Anthem

Medical Policy

Subject: Cell Transplantation (Mesencephalic, Adrenal-Brain and Fetal Xenograft)
Document #: TRANS.00004
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Description/Scope

This document addresses transplantation of cells from adrenal tissue, fetal mesencephalic tissue and xenograft fetal tissue (for example, from pigs or other animals) to the brain as a proposed treatment for advanced Parkinson's disease and other disorders.

Position Statement

Investigational and Not Medically Necessary:

Transplantation of adrenal, fetal mesencephalic and xenograft fetal tissues to the brain is considered**investigational and not medically necessary** for the treatment of Parkinson's disease and for all other indications.

Rationale

Parkinson's disease

Parkinson's disease (PD) is a motor system disorder resulting from the loss of dopamine-producing cells in the midbrain that innervate the caudate and putamen. Symptoms include resting tremor, rigidity, and the impaired ability to start and continue bodily movements. Because pharmacologic treatment does not provide sufficient long-term therapeutic benefit, surgical interventions to transplant dopamine-producing tissues into the brain are under study.

At this time, the medical literature regarding adrenal-to-brain transplantation for the treatment of PD is limited to the description of uncontrolled, short-term studies with small sample sizes or case studies. Although some of these studies report finding clinical improvements, high morbidity and mortality rates are frequent. A few pathologic reports on adrenal-to-brain recipients demonstrated very few to no surviving transplanted cells 6 months to a year following surgery. Due to the lack of long-term outcomes or data from large randomized controlled trials (RCTs), in conjunction with reports of high rates of complications and death in the existing literature, studies investigating adrenal-to-brain transplantation for the treatment of PD have diminished.

The evidence for the clinical impact of fetal mesencephalic transplantation is inadequate to support conclusions. Concerns related to small sample sizes and a limited number of controlled trials are joined with a wide array of methodological issues with the procedure itself.

The medical literature currently describes several different surgical approaches, such as open or stereotactic, and bilateral versus unilateral, in addition to variations in tissue preparation methods, the number of transplants, inclusion or exclusion of postoperative immunosuppressive therapy, and the type of screening used for tissue donors. While this procedure demonstrates low morbidity and mortality, significant improvements in short- and long-term physical symptoms, and that graft viability and function are maintained, with such a wide range of methods available and low level of evidence to support each, there is inadequate support for any one method at this time.

Investigations into the use of porcine fetal mesencephalic transplantation are being conducted. While similar methodological issues exist as with human fetal tissue transplantation, fewer concerns related to the use of porcine fetal tissue may make this type of procedure more widely accepted. At this time, only a few small clinical trials have been described in the literature with some promising results. Further RCTs must be conducted before this type of therapy may be adequately evaluated for use and long-term efficacy in the clinical setting.

The International Parkinson and Movement Disorder Society ([MDS]; Fox, 2011) updated their evidence-based medicine review of treatments for motor symptoms of PD. The MDS concluded that surgical outcomes of human fetal cell transplantation as a treatment for PD was investigational and evidence on efficacy was insufficient. In 2013, the MDS updated their Position Paper on the use of stem cell therapies for PD, reconfirming their earlier conclusion that human fetal cell transplantation remains investigational.

The MDS published a position paper in 2021 on stem-cell based therapy for PD. The authors summarized the following position and recommendations:

> Cell-based therapies should demonstrate efficacy and safety particularly lacking adverse immune reactions, tumor formation or dyskinesias. There have been great advances in the research of stem-cell therapy, especially for PD, and clinical trials are ongoing. However, for the time being there is still not enough evidence to support the widespread use of cell-based therapies for PD outside of carefully controlled clinical trials. We are hopeful for the future progress of such therapies based on extensive translational studies in proper animal models, and international clinical approaches with properly designed trials (Brundin, 2021).

While transplantation of tissues from the adrenal gland (adrenal-to-brain), fetal mesencephalic allograft and fetal xenografts have been proposed as a replacement source of dopamine-generating neurons to treat individuals with PD, data are lacking regarding the long-term safety and effectiveness of these proposed therapies and further RCTs must be conducted before this type of therapy may be adequately evaluated for use in the clinical setting.

Ischemic stroke

In 2019, Boncoraglio and colleagues published the results a Cochrane Review on the efficacy and safety of stem cell transplantation in people with ischemic stroke. The review included RCTs that recruited people with ischemic stroke (acute, subacute or chronic) or an ischemic lesion. All types of stem cell transplantation were included (autograft, allograft, or xenograft; embryonic, fetal, or adult; from brain or other tissues). The primary outcome was improvement in neurologic impairment or functional outcome at 6 months or longer. In total seven RCTs comprised of 401 participants were included in the analysis. Overall, stem cell transplantation was associated with a better clinical outcome compared to placebo when measured with the Health Stroke Scale (NIHSS) (5 studies, n=319; low-certainty evidence), but not with the modified Rankin Scale mRS (6 studies, n=371; very low-certainty evidence), or the

Barthel Index BI (3 studies, n=170; very low-certainty evidence). However, authors noted that the studies showing an improvement in function after transplantation were also more likely to have a higher risk of bias, and a limited sample size (32 or fewer participants). The study authors concluded:

> Overall, in participants with ischemic stroke, stem cell transplantation was associated with a reduced neurological impairment, but not with a better functional outcome. No obvious safety concerns were raised. However, these conclusions came mostly from small RCTs with high risk of bias, and the certainty of the evidence ranged from low to very low. More well designed trials are needed.

Background/Overview

Parkinson's disease (PD) is a progressive, incurable, disabling disease caused by slow continuous loss of nerve cells in a part of the brain called the substantia nigra that produces dopamine, a brain chemical critical for movement of the body. According to the National Institutes of Health (2011), approximately 1% to 2% of adults over the age of 60 are affected by PD.

Common symptoms of the disease include tremors or involuntary movement in the jaw and extremities, slowed movement, muscle stiffness, gradual loss of voluntary movement, gradual loss of automatic movement, postural instability and depression. The exact cause of PD is not known, but there is some evidence that there may be an inheritable component to the disease.

At this time, there is no known cure for PD. Primary management of the disease is through pharmacologic therapies. No drug has been shown to effectively slow the progression of the disease. As PD progresses, pharmacotherapy becomes less and less effective in managing the symptoms of the disease. Surgical procedures, such as pallidotomy and electrical deep brain stimulation, may be considered for severe cases. However, none of these treatments correct the underlying problem of nerve cell degeneration.

Several techniques have been proposed for the treatment of the underlying cause of PD in which tissue or cells from other sources are transplanted onto the candidate's brain at the location where cell degeneration is occurring or in nearby areas. Theoretically, the transplanted cells take the place of the dysfunctional brain cells by producing dopamine, thus improving the signs and symptoms of PD.

The transplantation of tissue from the adrenal glands, specifically adrenal medullary tissue, to a portion of the brain called the corpus striatum, called adrenal-to-brain transplantation, is intended to improve the motor and postural dysfunctions of PD. Adrenal-to-brain transplantation can involve either an autograft from the candidate or an allograft from an aborted fetus. When done with the individual's own adrenal tissue, a complicated double surgery, one to remove the adrenal tissue, and one to transplant it into the brain, is required.

Another type of transplant for PD, fetal mesencephalic transplantation, involves a surgical procedure to implant tissue harvested from fetal brains, specifically mesencephalic tissue, into portions of the candidate's brain known as the caudate and putamen areas.

Finally, surgery to transplant brain tissue from fetal pigs (xenografts) into the brains of individuals with PD has also been attempted. The goal of this procedure, as with the other procedures described, is to implant dopamine-producing cells into the brain, alleviating the symptoms of the condition.

Definitions

Autograft: The process of taking tissue from one part of the body and transplanting it into another part of the body with the goal of treating some specific disease or condition.

Fetal allograft: The process of taking tissue or cells from an aborted fetus and transplanting it into the body of a recipient with the goal of treating some specific disease or condition.

Mesencephalic: Pertaining to the mid-section of the brain.

Xenograft: The process of taking tissues from another species, such as pigs, transplanting it into the body of a human with the goal of treating some specific disease or condition.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
64999	Unlisted procedure, nervous system [when specified as adrenal tissue, fetal mesencephalic tissue or fetal xenograft tissue transplant to brain]
HCPCS	
S2103	Adrenal tissue transplant to brain
ICD-10 Diagnosis	
	All diagnoses including, but not limited to, the following:
G20.A1-G20.C	Parkinson's disease
G21.0-G21.9	Secondary parkinsonism

References

Peer Reviewed Publications:

1. Bhattacharya N, Chetri MK, Mukherjee KL, et al. Can human fetal cortical brain tissue transplant (up to 20 weeks) sustain its metabolic and oxygen requirements in a heterotopic site outside the brain? A study of 12 volunteers with Parkinson's disease. Clin Exp Obstet Gynecol. 2002; 29(4):259-266.
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4. Fink JS, Schumacher JM, Ellias SL, et al. Porcine xenografts in Parkinson's disease and Huntington's disease patients: preliminary results. Cell Transplant. 2000; 9(2):272-278.
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7. Kefalopoulou Z, Politis M, Piccini P, et al. Long-term clinical outcome of fetal cell transplantation for Parkinson disease: two case reports. JAMA Neurol. 2014; 71(1):83-87.
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14. Wang F, Sun Z, Peng D, et al. Cell-therapy for Parkinson's disease: a systematic review and meta-analysis. J Transl Med. 2023; 21(1):601.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Blue Cross and Blue Shield Association. Fetal mesencephalic transplantation for the treatment of Parkinson's disease. TEC Assessment, 1995; 10(1).
2. Blue Cross and Blue Shield Association. Embryonic mesencephalic transplantation for the treatment of Parkinson's disease. TEC Assessment, 2001; 16(8).
3. Boncoraglio GB, Ranieri M, Bersano A, et al. Stem cell transplantation for ischemic stroke. Cochrane Database Syst Rev. 2019; 5(5):CD007231.
4. Brundin P, Kalia L, Olsen A; et al. International Parkinson and Movement Disorder Society (MDS) Position Paper - Use of stem cell therapies for Parkinson's disease. January 2021. Available at: https://www.movementdisorders.org/MDS/News/News--Notices/News-Release---Stem-Cell-Therapies/MDS-Position-Paper-Use-of-Stem-Cell-Therapies-for-Parkinsons-Disease.htm. Accessed on December 09, 2023.
5. Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2011; 26 Suppl 3:S2-S41.
6. Hallet M, Litvan I. Evaluation of surgery for Parkinson's disease: a report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology. 1999; 53(9):1910-1921.

Websites for Additional Information

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2. National Institute of Health. National Human Genome Research Institute. Learning about Parkinson's. Updated April 29, 2020. Available at: https://www.genome.gov/Genetic-Disorders/Parkinsons-Disease. Accessed on December 09, 2023.
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Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References section.
	09/27/2023	Updated Coding section with 10/01/2023 ICD-10-CM changes; added G20.A1-G20.C replacing G20.
Reviewed	02/16/2023	MPTAC review. Updated References section.
Revised	02/17/2022	MPTAC review. Revised INV/NMN statement to include all indications and reformatted statement to a single statement. Updated Description/Scope, Rationale, Background/Overview and References sections.
Reviewed	08/12/2021	MPTAC review. Updated Rationale and References section.
Reviewed	08/13/2020	MPTAC review. Updated References section.
Reviewed	11/07/2019	MPTAC review. Updated References section.
Reviewed	01/24/2019	MPTAC review. Updated Description/Scope and References section.
Reviewed	01/25/2018	MPTAC review. The document header wording was updated from "Current Effective Date" to "Publish Date." Updated References section.
Reviewed	02/02/2017	MPTAC review. Updated Rationale and References sections.
Reviewed	02/04/2016	MPTAC review. Updated Rationale and References sections. Removed ICD-9 codes from Coding section.
Reviewed	02/05/2015	MPTAC review. Updated Rationale and References sections.

Reviewed	02/13/2014	MPTAC review. Updated Description, Rationale, Background and References sections.
Reviewed	02/14/2013	MPTAC review. Updated Rationale, Background, References and Websites sections .
Reviewed	02/16/2012	MPTAC review. Updated Description, Rationale, Background, References and Websites sections.
Reviewed	02/17/2011	MPTAC review. Updated References and Websites sections.
Reviewed	02/25/2010	MPTAC review. References updated.
Reviewed	02/26/2009	MPTAC review. References updated.
Reviewed	02/21/2008	MPTAC review. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary” at the November 29, 2007 MPTAC meeting. References updated.
Reviewed	03/08/2007	MPTAC review. References updated.
Reviewed	03/23/2006	MPTAC annual review. References updated.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	06/16/2003	TRANS.00004	Adrenal-to-Brain and Fetal Mesencephalic Transplantation
WellPoint Health Networks, Inc.	09/23/2004	7.10.01	Embryonic Mesencephalic Transplantation for the Treatment of Parkinson’s Disease

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Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.