

Case Report

Lysosomal Storage Disorders Presenting as Non-Immune Hydrops Fetalis: A Case Report

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Abstract

The frequency of NIHF (Non-immunological hydrops fetalis) and congenital ascites associated with LSD (Lysosomal storage disorders) is exceptionally rare. The reported incidence worldwide is about 1% with very limited reports from the MENA (Middle East and North Africa) region despite high incidence of consanguinity in the area. We report a case of NIHF with subcutaneous edema and congenital ascites as the main presenting sign which was diagnosed antenatally; subsequently LSD was diagnosed by enzymatic studies of amniotic fluid cultured cells after ruling out the most common conditions associated with fetal hydrops. A baby girl was delivered by spontaneous vaginal delivery at 33 weeks of gestation with generalized hydrops noted on physical examination. Diagnostic work up including lysosomal enzymes study confirmed the diagnosis of GM1 gangliosidosis. MRI (Magnetic resonance imaging) of the brain confirmed focal areas of hyper intensity with perivascular distribution consistent with dilated VR (Virchow Robin) spaces. LSD are serious and genetic conditions with poor outcome so efforts should be made to institute the best screening strategy in the MENA region because of the high rate of intermarriages. LSD should be considered in the diagnosis of NIHF which is essential for genetic counseling as there is a high chance of recurrence considering the high degree of consanguinity in the region.

INTRODUCTION

Hydrops fetalis defined as an abnormal accumulation of fluid in two or more compartments, including ascites, pleural and/or pericardial effusion and skin edema. Isolated congenital ascites is generally considered as part of the clinical picture of hydrops fetalis. It is a rare condition and predominantly occurs as an initial manifestation of hydrops fetalis in which the severity of peripheral edema is of a mild degree and ascites is the dominant clinical sign. Isolated congenital ascites without hydrops is usually due to intraabdominal disorders while congenital ascites associated with hydrops is usually due to an underlying systemic disorder [1-3].

The incidence of NIHF is reported as 1 in 2000–3000 pregnancies, comprising 85-90% of all described cases. The exact prevalence of hydrops fetalis is difficult to reveal, as many cases are not identified prior to intrauterine fetal death [4,5]. Despite the incidence being very low, NIHF accounts for 3% of the overall prenatal mortality [6-8] and the majority of cases are due to IEM mostly LSD. Several different LSD have been reported as being associated with NIHF and congenital ascites [9-11]

CASE REPORT

A G4P1L1A2 mother known to have type I diabetes on insulin analogues and hypothyroidism on thyroxine was followed-up at the antenatal clinic at our center. Her diabetic control was poor with recurrent admissions for diabetic ketoacidosis. She had one previous Cesarean section for failed induction of labour and the outcome was a live female 3.7 kg. She also had two previous first trimester miscarriages. The antenatal scan at 25 weeks of gestation revealed an isolated finding of abdominal ascites. Unfortunately this progressed to hydrops fetalis at 28 weeks of gestation. The couple was counseled at the fetal medicine unit and an amniocentesis was performed for chromosomal analysis and whole exome sequencing. TORCH infection screening was negative. Poor prognosis was explained to the couple. The mother went into spontaneous labour at 33 weeks of gestation and a live female neonate was born via spontaneous vaginal delivery with Apgar scores of 9/1 and 9/5. Her growth parameters were: Birth weight: 3.390 kg, Head circumference: 30.5 cm, and length: 48 cm.

The baby was evaluated on day 1 of life by the genetic team. Physical examination revealed generalized edema, bitemporal narrowing, puffy face with broad nasal bridge and bilateral epicanthic folds, mild micrognathia with hypertrophied gums, and hypo plastic toe nails with rudimentary 5th toe with very short 5th metatarsal. Dark mongolian spots were seen on low back, right shoulder and arm. Ascites was present. External genitalia were of normal female with vulval oedema. Rest of the general examination was normal.

Echocardiography and ophthalmological examination were normal. Ultrasound abdomen showed non focal hepatosplenomegaly. Analysis of lysosomal enzyme activities in cultivated amniotic cells point to a possibility of GM-1 gangliosidosis. The results of the lysosomal enzymes showed low Beta-galactosidase enzyme level of 0.13 nmol/min/ml (Normal range 1-5). MRI of brain showed decreased brain volume and abnormal sulci and gyri, with an impression of immature brain with prominent occipital horns. Few tiny focal areas of hyper intensity were identified with perivascular distribution consistent with dilated Virchow Robin spaces (Figure 1).

The patient was admitted for one month in the neonatal intensive care unit and was discharged home on NGT feeds and oxygen after being labeled DNR (Do not resuscitate). She died three months after discharge from the hospital.

DISCUSSION

LSD including MPS (Mucopolysaccharidosis); (MPS IVA, MPS VII), Sphingolipidoses, (Sialidosis Galactosialidosis: GM1-gangliosidosis, Niemann-Pick C, Gaucher Type II, Niemann-Pick A, Niemann-Pick C, Farber disease) Lysosomal transport defect (Infantile sialic acid storage disease) and others (Wolman disease and mucopolipidosis) are rare disorders [12].

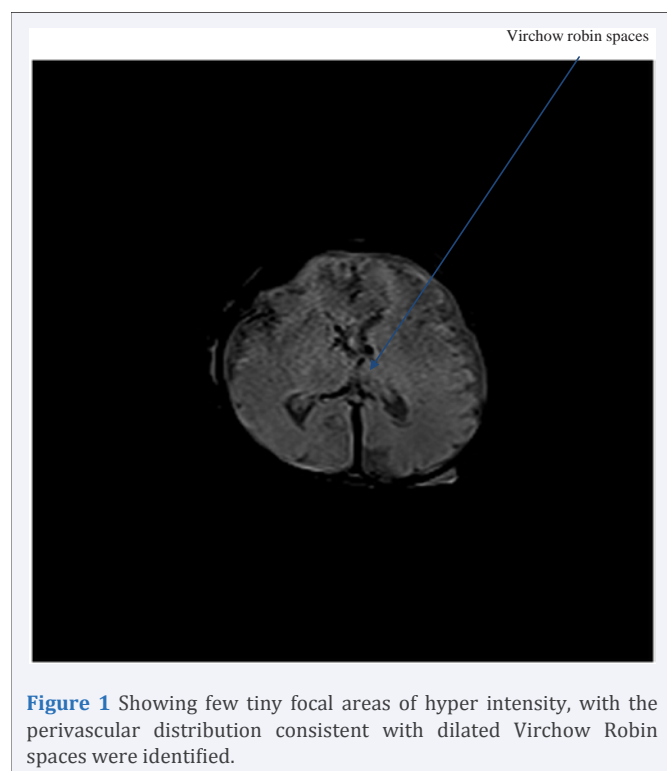


Figure 1 Showing few tiny focal areas of hyper intensity, with the perivascular distribution consistent with dilated Virchow Robin spaces were identified.

Sphingolipidoses account for a substantial proportion of neurometabolic disorders. The sphingolipidoses are genetic diseases which result from the mutation of a gene that is responsible for the production of the lysosomal hydrolases or activator proteins block sphingolipid degradation, leading to accumulation of the enzyme's specific sphingolipid substrate [12]. Glycosphingolipids are vital components of all cell membranes. Failing to metabolize and degrade these substances will result in their accumulation therefore initiating physiologic and morphologic change that produces specific clinical manifestations. GM1-gangliosidosis, was recognized and reported by O'Brien in 1965 for the first time [13]. It is a very uncommon autosomal recessive genetic-metabolic condition, triggered by the absence of the lysosomal enzyme gangliosidase- β -galactosidase which will result in buildup of glycoaminoglycans, oligosaccharides, and particularly GM1-ganglioside [14].

The prevalence of LSD is fluctuating from 12 to 25 per 100,000 live births (Pinto et al., 2004). LSD is autosomal recessive disorders with the exception of Fabry disease, and MPS II, which are X-linked recessive. The exact incidence of LSD in the MENA region is unknown. Al-Gazali et al has identified a mutation in isolated communities and certain tribes with a high degree of consanguinity which is likely to lead to increased disease prevalence in the region [15]. A recent report from UAE has revealed an incidence of 26.9 per 100,000 live births among emirates [15]. The relative incidence of GM1 gangliosidosis is not yet determined in the Omani population but because of consanguineous marriages, environmental and racial resemblances, the prevalence of this disease might be as high in Omani population too.

Ascites was the main presenting sign in our case. There have been prior reports of newborns with GM1 gangliosidosis presenting with NIHF or congenital ascites as the main presenting symptom sign [16,17]. Claeys et al., reported a similar case where he described a new born patient primarily presenting in the antenatal period with significant ascites and the diagnosis of galactosialidosis was only established after birth [18].

GM1-ganglioside significantly accumulates in the brain, liver and spleen. In addition, keratan sulfate- a mucopolysaccharide-accumulates in the liver and is excreted in the urine. Similarly we have seen brain involvement in our case. Virchow robin's spaces were identified in MRI in this case but can occur in various other pathologic conditions, including cystic periventricular leukomalacia, multiple sclerosis, mucopolysaccharidoses, cystic neoplasms, neurocysticercosis, arachnoid cysts, and neuroepithelial cysts [19].

We have to consider the importance of consanguinity in this case since the majority of LSD is inherited as an autosomal recessive disorder. In most of the reported cases the diagnosis was not established but had an antecedent sibling who was affected with the disease. For this reason, in cases of familial NIHF, one should consider the LSDs or other IEM (Inborn errors of metabolism). Despite of high rate of consanguineous marriage in Oman, there was no family history in this case of LSD or NIHF.

Other lysosomal storage disorders including cases of neonatal Sialidosis presenting as hydrops fetalis or with neonatal ascites have been published [20]. Some of the rare mucopolysaccharidosis like MPS IVA (Morquio disease) and MPS

It can also present prenatally with hydrops fetalis [21,22]. Though some of the LSDs tend to present with non immune hydrops or ascites there is great variability in the associated clinical and biochemical manifestations.

Several cases of LSD have been described in the literature with a higher prevalence rate in the Neighboring UAE (United Arab Emirates). The Omani population is ethnically diverse; Oman's presence on the Indian Ocean has established the settlement of many Baluchis along the northern coast as well as intermarriages with East African cultures. Considering the high degree of consanguinity in the country it is possible that the diagnosis of a high proportion of NIHF, and especially of LSD is missed

CONCLUSION

Consanguinity points towards a higher birth prevalence of autosomal recessive disorders which highlights the need for a population based screening program to ascertain the birth prevalence of LSD and subsequently the need for prenatal diagnosis and genetic counseling. This report also highlights the need to establish a genetic database system in all central institutions in the country and the MENA region considering the high incidence of consanguinity. This will therefore help to oversee the healthcare development within the country and the whole region.

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Author's Contribution

Mohamed reviewed the literature and prepared the manuscript and is the corresponding author, Asad helped to draft the manuscript, Khalid and Nihal made a critical reading of the manuscript and participated to revisions, Mariam helped to draft the manuscript.

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