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Sustained Functional Improvement in Progressive Multisystem Cerebellar Ataxia Following an Integrative Regenerative Medicine Approach: A Case Report

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Abstract

Background

Multisystem cerebellar ataxia is a progressive neurodegenerative disorder characterized by impaired motor coordination, postural instability, dysarthria, and a gradual decline in functional independence. Current therapeutic strategies are predominantly supportive in nature and do not target the fundamental biological mechanisms underlying neurodegeneration. Regenerative medicine approaches focusing on intercellular signaling, mitochondrial function, and neuroinflammation have been developed as prospective adjuncts to enhance neuronal function and biological stability.

Case presentation

We report the case of a patient with progressive multisystem cerebellar ataxia who underwent a structured integrative regenerative medicine protocol over a longitudinal follow-up period exceeding 12 months. The multimodal intervention included autologous and allogeneic mesenchymal stromal cells, extracellular vesicle therapy administered via injectable and inhaled routes, stress-enduring pluripotent regenerative cells, xenogeneic

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organ-derived biological signaling preparations, mitochondrial regulatory peptides, intravenous metabolic support, and photobiomodulation therapy. Clinical and functional assessments were performed longitudinally throughout treatment and follow-up.

Results

The patient demonstrated ongoing functional improvements and neurological stabilization, including enhanced postural stability, improved motor coordination, recovery of fine motor skills, refined speech articulation, and regained independence in daily activities. These advancements progressed gradually over the course of the treatment and were maintained during extended follow-up. No significant adverse events or noteworthy complications were reported. The temporal association between regenerative interventions and functional enhancements suggests a potential biological modulation of neurodegenerative mechanisms.

Conclusion

This case exemplifies sustained functional enhancement and clinical stabilization in progressive multisystem cerebellar ataxia, temporally correlated with a multimodal integrative regenerative medicine protocol. Although causality cannot be conclusively determined based on a single case report, these findings substantiate the need for further controlled clinical research into regenerative strategies targeting intercellular signaling, mitochondrial functionality, and neuroinflammatory pathways in neurodegenerative cerebellar disorders.

Keywords

Multisystem cerebellar ataxia; Neurodegeneration; Regenerative medicine; Mesenchymal stromal cells; Extracellular vesicles; Exosomes; Muse cells; Photobiomodulation; Mitochondrial dysfunction; Neuroinflammation; Stem cells; Mitochondrial peptides; European Wellness.

Introduction

Multisystem ataxia involving the cerebellum encompasses a collection of progressive neurodegenerative disorders characterized by impaired coordination, gait unsteadiness, dysarthria, and a gradual decline in fine motor skills. These conditions stem from dysfunction and degeneration within the cerebellum and its associated neural pathways. They notably compromise functional independence and quality of life, often concurrently affecting other neurological and autonomic systems. The pathophysiological mechanisms underlying these disorders include progressive neuronal loss, synaptic dysfunction, neuroinflammation, and disrupted neural network integration, all of which contribute to the deterioration of both motor and non-motor functions over time. At present, therapeutic modalities are limited, with conventional treatments primarily directed toward symptom relief and rehabilitative strategies. To date, no definitive disease-modifying therapies have been established for most forms of progressive cerebellar ataxia [1-4].

Progressive cerebellar ataxias are associated with intricate, multifactorial pathophysiological mechanisms that extend beyond mere neuronal loss. Increasing evidence indicates that chronic neuroinflammation, mitochondrial dysfunction, oxidative stress, and impaired intercellular signaling play significant roles in disease progression and functional decline. The persistent activation of microglia and astrocytes fosters a proinflammatory microenvironment that exacerbates neuronal vulnerability and hampers endogenous repair processes. Furthermore, mitochondrial impairment and energy deficits further jeopardize neuronal survival and synaptic functionality, particularly within cerebellar circuits that demand high metabolic

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resources. Collectively, these mechanisms impede the intrinsic regenerative capacity of the central nervous system and contribute to the progressive, often irreversible deterioration observed in neurodegenerative disorders of the cerebellum [5-9].

Given the limited regenerative capacity of the adult central nervous system, therapeutic strategies for progressive cerebellar ataxias have traditionally focused on symptomatic treatment, including physical therapy, speech therapy, and supportive neurological care. While these interventions may improve functional adaptation, they do not directly address the underlying biological mechanisms responsible for neuronal dysfunction and progressive degeneration. In recent years, advances in regenerative medicine have introduced new therapeutic paradigms aimed at modulating the neural microenvironment, reducing neuroinflammation, and enhancing endogenous repair processes. These approaches focus not only on cell replacement but also on paracrine signaling, immunomodulation, mitochondrial support, and restoration of intercellular communication, which are increasingly recognized as critical factors in maintaining neuronal function and promoting neural resilience in neurodegenerative conditions [10-14].

Among regenerative strategies, mesenchymal stromal cells have garnered substantial attention owing to their immunomodulatory, anti-inflammatory, and neuroprotective properties. Instead of primarily functioning through direct cell replacement, these cells predominantly exert their therapeutic effects via paracrine mechanisms, which include the secretion of bioactive molecules and extracellular vesicles that influence the neural microenvironment. These signaling pathways can modulate inflammatory responses, support mitochondrial function, promote neuronal survival, and enhance endogenous repair processes. Concurrently, extracellular vesicles such as exosomes have become recognized as essential mediators of intercellular communication, capable of transferring regulatory proteins, lipids, and nucleic acids that contribute to tissue homeostasis and functional recovery. Furthermore, greater emphasis has been placed on the utilization of biological preparations derived from cells and regulatory peptides, including tissue-specific and mitochondria-targeted signaling molecules, which can foster cellular resilience, metabolic function, and neuroendocrine regulation. Collectively, these approaches signify a paradigm shift from traditional replacement-based methods towards the modulation of biological systems that promote neural stability, adaptive repair, and the preservation of neurological function [15-22].

Given these emerging advances, integrative regenerative medicine approaches have been increasingly explored as potential strategies for modulating the biological environment underlying neurodegenerative disorders. By targeting multiple interconnected mechanisms, including neuroinflammation, mitochondrial dysfunction, impaired intercellular communication, and reduced adaptive repair capacity, these approaches aim to support neuronal function and preserve neurological integrity. Although growing experimental and clinical evidence suggests that these strategies may contribute to functional stabilization and improved biological resilience, clinical documentation on progressive cerebellar ataxia remains limited. Therefore, the present case report describes the longitudinal functional outcomes of a patient with progressive multisystemic cerebellar ataxia treated with a structured approach to integrative regenerative medicine, with an emphasis on neurological function, motor coordination, and restoration of daily activities autonomy [23-27].

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Methods

Patient description and initial clinical status

The patient was an adult woman with a confirmed diagnosis of progressive multisystemic cerebellar ataxia, established through neurological evaluation at a tertiary care center. The diagnosis was based on clinical presentation, neurological examination, and long-term follow-up, which revealed features including gait instability, impaired coordination, dysarthria, and progressive decline in fine motor skills. At the time of the comprehensive regenerative assessment, the patient had significant difficulty with activities requiring balance, postural control, and upper-extremity coordination, including handwriting, self-care tasks, and standing for extended periods. Despite ongoing conventional treatment, including physical and speech therapy, her functional decline persisted, consistent with the natural progression of progressive cerebellar neurodegeneration [28-31].

Initial functional limitations were documented through clinical assessment and structured functional observation. The patient exhibited impaired fine motor coordination, evident in decreased precision in writing and motor continuity, as well as postural instability when standing and during daily activities. He experienced a speech disorder called dysarthria, characterized by reduced articulation clarity and vocal control. These impairments considerably impacted his daily independence and quality of life, limiting his ability to perform routine activities such as cooking, grooming, and coordinating his upper limbs without assistance. At the time of evaluation, there were no conventional disease-modifying therapeutic options available, so treatment remained primarily supportive [32-34].

Ethical considerations and integrative treatment framework

All interventions were conducted within a clinical framework that prioritized patient safety, informed consent, and continuity of conventional medical care. The patient received a detailed explanation of the integrative regenerative approach, including its investigational nature, potential benefits, and possible risks, and provided written informed consent prior to initiation of treatment. Conventional neurological management, including physiotherapy and speech therapy, was maintained throughout the observation period, and no established treatments were discontinued. The therapeutic strategy was implemented as a complementary intervention aimed at supporting biological function and improving clinical outcomes without interfering with standard medical care [35-36].

The integrative regenerative approach was organized as a step-by-step protocol targeting key biological mechanisms involved in neurodegeneration, such as neuroinflammation, mitochondrial dysfunction, impaired intercellular communication, and decreased adaptive repair capacity. This multimodal framework included autologous and allogeneic cellular therapies, extracellular vesicle-based signaling support, cell-derived biological preparations, mitochondrial regulatory peptides, and metabolic optimization strategies. These interventions were implemented sequentially and over time with the aim of modifying the neural microenvironment, boosting cellular resilience, and enhancing functional stability. The treatment plan was personalized based on clinical response, functional assessments, and continuous safety monitoring over time [39-43].

Study design and longitudinal treatment framework

This study presents a longitudinal clinical case of a patient with progressive multisystemic cerebellar ataxia who received a structured protocol of integrative regenerative medicine over a 12-month period, with continuous follow-up. The therapeutic approach was implemented gradually and sequentially, with interventions applied at specific intervals and adjusted based on clinical response, functional assessments, and safety monitoring. The protocol was designed to target key biological mechanisms involved in neurodegeneration, including neuroinflammation, mitochondrial dysfunction, impaired intercellular signaling, oxidative stress, and diminished adaptive repair capacity [35-39].

Treatment protocol was commenced in December 2024 and continued through January 2026, beginning with biological preparation, followed by regenerative cellular procedures, extracellular vesicle-based signaling support, mitochondrial regulation therapies, and long-term biological maintenance. Clinical outcomes were monitored over time through neurological assessments, behavioral observations, and documentation of motor skills, speech abilities, postural stability, and daily living activities. Standard neurological treatments, including physical and speech therapy, were maintained throughout the treatment and follow-up periods. A detailed summary of the administered regenerative interventions, biological targets, and clinical observations is provided in (Table 1).

Biological preparations derived from organ-specific cells

As part of the integrative regenerative protocol, biological preparations derived from organ-specific cells were administered longitudinally to provide tissue-targeted regulatory signals. These preparations consisted of biological fractions containing peptides, growth factors, and regulatory molecules derived from xenogeneic mammalian tissues, including ovine and lagomorph sources, which had been clinically certified and processed under controlled biomedical manufacturing standards in accordance with established biological safety requirements for human use.

The ability of these preparations to influence cellular metabolism, intercellular communication, and tissue-specific functional regulation through signal-mediated mechanisms, rather than cell grafting, has been investigated.

Preparations aimed at augmenting central nervous system function, including those derived from brain and hypothalamic tissue sources, were administered to support neuroendocrine regulation, neuronal signal stability, and adaptive cellular responses. Additional preparations targeting peripheral nervous system structures were incorporated to enhance neural connectivity and neuromuscular coordination. Concurrently, systemic multi-organ biological preparations containing regulatory components derived from various tissue types—including brain, cardiovascular, hepatic, splenic, thymic, mesenchymal, osteoarticular, adrenal, placental, and reproductive tissues—were administered. These formulations were designed to furnish comprehensive support for biological signaling pathways that influence neuroendocrine homeostasis, immune regulation, and systemic metabolic processes.

These xenogeneic organ-derived biological preparations were administered sequentially throughout the treatment as part of a comprehensive strategy to modulate systemic and neuronal biological environments. Their inclusion in the protocol was based on the concept that tissue-derived regulatory

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molecules may promote cellular homeostasis, enhance adaptive biological responses, and contribute to functional stability in the context of progressive neurodegenerative conditions [50-53].

Stress-resistant mesenchymal stromal cells and pluripotent regenerative cells

The regenerative protocol involved administering autologous and allogeneic mesenchymal stromal cells. Autologous mesenchymal stromal cells were sourced from adipose tissue and delivered during the initial regenerative phase, with a total of approximately 100 million cells administered throughout the treatment. These cells were selected for their well-documented immunomodulatory, anti-inflammatory, and paracrine signaling properties, which have been demonstrated to influence the neural microenvironment, mitigate inflammatory signaling, and enhance neuronal survival and functional stability [54-58].

In addition to autologous cells, approximately 100 million allogeneic mesenchymal stromal cells were administered during the protocol to further enhance support for regenerative signaling. Allogeneic mesenchymal stromal cells have been extensively studied for their ability to exert biological effects through paracrine signaling mechanisms, including the secretion of growth factors, cytokines, and extracellular vesicles that contribute to the modulation of inflammation, mitochondrial function, and tissue homeostasis. Their use was intended to provide additional biological support for signaling to complement autologous cellular interventions.

The protocol also utilized stress-resistant pluripotent regenerative cells, known as MUSE-type cells, with about 40 million cells administered during the later treatment stages. These cells are notable for their non-tumorigenic pluripotent traits, innate stress tolerance, and capacity to migrate to tissue damage sites. Instead of directly replacing damaged tissue, they mainly exert therapeutic effects via regulatory signals that facilitate cellular repair, reduce inflammation, and improve cell resilience. Including these cells aimed to provide ongoing biological support and reinforce long-term functional stability in the neural environment [64-68].

All cell therapies were given in sequence as part of the long-term regenerative protocol, with timing and dosage tailored according to clinical response, functional assessments, and safety tracking. This step-by-step cell intervention approach aimed to enhance biological signaling support while ensuring patient safety and treatment tolerability during the entire observation period.

Extracellular vesicle therapy

Extracellular vesicle-based therapy was integrated as a crucial part of the regenerative protocol to enhance intercellular communication and biological signaling within the neural microenvironment. Extracellular vesicles were administered over time at specific treatment intervals. An initial dose of approximately 30 billion extracellular vesicles was given during the early regenerative phase. Follow-up administrations of about 70 billion extracellular vesicles were then carried out during the intermediate and later treatment phases. These vesicles included both autologous extracellular vesicles, obtained through clinical preparation from peripheral blood, and biological extracellular vesicle preparations administered as part of the integrative protocol [69-73].

The final administration of extracellular vesicles was conducted via inhalation, a noninvasive method that has been studied for its capacity to facilitate delivery to the central nervous system through the olfactory and respiratory pathways. This method has been associated with increased bioavailability of extracellular

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vesicles in neural tissues and has been investigated as a means to support neurological function and modulate neuroinflammatory processes. Inhalation administration was implemented during the maintenance phase of treatment to provide sustained support for biological signaling and to enhance the stability of the neural microenvironment [74-77].

Extracellular vesicles are acknowledged as vital mediators of intercellular communication, facilitating the transport of regulatory proteins, lipids, messenger RNAs, and microRNAs that modulate cellular metabolism, mitochondrial functionality, inflammatory pathways, and tissue homeostasis. Their sequential and ongoing administration aims to enhance adaptive cellular responses, bolster biological resilience, and support functional preservation in the context of advancing neurodegenerative disease [78-82].

Mitochondrial regulatory peptides and metabolic optimization

To advance cellular energy metabolism and mitigate oxidative stress, the regenerative protocol incorporated mitochondrial regulatory peptides alongside intravenous therapies aimed at metabolic optimization. Mitochondrial dysfunction and disruptions in cellular bioenergetics are acknowledged as principal factors contributing to neuronal susceptibility and the progressive decline of function in neurodegenerative disorders. Mitochondrial regulatory peptides, derived from xenogeneic tissues, were administered over a defined period, including formulations targeting regulatory pathways within the central nervous system and peripheral autonomic nervous system. These acellular, peptide-based biological preparations—obtained from xenogeneic mammalian neural tissues and produced in compliance with clinical safety standards—were employed to support mitochondrial functionality, enhance cellular respiration, and foster adaptive cellular responses to stress. The capacity of these regulatory peptides to influence mitochondrial integrity, modulate cellular metabolism, and augment cellular resilience under biological stress conditions has been thoroughly investigated [83-89].

In parallel, intravenous metabolic support was administered, including antioxidant and redox modulators such as glutathione, nicotinamide adenine dinucleotide (NAD^+) precursors, vitamin C, and amino acid formulations. These interventions were intended to enhance cellular antioxidant capacity, support mitochondrial energy production, and modulate oxidative and inflammatory pathways involved in neurodegeneration. Mitochondrial and metabolic optimization strategies have been investigated for their role in supporting neuronal function, improving cellular metabolism, and increasing biological resilience in neurodegenerative conditions [90-95].

These metabolic support and mitochondrial regulatory interventions were administered at predetermined intervals throughout the treatment protocol as part of the integrative regenerative strategy, with the aim of supporting cellular energy homeostasis, enhancing mitochondrial function, and fostering neurological functional stability.

Photobiomodulation therapy

Photobiomodulation therapy was incorporated as part of the integrative regenerative protocol to support mitochondrial function, cellular metabolism, and neuromodulatory processes. Multi-wavelength light therapy was administered longitudinally using defined spectral ranges, including red, yellow, and green wavelengths, applied in accordance with established clinical principles of photobiomodulation. The ability of these wavelengths to influence mitochondrial activity through interaction with chromophores involved

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in cellular respiration, particularly cytochrome c oxidase, has been investigated, resulting in increased adenosine triphosphate (ATP) production, modulation of reactive oxygen species, and improved cellular energy metabolism [96-100].

Photobiomodulation has also been associated with the modulation of inflammatory signaling pathways, improved microcirculation, and increased cellular resistance under conditions of physiological stress. In neurological contexts, light-based therapies have been investigated for their potential to promote neuronal survival, improve synaptic function, and promote functional recovery by modulating mitochondrial activity and cellular signaling pathways. The therapy was administered at defined intervals throughout the treatment period as part of the multimodal regenerative strategy, with the aim of supporting neural metabolic function and contributing to functional stabilization [101-105].

The inclusion of photobiomodulation therapy was based on its established safety profile and its role as a noninvasive intervention capable of supporting cellular bioenergetics and modulating biological processes relevant to the progression of neurodegenerative diseases.

Clinical assessment, functional assessment, and longitudinal follow-up

Clinical outcomes were evaluated longitudinally through structured neurological assessment, functional observation, and documentation of motor and functional performance throughout treatment and follow-up. The initial assessment was conducted prior to the commencement of the integrative regenerative protocol in December 2024, with subsequent follow-up assessments carried out at specified intervals throughout the treatment duration and during the maintenance phase, which extended until January 2026. The evaluation primarily concentrated on motor coordination, postural stability, speech function, fine motor control, and functional independence in activities of daily living [106-110].

The functional assessment comprised a comprehensive neurological examination and systematic observation of activities demanding coordinated motor functions. These activities included standing balance, upper limb coordination, handwriting, gait stability, and routine daily tasks such as personal grooming and cooking, which require sustained motor control. Variations in functional performance were monitored longitudinally through meticulous clinical observation and comparative analysis over time. Special emphasis was placed on indicators of cerebellar function, including coordination, motor precision, and speech articulation [111-115].

Safety was monitored throughout the treatment period, with clinical assessments to evaluate treatment tolerability and detect any potential adverse effects. The longitudinal design of the study allowed for the evaluation of both short-term and sustained functional changes, providing a comprehensive assessment of the clinical progression of patients during and after administration of the integrative regenerative therapy protocol. A detailed summary of the administered regenerative interventions, biological targets, and clinical observations is provided in (Table 1). The temporal sequence of regenerative interventions and clinical follow-up is summarized in (Figure 1).

Date	Intervention	Biological target	Dose / Quantity	Route of administration	Clinical observations
Dec-24	Organ-specific cell-derived biological preparations (central nervous system, hypothalamus, peripheral nervous system, and systemic multi-organ regulatory preparations)	Neural signaling, neuroendocrine regulation, mitochondrial support, systemic biological regulation	Standard clinical preparation	Injectable intramuscular	Initial improvement in postural stability, motor coordination, and fine motor control
Dec-24	Extracellular vesicles	Intercellular communication, neural microenvironment modulation	30 billion vesicles	Injectable intravenous	Early improvement in fine motor function and coordination
Jan-25	Autologous mesenchymal stromal cells (adipose-derived)	Immunomodulation, neuroprotection, paracrine signaling support	100 million cells	Injectable intravenous	Improved motor coordination, handwriting, and postural control
January 2025 – April 2025	Allogeneic mesenchymal stromal cells	Paracrine signaling support, neuroinflammatory modulation	100 million cells	Injectable intravenous	Progressive improvement in gait stability and motor integration
April 2025 – July 2025	Organ-specific biological preparations (brain, autonomic nervous system, and systemic preparations)	Neural regulation, mitochondrial function, neuroendocrine balance	Standard clinical preparation	Injectable intramuscular	Continued improvement in speech articulation and functional independence
Jul-25	Extracellular vesicles	Neural signaling, mitochondrial function, cellular communication	70 billion vesicles	Injectable intravenous	Improved speech clarity, motor coordination, and functional stability
July 2025 – January 2026	Mitochondrial regulatory peptides and metabolic optimization therapy	Mitochondrial function, oxidative stress reduction, cellular metabolism	Standard clinical preparation	Injectable intravenous; subcutaneous	Improved energy levels, neuromuscular coordination, and sustained functional improvement

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Jan-26	Stress-enduring pluripotent regenerative cells (MUSE-type cells)	Regenerative signaling, cellular resilience, neural repair support	40 million cells	Injectable intravenous	Sustained functional recovery and neurological stabilization
Jan-26	Extracellular vesicles	Neural signaling and central nervous system support	70 billion vesicles	Inhaled	Maintenance of neurological stability and functional independence
Throughout treatment period	Photobiomodulation therapy (multi-wavelength light therapy)	Mitochondrial activation, cellular metabolism, neuromodulation	Standard clinical protocol	Injectable intravenous light therapy	Contributed to overall functional stabilization and biological support

Table 1: reflects the longitudinal timeline of regenerative interventions, biological targets, administered doses, and associated clinical outcomes. This table summarizes the sequential integrative regenerative interventions administered between December 2024 and January 2026, including organ-specific cell-derived biological preparations, mesenchymal stromal cells, extracellular vesicles, mitochondrial regulatory peptides, and photobiomodulation therapy. Clinical observations reflect longitudinal functional changes in motor coordination, postural stability, speech function, and independence in activities of daily living.

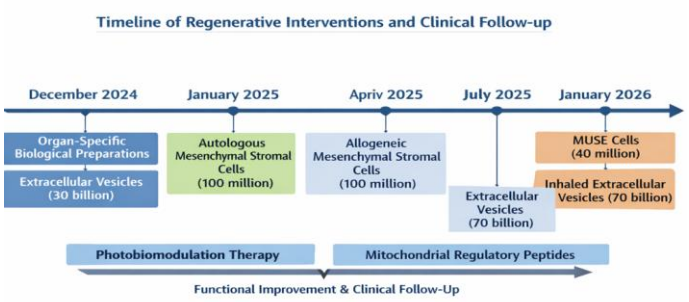

Figure 1: Timeline of regenerative interventions and clinical follow-up.

The diagram illustrates the sequence of regenerative interventions administered between December 2024 and January 2026, including organ-specific cell-derived biological preparations, mesenchymal stromal cells, extracellular vesicle therapy, mitochondrial regulatory peptides, and stress-enduring pluripotent regenerative cells. The timeline also reflects the longitudinal follow-up period during which functional improvements and neurological stabilization were observed.

Results

Baseline functional status

At the baseline evaluation in December 2024, the patient demonstrated significant neurological and functional impairment consistent with progressive multisystem cerebellar ataxia. Clinical examination revealed impaired postural stability, reduced coordination of voluntary movements, dysarthric speech, and marked deterioration of fine motor control. The patient exhibited difficulty in maintaining a stable upright posture and required increased effort to perform coordinated upper-extremity movements.

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Functional activities that necessitate balance, motor precision, and sustained neuromuscular coordination were markedly compromised.

Fine motor impairment was particularly evident in handwriting performance, which demonstrated irregular stroke formation, reduced motor continuity, and impaired spatial organization. These findings were consistent with cerebellar dysfunction affecting motor planning, coordination, and execution. Additionally, speech function was compromised, exhibiting decreased articulation clarity and vocal control characteristic of cerebellar dysarthria. These deficits significantly impacted the patient's daily independence and quality of life [120-123].

The patient also exhibited limitations in executing activities of daily living that necessitate coordinated motor functions and sustained postural control, such as grooming, cooking, and other routine functional tasks. These impairments exemplify the progressive nature of cerebellar conditions.

Early functional changes following initial regenerative interventions

Following the initiation of the integrative regenerative protocol, early functional changes were observed during the initial phase of treatment. Improvements in postural stability and motor coordination were documented, and the patient demonstrated an enhanced capacity to stand independently without external support. Motor control of the upper extremities exhibited measurable improvement, characterized by increased movement precision and a reduction in motor irregularities during coordinated tasks. These observations are indicative of improved neuromuscular coordination and functional motor integration [128-132].

Fine motor function showed early signs of recovery, especially in handwriting. Longitudinal documentation revealed improved stroke continuity, greater spatial organization, and increased motor consistency compared to the initial assessment. These findings indicated improved motor coordination and planning, suggesting functional improvement in cerebellum-related motor control. Speech function also showed progressive improvement, with increased clarity of articulation and greater vocal stability [133-137].

Meanwhile, the patient exhibited enhanced capacity to carry out activities of daily living involving coordinated movements and sustained postural control. Functional advancements were observed in activities such as standing unaided, executing upper limb movements above shoulder level, and sustaining postural stability during routine tasks. These preliminary changes suggest an improvement in motor function and an increase in overall functional independence during the initial stage of the regenerative protocol [138-141].

Intermediate and longitudinal functional improvements

Continuous functional improvement was observed during the intermediate and later phases of treatment. The patient demonstrated sustained improvement in postural stability and motor coordination, with the ability to maintain an upright position independently and perform coordinated upper limb movements with greater precision and control. Improvements in motor function were evident in tasks requiring axial stability and proximal muscle coordination, reflecting improved neuromuscular integration and functional motor control [142-146].

Functional recovery was further demonstrated by the patient's regained ability to perform activities of daily living that had previously been impaired. The patient was able to resume independent activities such as washing her hair, which requires sustained arm elevation and posture control, and cooking, necessitating prolonged standing, coordination of upper limb movements, and fine motor skills. Additionally, her walking ability improved, exhibiting greater fluidity, improved balance, and increased motor confidence. These functional enhancements signified a substantial restoration of autonomy and daily functional capacity [147-151].

Fine motor function continued to improve throughout the follow-up period, with sustained enhancements in handwriting, reflecting improvements in motor coordination, motor planning, and cerebellar function. Speech function also demonstrated continued progress, with increased clarity of articulation and vocal stability. These functional gains were maintained throughout the longitudinal follow-up extending until January 2026, indicating sustained functional stability and preservation of neurological function over time [152-156].

Representative clinical documentation demonstrating recovery of postural stability, motor coordination, and independence in activities of daily living is presented in (Figure 2).

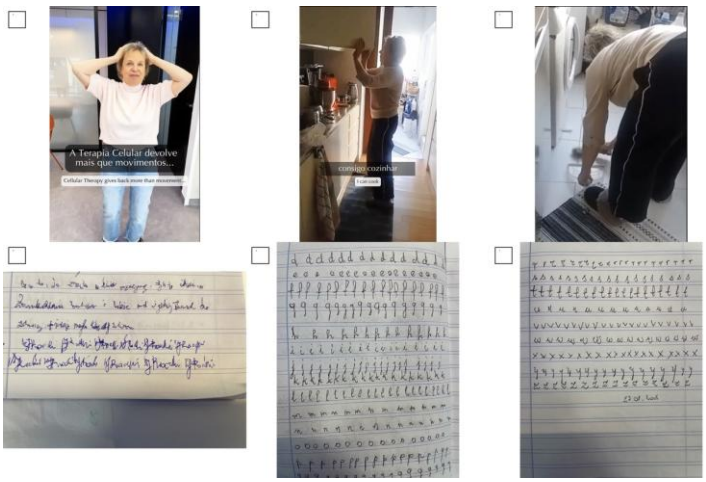

Figure 2: Functional recovery documentation (pre- and post-treatment comparison).

(Figure 2). Functional recovery and restoration of independence following multimodal regenerative therapy: Representative clinical documentation demonstrating recovery of postural stability, motor coordination, and functional independence. (A) Restoration of upright orthostatic posture without external support, indicating recovery of axial control and balance. (B) Bilateral upper-limb elevation above shoulder level, reflecting improved proximal neuromotor coordination and postural integration. (C) Independent performance of daily living activities, including cooking, demonstrating recovery of functional autonomy and coordinated motor planning. (D) Ability to perform complex coordinated tasks such as sweeping, requiring balance, trunk stability, and fine motor control. (E–F) Objective improvement in handwriting quality, demonstrating recovery of fine motor control, cerebellar coordination, and neuromuscular precision. These findings represent clinically meaningful functional recovery in a condition typically associated with progressive neurological decline.

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Safety and tolerability of treatment

All interventions administered were well tolerated during treatment and the follow-up period. No serious adverse events, neurological deterioration, or clinically significant complications were observed during or after the administration of cell therapies, extracellular vesicles, organ-specific cell-derived biological preparations, mitochondrial regulatory peptides, metabolic support therapies, or photobiomodulation interventions. The patient remained clinically stable throughout the protocol, and treatment did not need to be discontinued [157-160].

The minor transient effects associated with intravenous metabolic support were limited in scope and did not lead to clinically significant symptoms or functional impairment. There were no indications of immune rejection, systemic inflammatory responses, or neurological deterioration following the administration of autologous, allogeneic, or xenogeneic cell therapies or biological preparations derived from xenogeneic cells. Furthermore, the inhalation of extracellular vesicles was well tolerated, with no adverse effects on respiratory or neurological functions observed [161-164].

Longitudinal safety monitoring throughout treatment and follow-up demonstrated sustained tolerability of the treatment and the absence of clinically significant adverse outcomes. These findings support the favorable safety profile of the integrative regenerative protocol applied in this clinical case.

Correlation between treatment duration and functional outcomes

The functional enhancements observed throughout the treatment duration exhibited a temporal association with the sequential application of regenerative interventions. Following the inaugural treatment phase commenced in December 2024, which involved the administration of organ-specific cell-derived biological preparations targeting the central nervous system and systemic regulatory pathways, early enhancements in motor coordination, postural stability, and fine motor control were documented. These preliminary improvements were distinguished by an enhanced capacity to sustain an upright posture and increased motor coordination in the upper extremities [165-169].

The subsequent administration of autologous mesenchymal stromal cells and extracellular vesicle therapy during the early and intermediate phases of treatment was correlated with additional enhancements in functionality, encompassing progressive advancements in writing, speech articulation, and motor coordination. These enhancements are indicative of increased neuromuscular integration and enhanced motor planning, thereby suggesting an improvement in cerebellum-mediated motor control mechanisms [170-174].

During the intermediate and subsequent stages of treatment, including the administration of elevated doses of extracellular vesicle therapy and the subsequent deployment of stress-resistant pluripotent regenerative cells, ongoing enhancement and stabilization of neurological function were observed. The functional improvements encompassed sustained postural stability, increased walking fluency, and the restoration of independence in activities of daily living, such as cooking and personal grooming. These findings indicated a progressive recovery and stabilization of neurological function [175-179].

Importantly, these functional improvements were maintained throughout the maintenance phase, during which inhaled extracellular vesicle therapy was administered to enhance bioavailability within the central nervous system via non-invasive nose-to-brain delivery pathways, complemented by mitochondrial

regulatory support. Long-term follow-up extended through January 2026 indicated continued preservation of these functional gains, with no signs of neurological deterioration. This clinical course contrasts with the expected natural progression of multisystemic cerebellar ataxia, which is typically characterized by a progressive decline in function over time [180-184].

The observed temporal relationship between regenerative interventions and functional improvement, combined with sustained stabilization during long-term follow-up, supports the potential biological and clinical relevance of the integrative regenerative therapeutic approach in this patient. Longitudinal functional outcomes and neurological performance across the treatment and follow-up period are summarized in Table 2. Objective improvement in fine motor function is further demonstrated by comparison of handwriting performance before and after regenerative therapy, as shown in (Figure 3).

Functional domain	Baseline (Dec 2024)	Early phase (Jan–Apr 2025)	Intermediate phase (Apr–Jul 2025)	Late phase / Follow-up (Jan 2026)
Postural stability	Severely impaired; difficulty maintaining upright position	Improved ability to maintain upright posture	Stable upright posture without support	Maintained independent upright posture
Motor coordination	Markedly impaired coordination of voluntary movements	Improved coordination of upper extremities	Further improvement in coordinated movements	Sustained coordinated motor function
Fine motor function (handwriting)	Severely impaired; irregular strokes and poor motor control	Improved stroke continuity and motor control	Further improvement in precision and motor consistency	Maintained improved handwriting performance
Speech articulation	Dysarthric speech with reduced clarity	Improved articulation and vocal control	Further improvement in speech fluency	Sustained improved articulation and vocal stability
Gait stability	Impaired gait and reduced movement confidence	Improved walking stability	Further improvement in gait coordination	Maintained walking fluency and stability
Activities of daily living	Limited independence; difficulty performing routine tasks	Improved ability to perform self-care activities	Independent performance of daily activities, including cooking and grooming	Sustained independence and functional autonomy
Neurological functional stability	Progressive deterioration prior to treatment	Functional stabilization observed	Continued improvement and stabilization	Sustained neurological stability without deterioration

Table 2: Longitudinal functional outcomes and neurological performance over the treatment and follow-up period.

(Table 2) reflects the longitudinal functional outcomes and neurological performance over the treatment and follow-up period. This table summarizes the progression of neurological and functional parameters

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from baseline evaluation in December 2024 through longitudinal follow-up to January 2026. Functional domains assessed include postural stability, motor coordination, fine motor control, speech articulation, gait stability, and independence in activities of daily living.

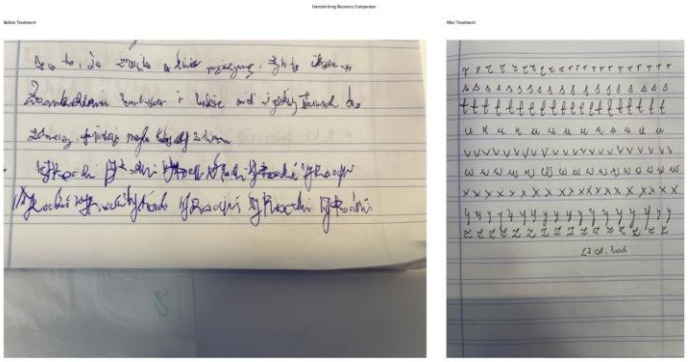

Figure 3: Objective improvement in handwriting performance following multimodal regenerative therapy.

(Figure 3) Representative comparison of handwriting performance before and after regenerative therapy. Baseline handwriting demonstrates impaired motor coordination, irregular stroke formation, and reduced motor control consistent with cerebellar dysfunction. Post-treatment handwriting demonstrates improved stroke continuity, enhanced motor precision, and improved neuromuscular coordination. These findings provide objective evidence of functional recovery of fine motor control and cerebellar-mediated motor function following multimodal regenerative intervention.

Discussion

Key findings and clinical relevance

This case report demonstrates sustained functional improvement and stabilization in a patient with progressive multisystemic cerebellar ataxia following administration of a structured protocol of integrative regenerative medicine. The improvements observed included increased postural stability, improved motor coordination, recovery of fine motor function, improved speech articulation, and restoration of independence in activities of daily living, such as cooking, grooming, and maintaining an upright posture. These functional improvements were maintained during longitudinal follow-up, which extended beyond 12 months [185-189].

It is important to observe that the clinical course documented here differs from the typical natural history of multisystem cerebellar ataxia, which is predominantly characterized by progressive neurological decline and increasing functional impairment over time. The gradual deterioration of motor coordination, balance, and independence in daily activities constitutes a hallmark of cerebellar neurodegeneration, with minimal prospects for spontaneous improvement. Within this framework, the sustained enhancements in functionality and stabilization observed in this patient are clinically significant findings, indicating a potential modulation of underlying biological mechanisms rather than mere transient symptomatic effects [190-194].

The temporal correlation between regenerative interventions and the subsequent progressive enhancement of functional capabilities, coupled with enduring stability over an extended follow-up period, corroborates the hypothesis that comprehensive regenerative strategies focusing on cell signaling,

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mitochondrial function, and neuroinflammatory pathways potentially aid in the preservation and recovery of neurological functions. These observations align with emerging evidence indicating that regenerative medicine approaches may impact the biological mechanisms underpinning the advancement of neurodegenerative disorders [195-199].

Mechanistic interpretation of regenerative interventions

The functional improvements observed in this case can be attributed to the combined biological effects of cellular therapies, extracellular vesicle signaling, mitochondrial regulatory support, and tissue-derived biological signaling interventions. Mesenchymal stromal cells are recognized for exerting their therapeutic effects primarily through paracrine mechanisms, including the secretion of growth factors, cytokines, and extracellular vesicles that modulate inflammation, support neuronal survival, and promote tissue homeostasis. These paracrine effects have been demonstrated to influence the neural microenvironment, enhance mitochondrial function, and support endogenous repair processes, which are essential factors in neurodegenerative conditions [200-205].

Extracellular vesicles constitute a fundamental element of intercellular communication and have been demonstrated to transport regulatory proteins, lipids, and nucleic acids capable of modulating cellular metabolism, mitochondrial function, and inflammatory pathways. Both experimental and clinical investigations have shown that extracellular vesicles can impact neuronal survival, facilitate synaptic stability, and promote neural functional recovery. The inhalation delivery of extracellular vesicles represents a non-invasive nose-to-brain administration strategy capable of enhancing central nervous system bioavailability via olfactory and respiratory neural pathways, thereby facilitating direct biological signaling support to neural tissues and potentially improving therapeutic targeting of neurodegenerative processes [206-211].

Stress-enduring pluripotent regenerative cells (MUSE-type cells) possess distinctive biological characteristics, including resilience to cellular stress, non-tumorigenic pluripotent potential, and the ability to migrate toward sites of tissue injury. These cells have been demonstrated to contribute to tissue repair predominantly through regulatory signaling mechanisms that promote cellular survival and modulate inflammatory responses. Their incorporation into regenerative protocols may have facilitated ongoing biological support and functional stabilization [212-216].

Furthermore, xenogeneic tissue-derived biological preparations containing regulatory peptides and signaling molecules may have contributed to the modulation of neuroendocrine function, mitochondrial activity, and cellular metabolism. Tissue-derived regulatory peptides have been studied for their role in influencing gene expression, cellular signaling pathways, and adaptive cellular responses. Mitochondrial regulatory peptides and metabolic optimization therapies may have further supported neuronal energy metabolism, reduced oxidative stress, and enhanced cellular resilience, which are critical factors in maintaining neuronal function in neurodegenerative conditions [217-223].

Photobiomodulation therapy may have offered supplementary support by enhancing mitochondrial function and modulating cellular signaling pathways. Light-based treatments have demonstrated the ability to influence cytochrome c oxidase activity, augment ATP synthesis, and regulate oxidative stress and inflammatory signaling. These effects potentially contribute to improved neuronal metabolic function and increased biological resilience [224-228].

The multimodal and integrative nature of the regenerative protocol, which targets multiple interconnected biological mechanisms, may elucidate the sustained functional improvements observed in this patient. Rather than operating through a single pathway, the combined interventions likely contributed synergistically to the modulation of the neural microenvironment and the preservation of neurological function. The proposed biological mechanisms underlying the observed functional recovery are illustrated in (Figure 4).

Innovation and relevance to advanced regenerative medicine

This clinical case exemplifies the potential of advanced integrative regenerative medicine techniques to impact functional outcomes in neurodegenerative diseases. Conventional therapeutic strategies for cerebellar ataxia have predominantly concentrated on symptomatic management and supportive care, with limited ability to influence the underlying biological mechanisms of disease progression. Conversely, regenerative medicine approaches seek to modulate essential cellular and molecular processes involved in neurodegeneration, such as inflammation, mitochondrial dysfunction, impaired cellular signaling, and diminished capacity for adaptive repair [229-233].

A significant innovative element of this protocol was the employment of a multimodal regenerative strategy that incorporates cellular therapies, extracellular vesicle signaling, xenogeneic tissue-derived regulatory peptides, mitochondrial regulatory support, and photobiomodulation. This integrative approach exemplifies a burgeoning paradigm within regenerative medicine that emphasizes the modulation of biological systems and the restoration of cellular communication networks rather than direct tissue replacement. Increasing evidence indicates that the modulation of the cellular microenvironment and the enhancement of endogenous repair mechanisms may play a crucial role in preserving neurological function and improving clinical outcomes in neurodegenerative conditions [234-238].

The utilization of extracellular vesicle therapies and stress-enduring pluripotent regenerative cells constitutes a particularly promising domain of research, as these methodologies provide the potential to deliver biological signaling support while mitigating risks linked to conventional cell transplantation. Likewise, tissue-derived regulatory peptides and mitochondrial support therapies exemplify emerging strategies focused on augmenting cellular resilience and enhancing biological functions at the molecular level [239-243].

This case offers clinical evidence endorsing the feasibility, safety, and prospective functional advantages of an advanced integrative regenerative medicine protocol. Although additional research is required to corroborate these findings within larger patient cohorts, the persistent functional enhancements documented in this case indicate that regenerative medicine strategies may present a promising therapeutic option for conditions generally regarded as progressive and irreversible.

Limitations and scientific considerations

This report describes a single clinical case, and its conclusions should be interpreted within the context of the inherent limitations associated with case report methodology. While the temporal association between regenerative interventions and functional improvement is noteworthy, a causal relationship cannot be definitively established. The clinical improvements observed may reflect the combined effects of multiple interventions, individual biological variability, and the complex interaction of regenerative and

adaptive biological processes. Therefore, the findings should be considered hypothesis-generating and interpreted with appropriate scientific caution.

Furthermore, the multimodal characteristics of the integrative regenerative protocol complicate the delineation of the specific contribution of each therapeutic component. The combined application of cell therapies, extracellular vesicles, mitochondrial regulatory peptides, tissue-derived biological preparations, metabolic support, and photobiomodulation constitutes a comprehensive biological intervention strategy. Although this integrative approach may yield synergistic benefits, additional controlled studies are required to ascertain the relative contributions and optimal therapeutic roles of each individual intervention [249-253].

The objective functional assessment in this case was conducted based on longitudinal clinical evaluation, structured observation, and documentation of functional performance. Although notable functional improvements were observed, future research incorporating standardized neurological rating scales, quantitative motor assessments, and biomarker analysis would further enhance the clinical evaluation and offer additional insights into the biological mechanisms underlying functional changes [254-258].

Notwithstanding these constraints, the persistent enhancement and stabilization of function observed in this patient are noteworthy, particularly within the context of a progressive neurodegenerative disorder that is generally linked to continuous functional deterioration. These findings underscore the necessity for additional investigation of regenerative medicine strategies in neurodegenerative diseases and emphasize the significance of ongoing clinical and translational research in this domain.

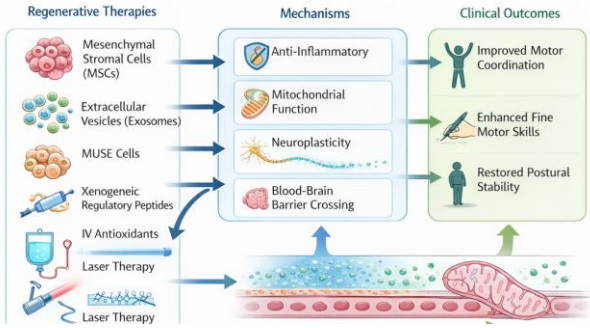

Figure 4: Proposed biological mechanisms underlying functional recovery following multimodal regenerative therapy.

(Figure 4). This schematic illustrates the proposed biological mechanisms associated with the observed functional recovery following multimodal regenerative therapy. Mesenchymal stromal cells and stress-enduring pluripotent regenerative cells contribute to immunomodulation, neuroprotection, and support of endogenous repair processes. Extracellular vesicles facilitate intercellular communication and deliver regulatory biomolecules, including proteins, lipids, and nucleic acids, that modulate inflammation and promote neural functional stability. Organ-specific cell-derived biological preparations and mitochondrial regulatory peptides support cellular metabolism, mitochondrial function, and adaptive repair capacity. Photobiomodulation enhances mitochondrial activity and cellular energy production. These mechanisms act synergistically to improve neural microenvironment stability, enhance cellular resilience, and support functional recovery.

A summary of the regenerative interventions and their associated biological mechanisms and therapeutic targets is presented in (Table 3).

Regenerative Intervention	Biological Mechanism	Therapeutic Target	Expected Clinical Effect
Autologous mesenchymal stromal cells	Immunomodulation, neurotrophic support, anti-inflammatory effects	Neuroinflammation, neural repair pathways	Improved motor coordination and functional recovery
Allogeneic mesenchymal stromal cells	Paracrine signaling, neuroprotection, microenvironment modulation	Neural microenvironment stability	Enhanced neurological stabilization
Stress-enduring pluripotent regenerative cells (MUSE cells)	Stress-resistant cellular repair, regenerative signaling	Cellular repair and neuroprotection	Improved functional resilience
Extracellular vesicles (exosomes)	Intercellular signaling, delivery of regulatory biomolecules	Neural communication and inflammation modulation	Improved neuromotor function
Organ-specific cell-derived biological preparations	Tissue-specific regulatory signaling, mitochondrial support	Cellular metabolism and adaptive repair	Improved neurological function
Mitochondrial regulatory peptides	Mitochondrial function optimization, reduction of oxidative stress	Cellular energy metabolism	Enhanced neuromuscular performance
Photobiomodulation therapy	Mitochondrial activation, ATP production, reduced oxidative stress	Cellular energy production and neural function	Improved functional stability

Table 3: Biological mechanisms and therapeutic targets of multimodal regenerative interventions.

(Table 3). This table summarizes the principal regenerative interventions administered in this clinical case and their associated biological mechanisms and therapeutic targets. Multimodal regenerative strategies, including mesenchymal stromal cells, stress-enduring pluripotent regenerative cells, extracellular vesicles, organ-specific cell-derived biological preparations, mitochondrial regulatory peptides, and photobiomodulation therapy, target key pathophysiological mechanisms involved in neurodegeneration. These mechanisms include modulation of neuroinflammation, mitochondrial support, enhancement of intercellular communication, promotion of neural repair processes, and stabilization of the neural microenvironment. The synergistic interaction between these interventions provides a biologically plausible framework for the observed functional recovery and neurological stabilization.

Future perspectives and clinical implications

The findings observed in this case emphasize the potential clinical significance of integrative regenerative medicine strategies that target multiple biological mechanisms implicated in neurodegenerative diseases. Progressive cerebellar ataxia is traditionally linked with irreversible neuronal dysfunction and ongoing functional decline, with few therapeutic options capable of altering disease progression. The sustained functional enhancement and stabilization observed in this patient imply that regenerative interventions focusing on cell signaling, mitochondrial function, and tissue homeostasis may constitute a promising therapeutic approach to support neurological function in neurodegenerative conditions.

This case further emphasizes the significance of multimodal regenerative strategies aimed at modulating the biological microenvironment, rather than depending solely on a single therapeutic intervention. The integration of cell therapies, extracellular vesicle signaling, mitochondrial regulatory support, and tissue-derived biological preparations exemplifies an emerging paradigm in regenerative medicine that concentrates on augmenting endogenous repair mechanisms and enhancing biological resilience. Such comprehensive approaches may provide advantages in managing the complex, multifactorial characteristics of neurodegenerative diseases [264-268].

Further research is required to advance the understanding of the safety, biological mechanisms, and clinical efficacy of regenerative medicine approaches in neurodegenerative disorders. Rigorous controlled clinical trials, standardized functional assessments, and biomarker analyses are crucial to establish the clinical significance of these interventions and to determine their optimal therapeutic roles. Moreover, additional investigations into extracellular vesicle therapies, stress-resistant pluripotent regenerative cells, mitochondrial regulatory peptides, and tissue-derived biological signaling methods may yield valuable insights into novel therapeutic strategies for neurological diseases [269-273].

This case substantiates the expanding body of evidence indicating that regenerative medicine potentially provides novel opportunities to influence the biological mechanisms involved in neurodegeneration and to enhance clinical outcomes. Although additional research is necessary, these findings advance the growing comprehension of regenerative therapeutic strategies and their prospective role in neurology.

Conclusion

This case report demonstrates sustained functional improvement and stabilization in a patient with progressive multisystem cerebellar ataxia following administration of a structured integrative regenerative medicine protocol. The patient exhibited significant improvements in postural stability, motor coordination, fine motor control, speech articulation, and independence in activities of daily living. These functional improvements were observed longitudinally and maintained throughout extended follow-up, indicating sustained preservation of neurological function.

The observed clinical course diverges from the anticipated natural progression of multisystem cerebellar ataxia, which is generally characterized by progressive neurological decline and loss of functional independence. Although causality cannot be definitively established based on a single case report, the temporal association between regenerative interventions and sustained functional improvement indicates that modulation of the underlying biological mechanisms involved in neurodegeneration may play a role in achieving functional stabilization.

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The multimodal regenerative approach utilized in this case targeted essential biological processes, including intercellular signaling, mitochondrial function, inflammatory modulation, and tissue-specific regulatory pathways. These findings substantiate the hypothesis that advanced integrative regenerative medicine strategies may serve as a promising complementary therapeutic approach for neurodegenerative diseases traditionally considered progressive and irreversible.

Further clinical research, including controlled studies and standardized functional assessments, is warranted to evaluate the safety, reproducibility, and clinical efficacy of regenerative medicine interventions in neurodegenerative disorders. This case contributes to the growing body of scientific evidence supporting the potential role of regenerative medicine in neurological conditions and highlights the importance of continued translational investigation in this evolving field.

Future Prospects

The findings observed in this case highlight the potential role of advanced regenerative medicine approaches in the management of neurodegenerative diseases characterized by progressive neuronal dysfunction and limited therapeutic options. The sustained functional improvement and stabilization documented suggest that modulation of intercellular signaling, mitochondrial function, and tissue-specific regulatory pathways may represent a promising therapeutic strategy for preserving neurological function.

Future research should focus on controlled clinical studies to evaluate the safety, reproducibility, and clinical efficacy of integrative regenerative medicine protocols in patients with cerebellar ataxia and other neurodegenerative disorders. Standardized neurological assessments, quantitative functional measurements, and biomarker analyses will be essential to further elucidate the biological mechanisms underlying the observed clinical improvements. Longitudinal studies involving larger patient populations will be necessary to determine the long-term therapeutic potential and optimal treatment parameters of regenerative interventions.

Furthermore, ongoing research into extracellular vesicle-based therapies, stress-resistant pluripotent regenerative cells, mitochondrial regulatory peptides, and tissue-derived biological signaling methods may offer significant insights into novel therapeutic strategies targeting the cellular and molecular mechanisms of neurodegeneration. Progress in regenerative medicine and translational neuroscience is anticipated to facilitate the development of innovative therapeutic approaches that can improve clinical outcomes and enhance the quality of life for patients suffering from neurological disorders.

This case advocates for ongoing scientific investigation into regenerative medicine as a therapeutic approach for neurodegenerative diseases and underscores the significance of translational research aimed at modulating the biological mechanisms that underlie neuronal dysfunction.

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Author contributions

Conceptualization, methodology, investigation, writing, and follow up were performed by RLM. Further editing, supervision, participation in the observational study, and statistical analysis were conducted by

DK. Data interpretation and laboratory analysis by MTKC and MBFW. All authors reviewed and approved the final version of the manuscript.

References

1. Klockgether T. (2011) Update on degenerative ataxias. Curr Opin Neurol. 24(4):339-45.
2. Manto M, Marmolino D. (2009) Cerebellar ataxias. Curr Opin Neurol. 22(4):419-29.
3. Schmahmann JD. (2019) The cerebellum and cognition. Neurosci Lett. 688:62-75.
4. Klockgether T. (2008) The clinical diagnosis of autosomal dominant spinocerebellar ataxias. Cerebellum. 7(2):101-5.
5. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. (2010) Mechanisms underlying inflammation in neurodegeneration. Nat Rev Neurosci. 11(10):703-15.
6. Heneka MT, Carson MJ, El Khoury J. (2015) Neuroinflammation in neurodegenerative disease. Lancet Neurol. 14(4):388-405.
7. Lin MT, Beal MF. (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 443(7113):787-95.
8. Nunnari J, Suomalainen A. (2012) Mitochondria: in sickness and in health. Cell. 148(6):1145-59.
9. Mattson MP, Gleichmann M, Cheng A. (2008) Mitochondria in neuroplasticity and neurological disorders. Neuron. 60(5):748-66.
10. Atala A, Lanza R, Mikos AG, Nerem RM. (2019) Principles of Regenerative Medicine. 3rd ed. Academic Press.
11. Pittenger MF, Discher DE, Peault BM, Phinney DG, Hare JM, et al. (2019) Mesenchymal stem cell perspective. NPJ Regen Med. 4:22.
12. Uccelli A, Moretta L, Pistoia V. (2008) Mesenchymal stem cells in health and disease. Nat Rev Immunol. 8(9):726-36.
13. Phinney DG, Pittenger MF. (2017) Concise review: MSC-derived exosomes. Stem Cells. 35(4):851-8.
14. Raposo G, Stoorvogel W. (2013) Extracellular vesicles. J Cell Biol. 200(4):373-83.
15. Théry C, Zitvogel L, Amigorena S. (2002) Exosomes: composition, biogenesis, and function. Nat Rev Immunol. 2(8):569-79.
16. Yáñez-Mó M, Siljander PRM, Andreu Z. (2015) Biological properties of extracellular vesicles. J Extracell Vesicles. 4:27066.
17. Toh WS, Lai RC, Hui JHP, Lim SK. (2017) MSC exosome as therapy. Nat Rev Rheumatol. 13(6):373-82.
18. Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R. (2017) Mesenchymal stem cell secretome. Int J Mol Sci. 18(9):1852.
19. Trounson A, McDonald C. (2015) Stem cell therapies in clinical trials. Cell Stem Cell. 17(1):11-22.
20. Squillaro T, Peluso G, Galderisi U. (2016) Clinical trials with MSC. Cell Transplant. 25(5):829-48.
21. Dezawa M. (2016) Muse cells. Proc Jpn Acad Ser B Phys Biol Sci. 92(8):297-312.
22. Wakao S, Kitada M, Kuroda Y. (2011) Muse cells identification. Proc Natl Acad Sci USA. 108(24):9875-80.
23. Kuroda Y, Wakao S, Kitada M, Murakami T, Dezawa M. (2013) Muse cells protocol. Nat Protoc. 8(7):1391-415.
24. Alvarez-Erviti L, Seow Y, Yin H. (2011) Exosome delivery to brain. Nat Biotechnol. 29(4):341-5.
25. Zhuang X, Xiang X, Grizzle W. (2011) Intranasal exosome delivery. Mol Ther. 19(10):1769-79.
26. Gizurarson S. (2012) Intranasal delivery. Curr Drug Deliv. 9(6):566-82.
27. Hamblin MR. (2017) Photobiomodulation. AIMS Biophys. 4(3):337-61.
28. Hamblin MR. (2017) Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophys. 4(3):337-61.
29. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, et al. (2012) The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng. 40(2):516-33.
30. Salehpour F, Rasta SH. (2017) The potential of transcranial photobiomodulation therapy for treatment of neurodegenerative diseases. Rev Neurosci. 28(4):453-71.
31. Rojas JC, Gonzalez-Lima F. (2011) Low-level light therapy of the eye and brain. Eye Brain. 3:49-67.
32. Raposo G, Stoorvogel W. (2013) Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 200(4):373-83.

33. Théry C, Witwer KW, Aikawa E. (2018) Minimal information for studies of extracellular vesicles 2018 (MISEV2018). J Extracell Vesicles. 7(1):1535750.
34. Valadi H, Ekström K, Bossios A. (2007) Exosome-mediated transfer of mRNAs and microRNAs. Nat Cell Biol. 9(6):654-9.
35. Lai RC, Yeo RWY, Lim SK. (2015) Mesenchymal stem cell exosomes. Semin Cell Dev Biol. 40:82-8.
36. Phinney DG, Pittenger MF. (2017) Concise review: MSC-derived exosomes. Stem Cells. 35(4):851-8.
37. Yáñez-Mó M, Siljander PRM, Andreu Z. (2015) Biological properties of extracellular vesicles. J Extracell Vesicles. 4:27066.
38. Toh WS, Lai RC, Hui JHP, Lim SK. (2017) MSC exosome therapy. Nat Rev Rheumatol. 13(6):373-82.
39. EL Andaloussi S, Mäger I, Breakefield XO, Wood MJ. (2013) Extracellular vesicles. Nat Rev Drug Discov. 12(5):347-57.
40. Colombo M, Raposo G, Théry C. (2014) Biogenesis, secretion, and intercellular interactions of exosomes. Annu Rev Cell Dev Biol. 30:255-89.
41. Pittenger MF, Mackay AM, Beck SC. (1999) Multilineage potential of adult human MSC. Science. 284(5411):143-7.
42. Caplan AI. (1991) Mesenchymal stem cells. J Orthop Res. 9(5):641-50.
43. Uccelli A, Moretta L, Pistoia V. (2008) Immunomodulatory function of MSC. Nat Rev Immunol. 8(9):726-36.
44. Squillaro T, Peluso G, Galderisi U. (2016) Clinical trials with mesenchymal stem cells. Cell Transplant. 25(5):829-48.
45. Trounson A, McDonald C. (2015) Stem cell therapies in clinical trials. Cell Stem Cell. 17(1):11-22.
46. Vizoso FJ, Eiro N, Cid S. (2017) MSC secretome: toward cell-free therapy. Int J Mol Sci. 18(9):1852.
47. Dezawa M. (2016) Muse cells: endogenous reparative pluripotent stem cells. Proc Jpn Acad Ser B. 92(8):297-312.
48. Wakao S, Kitada M, Kuroda Y. (2011) Muse cells are pluripotent. Proc Natl Acad Sci USA. 108(24):9875-80.
49. Kuroda Y, Wakao S, Kitada M. (2013) Isolation of Muse cells. Nat Protoc. 8(7):1391-415.
50. Alessio N, Squillaro T, Özcan S. (2018) Stress and stem cells. Int J Mol Sci. 19(6):1587.
51. Lin MT, Beal MF. (2006) Mitochondrial dysfunction and oxidative stress. Nature. 443(7113):787-95.
52. Nunnari J, Suomalainen A. (2012) Mitochondria in health and disease. Cell. 148(6):1145-59.
53. Mattson MP, Gleichmann M, Cheng A. (2008) Mitochondria in neurological disorders. Neuron. 60(5):748-66.
54. Picard M, McEwen BS. (2018) Psychological stress and mitochondria. Nat Rev Neurosci. 19(7):421-37.
55. Youle RJ, van der Bliek AM. (2012) Mitochondrial fission, fusion, and stress. Science. 337(6098):1062-5.
56. Heneka MT, Golenbock DT, Latz E. (2015) Innate immunity in neurodegeneration. Nat Immunol. 16(3):229-36.
57. Glass CK, Saijo K, Winner B. (2010) Mechanisms underlying inflammation in neurodegeneration. Nat Rev Neurosci. 11(10):703-15.
58. Atala A, Lanza R, Mikos AG, (2019) Nerem RM. Principles of Regenerative Medicine. 3rd ed. Academic Press;
59. Charbord P, Durand C. (2017) Stem Cell Biology and Regenerative Medicine. River Publishers.
60. Friedenstein AJ, Chailakhjan RK, Lalykina KS. (1970) Stromal stem cells. Cell Tissue Kinet. 3(4):393-403.
61. Alvarez-Erviti L, Seow Y, Yin H. (2011) Delivery of siRNA to brain by exosomes. Nat Biotechnol. 29(4):341-5.
62. Zhuang X, Xiang X, Grizzle W. (2011) Intranasal delivery of exosomes to brain. Mol Ther. 19(10):1769-79.
63. Gizurarson S. (2012) Intranasal drug delivery to CNS. Curr Drug Deliv. 9(6):566-82.
64. Banks WA. (2016) From blood–brain barrier to blood–brain interface. Exp Neurol. 283:4-7.
65. Pardridge WM. (2012) Blood–brain barrier drug delivery. J Neurochem. 121(4):531-42.
66. Hamblin MR. (2018) Photobiomodulation for brain disorders. Photonics. 5(4):1-17.
67. Banks WA. (2019) Extracellular vesicles: a new frontier in CNS drug delivery. Neurobiol Dis. 130:104538.
68. Théry C, Amigorena S, Raposo G, Clayton A. (2006) Isolation and characterization of exosomes. Curr Protoc Cell Biol. 2006;Chapter 3:Unit 3.22.
69. Johnsen KB, Gudbergsson JM, Skov MN. (2014) A comprehensive overview of exosomes. Int J Mol Sci. 15(8):15245-70.
70. Lässer C, Alikhani VS, Ekström K. (2011) Human saliva, plasma, and breast milk exosomes. J Extracell Vesicles. 1:10.

71. Robbins PD, Morelli AE. (2014) Regulation of immune responses by extracellular vesicles. Nat Rev Immunol. 14(3):195-208.
72. Kalluri R, LeBleu VS. (2020) The biology, function, and biomedical applications of exosomes. Science. 367(6478):eaau6977.
73. Pegtel DM, Gould SJ. (2019) Exosomes. Annu Rev Biochem. 88:487-514.
74. Mathieu M, Martin-Jaular L, Lavieu G, Théry C. (2019) Specificities of secretion and uptake of exosomes. Nat Cell Biol. 21(1):9-17.
75. Zhuang X, Deng ZB, Mu J. (2015) Ginger-derived nanoparticles protect against inflammation. Mol Ther. 23(1):134-43.
76. Ridder K, Keller S, Dams. (2014) Extracellular vesicle-mediated transfer of genetic information. Nat Commun. 5:1-11.
77. Tkach M, Théry C. (2016) Communication by extracellular vesicles. Cell. 164(6):1226-32.
78. Yeo RWY, Lai RC, Zhang B. (2013) Mesenchymal stem cell exosomes. Expert Opin Biol Ther. 13(5):713-24.
79. Théry C. (2011) Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep. 3:15.
80. Lai RC, Yeo RWY, Tan KH, Lim SK. (2013) Exosomes for regenerative medicine. Stem Cell Res Ther. 4(6):1-14.
81. Bruno S, Grange C, Deregibus MC. (2009) Mesenchymal stem cell-derived vesicles. Stem Cells Dev. 18(7):1053-63.
82. Phinney DG. (2012) Functional heterogeneity of mesenchymal stem cells. Sci Signal. 5(244):re7.
83. Caplan AI, Dennis JE. (2006) Mesenchymal stem cells as trophic mediators. J Cell Biochem. 98(5):1076-84.
84. Spees JL, Lee RH, Gregory CA. (2016) Mechanisms of mesenchymal stem cell function. Stem Cell Res Ther. 7:125.
85. Galipeau J, Sensébé L. (2018) Mesenchymal stromal cells. Nat Rev Immunol. 18(8):513-25.
86. Barry FP, Murphy JM. (2013) Mesenchymal stem cells in joint disease. Nat Rev Rheumatol. 9(10):584-94.
87. Wang Y, Chen X, Cao W, Shi Y. (2014) Plasticity of mesenchymal stem cells. J Cell Mol Med. 18(10):1909-17.
88. Dominici M, Le Blanc K, Mueller I. (2006) Minimal criteria for MSC. Cytotherapy. 8(4):315-17.
89. Friedenstein AJ. (1976) Stromal stem cells. Int Rev Cytol. 47:327-59.
90. Prockop DJ. (1997) Marrow stromal cells. Science. 276(5309):71-4.
91. Dezawa M, Kanno H, Hoshino M. (2004) Specific induction of neuronal cells. Dev Growth Differ. 46(2):149-57.
92. Kuroda Y, Wakao S, Kitada M. (2018) Muse cells. Adv Exp Med Biol. 1103:61-78.
93. Alessio N, Squillaro T, Özcan S. (2018) Muse cells and stress resistance. Int J Mol Sci. 19(6):1587.
94. Wakao S, Dezawa M. (2015) Muse cells in regenerative medicine. Regen Ther. 1:28-33.
95. Nunnari J, Suomalainen A. (2012) Mitochondria and disease. Cell. 148(6):1145-59.
96. Lin MT, Beal MF. (2006) Mitochondrial dysfunction in neurodegeneration. Nature. 443(7113):787-95.
97. Mattson MP. (2012) Energy metabolism and neuronal vulnerability. Nat Rev Neurosci. 13(10):701-12.
98. Youle RJ. (2012) Mitochondrial quality control. Science. 337(6098):1062-5.
99. Picard M. (2018) Mitochondrial plasticity. Nat Rev Neurosci. 19(7):421-37.
100. Hamblin MR. (2018) Photobiomodulation mechanisms. Photochem Photobiol. 94(2):199-212.
101. Hamblin MR. (2016) Shining light on the head. BBA Clin. 6:113-24.
102. Hamblin MR. (2016) Photobiomodulation and the brain: a new paradigm. Photomed Laser Surg. 34(12):559-60.
103. Naeser MA, Hamblin MR. (2016) Potential for transcranial photobiomodulation therapy. BBA Clin. 6:113-24.
104. Salehpour F, Cassano P, Rouhi N. (2018) Photobiomodulation therapy and neurological diseases. Mol Neurobiol. 55(8):6601-36.
105. Fitzgerald M, Hodgetts S, Van Den Heuvel C. (2013) Red/near-infrared irradiation therapy. Neural Regen Res. 8(30):2800-8.
106. Mitrofanis J. (2019) Why and how does photobiomodulation work? J Neural Transm. 126(6):741-52.
107. Trounson A, Thakar RG, Lomax G, Gibbons D. (2011) Clinical trials for stem cell therapies. BMC Med. 9:52.
108. Squillaro T, Peluso G, Galderisi U. (2016) Stem cell clinical trials update. Cell Transplant. 25(5):829-48.
109. Vizoso FJ, Eiro N, Cid S. (2017) MSC secretome therapeutic potential. Int J Mol Sci. 18(9):1852.

110. Gnecchi M, Zhang Z, Ni A, Dzau VJ. (2008) Paracrine mechanisms in stem cell therapy. Circ Res. 103(11):1204-19.
111. Caplan AI. (1991) MSC: cell-based reconstructive therapy. J Orthop Res. 9(5):641-50.
112. Caplan AI, Correa D. (2011) MSC as medicinal signaling cells. Cell Stem Cell. 9(1):11-15.
113. Phinney DG, Pittenger MF. (2017) MSC-derived extracellular vesicles. Stem Cells. 35(4):851-8.
114. Lai RC, Arslan F, Lee MM. (2010) Exosome secretome in regenerative medicine. Stem Cell Res. 4(3):214-22.
115. Bruno S, Grange C, Collino F. (2012) Microvesicles derived from MSC. Am J Pathol. 180(4):1375-87.
116. Katsuda T, Kosaka N, Takeshita F, Ochiya T. (2013) Exosome-mediated communication. Mol Ther. 21(1):22-32.
117. Colombo M, Raposo G, Théry C. (2014) Exosome biology overview. Annu Rev Cell Dev Biol. 30:255-89.
118. Robbins PD, Morelli AE. (2014) Extracellular vesicles in immune regulation. Nat Rev Immunol. 14(3):195-208.
119. Kalluri R. (2020) The biology of exosomes in cancer and regenerative medicine. Science. 367(6478):eaau6977.
120. Théry C. (2014) Exosomes and intercellular communication. Nat Rev Mol Cell Biol. 15(12):773-85.
121. Pegtel DM, Gould SJ. (2019) Exosome-mediated signaling. Annu Rev Biochem. 88:487-514.
122. Pittenger MF. (2009) MSC for CNS repair. J Cell Physiol. 221(1):1-6.
123. Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, et al. (2010) MSC neuroprotective effects. Stem Cells. 28(10):1792-8.
124. Uccelli A, Laroni A, Freedman MS. (2011) MSC and neurodegeneration. Nat Rev Neurol. 7(7):393-401.
125. Teixeira FG, Carvalho MM, Sousa N, Salgado AJ. (2013) MSC secretome and CNS regeneration. Front Cell Neurosci. 7:258.
126. Dezawa M. (2016) Muse cells regenerative potential. Proc Jpn Acad Ser B Phys Biol Sci. 92(8):297-313.
127. Wakao S, Dezawa M. (2018) Muse cells and tissue repair. Adv Exp Med Biol. 1103:61-78.
128. Alessio N. (2018) Muse cells pluripotency and regeneration. Int J Mol Sci. 19(6):1587.
129. Lin MT, Beal MF. (2006) Mitochondrial dysfunction and neurodegeneration. Nature. 443(7113):787-95.
130. Mattson MP. (2007) Mitochondrial regulation of neuronal survival. Nat Rev Neurosci. 8(9):663-74.
131. Picard M. (2018) Mitochondrial signaling in neurodegeneration. Nat Rev Neurosci. 19(7):421-37.
132. Nunnari J, Suomalainen A. (2012) Mitochondria and disease. Cell. 148(6):1145-59.
133. Youle RJ. (2012) Mitochondrial dynamics in neurodegeneration. Science. 337(6098):1062-5.
134. Heneka MT. (2015) Neuroinflammation in neurodegenerative diseases. Lancet Neurol. 14(4):388-405.
135. Glass CK. (2010) Mechanisms of neuroinflammation. Nat Rev Neurosci. 11(10):703-15.
136. Pardridge WM. (2005) Blood-brain barrier transport. NeuroRx. 2(1):3-14.
137. Banks WA. (2016) Blood-brain barrier physiology. Exp Neurol. 283:4-7.
138. Alvarez-Erviti L. (2011) Exosome delivery to CNS. Nat Biotechnol. 29(4):341-5.
139. Zhuang X. (2011) Intranasal exosome delivery. Mol Ther. 19(10):1769-79.
140. Gizurarson S. (2012) Intranasal drug delivery review. Curr Drug Deliv. 9(6):566-82.
141. Atala A, Lanza R. (2019) Principles of regenerative medicine. Academic Press.
142. Caplan AI. (2017) MSC biology and regenerative medicine applications. Stem Cells Transl Med. 6(6):1445-51.
143. Galipeau J, Sensébé L. (2018) Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Nat Rev Immunol. 18(8):513-25.
144. Squillaro T, Galderisi U, Peluso G. (2016) Aging and mesenchymal stem cells. Cell Transplant. 25(5):829-48.
145. Vizoso FJ, Eiro N, Schneider J, Perez-Fernandez R. (2017) Secretome of mesenchymal stem cells. Int J Mol Sci. 18(9):1852.
146. Spees JL, Lee RH, Gregory CA. (2016) Mechanisms of MSC-mediated repair. Stem Cell Res Ther. 7:125.
147. Phinney DG. (2012) Functional heterogeneity of mesenchymal stem cells. Sci Signal. 5(244):re7.
148. Lai RC, Chen TS, Lim SK. (2011) Mesenchymal stem cell exosome biology. Stem Cell Res Ther. 2(5):38.
149. Katsuda T, Ochiya T. (2015) Extracellular vesicles in regenerative medicine. Front Genet. 6:222.
150. Robbins PD. (2014) Extracellular vesicles and regenerative medicine. Nat Rev Immunol. 14(3):195-208.
151. EL Andaloussi S. (2013) Exosomes for therapeutic delivery. Nat Rev Drug Discov. 12(5):347-57.
152. Colombo M, Raposo G, Théry C. (2014) Exosome biology overview. Annu Rev Cell Dev Biol. 30:255-89.

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153. Pegtel DM, Gould SJ. (2019) Exosome function and biomedical applications. Annu Rev Biochem. 88:487-514.
154. Théry C. (2014) Exosome function in health and disease. Nat Rev Mol Cell Biol. 15(12):773-85.
155. Kalluri R, LeBleu VS. (2020) Exosomes in regenerative medicine. Science. 367(6478):eaau6977.
156. Tkach M, Théry C. (2016) Extracellular vesicles: communication mediators. Cell. 164(6):1226-32.
157. Yeo RWY, Lai RC, Tan KH, Lim SK. (2013) MSC exosomes therapeutic potential. Stem Cell Res Ther. 4(6):1-14.
158. Bruno S, Deregibus MC, Camussi G. (2015) Exosomes in regenerative medicine. Front Immunol.6:1-7.
159. Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, et al. (2010) MSC neuroprotective mechanisms. Stem Cells. 28(10):1792-8.
160. Uccelli A, Laroni A, Freedman MS. (2011) Mesenchymal stem cells in neurological diseases. Nat Rev Neurol. 7(7):393-401.
161. Teixeira FG, Carvalho MM, Sousa N, Salgado AJ. (2013) MSC secretome and CNS repair. Front Cell Neurosci. 7:258.
162. Dezawa M. (2016) Muse cells regenerative potential. Proc Jpn Acad Ser B Phys Biol Sci. 92(8):297-313.
163. Wakao S, Dezawa M. (2018) Muse cells and pluripotency. Adv Exp Med Biol. 1103:61-78.
164. Alessio N. (2018) Muse cells and regenerative medicine. Int J Mol Sci. 19(6):1587.
165. Lin MT, Beal MF. (2006) Mitochondrial dysfunction in neurodegeneration. Nature. 443(7113):787-95.
166. Mattson MP. (2007) Mitochondria and neuronal survival. Nat Rev Neurosci. 8(9):663-74.
167. Nunnari J, Suomalainen A. (2012) Mitochondrial biology and disease. Cell. 148(6):1145-59.
168. Youle RJ. (2012) Mitochondrial dynamics. Science. 337(6098):1062-5.
169. Picard M. (2018) Mitochondrial signaling in disease. Nat Rev Neurosci. 19(7):421-37.
170. Heneka MT. (2015) Neuroinflammation and neurodegeneration. Lancet Neurol. 14(4):388-405.
171. Glass CK. (2010) Neuroinflammation mechanisms. Nat Rev Neurosci. 11(10):703-15.
172. Hamblin MR. (2018) Photobiomodulation mechanisms. Photochem Photobiol. 94(2):199-212.
173. Mitrofanis J. (2019) Photobiomodulation therapy overview. J Neural Transm. 126(6):741-52.
174. Salehpour F. (2018) Photobiomodulation therapy review. Mol Neurobiol. 55(8):6601-36.
175. Fitzgerald M. (2013) Photobiomodulation and neural repair. Neural Regen Res. 8(30):2800-8.
176. Rojas JC. (2011) Light therapy and mitochondria. Eye Brain. 3:49-67.
177. Banks WA. (2016) Blood-brain barrier physiology. Exp Neurol. 283:4-7.
178. Pardridge WM. (2005) CNS drug delivery. NeuroRx. 2(1):3-14.
179. Alvarez-Erviti L. (2011) Exosome-mediated CNS delivery. Nat Biotechnol. 29(4):341-5.
180. Zhuang X. (2011) Intranasal delivery of exosomes. Mol Ther. 19(10):1769-79.
181. Atala A, Lanza R, Mikos AG. (2019) Principles of regenerative medicine. Academic Press.
182. Trounson A, McDonald C. (2015) Stem cell therapies in clinical trials: progress and challenges. Cell Stem Cell. 17(1):11-22.
183. Dominici M, Le Blanc K, Mueller I, et al. (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. Cytotherapy. 8(4):315-17.
184. Friedenstein AJ, Chailakhjan RK, Lalykina KS. (1970) Stromal stem cells in bone marrow. Cell Tissue Kinet. 3(4):393-403.
185. Prockop DJ. (1997) Marrow stromal cells as stem cells. Science. 276(5309):71-4.
186. Caplan AI, Dennis JE. (2006) Mesenchymal stem cells as trophic mediators. J Cell Biochem. 98(5):1076-84.
187. Phinney DG, Prockop DJ. (2007) Concise review: mesenchymal stem cells. Stem Cells. 25(11):2896-902.
188. Gnecchi M, He H, Noiseux N. (2005) Paracrine action accounts for MSC therapeutic effects. Circ Res. 97(11):1223-30.
189. Lai RC, Arslan F, Lee MM, et al. (2010) Exosome-mediated cardioprotection. Stem Cell Res. 4(3):214-22.
190. Katsuda T, Kosaka N, Takeshita F, Ochiya T. (2013) Exosome-based therapy. Mol Ther. 21(1):22-32.
191. EL Andaloussi S, Mäger I, Breakefield XO, Wood MJ. Exosomes for drug delivery. Nat Rev Drug Discov. 12(5):347-57.
192. Tkach M, Théry C. (2016) Communication by extracellular vesicles. Cell. 164(6):12260-32.
193. Robbins PD, Morelli AE. (2014) Regulation of immune responses by extracellular vesicles. Nat Rev Immunol. 14(3):195-208.

194. Pegtel DM, Gould SJ. (2019) Exosomes in disease and therapy. Annu Rev Biochem. 88:487-514.
195. Colombo M, Raposo G, Théry C. (2014) Biogenesis and function of exosomes. Annu Rev Cell Dev Biol. 30:255-89.
196. Kalluri R, LeBleu VS. (2020) Exosome biology. Science. 367(6478):eaau6977.
197. Lai RC, Yeo RWY, Lim SK. (2015) Mesenchymal stem cell exosomes. Semin Cell Dev Biol. 40:82-8.
198. Bruno S, Deregibus MC, Camussi G. (2015) MSC-derived extracellular vesicles. Front Immunol. 6:1-7.
199. Vizoso FJ, Eiro N, Schneider J, Perez-Fernandez R. (2017) MSC secretome applications. Int J Mol Sci. 18(9):1852.
200. Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, et al. (2010) MSC neuroprotection. Stem Cells. 28(10):1792-8.
201. Uccelli A, Laroni A, Freedman MS. (2011) MSC therapy for neurological diseases. Nat Rev Neurol.7(7):393-401.
202. Teixeira FG, Carvalho MM, Sousa N, Salgado AJ. (2013) MSC secretome neuroregeneration. Front Cell Neurosci. 7:258.
203. Dezawa M. (2016) Muse cells pluripotency and repair. Proc Jpn Acad Ser B Phys Biol Sci. 92(8):297-313.
204. Wakao S, Dezawa M. (2018) Muse cells regenerative medicine. Adv Exp Med Biol. 1103:61-78.
205. Alessio N. (2018) Muse cells stress resistance. Int J Mol Sci. 19(6):1587.
206. Lin MT, Beal MF. (2006) Mitochondrial dysfunction. Nature. 443(7113):787-95.
207. Mattson MP. (2007) Energy metabolism in neurodegeneration. Nat Rev Neurosci. 8(9):663-74.
208. Nunnari J, Suomalainen A. (2012) Mitochondria and disease. Cell. 148(6):1145-59.
209. Youle RJ, van der Bliek AM. (2012) Mitochondrial dynamics. Science. 337(6098):1062-5.
210. Picard M. (2018) Mitochondrial signaling. Nat Rev Neurosci. 19(7):421-37.
211. Heneka MT, Golenbock DT, Latz E. (2015) Neuroinflammation overview. Nat Immunol. 16(3):229-36.
212. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. (2010) Neuroinflammation mechanisms. Nat Rev Neurosci. 11(10):703-15.
213. Hamblin MR. (2018) Photobiomodulation mechanisms. Photochem Photobiol. 94(2):199-212.
214. Mitrofanis J. (2019) Photobiomodulation neuroprotection. J Neural Transm. 126(6):741-52.
215. Salehpour F, Rasta SH. (2017) Photobiomodulation therapy review. Rev Neurosci. 28(4):453-71.
216. Fitzgerald M. (2013) Photobiomodulation neural repair. Neural Regen Res. 8(30):2800-8.
217. Rojas JC, Gonzalez-Lima F. (2011) Light therapy mitochondrial effects. Eye Brain. 3:49-67.
218. Pardridge WM. (2005) Blood-brain barrier drug delivery. NeuroRx. 2(1):3-14.
219. Banks WA. (2016) Blood-brain barrier physiology. Exp Neurol. 283:4-7.
220. Alvarez-Erviti L. (2011) Exosome delivery to brain. Nat Biotechnol. 29(4):341-5.
221. Zhuang X. (2011) Intranasal exosome delivery. Mol Ther. 19(10):1769-79.
222. Gizurarson S. (2012) Intranasal CNS delivery. Curr Drug Deliv. 9(6):566-82.
223. Atala A, Lanza R, Mikos AG. (2019) Principles of Regenerative Medicine. Academic Press.
224. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, et al. (2014) CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. J Clin Epidemiol. 67(1):46-51.
225. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016.
226. World Medical Association. (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 310(20):2191-4.
227. Fanciulli A, Wenning GK. (2015) Multiple-system atrophy. N Engl J Med. 372(3):249-63.
228. Wenning GK, Colosimo C, Geser F, Poewe W. (2004) Multiple system atrophy. Lancet Neurol. 3(2):93-103.
229. Low PA, Reich SG, Jankovic J, Shults CW, Stern MB, et al. (2015) Natural history of multiple system atrophy in the USA: a prospective cohort study. Lancet Neurol. 14(7):710-9.
230. Stefanova N, Bucke P, Duerr S, Wenning GK. (2009) Multiple system atrophy: an update. Lancet Neurol. 8(12):1172-8.
231. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, et al. (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 71(9):670-6.

232. Schmitz-Hübsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, et al. (2006) Scale for the Assessment and Rating of Ataxia (SARA): development of a new clinical scale. Neurology. 66(11):1717-20.
233. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, et al. (1997) International Cooperative Ataxia Rating Scale. Neurology. 49(2):446-52.
234. Ilg W, Brötz D, Burkard S, Giese MA, Schöls L, et al. (2010) Long-term effects of coordinated physiotherapy in degenerative cerebellar disease: a randomized controlled trial. Neurology. 75(9).
235. Miyai I, Kang J, Kubota K, et al. (2012) Long-term effect of body-weight-supported treadmill training in patients with spinocerebellar degeneration. Arch Phys Med Rehabil. 93(7):1170-6.
236. Zesiewicz TA, Wilmot G, Kuo SH, Perlman S, Greenstein PE, et al. (2018) Comprehensive systematic review of treatment of cerebellar motor dysfunction and ataxia. Neurology. 90(10):464-71.
237. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, et al. (2001) Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 7(2):211-28.
238. Gimble JM, Katz AJ, Bunnell BA. (2007) Adipose-derived stem cells for regenerative medicine. Circ Res. 100(9):1249-60.
239. Bourin P, Bunnell BA, Casteilla L, Dominici M, Katz AJ, et al. (2013) Stromal cells from adipose tissue: a review. Cytotherapy. 15(6):641-8.
240. Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of cell therapy with mesenchymal stromal cells: a systematic review and meta-analysis. PLoS One. 2012;7(10):e47559.
241. Ankrum JA, Ong JF, Karp JM. (2014) Mesenchymal stem cells: immune evasive, not immune privileged. Nat Biotechnol. 32(3):252-60.
242. Le Blanc K, Mougiakakos D. (2012) Multipotent mesenchymal stromal cells and the innate immune system. Nat Rev Immunol. 12(5):383-96.
243. Galipeau J. (2013) The mesenchymal stromal cells dilemma—does a negative trial set us back? Cytotherapy. 15(1):2-3.
244. Xin H, Li Y, Buller B, Katakowski M, Zhang Y, et al. (2012) Exosome-mediated transfer of miR-133b from mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells. 30(7):1556-64.
245. Doeppner TR, Herz J, Görgens A, Schlechter J, Ludwig AK, et al. (2015) Extracellular vesicles improve post-stroke neuroregeneration and prevent postischemic immunosuppression. Stem Cells Transl Med. 4(10):1131-43.
246. Xin H, Li Y, Cui Y, Yang JJ, Zhang ZG, et al. (2013) Systemic administration of exosomes released from MSC promotes functional recovery and neurovascular plasticity after stroke in rats. J Cereb Blood Flow Metab. 33(11):1711-5.
247. Yang Y, Ye Y, Su X, He J, Bai W, et al. (2017) MSC-derived exosomes and their applications in nervous system disorders. Front Neurosci. 11: (Frontiers article).
248. Long Q, Upadhya D, Hattiangady B, Kim DK, An SY, et al. Intranasal MSC-derived exosomes promote brain repair after injury.
249. Perets N, Hertz S, London M, Offen D. Intranasal exosomes for CNS delivery: emerging strategy.
250. Lochhead JJ, Thorne RG. (2012) Intranasal delivery of biologics to the central nervous system. Adv Drug Deliv Rev. 64(7):614-28.
251. Cassano P, Petrie SR, Hamblin MR, Henderson TA, Iosifescu DV. (2019) Transcranial photobiomodulation for neuropsychiatric disorders. Psychiatr Clin North Am. 42(4):639-55.
252. Barrett DW, Gonzalez-Lima F. (2013) Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects. Neuroscience. 230:13-23.
253. Hamblin MR. (2018) Photobiomodulation for traumatic brain injury and stroke. J Neurosci Res. 96(4):731-43.
254. Verdin E. (2015) NAD+ in aging, metabolism, and neurodegeneration. Science. 350(6265):1208-13.
255. Rajman L, Chwalek K, Sinclair DA. (2018) Therapeutic potential of NAD-boosting molecules. Cell Metab. 27(3):529-47.
256. Covarrubias AJ, Perrone R, Grozio A, Verdin E. (2021) NAD+ metabolism and its roles in cellular processes. Nat Rev Mol Cell Biol. 22(2):119-41.
257. Dringen R. (2000) Metabolism and functions of glutathione in brain. Prog Neurobiol. 62(6):649-71.

258. Aoyama K, Nakaki T. (2013) Glutathione in cellular redox homeostasis and neurological disease. Oxid Med Cell Longev.
259. Sies H. (2015) Oxidative stress: a concept in redox biology and medicine. Redox Biol. 4:180-3.
260. Marx RE. (2004) Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 62(4):489-96.
261. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. (2009) Classification of platelet concentrates: from PRP to leukocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 27(3):158-67.
262. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. (2012) Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy. 28(3):429-39.
263. Friedenstein AJ. (1976) Precursor cells of mechanocytes. Int Rev Cytol. 47:327-59.
264. Caplan AI. (2017) New MSC: "Medicinal signaling cells". Cell Stem Cell. 21(2):137-8.
265. Théry C, Ostrowski M, Segura E. (2009) Membrane vesicles as conveyors of immune responses. Nat Rev Immunol. 9(8):581-93.
266. Soria FN, Pampliega O, Bourdenx M, Meissner WG, Bezard E, et al. (2017) Exosomes in neurodegeneration. Front Neurosci. 11:26.
267. Thompson AG, Gray E, Heman-Ackah SM, Mäger I, Talbot K, et al. (2016) Extracellular vesicles in neurodegenerative disease—pathogenesis to biomarkers. Nat Rev Neurol. 12(6):346-57.
268. Vella LJ, Hill AF, Cheng L. (2016) Focus on extracellular vesicles: exosomes and their role in protein trafficking in neurodegeneration. Front Neurosci. 10: (Frontiers article).
269. Lener T, Gimona M, Aigner L, Börger V, Buzas E, et al. (2015) Applying extracellular vesicles-based therapeutics in clinical trials. Adv Drug Deliv Rev. 88:83-95.
270. Mendt M, Rezvani K, Shpall E. (2019) Mesenchymal stem cell-derived exosomes for clinical use. Bone Marrow Transplant. 54(2):789-92.
271. van Niel G, D'Angelo G, Raposo G. (2018) Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 19(4):213-28.
272. Sipp D, Robey PG, Turner L. (2018) Clear up this stem-cell mess. Nature. 561(7724):455-7.
273. Aronson JK. (2005) Biomarkers and surrogate endpoints in clinical research. BMJ. 330(7493): (BMJ article).
274. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, et al. (2017) CARE guidelines for case reports: explanation and elaboration. J Clin Epidemiol. 89:218-35.