Hb-H disease-A diagnostic challenge

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- The α -thalassemia syndromes are among the most common single-gene disorders with more than 20% of the world population to be a carrier of some form of α –thalassemia, as estimated by The World Health Organization (WHO).
- Alfa thalassemia is very common in South East Asia, Middle East and South Asia such as India, Pakistan and Srilanka.

Table 1. Prevalence of haemoglobinopathies and populations at high risk

Haemoglobinopathy	High risk ethnic populations	Carrier frequency
β-thalassaemia	• Middle Eastern • Southern European • Indian subcontinent • Central and Southeast Asian • African	One in 5 to one in 12
α-thalassaemia	• Chinese • Southeast Asian • Southern European • Middle Eastern • Pakistani • African • Pacific Islander • Maori • Some Indigenous Australians in the Northern Territory and northern Western Australia	Approximately one in 20
Sickle cell disease	• African • African American • Middle Eastern • Southern European • Indian subcontinent • South American • Caribbean	Up to one in 4

- Hb H disease can occur if α^0 thalassemia (α α/--) is prevalent in the population.
- α^0 thalassemia is widely prevalent in South East Asia and India.
- A large number of individuals with HbH or even hydrops fetalis are reported in Pakistani and Iranian families.
- Extensive studies -conducted in India,Thailand and Malayasia regarding alfa thalassemia including genotype studies

- Thalassemia is a very neglected problem in our country
- Alpha-Thalassemia is probably a common genetic disorder in Bangladesh and Hb H disease is also prevalent.
- However, no comprehensive data is available.
- After Medline search we failed to find any case report on Hb H disease or HbBart's hydrops fetalis.

- Here we are reporting few cases of Hb H disease attending our centre (department of hematology, DMC&H)with chronic anaemia that were subsequently diagnosed as Hb H disease.

Case Study: Patient-1

- 34 years male developed high grade fever, continuous in nature,Tmax-105^0 F,
- Noticed yellow discoloration of the urine for the last 5days.
- He took antibiotic without prescription but developed extreme fatigue and got admitted in a specialized private hospital and treated in ICU.
- He was evaluated previously for elevated indirect bilirubin and was labelled as Gilberts Syndrome.
- Hb electrophoresis on 2 occasions were normal

Case Study: Patient-1…..cont

Investigation revealed

Hb 2.6 gm/dl,

S.bili-3.6mg/dl, with In bili 3.3

SLDH-1534U/L

Retics-0.13%(in autoanalyzer),

Film-microcytic hypochromic cells with anisocytosis,tear drop cells and occasional schistocytes.

Direct Coombs-negative,

Hb electrophoresis normal.

He received several unit of BT and antibiotics condition improved and discharged

He was referred to our hematology OPD for evaluation of his anemia and was diagnosed as a case of Hb H disease

Case Study:Patient-2

- 42 years female was referred from dept of Medicine for evaluation of MHA. She has been suffering for the last 9 years, not responding to oral & IV iron therapy & recently developed increasing fatigue, abdominal fullness and early satiety.
- Hb electrophoresis on multiple occasions were normal

Case Study: Patient-3

36 years female visited Gynae &Obs with 7 weeks pregnancy for MR.

She was found to have severe anemia and was referred to our OPD for evaluation.

On query she said, she developed severe anemia during her previous(2) pregnancies & her Hb dropped in spite of taking regular oral iron/folic acid replacement.

She was infused 4 unit RCC in her last pregnancy (4 years back)

In between her pregnancies she was asymptomatic.

Case Study: Patient-4

- An 18 years old boy visited our OPD with fever, cough and anemia.

  At 13 years of his age he had high fever & became severely anemic & got 4 unit BT. Since then, he got easily fatigued but didn’t receive any transfusion.

Summary of Clinical feature

Sl NO	Anemia	Jaundice	Skeletal change	Growth	Liver	Spleen
Pt-1	++	++	Mild facial change	Normal	Not palpable	6 cm
Pt-2	+++	Nil	Not apparent	Normal	Not palpable	9 cm
Pt-3	++	Nil	Not apparent	Normal	Not palpable	3 cm
Pt-4	+++	Nil	Not apparent	Normal	3 cm	6 cm

Summary of hematological feature

Sl NO	Hb% gm/dl	RBC NO	MCV	MCH	MCHC	RDW-CV%	Rtics%	Hb H inclusion body%
Pt-1	7.7	4.01	71	19	26.7	23.6	6%	40%
Pt-2	8.6	4.82	63	18	28	26	4.8%	30%
Pt-3	7.1	3.61	71.5	19.7	27.5	23.2	4.3%	40%
Pt-4	8.1	3.76	82.7	21.5	26	26	6%	50%

Hb Electrophoresis(gel)

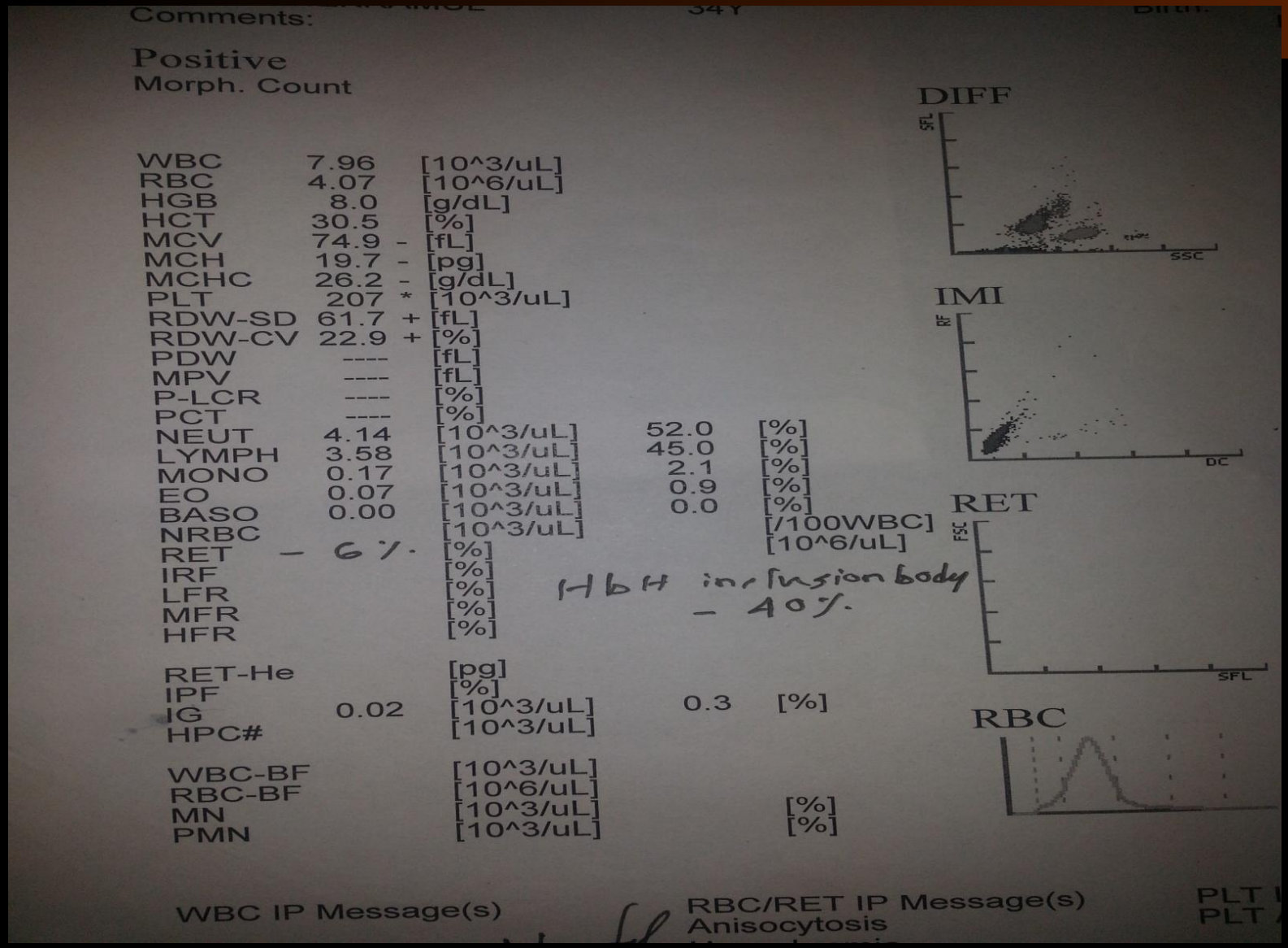
Sl NO	Hb A2	Hb F	Hb A	Hb H
Pt-1	1.8	<1	98.2	Not found
Pt-2	1.5	<1	98.5	Not found
Pt-3	1.3	0	98.7	Not found
Pt-4	1.1	<1	98.9	Not found

Hb Electrophoresis(Capillary)

Sl NO	Hb A2	Hb F	Hb A	Hb Barts	Hb H
Pt-1	1.1	0	94.5	0	4.4
Pt-2	1.1	<1	98.4	0	6.5
Pt-3	0.9	0	87.8	1.0	10.3
Pt-4	1.1	0.4	94.5	1.6	2.4

Picture of Pt-4

CBC of Hb H disease



Comments:

Positive
Morph. Count

WBC	7.96		[10^3/uL]		
RBC	4.07		[10^6/uL]		
HGB	8.0		[g/dL]		
HCT	30.5		[%]		
MCV	74.9	-	[fL]		
MCH	19.7	-	[pg]		
MCHC	26.2	-	[g/dL]		
PLT	207	*	[10^3/uL]		
RDW-SD	61.7	+	[fL]		
RDW-CV	22.9	+	[%]		
PDW	----		[fL]		
MPV	----		[fL]		
P-LCR	----		[%]		
PCT	----		[%]		
NEUT	4.14		[10^3/uL]	52.0	[%]
LYMPH	3.58		[10^3/uL]	45.0	[%]
MONO	0.17		[10^3/uL]	2.1	[%]
EO	0.07		[10^3/uL]	0.9	[%]
BASO	0.00		[10^3/uL]	0.0	[%]
NRBC			[10^3/uL]		[/100WBC]
RET	— 6 %.		[%]		[10^6/uL]
IRF			[%]		
LFR			[%]		
MFR			[%]		
HFR			[%]		
RET-He			[pg]		
IPF			[%]		
IG	0.02		[10^3/uL]	0.3	[%]
HPC#			[10^3/uL]		
WBC-BF			[10^3/uL]		
RBC-BF			[10^6/uL]		
MN			[10^3/uL]		[%]
PMN			[10^3/uL]		[%]

HbH inclusion body
— 40%.

DIFF
SFL
SSC

IMI
RF
DC

RET
FSC
SFL

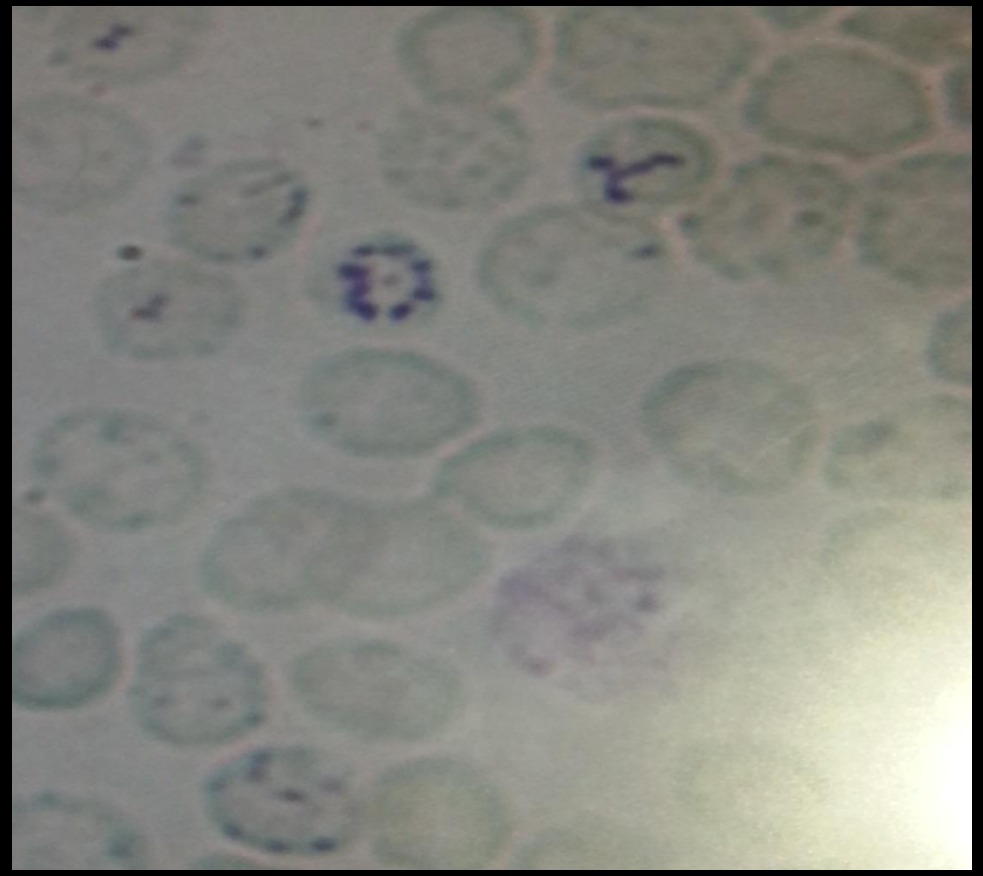
RBC

WBC IP Message(s)

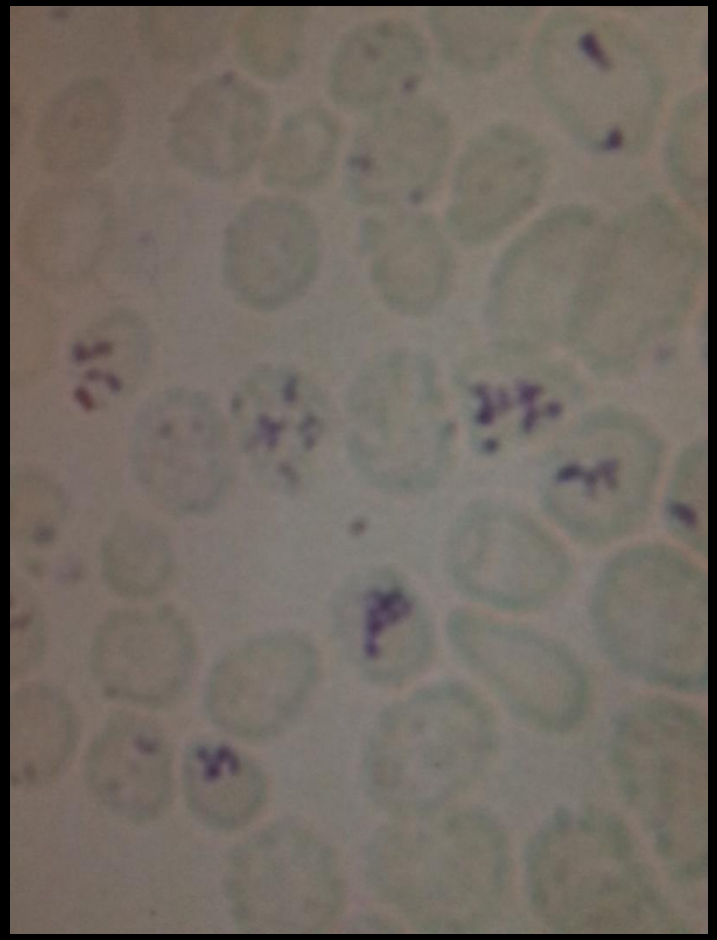
RBC/RET IP Message(s)
Anisocytosis

PLT
PLT

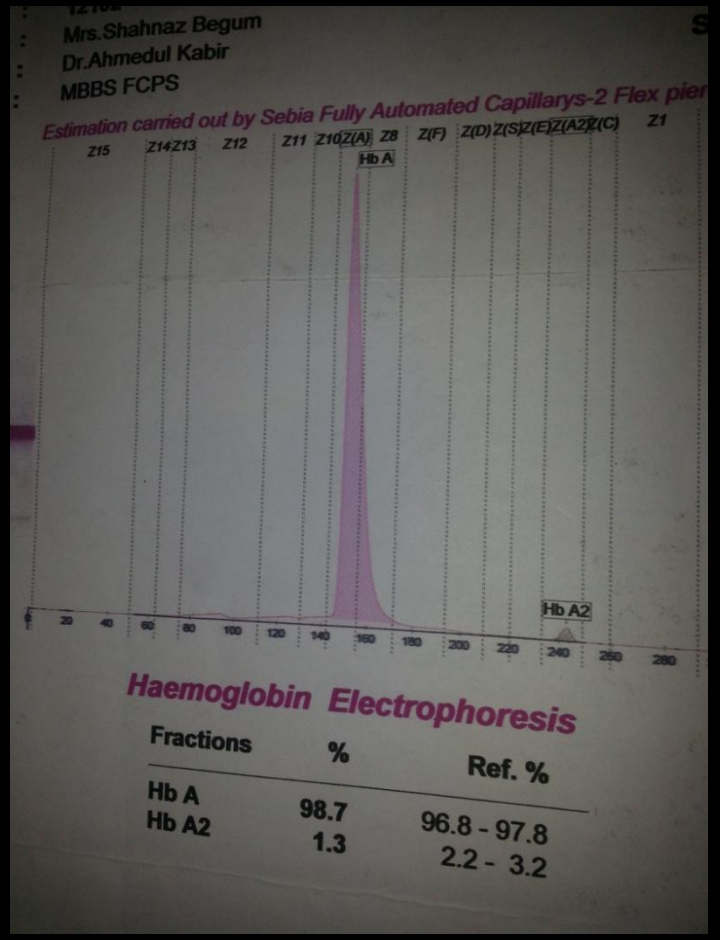
Hb H inclusions



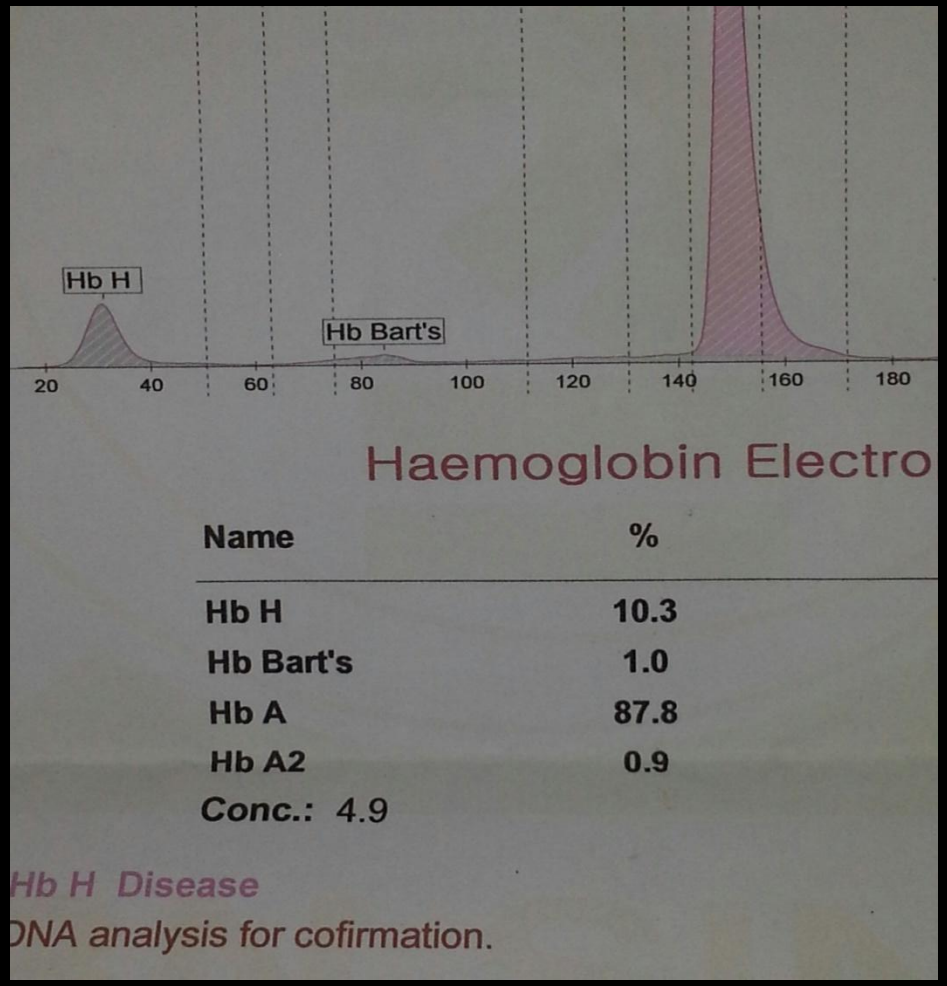
Hb H inclusions



Hb Electrophoresis(gel)



Hb Electrophoresis(capillary)



Discussion

- Hemoglobin H (Hb H) disease is the most common form of thalassemia intermedia
- Hb H disease results from double heterozygosity for α^0-thalassemia and deletional α^+-thalassemia from single α-globin gene deletions (--/–α).
- Hb H disease may occur from interactions between α^0-thalassemia with non-deletional mutations ($\alpha^T\alpha$ or α^T)

Discussion

α Thalassemia genetics:

- Deletion of one or more alpha genes from chromosome 16
- -α/αα: silent career with little signs
- --/αα: cis double deletion more common in SEA
- -α/-α: trans double deletion
- --/-α: Hb H disease
- --/--: Hb Bart's hydrops fetalis
- Hb Constant-Spring: elongation (discovered in Kingston, Jamaica; 2% of Thai have it)

Discussion

Pathogenesis

- Compound heterozygotes for α^0- and α^+-thalassemia (--/–α) with only one functional α globin gene
- Have a severe imbalance in globin chain synthesis.
- The excess β globin chains precipitate.
- Form a characteristic abnormal hemoglobin H (Hb H) or β globin tetramer (β_4).
- This causes a phenotype of mild to moderate chronic hemolytic anemia
- Characterized by Hb H inclusion bodies in the peripheral blood cells.

Discussion

Pathogenesis……cont

- Hb H inclusions bind with band 3 protein of the RBC cell membrane and causes damage
- Infections, pregnancy and intake of certain oxidant drugs increases Hb H inclusions leading to hemolysis.

Discussion

Clinical Presentation

- Clinical severity is widely variable
- Almost asymptomatic to a lethal hemolytic anemia
- Sometimes life threatening episode
- Requiring urgent blood transfusions
- Specially during times of infection, stress and pregnancy.

Discussion

All those cases had

- MHA with very high RDW-CV, like iron deficiency anaemia,
- PBF showed moderate anisipoikilocytosis with tear drop cells elliptocytes, fragmented cells, polychromatophils and few nucleated red blood cells.
- Reticulocyte counts were also moderately raised.
- But 24 hours incubation of peripheral blood of all patients with supravital staining with 1% brilliant cresyl blue showed 30-50% Hb H inclusions.

Discussion

- Hb electrophoresis done in gel electrophoresis in alkaline pH showed normal electrophoretic pattern except low Hb A2.
- Serum ferritin was also high.
- Repeat Hb electrophoresis in capillary method done with fresh sample revealed Hb H band.
- Molecular analysis for alfa thalassemia mutation detection was carried out only in one patient and revealed -α 3.7 homozygous.

Conclusion

- Hb H disease might not always benign.
- During hemolytic crisis which develops after acute infections with high fever, the hemoglobin level may drop significantly and patients can develop shock or renal shutdown.

Conclusion

We are presenting these cases to highlight

- Hb H disease is not a rare disease
- We would like to emphasize on the importance of early diagnosis of Hb H disease to avoid unnecessary investigations and prompt treatment of potentially serious haemolytic crisis.

Conclusion

Hb H disease should be suspected in chronic anaemia with

- MHA with reticulocytosis
- Normal or increased S ferritin
- Normal gel elctrophoresis or low Hb A2
- With or without splenomegaly

Hb H inclusion study should be done

Take home message

- Hb H are unstable
- May be missed in electrophoresis
- Hb H inclusions are **always** detected in red cells in Hb H disease
- **Hb H inclusion body test** is a simple, cheap and reliable test


THANK YOU ALL