RENAL DYSFUNCTION AND ELECTROLYTE IMBALANCE IN CHILDREN WITH BETA-THALASSEMIA MAJOR.

Gourav Kumar Goyal¹, Sameer Jagrwal₂*, Kalika Gupta³, SK Tak⁴

¹,² Assistant Professor, Department of Pediatrics, Ananta Hospital Associated with Ananta Institute of Medical Science & Research Centre, Rajsamand (Rajasthan) India.
³ Assistant Professor, Dept of PSM, AIMS & RC, Rajsamand
⁴ Professor & HOD, Department of Pediatrics, Ananta Hospital Associated with Ananta Institute of Medical Science & Research Centre, Rajsamand (Rajasthan) India.

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Corresponding author: Sameer Jagrwal

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Abstract

Background: Beta-thalassemia major (β-TM), is a type of chronic, microcytic anaemia that is characterized by impaired biosynthesis of the β-globin chain leading to accumulation of unpaired α-globin chain. Due to the severe anaemia caused in Thallasemia, patient must undergo repeated blood transfusions for survival. Repeated blood transfusions lead to built-up of iron overload which is responsible for tissue deposition of excess iron, ultimately resulting in iron toxicity. There are evidences of aminoaciduria, hypercalciuria, phosphaturia, magnesiuria, hyperuricosuria, low urine osmolality, and excess urinary secretion of markers of tubular damage such as N-acetyl-D-glucosaminidase in patients with beta-thalassemia major. In the present study, authors tried to investigate the proportion of patients diagnosed with β-Thalassemia Major manifesting renal dysfunction and electrolyte imbalance.

Material and Methods: It was a hospital based case-control study involving 100 patients coming to Department of Pediatric Medicine, and belonging to the age group 1 to 18 years. Equal number of healthy age and sex matched children were taken as controls.

Results: When cases and controls were compared with respect to albuminuria, blood pH, serum bicarbonate, phosphorus and blood urea, higher number of cases had deranged values as compared to the healthy controls [p<0.05].

Conclusion: Renal damage and tubular dysfunctions leading to electrolyte imbalances exist in children with β-thalassemia major.

Keywords: kidney, Thalassemia, Electrolytes, children.

Introduction:

Beta-thalassemia major (β-TM), is a type of chronic, inherited, microcytic anaemia that is characterized by impaired biosynthesis of the β-globin chain leading to accumulation of unpaired α-globin chain. Beta thalassemia major is the most prevalent type of thallasemia. It produces severe anaemia in its homozygous state.¹ Due to the severe anaemia caused in Thallasemia, patient must undergo repeated blood transfusions for survival. Repeated blood transfusions lead to built-up of iron overload which is responsible for tissue deposition of excess iron, ultimately resulting in iron toxicity.¹ Shortened red blood cells (RBCs) life span, rapid iron turnover, and tissue deposition of excess iron are major factors responsible for functional and physiological abnormalities found in various forms of thallasemia.

Iron-chelating therapy is largely responsible for doubling the life expectancy of patients with thalassemia major. it has been proven to prevent liver and heart damage, allow for normal growth and sexual development in children with thalassemia, and increase life span.² Although the prognosis for patients with thalassemia has greatly improved in recent decades with the use of modern newborn screening, blood transfusions and iron chelation therapy; organ dysfunction leading to electrolyte imbalance is still common. Iron deposition in the heart, liver, and multiple endocrine glands results in severe damage to these organs, with variable endocrine organ failure. Profound anemia and excess iron deposition leads to dysfunction of cardiovascular, reticuloendothelial, and other organ systems. In recent years, there are evidences of
aminoaciduria, hypercalciuria, phosphaturia, magnesiuria, hyperuricosuria, low urine osmolality, and excess urinary secretion of markers of tubular damage such as N-acetyl-D-glucosaminidase in patients with beta-thalassemia major. Renal dysfunction may occur in beta-thalassemia major patients showing no clinical symptoms and before the manifestations of any other complications. Renal dysfunction in these patients is not known well and seems to be multifactorial; attributed mainly to long-standing anemia, chronic hypoxia, iron overload and toxicity of iron chelators. There are limited studies on renal involvement in β-thalassemia, reporting both glomerular and tubular dysfunction.²

Early identification of patients at high risk of developing renal damage is of great importance as it may allow specific measures to be undertaken.

AIMS

To find out the proportion of patients diagnosed with β-Thalassemia Major manifesting renal dysfunction and electrolyte imbalance.

Material and Methods:

It was a hospital based case-control study done from June 2018 to June 2019. The study was conducted in Department of Pediatric Medicine, Ananta Institute of medical sciences and research centre, Rajsamand district, Rajasthan. Children coming to Department of Pediatric Medicine, and belonging to the age group 1 to 18 years were included in the study. Children diagnosed as β-thalassemia with standard methods, with or without chelation were taken as cases. Healthy age and sex matched children were taken as controls.

Exclusion Criteria included children <1 year of age, known cases of renal malformation or overt renal diseases, Systemic illness (cardiac, thyroid, hepatic diseases, diabetes mellitus or sepsis, etc.), need of renal replacement or diuretic therapy, history of intake of trimethoprim, corticosteroids or cephalosporin in the past 7 days and children whose guardians refused to give consent were excluded from this study.

For detection of minimum difference of at least 0.9 mg/dl serum phosphorus level in the β-Thalassemia Major patients and the control groups, the required sample size came out to be 32 in each group which was rounded off to 40 in each group. As the thalassemic patients were frequently encountered in the hospital during the study duration, 100 cases and 100 age and sex matched controls were finally included in the study.

Children diagnosed with Beta-thalassemia aged, 1 year to 18 years of either sex attending OPD and hematology clinic or admitted in thalassemia wards in the Department of Paediatrics were randomly selected to be included into study as cases. After applying inclusion and exclusion criteria, 100 thalassemic cases were included in the study, after taking informed consent from their parents. The patients selected were evaluated by taking clinical history, anthropometric measurements including weight, height, thorough physical examination, blood investigations [serum electrolyte and urine analysis] on preformed proforma. Healthy age and sex matched children who accompanied their family members to the same hospital were included in the study as controls, after taking informed consent from their guardians.

Statistical analysis was done using SPSS 21 version. Informed assent and consent were taken from the study subjects and their parents, respectively.

Results:

Baseline characteristics of the Subjects:

Table 1: Baseline characteristics of cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases [mean±SD]</th>
<th>Controls [mean±SD]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.7 ± 3.8</td>
<td>7.6 ± 3.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>22.8 ± 8.3</td>
<td>24.3 ± 8.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>119.1 ± 21.6</td>
<td>123.4 ± 22.7</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Chelation therapy

In the present study, around 70% Beta- thalassaemic cases were on Deferasirox and only 5% had been given Deferiprone. 23% cases were put on the combination of above two and the rest were not given any chelating agent.

Comparison of bio-chemical parameters between cases and controls

When cases and controls were compared with respect to albuminuria, blood pH, serum bicarbonate, serum phosphorus, blood urea and serum albumin, higher number of cases had deranged values as compared to the healthy controls. This result was found to be statistically significant [p<0.05].
**Figure 1:** Comparison of various bio-chemical parameters between cases and controls

**Table 2:** Comparison of means of various biochemical parameters between cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pH</td>
<td>7.36 ± 0.04</td>
<td>7.40 ± 0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum bicarbonate [mg/dl]</td>
<td>21.1 ± 1.4</td>
<td>24.1 ± 1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum phosphorus [mg/dl]</td>
<td>5.2 ± 0.6</td>
<td>4.1 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum albumin [g/dl]</td>
<td>4.03 ± 0.45</td>
<td>4.44 ± 0.62</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mean value of serum bicarbonate was 21.1 mg/L among cases whereas it was 24.1 mg/L among controls [p<0.05]. Mean serum phosphorus was found to be raised by 1.1 mg/dl among cases as compared to controls [p<0.05]. Serum albumin and blood pH was found to be deranged among cases and the result was statistically significant. [Table 2].

**Comparison of electrolyte imbalance with various chelators**

Among those patients, who were given deferasirox, 75% showed deranged serum electrolyte [p value>0.05].

On the above lines, 30%, 20% and 87% of cases put on Deferasirox, deferiprone and the combination, respectively, showed albuminuria [p value <0.001]. Patients who showed deranged blood pH and serum bicarbonate values were mostly either put on deferasirox or the combination of deferasirox and deferiprone [p <0.05].

**DISCUSSION**

In the current study, Beta-Thalassaemic cases and healthy controls in the age group 1 to 18 years old were included. Statistical analysis of baseline characteristics between cases and controls was found to be insignificant [p>0.05], proving that the two groups were almost similar.

The findings of the study were similar to Hamed E A etal⁴ and Grundy et al⁴ who reported deranged serum electrolytes among Beta –Thalassaemic patients.

The results of the present study showed signs of renal tubulopathy, such as increase in serum levels of inorganic phosphorus, blood urea, blood pH and urinary excretion of albumin, in thalassaemic patients with chelation therapy compared to healthy controls. On the similar lines, many investigators like Sumboonnanonda A etal⁵, Smolkin V etal⁶, Mohkam etal⁷ also reported statistically significant difference between means of several biochemical parameters between thalassaemic cases and healthy controls. Sumboonnanonda A etal⁵ reported mean S. Creatinine 0.6mg/dl, S. Bicarb 24.4mg/dl, serum ferritin 3293ng/ml among Thalassaemic cases. The increased serum levels of phosphate among cases can be explained by rapid erythrocyte turnover in combination with decreased reabsorption of filtered phosphate from damaged renal tubules. Lapatsanis et al⁸ reported phosphaturia and increase in serum phosphorus levels in βTM patients. In Turkey, Aldudak et al⁹ reported elevated urinary levels of protein/Cr and serum levels of UA and PO4 in βTM patients.

Behkit E O etal¹⁰ also confirmed that glomerular and tubular dysfunctions exist in children with beta-thalassemia major. This is in agreement with other studies⁵,⁵,⁶,⁷ that reported impairment in classical kidney functions (creatinine,albumin and GFR) and impairment in early glomerular function markers in beta-thalassemia major patients than controls. However, many other studies did not find any differences.¹¹,¹²

Brittenhaum etal¹³ showed that repeated blood transfusions were inevitably associated with iron overload that lead to multiple organ dysfunctions mainly in heart, liver and endocrine glands.

Hamed E A etal³ did correlation analysis and found, serum creatinine showed significant positive correlation with serum uric acid and Serum phosphorus (r = 0.391; r = 0.339). eGFR showed
significant positive correlation with age, height, weight and Serum total antioxidant capacity and negative correlation with serum phosphorus. Urine albumin/Creatinine showed significant positive correlation with serum uric acid. Cardiac, pulmonary, and endocrine complications in β-thalassemia major are well known and have repeatedly been discussed and described in the literature.  

Conclusion: The presented data confirms that renal damage and tubular dysfunctions leading to electrolyte imbalances exist in children with β-thalassemia major. The cause of this dysfunction is not known, but chronic anemia and oxidative stress due to tissue deposits of iron may be key factors. As dysfunction may not be detected by routine tests, use of early markers is recommended. In addition, we hope that the use of new-generation oral iron chelators may be beneficial for more effective removal of iron from cells, and thus reduce damage by iron overload.

References: