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# MESENCHYMAL STEM CELL THERAPY FOR PRADER-WILLI SYNDROME

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**ABSTRACT**
This study observed the effectiveness of UC-MSC Stem Cells in alleviating Prader-Willi syndromes. One good reason was that UC-MSC with a wide variety of stem cells is well-sourced and easy to collect and preserve. It also has the capability of multi-directional differentiation. It can differentiate into bone, adipose, cartilage, and other tissues and meet this endeavor's intended purpose. Besides it, UC-MSC is also the product of Celltech Stem Cell Laboratory & Banking (CSC) where this study is initiated. Experiments were applied on patients of different sexes to see the results of the treatments where both meet satisfactory expectations.

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## INTRODUCTION

In this assignment, Prader-Willi Syndrome will be discussed, specifically the various treatment options currently available and more novel treatments and therapies still in early development. Prader-Willi Syndrome refers to a multisystemic genetic disease that is paternally inherited (Fermin Gutierrez, M. A., Mendez, 2022). There are many negative repercussions that this syndrome has on the human body, impacting not only the endocrine, metabolic, and neurologic systems but also leading to both intellectual and behavioral problems (Fermin Gutierrez, M. A., Mendez, 2022). Some of the most frequently reported complications are dysmorphic features, failure to thrive prenatally, hypogonadism, short stature, hyperphagia, cognitive impairment, and behavioral disturbances (Angulo et al., 2015); (Fermin Gutierrez, M. A., Mendez 2022).

However, the syndrome is primarily characterized by extreme hypotonia that is associated with problems feeding during the first years of life, after which global developmental delays occur (Fermin Gutierrez, M. A., Mendez, 2022). By about the age of three, children have developed morbid obesity, and in fact, this syndrome is attributable to most cases of genetic obesity (Angulo et al., 2015); (Fermin Gutierrez, M. A., Mendez, 2022). Because of a deficiency in growth hormone, many patients are of short stature, with symptoms such as hypothalamic dysfunction that can ultimately cause several endocrinopathies (Angulo et al., 2015); (Heksch et al., 2017). These include central adrenal insufficiency, hypothyroidism, hypogonadism, and decreased bone mineral density (Angulo et al., 2015); (Heksch et al., 2017).

## METHOD

The researchers at CSC Laboratory & Banking in Jakarta, Indonesia using stem cells, conducted and produced the Prader-Willi symptom study. A literature study combined with the prime clinic's medical records (Vinski Regenerative Centre) enriched the analysis for the set-up mode of treatment. A pair consisting of a boy and a girl who have completed the treatments and recovered from some symptoms of Prader-Willi syndrome are then selected to represent in the report. Symptoms and technical results are in-line with the related section. The results of the study support the theory and are consistent.

## RESULT AND DISCUSSION

### Etiology of Prader-Willi Syndrome

The etiology of Prader-Willi Syndrome is associated with a lack of gene expression in the chromosomal region 15q11.2-q13, which are paternally inherited genes (G Butler et al., 2016). These chromosomal errors in genomic imprinting occur because of paternal deletion in roughly 70% of cases. In comparison, in about 25% of cases, the cause is maternal uniparental disomy (G Butler et al., 2016); (Heksch et al., 2017). For the 5% of other people with this syndrome, it results from defects in the imprinting center on chromosome 15, such as epimutations and microdeletions (G Butler et al., 2016); (Heksch et al., 2017). Most of these cases are sporadic. However, some familial cases may occur when the paternal genes carry a microdeletion in the imprinting center, which is inherited from the father's mother (G Butler et al., 2016); (Heksch et al., 2017).

### Epidemiology of Prader-Willi Syndrome

Prader-Willi Syndrome has an approximate incidence of 1:15,000 to 1:25,000 live births, with a prevalence of one in every 1:20,000 to 1:30,000 births (Pacoricona Alfaro et al., 2019). To diagnose cases, DNA methylation testing is employed to identify defects within the parental imprinting on chromosome 15, detecting over 99% of all people with Prader-Willi Syndrome (Fermin Gutierrez, M. A., Mendez, 2022). An infant can usually be diagnosed by about 8.6 weeks, even though the syndrome is not typically confirmed until around 3.9 years of age (Passone et al., 2018). Throughout the world, there are an estimated 400,000 people with Prader-Willi Syndrome, with about 20,000 of them in the United States (G Butler et al., 2016). As for gender, both males and females are equally impacted, while in race/ethnicity, no differences have been noted in studies (Bohonowych et al., 2019).

### Management of Prader-Willi Syndrome

To effectively manage Prader-Willi Syndrome, a multidisciplinary approach is needed, which may include various modalities such as nutritional management, growth hormone administration, as well as treatment for hypogonadism, hypothyroidism, and adrenal insufficiency (Cassidy et al., 2012); (Fermin Gutierrez, M. A., Mendez, 2022). For example, there will be different manifestations of this syndrome based on the age of the child, so management must address not only the consequences but also provide anticipatory guidance (Cassidy et al., 2012). Some patients also experience obstructive sleep apnea syndrome, which must be managed to decrease morbidity and mortality rates and improve quality of life (Fermin Gutierrez, M. A., Mendez, 2022).

Most clinical guidelines agree that Prader-Willi syndrome patients need to start growth hormones as early as possible, preferring when the child is first diagnosed between three and six months of age (Passone et al., 2018). In fact, if patients receive treatment when they are still young, they are expected to reach their projected final adult height (Angulo et al., 2015). Another possible medical treatment involves human chorionic gonadotropic hormone (hCG), which helps male patients to lower the position of the testicle; unfortunately, many will still require orchiopexy (Heksch et al., 2017). When patients reach about 15 or 16, they can receive testosterone treatment so long as they have either incomplete or delayed puberty (Heksch et al., 2017). Skeletal maturation and growth must be closely monitored in these patients (Heksch et al., 2017).

Similarly, female patients can be administered estrogen and prescribed low-dose transdermal patches to treat hypogonadism; they can receive this for two years or until menarche (Cassidy et al., 2012). Finally, both cognitive and behavioral strategies have been used successfully. They enable patients to understand their condition and how to manage it better, educating them about schedules, rules, and verbal cues (Passone et al., 2018). The goal is to reduce both aggressiveness and compulsiveness in these children and adolescents (Passone et al., 2018).

**Mesenchymal Stem Cell Therapy**

One novel treatment intervention that has received much research within the last few years involves using mesenchymal stem cell therapy for Prader-Willi Syndrome. Mesenchymal stem cells refer to non-specialized, primary cells that are not only nonhematopoietic but also plastic adherent; they have an extreme potential to proliferate with also engaging in both differentiation and self-renewal (Ullah et al., 2015). Mesenchymal stem cells can be isolated from various sources (Sarukhan et al., 2015); (Ullah et al., 2015). They have become an up-and-coming tool for tissue regeneration and cell therapy. These cells can easily separate into different cell types while possessing unique immunological properties (Musiał-Wysocka et al., 2019). Bone marrow represents the most frequently used source of mesenchymal stem cells (de Souza Fernandez & de Souza Fernandez, 2016), although adipose tissue is another common source (L Ramos et al., 2016).

When used in cell therapy, mesenchymal stem cells can accomplish many things, such as reconstructing cartilage and bone, treating joint degeneration, repairing damaged musculoskeletal tissues, and many more applications (Murphy et al., 2013). These stem cells are now employed in aesthetic medicine, plastic surgeries, and chronic disease management (e.g., cardiovascular, nervous, and endocrine system diseases) (Murphy et al., 2013). New clinical applications have also been tested, mainly because these stem cells can migrate into damaged sites in the body, proliferating and differentiating as needed (Murphy et al., 2013).

**Mesenchymal Stem Cell Therapy for Prader-Willi Syndrome**

According to the Foundation for Prader Willi Research (2023), genetic therapy is a strategy that uses or modifies genes to cure, treat, or prevent some medical condition. Many disorders and syndromes are now being treated with genetic therapy, which enables faulty genes responsible for diseases to be replaced with healthy copies of those genes (Research, 2023). Sometimes, genetic or gene therapy is used to modify a faulty gene, rather than replace it, as the gene is not working correctly (Research, 2023). Other times, new genes may be introduced instead, while genetic therapy can also apply to modifying the epigenome; this involves the chemical modifications that ascertain if a gene is silent or active (Research, 2023).

When considering gene therapy for Prader-Willi Syndrome, the focus is on the region where this syndrome is imprinted on chromosome 15 (Research, 2023). The genes will also act differently depending on whether the person inherits this syndrome from their mother or father (Research, 2023). In those who do not have Prader-Willi Syndrome, each cell contains a copy of chromosome 15 inherited from both the father and mother, meaning there are two (Research, 2023). However, chromosome 15's genes are only active on the paternal chromosome, as they are silent (i.e., inactive) on the maternal chromosome (Research, 2023). Therefore, the paternal chromosome 15 gene copy is missing for those with this syndrome.

In contrast, the full maternal chromosome 15 remains (Research, 2023). In rare cases, this syndrome is caused by uniparental disomy (UPD), as there is an imprinting defect, with the person having two copies of the maternal chromosome 15 (with no paternal chromosome 15) (Research, 2023). Nonetheless, it should be noted that everyone with this syndrome does contain at least one copy of the maternally inherited chromosome 15, even though the genes for the syndrome are inactive (Research, 2023).

Overall, two gene therapy strategies are being investigated to treat Prader-Willi Syndrome: Gene activation and Gene replacement (Research, 2023). Within the gene activation strategy, the maternal chromosome 15's epigenome is modified to turn on the present Prader-Willi Syndrome genes, as this may help restore normal cell function while improving the syndrome's clinical characteristics

(Research, 2023). The missing or inactive genes are replaced for gene replacement, although this is a very complex procedure (Research, 2023).

**Studies on Stem Cell Therapy for Prader-Willi Syndrome**

According to research, UBE3A refers to an E3 ubiquitin ligase on a maternally inherited allele that undergoes tissue-specific genomic imprinting (Chamberlain et al., 2010). The paternally inherited allele is not present in the brain's tissues, with the imprinted expression of UBE3A believed to happen because of reciprocal expression of a long noncoding antisense transcript, UBE3A-ATS (Chamberlain et al., 2010). UBE3A-ATS is a component of a >600-kb transcript present at the Prader-Willi Syndrome imprinting center, which is differentially methylated and located in the SNURF-SNRPN gene's exon 1 (Chamberlain et al., 2010). Again, within this syndrome, some species of small nucleolar RNAs (snoRNAs) are lost (Chamberlain et al., 2010). As no mouse model existed at the time that could summarize this syndrome's characteristics, a model was created through human induced pluripotent stem cell technology (Chamberlain et al., 2010). The researchers found that this model could be used to investigate how UBE3A-ATS's processing is regulated, including its impact on the paternal UBE3A promoter's chromatin structure during human neural development (Chamberlain et al., 2010). This research is possible because there are both expressions of paternal UBE3A-ATS and repression of paternal UBE3A in the human induced pluripotent stem cells during in vitro neurogenesis (Chamberlain et al., 2010).

Mesenchymal stem cells represent a preferred treatment for numerous types of disease, including immune disorders or conditions that require tissue regeneration (Welsh & Gallicchio, 2022). These types of stem cells can differentiate and self-renew into many different types of cellular lineages, such as multipotent stem cells, which can differentiate into the most vital bodily functions (Welsh & Gallicchio, 2022). As previously mentioned, mesenchymal stem cells are primarily sourced from human bone. However, other body locations, such as during and after childbirth, may be used with the placenta, amniotic fluid, and umbilical cord as critical places to extract these stem cells (Welsh & Gallicchio, 2022). These are specifically called adipose-derived mesenchymal stem cells, with researchers discovering their many benefits in treating obesity (Welsh & Gallicchio, 2022). After all, many adipose-derived mesenchymal stem cells in the body are easily accessed. These stem cells also have better long-term physical maintenance than bone marrow mesenchymal stem cells (Welsh & Gallicchio, 2022).

Adipose-derived mesenchymal stem cells may be the newest treatment option for patients with Prader-Willi Syndrome. Many studies have found that these stem cells treat numerous bodily physiologies, making them an excellent source of cell therapy (Welsh & Gallicchio, 2022). Unfortunately, there has not been as much research on using these stem cells for treating Prader-Willi Syndrome, with no in vivo studies yet (Kim et al., 2019). However, some other research has been undertaken on the application of epigenetic therapy for treating this syndrome (Kim et al., 2019). For example, since the genes involved in Prader-Willi Syndrome (in chromosome 15q11-q13) are silenced, their genetic structure should remain intact, even though the epigenetic mechanism causes them to be repressed transcriptionally well (Kim et al., 2019). Since Prader-Willi Syndrome is a genetic imprinting disorder, it is possible that a pharmacologic strategy would employ epigenetic modification, helping to reactivate the expression of the repressed genes (Kim et al., 2019).

**Case Studies**

Two case studies were conducted, with two patients – Patient A and Patient B – being treated for symptoms associated with Prader-Willi Syndrome. The treatment included Mesenchymal Stem Cell Therapy for both patients. Umbilical Cord Mesenchymal Stem Cells donors with the Allele gene test before where the MSC route through Intravenous and Intramuscular. First, it is essential to determine how these two pediatric patients were evaluated in order to diagnose this syndrome. DNA methylation

and molecular testing are recommended as early as possible. At the same time, chromosome analysis with fluorescence in situ hybridization may also detect 15q11-q13 (G Butler et al., 2016). Before starting any growth hormone therapy, a thyroid function test would be needed to rule out hypothyroidism; additionally, growth hormone deficiency can be identified through serum insulin-like growth factor-1 and liver function tests (G Butler et al., 2016). To rule out diabetes, an oral glucose tolerance test, and fasting glucose levels must both be analyzed. At the same time, bone composition and mineralization should be diagnosed using a Dual X-ray absorptiometry (DXA scan) (G Butler et al., 2016).

Additionally, management for these two patients with Prader-Willi Syndrome involved a combination of strategies and interventions. Considering the weight, height, and body mass index, adequate energy requirements must be created so patients can receive the nutrition they need without gaining weight (Cassidy et al., 2012). Daily food intake must be closely supervised, with dietician consultations recommended (Cassidy et al., 2012). These dieticians should also assess patients' mineral and vitamin intake, prescribing supplements if necessary (Cassidy et al., 2012). Patients with this syndrome only need to consume around 1,000–1,200 Kcal/day (Cassidy et al., 2012), so the parents of the children (Patients A and B) need to keep this in mind when planning daily food intake.

**Patient A**

Patient A is a two-year-old boy who was diagnosed with not only Prader-Willi Syndrome but also Somatomedin Deficiency Syndrome and Testosterone Deficiency. His primary symptoms included weak muscle tone, inability to speak, easily fatigued, and small penis size (based on age). He had testicular reduction surgery in the past. His initial weight was 12.5 kg, with a height of 89 cm. After Patient A received mesenchymal stem cell therapy, his development improved, with a more robust muscle tone noted. He interacts more with his surroundings, such as dancing when playing music. He has also learned to say words like "Uma," "Cucu" (Milk), and "Gak mau" (I do not want). He can also enjoy a long trip with his parents to umrah. And his genital (penis) was also grown commonly. Fine hairs on the body also started to grow after the first injection with low doses of Testosterone.

This patient has two other syndromes, which complicates his case and treatment. His body mass index is 15.8, an average, healthy weight for his gender, age, and size. The primary concern was weak muscle tone and not speaking. His problem seemed to be the defect of Growth hormone Factor-1; after Patient A received mesenchymal stem cell therapy, he improved physically and socially. This lends credence to using this stem cell therapy to treat Prader-Willi Syndrome.

**Patient B**

The second patient, Patient B, is a two-and-a-half-year-old girl. Upon arrival, she was also diagnosed with Prader-Willi Syndrome and Autism Spectrum Disorder. Her primary complaints included problems walking and being unable to talk to or interact with other people (besides her parents). Her initial weight was 16 kg, with a height of 85 cm. After undergoing mesenchymal stem cell therapy, Patient B also showed significant developments. Specifically, she could walk and communicate with simple words, as she is now more Willing to interact with the people around her.

Unlike Patient A, Patient B is obese, with her body mass index at 22.1. She is more significant than the 99th percentile for girls her age regarding her body mass index. She also has another disorder, again complicating the case with this comorbidity. She was having difficulties ambulating and socializing with others outside her family. She seemed to be more severe than Patient A. However, once she got mesenchymal stem cell therapy, her eating stability was gradually controlled and improved substantially as she walked more and even ran with assistance and talked with others. Her eye contact, especially with her parents and grandmother, improved.

## CONCLUSION

Patients A and B are receiving effective treatments with MSC and a combination of bioidentical hormonal, leading toward the condition that their prognosis may be more accepted. While this early clinical course is an advantage to both these patients' care. Numerous complications are associated with Prader-Willi Syndrome, the two most reported being endocrine (e.g., diabetes mellitus type 2) and cardiovascular (e.g., heart failure) diseases. Patients may only live past 40 if they care for themselves and manage their weight as they age. Nonetheless, the patients are closely monitored, with good treatment adherence and lifestyle choices. In that case, a patient can be expected to live an average lifespan. Therefore, with Patients A and B receiving some of the most recent and novel treatments in terms of stem cell therapy, their prognosis is excellent. Their parents and guardians will have to ensure that their children's other diagnosed conditions are also managed and treated, helping to prevent any other comorbidities (e.g., chronic illnesses that can be prevented).

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