J. Fetal Med. (September 2019) 6:147–150
https://doi.org/10.1007/s40556-019-00216-8

GENETICS IN FETAL MEDICINE

Gaucher Disease in Fetus: The Usual and the Unusual Presentations in a Family

Ranjana Mishra[1] · Sunita Bijarnia-Mahay[1] · Nidhish Sharma[2] · Nandita Dimri[2] · Renu Saxena[1] · Ratna Dua Puri[1] · I. C. Verma[1]

Received: 12 July 2019 / Accepted: 3 September 2019 / Published online: 17 September 2019

Abstract Gaucher disease is the most common of the lysosomal storage disorders, with a continuum of clinical features ranging from a perinatal lethal form to an asymptomatic form. Perinatal lethal Gaucher disease (PLGD), also known as fetal Gaucher disease is a distinct, severe form of type II Gaucher disease and typically presents as non- immune hydrops fetalis, hepatosplenomegaly and ichthyosiform abnormalities in the fetal life. We herein report a family with a spectrum of usual (i.e. hepatosplenomegaly) and unusual (i.e. absence of hydrops and presence of significant intrauterine growth restriction) features of PLGD with a genetic diagnosis of homozygous RecNciI mutation in the *GBA* gene.

✉ Sunita Bijarnia-Mahay
bijarnia@gmail.com

Ranjana Mishra
ranjanam312@gmail.com

Nidhish Sharma
nidhishsharma@yahoo.com

Nandita Dimri
dimnan@yahoo.com

Renu Saxena
renu2006@gmail.com

Ratna Dua Puri
ratnadpuri@yahoo.com

I. C. Verma
icverma@gmail.com

[1] Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, Delhi 110060, India

[2] Department of Fetal Medicine, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, Delhi 110060, India

Keywords Hydrops · Fetal · Perinatal-lethal · IUGR · Recombinant allele · RecNciI · Non immune-hydrops

Introduction

There are at least 20 inborn errors of metabolism (IEM) that are implicated in non-immune hydrops fetalis (NIHF), and lysosomal storage disorders (LSDs) form a major component of this IEM group [1]. As most IEM have autosomal recessive inheritance, consanguinity plays an important role in recurrent NIHF.

In a review article by Gimovsky et al. [2] the overall incidence of LSD reported was 5.2% (35 of 678) in all NIHF cases that tested for any LSD. The LSDs which are most commonly associated with NIHF include type II Gaucher disease, mucopolysaccharidosis (MPS) type VII, MPS type IV, GM1 gangliosidosis, Wolman disease, Galactosialidosis, Niemann-Pick disease type C, Farber disease, infantile free Sialic acid storage disease and Mucolipidosis II (I-cell disease) [1, 2]. Perinatal lethal Gaucher disease (PLGD), a severe form of type II Gaucher disease is one of the most common LSDs presenting as NIHF and contributes to 17% of all LSDs implicated in NIHF [2, 3]. We herein report a family with a spectrum of usual and unusual features of perinatal lethal Gaucher disease.

Case Report

The consultand (V4), a 33 years old second gravida was referred at 28 weeks period of gestation, to our genetic clinic for counselling regarding an antenatally diagnosed hepatosplenomegaly, cardiomegaly and intrauterine growth

restriction (IUGR) on ultrasound. Liver and spleen sizes were 57.8 mm and 52.45 mm respectively, both being above 95th centile and cardio-thoracic circumference ratio being 0.68 mm (Fig. 1a–c). The fetal biometry was suggestive of IUGR as the abdominal circumference of 207.3 mm and estimated fetal weight of 854 g were both below 3rd centile for 28 weeks of gestation. Nuchal fold thickness was 6 mm and there was no evidence of hydrops fetalis. The first trimester nuchal translucency was 1.2 mm at crown rump length of 58 mm which was normal and anomaly scan at 18 weeks was also normal. Her first pregnancy and delivery were uneventful.

The couple reported a distant consanguinity (Fig. 2). Consultand's husband (V5) and her sister's husband (V1) were brothers, and the sister's (V2) previous two pregnancies (V12 and VI3) were affected with hydrops fetalis. The sister's second (VI3) fetus was noted to have anemia and thrombocytopenia on evaluation. The fetal autopsy and NIHF/ LSD gene panel testing were done in that case by Bhutada et al. [4] who reported the identified homozygous RecNciI recombinant variant ([c.1448 T > C;1483G > C;1497G > C]) in the *GBA* (glucocerebrosidase) gene. The parents were heterozygote carriers for the identified variant.

With the above family history in mind, the couple was counselled that although their baby's presentation was different, there was a high suspicion of the same genetic condition as that identified in the sister's fetus. A prenatal diagnosis by amniocentesis and targeted molecular testing for the identified recombinant *GBA* variant was done which confirmed the fetus to be homozygous for the same. As the pregnancy had advanced beyond the legal gestational age of termination, the couple returned to their native city and continued with the pregnancy which resulted in intrauterine death (IUD) at 32 weeks. Baby girl (VI5) was noted to have skin peeling and edematous skin; however, a fetal autopsy could not be performed due to lack of facilities.

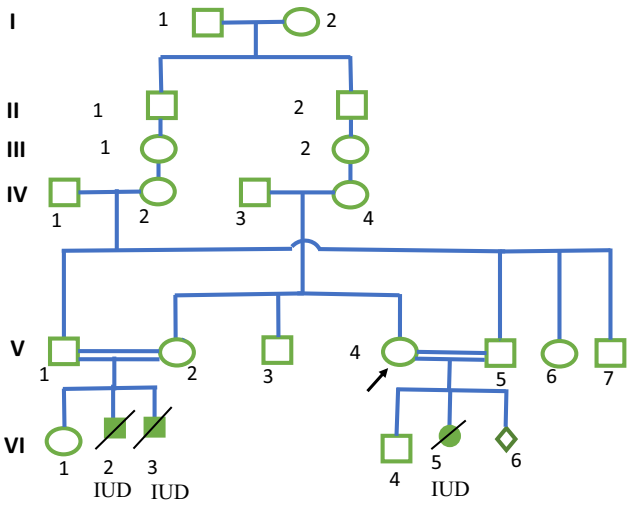

Fig. 2 Pedigree showing multiple fetuses affected with PLGD. Consultand marked with arrow

Prenatal diagnosis in a subsequent pregnancy (VI6) was performed by chorionic villus sampling at 11 weeks and targeted mutation testing, where the fetus was observed to be unaffected.

Discussion

Perinatal lethal Gaucher disease is a rare and poorly understood disorder. Mignot et al. [5] reported a series of 41 cases of perinatal lethal Gaucher disease. The various methods of diagnosis in that cohort were most commonly based on post-mortem pathological findings (59% of the 41 cases), followed by demonstration of enzymatic deficiency in cells from prenatal sample, in dead fetus, a living child or by the histopathological study of liver biopsy or bone-marrow aspiration. Few cases in that cohort were diagnosed retrospectively based on a positive family history. It is noticeable that NIHF as a classical finding in PLGD, was

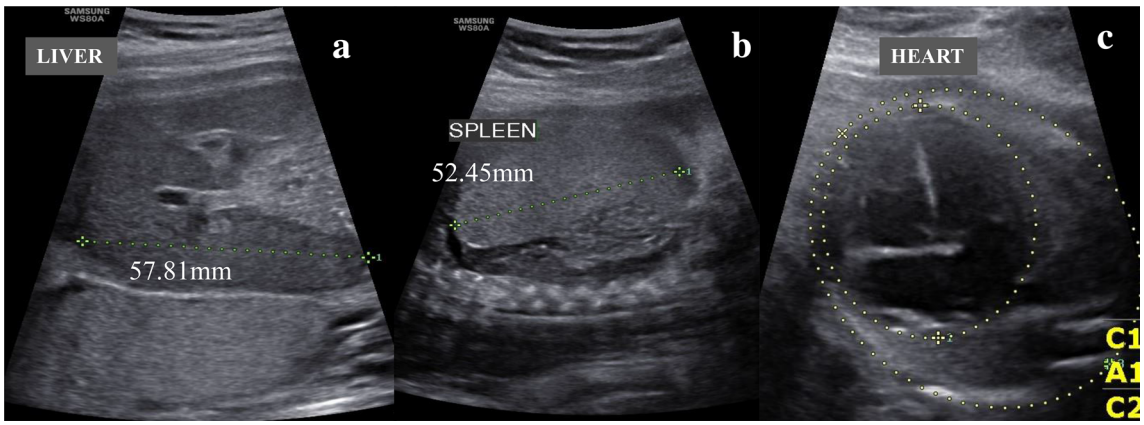

Fig. 1 Ultrasound images of fetus showing **a** hepatomegaly, **b**, splenomegaly **c** cardiomegaly

Table 1 Reported cases with homozygous RecNciI mutation presenting with NIHF

S. no	Study	No. of patients	Ethnicity	Hydrops at presentation
1	Present study	1	South Asian	No
2	Bhutada et al. [4]	2 (one family)	South Asian	2 of 2
3	Sidransky et al. [7]	2 (one family)	Afghani	1 of 2
4	Rowlands and Murray [8]	1	Lebanese	Yes
5	Stone et al. [9]	1	Lebanese	Yes
6	Stone et al. [6]	1	North American	Yes
7	Finn et al. [10]	1	Hispanic	No

absent in 34% (14/41) of fetuses in the above series. Hepatosplenomegaly was a major sign, and was associated with ichthyosis, arthrogryposis, and facial dysmorphology in 35–43% of cases.

In our family discussed above, although the familial mutation was same, significant phenotypic differences were noted between the fetuses. Hydrops fetalis was present in the two fetuses of the consultand's sister, but was conspicuously absent in the fetus of the consultand at the time of presentation. The skin edema seen at birth, could be a postmortem event and it is difficult to comment on its antemortem development. Another unusual feature seen in this fetus was significant IUGR which was seen in only two cases in Mignot's cohort of 41 PLGD fetuses. Although IUGR forms a part of the phenotypic spectrum of the PLGD (OMIM 608,013), it is possible that it is masked by the concomitant development of fetal hydrops. The RecNciI mutation identified in this family has been reported as the most frequent morbid allele in PLGD cases [5].

A RecNciI is one of seven different recombinant complex disease-causing alleles, derived from recombinant events between *GBA* and its pseudogene *GBAP*. RecNciI allele results in the common p.Leu483Pro (c.1448T > C) variant being co-allelic with both the p.Ala495Pro (c.1483G > C) and p.Val499Val (c.1497G > C) sequence variants located at end of exon 9 and beginning of intron 9. While there are limitations in genotype–phenotype correlations in PLGD, Stone et al. [6] have summarized 33 different pathogenic variants by characterizing all 62 alleles in 31 patients with type 2 Gaucher disease. It was observed that the most severe outcome of perinatal lethality due to hydrops fetalis often resulted from homozygosity for a recombinant allele (15 of 31 patients). Literature search has revealed that NIHF was the presenting feature in 6 of 8 fetuses with PLGD who were homozygous for RecNciI mutation (Table 1). This RecNciI mutation was not identified in homozygous form in any of the 17 patients with postnatal onset Gaucher type 2 disease in Stone's cohort [6] or in any other study in literature. This highlights the perinatal lethality of RecNciI allele in homozygous form.

In this case, it is the family history that simplified and expedited the diagnostic algorithm. A prenatal suspicion of PLGD would have been difficult in the absence of characteristic findings and more extensive work-up would have been required to arrive at the diagnosis. Herein lies the importance of extended pedigree charting during genetic counselling and taking cognizance of the fact that unusual presentation of a lethal disorder is possible.

Conclusion

The typical antenatal ultrasound features of NIHF, hepatosplenomegaly, arthrogryposis, IUGR and IUD are pointers towards an underlying storage disorder with PLGD being one of the most common differentials. PLGD should be suspected in a setting of organomegaly and IUGR even in the absence of hydrops in a fetus.

Compliance with Ethical Standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as received in 2008.

Informed Consent Patients' informed consents were obtained.

References

1. Kooper AJ, Janssens PM, de Groot AN, Liebrand-van Sambeek ML, van den Berg CJ, Tan-Sindhunata GB, van den Berg PP, Bijlsma EK, Smits AP, Wevers RA. Lysosomal storage diseases in non-immune hydrops fetalis pregnancies. Clin Chim Acta. 2006;371(1–2):176–82.
2. Gimovsky AC, Luzi P, Berghella V. Lysosomal storage disease as an etiology of non-immune hydrops. Am J Obstet Gynecol. 2015;212(3):281–90.
3. Stone DL, Sidransky E. Hydrops fetalis: lysosomal storage disorders in extremis. Adv Pediatr. 1999;46:409–40.
4. Bhutada E, Pyragius T, Petersen SG, Niemann F, Matsika A. Perinatal lethal Gaucher disease due to RecNciI recombinant

mutation in the GBA gene presenting with hydrops fetalis and severe congenital anemia. Case Rep Pathol. 2018;9:2549451.
5. Mignot C, Gelot A, Bessieres B, Daffos F, Voyer M, Menez F, Fallet Bianco C, Odent S, Le Duff D, Loget P, Fargier P, Costil J, Josset P, Roume J, Vanier MT, Maire I, de Villemeur TB. Perinatal-lethal Gaucher disease. Am J Med Genet. 2003;120A:338–44.
6. Stone DL, Tayebi N, Orvisky E, Stubblefield B, Madike V, Sidransky E. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. Hum Mutat. 2000;15:181–8.
7. Sidransky E, Tayebi N, Stubblefield BK, Eliason W, Klineburgess A, Pizzolato GP, Cox JN, Porta J, Bottani A, DeLozier-Blanchet CD. The clinical, molecular, and pathological characterisation of a family with two cases of lethal perinatal type 2 Gaucher disease. J Med Genet. 1996;33(2):132–6.
8. Rowlands S, Murray H. Prenatal ultrasound findings in a fetus diagnosed with Gaucher's disease (type 2) at birth. Prenat Diagn. 1997;17(8):765–9.
9. Stone DL, Carey WF, Christodoulou J, Sillence D, Nelson P, Callahan M, Tayebi N, Sidransky E. Type 2 Gaucher disease: the collodion baby phenotype revisited. Arch Dis Child Fetal Neonatal Ed. 2000;82(2):F163–F166166.
10. Finn LS, Zhang M, Chen SH, Scott CR. Severe type II Gaucher disease with ichthyosis, arthrogryposis and neuronal apoptosis: molecular and pathological analyses. Am J Med Genet. 2000;20(3):222–6.