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Exploring Long-Term Treatment Strategies in a Seven-Year-Old with Type 1 Gaucher Disease: A Case Report and Literature Review

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Review Article

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ABSTRACT

Background: Gaucher disease is a rare lysosomal disease that is caused by a mutation in the GBA gene, this leads to a deficiency in the enzyme glucocerebrosidase responsible for the breakdown of the lipid glucocerebroside, leading to its accumulation in body organs and cells.

Case presentation: Managing GD is a challenging procedure, due to its rare occurrence and high treatment cost. In this case report, we present a successfully managed case of a young boy, who has several complications including hepatosplenomegaly, bone deformities and other haematological abnormalities. His strong family support has helped him overcome these difficulties, with the help of the healthcare professionals who were always available to help.

Conclusions: This case highlights the need of a multidisciplinary team to manage rare diseases like GD and the need of continuous monitoring and strong social and psychological support.

Keywords: Gaucher disease; Lysosomal; Glucocerebrosidase; Glucocerebroside hepatosplenomegaly

INTRODUCTION

Gaucher Disease (GD) is an autosomal recessive Lysosomal Storage Disorder (LSD) resulting from biallelic pathogenic variants in the *GBA1* gene located on chromosome 1 (1q21), with over 400 variants in GBA documented in previous literature [1,2]. These variants result in a significant reduction in the activity of the lysosomal enzyme, glucocerebrosidase (GCase, also known as glucosylceramidase or acid β-glucosidase, EC: 4.2.1.25), which catalyzes the hydrolysis of glucosylceramide (GlcCer) into ceramide and glucose [3]. GD often presents as a multi-system disorder with type 1 as a non-neuronopathic form and acute and subacute, types 2 and 3, respectively, as neuronopathic forms. The global birth incidence of GD ranges globally between 0.45–25.0/100,000 live births depending on the type of GD and the region, yet is still considered a rare disease.

The signs and symptoms of GD often overlap with those of several other childhood diseases, which can lead to delays in reaching an accurate diagnosis, and they are also extremely heterogenous between patients, which could make diagnosis more difficult [4]. A study by Davidson et al. has shown that modifier genes could alter clinical phenotype in GD through four basic mechanisms: Changes in expressivity, in penetrance, dominance, and/or pleiotropy, which explains the variable presentation in GD. The most common signs and symptoms of GD could be classified into metabolic, hematologic, visceral, and skeletal, which collectively include hepatosplenomegaly, anemia, thrombocytopenia and/or splenomegaly and possibly, severe bone involvement [5]. Bone involvement often leads to acute and chronic pain episodes, while bleeding phenomena and gallstones are also observed [6]. Similar to all lysosomal diseases being progressive in their nature, the lysosomes in the macrophages of patients with GD progressively become filled and enlarged with undigested glucocerebroside, which subsequently resemble a “crumpled tissue paper” morphology upon visualization with electron microscopy. GD1 is often distinguished by the absence of neurological impairment. However, a 2017 study has demonstrated that GD1 patients are at 4-20 times more likely to develop Parkinson’s disease and at an earlier age than normal. Notably, Biegstraaten et al. have found that the prevalence of polyneuropathy is increased in GD1 patients relative to that in the general population, which also suggests that some neurological manifestations could be associated with GD1 [7].

Moreover, the prognosis of GD patients varies amongst the different types of GD, yet is generally considered good, where some people diagnosed with GD remain asymptomatic and have a normal life expectancy. However, some patients can have severe GD symptoms leading to early death such as GD2. Higher mortality rates in people with GD1 are associated with older age, splenectomy and malignancy complications; there is no gender difference in the mortality rates [8].

Treatment plans for GD involve lifelong administration, and usually comprises Enzyme-Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT) [9]. The goal of treatment is to keep all laboratory values in the normal range and prevent complications as much as possible, therefore, early treatment is crucial to identify sources of disease manifestation before deteriorating. ERT aims to replace the GCcase, whereas SRT is an orally consumable capsule that works by reducing the amount of substrate GlcCer and avoiding its accumulation in cells. Although SRT is oral, meaning it is less invasive than IV infusions, there is a chance of poor patient compliance, which hinders its effectiveness [10]. Advancements in the treatment have seen significant strides with the introduction of ERT, offering patients a chance at improved quality of life through intravenous infusions of the missing enzyme, albeit with the caveat of lifelong administration without a cure. However, recent developments have brought about a promising shift towards oral therapy with the FDA approval of eliglustat (Cerdelga), offering a more convenient treatment option. Moreover, ongoing exploration into SRT, exemplified for type 3 GD, signifies a potential alternative approach to addressing GD1. Current trials aim to implement gene therapy in the management of Gaucher disease, including “A Gene Therapy Study in Patients with Gaucher Disease Type 1 (GALILEO-1)” (NCT05324943) and “Phase 1/2 Clinical Trial of PR001 in Infants with Type 2 Gaucher Disease (PROVIDE)” (NCT04411654). Another phase 1/2 study, AVR-RD-02, compared ERT for the treatment of GD1 (NCT04145037 PROCEED) with intravenous administration of their construct.

Since GD is considered a condition that is managed by long-term administration of treatment and lifestyle changes, there must be adequate education provided to the family and patient regarding the formulation of the prescribed medication, timing, dosage, frequency, side effects and costs to ensure effective management. Other non-pharmaceutical factors must also be considered, such as mental health, which could have a significant impact on the life of patients as this condition often results in developmental delays, resulting in patients being perceived as younger than their peers, which could lead to mental distress. Another pivotal factor is also the physician-patient relationship, where strong communication and support could help improve the lives of patients with long term conditions as GD.

Our current study thus presents a case of GD in a seven-year-old and explores the effectiveness of Cerezyme treatment over a prolonged period of time as well as factors involving healthcare professionals and the family which ensure effective management of the condition. We also aim to explore what needs must be addressed in the future of treating GD and guide

future research and clinical practice to ensure optimal outcomes for patients.

LITERATURE REVIEW

A seven-year-old patient initially presented to the clinic at the age of two with persistent bone pain, general fatigue, and notable loss of appetite. Physical examination revealed splenomegaly (17 cm) and hepatomegaly (14 cm), confirmed by abdominal ultrasound, indicating hepatosplenomegaly. Haematological evaluations identified anaemia, thrombocytopenia, and neutropenia, prompting the initiation of treatment by the age of three.

A recent bone crisis underscored the ongoing severity of the condition. An X-ray during this period revealed a characteristic flask deformity of the femur with a ratio of 0.61, indicative of Gaucher Disease. Additionally, a DEXA scan confirmed osteoporosis with a Z-score of -1.8 at L1-L4. Neurological evaluations have consistently shown no abnormalities, and there are no manifestations of diabetes, hypertension, or atherosclerosis. Liver function tests initially showed ALT levels at 16.5 U/L and AST levels at 57 U/L; more recently, ALT levels were at 21.7 U/L and AST levels at 28.4 U/L, necessitating ongoing observation. The clinical and laboratory findings could be found.

During the treatment course, there was a marked improvement in the patient's symptoms; the anaemia and thrombocytopenia resolved and the patient became more active with a better appetite and reduced abdominal distention. However, the patient continues to manage osteoporosis and occasional bone pain, requiring regular monitoring and therapy adjustments.

The spleen, initially notably enlarged, has reduced in size with ongoing treatment but still requires regular monitoring for potential complications such as hypersplenism. The patient remains adherent to the treatment regimen, which has been critical in managing symptoms and preventing further complications. The treatment approach includes promoting regular physical activity and maintaining a healthy diet to support overall well-being and bone health.

Despite these challenges, the patient maintains a high level of school performance, rated at 4 out of 5, reflecting resilience and adaptability. The diagnosis of GD was conclusively confirmed through a beta-glucosidase leukocyte blood test, guiding the ongoing management plan aimed at maintaining the patient's quality of life and addressing any emerging symptoms effectively.

When interviewing the family, they mentioned that the patient was initially frustrated and had disbelief after being told his diagnosis of GD, he became less social with people around him, they reported that the patient has been more lethargic, lost appetite and felt fatigued following the diagnosis of GD, this has negatively impacted his participation in activities with children of his age, both at home and in school.

The family ensured to look at the disease in a positive way, by making sure that the patient's hospital appointments and treatment times get priority in their schedules. Moreover, they insisted on adjusting their lifestyles to provide a healthy diet and encouraged him to perform regular exercises, he slowly started accepting the disease and was able to engage with children of his age as well.

Some of the barriers faced by the family in terms of treatment adherence were the psychological barriers, where the patient was not willing to take his required medications, this was overcome by using a positive reinforcement system, by promising him a reward, the patient was willing to take his medications.

With strong family support and completion of treatment, the patient's symptoms have improved, he has more appetite, and increased activity, as well as reduced abdominal distention. However, his anaemia is still persistent and has developed osteoporosis, a known complication of Gaucher's disease. This experience has shaped his personality to look at challenges in a positive manner and is able to handle stressful times more effectively.

Access to healthcare was not a problem with the family, they were able to follow up with a paediatrician specialised in metabolic diseases in their country. The team of healthcare professionals were very considerate of the patient's condition, and treated the child in a very friendly manner "treated him as their son". The family is grateful for the continuous support and follow up provided by the healthcare team and they feel content when the doctors address their concerns and make sure they understand all the aspects of treatment.

Having a son diagnosed with GD has helped strengthen the personality of family members, they started being more resilient and positively accepting challenges. Furthermore, through faith in god, continuous prayers, psychological and financial support from family and friends, the patient was able to battle through Gaucher's disease and helped the family to stay positive during this time and overcome any challenges that may arise.

The family are open to discuss their case with others who might be going through the same issue, they will provide all the help they can by guiding them to the hospitals, and doctors who managed the case, as well as informing them of the places

of receiving treatment. The interview guide utilised to interview the family could be found.

DISCUSSION

This case report presents a seven-year-old patient with Type 1 Gaucher Disease (GD1), managed with Cerezyme (imiglucerase) over an extended period. The treatment demonstrated significant effectiveness, as evidenced by the resolution of anaemia, thrombocytopenia and improvement in appetite and activity levels. The patient's hepatosplenomegaly showed notable reduction, though osteoporosis and occasional bone pain persisted, indicating the need for ongoing management and monitoring.

Our findings on the effectiveness of Cerezyme (imiglucerase) align with extensive research highlighting its significant impact on managing GD1.

Cerezyme has consistently demonstrated efficacy in reducing spleen and liver size, correcting hematologic abnormalities, and enhancing patients' quality of life. Long-term treatment with imiglucerase leads to sustained improvements in hematologic parameters, with notable reductions in hepatosplenomegaly and an overall increase in patient well-being. Improvements in visceral and hematologic manifestations among patients undergoing Enzyme Replacement Therapy (ERT) have been observed.

Continuous enhancement in hematologic, visceral and skeletal manifestations has been reported over a decade of Cerezyme treatment. Despite its benefits, the management of skeletal complications remains a challenge, with many patients experiencing only partial resolution of bone disease.

In addition to pharmaceutical interventions, integrating non-pharmaceutical approaches significantly enhances the overall management of GD. This case report underscores the importance of a holistic treatment strategy, incorporating mental health support and lifestyle modifications such as regular physical activity and a balanced diet. The role of psychosocial support in improving treatment adherence and reducing the psychological burden of chronic disease is emphasised. Moreover, patient outcomes improve substantially when ERT is complemented with non-pharmaceutical interventions, indicating a multifaceted approach to GD management that addresses both the physical and psychological needs of patients.

The mechanism of action of Cerezyme involves providing a recombinant form of human β-glucocerebrosidase, the enzyme deficient in GD1. GD1 results from mutations in the *GBA1* gene, which lead to a deficiency in glucocerebrosidase, crucial for the breakdown of glucocerebroside into glucose and ceramide. The accumulation of glucocerebroside in macrophages results in the formation of Gaucher cells, which accumulate in various organs, causing hepatosplenomegaly, anaemia, thrombocytopenia and bone disease.

The therapy involves the intravenous administration of β-glucocerebrosidase, which is then taken up by macrophages through mannose receptors and transported to the lysosome, where it catalyses the hydrolysis of glucocerebroside; this enzymatic activity helps reduce the number of Gaucher cells, restoring normal cellular function and alleviating the pathological manifestations of the disease.

Cerezyme is generally well-tolerated, with a favourable safety profile. The most common adverse effects are mild to moderate infusion-related reactions, including fever, chills, rash and fatigue. These reactions can often be managed with premedication and adjustments to the infusion rate. In rare cases, patients may develop antibodies to the therapy, which can lead to a reduced therapeutic response.

The financial burden of Cerezyme therapy is significant, with annual costs for Enzyme Replacement Therapy (ERT) for GD1 in the United States ranging from approximately 384,814 $ to 705,493 $. A comprehensive study on the budget impact of ERT revealed that these expenses represent a major economic challenge for healthcare systems and patients. The high cost is attributable to the necessity for lifelong treatment, the complexity of the drug's manufacturing process and the requirement for regular infusions. Over a patient's lifetime, the cumulative expense can reach millions of dollars, emphasising the need for sustainable financial strategies and the potential for insurance coverage or patient assistance programs to alleviate the economic burden.

There are multiple areas of strengths and limitations within our study. Firstly, recording thorough family history and clinical examination has been helpful in providing insights on the improvement of the patient since diagnosis. Moreover, utilising multimodal imaging techniques, including abdominal ultrasound and DEXA scan, enhanced diagnostic accuracy by evaluating organomegaly, bone abnormalities and osteoporosis. Long-term follow-up provided valuable insights into treatment efficacy and disease progression, although the heterogeneous nature of GD1 presentations limits generalizability across diverse patient populations, which makes it necessary to delve into other cases to gain more comprehensive

understanding on the effectiveness of cerezyme treatment. As for highlighting the non-pharmaceutical factors which encourage better patient outcomes, such as support groups, positive communication between healthcare staff and the family and delving into how GD impacts the mental health of patients and families, a Quality of Life analysis (QoL) could provide more comprehensive insights and could help generate reproducible data which can be used in further studies, where the standardised QoL would avoid the biases involved with carrying out unstructured interviews. However, the interview conducted with the family still offers useful information regarding the factors which help improve the quality of life of GD patients, and light must be shed on the mental health and lifestyle of patients with chronic illnesses.

Looking forward, future research should further explore the multifaceted dimensions of GD1 management with a larger sample of patients. This includes further investigating the effectiveness of different treatment schemes as well as the impact of the doctor-patient relationship on treatment adherence and health outcomes. Addressing psychosocial aspects such as mental health, quality of life, and social support systems is also crucial for developing holistic treatment strategies. Moreover, investigating personalised medicine approaches could optimise outcomes for individuals with GD1, both on a physical and mental level. By integrating these insights, healthcare providers can enhance patient care, improve treatment adherence and ultimately, advance the quality of life for GD1 patients.

CONCLUSION

In conclusion, Gaucher disease is a rare but treatable condition, which needs strong clinical awareness to be identified, moreover, a multidisciplinary approach is required to help with the different manifestations of the disease. GD poses significant challenges both physiologically and psychologically, therefore it is necessary to have a strong support system to battle against the disease, as illustrated in this case.

One of the strongest enablers of successful management of this case was the healthy doctor patient relationship, which has facilitated the compliance to treatment and medical appointments. This highlights the importance of having a good rapport between the healthcare professionals and patients in cases like Gaucher where continuous follow ups and regular treatment modifications are required.

Furthermore, the family's positive attitude had a significant role in managing the barriers of successful management, they had great faith and resilience throughout their journey, which has reflected positively on their and their child's personality, making them stronger. In addition, their willingness to share their story further reiterates their strength and positive mindset.

SUPPLEMENTARY MATERIALS

All supplementary materials are available in Appendix A.

AUTHOR CONTRIBUTIONS

Conceptualization: K.A.A., M.R. and S.A.S.; Data curation: R.A.; Methodology: K.A.A., R.R.A. and R.A.; Resources: R.A., R.R.A. and R.A.; Supervision: K.A.A., M.R. and S.A.S.; Validation: K.A.A., M.R. and S.A.S.; Writing–original draft: M.R., R.A. and S.A.S.; Writing-review and editing: K.A.A., M.R., R.A. and S.A.S.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The World Medical Association's Declaration of Helsinki principles were followed to ensure ethical standards were upheld during the study. Informed consent was obtained from the family prior to writing the case report, they were informed that the report will be about their child, and that clinical information will be shared publicly, and the family understands that the patient's identity will remain anonymous.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

DATA AVAILABILITY STATEMENT

The datasets used and analysed during the current study are available from the corresponding author on request.

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The authors have no acknowledgements to declare.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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