Title: Autologous Mesenchymal Stem Cell Transplantation in Genetically Complex Cerebellar Ataxia

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Abstract:

Cerebellar ataxias are progressive neurodegenerative disorders with strong genetic underpinnings and limited treatment options. Variants in genes such as Synaptic Nuclear Envelope Protein 1 (*SYNE1*) and Multiple Inositol Polyphosphate Phosphatase 1 *(MINPP1)* have been implicated in distinct forms of hereditary ataxia. We report two siblings with cerebellar ataxia harboring distinct pathogenic variant combinations.: the brother was homozygous for both *SYNE1* and *MINPP1*, while the sister was heterozygous for *SYNE1* and homozygous for *MINPP1*. Notably, this represents the first report of heterozygous *SYNE1* and *MINPP1* variants co-occurring in ataxia.

Each patients underwent eight sessions of autologous mesenchymal stem cell (MSC) transplantation (MSCT) using bone marrow-derived MSCs (1×10^6 cells/kg), delivered via

combined intravenous and intrathecal routes at 1-, 3-, and 6-month intervals. Delivering MSCs via both intravenous and intrathecal routes may facilitate broader central nervous system engagement and improve delivery efficiency across neuroanatomical compartments. Each session was preceded by standardized safety screening to rule out infection or inflammation. Supportive therapy included physiotherapy, antioxidant supplementation, and a high-protein diet. Clinical response was monitored using the Scale for the Assessment and Rating of Ataxia (SARA).

The 22-year-old sister experienced sustained and progressive clinical improvement, with a total SARA score reduction from 5 to 0 over 24 months. She showed marked gains in balance, gait, fine and gross motor coordination, and speech fluency. Only transient adverse effects—such as fever, headache, and nausea—were observed. In contrast, her 15-year-old brother showed early improvements in gait and speech but experienced fluctuating SARA scores (range: 2–8) in later sessions, possibly due to disease progression or genotype-dependent therapeutic resistance. Her improvements persisted throughout the 12-month follow-up, suggesting a potential cumulative or durable therapeutic effect.

These findings suggest that MSCT may offer functional benefits in genetically complex cerebellar ataxia, potentially via paracrine mechanisms rather than cellular replacement. The sister's more favorable response may be partially explained by her preserved *SYNE1* allele, as *SYNE1* is known to support MSC survival, proliferation, and regenerative potential. This underscores the importance of genotype-specific responsiveness in stem cell therapies.

While MSCT is not curative, it may serve as a palliative strategy to improve quality of life and act as a bridge to future gene-targeted interventions. Controlled trials incorporating genetic stratification and biomarker profiling are essential to validate these early observations, optimize treatment protocols, and define predictors of therapeutic response.

Keywords: Mesenchymal Stem Cell Therapy, Cerebellar Ataxia, Neurodegenerative Disease, *SYNE1* Mutation, SARA score

Biography

I am Dr. Amirreza Boroumand, a neurologist, psychosomatic medicine specialist, and stem cell therapy expert. My career has been dedicated to advancing the understanding and treatment of neurological and psychosomatic disorders. I earned my medical degree from Mashhad University of Medical Sciences, where my thesis explored HTLV-I-infected T-cell lines. This early research sparked my passion for innovation in medicine.

Throughout my journey, I have sought knowledge across borders, completing a fellowship in psychosomatic medicine at Freiburg University in Germany and training in stem cell therapy for

neurological disorders at Münster University. My certifications, including RCT-GCP credentials from the USA-FDA and Iran-FDA, reflect my commitment to excellence in clinical research and practice.

I currently lead neurology departments at the International Center for Personalized Medicine in Düsseldorf, Germany, and the Parnia Stem Cell Institute in Mashhad, Iran. My private clinic specializes in neurodegenerative diseases and psychosomatic conditions, blending personalized care with cutting-edge therapies.

Research and education are central to my work. I have published extensively on topics ranging from stem cell applications in ALS to the psychosomatic dimensions of health. I have also authored books such as *Dementia: A Public Health Priority, Application of Stem Cells in Autoimmune Diseases,* and contributed to training the next generation of medical professionals.

My career has been enriched by international collaborations, workshops, and conferences, which have allowed me to share knowledge and integrate innovative treatments into medical practice. I remain committed to pushing the boundaries of neurology and psychosomatic medicine, always striving to improve patient outcomes through research, education, and compassionate care.