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Case Report

GAD+ Autoimmune Cerebellar Ataxia Following COVID-19 Vaccination: A Case Report and Therapeutic Approach

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Abstract

Cerebellar ataxias (CAs) are a heterogeneous group of disorders involving motor dysfunction, emotional symptoms, and cognitive impairment. Their etiologies range from paraneoplastic syndromes to autoimmune medical conditions. One of the initial presentations of immune-mediated cerebellar ataxia (IMCA) reported is acute cerebellitis following vaccination against COVID 19. The cerebellum is one of the regions of the central nervous system (CNS) that is most vulnerable to autoimmune injury. On the other hand, it also possesses a unique capacity for compensation and repair, known as cerebellar reserve. The aim of this study is to present stem cell and exosome therapy as a strategy to treat IMCA, based on the immunomodulatory and neuromodulatory properties of these cells and their components.

We present the case of a 48-year-old male who developed right upper limb ataxia in October 2021. Autoantibody testing was positive for anti-GAD antibodies. He was treated according to an immunotherapy-based protocol for autoimmune cerebellitis. Despite this treatment, his condition progressively worsened, resulting in gait instability, clumsiness, disabling tremor, dysarthria, swallowing difficulties and a significant loss of autonomy. He showed severe impairment on the Scale for the Assessment and Rating of Ataxia (SARA) and a significant decline in activities of daily living (ADLs).

Combined stem cell and exosome therapy is a novel approach for the treatment of IMCA. By leveraging the immunomodulatory and neuromodulatory properties of these therapies, meaningful clinical improvements were achieved in this patient. These findings present this therapy as a promising approach to treat this condition.

Keywords: *Cerebellar ataxias (CAs). Exosomes. Immune-mediated cerebellar ataxia (IMCA). Immunomodulation. Stem cells.*

Abbrevations

CAs: Cerebellar ataxias

IMCA: Immune-mediated cerebellar ataxia

CNS: Central nervous system

MRI: Magnetic resonance imaging

SARA: Scale for the Assessment and Rating of Ataxia

ADLs: Activities of daily living

FGF: Fibroblast growth factor

TERT: Telomerase reverse transcriptase

Background

Cerebellar ataxias (CAs) comprise a heterogeneous group of disorders characterised by motor, emotional, and higher cognitive function impairment (1). Their etiologies vary from paraneoplastic entities to autoimmune processes. As to the latter, the main pathophysiological mechanism is the presence of autoantibodies directed against cell surface and intracellular structures (2). One of the main antibodies is anti-GAD, directed against a key enzyme in the synthesis of the neurotransmitter GABA (3). This leads to an imbalance in neurotransmission, increasing glutamate levels and decreasing GABA levels. It is through this mechanism that cerebellar atrophy and neuronal death occur due to excessive levels of glutamate, a process called excitotoxicity (3).

One of the initial forms of presentation observed in immune-mediated cerebellar ataxia (IMCA) is acute cerebellitis following COVID-19 vaccination (4). There were several reports of neurological complications associated with COVID-19 vaccination, such as Guillain-Barré syndrome, Bell's palsy, and demyelinating or myasthenic events (5). The mechanisms by which the vaccine could induce autoimmunity range from molecular mimicry between vaccine antigens and autoantigens to polyclonal B-cell activation, promoting the production of cytokines and autoreactive T-cells (6).

The cerebellum is one of the most vulnerable areas of the central nervous system (CNS) with regard to autoimmune processes. On the other hand, the cerebellum has the ability to compensate for and repair damage caused by different medical conditions, a property unique to the CNS. This characteristic is known as cerebellar reserve (7). It is this premise that encourages early and appropriate treatments based on immunomodulation and neuromodulation. Therefore, the objective of this paper is to present stem cell and exosome therapy as a strategy for the treatment of IMCA, based on the immunomodulatory and neuromodulatory properties of these cells and their components.

Case Presentation

A 48-year-old patient with no significant medical history presented with ataxia mainly affecting the right upper limb in October 2021. As a temporal precedent, 40 days prior to the onset of symptoms, the patient had received COVID-19 vaccine. The patient's condition progressed with gait instability and an increased base of support, leading to his hospitalization.

Upon suspicion of acute cerebellitis, a diagnostic algorithm was performed to find the possible etiology. A brain magnetic resonance imaging (MRI), lumbar puncture, and Filmarray panel for encephalitis were requested. The lumbar puncture provided a fluid mainly containing mononuclear cells with hypercellularity. The MRI was reported as normal. The autoantibody testing proved positive for anti-GAD and anti-GM1. After the negative result in the FilmArray panel for encephalitis, the infectious etiology was ruled out and ampicillin/sulbactam and acyclovir therapy was discontinued. Due to the presence of autoantibodies, a therapeutic algorithm based on different strategies aimed at diagnosing acute autoimmune cerebellitis was established.

First, pulses of methylprednisolone were administered for 10 days, but due to the onset of intercurrent drug-induced pancreatitis, drug was discontinued. Right after, therapy with cycles of plasmapheresis was instituted, which had to be discontinued at the patient's request due to intolerance. Finally, intravenous immunoglobulin was administered, achieving temporary clinical improvement until February 2022, when he began to experience clumsiness, unsteadiness when walking, and paresthesia in both upper limbs. This year his symptoms increased, with the addition of incapacitating head tremors. He developed severe dysarthria with difficulty swallowing, disabling tremors, and limited autonomy, unable to sit or stand on his own.

In 2024, the patient contacted our team for treatment with stem cells and exosomes. Upon the first contact with the patient, he appeared to be severely impaired in some aspects of the Scale for the Assessment and Rating of Ataxia (SARA). His gait was weak and he could not walk more than 10 metres despite the help of aids or his caregiver, and he also had difficulty staying standing due to his tremor. On the other hand, he found it difficult to remain seated, kept rocking and with his head falling backwards due to poor cephalic support. At times, his speech was difficult to understand due to poor diction and drooling. His coordination was impaired in both upper and lower limbs, presenting dysmetria and tremors when performing coordination movements. Added to all this was his inability to perform rapid alternating movements (dysdiadochokinesia). The patient's autonomy was impaired, with inability to work or perform activities of daily living (ADLs) such as dressing, feeding, and moving around, among others.

After beginning stem cells and exosomes treatment from July to December of this year, the patient showed improvement, as observed by both the team and his family. His gross and fine motor skills improved, as well as his swallowing and speech articulation. The patient began to perform exercises to recover his gait, being

able to walk more than 10 metres with aids. This strengthened his axial muscles, allowing him to sit without assistance and maintain his posture without his head falling backwards. Of utmost importance was that the patient was able to regain autonomy in some activities of daily living, being able to feed and dress himself, begin driving his vehicle again, and return to work, something that was completely unthinkable at the time. Despite these improvements, consistent follow-up of the patient was lost due to reasons of geographic distance from our facility until December 2025, when he returned to restart therapy.

Discussion

The use of stem cells and exosomes in IMCA is based on two main foundations: immunomodulation and neuromodulation. Stem cells are undifferentiated cells that have the capacity of self-renewal and differentiation into various types of tissue. They maintain close interaction with the immune system and can act on the inflammatory microenvironment present in various diseases (8). In turn, they secrete a wide range of active biomolecules, such as proteins, nucleic acids, exosomes, and microvesicles, which altogether are released through structures known as secretomes (9). This complex complements the regenerative and therapeutic capacity of stem cells (9). Through cellular (action on Treg lymphocytes, macrophages) and humoral (exosomes, secretomes) mechanisms, stem cells exert an immunomodulatory action capable of regulating inflammation and promoting tissue repair (8).

On the other hand, in some patients, conventional therapies against autoimmune diseases, such as corticosteroids, plasmapheresis, or intravenous immunoglobulin, fail or are poorly tolerated (10). This was the case prior to treatment with stem cells and exosomes. Autologous stem cells stand out as a novel therapy in these processes thanks to their immunomodulatory properties, low immunogenicity, and regenerative capacity (10).

IMCA is characterised by the presence of a neurotoxic environment involving the accumulation of oxygen free radicals and mitochondrial impairment. The ability of stem cells to interact with damaged tissue cells has been studied. An essential mechanism that has been objectively verified is the transfer of mitochondria from stem cells to damaged tissue cells (11). This increased the amount of ATP present in these cells, enhancing their bioenergetic profile and functional capacity (11). This is a critical mechanism in the functional regeneration of damaged tissues.

We highlight the recent interest that has emerged in the superficial fascia as an important niche and reservoir for stem cells (12). It stands out as a biologically active environment capable of regulating stem cell survival, modulating the immune system, and with a strong regenerative potential (12). This tissue constitutes a biologically active platform and a communication pathway for the transport and circulation of stem cells, thus

being a strong enhancer of angiogenesis and cell survival. Its structure contains a high density of fibroblasts, which secrete multiple bioactive factors, especially the fibroblast growth factor (FGF) family (13). These factors interact with an enzyme called telomerase, over which they induce the expression of its TERT (telomerase reverse transcriptase) subunit, promoting the survival and differentiation of neuronal precursors, adult stem cells, and nerve cells (14). In these cells, it modulates excitotoxicity (14), a pathological mechanism that perpetuates extensive damage to nerve tissue.

These cellular, immunological, neuromodulatory, and functional basics help us understand how stem cell therapy can be positioned as a therapeutic strategy for IMCA. The advances achieved during the year 2025 are shown below.

The patient showed remarkable progress in both SARA and ADLs. Functional improvement was mainly observed in areas such as: remaining seated, speech ability and absence of tremors. On the other hand, his autonomy had improved, allowing him to get dressed, eat by himself, drive his car and return to work.

The stem cell extraction procedure was again performed and completed successfully. After that, stem cells and exosomes were administered for 3 consecutive days. The patient was discharged showing a noticeable improvement, accompanied by the prior advances described above. His muscle tone and trophism were normal, with 5/5 muscle strength in the upper and lower limbs. The patient could perform the heel-to-shin test on both lower limbs, something that was previously unthinkable. His disabling tremor had disappeared, and he was able to maintain a good posture while sitting and drink a glass of water without spilling it. Along with this, his swallowing had improved, and he was able to feed himself with good swallowing dynamics. His speech was well articulated, using a wide range of words, and drooling had decreased to only occasional events. These advances had also allowed him to stay standing for longer periods of time, intensifying his exercises to recover his gait. Finally, he regained some of his autonomy, being able to drive his car and return to work. Upon continuing therapy, emphasis will be placed on consolidating his gait to achieve even greater functional improvements and autonomy.

Overall, clinical and functional improvement was observed, allowing the patient to perform previously unthinkable tasks such as maintaining posture, performing coordination exercises, articulating words correctly, feeding himself, and improving a highly disabling symptom such as tremor. In addition, he has greater autonomy, being able to drive his own vehicle and return to work. These advances are extremely promising given the disabling nature of IMCA.

Conclusion

CAs are complex medical conditions with heterogeneous clinical features and etiologies. Among them, we focus on IMCA as a cause of disability and loss of autonomy in activities of daily living. Despite this, the

cerebellum exhibits a great capacity for regeneration from the damage it sustains. This property, known as cerebellar reserve, is critical for the onset of functional and structural regeneration through immunomodulation and neuromodulation strategies.

Stem cells have immunomodulatory properties and can promote an anti-inflammatory profile at both the cellular and humoral levels. On the other hand, elements such as fibroblasts, FGF, telomerase, exosomes, and secretomes play a vital role in cell proliferation, neuronal development, and neurogenesis. This further enhances the unique feature of the cerebellum in terms of tissue regeneration.

The patient showed significant advances as measured by the SARA and ADLs, promoting his autonomy in daily living activities such as dressing, eating, driving and working. His clinical improvement was measured by parameters such as coordination, absence of tremor, swallowing, speech, and motor tests such as muscle strength or the heel-to-shin test, all of which showed improvement.

The combined therapy with stem cells and exosomes represents a novel therapy for IMCA, promoting clinical advances through immunomodulation and neuromodulation that position it as a promising treatment for this condition.

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