Hyperhomocyst(e)inaemia in children with chronic renal failure

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Abstract

Background. Hyperhomocyst(e)inaemia has been identified as a significant risk factor for the occurrence of atherosclerosis in adults with chronic renal failure. Because of its presumed direct toxic effect on the vascular wall, long-standing hyperhomocyst(e)inaemia in children with chronic renal failure might have an important influence on their risk of future development of atherosclerosis. Hitherto no data on hyperhomocyst(e)inaemia in children with renal failure have been published.

Methods. We investigated 16 children with chronic renal failure on conservative management, 12 children on haemodialysis and 17 children with a renal transplant. Age-matched controls were used for comparison. Plasma homocyst(e)ine levels after an overnight fast were determined by HPLC. Glomerular filtration rate was estimated by the Schwartz formula.

Results. Mean plasma homocyst(e)ine levels were 12.6 ± 5.2 μmol/l in the conservatively managed group, 22.2 ± 13.5 μmol/l in the haemodialysed group, 14.2 ± 2.1 μmol/l in transplanted children with an estimated GFR > 60 ml/min/1.73 m² and 17.5 ± 5.1 μmol/l in transplanted children with a lower estimated GFR. In all groups homocyst(e)ine levels were significantly elevated as compared to controls. Homocyst(e)ine levels were significantly correlated with age and negatively correlated with estimated GFR and serum folate levels.

Conclusions. Hyperhomocyst(e)inaemia is a feature of chronic renal failure in children as well as in adults. Elevated homocyst(e)ine levels can already be demonstrated in children with renal failure before end-stage renal disease has developed and persist after renal transplantation. Whether treatment of hyperhomocyst(e)inaemia in children with renal failure decreases the risk for future atherosclerosis remains to be proven.

Key words: children; chronic renal failure; folate; haemodialysis; homocyst(e)ine; renal transplant

Introduction

Hyperhomocyst(e)inaemia is frequently found in adults with end-stage renal disease [1,2]. No published data exist on hyperhomocyst(e)inaemia in children with ESRD. The first objective of this study was to investigate whether plasma homocyst(e)ine (tHcy) levels are elevated in children with chronic renal failure, in pre-end-stage and end-stage renal disease and after renal transplantation. The second objective was to investigate whether a significant correlation exists between plasma homocyst(e)ine levels and (i) the level of renal insufficiency as estimated by the Schwartz formula and (ii) the age of the child.

Subjects and methods

Patients and data collection

Sixteen children (4 girls) with chronic renal failure on conservative management, 12 children (7 girls) on haemodialysis and 17 children (9 girls) with a functioning renal transplant participated in this study after informed consent. Of the children with a renal transplant six (2 girls) had a GFR estimated by the Schwartz formula of more than 60 ml/min/1.73 m² (Tx high group). These children were analysed separately. Data on age and renal function of all patient groups are represented in Table 1.

Children on conservative management were prescribed diets containing 1.3–1.5 times the RDA of protein for age. None of these children were receiving folic acid supplementation. All children on haemodialysis were pre-
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The results were expressed as mean ± SD. Differences between patients and controls were analysed by Student’s t test. The relationships between plasma homocyst(e)ine levels and variables age, estimated GFR and plasma folate levels were analysed by linear and multiple linear regression analysis. A P value of <0.05 was considered as statistically significant.

Results

High plasma homocyst(e)ine levels were observed in all patients groups (Table 2) and were above the 95th percentile of published normal values [4] in 67% of conservatively managed patients, in 92% of patients on haemodialysis, in 100% of patients in the Tx high group, and in 91% of the patients in the Tx low group. Plasma homocyst(e)ine levels were elevated in all patient groups as compared to controls (Table 2). There was a significant correlation between plasma homocyst(e)ine level and age (Figure 1). This is in accordance with published data on normal children [4]. Folate levels in patients ranged from 7.0 to 92.1 nmol/l. None of the patients had a folate deficiency (normal range 4.1–20.4 nmol/l). Folate levels were significantly higher in haemodialysis patients (45.8 ± 23.7 nmol/l) as compared to the other patients (14.0 ± 8.3 nmol/l, P < 0.0001). In multiple linear regression analysis a significant correlation was found between homocyst(e)ine plasma levels and age (P = 0.001), a significant negative correlation with estimated GFR (P = 0.016) and a tendency toward a negative correlation with serum folate level (P = 0.06).

Discussion

In this study we found that homocyst(e)ine levels in children with chronic renal failure are significantly elevated as compared to normal controls. Homocyst(e)ine levels were higher than the 95th percentile of published data in the great majority of patients in all studied groups. As in normal children there is a significant increase of plasma homocyst(e)ine level with age. This latter point has to be taken in consideration when evaluating homocyst(e)ine levels in children with renal failure.

Elevated homocyst(e)ine levels can already be demonstrated before end-stage renal disease has developed and seem to increase with loss of renal function. After renal transplantation hyperhomocyst(e)inaemia seems to persist, even in those children with a good transplant function. The use of cyclosporin A in renal transplant recipients has been implicated as an additional risk factor for hyperhomocyst(e)inaemia [5], although a more recent study could not demonstrate a difference in plasma homocyst(e)ine levels between renal transplant recipients on cyclosporin A as opposed to those without cyclosporin A with comparable renal function [6]. As the majority of our patients were taking cyclosporin A, it is not possible to draw a conclusion on the effect of cyclosporin A on plasma homocyst(e)ine levels from our data.

Folate status is an important determinant of plasma homocyst(e)ine level [7]. None of the patients tested had evidence of folate deficiency. In fact, in the group of haemodialysed patients folate levels were above normal and significantly elevated as compared to the other patient groups, but their homocyst(e)ine levels were the highest. Administration of a supraphysiological dose of folic acid can lower homocyst(e)ine levels in adults in dialysis [8,9] as in children [10]. In our group of dialysis patients the dosage of folic acid, prescribed to prevent deficiency, probably was not high enough to prevent hyperhomocyst(e)inaemia.

Whether lowering of homocyst(e)ine levels by administration of a supraphysiological dose of folic acid actually decreases the risk of developing atherosclerosis remains to be proven. The administration of folic acid is, however, an inexpensive and safe therapy. Because of the long standing of hyperhomocyst(e)inaemia in individuals with chronic renal insufficiency from described B-vitamin supplementation after each haemodialysis session. They also received folic acid supplementation, 1 mg after each dialysis treatment. All children were dialysed three times weekly for 4 h. Transplanted children did not have any dietary restrictions or vitamin supplementation. Immunosuppressive therapy consisted of prednisone, azathioprine and cyclosporin A. In the Tx low group median daily prednisone dosage was 0.15 mg/kg body weight (range 0.08–0.55); median daily cyclosporin A dosage was 4.8 mg/kg body weight (range 0–9.1). two children did not receive cyclosporin A and three of these patients had a live-related donor kidney. In the Tx high group median daily prednisone dosage was 0.13 mg/kg body weight (range 0.06–0.15); median daily cyclosporin A dosage was 4.5 mg/kg body weight (range 0–6.4), one child did not receive cyclosporin A and one of these patients had a live-related donor kidney.

Blood samples were taken after an overnight fast. In children on haemodialysis, samples were taken predialysis after the long interdialytic interval. Creatinine levels were measured by standard analytical methods. An estimation of GFR was made by the Schwartz formula. Homocyst(e)ine levels were determined by HPLC using the SBDF reagent with fluorescence detection as described by Araki and Sako [3]. Control values for homocyst(e)ine were taken from normal children admitted for minor surgery.

Table 2. Homocyst(e)ine levels in patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients µmol/l</th>
<th>Controls µmol/l</th>
<th>P*</th>
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<tbody>
<tr>
<td>Conservative</td>
<td>12.6 ± 5.2</td>
<td>8.2 ± 3.3</td>
<td>0.004</td>
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<tr>
<td>Haemodialysis</td>
<td>22.2 ± 13.5</td>
<td>9.6 ± 2.7</td>
<td>0.002</td>
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<tr>
<td>Tx high</td>
<td>14.2 ± 2.1</td>
<td>9.4 ± 2.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Tx low</td>
<td>17.5 ± 5.1</td>
<td>9.9 ± 2.7</td>
<td>0.0001</td>
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</tbody>
</table>

Data are means ± standard deviation. *Student’s t test.
childhood onward, lowering homocyst(e)ine levels in these individuals may have a clinically more significant effect than in those who develop renal failure at a later age.

References


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