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Gaucher's Disease: Prenatal and Post Natal Diagnostic Dilemma and Biochemical Aid - Case Series and Review of Literature

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Authors' contributions

This work was carried out in collaboration between all authors. Author MIK designed the case series and literary reviews and wrote the first draft of the manuscript. Author SE managed the literature searches. Author AY managed the introduction and references and author SZ managed the discussion and conclusion. All authors read and approved the final manuscript.

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ABSTRACT

Background: Gaucher's Disease (GD) is a rare genetically inherited, autosomal recessive disorder. It is classified as a lysosomal storage disorder and is characterized by the accumulation of glycolipids. This is due to the deficiency of lysosomal hydrolase β – glucocerebrosidase. The gene responsible for synthesizing this enzyme is encoded by *GBA1* on chromosome 1q21.
Case Series: We present a case series of a Gravida-5 Para-3 Live-1 Death-2 Abortion-1

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(G5P3L1D2A1) patient, with 19 weeks amenorrhea with prenatal diagnosis suggestive of GD clinically being planned for termination. The past obstetrics history is as follow; First pregnancy – full-term normal vaginal delivery (FTNVD) with male baby diagnosed as type 2 GD at 8 months after birth and died at 9 months 14 days; Second pregnancy – FTNVD with female baby presently 3 years 6 months and healthy and enzymatic assay and mutational analysis for GD negative; Third pregnancy – full-term lower segment cesarean section (FTLSCS) with male baby diagnosed as type 2 GD at 7 months after birth and died at 1 year 8 days; Fourth pregnancy – chorionic villus sampling (CVS) done at 12 weeks and enzymatic assay positive for GD and terminated at 17 weeks.

Conclusions: We report a case of a lady presenting with two children diagnosed with type 2 GD after birth who died within a year of birth. Another two pregnancies diagnosed prenatally with GD and terminated and one healthy live child. Case series and Literature Review is presented together with an objective to emphasize that a rare disease like GD can have bad infant prognosis and that prenatal diagnostics can help in the diagnosis of the disease in intrauterine life, to facilitate making a timely decision. It also highlights the importance of genetic counseling to avoid dismal outcomes.

Keywords: Lysosomal storage disorder; glucocerebroside; type 2 gaucher's disease; chorionic villus sampling; amniocentesis.

1. INTRODUCTION

Gaucher's Disease (GD) is a lipid storage disorder in which glucocerebroside, a component of the cell membrane in various tissues, accumulates due to deficiency of hydrolytic lysosomal enzyme β glucocerebrosidase (βGC) [Enzyme Code 3.2.1.45], hence also referred to as a lysosomal storage disorder. Though GD is a rare disease it is the commonest enzyme deficiency disorder among the group of inherited lysosomal storage disorders [1]. The clinical component of the disease was first described by a French physician Philippe Gaucher, in 1882 [2]. Epstein in 1924 first described the accumulation of glucocerebrosides [3]. In 1965 Brady et al. [4] elucidated the biochemical enzyme deficiency responsible for the disease.

The enzyme βGC causes the hydrolytic cleavage of glucose from glucocerebroside [4]. The activity of this enzyme is reduced in GD [4]. The gene involved in this disease process is the *GBA1* gene and it is located on chromosome 1q21 [5]. Sidransky et al. [6] have described about 200 mutant alleles and Somaya et al. [7] have described about 300 mutant alleles responsible for the condition but the most common mutation causing this genetic disorder is L444P [7].

There are three clinical subtypes of GD, classified on the basis of absence or presence, and if present on the degree of severity and progression of neurological symptoms [8]. The severity of the disease doesn't correlate with either the amount of lipid stored or with the residual enzyme activity measured [9]

Type 1 GD is the nonneuronopathic form. It is the most common form and presents from childhood to early adulthood. The affected individuals survive into adulthood but survival is variable depending on the severity. It is mainly characterized by visceral involvement but nervous system is not involved [10,11].

Type 2 is the acute neuronopathic form. It is rare in occurrence and presents by 6 months of life. The child usually dies by 2 years in the absence of treatment. It is characterized by precocious and rapid neuronal degeneration and is associated with visceral involvement [10,11].

Type 3 is the chronic neuronopathic form. It is rare in occurrence and presents in childhood before 2 years. The affected person sometimes survives till third to fourth decade of life [12]. It is a heterogenous subtype involving visceral and neurological effects [10,11].

2. MATERIALS AND METHODS

A non consanguineous, married couple with no family history of GD was closely followed for a 6 year period. The obstetric history of the mother and the pediatric history of the children was monitored and recorded.

The post natal diagnosis of GD was confirmed by a peripheral blood sampling and assessment of leukocytes for the amount of βGC. The assessment was done biochemically by a fluorimetric assay using 4 – Methyl Umbelliferon with a normal enzymatic activity range of 6.0 to 9.0 nmol/hr/mg and a control of 7.2 nmol/hr/mg.

The procedure as described by Beutler E, et al. [13] in 1970 and Peters et al. [14] in 1976 [15].

The prenatal diagnosis of GD was done by cells from chorionic villus sampling and placental biopsy, by a fluorimetric analysis using 4 – Methyl Umbelliferon for βGC enzyme activity with a normal range of 320 – 550 nmol/hr/mg and a control of 600 nmol/hr/mg. The procedure as described by Beutler E, et al. [13] in 1970 and Peters et al. [14] in 1976 was used [15] .

Chorionic Villus Sampling (CVS) was done under ultrasound guidance after obtaining informed consent in a specialized fetal medicine unit with emergency obstetric backup.

Termination of pregnancy for medically recognized conditions on eugenic grounds was performed by intrauterine extra amniotic instillation of 170 ml of ethacridine lactate using a simple foley's catheter and later by induction with Prostaglandin E1 (PG E_1) – Misoprostol, which was placed per vaginally in the posterior fornix of vagina after obtaining the informed consent of both the parents.

3. CASE SERIES

In this case series, the authors describe a couple of Indian origin, who had more than one pregnancy and more than one child affected with GD. This paper is important in that it highlights the importance of prenatal testing and genetic counseling in families that have affected individuals with GD. Our patient is the mother who is G5P3L1D2A1 from a low socioeconomic background married for 6 years in a non consanguineous marriage. The patient presents with 4 months amenorrhoea with last menstrual period on 16/01/2016. She comes for the first time at 14 weeks 5 days to the outpatient with urine pregnancy test (UPT) positive for β human chorionic gonadotrophin. Pregnancy had been asymptomatic with no exposure to radiation, teratogenic drugs or infections. There is no significant family history of genetic and inherited disorders in both the parents and families of both the parents. No Folic acid intake during the first trimester and iron-folate intake during the second trimester were reported. She was found to be normal on general and obstetric examination. Upon enquiring, she revealed the following past obstetric history with well preserved medical records. The following is also demonstrated by the pedigree below in Fig. 1.

First Pregnancy & Child: Conceived spontaneously, pregnancy uneventful and delivered a live term male baby weighing 3.5 kg vaginally. Baby was healthy at and after birth and was breast fed and immunized and remained so until 5 months. Milestones were delayed. At the fifth month of life, the child had an episode of respiratory tract infection (RTI) and developed neck rigidity and threw a seizure for which the child was managed on the lines of febrile seizure in the emergency room and discharged. Over the next two months, the child had repeated episodes of RTI and seizures. Hepatomegaly and splenomegaly were palpable on examination. A simple blood investigation revealed anaemia (Haemoglobin Hb – 8 gm/dl). The child was managed medically with haematinics, anticonvulsants and antibiotics to which the child didn't respond. A differential diagnosis of malaria and kala-azar were ruled out given their high prevalence in the tropics. A bone marrow biopsy was also taken which was found to be normal. Later storage disorder was considered and a leucocytic enzymatic assay was done for βGC and β–galactocerebrosidase. This revealed a reduced enzymatic activity of βGC i.e. 1.7 nmol/hr/mg (normal range 6.0 – 9.0 nmol/hr/mg) confirming the diagnosis of GD. The age of onset of the symptoms and neurological involvement classified the child as having type 2 GD. As the disease progressed the frequency of seizures increased and the child started having episodes of apnea after each seizure. After 25 days of hospitalization the child died at the age of 9 months and 14 days.

Second Pregnancy & Child: Conceived spontaneously, pregnancy was uneventful and the patient and her husband didn't consent for prenatal diagnosis when they were told about the inherent procedural risk of spontaneous abortion. She delivered a live female baby weighing 3.2 kg by spontaneous vaginal delivery. The child was healthy at and after birth and was breast fed and immunized. The child complained of excessive fatigue at the age of two and a half years. Complete blood counts revealed anaemia (Hb – 6 gm/dL) and erythrocytopenia (3.1 million/mm^3). The child was further investigated and following were the findings, packed cell volume – 20.5% [low], serum iron – 17 mcg/dL [low] (50 – 175 mcg/dL), percentage saturation – 3.6% [low](12 – 45%), serum transferrin – 366 mg/dL [high] (202 – 364 mg/dL), total iron binding capacity – 471 mcg/dL [high] (250 – 450 mcg/dL), high performance liquid chromatography for Hb variants – normal, serum folic acid - 14.228

ng/ml [normal] (5.21 – 20 ng/ml) and serum vitamin B12 321.429 pg/ml [normal] (200 – 1100 pg/ml) and haemoglobin electrophoresis was done and found to be normal. Bone marrow examination was normal. Ultrasonography (USG) was done and no organomegaly was detected. βGC activity tested and found normal - 8.7 nmol/hr/mg (6.0 – 9.0 nmol/hr/mg). A genetic mutation analysis for GD revealed absence of specific mutation. The final diagnosis was iron deficiency anaemia for which the child was appropriately managed and presently she is three and a half years and healthy.

Third Pregnancy & Child: Conceived spontaneously and delivered a live male child at term by an elective Lower Segment Cesarean Section (LSCS), the indication being transverse lie and oligohydramnios. The child was exclusively breast fed for 6 months and was appropriately immunized and remained healthy for such a period after which he developed strabismus and frothing at the mouth. The child was then bought to us with RTI and on examination was found to have hepatomegaly and splenomegaly. An enzymatic assay on leucocytes showed abnormally lowered activity of βGC ie 0.88 nmol/hr/mg (normal range 6.0 – 9.0 nmol/hr/mg) at 7th months of life. Similar problems continued for the next 6 months and the child died at the age of 1 year 8 days, minutes after a single episode of myoclonic seizure.

Fourth Pregnancy: Conceived spontaneously and confirmed by UPT and USG. The patient agreed to prenatal testing for GD and a CVS was done per abdominally at 12 weeks of gestation. The values of βGC were found to be significantly lower at 23.2 nmol/hr/mg, given the normal range of 320 – 550 nmol/hr/mg. The couple was explained about the diagnosis and with their consent, the pregnancy was terminated at 17 weeks on eugenic grounds by intrauterine extra-amniotic instillation of 170ml of ethacridine lactate. The delivered foetus was male.

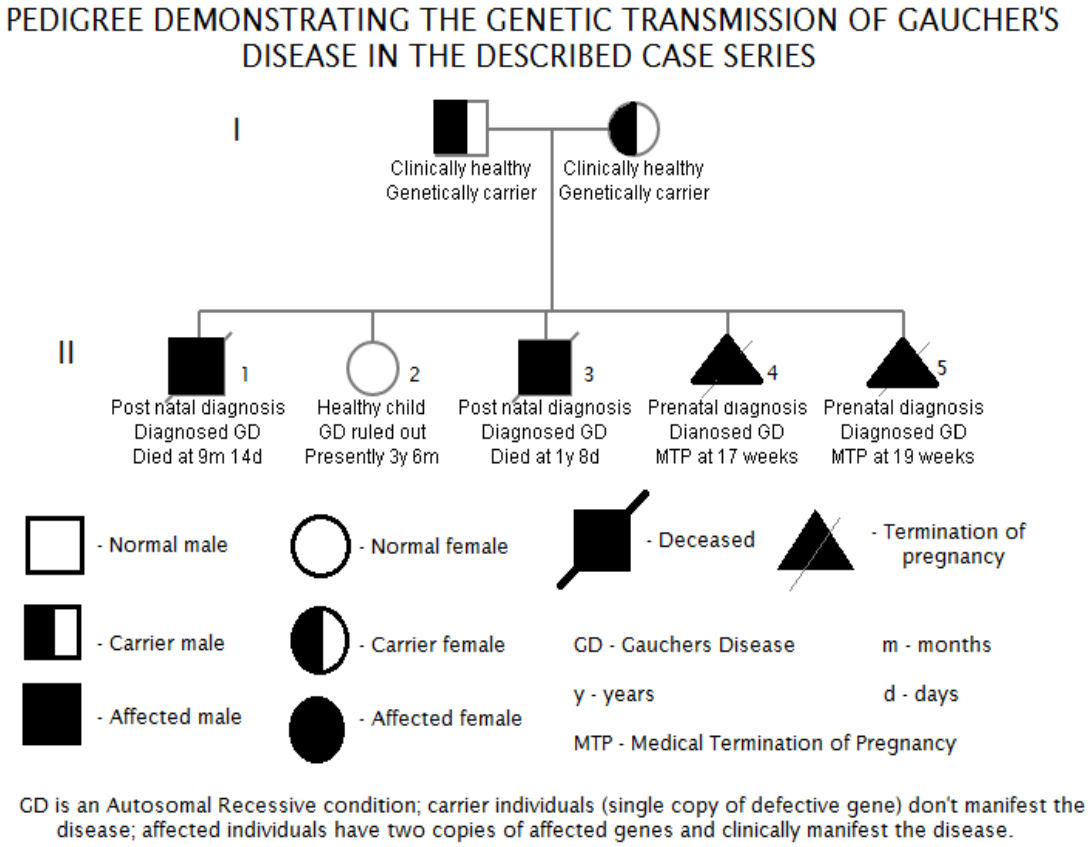

Fig. 1. Pedigree demonstrating the transmission of GD in the above described family

Fifth Pregnancy: Conceived spontaneously and confirmed by UPT. The first antenatal visit was registered at 14 weeks. The patient consented for amniocentesis which was attempted at 16 weeks but was abandoned due to tenting of membranes, a second attempt was made at 18 weeks, which was successful and simultaneously placental biopsy was also taken. Enzyme assay done on tissues obtained by placental biopsy was suggestive of GD as βGC levels were abnormally low ie. 14.2 nmol/hr/mg (320 – 550 nmol/hr/mg). Karyotyping done on cultured amniocytes revealed normal results. The parents were counseled about the diagnosis and with their informed consent pregnancy was terminated on eugenic grounds at 19 weeks by induction with misoprostol. Upon examination the gender of the delivered foetus was found to be female.

4. DISCUSSION

4.1 Incidence and Geographical Distribution

GD is a rare but a potentially life-threatening disease with a heavy psychological burden on the parents of the children affected with GD, especially if more than one pregnancy or more than a child is affected with GD. The incidence of type 1 GD in general population is 1 in 60,000 but is very high in Ashkenazi Jewish population to the tune of 1 in 450 [16]. Type 2 GD is very rare and its incidence is 1 in 150,000 populations and has no ethnic predisposition [17]. Type 3 is low in incidence and is pan-ethnic but an endemic cohort of Swedish patients with chronic neuronopathic GD lives in Northern Sweden in the county of Norrbotten, an area of approximately 100,000 square km, which is inhabited by approximately 250,000 people. This unique form of Gaucher disease is called the Norrbottnian form of Gaucher disease. In Sweden, it accounts for approximately 40% of all known cases of GD [18].

In a study by Jayesh Sheth et al. [19] over an eleven year period in India, 1,110 children with coarse facial features, hepatomegaly or hepatosplenomegaly, skeletal dysplasia, neuroregression, leukodystrophy, developmental delay, cerebral-cerebellar atrophy, and abnormal ophthalmic findings were worked up for storage disorders. Storage disorders were detected in 387 children (34.8%). In this the highest contributors were the group of glycolipid storage disorders, to the tune of 48%. A higher incidence of GD (16%) was reported in this study followed by Ganglioside Monosialic - GM2 gangliosidosis [Tay-Sachs disease (10%) and Sandhoff disease (7.8%)] and mucopolysaccharide disorders among all lysosomal storage disorders.

4.2 Clinical Classification

GD presents with variable phenotypic presentation ranging from neonatal lethality to asymptomatic octogenarians. The earlier the age of onset, the more severe and progressive is the phenotype of disease [20].

The neuronopathic forms of GD are characterized by severe neuronal damage, astrocytosis, and microglial proliferation. Experimental studies in mice with neuronopathic forms of GD have suggested that on accumulation of glucocerebroside over a critical threshold level in neurons, a cascade of reactions is activated in the microglial cells which release inflammatory cytokines. This amplifies inflammatory response that causes neuronal death [21]. Epilepsy, Myoclonus or myoclonic epilepsy is a well-known feature of neuronopathic GD [10]. Brain stem involvement occurs early which explains the early onset of hyperextension of the neck, strabismus and feeding difficulties [22]. Apneas, stridor, and trismus occur late and are less frequent. Oculomotor impairment occurs due to strabismus and not due to oculomotor apraxia though it is commonly associated with neuronopathic GD [23]. The presence of at least one N370s allele rules out the neuronopathic form of the disease [24].

The criterion for assigning a patient as GD type 2 requires the fulfillment of neuro-degeneration and death before the second year of life, in the absence of management [10]. Mingyi Chen et al. [25] describe that most of the GD type 2 children die before 5 years. Death occurs mostly due to aspiration or respiratory impairment [6]

Type 1 GD without primary neurological involvement is treatable with enzyme replacement therapy (ERT) but ERT does not stop the fatal neurological progression of type 2 GD. In type 3 GD, neurological progression may be slowed down or possibly halted in some cases by higher doses of ERT [26]. Therefore, it is essential to distinguish between type 1 GD and type 3 GD for initiating management. Saccade initiation failure (SIF) i.e. ocular motor apraxia and supranuclear gaze palsy is often the earliest neurological sign in type 3 GD [26]. This sign can

be difficult to detect clinically, but is readily revealed as missed quick-phases during induced optokinetic and vestibular nystagmus [26].

Table – 1 demonstrates the differentiating features of type 1, 2 and 3 GD.

4.3 Clinical Features and Correlation with the Case

Enzymatic deficiency leads to accumulation of glucocerebrosides in several tissues and organs, notably the spleen, liver, bone marrow and leukocytes. The earliest manifestation of GD is splenomegaly, though the liver also becomes enlarged it is not to the magnitude exhibited by the spleen. Bone infiltration may cause under mineralization leading to easy fracturing. Bone involvement also cases haematological manifestations like severe anaemia and thrombocytopenia [27]. Pulmonary involvement compromises respiratory gas exchange [27].

Type 2 GD is the acute and fulminant neuronopathic type characterized by the onset of symptoms after 3 – 6 months of life as seen in our case, the first child remained asymptomatic until 5 months and third child until 6 months. The first signs to appear are those of brain stem affection as seen in our case wherein the first child had hyperextension of the neck and, the third child had constant frothing at mouth and strabismus to start with. Neuro degeneration is characteristic of type 2 GD and was present in our case as delayed milestones and multiple seizure episodes in the first child and, death following a myoclonic seizure in the third child. Organ involvement manifesting as splenomegaly and hepatomegaly was evident in both the children clinically and radiologically. Apnea which is a late feature was seen in the first child as post seizure apnoea, late during the disease. Bone marrow infiltration leads to anaemia which was evident in both the children. Both of them cried incessantly and had repeated episodes of pneumonia. The cause of death was respiratory compromise and both children expired before the first year of life. This highlights the importance of considering lipid storage disorders as a differential diagnosis when a child presents with neurological symptoms and organomegaly, and the need to follow up with investigative workup aimed at detecting the same thereafter so that therapeutic interventions can be planned appropriately.

4.4 Inheritance

GD is inherited as an autosomal recessive genetic disorder, so the offspring will be affected only if both the parents carry the mutant allele. Those carrying one copy of mutant allele and one copy of normal allele are called as heterozygotes or carriers and such parents have a 25% probability of having a homozygote with both the copies affected. Only homozygotes manifest GD clinically whereas heterozygotes don't as it is a recessive trait.

4.5 Investigative Workup

The investigative modalities include an enzymatic assay for βGC activity in leukocytes [28] or cultured fibroblast [13] followed by

Table 1. Classification of GD

Feature	Type 1 GD	Type 2 GD	Type 3 GD
Synonyms	Nonneuronopathic	Neuronopathic	Neuronopathic
Onset	Chronic	Acute	Chronic
Visceral involvement	Present	Present	Present
Neurological involvement	Absent	Present	Present
Bone involvement	Present	Absent	Present
Predisposed populations	Panethnic	Panethnic	Panethnic
	Ashkenazi jews		Swedish norbottnians
Slow horizontal saccades	Absent	Absent	Present
Onset	Childhood	Infanthood	Childhood
	Adulthood		Adolescence
Death	Childhood	Usually below 2 years	Usually childhood or early adulthood
	Adulthood	Latest evidence – below 5 years [46]	Latest evidence - 30 – 40 years [43]

molecular diagnosis for the mutant allele in homozygous affected patients. Brady et al. [29] in 1971 described that carriers may be diagnosed by enzymatic assay but molecular genetic testing for the mutant allele is the more preferred modality for the diagnosis of carrier state [7]. Schneider in 1972 first diagnosed GD in a foetus in utero [30]. CVS and amniocentesis are well accepted procedures for prenatal diagnosis.

4.5.1 Work-up in suspected cases

The diagnosis of all types of GD is based upon the enzymatic assay for βGC activity in leukocytes [28] or cultured skin fibroblasts. [13] Diagnosis is considered when the activity is significantly lower than 30% of normal [31]. Leukocytes have a glucocerebroside rich membrane [10]. The biochemical enzyme assay is done fluorometrically using a fluorogenic substrate 4–methylumbelliferyl beta-D-glucopyranoside as described by Beutler E, et al. [13] in 1970 and Peters et al. in 1976 [14,15]. Genetic testing for mutation is possible by mutation analysis, by the use of several genetic techniques like Polymerase Chain Reaction, Restriction Digestion Method and Reverse Hybridization [32] for homozygous patients.

Gaucher's cell with its characteristic crinkled or crumpled paper appearance, which was considered a typical finding for GD, which is seen on bone marrow aspirate is seen late in the disease and as such may cause diagnostic delay when depended upon as the first or only diagnostic modality in type 2 GD [33]. Histology from the affected tissues may show macrophages engorged with lipids and eccentric nuclei [34]. Bone Marrow aspiration or liver biopsy may identify Gaucher's cell but enzyme assay is a sensitive, specific and a much less invasive technique [6].

4.5.2 Work-up in suspected carriers

All homozygous patients inherit the mutant alleles from their heterozygous parents, and heterozygous individuals have one copy of the unaffected gene. These heterozygous carriers don't manifest the disease clinically so it is required that they are tested by mutation analysis which is described as the method of choice [7]. Enzyme assay for heterozygous carriers reveals half the normal enzyme activity [6] but enzymatic assay is unreliable in this group because 20% of carriers have normal enzyme activity [7]. Our couple was advised to get tested for the mutation but they refused as they think it may cause marital discord.

4.5.3 Pre-natal diagnosis

There is a 25% probability of every pregnancy being affected with GD if both the parents are carriers. Hence they should be offered prenatal diagnosis and genetic counseling so that they can take an informed decision. Prenatal diagnosis can be done by enzyme assay directly on cells obtained by CVS at 10–12 weeks of gestation and cell cultures from amniotic fluid at 15 – 18 weeks of gestation [35]. The RCOG suggests that amniocentesis should be performed after 15 weeks of gestation as early amniocentesis has a higher rate of fetal loss, an increased incidence of fetal talipes and respiratory morbidity [36]. The RCOG guidelines also recommend that CVS should not be performed before 10 completed weeks of gestation as it is associated with oromandibular limb hypoplasia and isolated limb disruption defects [36]. Enzymatic assay on CVS gives immediate results whereas amniocentesis takes time because the cells obtained after amniocentesis need to be cultured which takes 2 – 3 weeks [37].

In our case CVS was performed in the 4th pregnancy at 12 weeks which lead to the detection of GD. In the 5th pregnancy as the patient presented late and due to technical difficulties, amniocentesis was attempted at 18 weeks and simultaneously placental biopsy was also taken as amniotic fluid cell culture takes time and termination of pregnancy is not allowed after 20 weeks of gestation in India in accordance with the Medical Termination of Pregnancy Act 1971.

4.6 Genetic Counseling

Prenatal diagnosis should be offered with genetic counseling [38]. All suspected carriers and the families which have GD should also be offered testing for carrier state followed by genetic counseling [38].

4.7 Treatment

Treatment is Enzyme Replacement therapy (ERT) with recombinant enzyme imiglucerase which is highly effective in reversing the haematologic and visceral manifestations of type 1 and type 3 GD [39] but for children with type 2 treatment is only supportive [40] because ERT

cannot reverse neurological manifestations as the recombinant enzyme can't cross the blood brain barrier [41]. This provides enough grounds to consider termination of pregnancy on Eugenic grounds when the foetus is prenatally diagnosed. Currently velaglucerase (produced from fibrosarcoma cell line) and taliglucerase alpha (produced from carrot root cells) are also available [27].

5. CONCLUSIONS

Though GD is a rare disease it is a potentially lethal one. GD should be suspected in a child presenting with organomegaly or neurological symptoms. Prenatal diagnostics and genetic counseling should be offered if GD runs in the family or if a sibling is affected with GD. Premarital and preconception genetic counseling would be of help in families with a history of GD.

6. FUTURE PROSPECTS

To prevent recurrent terminations, earlier preventive approaches such as preimplantation genetic diagnosis followed by Intra Cytoplasmic Sperm injection (ICSI) is being highlighted [7]. Substrate reduction therapy using Miglustat and Eliglustat which aim at reducing the synthesis of glucocerebroside by inhibiting the enzyme glucosylceramide synthetase is under study [42-44]. Research is underway for molecular chaperone therapy that prevents the misfolding and subsequent destruction of the mutated enzyme [45]. Inhibiting histone deacetylase helps in restoring the activity of the mutant enzyme [46]. Gene therapy using viral vectors to increase the gene expression for enzyme production is underway. Therapeutic application of plant glucocerebrosidase as a carrot cell suspension has been developed [27]. Transcription Activator Like Effector Nuclease (TALEN), which are gene editing nucleases are also being investigated. Human Induced Pleuripotent Stem Cells from type 2 GD [homozygous for β-glucocerebrosidase (*GBA*) 1448T>C mutation] have shown 'targeted genetic manipulation' by Chemokine Receptor Type - 5 (CCR- 5) specific TALEN [47].

Table 2 shows the possible therapeutic interventions for GD.

Table 2. Possible therapeutic interventions for GD with their mechanism of actions

S. no	Drug class	Mechanism of action	Drugs	Properties
1.	Recombinant Glucocerebrosidase	Replacement of deficient enzyme ie. Enzyme Replacement Therapy (ERT)	Aglucerase	Harvested from tissues – now not available
			Imiglucerase	Recombinant DNA Technology – Chinese Hamster Ovary
			Velaglucerase	Recombinant DNA Technology – Fibrosarcoma Cell Line
			Taliglucerase alfa	Recombinant DNA Technology – Plant Derived
2.	Substrate reduction therapy	Inhibition of glucosylceramide synthetase	Eliglustat	Synthetic – Hemitartrate salt
			Miglustat	Synthetic – Iminosugar
3.	Pharmacological chaperone	Facilitates the correct folding of the enzyme hence the enzyme is trafficked to lysosomes (cf. to defective enzyme degraded by endoplasmic reticulum associated degradation)	Ambroxol	Synthetic
4.	Histone deacetylase inhibitor (HDACi)	Decrease in degradation of the enzyme via ubiquitin proteasome pathway (cf. Defective enzyme degraded by ubiquitin proteasome pathway through hsp 90)	Suberoylanilide Hydroxamic Acid (SAHA) and LB-205	Synthetic
5.	Transcription activator like effector nuclease (TALEN)	Gene editing nucleases	CCR- 5 specific TALEN	Nuclease – Molecular genetics technology

7. RESEARCH INVOLVING HUMAN PARTICIPANTS

- All procedures performed on the patient were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
- All treatment protocols followed are in accordance with the latest accepted Evidence Based Medicine Norms.
- Medical Termination of Pregnancy which was carried out was after obtaining a well informed consent of the patient and in accordance with the MTP Act 1971, which allows termination on Eugenic Grounds and is the accepted law of the land.

INFORMED CONSENT

- All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.
- Informed consent was obtained from the patient / couple.
- The patient and her husband have given well informed consent for all diagnostic and management procedures that were carried out and these documents have been well preserved and can be produced on demand.
- The patient and her husband have given informed consent for any type of electronic or paper storage, transmission, and publishing of their records / case histories for the purpose of scientific advancement and these documents have been well preserved and can be produced on demand.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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