



Serum Aluminum Level and Its Relation with Parathyroid Hormone and Anemia in Children on Maintenance Hemodialysis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AAH and MAES designed the study, wrote the protocol, wrote the first draft of the manuscript and managed the literature searches. Author GESI managed the analyses of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/16146

Editor(s):

(1) Toru Watanabe, Department of Pediatrics, Niigata City General Hospital, Japan.

Reviewers:

(1) Anonymous, Spain.

(2) M. M. Suchitra, Department of Biochemistry, Sri Venkateswara Institute of Medical Sciences, India.

Complete Peer review History: <http://www.sciencedomain.org/review-history.php?iid=946&id=12&aid=8299>

Original Research Article

Received 10th January 2015
Accepted 18th February 2015
Published 27th February 2015

ABSTRACT

Aim: Renal excretion of aluminum is impaired in patients with chronic kidney disease, thereby increasing the risk of toxicity. Our aims were to determine the serum aluminum level in children on regular haemodialysis and to assess the effect of aluminum on PTH and blood parameters.

Methodology: This is a case control study was done on 120 children, a group of 60 cases on regular hemodialysis, their ages ranged from 3 to 16 year. They were 27 males (45%) and 33 females (55%) they were selected from the hemodialysis unit and outpatient clinic of Al-Zahraa hospital, AL-Azhar University during the period from January 2014 to September 2014. The studied cases were divided into two groups according to the serum aluminum level; group A $\leq 50 \mu\text{g/L}$, and group B $> 50 \mu\text{g/L}$. Another group of 60 apparently healthy children with matched age and sex with the patient group served as a control. All subjects underwent thorough history taking, clinical examination and the following investigations: complete blood count, blood urea, serum creatinine,

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total serum calcium, serum phosphorus, serum aluminum, ferritin, PTH and aluminum level of drinking water and water for dialysis.

Results: In this study serum aluminum level was significantly higher in cases compared with controls, it was (60 ± 20 $\mu\text{g/L}$) and (20 ± 10 $\mu\text{g/L}$) respectively ($P=.000$). Also we found serum PTH was significantly higher while serum calcium was significantly lower in cases compared to controls particularly in children whose aluminum >50 $\mu\text{g/L}$. We found a significant positive correlation between serum aluminum levels with PTH ($r=.50$, $P=.001$). Also our study reported that the aluminum level in both tap water (for drinking) and water from the dialysis unit their levels were 300 $\mu\text{g/L}$ and 1 $\mu\text{g/L}$ respectively.

Conclusion: Drinking water is the main source of high aluminum level in our study and its overload is still a serious health problem in hemodialysis children. So aluminum should be diminished from drinking water to reach the permissible limit; routine monitoring of aluminum level and new modalities of hemodialysis is recommended.

Keywords: Aluminum; parathyroid hormone; PTH; hemodialysis; children.

1. INTRODUCTION

Although the prevalence of aluminum (Al) overload in dialysis patients is decreasing, it is still an insidious problem worldwide, especially in these dialysis patients still often exposed to aluminum-containing medications [1].

Aluminum is considering one of the trace elements. Trace element is defined as one that makes up less than 0.01% of body's mass. Those present at $\mu\text{g/dl}$ in body fluids and at mg/kg in tissues are referred to as trace elements [2].

In end stage renal disease patients different factors affect serum concentrations of trace elements like increased oral intake, failure of renal excretion, degree of renal failure, use of medications, contamination of dialysate, quality of water used for dialysis and metabolic alterations associated with renal failure [3-5].

Aluminum toxicity can cause osteomalacia, anemia, and dementia in hemodialysis patients and has historically been associated with exposure to contaminated water or dialysate preparations or ingestion of aluminum-containing phosphate binders. Since 2002, improvements in water treatment methods and use of non-aluminum-containing phosphate binders have resulted in low prevalence ($<1\%$) of aluminum toxicity among hemodialysis patients [6].

Water source, some domestic tap water contains aluminum in high concentration, either naturally or because aluminum has been added as a flocculent in the purification process [7].

Concentrations of aluminum in food range widely (means range from <0.001 to 69.5 $\text{mg}/100$ g),

depending on the nature of the foodstuffs. The highest levels are found in nuts, grains and dairy products, particularly processed cheeses [8].

The aluminum entering the body accumulates in various tissues, including bone, brain, parathyroid glands, and other organs. Such accumulation of aluminum can produce toxicity [9].

Aluminum toxicity generally leads to an accelerated cell death due to chronic disruption of cell metabolism. Among the effects, aluminum can lead to an interference with the glucose transphosphatase cycle, disturbance in parathyroid hormone (PTH), bone metabolism and changes in serum essential elements as calcium and phosphorus [10].

Aluminum induced direct and indirect effect on the parathyroid gland, acting through different mechanisms. Aluminum accumulation in the parathyroid glands can reduce the parathyroid response to hypocalcaemia and prevents release of PTH [11]. Also it interferes with synthesis of PTH [12] and has an inhibitory effect on parathyroid cell proliferation [13].

Anemia is common in people with kidney disease. Healthy kidneys produce a hormone called erythropoietin (EPO), which stimulates the bone marrow to produce the proper number of red blood cells needed to carry oxygen to vital organs. Diseased kidneys, however, often don't make enough EPO. As a result, the bone marrow makes fewer red blood cells [14].

We conduct this study to determine the serum aluminum level in haemodialysis children and to assess the effect of aluminum on parathyroid hormone (PTH) and blood parameter.

2. SUBJECTS AND METHODS

This is a case control study; it was carried out on 120 children from pediatric hemodialysis unit and the outpatient clinic of Al-Zhraa hospital, Al-Azhar University during the period from January 2014 to September 2014.

The study included 60 children with chronic kidney disease (CKD) on regular hemodialysis more than three months, for 4 hours/setting, 3 times weekly, with low flux polysulphone dialyzer by 4008 Fresenius machine. The most common cause of CKD in the patients group was unknown (44%) followed by focal segmental glomerulosclerosis (20%), their ages ranged from 3 to 16 year. They were 27 males (45%) and 33 females (55%).

The studied cases were divided into two groups according to the serum aluminum level; group A $\leq 50 \mu\text{g/L}$, and group B $> 50 \mu\text{g/L}$. $50 \mu\text{g/L}$, this highest level before occurrence of aluminum toxicity.

A group of 60 apparently healthy children with matched age and sex with the patient group served as a control. Children with acute kidney injury and on peritoneal dialysis were excluded from the study; they were subjected to full history taking including etiology, onset of CKD and the duration of hemodialysis, and Laboratory investigations. Informed consent was obtained from the participating parents in adherence with the guidelines of the ethical committee of AL-Zahraa hospital, AL-Azhar University, Cairo, Egypt.

2.1 Sample Collection

7 ml venous blood samples were withdrawn, 2 ml for complete blood picture were taken on EDTA solution for CBC; 5 ml of the samples were put in a plain tube and left to clot and sera were separated without delay. Separates sample divided into two portions; one for (serum urea, creatinine, calcium and phosphorus) were done on the same day. The other serum sample divided into two portions ;one for serum ferritin and PTH and the other portion for serum aluminum that stored in a special tube, red-top vacutainer tubes (Becton Dickinson Co., Rutherford, NJ07070), to avoid false positives due to contaminates. Both serum samples were stored at -20°C after careful labeling till the time of assay.

2.2 Water Sampling

Two samples of water were taken; the first one was from the water of dialysis unit which is used for dialysis and the second sample from the tap of drinking water.

2.3 Routine Investigations

- Complete blood picture was done automatically by coulter MD 18 automated hematological counters [15].
- Serum urea and creatinine were done on AVL.988
- Serum calcium (Ca) and serum phosphorus (Ph) were done on HITACHI auto analyzer.
- Serum ferritin. Was measured quantitatively by enzyme-linked immuno-sorbent assay (ELISA).
- PTH assay was done on Elecsoys 1010 electrochemilumescence autoanalyzer.

2.4 Specific Investigations

- 1- Serum Aluminum for the patients and the controls.
- 2- Aluminum concentration in water pipe system used for drinking and from the dialysis water unit.

The two samples were used for detection of aluminum level using perkin Elmer 2380, atomic absorption spectrophotometer according to the method of AOAC [16].

2.5 Statistical Analysis

The data of collected questionnaire was entered and analyzed using SPSS 16.0 (Statistical Package for Social Sciences). Mean and standard deviation was given for normally distributed quantitative variables. Frequencies and percentages were given for qualitative variables. Two – independent sample t test was applied to observe group mean differences. Pearson correlation was applied to observe correlation between quantitative variables. A *P* value of $<.05$ was considered statistically significant. Receiver operating characteristic curve (ROC) was used to assess the best cut off point with sensitivity, specificity, positive predictive value (+PV) and negative predictive value (-PV).

3. RESULTS

Our study reported no statistical significant difference between cases compared with the

controls as regard gender and age, Table 1. However Table 2 revealed a statistically significant decrease in RBC, Hb, Hct% in cases when compared to the controls, while it shows a significant increase in serum urea, creatinine and Ph levels in cases than the control group. The same table shows no significant difference regarding serum calcium level between both groups.

This work showed significant increase in the serum ferritin, PTH and aluminum levels in patients group compared with the controls, Table 3.

Also our study reported that the aluminum level in both water pipe system (for drinking) and water from the dialysis unit their levels were 300 µg/L and 1 µg/L respectively, Table 4.

Our result showed comparison between group A (≤ 50 µg/L) and group B (> 50 µg/L) regarding laboratory parameters. There was a statistical significant difference between both groups

regarding the serum calcium, PTH and ferritin levels. The mean serum Ca level in group A and group B were 9.43 ± 3.79 mg/dl and 7.67 ± 1.29 mg/dl respectively with $P=.04$; while the median PTH in group A and group B were 338 pg/ml and 691 pg/ml respectively, with $P=.000$ Also the median of ferritin in both groups was 510 µg/dL and 983 µg/dL respectively. With $P=.000$. However there was no statistical significant difference with other parameters, Table 5.

The correlation between serum aluminum level and the studied parameters are shown in Table 6; it revealed a positive correlation between serum aluminum level with PTH and age. However there was no significant correlation with the other parameters.

The cut of points for aluminum between cases and the controls are noticed in Table 7 and Fig. 1; it revealed that aluminum 80% sensitive and 100% specific in prediction of case group.

Table 1. Comparison between patients group and the controls regarding age and gender

Variable	Controls (n=60)		Cases (n=60)		Chi-square test		
	No.	%	No.	%	X ²	P-value	
Gender:	Female	36	60%	33	55%	0.205	.651
	Male	24	40%	27	45%		
Age (year):	Mean±SD		Mean±SD		t-test	P-value	
	11±3.42		10.1±4.32		1.035	.304	
Range	4-15		3-16				

Table 2. Comparison between the two studied groups regarding laboratory data

Variable	Control group (n=60)		Cases group (n=60)		Independent t-test	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	t	P-value
RBCs (10 ⁶ /mm ³)	4.90±0.28	3.97±1.15	4.90±0.28	3.97±1.15	4.980	.000*
Hb mg/dl	11.99±2.94	10.17±1.48	11.99±2.94	10.17±1.48	3.502	.001*
(Hct)%	40.00±0.88	31.15±4.04	40.00±0.88	31.15±4.04	13.539	.000*
MCV(fl)	83.64±3.65	83.00±3.55	83.64±3.65	83.00±3.55	0.795	.429
Urea mg/dl	21.60±6.89	162.22±35.77	21.60±6.89	162.22±35.77	-24.417	.000*
Creainine mg/dl	0.35±0.11	7.86±2.08	0.35±0.11	7.86±2.08	-22.796	.000*
Calcium (mg/dl)	9.17±0.37	8.47±2.82	9.17±0.37	8.47±2.82	1.568	.121
Phosphorus (mg/dl)	4.39±0.39	5.84±1.83	4.39±0.39	5.84±1.83	-4.901	.000*

* Statistically significant

Table 3. Comparison between cases group and the controls as regard serum levels of ferritin, parathyroid hormone (PTH) and aluminum (Al)

Variable	Controls group (n=60)	Cases group (n=60)	Test of significance	
			t/z*	P-value
Ferritin (µg/dl), median (IQR)	84(78-89)	718(356-1908)	6.594*	.000*
PTH (pg/ml), median (IQR)	37.5(32-45)	557.5(309-827)	6.164*	.000*
Al (µg/L), mean ± SD	20±10	60±20	-11.217	.000*

* Mann-Whitney test; *Statically Significant

Table 4. Aluminum level in tap water (for dinking) and hemodialysis water unit

Aluminum in water samples	Tap water (drinking water) 300 µg/L	Hemodialysis water 1 µg/L
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Table 5. Comparison between group A and group B regarding laboratory data

Variable	Group A (aluminum ≤ 50 µg/L) (n=27)	Group B (aluminum >50 µg/L) (n=33)	Test of significance	
	Mean±SD	Mean±SD	t/z*	P-value
RBCs (10 ⁶ /mm ³)	4.32±1.55	3.68±0.58	1.785	.082
Hb (gm/dl)	10.21±1.75	10.13±1.26	0.176	.861
Urea (mg/dl)	156.93±27.60	166.55±41.42	-0.842	.405
Creatinine (mg/dl)	7.57±2.54	8.10±1.63	-0.803	.427
Ca (mg/dl)	9.43±3.79	7.67±1.29	2.044	.048*
Ph (mg/dl)	6.30±1.87	5.43±1.74	1.486	.146
Ferritin(µg/dl), median (IQR)	510(312-1001)	983(400-1908)	-5.073*	.000*
PTH (pg/ml), median (IQR)	338(76-929)	691(401-1001)	-3.991*	.000*

* Mann-Whitney test; *Statistically significant

Table 6. Correlation between serum aluminum level and the studied parameters

Variable	AI	
	r	p-value
Age (year)	0.33	.041*
Duration of disease (month)	0.04	.805
RBC (10 ⁶ /mm ³)	-0.13	.415
Hb (mg/dl)	0.04	.824
Urea(mg/dl)	0.00	.975
Creatinine (mg/dl)	0.21	.204
Ca (mg/dl)	-0.30	.058
Ph (mg/dl)	-0.19	.259
Ferritin(µg/dL)	0.09	.597
PTH (pg/ml)	0.50	.001*

*Statistically significant

Table 7. Cut off point for the serum level of aluminum in prediction of the case group

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>40 µg/L	98.1	80.00	100.00	100.0	83.3

4. DISCUSSION

Ingested aluminum is normally excreted by the kidney. When there is a markedly reduced or absent kidney function, there is little or no ability to excrete aluminum and hence accumulation can occur [17]. In this study serum aluminum level was significantly higher in cases with CKD on regular hemodialysis than in controls, it was (60±20 µg/L) and (20±10 µg/L) respectively (P=.000). Our results are in accordance with Anees et al. Lee et al. and Skarupskiene et al. [18,2,19], they reported that significant high level of serum aluminum in cases compared to controls.

Aluminum level at the beginning of dialysis should be 20 µg/L, and toxicity can occur at levels 60 µg/L [20]. In the present study, the prevalence of aluminum overload (serum aluminum >50 µg/L) was observed in 33 (55%) of cases, serum aluminum values were greater than the recommended baseline by National Kidney Foundation- Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and accordingly most of our patients had Aluminum overload that is a shocking result.

In the current study high serum aluminum level in cases may be due to high aluminum concentration in drinking water, it is surprising to find that the

aluminum concentration in water tap used for drinking is 300 µg/L, this amount exceeds the permissible limit. Source of drinking water in hospital is the same source which serves the residents of the area in the hospital district. Most of the children in the study live in the same district, so they have the same water source in their homes. In Egypt, they add aluminum as a flocculent in the purification process of drinking water. Also, the water source used for hemodialysis is from tap water but it is enter to special filtration unit before using. In addition to cooking in aluminum utensils, using of foils for packaging and beverage cans may be another source of aluminum.

In a survey of 186 community water supplies in the USA, median aluminum concentrations for all finished drinking-water samples ranged from 30 to 100 µg/L.

The urine is the most important route of aluminum excretion [21,22]. Our patients can not excrete aluminum as most of them are anuric but not all and this may explain the difference in aluminum serum levels, also the composition of the food eaten in conjunction with drinking water that contains aluminum has a strong effect on the absorption of aluminum [23].

The aluminum level in dialysis water was 1 µg/L, which is within the value recommended by US and Europe, they recommended keeping the concentration of aluminum in dialysis fluid below 2 µg/L, which has nearly eradicated dialysate linked aluminum intoxication [24].

The cases in this study do not take any drugs containing aluminum (aluminum hydroxide). Routinely calcium based phosphate binders are used to control this complication, so drinking water in our study is considered the main source of high aluminum level in our cases.

Nearly everyone with end-stage kidney failure has anemia. The most likely cause of anemia is decreased erythropoietin hormone (EPO) production, in our study there was decrease in RBC, Hb, Hct % in cases when compared to controls. Our results are in agreement with several studies [25-28].

In spite of anemia observed in our patients in this study we found significant high level of serum ferritin in patients group. The serum ferritin is an 'acute phase reactant'. It may be elevated secondary to chronic inflammation or infection

and, thus, is not always a reliable index of iron deficiency in chronic kidney disease patients, in contrast to normal individuals without underlying renal disease [29].

Also we found no correlation between serum aluminum and ferritin. High serum ferritin in the present study does not reflect the state of anemia as it is considered one of the inflammatory markers in end stage renal disease (ESRD).

Aluminum may cause anemia through decreased heme synthesis, decreased globulin synthesis, and increased hemolysis. It may also have a direct effect on iron metabolism: it influences absorption of iron via the intestine, it hinders iron's transport in the serum, and it displaces iron's binding to transferrin. Excess aluminum has been shown to induce microcytic anemia [30].

Functional iron deficiency is likely to develop in most patients leading to iron-limited erythropoiesis. Iron stores are adequate in functional iron deficiency; however, there is an inability to adequately mobilize it from the reticuloendothelial system to support erythropoiesis [31]. Both functional iron deficiency and reticuloendothelial blockade may lead to erythropoietin resistance [32]. Therefore, dialysis patients with an obvious aluminum overload may need larger doses of recombinant human erythropoietin (rHuEPO) to overcome this resistance, which significantly increases the cost of patient care [33].

In our study, serum PTH was significantly higher in cases compared to controls particularly in children whose aluminum >50 µg/L; our results are in accordance with several studies [34-36]. On the contrary, some studies suggested that lower level of PTH in cases compared to controls [10,12,24]. Our explanation of increased PTH is uremia may be associated with the development of severe secondary hyperparathyroidism (HPT). HPT is associated with an increase in PTH synthesis and secretion and with proliferation of the parathyroid cells.

Elevated aluminum levels in humans, primarily in individuals with impaired renal function have been associated with several bone disorders. The mechanism by which aluminum exerts its effects on bone tissue may be due to inhibition of osteoblast proliferation, function and mineralization of osteoid tissue [37].

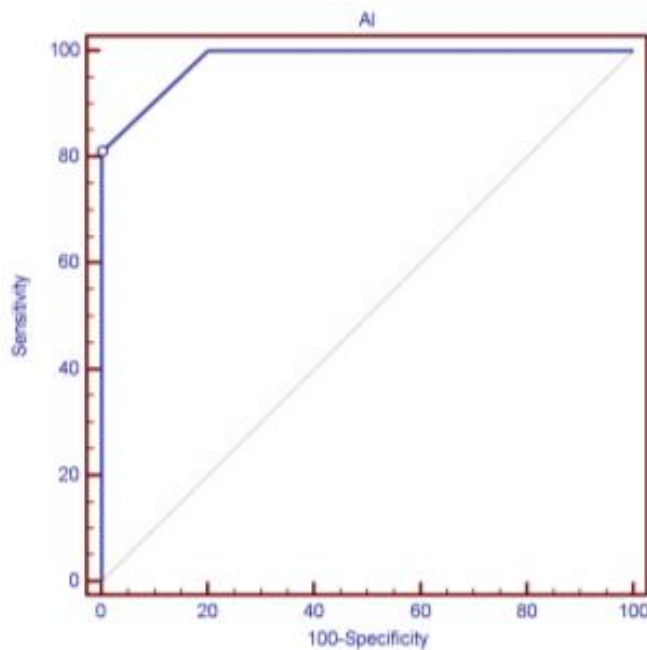


Fig. 1. ROC curve for serum level of aluminum between cases and the controls

There is clear evidence that sustained exposure to high aluminum levels can cause bone abnormalities, our results are similar to that obtained by Mjoberg et al. [38]; who reported that aluminum exposure greatly increased the risk of fragility fractures and bone disorders due to the fact that aluminum decreases serum calcium and inhibits bone mineralization.

Also in the present study in spite of highly elevated PTH in CKD patients, hypocalcemia is still observed particularly in children whose aluminum >50 µg/L. Aluminum accumulation in the parathyroid glands can reduce the parathyroid response to hypocalcaemia and prevents release of PTH [11]; the observed hypocalcaemia particularly in these patients may attributed to the effect of aluminum as it impairs parathyroid function through a calcium-like mechanism due to the lack of specificity of the calcium-sensing receptor. Accordingly we found a positive correlation between PTH and aluminum level, while a negative correlation between serum aluminum and calcium was reported but not reached to be of statistical significant value and it may due to small sample size and it is one of the study limitations. Also the study reported positive correlation between aluminum with age and consequently the abnormalities occurring with aluminum accumulation.

5. CONCLUSION AND RECOMMENDATIONS

Drinking water is the main source of high aluminum level in our cases and it is major health problem for children either healthy or with CKD and general population as a whole. Also cooking in aluminum utensils, using of foils for packaging and beverage cans may be another source of aluminum, so we need further study to detect other sources of aluminum intoxication. Aluminum should be diminished from tap water (drinking water) to reach the permissible limit according to the specifications of the World Health Organization. Health education for people about the sources, uses and toxicity of aluminum is important. Aluminum overload is an ignored problem in many of dialysis unit. Routine monitoring of aluminum level and new modalities of hemodialysis is recommended to reduce aluminum overload and consequently improve aluminum overload sequels particularly related to anemia and bone disorders.

CONSENT

Informed consent was obtained from the participating parents in adherence with the guidelines of the ethical committee of AL-Zahraa hospital, AL-Azhar University, Cairo, Egypt.

ETHICAL APPROVAL

Consent was obtained from the ethical committee of AL-Zahraa hospital, AL-Azhar University, Cairo, Egypt. Participation in the study was voluntary and nobody was coerced into participation. The data will be Confidential and used only in this research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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