An Early Presentation of a Genomic Variant of Mucopolysaccharidoses II in a Female Newborn Baby

Ritesh[1], Singh HM[2]

Abstract

Mucopolysaccharidoses II is a X-linked genetic disorder caused by the deficiency of lysosomal enzyme Iduronate sulfate sulfatase due to mutations of Iduronate 2-sulfatase (IDS) gene which results in accumulation of intralysosomal glycosaminoglycan. X inactivation and gene alterations are known to cause this entity in a female child. We report an unusual case of missense mutation of IDS gene in heterozygous variant with dominant expression in a female neonate presented in early newborn period with incurable severity. X-linked recessive (heterozygous) missense mutation of Exon 8 in IDS gene confirmed a case of Mucopolysaccharidoses II by Sanger sequencing.

Key words: Blueberry muffin lesions; female hunter Syndrome; iduronate 2-sulfatase; missense mutation; Mucopolysaccharidoses II (OMIM 309900).

Introduction

Mucopolysaccharidoses II (MPS II) is also known as Hunter Syndrome and was first described in 1917 by Hunter C.[1] MPS II in a female child is a recognised entity and several cases have been reported with variable clinical presentation and outcome.[2-5] The multi exon deletion and missense mutation on specific location are the major deciding factors for severity and early presentation of the disease.[6] The case reported here presented in newborn period with utmost severity in a female neonate.

Case Report

A female neonate, first product of non-consanguineous marriage was born through thick meconium stained liquor and required resuscitation at birth. Birth weight of the baby was 2.34 kg and head circumference was 33 cm. Antenatal sonography scan was unremarkable. The baby had multiple blueberry muffin spots, ecchymosis, dilated tortuous vein over scalp and Mongolian spots [Figure 1].

Crackles were heard on both sides of chest and the abdomen was distended due to enlarged liver and spleen. Apt test in gastric lavage was positive for neonatal blood. Blood investigation at birth reported as platelets-35,000, reticulocytes–8.2%, international normalised ratio-4.9 and elevated liver enzymes. Direct anti-globulin test was negative.

[1]Ritesh, Department of Paediatrics, ITFH Tajikistan; [2]Harsh Mohinder Singh, BaseHospital Barrackpore, North Parganas, West Bengal, India.

Address for correspondence
Ritesh,
Department of Paediatrics,
ITFH Tajikistan.
E-mail: ritesh2000sriji@yahoo.com

Acknowledgements: None
Funding: Nil
Conflict of Interest: None
Permission from IRB: Yes

How to cite
Ritesh, Singh HM. An Early Presentation of a Genomic Variant of Mucopolysaccharidoses II in a Female Newborn Baby. J Nepal Paediatr Soc 2018;38(3):190-2.

doi: http://dx.doi.org/10.3126/jnps.v38i3.27320

Submitted on: 2020-01-19
Accepted on: 2020-02-12

Kidigram showed cardiomegaly and only midline bowel gas due to massive hepatosplenomegaly. At six hours of life, the baby started to have profuse bleeding from all natural orifices. The baby was ventilated and all possible intensive management were instituted but she continued to deteriorate and succumbed to her illness.

The clinical presentation prompted to investigate for congenital infections, metabolic disorders and neonatal malignancy. Blood samples were taken before blood and component transfusion. TORCH titer of the baby was nonreactive. There were no abnormal cells in peripheral blood smear. Suspecting a metabolic disorder Clinical Exon Sequencing test was done which revealed X-linked recessive variant (heterozygous) missense mutation c. C1083G (p.Phe 361Leu) of Exon 8 (NM_000202) in the IDS gene. Additional findings were also reported as recessive (compound heterozygous) variant (c.C3659t/p.Ser 1220 Phe and c.G7181A/) in NBEAL2 gene and dominant (heterozygous) missense variant (c.G2511C/p.Gln 837 His) in ITGA2B gene. This was further confirmed by Sanger Sequencing (Figure 2).

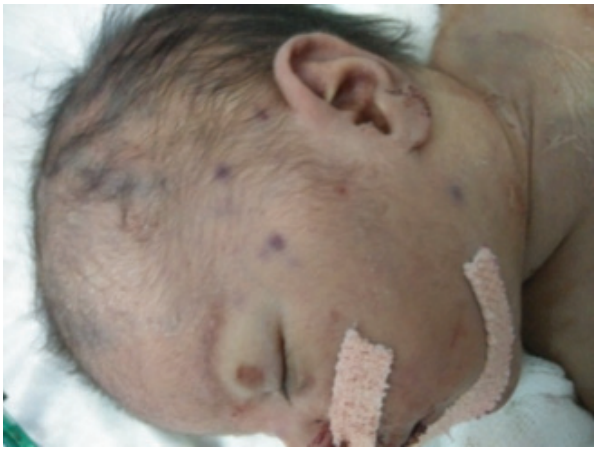

Fig. 1: Blueberry muffin spots and bleeding from natural orifices (Nose, mouth and ear)

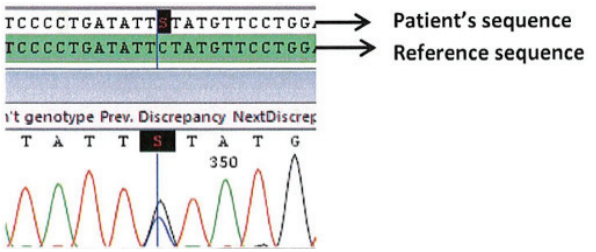

Fig. 2: X-linked recessive (heterozygous) missense mutation c.C1083G (p.Phe361Leu) of Exon 8 (NM_000202) in IDS gene confirmed by Sanger Sequencing.

Discussion

MPS II heterozygous females are rarely affected unless either there is a simultaneous presence of two mutant alleles or a coincidental genetic defect leading to skewed X-inactivation or hemizygosity in heterozygote condition with dominant expression of the mutant IDS allele.[7-9] In MPS II the pattern of skewed X- chromosome inactivation is a major factor in determining the phenotype in heterozygotes and affected females.[7,10] As a rule, gene deletion correlates with clinical severity and age of presentation, whereas missense mutation of IDS gene alone is responsible for less severe variant.[8] In contrast to this general rule, the missense mutation can also present with variable phenotype and as a fact, clinical severity depends on the location of specific mutation.[6] The index case had X-linked recessive variant (heterozygous) missense mutation c.C1083G (p.Phe 361Leu) of Exon 8 (NM_000202) in the IDS gene along with compound heterozygous variant in NBEAL2 gene and dominant heterozygous missense variant.

Extra medullary haematopoiesis in dermis is seen as blueberry muffin eruptions which are reddish blue or magenta coloured non blanching purpuric lesions. Such extra medullary haematopoiesis occurs as a manifestation of increased demand of haematopoiesis which may be due to loss of cellular blood element or dysfunction of bone marrow. The differential diagnosis of blueberry muffin lesions is huge. In our case the common possible causes of blueberry muffin lesions presenting at birth were ruled out like congenital rubella and cytomegalovirus infections and blood dyscrasias. Some neonatal malignant conditions can also have the similar dermal lesions at birth, as it is seen in congenital monoblastic leukemia. Peripheral blood smear of this baby was not suggestive of malignancy but flow cytometry definitely would have been a better choice for exclusion of haematological malignancy.

Structural alteration and simultaneous presence of more than two mutant alleles in heterozygous variant with dominant expression were presumably responsible for the severity and early presentation in this case. Analysis for X chromosome inactivation was not done due to financial constraints, which could have better explain the reason for early presentation and severity of the disease in this case. Parental genomic sequencing was also not done to find out whether the obtained variant in patient was inherited or de-novo mutation. This was a limitation to this case.

Conclusion

Inborn errors of metabolism should be considered in differential diagnosis of a severely ill new born baby.

We reported this case to promulgate the fact that contrary to presently known genetic substantiation, a missense mutation of IDS gene may also lead to severe and early presentation of MPS II in neonatal age even in a female baby.

References

1. Hunter C. A Rare Disease in Two Brothers. Proc RSoc Med.1917;10:104-16. DOI: https://DOI.org/10.1177/003591571701001833.
2. Sukegawa K, Song XQ, Masuno M. Hunter disease in a girl caused by R468Q mutation in the iduronate-2-sulfatase gene and skewed inactivation of the X chromosome carrying normal allele. Hum Mutat. 1997;10:361-7. DOI: https://DOI.org/10.1002/(SICI)1098-1004(1997)10:5%3C361::AID-HUMU5%3E3.0.CO;2-I.
3. Tuschl K, Gal A, Paschke E, Kircher S, Bodamer OA. Mucopolysaccharidosis type II in females: Case report and review of literature. Pediatr Neurol.2005;32:270–72. DOI: https://DOI.org/10.1016/j.pediatrneurol.2004.10.009
4. Winchester B, Young E, Geddes S. Female twin withHunter disease due to nonrandom inactivation of the X-chromosome: Aconsequence of twinning. Am J Med Genet.1992;44:834–8. DOI: https://DOI.org/10.1002/ajmg.1320440625.
5. Sohn YB, Kim SJ, Park SW. A mother and daughter with the p.R443X mutation of mucopolysaccharidosis type II:Genotype and phenotype analysis. Am J Med Genet. 2010;152:3129–32. DOI: https://DOI.org/10.1002/ajmg.a.33589.
6. Jurecka A, Krumina Z, Żuber Z. Mucopolysaccharidosis Type II in females and response to enzyme replacement therapy. Am J Med Genet. 2012;158:450-4. DOI: https://DOI.org/10.1002/ajmg.a.34415.
7. Pina-Aguilar RE, Zaragoza-Arevalo GR, Isabella RC. Mucopolysaccharidosis type II in a female carrying a heterozygous stop mutation of the iduronate-2-sulfatase gene and showing a skewed X chromosome inactivation. Eur J Med Genet.2013; 56: 159-62. DOI: https://DOI.org/10.1016/j.ejmg.2012.11.006.
8. Khan SA, Peracha H, Ballhausen D. Epidemiology of mucopolysaccharidoses. Mol Genet Metab. 2017;121: 227-40. DOI: https://DOI.org/10.1016/j.ymgme.2017.05.016.
9. Pinto LLC, Maluf SW, Leistner-Segal S, da Silva Z. Are MPS II heterozygotes actually asymptomatic? A study based on clinical and biochemical data, X-inactivation analysis and imaging evaluations. Am J Med Genet. 2011;155:50-7. DOI: https://DOI.org/10.1002/ajmg.a.33770.
10. Schwartz IVD, Pinto LLC, Ribeiro MG. Clinical and Biochemical Studies in Mucopolysaccharidosis type II Carriers. J Inherit Metab Dis. 2009; 32:732–38. DOI: https://DOI.org/10.1007/s10545-009-1275-9.