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Sporadic Cause of Hemolytic Anemia - A Case Report

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Abstract: ***Hemoglobin J (Hb J) is a rare variant of normal hemoglobin (Hb A) that belongs to distinct group of fast moving Haemoglobin (FMH). It is identified by its unique fast movement on Alkaline Gel Electrophoresis, towards anode when compared with the normal Hb A. Hb J can be differentiated and identified solely from its retention time. Though Hb J cases are often clinically silent, most of them are detected during routine screening or in conjunction with other hemoglobinopathies. Sometimes they can present with life threatening anemia requiring medical intervention. Most often Hb J is associated with other disorders like alpha thalassemia or other hemoglobin variants. We present here a case report of isolated HbJ which is diagnosed after thorough evaluation for recurrent anemia. This is probably first case of Hb J to be reported from our region. This case report demonstrates the need of in - depth evaluation of a case of recurrent anemia.***

Keywords: Fast Moving Haemoglobin, Hb J, Hemoglobin J, Coombs Negative Hemolytic anemia, Recurrent Anemia, Hemoglobinopathy

1. Case Report

A 19yr old male presented with complaints of progressive generalized weakness, intermittent episodes of headache, palpitations and easy fatigability since 1 1/2yrs and shortness of breath, which is worsening on exertion since few weeks. No history of pica, melena, cough and chest pain. His past history is significant for undergoing blood transfusion for anemia elsewhere without complete evaluation for anemia. He is born into a consanguineous marriage, with his elder sibling free from any complaints. His vitals are stable except for resting tachycardia. General examination revealed gross pallor. His systemic examination was unremarkable.

Further Lab workup - Hemogram showed Bicytopenia (microcytic hypochromic anemia and leucopenia) with relative lymphocytosis and thrombocytosis. Reticulocyte count and LDH were elevated. Sickling test, Direct and Indirect Coombs test were negative. Osmotic fragility test, iron studies, ESR, serum vitamin B12, Folic acid levels, Renal, Thyroid, Liver function tests and Complete Urine examination were within normal limits. Stool for occult blood was negative. Stool for ova, cyst and parasites were negative.

CT brain study was normal. Ultrasound whole abdomen study showed horseshoe kidney with fused lower poles. Bone marrow aspiration was suggestive of erythroid hyperplasia [Fig.1]. With a provisional diagnosis of Coombs negative hemolytic anemia, an HPLC (High Performance Liquid Chromatography) was performed showing a **P3 peak** at a retention time of 1.73 minutes [Fig 2&3] with slightly decreased Hb A2 levels (1.5%) [N – 2 - 3%], suggesting the diagnosis of Hb J (an alpha chain variant). Presence of rare Hemoglobin J and horse shoe kidney implies congenital nature. DNA analysis and Parental screening which were advised for definite diagnosis could not be performed due to financial constraints. He was treated conservatively with oral hematinics and blood transfusions and he improved well.2 months follow up he is doing fine and his hemoglobin is stable.

Lab reports:

Blood Tests	Value	Biological Reference Interval
Hemoglobin	**4.6**	13.00 - 17.00 g/dl
MCV	**59**	80.00 - 100.00 fl
MCH	**16**	27.00 - 32.00 pg
MCHC	**25.3**	32.00 - 35.00 g/dl
Total count	**3100**	4.00 - 10.00 thou/mm^3
Platelet count	**5, 00, 000**	150.00 - 450.00 thou/mm^3
ESR	10	0 - 20mm/1^{st} hr
Serum B12	334	191 – 663 pg/ml
Serum Folic acid	7.5	>5.38 ng/ml
Serum Uric acid	4.8	2.4 – 5.75 mg/dl
Total Bilirubin	0.80	<1.2 mg/dl
Indirect Bilirubin	0.30	<1 mg/dl
SGOT	15	<40 U/L
SGPT	18	<41 U/L
PCV	25	40.00 - 50.00 %
Serum Iron	95	65.00 - 175.00 µg/dL
TIBC	292	250.00 - 425.00 µg/dL
Transferrin saturation	25	20.00 - 50.00 %
LDH	**356**	<248 U/L
Reticulocyte count	**4.5**	0.5 - 2.5%
TSH	3.2	0.4 - 4.0 mIU/L

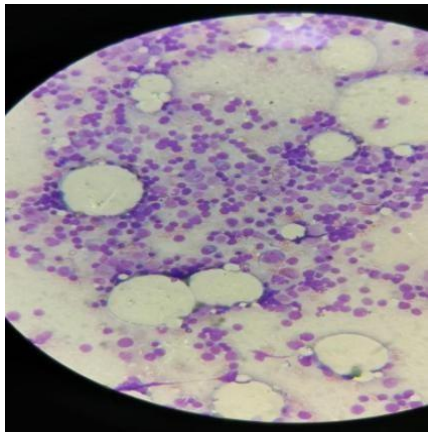

Figure 1: Bone marrow aspiration showing normoblastic erythroidhyperplasia

Peak Name	Calibrated Area %	Area %	Retention Time (min)	Peak Area
P1	---	0.5	0.80	6781
Unknown	---	0.3	1.02	4138
F	1.5	---	1.15	19623
P2	---	5.4	1.34	70887
P3	---	26.4	1.73	343968
Ao	---	64.4	2.43	840188
A2	1.5	---	3.66	18603
			Total Area:	1,304,188

Fig. 2

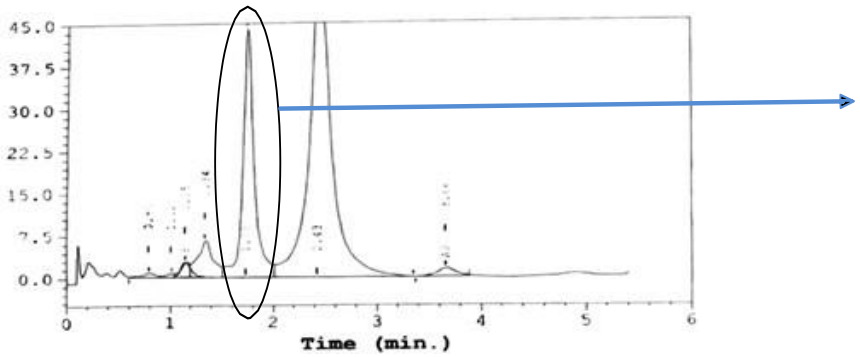

Fig. 3

Abnormal Haemoglobin StudiesHb VariantsBlood
(EDTA Whole Blood)

Investigation	Observed Value	Unit	Biological Reference Interval
Foetal Haemoglobin (HbF)	1.5	%	0.0-2.0
Haemoglobin A0 (Hb A0)	70.6	%	94.3-98.5
Haemoglobin A2 (HbA2)	1.5	%	1.5-3.7
Other	26.4		
Impression	An abnormal Hb (26.4%) identified at retention time (1.73 mins) Most likely suggestive of HbJ (an alpha chain variant) Advice : DNA analysis and parental screening for definite opinion.		
Comment	See Remark 1 and 2.		
Method	HPLC		

2. Discussion

Most common genetic cause of anemia was Hemoglobinopathies. The cumulative gene frequency of hemoglobinopathies in India is 4.2%.1 Hemoglobin is composed of heme, which made up of iron with porphyrin rings and globin chains, which are made up of two alpha and two non - alpha chains. Numerous variants of hemoglobin have been described which are primarily due to changes in the amino acid composition of the alpha and beta chains. Hemoglobin J is one of such variants, and it itself has 71 further variants defined by changes in their amino acid composition.2 Most cases of Hb J are clinically silent and mostly discovered incidentally during routine investigations or in conjunction with other hemoglobinopathies such as thalassemia and sickle cell anemia[3] while investigating these diseases, or accidentally during family or antenatal screening by alkaline gel electrophoresis and/or CE - HPLC [Cation Exchange - High Performance Liquid Chromatography].

Hemoglobin (Hb) J derived its name as “Fast Moving Hemoglobin (FMH) ” due to its characteristic fast anodal movement compared to Hb A on gel electrophoresis. It results from a mutation leading to substitution of a negatively charged amino acid in the α, β, or ϒ globin chain[2]. Fast - moving hemoglobin’s are a heterogenous group of rare hemoglobin variants which belong to hemoglobin J family comprising of Hb J Meerut/Hb J

Birmingham (a) [4], Hb J - Bangkok (b) [5], Hb J Baltimore (b) [6], to name a few. Oscar A. Throup and his colleagues assigned the name Hemoglobin J, while studying this characteristic feature[7]. Population studies conducted showed only nine out of a total of sixty thousand[8] and one out of twenty - six hundred[9] had hemoglobin J, thus, depicting rarity of Hb J. Hemoglobin J reported from Meerut India shows the mutation of 120th alanine to glutamic acid on alpha chain (a 120 Ala - Glu). Blackwell et al. first reported this Hb variant in two sisters from Meerut, India.1[0] Hemoglobin J was also reported from Chhattisgarh, Central India as revealed by Lingojwar and coworkers in 2016.

Electrophoresis is the standard screening test for detecting hemoglobin variants in many laboratories especially in developing countries. Though these hemoglobin's are detected and quantitated by CE HPLC by their characteristic Retention Times (RT's); their fast moving nature is demonstrable only on alkaline gel electrophoresis at pH 8.6.1[1] Thus, both these techniques are mutually complimentary in detection, quantitation, and nomenclature of the hemoglobin variant. CE - HPLC stands as a standard for these hemoglobin variants differentiations. Hb J presents as elevated P3 peak on HPLC, while thalassemia is detected by the presence of eluted proteins at the retention time between 0 and 1 minutes. P3 peak up to 6% is considered normal, values 6%–12% indicates suboptimal specimen and values greater than 15% indicates Hb J. Anemia when associated with HbJ should be searched for concomitant hemoglobinopathy.

Glycosylated hemoglobin (HbA1C), though not generally considered as true fast hemoglobin variants, should be kept in mind as it can occur in uncontrolled diabetes mellitus patients which can mislead to a diagnosis of FMH's.1[2] A CE - HPLC can differentiate it from inherited FMH's by their characteristic RT's. Many other alpha - and beta - globin chain variants can also lead to elevated P3 peak, (HbJ Mexico, HbJ Oxford, HbJ Paris, HbJ Baltimore and HbJ Bangkok) and are distinguished based on the differences in retention time.1

Although the HbJ variant carries little clinical significance, it is important to be aware of this abnormal Hb variant, which may sometimes present as falsely low values of HbA1c in diabetic patients.

3. Conclusion

To Conclude Hb J is a rare variant of hemoglobin, the research is going on fast pace. Till now 71 new variants are identified. On most of the occasions Hb J is clinically silent. Sometimes it may present with severe anemia from hemolysis. CE - HPLC is the standard method for diagnosing and differentiating hemoglobin variants where Hb J presents as a P3 peak. Whenever encountered a case of anemia with Hb J, we should look for a concomitant hemoglobinopathy or the presence of unstable hemoglobin. This case prompts us to consider of Hb J as a potential cause when evaluating for cause of anemia.

Financial Disclosures: None

Conflicts of Interest: None

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