Review Article
Renal complications of beta-thalassemia major in children

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Abstract: The success that has been made in the care of patients with thalassemia has led to the emergence of unrecognized complications including several renal abnormalities. Chronic anemia and iron overload as well as the use of iron chelator are believed to lie behind these abnormalities. Many investigators document the presence of tubular dysfunction and abnormalities in glomerular filtration rate in these patients. In this review we will discuss the updates in the diagnosis, pathogenesis and prevention of renal complications of thalassemia.

Keywords: Children, thalassemia, renal complications

Introduction

Thalassemias are defined as a heterogeneous group of genetic disorders of hemoglobin synthesis all of which result from a reduced rate of production of one or more of the globin chains of hemoglobin. This basic defect results in imbalanced globin chain synthesis, which is the hallmark of all forms of thalassemia. Beta thalassemia is due to impaired production of beta globin chains, leading to a relative excess of alpha globin chains. The degree of alpha globin chain excess and the beta gene mutations are two major determinants of the severity of subsequent clinical manifestations. Most patients with homozygous beta thalassemia (thalassemia major) have profound progressive anemia necessitating regular blood transfusions to preserve life, but a few remain transfusion independent (thalassemia intermedia) [1].

Patients with Beta thalassemia major (β-TM) usually present early in life with profound anemia that necessitates regular blood transfusion to survive. Repeated blood transfusions are inevitably associated with iron overload that leads to multiple organ dysfunctions namely heart, liver and endocrine glands [2].

Historically, renal diseases have not been a major issue in patients with β-TM because sur-

vival was limited by severe cardiac iron loading from chronic transfusion therapy leading to premature early death, and simply patients did not live long enough to develop conditions linked to kidney dysfunction [3].

Although advances in the care of patients with β-TM, especially with the advent of effective chelating agents that can reduce the iron burden and its consequences, translate into better patient survival, this success has allowed previously unrecognized complications to emerge, including several renal abnormalities [4].

In this review we are going to discuss the underlying mechanisms of renal abnormalities in patients with β-TM, their different manifestations and guidelines for prevention.

Mechanisms of renal disease in β-TM

Several major factors are responsible for functional abnormalities found in β-TM which include shortened red cell life span, rapid iron turnover, and tissue deposition of excess iron. Moreover, the uses of specific iron chelators are not without harm to the kidney [5].

Chronic anemia and hypoxia

In anemic rats, Kaissling et al [6] observed that the most striking effects of anemia on renal

morphology were damages in the proximal tubules and a volume increase of the peri-tubular spaces. A good correlation between the severity of anemia and markers of tubular abnormalities are reported in patients with β-TM [7]. Likewise Ali and Sultan reported that patients with β-TM had significantly higher levels of cystatin C-as a marker of glomerular dysfunction [8].

Chronic anemia and hypoxia are associated with oxidative stress and lipid peroxidation that are correlated to functional abnormalities in tubular cells [9]. Moreover, anemia may accelerate the decline in renal function by inducing tubulo-interstitial hypoxia. Chronic hypoxia of tubular cells with increased metabolic demand causes apoptosis or epithelial-mesenchymal transition, leading to the development of tubulo-interstitial injury and consequent glomerulosclerosis and kidney fibrosis [6, 10].

Hyperfiltration has been noted in some studies in patients with β thalassemia [11, 12]. It is demonstrated that fetal sheep subjected to chronic anemia showed reduced systemic vascular resistance that leads to hyperdynamic circulation that increases renal plasma flow and glomerular filtration rate (GFR). These changes can eventually lead to stretching of the glomerular capillary wall and subsequent endothelial and epithelial injury, together with transudation of macromolecules into the mesangium associated with glomerular dysfunction. In the long-term, such changes may lead to a progressive decline in GFR [13].

Iron overload

Extensive intra-medullary destruction of red cell precursors, shortened red cell life span, rapid iron turnover and regular blood transfusions leads to iron overload in patients with β-TM [14]. Autopathy series from 18 patients with β-TM showed hemosiderin deposits in visceral and parietal glomerular epithelial cells [15]. Koliakos et al [15] showed that the urine markers of tubular dysfunctions correlated positively with serum ferritin concentration and liver iron deposition, as detected by MRI T2 values, in children with β-TM. Similarly serum Cystatin C levels had a highly significant strong positive correlation with serum ferritin in patients with β-TM [8].

Many investigators [17, 18] proved that the cellular injury of renal cells secondary to iron deposition is induced by the release of free reactive iron that stimulates the production of reactive oxygen species.

Chelation therapy

Iron chelators are one of cornerstones of the treatment of chronic iron overload in patients with thalassemia. Three iron chelators are currently available: parenteral deferoxamine and oral deferiprone and deferasirox. All three chelators can potentially lead to consequences on renal function. The glomerular dysfunctions range from mild transient increase in serum creatinine up to acute kidney injury (AKI).

Many investigators [5, 19] documented a reversible non-progressive increase in serum creatinine in 14% of the β-TM cohort given deferoxamine and 38% of patients receiving deferasirox. These changes may be explained partially by iron depletion. GFR was reduced in the iron deprived nephrons via impaired mitochondrial function and consequent production of adenosine and adenosine triphosphate that lead to activation of the tubulo-glomerular feedback, vasoconstriction of the afferent pre-glomerular arterioles.

AKI and acute changes in renal function have been reported in up to 40% of patients given deferoxamine when higher doses and overdoses occurred. Diarrhea and vomiting are common, and this may lead to volume depletion and pre-renal AKI [20, 21]. The relatively high incidence of Yersinia infection with deferoxamine therapy should be considered to cause AKI if sepsis follows [21]. Likewise, deferiprone may cause, in about 1% of the treated patients, agranulocytosis which might lead to severe sepsis and acute tubular necrosis [23].

Others

The cardiorenal syndrome, hepatorenal syndrome and hepatitis induced glomerulonephritis should be remembered as potential causes of renal diseases in patients with thalassemia [24, 25]. Renal stones are not uncommon in thalassemic patients. This finding is related to the increased uric acid in the urine as a consequence of high erythrocyte turnover and the increased hypercalciuria from vitamin D and

calcium replacement for deficiency and hypoparathyroidism [26, 27].

Manifestations of renal dysfunction in thalassemia

Tubular dysfunction: Sadeghi-Bojd et al [28] studied 166 children with β-TM. Patients showed significant signs of renal tubulopathy, such as hypercalciuria (12.9%), proteinuria (8.6%), phosphaturia (9.2%), magnesiumuria (8.6%) and hyperuricosuria (38%). Likewise, in a study by Sumboonnanonda et al [7] aminoaciduria was detected in one-third of 104 β-TM patients and low molecular weight proteinuria was found in all patients. Moreover, proximal tubular dysfunction was reported in children with β-TM after treatment with deferasirox [29]. In a prospective study done on ten children treated with β-TM receiving deferasirox, Dubourg et al. showed a generalized proximal tubular dysfunction in two patients whereas nine patients presented at least one sign of proximal tubular dysfunction [30].

Many studies in thalassemia, including major, [31, 32] have identified an increase in biomarkers of proximal tubular damage leading to increased urinary excretion of N-acetyl-D-glucosaminidase (NAG) and beta-2 microglobulin. A recent study by Sumboonnanonda et al [33] showed that the secretion of such markers was significantly reduced in patients with β-TM who had undergone curative hematopoietic stem-cell transplantation compared with age-matched patients who had not had transplantation.

Glomerular dysfunction: Many investigators [11, 12] reported that mean values of creatinine clearance and GFR are higher than normal in patients with β-TM. This mimics the early changes seen in diabetic nephropathy.

AKI has been reported in thalassemia with deferoxamine therapy [21]. In some studies, deferoxamine overdose secondary to administration-pump malfunction or inadequate dosage monitoring resulted in AKI necessitating dialysis. Renal biopsy was only performed in a single patient and showed tubular necrosis and severe damage to tubular mitochondria on electron microscopy [5]. Several cases of AKI have also been reported in post-marketing surveillance of the oral chelator deferasirox [5].

Historical data have shown that thalassemia has represented a small proportion of dialysis patients. Indeed, significant renal involvement is not a frequent complication in children and young adults suffering from thalassemia. These estimates may change with the future ageing thalassemic population and use of medications, which may potentially affect the kidney [25].

Hamed and El-Melegy [34] studied the biochemical markers of glomerular dysfunction in 69 children with β-TM. In this study, reduced estimated GFR (< 90 mL/minute/1.73 m^2) was found in 58.8% and 45.7% of patients with and without chelation therapy. Proteinuria was reported in patients with (47.1%) and without chelation therapy (45.7%). Significant higher levels of early biomarkers of glomerular injury as microalbuminuria and serum cystatin levels were also documented in these patients.

An observational study of children under 5 years exposed to deferoxamine for a median 2.3 years [35] demonstrated that 5.1% of patients developed non-progressive increases in serum creatinine and 5% had a more than 50% increase in serum creatinine values and 2.5% having values greater than the upper limit of normal. Al-Khabori et al reported that deferasirox was discontinued in 7 out of 72 children with β-TM due to persistent progressive rise(s) in serum creatinine (40% mean serum creatinine rise from baseline) [36] Likewise, it was shown that 8 out 10 children with β-TM received deferasirox for 17.2 ± 8.9 months experienced a > 10% decrease in inulin clearance [30].

Hematuria: The prevalence of hematuria in β thalassemia major is not yet fully investigated. In one study from Iran [37], the authors compared 58 patients with β thalassemia major and 50 patients with thalassemia intermedia and reported hematuria in 2 patients of the former group (3.4%). In another study [38], urinalysis was performed in 500 patients with β thalassemia major ranged in age from 6 months to 32 years. Hematuria was detected in 55 (10.6%), including 9.8% of those younger than 20 years. Sterile pyuria was detected in 4% and proteinuria in 16% of the patients with hematuria. The presence of hematuria may relate to an increased incidence of renal stone disease directly causing hematuria from trauma to the renal tract or causing obstructions [31].

Monitoring

The increased awareness of the kidney and an understanding of the potential mechanisms of renal injury have led to increased monitoring of the kidneys, especially in chelated patients. Particular attention should be given to monitoring renal function in patients who are at an increased risk of complications (patients with diabetes), have pre-existing renal conditions (or an GFR < 60 mL/min/1.73 m^2 and proteinuria), have co-morbidities or are on medications, which may affect renal function [24]. Although there are no strong evidence about the ideal way of monitoring these patients, a 3 monthly serum creatinine/measurements, a simple urine dipstick to detect non-visible blood and a protein/creatinine ratio (in a morning urine sample) should be performed. More frequent measurements (monthly) in chelated patients should be performed [24].

It is well known that serum creatinine is recognized as an unreliable measure of early renal dysfunction therefore estimated GFR, based on Schwartz equation, is more reliable. On the other hand, many investigators suggest that cystatin C is a poor biomarker of renal function in patients with thalassemia, however these data need to be validated [39, 40].

Tubular function assessment using beta-2 microglobulin and NAG may be useful [24].

Prevention and management

The increased awareness of hematologists that in thalassemic patients the kidney may be affected due to the disease itself or the chelation therapy is the corner stone in preventing the renal complications of thalassemia. Frequent monitoring according to the mentioned guidelines helps in early picking up of patients. Referral to a nephrologist is perhaps advised, especially if haematoproteinuria is present [24].

Choice of iron chelator therapy should be individualized for each patient according to requirements and the clinical situation [41]. The use of chelators flexibly, alternating use between chelators, at lower doses or in combination, to limit potential adverse effects is recommended [24]. Balocco et al. [42] demonstrated alternate use of deferasirox and deferiprone allowed tolera-

bility with no adverse effects and similar efficacy in reducing serum ferritin. Chelator avoidance in high-risk groups (patients with diabetic, established renal insufficiency, significant proteinuria) remains debatable and a risk benefit consideration is necessary [24]. Ponticelli et al [5] stated that in thalassemic children using Deferasirox, dose should be reduced by 10 mg/kg if serum creatinine raises by 33% above pretreatment values and above the age-appropriate upper limit of normal at two consecutive visits.

Disclosure of conflict of interest

None.

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References

[1] Shinar E, Rachmilewitz EA. Differences in the pathophysiology of hemolysis of alpha- and beta-thalassemic red blood cells. Ann N Y Acad Sci 1990; 612: 118-126.

[2] Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med 1994; 331: 567-573.

[3] Borgna-Pignatti C, Cappellini MD, De Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, Ghilardi R, Piga A, Romeo MA, Zhao H, Cnaan A. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood 2006; 107: 3733-3737.

[4] Musallam KM, Taher TA. Mechanisms of renal disease in β-thalassemia. J Am Soc Nephrol 2012; 23: 1299-1302.

[5] Ponticelli C, Musallam KM, Cianciulli P, Appellini MD. Renal complications in transfusion-dependent beta thalassemia. Blood Rev 2010; 24: 239-244.

[6] Kaissling B, Piess S, Rinne B, Le Hir M. Effects of anemia on morphology of rat renal cortex. Am J Physiol 1993; 264: F608-617.

[7] Sumboonnanonda A, Malasit P, Tanphaichitr VS, Ong-ajyooth S, Sunthornchart S, Pattanakitsakul S, Petrarat S, Assateerawatt A, Vongjirad A. Renal tubular functions in beta-thalassemia. Pediatr Nephrol 1998; 12: 280-283.

[8] Ali BA and Sultan AM. Frequency of Glomerular Dysfunction in Children with Beta Thalassaemia Major. Sultan Qaboos Univ Med J 2014; 14: e88-94.

[9] Nagababu E, Gulyani S, Earley CJ, Cutler RG, Mattson MP, Rifkind JM. Iron-deficiency anemia enhances red blood cell oxidative stress. Free Radical Res 2008; 42: 824-829.

[10] Zhou XJ, Laszik Z, Wang XQ, Silva FG, Vaziri ND. Association of renal injury with increased oxygen free radical activity and altered nitric oxide metabolism in chronic experimental hemosiderosis. Lab Invest 2000; 80: 1905-1914.

[11] Aldudak B, Karabay Bayazit A, Noyan A, Ozel A, Anarat A, Sasmaz I, Kilinç Y, Gali E, Anarat R, Dikmen N. Renal function in pediatric patients with beta-thalassemia major. Pediatr Nephrol 2000; 15: 109-112.

[12] Grossman H, Dische MR, Winchester PH, Canale V. Renal enlargement in thalassemia major. Radiology 1971; 100: 645-648.

[13] Nangaku M. Chronic hypoxia and tubulointerstitial Injury: A final common pathway to end-stage renal failure. J Am Soc Nephrol 2006; 17: 17-25.

[14] Weatherall DJ, Clegg JB, eds. The Thalassemia Syndromes. 4th edn. Oxford: Blackwell Science; 2001.

[15] Landing BH, Gonick HC, Nadorra RL, Hyman CB, Wells TR, Villarreal-Engelhardt G, Mersch J, Agness CL. Renal lesions and clinical findings in thalassemia major and other chronic anemias with hemosiderosis. Pediatr Pathol 1989; 9: 479-500.

[16] Koliakos G, Papachristou F, Koussi A, Perifanis V, Tsatra I, Souliou E, Athanasiou M. Urine biochemical markers of early renal dysfunction are associated with iron overload in beta-thalassemia. Clin Lab Haematol 2003; 25: 105-109.

[17] Kassab-Chekir A, Laradi S, Ferchichi S, Haj Khelil A, Feki M, Amri F, Selmi H, Bejaoui M, Miled A. Oxidant, antioxidant status and metabolic data in patients with beta-thalassemia. Clin Chim Acta 2003; 338: 79-86.

[18] Zager RA, Johnson AC, Hanson SY. Proximal tubular cytochrome c efflux: Determinant, and potential marker of mitochondrial injury. Kidney Int 2004; 65: 2123-2134.

[19] Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M, Gattermann N, Giraudier S, Lee JW, Chan LL, Lin KH, Rose C, Taher A, Thein SL, Viprakasit V, Habr D, Domokos G, Roubert B, Kattamis A; EPIC Study Investigators. Tailoring iron chelation by iron intake and serum ferritin: The prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica 2010; 95: 557-566.

[20] Prasannan L, Flynn JT, Levine JE. Acute renal failure following deferoxamine overdose. Pediatr Nephrol 2003; 18: 283-285.

[21] Volti SL, Maccarone C, Volti GL, Romeo MA. Acute renal failure following deferoxamine overdose. Pediatr Nephrol 2003; 18: 1078-1079.

[22] Robins-Browne RM, Prpic JK. Effects of iron and deferoxamine on infections with Yersinia enterocolitica. Infect Immun 1985; 47: 774-779.

[23] Galanello R. Deferiprone in the treatment of transfusion-dependent thalassemia: a review and perspective. Ther Clin Risk Manag 2007; 3: 795-805.

[24] Bhandari S, Galanello R. Renal aspects of thalassemia a changing paradigm. Eur J Haematol 2012; 89: 187-197.

[25] Mastrangelo F, Lopez T, Rizzelli S, Manisco G, Corlianò C, Alfonso L. Function of the kidney in adult patients with Cooley's disease. A preliminary report. Nephron 1975; 14: 229-236.

[26] Smolkin V, Halevy R, Levin C, Mines M, Sakran W, Ilia K, Koren A. Renal function in children with beta-thalassemia major and thalassemia intermedia. Pediatr Nephrol 2008; 23: 1847-151.

[27] Koren G, Bentur Y, Strong D, Harvey E, Klein J, Baumal R, Spielberg SP, Freedman MH. Acute changes in renal function associated with deferoxamine therapy. Am J Dis Child 1989; 143: 1077-1080.

[28] Sadeghi-Bojd S, Hashemi M, Karimi M. Renal tubular function in patients with beta-thalassemia major in Zahedan, southeast Iran. Singapore Med J 2008; 49: 410-412.

[29] Rheault MN, Bechtel H, Neglia JP, Kashtan DCE. Reversible Fanconi syndrome in a pediatric patient on deferasirox. Pediatr Blood Cancer 2011; 56: 674-676.

[30] Dubourg L, Laurain C, Ranchin B, Pondarré C, Hadj-Aïssa A, Sigaudo-Roussel D, Cochat P. Deferasirox-induced renal impairment in children: an increasing concern for pediatricians. Laurence Pediatr Nephrol 2012; 27: 2115-2122.

[31] Ali D, Mehran K, Moghaddam AG. Comparative evaluation of renal findings in Beta-thalassemia major and intermedia. Saudi J Kidney Dis Transpl 2006; 19: 206-226.

[32] Safaeiasl A, Maleknejad S, Heidarzadeh A, Ghandi Y. Urine β2 Microglobulin and other biochemical Indices in β Thalassemia Major. Acta Medica Iranica 2009; 47: 443-446.

[33] Sumboonnanonda A, Sanpakit K, Piyaphanee N. Renal tubule function in beta-thalassemia after hematopoietic stem cell transplantation. Pediatr Nephrol 2009; 24: 183-187.

[34] Hamed EA, El-Melegy TN. Renal functions in pediatric patients with beta-thalassemia ma-

jor: relation to chelation therapy: original prospective study. Ital J Pediatr 2010; 36: 39.

[35] Aydinok Y, Unal S, Oymak Y, Vergin C, Türker ZD, Yildiz D, Yesilipek A. Observational study comparing long-term safety and efficacy of Deferasirox with deferoxamine therapy in chelation-naïve children with transfusional iron overload. Eur J Haematol 2012; 88: 431-438.

[36] Al-Khabori M, Bhandari S, Al-Huneini M, Al-Farsi K, Panjwani V, Daar S. Side effects of deferasirox iron chelation in patients with beta thalassemia major or intermedia. Oman Med J 2013; 28: 121-124.

[37] Derakhshan A, Karimi M, Ghadimi AM. Comparative evaluation of renal findings in beta thalassemia major and intermedia. Saudi J Kidney Dis Transpl 2008; 19: 206-209.

[38] Mohammad HF, Mohammad KF, Shahriari M, Shervin R. Hematuria in patients with beta-thalassemia major. Iran J Kidney Dis 2010; 4: 133-136.

[39] Astor BC, Levey AS, Stevens LA, Van Lente F, Selvin E, Coresh J. Method of glomerular filtration rate estimation affects prediction of mortality risk. J Am Soc Nephrol 2009; 20: 2214-2222.

[40] Papassotiriou I, Margeli A, Hantzi E, Delaporta P, Sergounioti A, Goussetis E, Ladis V, Kattamis A. Cystatin C levels in patients with beta-thalassemia during deferasirox treatment. Blood Cells Mol Dis 2010; 44: 152-155.

[41] Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med 2011; 364: 146-156.

[42] Balocco M, Carrara P, Pinto V, Forni GL. Daily alternating deferasirox and deferiprone therapy for "hard-to-chelate" beta-thalassemia major patients. Am J Hematol 2010; 85: 460-461.