

Ain-Shams University
Faculty of Medicine
ENT Department
Phoniatrics Unit

STEM CELL THERAPY IN COMMUNICATION DISORDERS

(Systematic Critical Review)

Submitted for the Partial Fulfillment for Master Degree
in Phoniatrics

By

Nermeen Atef Elhusseiny Ahmed

M.B., B.Ch Faculty of Medicine- Zagazig University
Resident of Phoniatrics at Zagazig University Hospitals

Under Supervision of

Prof. Dr. Nahla Abd El-Aziz Rifaie

*Professor and head of Phoniatrics Unit – ENT Department
Faculty of Medicine, Ain Shams University*

Dr. Dina Ahmed Elsayed Elrefaie

*Lecturer of Phoniatrics - ENT Department
Phoniatrics Unit, Faculty of Medicine, Ain Shams University*

Dr. Elham Magdy Hafiz

*Lecturer of Phoniatrics - ENT Department
Phoniatrics Unit, Faculty of Medicine, Zagazig University*

2018

Acknowledgement

Firstly and for most, all gratitude goes in the first place to **ALLAH**, the merciful and compassionate, he always guide me all over my life.

I would like to express my deepest appreciation and profound gratitude to *Prof. Dr. Nahla Abd El-Aziz Rifaie*, professor of phoniatics, Faculty of medicine, Ain Shams University, who devoted her time and efforts to this work. I am truly grateful to her for her kind supervision and ultimate support and whatever has been said is little to express my respect and thanks.

I am also deeply grateful to *Dr. Dina Ahmed Elsayed Ebrefaie* Lecturer of Phoniatics, Faculty of Medicine, Ain Shams University for her constructive guidance, valuable advice and for her kindness and keen supervision.

I am greatly indebted to *Dr. Elham Magdy Hafiz* Lecturer of Phoniatics, Faculty of Medicine, Zagazig University for her valuable advice and for her help and constant encouragement all through this work.

I am also thankful for all staff members of the phoniatics unit at Zagazig Hospital and Ain Shams University for their kind help and great support.

Finally, I would like to thank my family for supporting me all the time

List of Contents

	Page No.
1-Introduction	1
2-Aim of the work	4
3-Review of literature	5
4-Materials and methods	53
5-Results:	
a- Autism	57
b- Stroke	67
c- BDMH	88
d- TBI	103
e- Vocal fold regeneration	115
6-Discussion	122
7-Conclusion	136
8- Summary	139
9-Reference	142
Arabic Summary	—

List of Abbreviations

- ¹⁸F-FDG-PET/CT...** Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography.
- ABA.....** Applied behavior analysis
- ABC.....** Aberrant Behavior Checklist to measure behavior improvement after treatment.
- ASD** Autism spectrum disorders.
- ATEC** Autism Treatment Evaluation Checklist to evaluate the effectiveness of treatment of autism.
- BBS.....** Berg Balance Scale for balance
- BDI.....** Battelle Developmental Inventory.
- BDI.....** Battelle Developmental Inventory.
- BDMH.....** Brain damaged motory handicapped.
- BDNF** Brain deived neurotrophic factor.
- BDNF-UCMSC...** Brain derived neurotrophic factor from umblical cord mesenchymal stem cells.
- BI.....** Barthel Index.
- BMMC** Bone marrow derived mononuclear stem cells
- BMMC** Bone marrow mononuclear cells.
- BMMNC** Bone marrow mononuclear cells.
- BMSC.....** Bone marrow mesenchymal stem cells
- BTBR T+tf/J mice ...**Model of mice has distinct behavioral pattern as ASD.

CBMNC Human cord blood mononuclear cells,

CD133..... Stem cell marker

CGI Computer-generated imagery

CGI..... Clinical global impression scale to measure severity of autism.

CNTF Ciliary neurotrophic factor

CNTF Ciliary neurotrophic factor,

CT..... Computed tomography

CXCR4..... Chemokine receptor type 4.

DC Dendritic cells

DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

Epo Group take placebo and erythropoietin

Epo Group take placebo and erythropoietin.

ESCs..... Embryonic stem cells

FAM Functional Assessment Measure to measure cognition, communication and behavior

FDG-PET Fluorodeoxyglucose-positron emission tomography for detection of active malignant cells.

FIM Functional Independence Measure for motor abilities assessment.

FIM Functional Independence Measure to measure the degree of disability

FIM Functional independence measures to measure functional independence

Floor time /DIR (Developmental Individual-difference Relationship-based model)

FMA.....Fuel-Mayer Assessment for motor, sensory scores and balance.

FMFM.....Fine motor function movement,

FMRIFunctional magnetic resonance imaging

GDNF.....Glial –cell-line derived neurotrophic factor.

GMFCS.....Gross Motor Function Classification System

GMFCS.....Growth motor function classification system.

GMFCS.....Growth motor function classification system.

GMFMGrowth motor function measure,

GMFM.....Growth motor function measure

GMFM.....growth motor function movements.

HA/ALG.....Hyaluronic acid/mildly cross linked alginate hydrogel.

hASCHuman adipose derived stem cell

hASCHuman adipose derived stem cell.

Health stroke scale score ...A tool used to objectively quantify the impairment caused by a stroke.

HIV.....Human immunodeficiency virus

hMSCHuman mesenchymal stem cells.

ICU.....Intensive Care Unit

IFN-gamma....Interferon gamma

IL-1 β Interleukin -1 beta.

IL-10.....Interleukin-10

INF- γ Interferon gamma.

IPSC Induced pluripotent stem cells,

iPSCs Induced pluripotent stem cells.

ISAA..... Indian scale for assessment of autism for diagnosis and measuring severity of autism

MCP-1..... Monocyte chemoattractant protein-1

MFCs Growth motor function classification system.
FMFM Fine motor function measure.

MNCs Mononuclear cells

mNSS..... Modified neurologic severity score for behavior assessment

mNSS..... Modified neurological severity scale.

Modified Rankin Scale Scale to measure the degree of disability/dependence in daily activities after stroke.

MRI..... Magnetic resonance imaging

mRS..... Modified Rankin Scale

MSC Mesenchymal stem cells.

MSCs..... Mesenchymal stem cells

MWM..... Morris Water Maze for memory assessment.

NIHSS National Institute of Health Stroke Scale

NK Natural killer.

NSS..... Neurological severity score.

Nur own..... Neurotrophic factor from mesenchymal stem cells.

PET Positron emission tomography

PET.CT Positron emission tomography–computed tomography,

PET-CT scan . Positron Emission Tomography – Computed Tomography.

PET-CT scan . Positron emission tomography-computed tomography

PKU..... Phenylketonuria

Pucb..... Group take umbilical cord blood stem cells and erythropoietin.

Pucb..... Group take umbilical cord blood stem cells and erythropoietin.

RA Retinoic acid.

RT-PCR Reverse transcription polymerase chain reaction.

SCERTS..... Social Communication- Emotional Regulation- Transactional Support

SORT Spatial operant reversal task to measure cognition level

SPECT scan... A Single Photon Emission Computed Tomography.

TBI Traumatic brain injury

TGF-beta..... Tumor growth factor-beta

TNF- α Tumor necrosing factor alpha.

TNF-alpha..... Tumor necrosis factor alpha

TUNEL..... (Terminal deoxynucleotidyltransferase mediated DUTP nick end-labeling) to measure apoptotic cells as TUNEL –positive nucleus with condensed nuclear morphology.

UCB..... Umbilical cord blood

UCBSC..... Umbilical cord blood stem cells.

UCMSC..... Umbilical cord derived mesenchymal stem cells

UCMSC..... Umbilical cord mesenchymal stem cells

VEGF Vascular endothelial growth factor

VEGF Vascular endothelial growth factor

VEGF Vascular endothelial growth factor.

VF..... Vocal fold

VF..... Vocal Folds

VPA-treated mice Mice injected by valporic acid to be ASD mouse model

WMT..... Morris water maze test for assessment of memory.

List of Tables

Table 1-1: Results of autism	58
Table 1-2: Results of autism	60
Table 1-3: Results of autism	62
Table 1-4: Level of evidence of autism	64
Table 2-1: Results of stroke	68
Table 2-2: Results of stroke	70
Table 2-3: Results of stroke	72
Table 2-4: Results of stroke	74
Table 2-5: Results of stroke	77
Table 2-6: Results of stroke	79
Table 2-7: Results of stroke	81
Table 2-8: Level of evidence of stroke	83
Table 3-1: Results of BDMH	89
Table 3-2: Results of BDMH	91
Table 3-3: Results of BDMH	93

Table 3-4: Results of BDMH	95
Table 3-5: Results of BDMH	97
Table 3-6: Level of evidence of BDMH	99
Table 4-1: Results of TBI	104
Table 4-2: Results of TBI	106
Table 4-3: Results of TBI	108
Table 4-4: Results of TBI	110
Table 4-5: Level of evidence of TBI	112
Table 5-1: Results of vocal fold regeneration .	116
Table 5-2: Results of vocal fold regeneration .	118
Table 5-3: Level of evidence of vocal fold regeneration	120

List of flow Charts

1-Flow chart of autism	57
2-Flow chart of stroke	67
3-Flow chart of BDMH	88
4-Flow chart of TBI	103
5-Flow chart of vocal fold regeneration	115

INTRODUCTION

Stem cells are un-differentiated cells that can proliferate into specialized cells and can divide to produce more stem cells. There are five main types of stem cells: embryonic stem cells, from the inner cell mass of blastocysts, adult stem cells, from various tissues, fetal stem cells, induced pluripotent stem cells (iPSCs) and amniotic stem cells. Stem cells act as a repair system for the body, replenishing adult tissues **(Tuch, 2006)**.

The role of stem cell appear in different communication disorders as in autism, brain damaged motory handicaped, aphasia following stroke, traumatic brain injury, and regeneration of vocal fold after vocal fold scar, atrophy or sulcus vocalis.

Autism spectrum disorders (ASD) are a group of neuro- developmental disorders as problems in verbal, nonverbal communication, social relationship, and appearance of stereotypical repetitive behavior **(Geschwind, 2008)**.

In autism, Stem cells act by Angiogenesis and Immuno-regulation. Angiogenesis means that Stem cell transplantation can increase local blood supply and restoration of function to damaged areas **(Park et al., 2009)**.

Immuno-regulation occurs by inhibition of T cells, B cells, and natural killer (NK) cells, increase activity of dendritic cells, inhibition of T lymphocyte pro-inflammatory cytokine production and regulate anti-inflammatory IL-10 and TGF-beta. This leads to decrease the damage with improvement of function (**Siniscalco et al., 2012**).

Aphasia is a neurological disorder that appears as difficulty in comprehension and formulation of language due to dysfunction in specific brain regions as in stroke (**Stahl et al., 2015**).

Mononuclear cell (MNCs) can decrease the site of lesion and restore the function. Stem cells are chemo attracted to the lesion area and stimulate the production of different cytokines and growth factors 8, 9, building of new blood vessels and repair of injured endothelium, decrease damage of neural tissues, prevent apoptosis, cell death and inflammation (**Prasada et al., 2012**).

In case of traumatic brain injury, neural stem cells are able to build a bridge between the damaged region and healthy regions of the brain. This bridge is called bio-bridge so, can replace injured tissues and produce growth factors. Stem cells stimulate the migration of brain own stem cells to the injured area (**Naoki et al., 2013**).

Brain damage with motor handicappness is a group of permanent motor disorders that appear in early childhood. Stem cell has its neuro-protective properties by its ability to decrease inflammation and apoptosis. The production of neuro-tropic factors may stimulate cell therapy efficacy (**Oskoui et al., 2013**).

Regeneration of vocal fold atrophy occurs by injection of stem cells in vocal fold, that enhance regeneration, reduction in scar tissue and fibrosis, deposition of type I collagen, improvement of vocal fold viscoelastic properties, stimulating wound healing and restoring the anatomical and physiological structure of VF. Mesenchymal stem cells can produce multiple growth factors as hepatocyte growth factor, vascular endothelial growth factor and collagen that lead to regeneration of tissue (**Kim et al., 2014**).