

Iron and aluminum status in dialysis patients

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Abstract

We undertook a retrospective survey of 119 hemodialysis (HD) and 35 continuous ambulatory peritoneal dialysis (CAPD) patients to evaluate the association between the major histocompatibility complex and iron and aluminum status. Furthermore, we evaluated the relationship between serum aluminum and ferritin concentrations. We confirm previous studies which showed an association between ferritin and HLA A₃, B₇, B₁₄. There also appeared to be an association between serum aluminum concentrations greater than 50 mcg/L and HLA B₄₄ in the CAPD patients, however this association was not present when the HD and CAPD patients were taken together. HD patients had serum aluminum concentrations higher than CAPD patient and, therefore, they may be at higher risk of developing aluminum overload. We found no correlation between serum aluminum and ferritin concentrations.

KEY WORDS: Iron. Aluminum. Hemodialysis. Peritoneal dialysis. HLA.

Hierro y aluminio en los pacientes en diálisis

Hemos realizado un estudio retrospectivo de 119 pacientes en hemodiálisis (HD) y 35 pacientes en diálisis peritoneal continua ambulatoria (CAPD) para evaluar la asociación entre los complejos de histocompatibilidad y el estado del hierro y el aluminio. Además, hemos evaluado la relación entre las concentraciones de ferritina y aluminio séricos. Hemos confirmado los estudios previos, los cuales mostraban una asociación entre ferritina y los antígenos HLA, A₃, B₇ y B₁₄. También parece existir una asociación entre la concentración de aluminio sérico mayor de 50 mcg/l y el antígeno HLA B₄₄ en los pacientes en CAPD, sin embargo esta asociación no está presente cuando se consideraban conjuntamente los pacientes

en HD y en CAPD. Los pacientes en HD tenían una concentración sérica de aluminio mayor que los pacientes en CAPD y, además, tenían un mayor riesgo de sufrir una intoxicación aluminica. No hallamos correlación entre las concentraciones séricas de aluminio y ferritina.

PALABRAS CLAVE: Hierro. Aluminio. Hemodiálisis. Diálisis peritoneal. HLA.

Introduction

Several factors are involved in the common problem of anemia in dialysis patients (1), including reduction in erythropoietin synthesis, decrease in red blood cell survival, blood losses, iron deficiency, aluminum intoxication etc. (2, 3). Many dialysis patients require intermittent blood transfusions with the risk of inducing iron overload. Patients with the human leukocyte antigens (HLA) A₃, B₇ and B₁₄ seem to be at greater risk of developing iron overload (4, 5-6).

Aluminum (Al) overload, in dialysis patients, is a recognized complication of oral intake of aluminum hydroxide phosphate binders, and/or high Al content of the dialysis water (7, 8). It has been observed that patients with low serum ferritin concentrations, absorb more Al than those with high serum ferritin (9), a more accurate measure of iron (Fe) status than serum iron (10), suggesting that there is a link between Al and Fe cation absorption and metabolism.

We undertook a retrospective survey of hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients to determine if there was a link between the major histocompatibility complex and serum Al concentrations. Furthermore we evaluated the relationship between serum Al and ferritin concentrations.

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Patients and methods

The study included 119 HD patients, and 35 CAPD patients. The mean (\pm SD) age of the HD patients was 57 ± 13 years (60 male, 59 female), who had been receiving dialysis for a mean of 6.5 ± 3.5 years (range: 2 months to 14 years). Twenty five percent (25 %) of HD patients had been on dialysis for more than 10 years. The mean age of the CAPD patients was 50 ± 15 years (21 male, 14 female), and their average time on dialysis was 4.3 ± 3.4 years (range: 4 months to 13 years, with 8.3 % of these patients having been on dialysis for more than 10 years). Some of the CAPD patients were previously on HD.

HD had been performed three times a week for four hours using hollow fiber dialyzers and reverse osmosis for treatment of the water. Four 2 liters daily CAPD exchanges were performed by the patients using dextrose dialysis fluid (Dianeal, Baxter, IL). Oral iron supplements (intravenous iron was used in the past), aluminum hydroxide and calcium carbonate were given as needed to maintain adequate serum ferritin, phosphate and calcium concentrations. Parenteral androgens were used regularly, for the treatment of anemia. Blood transfusions were performed only when the patients were symptomatic and/or had an hematocrit lower than 16 %. Serum ferritin concentration was measured by radioimmunoassay (RIA) using mouse and rabbit antibodies (normal values range between 10 and 350 ng/mL). Serum Al concentration was measured by electrothermal (graphite furnace) atomic absorption spectrophotometry. Serum Al and ferritin levels were measured within two months of each other.

Unpaired t-test, linear regression and Fisher's exact test were used for statistical analysis.

Results

Serum Al and ferritin concentrations of HD and CAPD patients taken together, were 73 ± 43 mcg/L and 347 ± 378 ng/mL respectively. There was no correlation between serum Al and ferritin concentrations ($t = 0.44$, $p = 0.65$), nor, was there a correlation between time on dialysis and either serum Al or ferritin concentrations. ($t = 0.62$, $p = 0.53$; and $t = 0.18$, $p = 0.85$, respectively).

Serum Al and ferritin concentration were compared for 35 CAPD and 35 HD patients matched for time on dialysis. Twenty six (74 %) of these CAPD patients were on CAPD for at least 2 years (mean time 3.3 years; range between 3 months to 6.25 years). There was no difference in serum ferritin concentrations between the two groups. However, serum Al concentrations were higher in the HD than in the

CAPD patients (75 ± 43 mcg/L versus 52 ± 53 mcg/L, $p < 0.05$). Table I.

TABLE I

Serum ferritin and Al concentration in HD and CAPD patients, matched for time on dialysis

	CAPD (n = 35)	HD (n = 35)
Years on dialysis	5.5 ± 3.4	4.4 ± 2.2
Serum Ferritin ng/mL	411 ± 402	317 ± 422
Serum Al mcg/L	52 ± 53	$75 \pm 43^*$

Values are expressed in Mean \pm SD. $8 p < 0.05$

Only 9 (6 HD and 3 CAPD) of 147 patients (6.1 %) had serum ferritin concentrations over 1,000 ng/mL. In only 4 of these 9 patients was HLA typing available and 3 of the 4 had at least one of the "haemochromatosis alleles" (HLA A₃, B₇ or B₁₄) present. We could find no association between HLA alleles, and high serum Al concentration in HD (29 patients) and CAPD (32 patients) patients taken together ($p = 0.052$). However, when the CAPD group (32 patients) was studied independently of the HD group, we found a significant association between HLA B₄₄ and serum Al concentrations greater than 50 mcg/L ($p < 0.01$), with a prevalence of the allele of 55 %. Table II.

TABLE II

Comparison of HLA B₄₄ and serum Al in 32 CAPD patients

Serum Al	HLA B ₄₄ present	HLA B ₄₄ absent
> 50 mcg/L	6	5
< 50 mcg/L	2	19

Values are expressed in Mean \pm SD. $8 p < 0.05$

Discussion

Patients on dialysis are at high risk of developing both iron and Al overload secondary to exogenous administration (2, 6, 7). Several studies have shown a link between HLA A₃, B₇, B₁₄ and iron overload (4, 5, 11). Only 9 of our patients had serum ferritin levels over 1,000 ng/mL and none had symptoms of iron overload. HLA typing was available in only 4 of these patients (3 CAPD and 1 HD) and three of them had at least one of the "hemochromatosis alleles" confirming previous studies (4, 5, 11). When the CAPD patients were considered alone we found a significant association between HLA B₄₄ and serum Al concentration greater than 50 mcg/L, with a prevalence of

the allele of 55 % (the prevalence of HLA B₄₄ in the American and European Caucasian population is approximately 20 % (12). But when both CAPD and HD patients were considered together this association almost, but did not, reach statistical significance ($p = 0.052$). Therefore it does not seem to be a clear association between the major histocompatibility complex and Al status in patients on dialysis. However, we believe that further studies are warranted to evaluate, if such association becomes apparent in patients with clinical signs of Al toxicity.

Hakim et al (13) recently reported that 41% of their 150 HD patients had serum ferritin concentrations greater than 2,000 ng/mL and they suggested this was likely a reflection of the large number of long-term HD patients and their "liberal criteria for transfusions". In our study 25 % of the HD patients were on dialysis for more than 10 years and yet the mean serum ferritin concentration was 327 ng/mL (range 17 - 1,857 ng/mL) with only 5 % of patients having serum ferritin concentrations over 1,000 ng/mL; furthermore we could find no correlation between time on dialysis and ferritin levels. It has been well documented, that there is a close correlation between the number of transfusions, parenteral iron administration, and the risk of iron overload (14). Since our original study (5), we have had strict criteria for blood transfusions, as well as abandoning parenteral iron, preferring instead to use parenteral androgens for the treatment of anemia, and minimizing patient blood loss with thorough dialyzer rinsing procedures. Patients with HLA A₃, B₇ and B₁₄, may well be at higher risk for developing iron overload, but routine screening for all patients is clearly not feasible.

Cannata et al (9) reported an inverse correlation between serum ferritin and Al concentrations, suggesting that there is a common pathway for gastrointestinal absorption of iron, lead, cadmium, cobalt and aluminum; they concluded that patients with high iron stores would absorb less Al and therefore, would be at lower risk for developing Al overload than those with low iron stores. However, in our study we could find no correlation between serum ferritin and Al concentrations. While serum ferritin correlates strongly with tissue iron stores, there is a less clear relationship between serum Al concentrations and tissue Al concentration (15). At very high serum aluminum concentrations, however, it has been shown that there is a close association between serum Al levels greater than 200 mcg/L and bone Al deposits (16). According to Cannata et al (9), these patients should have low serum ferritin concentrations. Only 2 % of our patients had serum Al levels in this range and we could not find such a correlation. It is interesting to note that the CAPD patients have lower serum Al concentrations than HD patients when matched for

time on dialysis. This may be related to a better Al clearance with peritoneal dialysis, less total aluminum exposure in dialysis water, or to less oral Al intake. It is difficult to compare the aluminum hydroxide doses used as phosphate binders in both groups, but if, indeed, hyperphosphataemia is better controlled with CAPD than with HD (17), it may mean that lower doses of oral Al hydroxide are required during CAPD, and these patients may, therefore, be at lower risk of developing Al overload.

In conclusion, we believe that iron overload can be avoided in dialysis patients if blood transfusions are used only when it is absolutely necessary. Administration of parenteral androgens help to reduce the number of transfusions per patient per year. Serum Al concentration is higher in the HD than in the CAPD patients, therefore patients on HD are at higher risk of developing Al overload. However, further studies are needed to evaluate the association between high serum Al concentrations and the major histocompatibility complex.

We could find no correlation between serum Al and ferritin and, therefore, further studies are required to confirm if, indeed, trace elements share the same intestinal pathway for absorption.

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