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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/20177
DOI URL: http://dx.doi.org/10.21474/IJAR01/20177

RESEARCH ARTICLE

HBE BETA-THALASSEMIA IS ASSOCIATED WITH IGA NEPHROPATHY

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Manuscript Info

Manuscript History
Received: 06 November 2024
Final Accepted: 10 December 2024
Published: January 2025

Key words:-
β-Thalassemia, IgA Nephropathy (IgAN), Glomerulonephritis, Berger's Disease

Abstract

β-thalassemia are a group of autosomal recessive inherited disorders of haemoglobin synthesis where in mutations of the β-globin gene lead to various degrees of defective β-chain production, an imbalance in α/β-globin chain synthesis, ineffective erythropoiesis and anaemia. Improved survival in thalassaemic patients has led to the emergence of previously unrecognized complications, such as renal disease. Renal disease is considered the 4th cause of morbidity among patients with transfusion dependent thalassemia. IgA nephropathy (IgAN) is an immune complex-mediated glomerulonephritis, defined morphogically by the constant presence of dominant or co-dominant mesangial deposists of IgA and accompanied by avariety of histopathological lesions. It is the most common pattern of primary glomerulonephritis seen in the world and represents a significant cause of renal insufficiency in young adults. Here we report a case of 24 year old male known case of E beta thalassemia since his 8 years of age with IgA nephropathy.

Introduction:-

Thalassemia refers to a group of hereditary haemolytic anaemia, wherein mutations or deletions of the globin gene lead to various degrees of inhibition in α or β globin synthesis[1,2]. The manifestations primarily include anaemia, jaundice and hepatosplenomegaly[2]. The clinical and haematological spectrum of β-thalassemia disease ranges from mild to clinically overt conditions including transfusion dependent (TDT) β-thalassemia major (TM) and non-transfusion dependent (NTDT), β-thalassemia intermedia (TI) or thalassemia minor (TMin)[3,4,5]. HbE is characterized by a point mutation in exon 1 at codon 26 (GAG to AAG) on chromosome11, which results in the substitution of lysine for glutamic acid[6]. The interaction of HbE and beta thalassemia gives rise to HbE beta thalassemia which is a very heterogenous condition with clinical diverse phenotypes[6].

IgA nephropathy (IgAN) is an immune complex-mediated glomerulonephritis defined morphogically by the constant presence of dominant or co-dominant mesangial deposits of IgA and followed by IgA associated

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histopathological lesions[7]. It is the most common pattern of primary glomerulonephritis seen in the world and represents a significant cause of renal insufficiency in young adults[7,8]. Microscopic hematuria is frequently observed in thalassemia patients, and is considered to be the result of tubular damage induced by iron deposition, hypercalciuria, hyperuricosuria and deferoxamine uses[1,6].

Case report :

A 24 year old , non diabetic, non hypertensive non smoker male student from Darjeeling, West Bengal, India, was admitted with swelling of his face and decrease urine output with hematuria for last 3 days. The disease was acute in onset and progressive in nature. He notied the puffiness of face (periorbital) in the morning after getting up from the bed. He complained of oliguria and hematuria from the same day. There was no history of fever, anorexia, respiratory distress , convulsion, anuria. He did not complain of any burning micturation or loin pain, sore throat. He is a known to have HbE beta Thalassemia, in which, he has been required transfusion of PRBC yearly since the age of 8years. He denied any past or current addictions, and had no family history of thalassemia.

On arrival his pulse was 88/minute, regular and high volume, with no special character, all peripheral pulses well palpable, and no radioradial or radiofemoral delay. The BP was 148/92 mmHg measured at right upper arm supine position, respiration 16/minute, and SpO2 99% in room air. Vital signs suggestive of periorbital and bilateral pedal oedema with mild pallor. On Gastrointestinal examination flanks were full and hepatospenomegaly.

Laboratory investigations showed microcytic hypochromic anaemia (Hb- 7.5 g/dL, TLC – 5700/µL, Platelet- 188,000/µL, MCV- 74.8 fL, RDW –CV 25.2%). Biochemical and microbiological investigations are showed on table 1. Digital chest x-ray (PA view) and 12 lead ECG were normal. Echocardiography showed no RWMA with normal LV systolic function, mild mitral regurgitation, chink of pericardial effusion and LA dilated (4mm), ejection fraction 71%. USG of whole abdomen demonstrated hepatosplenomegaly (liver 158mm, spleen 150mm) with asicites (++) and right kidney 93mm, left kidney 90mm with raised cortical echogenecity and normal CMD without any features of obstructive uropathy. ANA in hep 2 cell line and Anti dsDNA (ELISA) were negative. ABG suggestive of normal study.

In this case the patient didn't show any evidence of iron chelation theray and nephrotoxic drugs intake. Laboratory test showed normal C3, C4 complement level. Urine analysis suggestive of hematuria with sediments and proteinuria. Ultrasound of whole abdomen demonstrated asicites with hepatospleenomegaly. A decision was made to perform a renal biopsy. Two cores of renal cortex containing up to 11 glomeruli were analyzed. They showed mesangial and focal endocapillary proliferative glomerulonephritis featuring cellular crescents over 4/11 (36.3%) glomeruli. Immunofluorescence revealed dominant glomerular staining for IgA (3+ mesangial, capillary wall, granular) and C3 (1+, mesangial, capillary wall, granular) , also acute tubular inury is observed. On the basis of these findings, a diagnosis of IgA nephropathy-induced nephrotic syndrome was made. Patients was given IV antibiotics, PPI and 3 units PRBC transfutions with Tab Folic acid 5mg once OD and also put him on pulsed with intravenous methylprednisolone 500 mg daily for 3 days followed by oral prednisolone 1 mg/ kg daily for a month which was then tapered gradually based on response. His proteinuria and renal function improved significantly. Currently, he is on 4 month follow up at the thalassemia and nephrology clinics.

Discussion:-

Thalassemia is a common inherited disease of haemoglobin synthesis worldwide[2]. Patients with thalassemia have a widespectrum of clinical phenotypes depending on their respective genotype characteristics[2]. There arenumerous factors that could contribute to renal disease in a patient with thalassemia[5,6]. Among them are iron overload, chronic anaemia, hypoxia, acquired Fanconi syndrome, inappropriate use of iron chelation, nephrotoxic drugs, infectious agents, postsplenectomy and nephrolithiasis[5,6,7,].

IgA nephropathy which is also known as Berger's diseaseas seen in this patient is the most common glomerulonephritis globally[5,6,7]. It is characterized by the presenceof circulating and glomerular immune complexes consisting of galactose-deficient IgA1 and C3[6]. These immune complexes contribute to

glomerular inflammation and proliferation in the mesangium. Stimulation of therenin-angiotensin system further results in glomerulosclerosis and tubulointerstitial fibrosis[5,6]. In non thalassemic humans, these immune complexes bind to the erythrocyte complement receptors, thereby removing them from the circulation via the liver and spleen[6]. The lower levels of erythrocyte complement receptors in patients with thalassemia compromise clearance of these immune complexes, thus leading to IgAN[1,6].

Thalassemia associated with IgAN is relatively rare. In 1994, Harada [09] reported a case of a beta-thalassemiapatient with microscopic hematuria, which was later diagnosed with IgAN. Jung Hyun Kang et al. [10] reporteda case of a beta-thalassemia minor patient who did not receive any specific treatment for anaemia. During thefollow-up, the patient exhibited overt microscopic hematuria and proteinuria with elevated serum IgA levels and was diagnosed with IgAN after renal biopsy. In 2016, Mrabet [11] also reported a case of a beta thalassemia minor patient associated with IgAN who showed persistent microscopic hematuria and new-onset overt proteinuria.

Table 1:- Metabolic parameters.

CRP	12.72 mg/dL	Ferritin	827.0 µg/L (20 – 250)
ESR	25 mm 1st hour	Serum LDH	148 U/L
Ur / Cr	218 / 2.0 mg/dL	Corrected calcium	9.2 mg/dL
Na+ / K+	133 / 3.9 mEq/L	DCT	Negative
Total bilirubin / Direct bilirubin	1.2 / 0.4 mg/dL	Fasting lipid profile	Normal
SGOT/ SGPT	23 / 10 U/L	Serum C3	98.10 mg/dL (90 – 180)
Total protein/ Albumin	5.5 / 2.5 gm/dL	Serum C4	10.00 mg/dL (10 – 40)

Table 2:- Ascitic fluid analysis.

Parameters	Results
Colour	Pale yellow
Cell count	100 cumm
Cell type	Polymorphs -25%, lymphocytes – 75%
Glucose	121 mg/dL
Protein/ Albumin	3.1/1.7 mg/dL
ADA	14.39 U/L (normal upto 40)
SAAG	Low

Table 3:- Urine analysis.

Parameters	Results
Protein	Present (+)
RBC	Present (+++), 13-15 /HPF
Semiment	Present
Cast	Granular cast
Pus cell	2 - 3 /HPF
C/S	NO growth after 48 hours
24 hours urinary protein	2080 mg/ 24 hours (volume 1800ml)

Conclusion:-

IgAN should be considered as one of the main causes of renal dysfunction in a patient with thalassemia. Disease progression and end-stage kidney disease can be prevented by reaching an early diagnosis and instituting prompt therapy.

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