International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Ataxia as Symptom or Disease: A Review of Mechanisms of Primary Ataxia and Acquired Ataxia

Katherina Tereshchenkov

Student

Abstract

This review examines the mechanisms underlying acquired and primary ataxias, emphasizing both their shared features and distinctions. In both primary and acquired forms, cerebellar dysfunction develops through damage to Purkinje neurons and disruptions in calcium
signaling pathways that regulate excitability and motor coordination. Acquired ataxias most often result from external factors such as toxins, immune reactions, or neurodegenerative processes.
Because these causes can sometimes be identified and treated, acquired ataxias may stabilize or even improve when addressed early. Primary ataxias, in contrast, arise from genetic mutations
that drive progressive and irreversible cerebellar degeneration. Current treatments are largely supportive, though new research is investigating gene modulation, calcium channel regulation, and mitochondrial protection as potential therapeutic strategies. Recent advances in genetic testing and neuroimaging have improved classification and diagnostic accuracy. However,
reliable biomarkers that clearly separate primary and acquired ataxias remain limited. By comparing overlapping and distinct mechanisms, this review emphasizes the importance of early diagnosis and ongoing research into calcium signaling and Purkinje neuron biology to guide future therapies for movement disorders.

Keywords: ataxia, Purkinje neurons, calcium signaling, acquired ataxia, primary ataxia

Introduction

Movement is a complex neurophysiological process involving the coordinated activity of multiple brain regions to plan, initiate, and modulate motor control. The primary motor cortex, found in the brain's frontal lobe, sends signals through nerve pathways to the spinal cord, where they reach motor neurons that connect directly to muscles (Sanes & Lichtman, 2001). These motor neurons form neuromuscular junctions or specialized synapses releasing the neurotransmitter acetylcholine to activate muscle fibers. This release causes the muscle to contract, allowing movement to occur (Sanes & Lichtman, 2001). While the primary motor cortex generates motor commands that activate spinal motor neurons and skeletal muscles, the cerebellum plays a crucial role in refining these outputs. Located at the hindbrain, within the posterior cranial fossa, the cerebellum integrates sensory and motor information to ensure precision, timing, and stability in voluntary movements. The basal ganglia are primarily involved in the initiation and selection of voluntary motor actions by modulating activity in the motor cortex through cortico-basal ganglia-thalamo-cortical loops (DeLong & Wichmann, 2007). They facilitate desired

movements while inhibiting competing or unnecessary motor programs, contributing to smooth and purposeful execution of motion. In contrast, the cerebellum is essential for motor coordination, timing, and precision. It integrates sensory feedback with motor commands to fine-tune movements and ensure postural stability and accuracy (Manto et al., 2012).

The cerebellum includes a complex structure composed of nuclei, which transmit information to induce movement. These nuclei relay cerebellar signals to other motor areas, including the thalamus and brainstem. Granule cells receive excitatory input from mossy fibers carrying sensory and proprioceptive data. The cerebellum's circuitry is highly structured, with Purkinje cells acting as the primary inhibitory output neurons projecting to the deep cerebellar nuclei (Gao et al., 2012; Ito 2006). The parallel fibers synapse onto Purkinje cells, shaping cerebellar output. These inhibitory neurons integrate signals from climbing fibers, which originate in the inferior olive, and parallel fibers, which derive from granule cells. Climbing fibers from the inferior olive form powerful synapses on Purkinje cells and play a key role in motor error correction and plasticity (Schwartz, 2016). This architecture allows the cerebellum to compare intended motor output with actual performance and make rapid, real-time adjustments.

Calcium plays a fundamental role in synaptic transmission by triggering the release of neurotransmitters at the presynaptic terminal. Intracellular calcium signaling within Purkinje cells is central to this function. It regulates both neuronal excitability and synaptic plasticity, which are essential for motor learning and adaptation (Manto, 2022). The cerebellum also interacts with cortical and subcortical centers, including the basal ganglia, forming integrated networks involved in both motor control and higher cognitive functions.

The cerebellum’s function depends on tightly regulated chemical communication.

Neurotransmitters and neuromodulators are the key messengers in these processes.

Neurotransmitters, such as glutamate and GABA, act quickly and locally. Glutamate provides excitatory signaling from granule cells and mossy fibers, while GABA, released by Purkinje cells, inhibits the deep cerebellar nuclei (Manto & Jissendi, 2012). Neuromodulators, including dopamine, serotonin, and acetylcholine, operate over broader timescales and larger areas of the brain. Rather than directly triggering neuronal firing, neuromodulators influence how excitable neurons become or how effectively they transmit signals (Teleanu et al. 2022). This modulation affects circuit behavior, synaptic plasticity, and movement patterns based on behavioral context and internal states (Warthen et al., 2009). Dopaminergic and serotonergic inputs modulate the excitability of Purkinje cells and interneurons, altering the timing and strength of signals relayed to deep cerebellar nuclei and affecting motor coordination and timing (Teleanu et al., 2022). By regulating neuronal responsiveness and synaptic transmission, neuromodulators ensure the cerebellum can dynamically adjust motor commands in response to sensory input and task demands Coordinated movement results from the integration of motor commands, sensory input, and cerebellar modulation, producing smooth and purposeful actions with accurate force and timing. Markin uncoordinated movement is irregular timing, tremors, imprecise targeting (dysmetria), and instability. These impairments typically result from disrupted cerebellar signaling, especially due to altered Purkinje cell output or imbalanced neurotransmitter activity (Manto 2022). This highlights the importance of precise regulation within the cerebellar system for normal motor function.

Ataxia

Ataxia refers to a neurological condition characterized by impaired coordination of voluntary

movements, often resulting from dysfunction or damage to the cerebellum or its associated pathways. Ataxia can present with gait instability, balance impairment, slurred speech, and abnormal eye movements (Lin & Kuo 2023). Ataxia can occur because of a genetic disorder, autoimmune disease, vitamin deficiency, tumor, stroke, and more. However, as the causes differ, ataxia can either be its own individual condition or resulting from an already occurring disruption. Therefore, ataxia may occur as a primary disorder, as seen in hereditary spinocerebellar ataxias or as an acquired symptom. Estimates suggested that hereditary ataxias affect approximately 26 per 100,000 individuals globally, though rates vary depending on region and genetic subtype (Hafiz & De Jesus 2023). There are also sporadic ataxias, which are not inherited and occur frequently in older adults, often lacking a clearly identifiable cause (Lieto et al., 2019). Since the estimate accounts only for hereditary ataxias, it is important to remember that other forms, such as sporadic ataxias, also contribute significantly to the overall prevalence.

Medically, ataxia is highly significant because it often signals deeper dysfunction within the cerebellum or its associated pathways. In many cases ataxia, whether primary or acquired, is progressive and can severely impair a person's quality of life. Early recognition and accurate identification of the underlying cause are essential for determining the course of the disease, planning treatment, and providing appropriate support, especially due to treatment variations between acquired and primary ataxias. Additionally, recognizing whether ataxia is a stand-alone neurodegenerative disorder or a symptom of another condition helps clinicians design more personalized and effective interventions.

Although cerebellar research has advanced in recent decades, there is still a lack of clarity on how the mechanisms of ataxia differ between its presentation as a symptom and as a primary disorder. While both forms share similar motor features such as imbalance, tremor, and poor coordination, the underlying biological processes may be quite different. Acquired ataxia, often occur from external insults like stroke or substance abuse, where cerebellar function is temporarily or partially impaired without widespread degeneration. In contrast, primary cerebellar ataxias such as spinocerebellar ataxias involve progressive, cell-specific degeneration and early disruption of Purkinje cell signaling (Lin & Kuo, 2023). Despite these differences, much of the existing literature treats ataxia as a uniform clinical condition (Warthen et al., 2024).

This limits the development of more nuanced treatment strategies and contributes to diagnostic uncertainty. Furthermore, in clinical practice, the boundary between ataxia as a symptom and as a disorder may not have a clear definition, making classification and treatment planning more challenging.

The aim of this review is to describe differing mechanisms of when ataxia occurs as a symptom of broader neurological disruption compared to when it arises as a primary neurodegenerative process. By addressing this distinction, there can be additional clarity to cerebellar pathophysiology and support to the development of targeted research, diagnostics, and therapeutic approaches in the study of movement disorders.

Ataxia as a Symptom

Etiology of Acquired Ataxias

Acquired ataxias are conditions in which cerebellar impairment arises because of another underlying disorder, rather than from a primary cerebellar disease. They develop when external influences disrupt cerebellar function either through direct effects on cerebellar pathways or by altering the physiological conditions necessary for normal cerebellar output (Hafiz & De Jesus, 2025). These conditions include a wide range of inflammatory, vascular, neoplastic, metabolic, toxic, and infectious etiologies. A key

feature of many acquired ataxias is their potential reversibility with the prompt identification and effective management of the underlying cause.

Multiple Sclerosis. Multiple sclerosis (MS) represents one of the most frequent causes of acquired cerebellar symptoms in young adults. MS involves the immune system attacking the myelin sheath within the central nervous system, thereby disrupting the propagation of neural signals. When demyelination occurs in the cerebellum, cerebellar peduncles, or brainstem, patients may develop symptoms including gait unsteadiness, limb incoordination, or slurred speech. These symptoms can fluctuate over time and are particularly prominent during disease flare-ups. The cerebellum itself is not always permanently damaged in such cases, which helps explain why symptoms often improve with corticosteroids or disease-modifying immunotherapies (Zengin, 2024).

Stroke. Infarction involving the cerebellum, particularly within the vascular territory of the posterior inferior cerebellar artery (PICA), can lead to the sudden onset of cerebellar ataxia, often presenting as dysmetria, truncal instability, and vertigo. These signs reflect impaired motor coordination resulting from ischemic injury to cerebellar neurons due to the loss of blood supply (Lee, 2009). In more severe cases, post-stroke swelling in the posterior fossa may exert pressure on nearby structures such as the brainstem and fourth ventricle. This overall effect can lead to additional neurological deterioration or obstructive hydrocephalus, occasionally requiring emergency surgical intervention. Nevertheless, if managed promptly, ataxic symptoms may improve significantly, especially if the damage is localized and compensatory neuroplasticity is preserved (Lee 2009).

Tumors. Cerebellar ataxia symptoms can also appear in association with malignancies, either as a direct consequence of tumor growth or due to immune responses triggered by the presence of cancer. Tumors located in the posterior fossa or metastatic lesions involving cerebellar tissue can directly interfere with cerebellar circuits by compressing or infiltrating neural structures. Pilocytic astrocytomas are benign, slow-growing tumors that frequently arise in the cerebellum, particularly in children and young adults, and often present with symptoms of ataxia due to compression of cerebellar structures or obstruction of cerebrospinal fluid flow (Dasgupta & Gupta, 2024). Surgical resection is the primary treatment and often results not only in halting symptom progression but also in reversal of ataxic symptoms, particularly when intervention occurs before irreversible neuronal damage has occurred. In paraneoplastic cerebellar degeneration, the immune system mistakenly targets cerebellar neurons in response to antigens expressed by tumors. This form of ataxia is often associated with small-cell lung carcinoma, breast cancer, and gynecological malignancies. Onset is usually subacute and can be rapidly progressive, but prompt identification and treatment of the underlying tumor, along with immunotherapy, may limit further cerebellar damage. In most cases, significant cerebellar damage, especially Purkinje cell loss, is irreversible, and patients have persistent ataxia and coordination deficits. Some partial improvement may occur if initiation of treatment occurs early, before extensive neuronal loss (Dasgupta & Gupta, 2024).

Toxins. Exposure to certain toxins or drugs can interfere with cerebellar processing and produce ataxia. Implicated in causing cerebellar toxicity include chemotherapeutic agents such as cytarabine and 5-fluorouracil (Lieto et al., 2019). Chronic alcohol consumption has a strong associated with cerebellar degeneration, especially affecting the anterior superior vermis, which contributes to gait instability (Andersen, 2004). Environmental toxins, including heavy metals like mercury or organic solvents such as toluene, may disrupt cerebellar function either through direct neuronal toxicity or by altering systemic metabolism. In many cases, the effects of toxins are dose-dependent and may be partially reversible with cessation of exposure and appropriate medical management (Lieto et al., 2019).

Infections. Cerebellar symptoms may arise in the context of infections affecting the central nervous system. In children, acute post-viral cerebellar ataxia often follows infections such as Epstein-Barr virus. This condition typically resolves spontaneously within a few weeks and result from transient immune-mediated inflammation rather than direct viral invasion (Branes & Brew 2019). Bacterial cerebellitis and chronic infection with neurotropic viruses such as John Cunningham virus (JCV) may cause more severe and longer-lasting cerebellar damage than the typical post-viral ataxia seen in children. JCV infection in immunocompromised individuals can directly injure cerebellar neurons, including the granule cell layer, and lead to cerebellar atrophy (Sharma et al., 2025). The immune response triggered by JCV reactivation, involving both T-cell and antibody activity, may persist beyond initial viral clearance and continue to impair cerebellar function (Holroyd et al., 2017). In such scenarios, patients may experience persistent ataxia even after the infectious agent is no longer detectable, suggesting that prolonged cerebellar dysfunction arises from sustained inflammatory or immune-mediated injury rather than ongoing infection.

A defining feature of many acquired ataxias is their variable and often reversible course.

Unlike genetic or primary neurodegenerative ataxias that tend to progress slowly and irreversibly, acquired ataxias frequently improve or resolve after addressing the inciting factor.

Across forms of acquired ataxia most cases involve impairments to cerebellar neurons. However, symptoms often fluctuate. This variability is especially noticeable in conditions such as multiple sclerosis or toxin-related syndromes, where changes in systemic physiology or treatment status can alter the degree of cerebellar impairment. This dynamic nature highlights the importance of early recognition and intervention.

Mechanisms of Acquired Ataxia

The functional disruption of cerebellar output in acquired ataxias typically occurs through mechanisms that impair the integrity or signaling capacity of key cerebellar neurons. Two critical contributors to this process are changes in Purkinje cell function and disturbances in calcium signaling. These mechanisms often occur without overt structural degeneration and may be reversible depending on the context and severity of the underlying condition.

Purkinje cells are the primary output neurons of the cerebellar cortex and are crucial for the coordination and timing of motor activities. The integrated output of Purkinje cells modulates the activity of deep cerebellar nuclei, which then projects to motor centers in the brainstem and thalamus. When disruption occurs in Purkinje cell activity, either due to direct interference or changes in the surrounding neural environment, the result is a breakdown in the precision of motor control. In acquired ataxias, Purkinje cells may remain structurally intact but become functionally impaired. For example, chronic alcohol consumption impairs Purkinje cell signaling through multiple mechanisms: ethanol and its metabolites disrupt synaptic function, alter neurotransmitter balance, such as enhanced GABAergic inhibition, and contribute to nutritional deficiencies that impair cerebellar function, even before overt neuron loss occurs (Karhunen et al., 1994). Despite these functional disruptions, Purkinje cells may recover with the removal of the toxic agent and nutritional status restored. This explains why many acquired ataxias improve with timely medical intervention.

Calcium ions play a fundamental role in neuronal activity, influencing processes such as neurotransmitter release, synaptic plasticity, and gene expression. Within Purkinje cells, there is a tight regulation of calcium through channels, intracellular stores, and buffering proteins.

Disruption of calcium homeostasis is a common pathological feature in many forms of acquired cerebellar dysfunction. In ischemic stroke, for instance, a lack of oxygen and glucose deprives neurons of the energy required to maintain calcium gradients, leading to intracellular calcium accumulation. This triggers a cascade of harmful processes including activation of proteases, generation of reactive oxygen species, and even cell damage (Qin et al., 2022). In multiple sclerosis, demyelination and inflammation alter the function of sodium and calcium channels along axons, leading to abnormal calcium influx and potential excitotoxic damage (O'Malley et al., 2008). Systemic inflammation associated with infections or autoimmune disorders may also disrupt calcium buffering within neurons, impairing signal transmission, and plasticity (Parvez & Ohtsuki, 2022).

In acquired ataxias, disruptions in calcium signaling often stem from broader pathological processes such as inflammation, ischemia, or metabolic imbalance. These systemic disturbances
interfere with the cerebellum's ability to regulate intracellular calcium, which is essential for maintaining neuronal excitability and synaptic transmission. While these changes are typically indirect, they can significantly impair cerebellar output.

Clinical Implications

When ataxia emerges as a symptom within the broader landscape of systemic or neurological disease, it presents a unique set of diagnostic and therapeutic challenges. Unlike conditions where cerebellar dysfunction is the central pathological process, acquired ataxia requires clinicians to look beyond the cerebellum and consider a wide array of potential causes. This demands a careful balance between recognizing the signs of cerebellar involvement and identifying the upstream disease mechanisms responsible for that dysfunction.

As such a diverse range of etiologies can trigger acquired ataxia, it is essential to evaluate the clinical presentation in its full context. The sudden onset of ataxia in an otherwise healthy individual may suggest an acute cause such as stroke, viral cerebellitis, or intoxication. In contrast, fluctuating or episodic symptoms might point to autoimmune demyelination or metabolic instability. The time course associated neurological signs, recent medical history, and systemic symptoms all provide importance in the diagnostic process.

The presence of ataxia as a symptom rarely necessitates direct treatment aimed at the cerebellum itself. Instead, clinical management shifts toward correcting or controlling the underlying condition that has disrupted cerebellar function. Immunomodulatory therapy can reduce cerebellar symptoms in multiple sclerosis or paraneoplastic syndromes. In the setting of cerebellar infarction, interventions may include antithrombotic therapy or surgical decompression, depending on the extent and location of the damage. While supportive care and physical therapy can assist in regaining motor coordination and balance, these measures are typically adjunctive and offer only partial or compensatory benefit. The most effective improvement in cerebellar symptoms results from successful resolution or mitigation of the primary disease process. This might include treating an underlying infection, removing a tumor, correcting a metabolic imbalance, or achieving abstinence in cases of alcohol-induced cerebellar dysfunction. In such cases, the intervention targets the root cause of cerebellar dysfunction and can allow Purkinje cells and neural circuits to recover their function with limited structural damage. On the other hand, interventions that focus only on symptoms, such as balance training or medications to reduce tremors, rarely result in meaningful or lasting improvement without addressing the underlying pathology. This underscores the importance of identifying and directly treating the cause of acquired ataxia, since the cerebellar

symptoms are often a downstream effect of a broader disease process. This further reinforces the importance of early recognition and intervention in acquired ataxias.

Ataxia as a Primary Disorder

Overview of Hereditary and Idiopathic Ataxias

Cerebellar ataxia represents a spectrum of disorders marked by impaired motor coordination, gait instability, and balance disturbances, all arising from cerebellar dysfunction. Ataxia may emerge from acquired, idiopathic, or hereditary causes, but this review focuses primarily on hereditary forms that implicate molecular and genetic disturbances, particularly those targeting the cerebellum. These include autosomal dominant spinocerebellar ataxias (SCAs), autosomal recessive cerebellar ataxias (ARCAs), and Friedreich's ataxia. Characteristics of each of these conditions is progressive neurodegeneration, with the cerebellum being the main site of pathology. There are other lesser known forms of genetic ataxia but for the purpose of this review they will not be discussed in depth.

The global epidemiology of hereditary cerebellar ataxias remains difficult to quantify due to regional differences in genetic composition and variations in diagnostic practices. A systematic review by Ruano et al. (2014) estimated that the average prevalence of dominant hereditary cerebellar ataxias was approximately 2.7 per 100,000 people, while autosomal recessive forms affected roughly 3.3 per 100,000. These estimates suggested that around one in every 10,000 individuals globally may be affected by some form of hereditary cerebellar ataxia. However, a considerable proportion of cases remain without a known genetic diagnosis even after extensive testing, indicating that the true prevalence is likely higher and that additional causative genes remain undiscovered.

Spinocerebellar ataxia

Hereditary ataxias result from monogenic mutations, many of which have been identified through advances in genetic technologies. Spinocerebellar ataxias are genetically heterogeneous and most inherited in an autosomal dominant pattern. More than 30 distinct SCA subtypes have been described, including SCA1, SCA2, SCA3 (also known as Machado-Joseph disease), and SCA6, each linked to specific gene mutations affecting neuronal homeostasis (Meera et al., 2016). Despite genetic variability, these disorders often converge on a shared pathological hallmark, which is selective degeneration of cerebellar Purkinje neurons.

Autosomal recessive cerebellar ataxia

Autosomal recessive cerebellar ataxias are less common but include highly penetrant forms such as Friedreich's ataxia, ataxia-telangiectasia, and ataxia with oculomotor apraxia.

Friedreich's ataxia, the most prevalent of the recessive ataxias, typically presents in adolescence and involves expanded GAA repeats in the FXN gene. This expansion leads to frataxin deficiency, mitochondrial dysfunction, and neurodegeneration. Although the affected gene products vary considerably across both dominant and recessive forms, the common endpoint remains the same: degeneration of neurons within cerebellar circuits, especially Purkinje cells and deep cerebellar nuclei. In some ARCAs with known metabolic or mitochondrial dysfunction, such as Friedreich's ataxia, certain drugs show disease-modifying potential by enhancing antioxidant responses, yet even these therapies do not appear to reverse existing cerebellar injury. Overall, current treatments aim to stabilize or slow progression, rather than restore lost neuronal function.

Idiopathic forms

Beyond the hereditary forms, idiopathic cerebellar ataxias remain a challenging clinical entity, as there is

no clear identifiable genetic or acquired cause thorough evaluation. Advances in sequencing technologies have revealed that some cases once considered idiopathic are actually genetic, while others remain without a known cause, highlighting that idiopathic ataxias can
reflect both hereditary and non-hereditary processes (Lin & Kuo, 2023).

Etiology of Primary Ataxia

Purkinje neurons play a critical role in cerebellar function, serving as the primary output neurons of the cerebellar cortex. They receive synaptic input from parallel and climbing fibers and exert inhibitory control on cerebellar nuclei, which in turn modulate motor pathways. These neurons are uniquely vulnerable to insults due to their extensive dendritic arbor, high metabolic demand, and reliance on tightly regulated ion channel function. In many forms of ataxia, dysfunction in Purkinje cell signaling precedes detectable neurodegeneration, highlighting the significance of electrophysiological disturbances as early pathogenic events. Across various SCA mouse models, abnormalities in Purkinje neuron firing patterns have been consistently observed. Even before morphological degeneration becomes apparent, these neurons show reduced firing frequency and increased irregularity, which strongly correlates with the onset of ataxic symptoms (Meera et al., 2016). For instance, in mutant mice with altered P-type calcium channel genes, researchers have demonstrated that Purkinje neurons maintain their average firing frequency but lose the temporal precision of their spiking (Meera et al., 2016). This irregularity in firing disrupts the delicate timing necessary for cerebellar output and is sufficient to cause motor impairment.

Dendritic arborization defects are another common feature across multiple forms of ataxia. In mice, which lack the β_4 subunit of voltage-gated calcium channels, Purkinje cells display reduced dendritic complexity and altered synaptic input from parallel fibers (Benedetti et al., 2016). These structural changes compromise the integrative capacity of Purkinje neurons, diminishing their ability to process excitatory input and maintain output to the cerebellar nuclei.

Importantly, these deficits emerge during late developmental stages, indicating that even postnatal maturation of Purkinje cells is dependent on proper ion channel function and synaptic organization.

Purkinje neuron vulnerability also occurs in autosomal recessive spinocerebellar ataxia 20, caused by mutations in the SNX14 gene. SNX14 deficiency leads to impaired axonal transport and mitochondrial dysfunction within Purkinje neurons, compromising cellular energy supply and contributing to neuronal degeneration (Zhang et al., 2021). The affected neurons show signs of disrupted microtubule organization and mitochondrial distribution, further illustrating the complex interdependence between cytoskeletal integrity, organelle transport, and neuronal survival.

In summary, disrupted firing patterns, dendritic simplification, and impaired axonal transport represent early markers of Purkinje neuron dysfunction in cerebellar ataxia. These alterations often occur before cell death and contribute directly to motor impairments. Across genetically diverse ataxias, Purkinje neurons emerge as a common site of vulnerability, where disruptions in intracellular signaling, synaptic architecture, and energy metabolism converge. Numerous ataxia-associated genes encode components of the calcium signaling pathway. The CACNA1A gene encodes the alpha subunit of P/Q-type calcium channels (CaV2.1), which are highly enriched in cerebellar neurons and crucial for both synaptic transmission and intrinsic excitability. Mutations in CACNA1A implicated in episodic ataxia type 2 and spinocerebellar ataxia type 6. Loss-of-function mutations in this channel reduce calcium influx, leading to impaired neurotransmitter release and irregular Purkinje neuron firing. Conversely, gain-of-

function mutations can cause excessive calcium entry, triggering excitotoxicity and cellular stress (Huang & Shakkottai, 2023; Rajakulendran et al., 2010).

Disrupted calcium homeostasis also impairs mitochondrial function. In mice models, which harbor mutations in the α_1A subunit of CaV2.1, cerebellar granule cells show altered calcium handling, mitochondrial depolarization, and increased apoptotic markers (Bawa & Abbott, 2008). Although reactive oxygen species were not significantly elevated, the findings indicated that mitochondrial dysfunction driven by calcium imbalance may underlie cell vulnerability in these models. Calcium-activated potassium channels serve as essential regulators of neuronal excitability by shaping action potential afterhyperpolarization. These include the

large conductance BK channels (KCNMA1) and small conductance SK2 channels (KCNN2). Downregulation or dysfunction of these channels is observed in multiple SCA models and leads to impaired repolarization, reduced firing regularity, and motor deficits (Huang & Shakkottai, 2023). Experimental restoration of BK and SK2 channel activity improves Purkinje neuron

spiking precision and ameliorates behavioral impairments, highlighting the therapeutic potential of modulating calcium-activated potassium channels.

Several components of the calcium signaling cascade have been implicated in cerebellar ataxias, demonstrating the complexity of calcium regulation in Purkinje neuron function. The TRPC3 channel, mutated in spinocerebellar ataxia type 41 (SCA41), results in a gain of function that causes excessive calcium influx and Purkinje neuron hyperexcitability, contributing to neuronal degeneration. The inositol 1,4,5-trisphosphate receptor type 1 (IP3R1) is responsible for calcium release from intracellular stores within the endoplasmic reticulum. Mutations or dysregulation of IP3R1 have a link to ataxias including SCA15, SCA29, and some autoimmune forms. Excessive IP3R1 activity leads to abnormal intracellular calcium overload, which disrupts cellular homeostasis and triggers excitotoxicity. Mutations in plasma membrane calcium ATPases PMCA2 and PMCA3 impair the cell's ability to pump excess calcium out, resulting in elevated intracellular calcium levels (Huang & Shakkottai, 2023). This imbalance disturbs Purkinje neuron firing and contributes to motor dysfunction characteristic of ataxia. Disruptions throughout the calcium signaling pathway, from calcium entry through channels to intracellular release and extrusion, converge to impair Purkinje neuron function and survival, highlighting calcium regulation as a critical factor in cerebellar health and ataxia progression (Huang & Shakkottai, 2023). Together, these findings support a model in which disrupted calcium homeostasis initiates a cascade of harmful processes, including mitochondrial damage, oxidative stress, and excitotoxicity. The convergence of diverse genetic mutations on calcium signaling pathways underscores its pivotal role in Purkinje neuron health and ataxia pathogenesis.

Clinical Implications

Although no cure currently exists for hereditary cerebellar ataxias, recent insights into their molecular mechanisms have opened the door to therapeutic strategies. These include pharmacological agents aimed at restoring neuronal excitability, gene-based therapies targeting mutant alleles, and drugs that protect against mitochondrial stress. Because early dysfunction often precedes irreversible cell loss, timely diagnosis and intervention are critical for altering disease trajectories.

Ion channel modulators have shown promising results in preclinical models and some human trials. For example, 4-aminopyridine, a potassium channel blocker, enhances action potential precision and can reduce symptoms in episodic ataxia type 2 and spinocerebellar ataxia type 6. However, its non-specific

effects on other neurons limit its broader utility and may induce adverse outcomes (Huang & Shakkottai, 2023). More selective combinations, such as chlorzoxazone and baclofen, have demonstrated superior efficacy. Chlorzoxazone activates BK and SK2 channels, restoring afterhyperpolarization, while baclofen, a GABA-B receptor agonist, indirectly supports potassium channel activation. These agents improve motor performance and neuronal firing across multiple SCA models, including SCA1, SCA2, and SCA6.

Gene suppression technologies such as antisense oligonucleotides (ASOs) and RNA interference offer a complementary approach. These strategies aim to selectively reduce the expression of mutant alleles, such as ATXN1, ATXN2, and ATXN3. In experimental models, gene suppression has normalized ion channel transcripts, restored Purkinje neuron excitability, and improved motor function (Huang & Shakkottai, 2023). Although clinical translation remains ongoing, these results indicate the potential for gene-based precision therapies.

Mitochondrial protection is another critical avenue of research. In models of SNX14 deficiency, the antiepileptic drug valproate can restore mitochondrial transport in Purkinje neurons and reduce motor deficits (Zhang et al., 2021). For patients with Friedreich's ataxia, omaveloxolone, an NRF2 activator, has demonstrated clinical benefit by enhancing antioxidant capacity and mitochondrial resilience. Given that mitochondrial dysfunction is common in multiple SCA and ARCA subtypes, this strategy may have broader applications.

Treatment options for primary cerebellar ataxias, including spinocerebellar ataxias (SCAs) and autosomal recessive cerebellar ataxias (ARCAs), are similarly constrained and largely focus on symptom relief rather than reversing cerebellar degeneration. Supportive measures such as balance training, assistive devices, and pharmacologic agents may help manage tremor, gait instability, or spasticity, but they do not halt the progression of neuronal loss.

Although emerging therapies, such as gene-targeted approaches and calcium channel modulators, hold promise for modifying disease course, none have yet demonstrated the ability to regenerate damaged cerebellar circuits or fully restore Purkinje cell function. As a result, current treatment strategies remain largely palliative, aimed at improving quality of life while efforts continue to identify disease-modifying interventions.

In conclusion, recent advances in our understanding of ataxia pathogenesis point to shared cellular vulnerabilities despite genetic diversity. The central role of calcium signaling and Purkinje neuron excitability offers a unifying framework for therapeutic development. Unlike acquired ataxias, which often allow for targeted treatment of underlying causes and may show some reversibility, primary ataxias generally require genetic diagnosis and focus on symptom management and slowing progression due to their intrinsic neurodegenerative nature. While no treatments currently reverse cerebellar degeneration, strategies targeting these common mechanisms may offer disease-modifying benefits.

Discussion

This review describes the differing mechanisms underlying ataxia when it manifests as a symptom of broader neurological disruption, known as acquired ataxia, versus when it arises as a primary neurodegenerative disorder. By addressing this fundamental distinction, the review clarifies an often underexplored aspect of cerebellar pathophysiology. With the aim to support the development of more targeted research, diagnostic tools, and therapeutic strategies in the study of movement disorders.

Several key points emerge from this comparative analysis. Both primary and acquired ataxias share a

common endpoint of cerebellar dysfunction, particularly involving impairment of Purkinje neurons and disruptions in calcium signaling pathways. These pathways are essential for maintaining the delicate balance of neuronal excitability and synaptic integration within the cerebellar cortex, which underlies coordinated motor function. Dysregulation of intracellular calcium homeostasis can arise from genetic mutations affecting calcium channels and related proteins, or from acquired insults such as toxins or immune-mediated damage. In either case, the disruption impairs Purkinje neuron function and eventually contributes to neurodegeneration.

Notably, neoplastic processes can also contribute to ataxia, as tumor infiltration or paraneoplastic immune responses may directly damage cerebellar tissue. In addition, certain chemotherapeutic agents, particularly those that cross the blood-brain barrier, have an association with neurotoxicity and the development of cerebellar symptoms including ataxia. These dual effects underscore the importance of carefully balancing oncologic treatment efficacy with neuroprotective strategies in vulnerable patients. This convergence highlights a unifying biological framework that may guide future therapeutic development across different ataxia types.

However, significant differences exist between primary and acquired ataxias that are critical for clinical management and research focus. Acquired ataxias typically arise from systemic or external factors that affect cerebellar function indirectly. Because these underlying causes, including nutritional deficiencies, autoimmune reactions, or exposure to toxins, are often modifiable or treatable, acquired ataxias frequently exhibit reversibility or stabilization with early intervention of the primary condition. This potential for recovery underscores the importance of comprehensive diagnostic evaluation to identify treatable acquired causes promptly. In contrast, primary ataxias are in all cases caused by intrinsic genetic mutations that result in progressive and irreversible cerebellar degeneration. These hereditary ataxias, including various forms of spinocerebellar ataxias and autosomal recessive cerebellar ataxias, pose a greater challenge due to their relentless progression and the current lack of curative therapies. Treatment strategies are supportive, aiming to manage symptoms and improve quality of life while experimental therapies focused on disease modification, such as gene-silencing technologies, calcium channel modulators, and mitochondrial protectants, are actively being investigated. The irreversible nature of neuronal loss in primary ataxias emphasizes the critical need for early diagnosis, as interventions initiated prior to extensive neurodegeneration may offer the greatest potential benefit.

Despite these advances, many questions remain unanswered. The precise molecular cascades by which diverse genetic mutations converge on Purkinje neuron vulnerability are not fully delineated. The role of non-neuronal cells, such as glia and immune components, in ataxia pathogenesis warrants further exploration. Additionally, the development of reliable biomarkers that can differentiate primary from acquired ataxias at early disease stages remains an unmet clinical need. Such biomarkers could assist in facilitating timely and more accurate diagnosis, enabling patient stratification in clinical trials, and improving monitoring of disease progression and therapeutic response.

Future research efforts should prioritize the integration of genetic, molecular, and clinical data to refine ataxia classification and diagnosis. Advances in next-generation sequencing, coupled with improved neuroimaging methods, show promise in enhancing our ability to detect ataxia subtypes and identify novel causative mutations. On the therapeutic front, continued development and rigorous testing of targeted agents that restore calcium signaling balance, protect mitochondrial function, and modulate gene expression hold significant promise.

Moreover, fostering multidisciplinary collaboration between neurologists, geneticists, and

neuroscientists will be essential to accelerate translational research from bench to bedside.

Improving diagnostic accuracy remains an essential clinical priority. The identification of novel causative genes and impsrovements in genetic testing have transformed ataxia diagnosis, but many patients remain undiagnosed (Ruano et al., 2014). Multimodal approaches that incorporate clinical history, neuroimaging, metabolic screening, and next-generation sequencing are becoming standard practice (Lin & Kuo, 2023). Early identification of ataxia subtypes not only aids in predicting disease course but also permits timely initiation of targeted therapies, which may be most effective before irreversible cerebellar damage occurs.

Conclusion

Ataxia remains comparatively understudied to other neurodegenerative disorders, partly due to its lower prevalence and the complexity of its diverse etiologies. However, the emerging understanding of calcium signaling and Purkinje neuron physiology provides a powerful framework to unite disparate ataxia subtypes and guide the development of effective treatments. This review serves as a step toward bridging the knowledge gap and highlights the urgency of expanding research in this field.

Differentiating primary from acquired ataxias and elucidating their overlapping and distinct mechanisms are vital for improving diagnosis and treatment. By advancing targeted research in calcium signaling pathways and cerebellar neurobiology, there is hope for developing disease-modifying therapies that can slow or prevent neurodegeneration. This work aims to enhance and emphasize the importance of mechanism distinctions towards movement disorder diagnostics and treatment, underscoring the importance of continued investigation into the pathophysiology and management of cerebellar ataxias.

References

1. Andersen, B. B. (2004). Reduction of Purkinje cell volume in cerebellum of alcoholics. *Brain Research, 1007*(1–2), 10–18. https://doi.org/10.1016/j.brainres.2004.01.058 Bawa, B., & Abbott, L. C. (2008). Analysis of calcium ion homeostasis and mitochondrial function in cerebellar granule cells of adult CaV 2.1 calcium ion channel mutant mice. *Neurotoxicity Research, 13*(1), 1–18. https://doi.org/10.1007/BF03033363
2. Benedetti, B., Benedetti, A., Flucher, B. E., & Acsády, L. (2016). Loss of the calcium channel β4 subunit impairs parallel fibre volley and Purkinje cell firing in cerebellum of adult ataxic mice. *European Journal of Neuroscience, 43*(11), 1486–1498. https://doi.org/10.1111/ejn.13241
3. DeLong, M. R., & Wichmann, T. (2007). Circuits and Circuit Disorders of the Basal Ganglia. *Archives of Neurology, 64*(1), 20–24. https://doi.org/10.1001/archneur.64.1.20
4. Gao, Z., van Beugen, B. J., & De Zeeuw, C. I. (2012). Distributed synergistic plasticity and cerebellar learning. *Nature Reviews Neuroscience, 13*(9), 619–635. https://doi.org/10.1038/nrn3312
5. Hafiz, S. & De Jesus, O. Ataxia. [Updated 2023 Aug 23]. In: StatPearls [Internet]. StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562284/
6. Holroyd, K. B., Sotirchos, E. S., DeBoer, S. R., Mills, K. A., & Newsome, S. D. (2017). JC virus granule cell neuronopathy onset two months after chemotherapy for low-grade lymphoma. *Cerebellum & Ataxias, 4*(1), 8. https://doi.org/10.1186/s40673-017-0066-6
7. Huang, H., & Shakkottai, V. G. (2023). Targeting ion channels and Purkinje neuron intrinsic membrane excitability as a therapeutic strategy for cerebellar ataxia. *Life, 13*(6), 1350. https://doi.org/10.3390/life13061350

8. Ito, M. (2006). Cerebellar circuitry as a neuronal machine. *Progress in Neurobiology, 78*(3), 272–303. https://doi.org/10.1016/j.pneurobio.2006.02.006
9. Karhunen, P. J., Erkinjuntti, T., & Laippala, P. (1994). Moderate alcohol consumption and loss of cerebellar Purkinje cells. *British Medical Journal, 308*(6945), 1663–1667. https://doi.org/10.1136/bmj.308.6945.1663
10. Lee, H. (2009). Neuro-otological aspects of cerebellar stroke syndrome. *Journal of Clinical Neurology, 5*(2), 65–73. https://doi.org/10.3988/jcn.2009.5.2.65
11. Lieto, M., Roca, A., Santorelli, F. M., Fico, T., De Michele, G., Bellofatto, M., Saccà, F., De Michele, G., & Filla, A. (2019). Degenerative and acquired sporadic adult onset ataxia. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 40*(7), 1335–1342. https://doi.org/10.1007/s10072-019-03856-w
12. Lin, C.-Y. R., & Kuo, S.-H. (2023). Ataxias: Hereditary, acquired, and reversible etiologies. *Seminars in Neurology, 43*(1), 48–64. https://doi.org/10.1055/s-0043-1763511
13. Manto, M. (2022). The underpinnings of cerebellar ataxias. *Clinical Neurophysiology Practice, 7*, 372–387. https://doi.org/10.1016/j.cnp.2022.11.002
14. Manto, M., Bower, J. M., Conforto, A. B., Delgado-García, J. M., da Guarda, S. N. F., Gerwig, M., Habas, C., Hagura, N., Ivry, R. B., Mariën, P., Molinari, M., Naito, E., Nowak, D. A., Oulad Ben Taib, N., Pelisson, D., Tesche, C. D., Tilikete, C., & Timmann, D. (2012).
15. Consensus Paper: Roles of the Cerebellum in Motor Control—The Diversity of Ideas on Cerebellar Involvement in Movement. *The Cerebellum, 11*(2), 457–487. https://doi.org/10.1007/s12311-011-0331-9
16. Manto, M. U., & Jissendi, P. (2012). Cerebellum: Links between development, developmental disorders and motor learning. Frontiers in Neuroanatomy, 6. https://doi.org/10.3389/fnana.2012.00001
17. Meera, P., Pulst, S. M., & Otis, T. S. (2016). Cellular and circuit mechanisms underlying spinocerebellar ataxias. *The Journal of Physiology, 594*(16), 4653–4660. https://doi.org/10.1113/JP271897
18. O'Malley, H. A., Shreiner, A. B., Chen, G.-H., Huffnagle, G. B., & Isom, L. L. (2009). Loss of Na+ channel β2 subunits is neuroprotective in a mouse model of Multiple Sclerosis. *Molecular and Cellular Neurosciences, 40*(2), 143–155. https://doi.org/10.1016/j.mcn.2008.10.001
19. Parvez, Md. S. A., & Ohtsuki, G. (2022). Acute cerebellar inflammation and related ataxia: Mechanisms and pathophysiology. *Brain Sciences, 12*(3), 367. https://doi.org/10.3390/brainsci12030367
20. Qin, C., Yang, S., Chu, Y.-H., Zhang, H., Pang, X.-W., Chen, L., Zhou, L.-Q., Chen, M., Tian, D.-S., & Wang, W. (2022). Signaling pathways involved in ischemic stroke: Molecular mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy, 7, 215. https://doi.org/10.1038/s41392-022-01064-1
21. Rajakulendran, S., Schorge, S., Kullmann, D. M., & Hanna, M. G. (2010). Dysfunction of the CaV2.1 calcium channel in cerebellar ataxias. *F1000 Biology Reports, 2*, 4. https://doi.org/10.3410/B2-4
22. Ruano, L., Melo, C., Silva, M. C., & Coutinho, P. (2014). The global epidemiology of hereditary ataxia and spastic paraplegia: A systematic review of prevalence studies. *Neuroepidemiology, 42*(3), 174–183. https://doi.org/10.1159/000358801

23. Sanes, J. R., & Lichtman, J. W. (2001). Induction, assembly, maturation and maintenance of a postsynaptic apparatus. *Nature Reviews Neuroscience, 2*(11), 791–805. https://doi.org/10.1038/35097557
24. Schwartz, A. B. (2016). Movement: How the Brain Communicates with the World. Cell, 164(6), 1122–1135. https://doi.org/10.1016/j.cell.2016.02.038
25. Sharma. R., Garnham, J., & Campos, A. (2019). JC virus granule cell neuronopathy. Reference article, Radiopaedia.org. (Updated June 8, 2025, Accessed on 17 Sep 2025) https://doi.org/10.53347/rID-67267
26. Teleanu, R. I., Niculescu, A.-G., Roza, E., Vladâcenco, O., Grumezescu, A. M., & Teleanu, D. M. (2022). Neurotransmitters—Key factors in neurological and neurodegenerative disorders of the central nervous system. *International Journal of Molecular Sciences, 23*(11), 5954. https://doi.org/10.3390/ijms23115954
27. Warthen, K., Walker, N., Wicklund, B. D., Gonzalez, M., Ramirez, N., Gee, S., Al-Dasouqi, H., & Madore, M. (n.d.). Neuromodulation of cerebellum for motor applications review. *25 October 2024*. https://article.imrpress.com/journal/JIN/23/10/10.31083/j.jin2310195/a26fea19a41e7498 b5fd07eade01ce30.pdf
28. Zengin, E. S. (2024). Ataxia in patients with Multiple Sclerosis: A brief review. *Journal of Multiple Sclerosis Research.* https://doi.org/10.4274/jmsr.galenos.2024.2024-4-1 Zhang, H., Hong, Y., Yang, W., Wang, R., Yao, T., Wang, J., Liu, K., Yuan, H., Xu, C., Zhou, Y.,
29. Li, G., Zhang, L., Luo, H., Zhang, X., Du, D., Sun, H., Zheng, Q., Zhang, Y.-W., Zhao, Y., & Zhou, Y. (2021). SNX14 deficiency-induced defective axonal mitochondrial transport in Purkinje cells underlies cerebellar ataxia and can be reversed by valproate. *National Science Review, 8*(7), 1–14. https://doi.org/10.1093/nsr/nwab024