Prenatal counseling and diagnosis of Gaucher disease in Egypt: an 18-year experience

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Objective
To provide prenatal counseling (PC) and prenatal diagnosis (PD) of Gaucher disease in pregnant women with previous affected sibling (s).

Patients and methods
PC was done in 154 pregnancies among 109 females from June 2000 to July 2018. Positive consanguinity was found in 98 (89.9%) couples. Chorionic villus sampling (CVS) was done between 11 and 12 weeks of gestational age in 115 pregnancies among 84 women. Two women had CVS in four pregnancies, five in three pregnancies, and 15 in two pregnancies. β-glucocerebrosidase activity was measured in chorionic villi.

Results
Of 154 pregnancies, 115 (74.68%) proceeded to CVS and 39 (25.32%) did not. Of the 39, 18 did not show up, eight already came late for PD, nine had missed or spontaneous abortion, three refused, and one had induced abortion before PD. In 110 (95.65%) pregnancies, enough chorionic villi were retrieved, and β-glucocerebrosidase was measured; 79 (71.82%) had normal enzyme activity and 31 (28.18%) had low activity. In five cases, we could not retrieve enough villi.

Conclusion
In spite of the presence of enzyme replacement therapy for Gaucher disease, it is not effective for all types, in addition to high cost and variable response. So, our responsibility in PC is to offer early diagnosis by CVS, as one of the options, to the pregnant women/couples.

Keywords:
chorionic villus sampling, Gaucher disease in Egypt, prenatal counseling and diagnosis, β-glucocerebrosidase

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Introduction

Gaucher disease (GD) is an autosomal recessive disorder caused by a genetic deficiency of the lysosomal enzyme β-glucocerebrosidase which leads to the storage of glucocerebroside and other glycolipids in various tissues that cause damage to several organ systems (Grabowski, 2008; Grabowski *et al.*, 2013).

GD is classified based on clinical characteristics into three types: type 1 is nonneuropathic, type 2 is acute neuropathic, and type 3 is chronic neuropathic (Grabowsky *et al.*, 2004).

Type 1, which affects most patients, is characterized by organomegaly. The main cause of the anemia, cytopenia, hepatosplenomegaly, and the bone lesions associated with the disease is considered to be the infiltration of the bone marrow, spleen, and liver by Gaucher cells (Stirnemann *et al.*, 2017).

The definitive diagnosis of GD is by the measurement of β-glucosidase enzyme activity in leukocytes or skin fibroblasts (Ho *et al.*, 1972; Di Rocco *et al.*, 2014). There is no role for histological examination of the bone marrow, liver, or spleen for the diagnosis of the disease (Nagral, 2014).

Prenatal diagnosis (PD) of GD is possible by direct measurement of glucosidase activity in chorionic villus sample (CVS) (Besley and Broadhead, 1989).

Our objective was prenatal counseling (PC) and diagnosis of GD in pregnant women with previous affected sibling(s).

Patients and methods

Primary intervention: prenatal counseling

This is a retrospective study. PC was done in the period from June 2000 to July 2018 in 154 pregnancies among 109 females: one female was counseled in five pregnancies, three females were

counseled in four pregnancies, 10 were counseled in three pregnancies, and 12 women were counseled in two pregnancies. The age of the women ranged from 18 to 38 years.

All the pregnant women were subjected to history taking, pedigree construction, clinical examination, and ultrasound scan.

All the 109 pregnant women have an affected sibling with GD, except two with family history in a close relative. Overall, five have three affected siblings, and 14 have two affected siblings.

At first visit counseling, 67 (51.15%) affected siblings were living and 64 (48.85%) were dead. Among the 67 affected living siblings, 35 (52.24%) were under enzyme replacement therapy (ERT), and 32 (47.76%) did not receive treatment.

Among the 64 affected dead siblings, nine were under ERT before death: six died after variable period of ERT (11, 5, 2.5, 2 years, and 6 months, correspondingly), two died after few injections of ERT, and another died 3 days after ERT from bloody diarrhea.

Among the 109 pregnant women, at their first visit, 57 (52.3%) had no normal child and 52 (47.7%) had normal children (25 have girls, 21 have boys, and six have girls and boys). Accordingly, 82 (75.23%) families have no normal boys.

Of the 109 pregnant women/couples, 98 (89.9%) have positive consanguinity and only 11 (10.1%) have negative consanguinity. Among the 154 pregnancies, 137 (88.96%) were positive and 17 (11.04%) were negative.

Proper counseling was done explaining the following items:
(1) The nature of GD
(2) The possibility of recurrence in each pregnancy
(3) The idea (rationale) of PD
(4) The procedure of CVS.

Finally, an informed consent was provided by the pregnant women, and they were scheduled for PD by CVS.

Secondary intervention: prenatal diagnosis

CVS was done between 11 and 12 weeks of gestational age in 115 pregnancies among 84 women: four times in two women, three times in five women, and two times in 15 women.

Chorionic villi were sampled by transabdominal route using the free-hand, fine-needle aspiration method with 20-G needle under simultaneous ultrasound guidance. If sufficient villi were not obtained in the first attempt, a second one was made with another needle with a maximum of three attempts.

Chorionic villi were retrieved successfully in 110 (95.65%) cases by one CVS puncture in 49 (44.55%) cases, two CVS punctures in 37 (33.64%), and three CVS punctures in 24 (21.81%) cases.

The retrieved chorionic villi were immediately dissected from the maternal decidua. The importance of the immediate separation of decidua from chorionic villi is highly stressed (Besley *et al.*, 1988). The sample was placed in sterile medium or saline and frozen. After thawing, β-glucosidase activity was measured in the chorionic villi fluorometrically.

Results

Primary outcome: cases subjected to chorionic villus sampling

Of the 154 counseled pregnancies, 115 (74.68%) proceeded to CVS and 39 (25.32%) were not subjected to CVS. Among these 39 pregnancies, 18 (46.15%) did not show up at scheduled time, nine (23.08%) had missed or spontaneous abortion, eight (20.51%) already come late for PD, three (7.69%) refused, and one (2.56%) had induced abortion before PD.

Secondary outcome: enzyme activity measurement

β-glucosidase activity was measured in 110 CVS. Normal enzyme activity, denoting normal fetus, was found in 79 (71.82%) cases, and low enzyme activity, denoting affected fetus, was found in 31 (28.18%) cases. In five cases subjected to CVS, we could not retrieve enough chorionic villi for the biochemical diagnosis. Three patients were not cooperative (moving during puncture), one patient was very obese (needle could not reach the placenta) and one patient had a posterior and very low lying placenta (inaccessible placenta).

Discussion

In our study, many factors affected the decision-making process of the parents to do PD. The following are among these factors:
(1) Personal experience and suffering with the affected sibling
(2) Absence of a normal boy
(3) Proper PC
(4) Family and society pressures
(5) Negative influence of other doctors.

Overall, 154 pregnancies were counseled; however, 39 pregnancies were not subjected to CVS. Table 1 illustrates the reasons and the proposed explanations of these cases.

Many of our patients came from rural areas where they were dealing with other physicians, general practitioners, or even obstetricians. These physicians may have negatively influenced the patient's decision to do PD.

The following are examples of other physicians' opinions that may affect negatively patient's decision:
(1) No PD for such disease
(2) Tests are neither accurate nor conclusive
(3) Tests are for research and not for clinical practice
(4) Placenta is not formed in third month for CVS
(5) CVS will harm the fetus
(6) CVS will definitely cause abortion.

As a prerequisite for PD and before PD can be offered, the diagnosis in the proband must be precisely established. A clinical diagnosis alone is not sufficient (Kleijer and Verheijen, 2009). In all cases, it is important to establish the enzyme deficiency in the proband (Besley and Wraith, 1997).

GD is the commonest type of lipidoses in Egypt. However, if GD and/or Niemann–Pick disease are suspected clinically in an affected child with hepatosplenomegaly, three enzymes, namely, β-glucosidase, sphingomyelinase, and chitotriosidase, should be estimated simultaneously for better evaluation of the case and to exclude the possibility of Niemann–Pick disease. Chitotriosidase is an important enzymatic biomarker in all cases of hepatosplenomegaly accompanied with or without neurologic manifestations (AboulNasr and Fateen, 2008).

Table 1 Reasons and the proposed explanations of 39 cases not subjected to chorionic villus sampling

Reasons	*n*/%	Proposed explanations
No show up at scheduled time	18 cases	Spontaneous abortion
	46.15	Discouraging family influence
		Negative influence of other doctors
		Fear from procedure or facing results
Spontaneous or missed abortion	9 cases	Abortion rate is high in genetic diseases
	23.08	
Came late for PD	8 cases	Lack of knowledge about availability and accuracy of PD
	20.51	Discouraging family influence
		Negative influence of other doctors
		Hesitation to come for counseling.
Refusing PD	3 cases	Fear from procedure of PD
	7.69	Not convinced by rationale of PD
Induced abortion before PD	1 case	
	2.56	

CVS, chorionic villus sampling; PD, prenatal diagnosis.

Consanguineous marriage is common in Egypt. It varies from 29 to 40% in different areas (Temtamy and Aglan, 2012). This explains the high consanguineous rate among couples with children of autosomal recessive diseases such as GD in our study.

Concerning the motivation of the pregnant women/couples for PD. A previous study of PD for mucopolysaccharidoses among pregnant Egyptian women found out that parents were keen to do PD to have a normal child (AboulNasr and Fateen, 2004). In the present study, we found that pregnant women/couples were eager not only to have a normal child or to avoid having an affected one but more importantly sometimes to have a normal boy as they have already normal girls.

We will try in the following discussion to answer three important controversial questions concerning PD of GD by measuring β-glucosidase enzyme activity in chorionic villi:
(1) Why PD in spite of the presence of ERT?
(2) Why CVS and not amniocentesis?
(3) Why enzyme assay and not mutation analysis?

First question: why prenatal diagnosis?

Parents having an affected child with GD will have a 25% recurrence risk in subsequent pregnancies. Therefore, they may refrain from having further children unless PD is available with the option of termination of the affected pregnancy (Kleijer and Verheijen, 2009).

Prenatal testing for couples with family history of GD should be offered in conjunction with genetic counseling so that they can be aware of available options and can make informed decisions (Zuckerman *et al.*, 2008).

The cost of ERT is very high and may reach hundreds of thousands of US dollars annually for a single patient in addition that it is to be continued for life (Singh *et al.*, 2010). Moreover, ERT cannot reverse the neurological manifestations in type 2 or type 3 GD (Germain and Benistan, 2007).

GD may be associated with other serious conditions. Increased risk of multiple myeloma and hematological and nonhematological malignancies has been reported with type 1 GD (Cappellini, 2015). The pathophysiology of cancer development in GD is not well understood (Astudillo *et al.*, 2015).

There is a recent discovery of association between GD and Parkinson's disease. This association has now refocused research toward delineating the role of glucocerebrosidase in the brain (Lal and Sidransky, 2017).

So, PD is the option that should be discussed and offered for every pregnant woman with a history of an affected sibling (AboulNasr and Fateen, 2008).

Second question: why chorionic villus sampling?

Chorionic villi has been proved to be suitable for direct enzyme assay in different metabolic disorders (Poenaru *et al.*, 1979; Desnick *et al.*, 1992). It is agreed that PD of GD can be done by measuring β-glucosidase activity in fresh chorionic villi (Stirnemann *et al.*, 2017). Many have recommended uncultured chorionic villi for reliable prenatal enzymatic diagnosis of various lysosomal disorders including GD (Verma *et al.*, 2015).

Direct enzyme assay in CVSs between 11 and 12 weeks of gestational age should provide early diagnosis. This is more favorable than later diagnosis by amniocentesis between 14 and 15 weeks of gestational age, from medical, ethical, and psychological aspects (AboulNasr and Fateen, 2002).

Third question: why enzyme assay?

Clinical phenotype of GD cannot be discerned from the genotype (Goker-Alpan *et al.*, 2003). There seem to be factors other than genotype affecting the phenotypic expression as severity may vary among siblings, even identical twins (Lachmann *et al.*, 2004).

It is challenging to understand genotype-phenotype correlation in GD as individuals sharing the same genotype, even siblings or twins, can differ in their disease manifestations, clinical course, and response to therapy (Biegstraaten *et al.*, 2011).

β-glucosidase assay is accurate with rapid result. Detection of many mutations is more expensive and time consuming. In addition, mutation analysis does not add more information relevant to the decision making in PD.

Although, the benefits of PD procedures are well documented, the investigation of psychological consequences related to these procedures has remained a surprisingly neglected area of research (Leithner *et al.*, 2004).

PC is not a one-way meeting. Enough time should be given for listening to couples, understanding their problems and fears, and explaining clearly and patiently all the available options including PD. PC should be comprehensive, nondirective, and nonjudgmental. PC should be considered as a psychoanalysis session (Table 2).

PC is not only a prediagnostic process but also a postdiagnostic one (Table 3).

In any medical issue with an ethical aspect, there is what we call 'the ethical puzzle.' It comprises the three sides interinfluencing each other and finally affecting the decision making. These sides are the society, the patient, and the physician. We should consider and respect every side and avoid conflicts of interests between them.

Obstetricians working in the field of PD should be aware of the scientific, psychological, and ethical aspects of each disease-patient condition; considering collectively these aspects in the decision making is mandatory. Counseling is a dynamic and nondogmatic process helping couple's decision and not doctor's decision imposing.

CVS between 11 and 12 weeks of gestational age will provide early diagnosis and consequently give the patient the option and opportunity of an early termination which is medically safer. In addition, many Muslims believe that 'the Soul' comes to the fetus after the first four months (i.e., 120 days) of pregnancy. So, if termination is to be done, it should be in that gestational period, that is, before ensoulment of the fetus.

Obstetricians offering PD bear a heavy responsibility. Diagnostic errors may result in loss of normal pregnancies or the avoidable birth of affected children. Obstetricians must be aware of the test available so that they can counsel their patients accordingly. Our

Table 2 The application of psychoanalysis in prenatal counseling

Tool	Technique (act by)	Aim
Listening to patient	Expressing her thoughts and inner conflicts	Talking relief
Analysis by counselor	Liberation from outer pressures (e.g. family, society)	Removing negative thoughts and influences
Explaining medical options	Offering help	Finding solutions and encouraging positive attitude

Table 3 Prediagnostic and postdiagnostic processes of prenatal counseling

Item	Prediagnostic counseling	Postdiagnostic counseling
Explain	Presumptive possibilities	Definitive result
Speak about	Percentages	Negative or positive
Decision	To do prenatal diagnosis or not	To continue pregnancy or not

duty and responsibility as physicians/counselors is to offer all the available options to the patients/couples.

Conclusion

In spite of the presence of ERT for GD, it is not effective for all types in addition to high cost and variable response. It is the right of the couple with history of an affected child with GD to understand that PD is possible and available. So, PC should offer early PD of GD by CVS to measure β-glucosidase activity in chorionic villi as an option to allow couples at risk to make an informed reproductive decision.

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Conflicts of interest

There are no conflicts of interest.

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