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A Case of G6pd Deficiency with Kernicterus

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Abstract:
Background*:G6PD deficiency is the most common enzyme deficiency in humans affecting around 400 million people worldwide. It is inherited as an x linked fashion. The enzyme glucose 6 phosphate dehydrogenase (G6PD) when deficient leads to impaired production of reduced glutathione and predisposes the red cells to damage by oxidative metabolites causing haemolysis.[1]Deficient neonates may manifest clinically with indirect hyperbilirubinemia or even kernicterus*
Case Report:Here is a second born male baby born to non-consanguineous parents, through normal vaginal delivery, cried immediately after birth,Inj. Vitamin K given at birth, started on breastfeeding, baby blood group is O positive and mothers blood group is B positive. Baby was discharged at the end of 24 hours. At 72 hours of life baby presented with features of opisthotonos and seizures with jaundice involving palms and soles.G6PD quantitative assay was done which showedlow levels of the enzyme (48IU) which shows G6PD deficiency mediated kernicterus.
Conclusion: *Early detection of G6PD deficiency in the affected new-born's may be important for reducing the risk of severe hyperbilirubinemia, kernicterus, and the need for exchange transfusion*
Keywords: *G6PD deficiency, jaundice, vitamin k,kernicterus*

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I. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited disorder that may cause neonatal hyperbilirubinemia and kernicterus[2]. G6PD deficiency is the most common enzyme deficiency in humans affecting around 400 million people worldwide.

It is inherited as an x linked recessive fashion. Resurgence of kernicterus is due to less aggressive treatment of jaundice and from unrecognized G6PD deficiency. Kernicterus due to G6PD deficiency is preventable, provided jaundice is detected early and adequate interventions are instituted promptly. The enzyme glucose 6 phosphate dehydrogenase (G6PD) when deficient leads to impaired production of reduced glutathione and predisposes the red cells to damage by oxidative metabolites causing haemolysis.

The prevalence of G6PD deficiency in India varies from 2.3% to 27.0%. Even when, WHO recommends G6PD screening via fluorescent spot test among populations where 3-5 % of males are affected, it is impractical in resource poor developing countries. Deficient neonates may manifest clinically with indirect hyperbilirubinemia[3] or even kernicterus.

As vitamin K may decrease glutathione concentrations in normal infant erythrocytes, it is suggested that it may trigger haemolysis in G6PD deficient infants. The most effective management of G6PD deficiency is to prevent haemolysis by avoiding oxidative stress. Screening programmes for the disorder are undertaken, depending on the prevalence of G6PD deficiency in a particular community.[4]

II. Case Report

Second order male baby born to non-consanguineous parents, through normal vaginal delivery, cried immediately after birth, Inj. Vitamin K given at birth, started on breastfeeding, baby blood group is O positive and mothers blood group is B positive. Baby was discharged at the end of 24 hours. At 72 hours of life baby presented with features of opisthotonos and seizures with jaundice involving palms and soles.

There was no family history of jaundice in either parents or neonatal jaundice in the elder female sibling. On evaluation, CBC and peripheral smear were normal, DCT- negative, bilirubin levels- total bilirubin-34.8mg\dl, indirect bilirubin- 33.8mg\dl. USG abdomen showed mild hepatomegaly, USG cranium showed features of cerebral oedema, Septic screen was negative.Baby received exchange transfusion and phototherapy for 1.5 days. At discharge total bilirubin was 6.5mg\dl and indirect bilirubin was 6mg\dl

At **4months of life**baby evaluated for FTT and abnormal posturing, MRI brain with MRS done and it was normal. In view of persisting neurological issues and normal MRI, G6PD quantitative assay was done which showedlow levels of the enzyme (48IU) and**clinical exome sequencing** was done which showed **G6PD deficiency** (exon 3- variant c.131C>G, hemizygous)

MedGenome Labs Ltd.
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MEDGENOME

DNA TEST REPORT - MEDGENOME LABORATORIES

Full Name / Ref No:	[redacted]	Order ID/Sample ID:	254838/575188
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	4 months	Date of Sample Collection:	8th March 2021
Referring Clinician:	Dr. T. Vasanthi, Kanchi Kamakoti Child Trust Hospital, Chennai	Date of Sample Receipt:	9th March 2021
		Date of Order Booking:	9th March 2021
		Date of Report:	5th April 2021
Test Requested:	Clinical Exome		

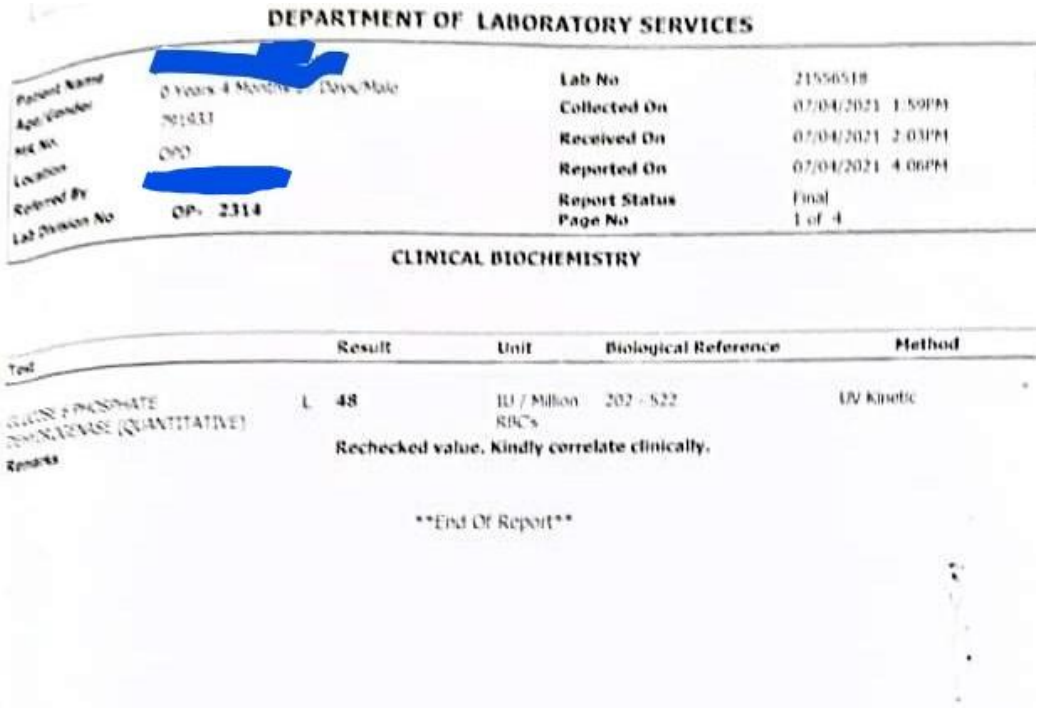
CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

[redacted] born of a non-consanguineous marriage, presented with clinical indications of dystonia, athetoid movements, severe opisthotonus and stridor. He has a history of neonatal jaundice and increased bilirubin on day 5 of life. He is suspected to be affected with bilirubin encephalopathy or mitochondrial or neurometabolic disorder or post keenicteric sequelae and has been evaluated for pathogenic variations.

RESULTS

PATHOGENIC AND LIKELY PATHOGENIC VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE WERE DETECTED

Gene (Transcript) *	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
G6PD (-) (ENST00000393562.10)	Exon 3	c.131C>G (p.Ala44Gly)	Hemizygous	Hemolytic anemia, G6PD deficient (favism)	X-linked dominant	Pathogenic



DEPARTMENT OF LABORATORY SERVICES

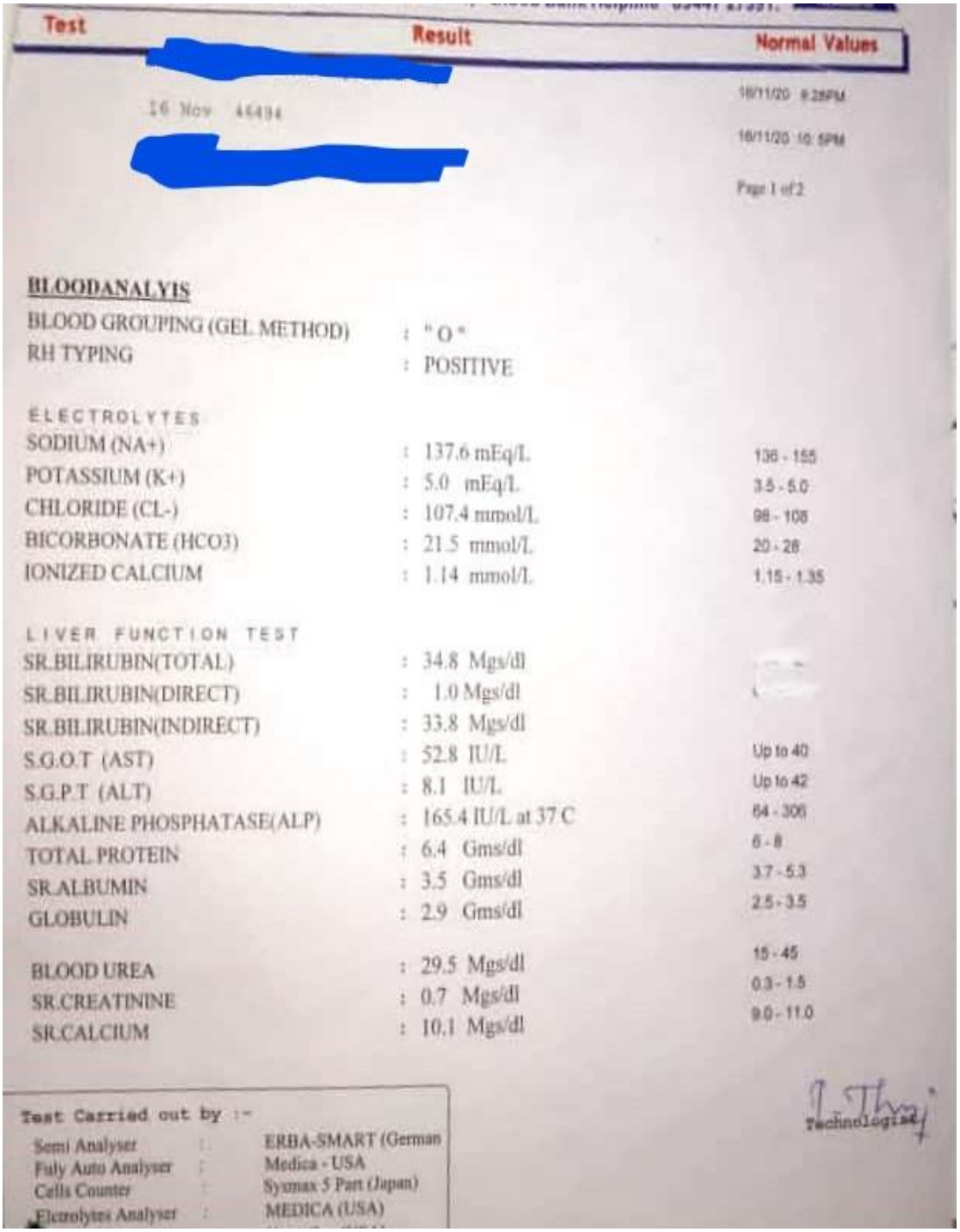
Patient Name	[redacted]	Lab No	21556518
Age/Gender	0 Years 4 Months 7 Days/Male	Collected On	07/04/2021 1:59PM
MR No	501433	Received On	07/04/2021 2:03PM
Location	OPD	Reported On	07/04/2021 4:06PM
Referred By	[redacted]	Report Status	Final
Lab Division No	OP- 2314	Page No	1 of 4

CLINICAL BIOCHEMISTRY

Test		Result	Unit	Biological Reference	Method
GLUCOSE 6 PHOSPHATE DEHYDROGENASE (QUANTITATIVE)	L	48	IU / Million RBCs	202 - 522	UV Kinetic

Remarks: **Rechecked value. Kindly correlate clinically.**

End Of Report



Test	Result	Normal Values
[redacted]		
16 Nov 46434		16/11/20 9:28PM
[redacted]		16/11/20 10:5PM
		Page 1 of 2

BLOODANALYIS

BLOOD GROUPING (GEL METHOD)	: "O"	
RH TYPING	: POSITIVE	
ELECTROLYTES		
SODIUM (NA+)	: 137.6 mEq/L	136 - 155
POTASSIUM (K+)	: 5.0 mEq/L	3.5 - 5.0
CHLORIDE (CL-)	: 107.4 mmol/L	98 - 108
BICORBONATE (HCO3)	: 21.5 mmol/L	20 - 28
IONIZED CALCIUM	: 1.14 mmol/L	1.15 - 1.35
LIVER FUNCTION TEST		
SR.BILIRUBIN(TOTAL)	: 34.8 Mgs/dl	
SR.BILIRUBIN(DIRECT)	: 1.0 Mgs/dl	
SR.BILIRUBIN(INDIRECT)	: 33.8 Mgs/dl	
S.G.O.T (AST)	: 52.8 IU/L	Up to 40
S.G.P.T (ALT)	: 8.1 IU/L	Up to 42
ALKALINE PHOSPHATASE(ALP)	: 165.4 IU/L at 37 C	64 - 306
TOTAL PROTEIN	: 6.4 Gms/dl	6 - 8
SR.ALBUMIN	: 3.5 Gms/dl	3.7 - 5.3
GLOBULIN	: 2.9 Gms/dl	2.5 - 3.5
BLOOD UREA	: 29.5 Mgs/dl	15 - 45
SR.CREATININE	: 0.7 Mgs/dl	0.3 - 1.5
SR.CALCIUM	: 10.1 Mgs/dl	9.0 - 11.0

Test Carried out by :-

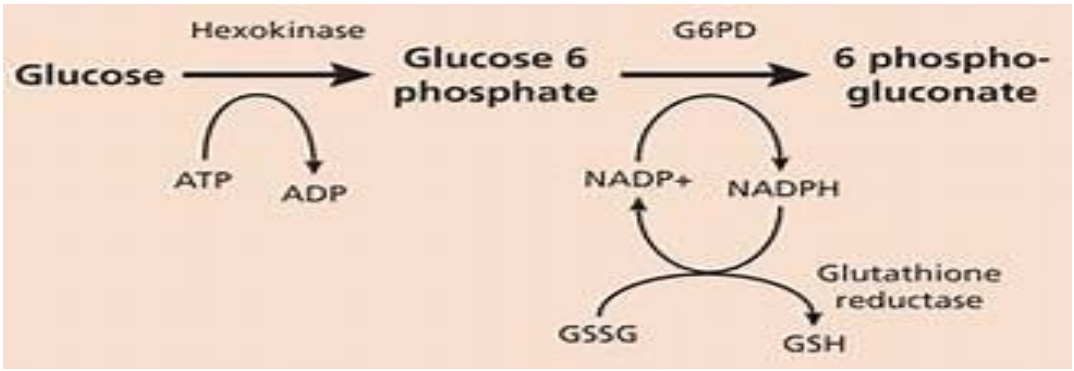
Semi Analyser	:	ERBA-SMART (German
Fuly Auto Analyser	:	Medica - USA
Cells Counter	:	Sysmax 5 Part (Japan)
Electrolytes Analyser	:	MEDICA (USA)

Technologist

III. Discussion

G6PD deficiency is an X-linked disorder resulting from an alteration or mutation of the G6PD gene located at the distal end of the long arm of the X chromosome [5,6].About 140 mutations have been described, most are single base changes, leading to amino acid substitutions.

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme that catalyses the first reaction in the pentose phosphate pathway, providing reducing power to all cells in the form of NADPH.The conversion of NADP to NADPH is critical to produce glutathione, an important antioxidant that helps protect erythrocytes against oxidative stress[7].Reticulocytes have five times higher G6PD Enzyme activity than oldest erythrocytes.



WHO Classification of G6PD variants into **FIVE** classes

Class	Severity	Enzyme Activity
Class 1	Severe enzyme deficiency with chronic non spherocytic haemolytic anaemia	<10% of Normal
Class 2	Severe enzyme deficiency	<10% of Normal
Class 3	Moderate to Mild enzyme deficiency	10-60% of Normal
Class 4	Mild or no enzyme deficiency	60-100% of Normal
Class 5	Increased enzyme activity more than twice normal	>100% of Normal

The most common clinical features of G6PD deficiency usually presents as
1)Drug-induced or infection-induced acute haemolytic anaemia
2)**Favism**
3) Neonatal jaundice
4) Chronic non-spherocytic haemolytic anaemia
5) Kernicterus.

1)Drug-induced or infection-induced acute haemolytic anaemia
The Severity of the haemolytic episode induced by a particular drug depends on its dose. It is self-limiting haemolysis, commencing in 2-3 days lasting for 7days followed by a return of haemoglobin value to normal after 20-30 days despite continuous drug administration.
Administration of vit k -3 and application of henna[11] over abdomen and legs triggers the haemolysis in G6PD deficiency patients

Antimalarial	primaquine
Sulfonamides	Sulfacetamide Sulfamethoxazole Sulfapyridine Sulfasalazine
Antibiotics	Nitrofurantoin Nitrofurans
Analgesics	Acetanilide

2)Favism[9]:causes acute haemolytic anaemia, haemoglobinuria usually around 24 hr after the bean's ingestion. Favism[6] most frequently associated with the Mediterranean variant of G6PD deficiency

3)Neonatal jaundice: The principal cause neonatal icterus in G6PD-deficient infants is inability of the liver to adequately conjugate bilirubin. One third of all male new-born babies with neonatal jaundice haveG6PDdeficiency; less common in female neonates with jaundice, usually seen in 1 -4 days of life. Kernicterus is seen in Mediterranean and Chinese infants. The relationship between G-6-PD deficiency and jaundice in the new-born period is well recognized

4)Kernicterus[8]: Kernicterus is a severe neurological condition, caused by bilirubin-induced damage in the basal ganglia. The neurological outcome is often poor.Neurotoxic agent is free unconjugated bilirubin.in the Central Nervous System, neither high Total Serum Bilirubin (TSB) nor high serum Unconjugated Bilirubin (UCB) are the relevant neurotoxic agents[12]. The characteristic signs of kernicterus are jaundice associated with lethargy and

poor sucking, followed by seizures, choreoathetosis, spasticity, and high-pitched cry**. Increasing incidence of kernicterus all over the world is mainly due to unrecognized G6PD deficiency and early discharge from hospital after birth.**

Screening tests[10]: The principle of the test to demonstrates the presence or absence of G6PD by testing it ability of RBCs to generate NADPH from NADP, a reaction that directly depends on the availability of G6PD

1) Brilliant Cresyl Blue Dye Test
2) Methaemoglobin Reduction Test
3) Fluorescent Spot Test

Enzyme Assay: The enzymatic activity of G6PD can be assessed by quantitative spectrophotometric analysis

Genetic Analysis- Clinical exome sequencing

Avoiding neurological damage is the driving force behind understanding, screening, preventing and treating neonatal hyperbilirubinemia.Early assessment of G6PD activity may provide an etiologic diagnosis for neonatal jaundice. WHO recommends neonatal screening of cord blood samples in populations where G6PD deficiency is common[1n.] Screening of cord blood for G6PD deficiency will improve awareness among families and health care professionals due to danger of severe hyperbilirubinemiaandfacilitates earlier treatment.

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