ORIGINAL ARTICLE

"A Tale of 'AR': A Rare All-round Review of Obstetric Autosomal Recessive Disorders"

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Abstract

Aim: The aim of this study was to understand the obstetric management of autosomal recessive (AR) disorders.

Background: Pregnancy is fickle in nature. While it can put a veil on a few diseases and cause their remissions, it can as well unmask several other disorders, making itself a window for diagnosis. Not only does it help salvage the mother from further complications of such disorders but also provides the obstetricians an opportunity to know whether her future progeny, nurturing within her currently, shall be affected by those disorders.

Case description: Hereby, we discuss six cases of rare disorders of autosomal recessive origin in our case series that can possibly cause profound morbidity to both the fetus and the mother.

Conclusion: While not encountered routinely, a knowledge of these goes a long way in securing the loose ends of the finer aspects of maternal and fetal outcomes in maternal autosomal recessive disorders.

Clinical significance: Not only do these disorders cause poor outcomes on their own, but the drugs used to maintain their remissions are also often teratogenic and require reconsideration with astute preconceptional counseling. In lieu of the paucity of literature on this subject, this case series will be an invaluable addition to the obstetric management of autosomal recessive disorders.

Keywords: Autosomal recessive, Bloom syndrome, Dubin–Johnson syndrome, Genetic disorder, Homocysteinemia, Preconception care, Sickle cell disease, Wilson disease.

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Cases

Case 1: Sickle Cell Disease with a Suboptimal Perinatal Outcome

A 22-year-old primigravida came for antenatal booking at 18 weeks of gestation. She was diagnosed with sickle cell disease several years ago and was on hydroxyurea dosed at 500 mg/day which she had consumed during the period of fetal organogenesis as well. She was started on folic acid 5 mg/day, aspirin 75 mg/day, and oral penicillin prophylaxis,[1] and anomaly scan was carried out, which was normal. She was already immunized against capsulated organisms and hepatitis B. Monthly urine cultures were performed to look for urinary tract infections. Renal function was monitored routinely with screening for retinopathy done at booking as well. Echocardiography was done to check for pulmonary hypertension, which showed normal cardiac function. Growth monitoring scans were done for the fetus from 24 weeks of gestation monthly, which showed intrauterine growth restriction, although with normal Doppler studies. Regular blood pressure monitoring was done owing to her increased risk of developing hypertension during pregnancy. She and her partner's hemoglobin electrophoresis was performed to check for partner carrier status and the presence of concomitant other hemoglobinopathies as seen in Figure 1A. Since the partner tested negative for it, invasive prenatal testing was not performed. The patient had an admission at 28 weeks of gestation for a painful crisis, for which she was hydrated and oxygenated well and even transfused with packed red cells. She was started on low molecular weight heparin (LMWH) on admission according to her weight category. The patient had an absence of umbilical artery flows in the Doppler study at 32 weeks of gestation and an emergency cesarean section was done which gave birth to a 900-g fetus, who after shifting to the neonatal intensive care unit (ICU) had a successful outcome later. The baby was tested for sickle cell disease and it showed the presence of sickle cell trait. The mother had an uneventful postoperative course and was continued on LMWH till 6 weeks.

Case 2: Sickle Cell Disease and Spontaneous Miscarriage

A 29-year-old primigravida with a known case of sickle case disease, an autosomal recessive (AR) disorder, diagnosed in childhood, presented to the emergency unit with incomplete abortion. The patient gave a history of bilateral hip joint

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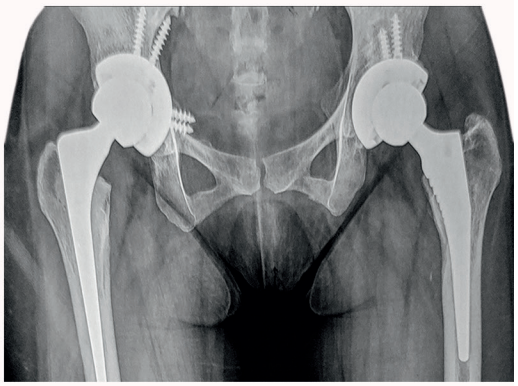
Conflict of interest: None

	Diameter	Parameter	Reference remark	Remark	Limit	Remarks
1	Sickle Cell Disease	S-Band	ND	66.77	%	Positive
		C-Band	ND	ND		
		E-Band	ND	ND		
		F-Band	<–2	1.88		
		D-Band	ND	ND		
		A-Band	60-98	27.92		
2	Sickle Cell Anemia (35-99)	S-Band	ND	66.77	%	Positive
		F-Band	<–2	1.88		
		A-Band	60-98	27.92		
		A2-Band	13-35	3.43		
3	Beta Bilirubinemia	A2-Band	13-35	3.43	%	Negative
		F-Band	<–2	1.88		
		A-Band	60-98	27.92		
4	Variant hemoglobinopathies (C,D,H bart band) including Hb E (Var Hb)	F-Band	<–2	1.88	%	Negative
		C-Band	ND	ND		
		E-Band	ND	ND		
		A-Band	60-98	27.92		
		D-Band	ND	ND		

A



B

Figs 1A and B: Sickle cell disease

replacement as seen in Figure 1B in the past due to avascular necrosis of the hip joint. She also had multiple hospital admissions since childhood due to painful sickling crisis episodes and a splenectomy was done. She was vaccinated against capsulated organisms and was receiving intramuscular penicillin prophylaxis. She currently consumed hydroxyurea at a dose of 500 mg/day and had not stopped it after conceiving. She was provided with preconceptional counseling later regarding the teratogenicity associated with it. Sickle cell disease is caused by a single-nucleotide polymorphism that leads to glutamate-to-valine substitution at position 6, thereby β-globin chains being substituted in hemoglobin A to form hemoglobin S.

Case 3: Bloom Syndrome

A 29-year-old multigravida in a second-degree consanguineous marriage, with two living children on antenatal booking at 15 weeks of gestation gave a history of Bloom syndrome in the first child. Its common variable immunodeficiency led to the recurrent chest and abdominal infections, necessitating monthly hospital admissions for intravenous immunoglobulin administration.[2] The second child was unaffected. Since the proband was recognized, Sanger sequencing was done for the parents for the BLM gene on chromosome 15, which showed both of them to be heterozygous for the condition. Invasive prenatal diagnostic testing was offered and amniocentesis was carried out at 16 weeks of gestation, and target Sanger sequencing and mutation analysis for the same gene revealed the fetus to be heterozygous to this autosomal recessive condition as seen in Figure 2, thereby reassuring the parents of its condition.

Case 4: Wilson's Disease

A 21-year-old primigravida, known case of Wilson's disease for 8 years,[3] on D-penicillamine initially dosed at 500 mg/day and later changed to 250 mg/day till pregnant and zinc sulfate 50 mg/day, presented to our outpatient department for antenatal booking at 17 weeks of gestation. It is an autosomal recessive characterized by ATP7B enzyme deficiency in the liver which leads to the impaired pairing of copper with ceruloplasmin, thereby increasing copper deposition in the body, and excretion through urine (134 μg/24 hours, normal levels: <50 μg/24 hours) and decreased serum ceruloplasmin levels (2.59 mg/dL, normal levels: 14–40 mg/dL). Devoid of any symptoms, the patient's abdomen ultrasound showed splenomegaly with dilated splenic vessels and chronic liver disease. There was also a presence of hyperintense lesions on magnetic resonance imaging (MRI) of various parts of the brain. Ophthalmic examination showed the presence of classical Kayser–Fleischer rings as seen in Figure 3, and neurological examination demonstrated mild dysarthria and moderate ataxia. Since penicillamine is a category D drug during pregnancy, the patient was counseled regarding the same and the consent was taken for the continuation of pregnancy. The patient had a spontaneous vaginal delivery which required a transfusion of platelets due to thrombocytopenia caused by the splenomegaly with normal autoimmune workup, at 37 weeks of gestation and a baby cried immediately at birth. Copper chelation was resumed to pre-pregnancy doses on discharge. Gastroenterology follow-up was done to look for variances, which were absent. Since the partner was tested to be negative for enzyme deficiency, the baby was not tested for it.

Case 5: Dubin–Johnson Syndrome

A 19-year-old primigravida, referred to our hospital at 34 weeks of gestation,[4] with icterus since childhood, not evaluated ever before due to lack of any other distressing symptoms. The patient gave no history of nausea or fever, altered urine or stool color, premonitory symptoms or history of blood transfusions, inadvertent needle stick injury, or illicit drug consumption. On examination, the presence of icterus was seen only on the sclera. On investigating further, the liver function tests showed total hyperbilirubinemia (3.5–4.5 mg/dL consistently) with a predilection to direct bilirubinemia but normal transaminases. Hepatic viral markers, autoimmune and hemolytic workup were

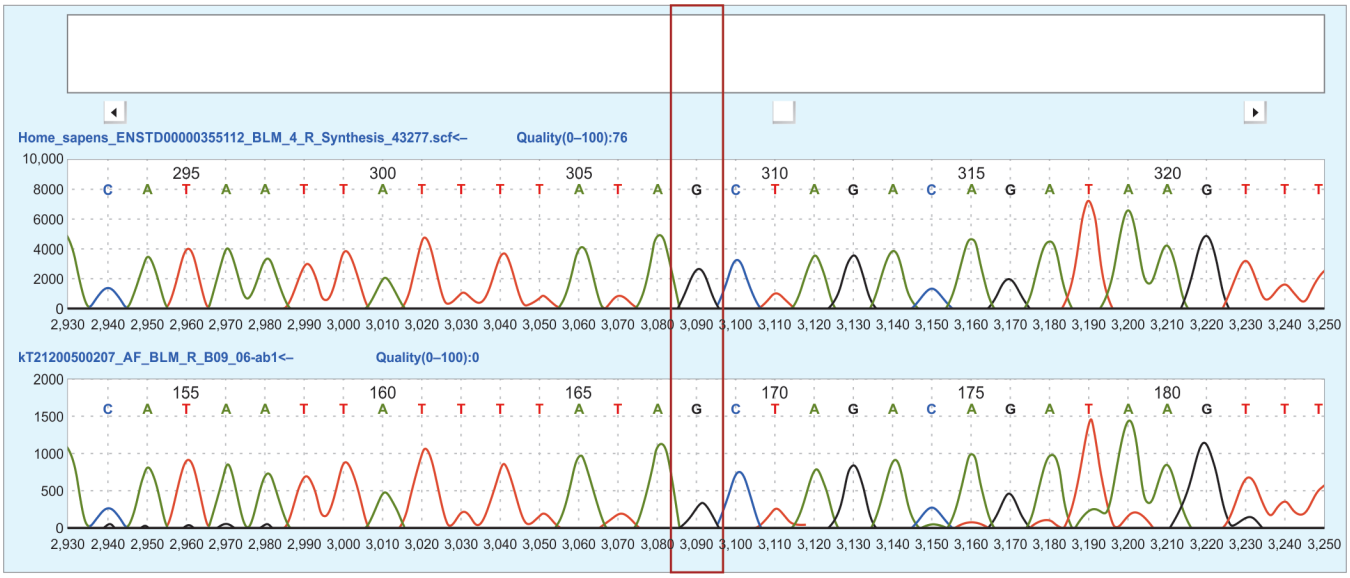


Fig. 2: Prenatal diagnostic testing report for Bloom syndrome

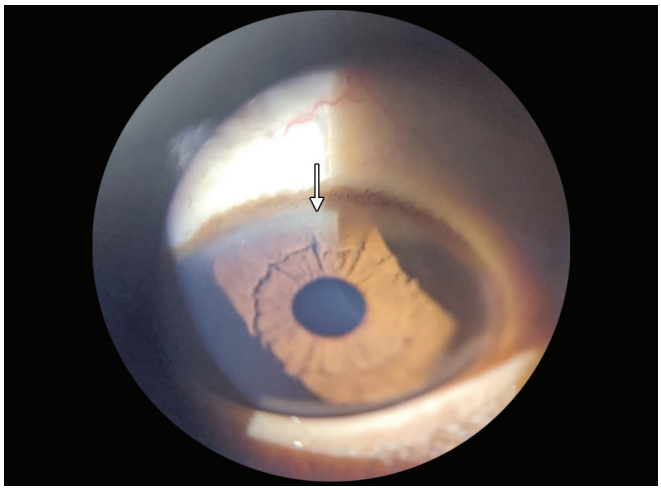


Fig. 3: Kayser–Fleischer (KF) rings seen in Wilson's disease

within normal limits. Ultrasound revealed no organomegaly either. The patient eventually had a spontaneous vaginal birth at term and had a good fetal outcome. A liver biopsy done postnatally showed the presence of staining of the tissue on Masson Fontana staining, which gave us the diagnosis of Dubin–Johnson syndrome as seen in Figure 4. Dubin–Johnson syndrome is an autosomal recessive disorder and is caused by a mutation in the ABCC2 gene. The ABCC2 gene produces a malfunctioning multidrug-resistant protein 2 that leads to impaired conjugated bilirubin excretion. It is a benign disorder that does not require any active intervention unless complicated by a concomitant pregnancy or nonpregnancy-related hepatic disorder.

Case 6: Homocystinuria

A 22-year-old primigravida, with chronic hypertension of unknown cause, presented to our emergency unit in the first trimester with inevitable abortion. After surgical evacuation, the hypertensive component was investigated and the patient had the presence of raised serum homocysteine (110 µmol/L, normal levels: 5–15 µmol/L) and homocystinuria. She was started on antihypertensive agents and pyridoxine, folic acid, and methyl-cyanocobalamin

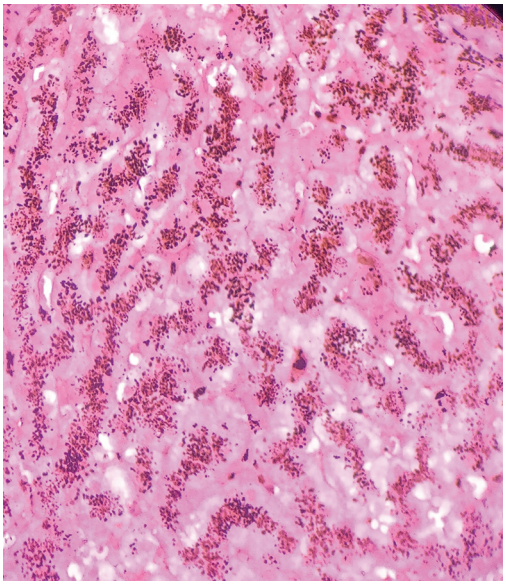


Fig. 4: Masson Fontana staining of liver biopsy for Dubin–Johnson syndrome

supplementation. The patient was later lost to follow-up. Homocystinuria is an autosomal recessive disorder that showed the absence of an enzyme cystathionine β-synthase and more similar enzymes involved in the metabolism of methionine.

Discussion and Conclusion

The above cohort of cases shows various autosomal recessive disorders encountered in our clinical practice. Most, if not all, carry a morbid quality of life for patients, and hence preconceptional genetic counseling that includes discouraging marriages between heterozygotes or homozygotes, or use of preimplantation genetic screening during assisted reproductive techniques serves a massive purpose of preventing propagation of these disorders to subsequent generations. Also, eliciting histories of previous pregnancies in obstetric patients and their fetal outcomes can help us direct the need for prenatal investigations.

To diagnose mendelian disorders, a pedigree chart can help trace and predict the prevalence of these disorders in a family. Not only do a few of these disorders themselves disrupt the quality of life, conditions mentioned above required potentially teratogenic drug consumption like D-penicillamine[5] and hydroxyurea,[6] which requires to be halted 1–3 months prior to pregnancy, or their dosage altered. Since most patients in our study got their antenatal booking done much after the period of organogenesis, a vital process of preconceptional counseling plays a major role in their subsequent pregnancies. Awareness and a mindful approach can thus help from preventing skipping these disorders from diagnosis and make pregnancy a turning point for the future course of maternal health. Table 1 summarizes the cases in a nutshell.

Table 1: Autosomal Recessive Disorders and their Obstetric Outcomes

S. No.	*Diagnosis*	*Investigations*	*Treatment*	*Maternal outcome*	*Fetal outcome*
1.	Sickle cell disease	(a) Complete hemogram (b) Renal function tests (c) Couple hemoglobin electrophoresis (d) Ophthalmic examination for retinopathy (e) Echocardiogram (f) Urine cultures (e) Fetal Doppler scans for growth (g) Fetal anomaly scan	(a) Aspirin (b) Hydroxyurea (c) LMWH (d) Hydration and oxygen therapy (e) Folic acid supplementation (f) Analgesics during painful crisis (NSAIDs avoided) (g) Penicillin prophylaxis (h) Blood transfusion	Emergency cesarean section due to Doppler changes suggestive of fetoplacental insufficiency	Extreme low-birth weight (900 gm), cried at birth APGAR score of 6/10 Prolonged NICU stay, discharged later
2.	Bloom syndrome	Sanger Sequencing done for BLM gene on chromosome 15, for parents and fetus (via amniocentesis)	None required for the mother, affected child required monthly immunoglobulin administration	Still in her antenatal follow-up	Sanger sequencing showed fetus to be heterozygous for Bloom syndrome
3.	Wilson's disease	(a) Complete hemogram (b) Liver function tests (c) Urine copper (d) Serum ceruloplasmin (e) Anti-nuclear antibodies and immature platelet fraction (f) Slit-lamp ophthalmic examination (g) MRI of brain (h) Abdominal ultrasound and Doppler studies (i) Endoscopy for varices (j) Fetal anomaly scan. (k) Partner ATP7B enzyme assay	(a) D-penicillamine (b) Zinc sulfate	Spontaneous vaginal delivery at term with need for transfusion of platelets for thrombocytopenia	Male baby weighing 2.8 kg, cried at birth, APGAR score of 9/10
4.	Dubin–Johnson syndrome	(a) Complete hemogram (b) Liver function tests (c) Antinuclear antibody (d) Antimicrosomal antibody (e) Urine copper and serum ceruloplasmin (f) Abdominal ultrasound (g) Fetal ultrasound for growth monitoring (h) Magnetic resonance cholangiopancreatography (i) Liver biopsy	Trial of ursodeoxycholic acid supplementation was given, without much benefit	Spontaneous vaginal delivery at term	Male baby weighing 2.8 kg, cried at birth, APGAR score of 10/10
5.	Homocystinuria	(a) Serum homocysteine levels (b) Urine homocysteine levels	Supplementation with (a) Folic acid (b) Pyridoxine (c) Methyl-cyanocobalamine	Surgical evacuation for spontaneous inevitable abortion and later lost to follow-up	Aborted in the first trimester
6.	Sickle cell disease	(a) Complete hemogram (b) Renal function tests (c) X-ray of the hip joint	(a) Hydroxyurea (b) Hydration and oxygen therapy (c) Penicillin prophylaxis	Surgical evacuation for spontaneous incomplete abortion	Aborted in the first trimester

APGAR, appearance, pulse, grimace, activity, and respiration; LMWH, low molecular weight heparin; MRI, magnetic resonance imaging; NSAID, non steroidal anti-inflammatory drug

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