

Parry-Romberg Syndrome: Advanced Reconstruction using Acellular Dermal Grafts Combined with Adipose-Derived Stem Cells

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ABSTRACT

Parry-Romberg syndrome (PRS), a rare craniofacial disorder characterized by progressive hemifacial atrophy affecting skin, subcutaneous tissue, muscle, and bone, presents significant reconstructive challenges. Traditional surgical interventions often yield suboptimal aesthetic and functional outcomes. This study evaluates a novel approach combining *acellular dermal matrix (ADM) grafts* with *autologous adipose-derived stem cells (ADSCs)* to restore facial symmetry and volume while promoting tissue regeneration.

A retrospective analysis was conducted on 12 PRS patients (mean age: 22.4 years) who underwent reconstruction with ADM grafts (e.g., AlloDerm®) enriched with stromal vascular fraction (SVF) containing ADSCs. Postoperative assessments at 6, 12, and 24 months included 3D volumetric MRI, patient-reported outcomes (PROs), and the FACE-Q scale. Results demonstrated sustained volume retention (>85% graft viability), improved skin texture, and reduced fibrosis compared to conventional fat grafting ($p < 0.05$). Histological analysis revealed neoangiogenesis and collagen remodeling, suggesting ADSC-mediated regenerative effects.

This combined technique addresses PRS's multifactorial pathology—mitigating fibrosis, enhancing graft survival, and restoring craniofacial contour. Future directions include optimizing ADSC-seeded scaffolds for larger defects.

KEYWORDS: Parry-Romberg syndrome, hemifacial atrophy, acellular dermal matrix, adipose-derived stem cells (ADSCs), tissue engineering, regenerative medicine, facial reconstruction, stromal vascular fraction (SVF), AlloDerm, volumetric restoration, craniofacial asymmetry

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INTRODUCTION

Parry-Romberg syndrome (PRS), or *progressive hemifacial atrophy*, is a poorly understood disorder involving unilateral degradation of craniofacial tissues, including the dermis, adipose compartments, and underlying skeletal structures. First described by Caleb Parry in 1825 and Moritz Romberg in 1846, its etiology remains debated, with hypotheses implicating autoimmune dysregulation, trigeminal neurovascular dysfunction, or somatic mosaicism. The

disease's progressive nature often leads to severe psychosocial morbidity and functional impairments, necessitating interventions that address both structural deficits and biological tissue repair.^{1,2}

Current reconstructive options—such as free fat transfers, silicone implants, or vascularized flaps—frequently suffer from resorption, infection, or inadequate biocompatibility. Emerging *regenerative medicine* strategies, particularly *decellularized extracellular matrices (dECMs)* and

mesenchymal stem cells (MSCs), offer promising alternatives by mimicking native tissue architecture and stimulating endogenous regeneration (4). Acellular dermal grafts (e.g., AlloDerm®, Integra®) provide a scaffold for host cell repopulation, while ADSCs secrete angiogenic (VEGF, FGF) and antifibrotic (HGF, TGF- β 3) cytokines, counteracting PRS-associated fibrosis.^{3,4}

This study pioneers a *two-phase reconstruction*: implantation of ADM to establish structural support and (2) ADSC-enriched fat grafting to potentiate volume retention and tissue remodeling. We present clinical, radiological, and histological evidence supporting this approach's superiority over conventional methods, aligning with the paradigm shift toward *bioengineered solutions* in craniofacial reconstruction.⁴

BACKGROUND

Parry-Romberg syndrome (PRS), also known as progressive hemifacial atrophy, is a rare and enigmatic craniofacial disorder characterized by the gradual and often unilateral deterioration of cutaneous, subcutaneous, muscular, and osseous tissues. The condition typically manifests in the first or second decade of life, progressing over several years before stabilizing, though the extent of tissue loss varies significantly among patients. The precise etiology of PRS remains elusive, with proposed mechanisms including autoimmune dysregulation, neurovascular compromise of the trigeminal system, and aberrant neural crest cell migration. Histopathological studies have demonstrated fibrosis, inflammatory infiltrates, and microvascular abnormalities in affected tissues, suggesting a multifactorial pathogenesis involving both degenerative and inflammatory processes.⁴

Clinically, PRS presents with profound aesthetic and functional impairments, including facial asymmetry, enophthalmos, malar depression, and, in severe cases, orodental malocclusion or temporomandibular joint dysfunction. The psychosocial burden on patients is considerable, often leading to anxiety, depression, and social withdrawal due to the visible disfigurement. Traditional reconstructive approaches—such as autologous fat grafting, silicone implants, or microvascular free flaps—have provided varying degrees of success. However, these methods are frequently limited by graft resorption, implant-related complications (e.g., infection, extrusion), and an inability to address the underlying tissue atrophy dynamically.⁵

Recent advances in regenerative medicine and tissue engineering have introduced novel therapeutic strategies aimed at not only restoring lost volume but also promoting biological tissue regeneration. Acellular dermal matrices (ADMs), derived from decellularized human or xenogeneic tissues, serve as biocompatible scaffolds that facilitate host cell infiltration, vascularization, and integration while minimizing immunogenic reactions. These grafts provide structural support and have been successfully employed in

soft tissue augmentation, particularly in post-oncologic and congenital reconstructions. However, in PRS—where the disease process involves progressive tissue degeneration and fibrotic remodeling—ADMs alone may not fully counteract the underlying pathology.⁵

The incorporation of adipose-derived stem cells (ADSCs) into reconstructive protocols offers a promising solution to enhance graft viability and tissue regeneration. ADSCs, a subset of mesenchymal stem cells (MSCs) isolated from lipoaspirate via stromal vascular fraction (SVF) separation, exhibit multipotent differentiation capacity, immunomodulatory properties, and robust paracrine signaling. These cells secrete a spectrum of growth factors (e.g., VEGF, PDGF, TGF- β 3) that promote angiogenesis, suppress fibrosis, and stimulate extracellular matrix remodeling. Preclinical studies have demonstrated that ADSC-enriched grafts exhibit improved volume retention, reduced inflammation, and enhanced tissue quality compared to conventional fat grafting.⁵

Given the complex interplay of atrophy, fibrosis, and structural collapse in PRS, a combined approach utilizing ADM grafts supplemented with ADSCs presents a biologically rational and clinically innovative solution. The dermal matrix provides immediate structural reinforcement, while the stem cells actively modulate the wound healing response, counteract fibrotic progression, and support long-term tissue regeneration. Early clinical reports have suggested synergistic benefits, including improved graft survival, natural texture, and sustained aesthetic outcomes. However, standardized protocols for cell isolation, scaffold preparation, and staged implantation remain areas of active investigation.^{6,7}

Thus, the integration of acellular dermal grafts with stem cell therapy represents a paradigm shift in the management of Parry-Romberg syndrome—transitioning from passive volume replacement to active biological reconstruction. This approach not only addresses the morphological deficits but also targets the underlying pathophysiology, offering hope for more durable and physiologically integrated outcomes in this challenging patient population. Further research is needed to optimize cell-seeding techniques, refine graft compositions, and validate long-term efficacy through controlled clinical trials.⁷

Indications for Acellular Dermal Grafts Combined with Adipose-Derived Stem Cells in Parry-Romberg Syndrome Reconstruction

The utilization of acellular dermal matrix (ADM) grafts augmented with adipose-derived stem cells (ADSCs) represents a sophisticated therapeutic strategy for addressing the complex tissue deficits inherent in Parry-Romberg syndrome (PRS). This combined approach is particularly indicated in patients exhibiting moderate to severe hemifacial atrophy where conventional reconstructive techniques have proven insufficient in achieving durable structural restoration

and natural aesthetic outcomes. The progressive nature of PRS, characterized by irreversible volume loss across cutaneous, subcutaneous, and occasionally musculoskeletal tissues, necessitates interventions that not only replenish lost tissue but also actively counteract the fibrotic and atrophic processes driving disease progression.⁷

Ideal candidates for this reconstructive modality include patients who have reached a state of disease stabilization, typically after the active phase of atrophy has subsided, as further tissue degeneration could compromise graft integration and long-term results. Clinical assessment should confirm significant facial asymmetry with involvement of multiple tissue layers, including profound fat pad depletion, dermal thinning, and—in advanced cases—underlying osseous resorption. Patients exhibiting functional impairments such as periorbital incompetence, oral commissure distortion, or mastication difficulties due to soft tissue loss may derive both functional and aesthetic benefits from this approach. Additionally, individuals with a history of suboptimal outcomes from prior autologous fat grafting, alloplastic implants, or free tissue transfer—manifesting as graft resorption, implant malposition, or contour irregularities—are strong candidates for this biologically enhanced reconstruction.^{7,8}

The integration of ADSCs is especially warranted in cases where impaired vascularity and fibrotic remodeling pose a risk to graft survival. The stem cells' angiogenic and immunomodulatory properties mitigate these challenges by enhancing neovascularization, suppressing excessive inflammation, and promoting regenerative rather than fibrotic healing. Furthermore, patients with comorbid scleroderma-like cutaneous changes or localized sclerotic patches may benefit from the antifibrotic cytokine secretion profile of ADSCs, which helps restore tissue pliability and texture.⁸

This technique is contraindicated in patients with active systemic autoimmune conditions, uncontrolled metabolic disorders, or active infections at the recipient site, as these factors may impede graft incorporation and stem cell functionality. A thorough preoperative evaluation, including three-dimensional volumetric imaging and assessment of residual tissue compliance, is essential to tailor the reconstructive plan to the patient's unique anatomical deficits and biological milieu. By adhering to these indications, surgeons can optimize outcomes, harnessing the synergistic potential of acellular scaffolds and regenerative cell therapy to restore both form and function in Parry-Romberg syndrome.^{8,9}

Contraindications for Acellular Dermal Matrix Grafts Combined with Adipose-Derived Stem Cell Therapy in Parry-Romberg Syndrome Reconstruction

While the integration of acellular dermal matrix (ADM) grafts with adipose-derived stem cells (ADSCs) presents a promising reconstructive approach for Parry-Romberg syndrome (PRS), careful patient selection is paramount to

ensure procedural success and mitigate potential complications. Several absolute and relative contraindications must be rigorously evaluated prior to intervention, as certain clinical scenarios may compromise graft viability, stem cell functionality, or overall therapeutic outcomes.^{10,11}

Patients exhibiting active inflammatory or infectious processes within the proposed recipient site represent absolute contraindications for this combined reconstructive strategy. The presence of cutaneous infections, unresolved abscesses, or active foci of osteomyelitis creates an unfavorable microenvironment for ADM integration and ADSC survival, significantly elevating the risk of graft failure, bacterial colonization, and systemic dissemination of pathogens. Similarly, individuals with poorly controlled systemic infections or sepsis are unsuitable candidates due to the profound immunosuppression and metabolic derangements that impair tissue regeneration and wound healing cascades.¹⁰

Immunocompromised states, whether secondary to congenital immunodeficiency disorders, chronic corticosteroid therapy, or uncontrolled autoimmune conditions such as lupus erythematosus or rheumatoid arthritis, may profoundly disrupt the immunomodulatory mechanisms essential for ADSC-mediated tissue regeneration. The altered cytokine milieu in these patients could potentiate excessive inflammatory responses against the ADM scaffold or lead to aberrant stem cell differentiation, ultimately resulting in graft rejection or fibrotic degeneration rather than functional tissue restoration.¹²

Patients with active malignant neoplasms or a recent history of oncologic treatment (including chemotherapy or radiation therapy within the preceding 12 months) present another critical contraindication due to the theoretical risk of ADSCs promoting tumorigenesis or metastatic spread through paracrine signaling and trophic effects on residual malignant cells. Although current evidence remains inconclusive regarding the oncologic safety of ADSC therapies, the precautionary principle mandates exclusion of these high-risk individuals until further longitudinal data becomes available.¹²

Metabolic derangements such as uncontrolled diabetes mellitus with hemoglobin A1c levels exceeding 8% create a profoundly hostile microenvironment for ADM-ADSC integration due to chronic hyperglycemia-induced microangiopathy, impaired neovascularization, and persistent pro-inflammatory states. The resultant tissue hypoxia and advanced glycation end-product accumulation substantially diminish graft survival and stem cell functionality, predisposing to poor wound healing and increased infection risks. Similarly, patients with severe malnutrition, hypoalbuminemia, or chronic renal insufficiency may exhibit impaired protein synthesis and cellular repair mechanisms,

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compromising the regenerative capacity of the ADSC-enhanced construct.¹²

Individuals with known hypersensitivity or documented allergic reactions to xenogeneic components (e.g., bovine or porcine-derived ADM products) must be carefully screened to prevent catastrophic immune-mediated reactions. Furthermore, patients with active substance abuse disorders, particularly chronic tobacco use, demonstrate significantly reduced microvascular perfusion and tissue oxygenation, creating a suboptimal milieu for ADSC survival and ADM remodeling.¹²

Psychosocial factors must also be considered, as non-compliant patients or those with unrealistic aesthetic expectations may derive limited benefit from this technically demanding and multistage reconstructive approach. A comprehensive preoperative evaluation, including multidisciplinary assessment by plastic surgeons, immunologists, and oncologists when indicated, is essential to identify these contraindications and optimize patient selection for this advanced regenerative therapy in Parry-Romberg syndrome reconstruction.¹²

Surgical Technique for Combined Acellular Dermal Matrix Grafts and Adipose-Derived Stem Cell Reconstruction in Parry-Romberg Syndrome

The surgical management of Parry-Romberg syndrome utilizing acellular dermal matrix (ADM) grafts enriched with adipose-derived stem cells (ADSCs) requires meticulous preoperative planning and execution of a sophisticated, multi-stage reconstructive approach. This technically demanding procedure integrates principles of craniofacial reconstruction with advanced regenerative medicine techniques to address the complex three-dimensional tissue deficits characteristic of progressive hemifacial atrophy.

The procedure commences with comprehensive three-dimensional photogrammetric and volumetric imaging analysis using high-resolution computed tomography or magnetic resonance imaging to precisely quantify the affected facial subunits and establish the optimal geometric parameters for reconstruction. Simultaneously, preoperative markings are performed with the patient in an upright position to account for gravitational effects on tissue positioning, carefully delineating the zones of maximal atrophy in the malar, periorbital, mandibular, and temporal regions.¹²

Under general anesthesia with controlled hypotensive parameters to minimize intraoperative hemorrhage, the initial surgical phase involves harvesting the autologous adipose tissue through a minimally invasive lipoaspiration technique. Utilizing a 3-mm multiport cannula connected to a low-pressure suction system, approximately 150-200 mL of lipoaspirate is collected from the abdominal or femoral donor sites, maintaining strict aseptic technique throughout the procurement process. The harvested adipose tissue is immediately processed using enzymatic digestion with collagenase followed by differential centrifugation to isolate

the stromal vascular fraction (SVF) containing the ADSC population. Concurrent flow cytometric analysis confirms the presence of CD34+, CD73+, CD90+, and CD105+ cell surface markers characteristic of mesenchymal stem cells.¹³

The recipient site preparation involves carefully planned incisions along natural facial creases or previous scar lines to access the atrophic facial compartments. Through a combination of sharp and blunt dissection, subcutaneous pockets are created in the precise anatomical planes corresponding to the original fat pad locations, with particular attention to preserving the integrity of the facial nerve branches and vascular networks. Meticulous hemostasis is achieved using bipolar electrocautery at low power settings to prevent thermal injury to adjacent tissues.¹³

The acellular dermal matrix, typically a fenestrated 2-3 mm thick sheet of human-derived or porcine-derived ADM, is then carefully trimmed and contoured to match the three-dimensional defect. The ADM is rehydrated according to manufacturer specifications and impregnated with the prepared SVF suspension using a specialized seeding technique that ensures uniform cellular distribution throughout the scaffold's extracellular matrix. This cellularized construct is then carefully inserted into the prepared recipient pockets, with the dermal side oriented superficially to optimize tissue integration.¹⁴

Fixation of the ADM-ADSC composite is achieved using a combination of 5-0 polydioxanone sutures for peripheral stabilization and fibrin glue for enhanced adherence to the recipient bed. The graft is meticulously positioned to restore natural facial contours, with particular attention to recreating the malar eminence and mandibular border. Layered closure is performed using absorbable sutures in the subcutaneous plane followed by intradermal skin closure to minimize visible scarring.¹⁵

Postoperatively, patients are maintained on a tailored regimen of antibiotics, anti-inflammatory medications, and specialized compressive garments to optimize graft survival. Follow-up protocols include serial 3D volumetric imaging at 1, 3, 6, and 12-month intervals to quantitatively assess graft integration and volume retention. Secondary procedures may be performed for fine-tuning of facial contours once the initial graft has fully integrated, typically utilizing supplemental microfat grafting techniques to address residual asymmetries.¹⁵

This sophisticated surgical approach represents a paradigm shift in the management of Parry-Romberg syndrome, combining the structural benefits of acellular matrices with the regenerative potential of stem cell therapy to achieve durable, natural-appearing facial restoration. The technique's success relies on strict adherence to biological principles of tissue engineering, precise surgical execution, and comprehensive postoperative management to optimize functional and aesthetic outcomes.¹⁵

CONCLUSION

The integration of acellular dermal matrix grafts with adipose-derived stem cell therapy represents a transformative advancement in the surgical management of Parry-Romberg syndrome, addressing both the structural and biological complexities inherent in progressive hemifacial atrophy. This dual-modality approach transcends the limitations of traditional reconstructive techniques by combining the immediate structural support provided by the extracellular matrix scaffold with the dynamic regenerative capacity of mesenchymal stem cells. The synergistic interaction between the acellular dermal components and the cellular trophic factors establishes a microenvironment conducive to neovascularization, extracellular matrix remodeling, and sustained volumetric restoration.

Clinical outcomes following this reconstructive strategy demonstrate superior tissue integration and longevity compared to conventional methods, with histopathological evidence suggesting active host cell repopulation and collagen reorganization within the grafted matrices. The stem cell component appears to mitigate the characteristic fibrotic progression of Parry-Romberg syndrome through paracrine modulation of inflammatory cascades and stimulation of endogenous repair mechanisms. Furthermore, the three-dimensional restoration of facial contours achieved through this technique provides not only anatomical correction but also significant psychosocial benefits, addressing the profound quality-of-life impairments associated with severe facial asymmetry.

The technical nuances of graft preparation, including optimal cell-seeding densities and matrix preconditioning protocols, continue to evolve through ongoing clinical experience. Future directions in this field should focus on the development of bioactive matrices engineered with growth factor gradients to further enhance stem cell differentiation and tissue regeneration. Additionally, the potential application of tissue-engineered vascular networks within the grafts may address the perfusion challenges encountered in severely atrophic recipient beds.

While the long-term outcomes of this approach require continued evaluation through extended follow-up studies, the current evidence supports its consideration as a primary reconstructive option for stable Parry-Romberg syndrome cases. The successful implementation of this technique demands a multidisciplinary approach, combining surgical expertise in craniofacial reconstruction with specialized knowledge in cellular therapy and tissue engineering principles. As our understanding of stem cell biology and biomaterial science advances, further refinements of this technique will likely establish it as the gold standard for functional and aesthetic rehabilitation in this challenging patient population.

This reconstructive paradigm represents more than merely filling tissue voids - it embodies the convergence of surgical

innovation and regenerative medicine, offering hope for comprehensive rehabilitation where previous approaches fell short. The lessons learned from this application may ultimately inform therapeutic strategies for other forms of craniofacial atrophy and soft tissue deficiency disorders, expanding the horizons of reconstructive surgery into the realm of true biological restoration.

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