can have a positive or negative impact on an individual's dietary intake. The amount and quality of dietary intake is directly linked to nutritional profile of individuals. Considering the deteriorating neurological features of the ataxia condition, health and wellness maintenance is paramount. Dietary intake is guided by set of recommendations/standards for the daily intake of nutrients and other food components based on the recommended daily allowances. These measurements are used to assess or track food, nutrient or any non-nutritional intake by individuals. The main purpose for assessing an individual's dietary intake is for nutritional screening and surveillance, which can be used to guide research. In individuals with neurological disorders, resting energy expenditure due to hypermetabolism is increased [76].

Diet and nutrition is featured heavily in its effect on clinical outcomes of this condition. Spinocerebellar Ataxia may have important health impact and nutritional risk profile effect due challenges with swallowing, dysphagia, dependence in meal preparations, muscle and coordination challenges. These physiological changes that are characteristic of spinocerebellar ataxia impact dietary intake and negatively affect lean body [77].

While there is no specific diet that can cure ataxia, certain dietary changes may help manage symptoms and support overall health in individuals with ataxia. Here are some considerations: a) Maintaining a well-balanced diet is essential for overall health. Include a variety of fruits, vegetables, whole grains, lean proteins, and healthy fats in your meals. This ensures you receive essential nutrients, vitamins, and minerals necessary for optimal functioning of the body and brain. b) consuming antioxidant-rich foods as berries, leafy greens, nuts, and seeds, may help combat oxidative stress and reduce inflammation. c) Omega-3 fatty acids, found in fatty fish (e.g., salmon, mackerel,

and sardines), walnuts, flaxseeds, and chia seeds, have anti-inflammatory properties and may promote brain health. Including these foods in the diet may be beneficial for managing ataxia symptoms. d) Adequate hydration is important for overall health and can help support proper brain function. Aim to drink an adequate amount of water throughout the day and limit sugary beverages. e) Including high-fiber foods like whole grains, fruits, vegetables, and legumes in your diet can help support gut health and regular bowel movements, which can be beneficial for individuals with ataxia who may experience digestive issues.

It is important to note that dietary changes should be discussed with a healthcare professional to ensure they are appropriate for your individual situation and do not interfere with any other treatments or medications you may be taking [78].

Gene therapy

Currently, there are no symptomatic or neuroprotective treatments approved by the United States (US) Food and Drug Administration (FDA) for SCAs, although research has dramatically expanded in the past decade. Novel future treatments of SCAs may include gene therapy, clustered regularly interspaced short palindromic repeats (CRISPR) gene editing, stem cell therapy, antisense oligonucleotides (ASOs), and pharmacologic agents.

The research by Ocana-Santero., *et al*. (2021) discusses the potential role of gene therapy in the treatment of Friedreich's ataxia, a genetic form of ataxia caused by mutations in the frataxin gene. The authors note that current treatments for Friedreich's ataxia are limited, and there is no cure for this condition. The authors suggest that gene therapy, which involves the delivery of a functional copy of the frataxin gene to affected cells, may be a promising treatment option for Friedreich's ataxia. The authors discuss several approaches to gene therapy, including viral vectors, non-viral vectors, and genome editing technologies. The authors note that while gene therapy is still in the experimental stages for Friedreich's ataxia, preclinical studies have shown promising results in animal models of the disease. Further research is recommended and needed to evaluate the safety and effectiveness of gene therapy in humans, and to identify the optimal delivery strategies and dosages for this treatment approach. Overall, the research by Ocana-Santero., *et al*. highlights the potential of gene therapy as a future treatment option for Friedreich's ataxia, and underscores the need for continued research in this area [79].

Repurposed drugs

The research by Ogawa (2004) discusses the potential of repurposed drugs in the treatment of cerebellar ataxia. The author notes that there are currently no specific pharmacological treatments for ataxia, and that most treatments are directed towards managing symptoms or underlying conditions. The author suggests that repurposed drugs, which are drugs that have been approved for other uses but have potential therapeutic effects in ataxia, may be a promising avenue for treatment. The author notes several examples of repurposed drugs that have shown potential in preclinical or clinical studies, including Riluzole that is used to treat amyotrophic lateral sclerosis (ALS), which has been shown to improve motor function and reduce cerebellar atrophy in animal models of ataxia. Alternatively, Acetyl-DL-leucine is used to treat vertigo, which has been shown to improve gait and balance in patients with cerebellar ataxia in clinical studies.

Also 4-aminopyridine is used to treat multiple sclerosis, which has been shown to improve motor function and reduce ataxia symptoms in animal models of ataxia.

The author notes that while repurposed drugs may offer a promising treatment approach for ataxia, further research is needed to fully evaluate their safety and effectiveness in humans. The author also highlights the need for continued research into the underlying mechanisms of ataxia, in order to identify new drug targets and develop more specific pharmacological treatments for this condition [80].

Virtual reality therapy

Virtual reality therapy (VRT), also known as simulation for therapy, has emerged as a promising approach in the rehabilitation of various neurological conditions, including ataxia. It is a form of Virtual reality exposure therapy to help decrease the intensity of the stress

responses you might have to situations, thoughts, or memories which provoke anxiety or fear. Although research on the specific use of VR therapy for ataxia is still limited, it shows potential in improving motor coordination, balance, and functional abilities. Here are some key points regarding the use of virtual reality therapy in ataxia:

- Balance and coordination training: VR technology can create immersive and interactive environments that simulate real-world scenarios. These virtual environments can be designed to challenge an individual's balance and coordination, providing a controlled and safe setting for practicing movements and improving motor skills affected by ataxia.
- Visual feedback: One of the advantages of VR therapy is the provision of real-time visual feedback. This feedback can enhance proprioception (awareness of body position) and visual-motor integration, which are often impaired in individuals with ataxia. Visual cues, such as targets or virtual guides, can help individuals with ataxia improve their movement accuracy and coordination.
- Task-specific training: VR therapy can offer task-specific training that focuses on activities relevant to daily life. For example, exercises can be designed to simulate reaching, grasping, and manipulating objects, mimicking functional movements and tasks that individuals with ataxia may find challenging. The goal is to improve motor planning, execution, and coordination in a virtual environment that can be adjusted to match individual needs and abilities.
- Motivation and engagement: VR therapy can provide an engaging and motivating platform for rehabilitation. The immersive and interactive nature of virtual environments can enhance individuals' motivation to participate in therapy and adhere to their treatment plans, potentially leading to more effective outcomes.
- Adaptability and progression: Virtual reality systems can be adjusted and customized to meet the changing needs and progression of individuals with ataxia. The level of difficulty, complexity, and intensity of the exercises can be modified based on an individual's abilities and progress, allowing for personalized and adaptive training programs.

It is important to note that while VR therapy shows promise in the rehabilitation of ataxia, it should be used as part of a comprehensive treatment plan that may include other conventional therapies, such as physical therapy and occupational therapy. Additionally, the specific VR systems, programs, and protocols used may vary depending on the availability of resources and the expertise of the healthcare professionals involved.

Research by Takimoto., *et al*. (2021) describes a case of cerebellar ataxia that was successfully treated using virtual reality (VR)-guided rehabilitation. The patient, a 78-year-old woman with cerebellar ataxia caused by cerebellar infarction, underwent a 4-week VR-guided rehabilitation program that involved interactive exercises to improve balance, gait, and coordination. The VR system used in the rehabilitation program provided the patient with visual and auditory feedback, as well as real-time monitoring of her movements. The exercises were tailored to the patient's individual needs and level of ability and progressed in difficulty over the course of the program. The authors report that the patient showed significant improvements in her gait, balance, and coordination after the 4-week rehabilitation program, as measured by a range of outcome measures. The authors note that the VR-guided rehabilitation program was well tolerated by the patient, and that she reported feeling more confident and independent in her daily activities. The authors suggest that VR-guided rehabilitation may be a promising treatment approach for individuals with ataxia, particularly in cases where traditional physical therapy approaches may not be feasible or effective. They note that VR-guided rehabilitation has several potential advantages, including the ability to provide real-time feedback and monitoring, as well as the ability to tailor exercises to the individual needs and abilities of the patient. Overall, the research by Takimoto., *et al*. highlights the potential of VR-guided rehabilitation as a treatment option for ataxia, and underscores the importance of developing tailored and individualized approaches to rehabilitation for affected individuals [81].

Conclusion

Ataxia refers to a group of neurological disorders characterized by the patient's coordination problems, gait disturbance and trouble speaking. However, the investigation of underlying causes requires systematic evaluation. These disorders can affect various parts of the

body, including the limbs, trunk, and even eye movements. In acute settings, the clinician's main mission is to recognize life-threatening events. There are different types of ataxia, including hereditary ataxias (such as Friedreich's ataxia and spinocerebellar ataxias) and acquired ataxias (caused by conditions like stroke, which typically happens suddenly with headache, nausea, and vomiting, multiple sclerosis, or head trauma). In nonacute settings, no simple algorithm or guideline to follow exists. Conclusions about ataxia can vary depending on the specific type and underlying cause. Because this condition is complex and multifactorial diagnosing ataxia involves a comprehensive medical evaluation, including a detailed medical history, physical examination, which can often prompt appropriate laboratory and diagnostic tests to confirm a clinical working diagnosis. In certain situations, finding an etiology can become a daunting task. On the other hand Genetic counseling in cases of hereditary ataxia is crucial. It helps individuals and their families understand the inheritance pattern, risk factors, and available options for family planning.

It is important to note that ataxia is a complex condition with a wide range of underlying causes and individual experiences. Therefore, treatment and management strategies should be tailored to each person's specific needs and circumstances and regular follow-up with healthcare professionals is essential to monitor the progression of the condition and adjust interventions accordingly.

Further research and clinical trials are needed to establish the efficacy and optimal utilization of virtual reality therapy for ataxia. Consulting with a healthcare professional experienced in VR rehabilitation or a specialized neurological rehabilitation center can provide more specific guidance and recommendations based on individual needs and circumstances.

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Conflict of Interest

Authors declare no conflict of interest.

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