Review Article ISSN 2689-1077

Genetics & Molecular Medicine

# Effectiveness of Enzyme Replacement and Enhancement Therapies on the Management of Tay-Sachs

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**Received:** 15 July 2021; **Accepted:** 10 August 2021

**Citation:** Peterchris Okpala, Sandra Okpala. Effectiveness of Enzyme Replacement and Enhancement Therapies on the Management of Tay-Sachs. Genet Mol Med. 2021; 3(1) 02: 1-4.

## ABSTRACT

*Tay-Sachs is a hereditary syndrome that damages the spinal cord and brain nerve cells. This rare type of disease is mainly manifested in infants at the ages of three to six months. Affected infants lose all their motor skills, such as sitting and crawling. As the disease evolves, kids infected will experience seizures, blindness, deafness, and eventually paralysis. Solovyeva et al., 2018). Currently, there is no treatment for TSD, and different therapies are joined to improve symptoms in patients with the late-onset form. Infant TSD patients do not survive beyond five years. These therapies can also defer the progression of TSD in late-onset form patients. Enzyme replacement therapy (ERT) and enzyme enhancement therapies (EET) are encouraging therapies that could finally cure the disease. Smith (2021) demonstrated the efficiency of ERT and EET therapies using α and β subunits of Hex A using rats and a rare form of sheep known as Jacob sheep. This evaluation discourses the effectiveness of Enzyme replacement and Enhancement therapies in preventing neuroinflammation and non-neurologic symptoms of the TSD.*

## Keywords

Tay-Sachs, Enzyme replacement, Enzyme Enhancement, Mice, Jacob Sheep.

## Introduction

Tay Sachs is a very sporadic disease that is congenital from parents to the offspring. Affected children are incapable of breaking down fatty substances. The buildup of fatty substances (gangliosides) to lethal levels in the brain of infants results in the massive destruction of nerve cells, crippling their functions. The lifespan of affected children is no more than five years. In most cases, the disease manifests in early infancy as a severe disorder of the nervous system [1]. The Juvenile form manifests in teenage years, with a rare type that manifests in late adulthood. The severity of the clinical symptoms will depend on lingering HexA enzymatic activity. This is a deadly illness without any curative medicines and treatment options available to manage the severity of symptoms. They include enzyme replacement therapy, gene therapy, enzyme enhancing therapy, substrate reduction therapy, and cell transplantation. This review will evaluate the effectiveness of investigative therapies Enzyme replacement therapy and Enzyme enhancement therapy in the management of Tay-Sachs disease. ERT involves injecting the enzyme deficient in the brain. With TSD, ERT is a complicated process as the enzymes are supposed to be injected into the brain. Researchers undertaking clinical trials have to ensure the enzyme is of high quality and responds well to white blood cells. Vu et al. [2] revealed that ERT therapy on TSD relieved the signs provisionally as the influence of inoculated enzymes wears off with time. ERT therapy must be repeated several times as it may delay progression in the late onset form of TSD. Therefore, research on ERT should be taken seriously as it could eventually lead to a cure for the disease.

Gualdrón-Frías & Calderón-Nossa [3] establish that ERT research has been constrained because the enzyme is huge and cannot cross the barrier between the blood and brain as needed. Research is still ongoing on whether the HEXA enzyme can be inoculated straight into the central nervous system to alleviate this problem. Existing study models have failed to demonstrate the successful uptake of the enzyme when inoculated straight through the central

nervous system. Nevertheless, according to Solovyeva et al. [4], researchers are still working on effective apparatuses to administer ERT as it considerably helps manage symptoms of the disease. Solovyeva et al. study revealed that Enzyme enhancing therapy using chaperones to steady the enzyme increases HEXA levels, but medical benefits are yet to be realized [4].

## Purpose of the Review

This review was done to investigate the effectiveness of Enzyme Replacement Therapy (ERT) and Enzyme enhancement therapy (EET) in managing Tay-Sachs disease. These two therapies are promising options for Tay-Sachs patients with the late onset of the disease. It is essential to evaluate how these two therapies can effectively reduce the severity of symptoms. Nothing has been found to reduce the neuro-progression of the disease in infants, with most of them dying before the age of five years. This review will also illustrate the gaps of research in ERT and EET and suggest future research topics on the subject.

## Objectives

- To gain knowledge on research evidence supporting the use of Enzyme replacement therapy (ERT) in managing Tay-Sach disease as it has proven effective in treating lysosomal storage diseases
- Gain an understanding of how Enzyme enhancement therapy (EET) can manage Tay-Sachs disease
- Gain an understanding of other current treatment options being evaluated for Tay-Sach disease and how they can be used together with ERT and EET to maximize clinical benefits on the patient
- Identify gaps in research that could guide other researchers on the areas that need to be explored further to improve patient outcomes
- To suggest areas of research that could help on the research topic.

## Background / Overview

TSD is a rare genetic disorder that manifests when an infant gets several defective HEXA genes from both parentages. Infected kids lack hexosaminidase A enzyme, and this causes a biochemical response that destroys the nerve cells in the brain and spine. With no treatment in sight, caregivers must embrace the management options available to relieve non-neurologic symptoms. NAD [5], a Nationwide body that reviews research on TSD, reveals that the absence of this hormone activates irregular growth of gangliosides in neurons leading to cell death after the disease develops. According to Gualdrón-Frías & Calderón-Nossa [3], accepted ERT and EET therapies are presently being used to treat the non-neurological symptoms of the disease. ERT delivers the lost deficient enzyme through steady IV infusions. ERT delays progression in patients with the rare late onset of the disease. Renna reveals the current status of ERT therapy as being a success in the management of Gaucher Type I for the last two decades. It also cures Fabry and some types of Mucopolysaccharidosis (MPS) [6]. According to Vu et al. (2018), there is a need for substantial research into therapeutic techniques such as Enzyme replacement therapy and Enzyme enhancement therapy and how they could be beneficial in the management and eventual cure of the disease. ERT has been proven successful in the treatment of other lysosomal storage disorders [7]. At present, the treatment of Tay-Sach is aimed at providing a sufficient diet, monitoring seizures, and monitoring the recurrent communicable diseases in infant patients [1]. Infant and teenage patients need their airways to be protected and occupational therapies to recover some of their lost motor skills.

ERT in TSD involves the replacement of absent hexosaminidase A hormone. The incapability to find a route to distribute the replacement molecule due to its large size is a restrictive factor as the molecule needs to cross the blood-brain barrier. This continues to present neurological complications to date. Lew et al. [8] revealed the challenges facing researchers concerning the synthesis of both subunits. They have to uncover the six filtrates of mannose by treating the Artificial Hexa A with α mannose. Researchers' attempts to sidestep the blood-brain barrier by inoculating the enzyme directly into the spinal cord, a process referred to as "intrathecal delivery," have been promising on animal models [1]. Clinical trials on humans are very early, and results have been inconclusive, with more controlled clinical trials needed.

Enzyme enhancing therapy (EET) of chaperone therapy is still being explored. Minute molecules known as chaperones are attached to recently synthesized hexosaminidase A enzyme. This is intended to protect the dilapidation of the hexosaminidase A within the cells before it is ruined, allowing the hexosaminidase A albeit deficient, to use its activity for extended periods. Patients with the late-onset version of TSD who took the treatment during clinical trials exhibited improved activity of hexosaminidase A, and this did not result in any visible signs of progress on the indicators. Vu et al. [2] revealed that EET also presented many adverse side effects which needed to be eliminated before it can fully be approved for patients. The numerous mutations caused by Tay-Sachs are not confined to dynamic sites, and this is the leading cause of variability in the natively folded protein [1]. An approach intricate in the decrease of the substrate includes the use of molecules known as chaperones.

What prompted the research is that the increased manifestation of Tay-Sachs has been rising in other cultural groups other than people of Jews descent. This review will give valuable insights to caregivers and patients considering ERT and EET for their loved ones to manage some symptoms. The public needs to know how they can diminish the incidence through communal therapy and screening efforts. Caregivers of Infants and older patients need to know something to address this debilitating disease killing their loved ones. Various investigative therapies such as ERT and EET can help manage the non-neurological symptoms of the disease.

## Materials and Methods Used

This is a review that involved evaluating research articles to

understand the latest information on the effectiveness of ERT and EET therapies on TSD patients. The latest peer-reviewed journals and medical library articles were analyzed to determine the steps and materials researchers are using to determine the effectiveness of ERT and EET therapies in the management of Tay- Sach disease. Citations were sifted to contain the most recent articles not older than six years on ERT and EET therapies. The articles used were grouped into case studies, medical news articles, experimental tests, periodical articles, and chronicle reviews. A total of 10 articles were selected. A review of the materials used by Solovyeva et al. [4] and Vu et al. [2] to investigate the efficiency of ERT and EET therapies on Tay-Sach patients is highlighted below. Solovyeva et al. [4] utilized mice and sheep models to examine the efficacy of ERT and EET in the management of TSD. Induced stem cells from infant patients of TSD were used. When HEXA defective mice models were used, they did portray characteristics of TSD without destruction to the brain and spinal cord nerves.

Mice with Jacob Sheep were the main in vivo models used for TSD research models because of their vulnerability to the disease. The models' pathophysiology and specific gene mutations are matching to those of humans with TSD.HEXA Knockout on mice had standard lifespans and no clinical indicators of TSD. Gualdrón-Frías & Calderón-Nossa [3] reveal that Hex B mice with TSD manifested features of TSD degeneration of the nerves. They manifested clinical symptoms such as general weaknesses in body muscles and shivering. Future researchers are advised to use Hex B lacking mice to analyze the viability of a gangliosidosis cure to explore this further. There were challenges in generating the Hex A-based ERT due to the need to synthesize the enzyme subunits. Udwadia-Hegde & Hajirnis [9] evaluated the effectiveness of EET therapies by using models that inhibited Hex A to reduce the metabolism of the ganglioside. This proved successful in mice simulations with clinical trials on humans unfruitful.

## Discussion/Body

The findings regarding the effectiveness of ERT and EET therapies in the management of Tay-Sachs disease are discussed below. They focus on treating the non-neurologic aspects of the disease. Advances on the intravenous use of ERT and EET therapies are also deliberated. This section also highlights that the FDA has approved only a few ERT and EET therapies to manage Tay-Sachs disease as currently, there is no known cure for the disease. Several investigational methods that seek to reinstate enzyme functions have been presented and are still under research and authentication [3]. In infantile TSD, the children are very vulnerable to many contagious infections, and they succumb to pneumonia caused by aspiration before their fifth birthday. For these therapies to be fruitful in the overall management of TSD, the two components of Hex A α and Hex A β must assimilate with the gangliosides within the lysosomes. Gualdrón-Frías & Calderón-Nossa [3] faced many limitations that did not allow the two components to integrate successfully. Solovyeva et al. [4] reviewed study models that used Hex A comprised of Neu3 DNA segments. When ERT and EET therapies were done on the study models, there was an accumulation of the toxic fatty acids (gangliosides) in the brain nerve cells of the mice. In addition, researchers noted cytoplasmic membrane materials in the neurons. The Hex A and Neu3 mice models portrayed irregularities in bone configuration and deterioration of the neurons characterized by slow movements [4].

In the mouse models used, the therapeutic usefulness of recombining and HexA was established with progress in motor function and reduced lifespan. The healing effects of ERT and EET therapies were evidently verified by the SD prototype of mice or the Hex B prototype [4]. The mutations of the Hex A enzyme make it difficult for ERT and EET therapies to stop the neurodegeneration of TSD because the mutations increase the accumulation of toxic fatty acids on the brain and spine neurons. The review also analyzed other TSD study models, such as the flamingo. TSD developed impulsively, just like in sheep models, and the Hex A action lacked the buildup of gangliosides. Nevertheless, the flamingo study model had too many limitations because the pathogenesis of humans and flamingoes are very diverse. When TSD patients were treated with a prototype of chimeric Hex B cells, the accumulation of the gangliosides was reduced. This was very encouraging as some brain activity in the brain of the sheep and mice prototypes used was reinstated. There was also an improvement in motor functions and a higher survival rate of those with the late-onset of TSD. More research on ERT and EET therapies is recommended because they showed some little protective effect on the neurons and reinstated the functions of the lacking enzyme. This could eventually slow the deteriorating process of TSD. ERT and EET therapies can reduce the accumulation of fatty acid residues in the brains of TSD patients, which could relieve symptoms considerably.

## Gaps in the Literature Review

There were few case studies to demonstrate how ERT and EET therapies manage non-neurologic symptoms of TSD. The review also gives little insight into EET therapy as it is still undergoing clinical trials. It also gives scanty information on how ERT and EET therapies can assist patients with juvenile forms of the disease, proving to be the severest with a short lifespan, not longer than five years. The review disregards other therapies like gene therapies and stem cell therapy, which can prevent disease progression for those with the late-onset form when combined with ERT and EET therapies. Central themes give insights on ERT and EET therapies. It is essential to note that TSD as a disease is under-researched since it affects a small fraction of the population.

## Questions for Further Research

- How ERT could restore the functions of β-hexosaminidase A.
- What additional research, on the pathology of Tay-Sachs disease, can yield more insights that researchers can use to achieve appropriate treatment and progress patient outcomes
- How to administer ERT Therapies successfully through the blood-brain barrier
- Possible Therapies that could delay the progression of the disease in infants and prolong their short lifespan

- More case studies on clinical trials of ERT and EET therapies in the three types of TSD

## Suggestions for Future Studies

Future studies must focus more on ways to penetrate the blood-brain barrier in the administration of enzyme replacement therapy. There is a need to research therapeutic techniques and how they can slow the progression of the disease. More needs to be done to understand the pathology of the degenerative neurological aspects of Tay-Sachs disease. More research on gangliosidosis is needed to find standard treatments. Research on the pathology of TSD and treatment options is increasingly scanty, hence the long wait without a definitive form of treatment. There is also a need to establish the prevalence of TSD in other ethnic communities. More Researchers should be encouraged to investigate TSD as this could quicken the search for a cure.

## Clinical Significance

This review will make specialists of TSD make more informed decisions when managing their patients with TSD. The modified version of ERT is also very promising in managing symptoms. Physicians will give caregivers and patients insights to make informed decisions on the acceptance of ERT and EET therapies. It will also encourage other researchers in the medical field to research more to break the barriers that could eventually lead to a cure. Without curative therapies, substantial research into therapeutic procedures could be valuable in the management of the disease. Since babies affected by TSD are born without the enzyme hexosaminidase A (HEXA), ERT therapy research could offer breakthroughs on how this enzyme can be enhanced or replaced to improve health outcomes and prolong life in infantile TSD patients.

## Conclusion

The findings from the review offer promising insights on the use of ERT and EET therapies in the management of TSD. Therapeutic effect on the treatment of TSD can only be achieved by replacing and distributing the deficient Hex A enzyme in the central nervous system. ERT and EET article therapies reviewed confirmed the therapies offered little assistance in stopping the destruction of the neurons in the central nervous system. However, they could moderately reinstate Hex A enzyme and relieve some symptoms momentarily. ERT and EET therapies should be started at the earliest possible after the disease is diagnosed. The review is relevant for students in the medical field. It gives significant insights into a rare disease that has baffled many in the medical field and community. These insights can assist caregivers and patients in making informed choices that could significantly improve their quality of life.

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