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Lead poisoning and cystatin-C in children

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Abstract

Background Lead pollution is a global problem both in developed and developing countries. Lead poisoning is associated with decreased glomerular filtration rate (GFR) and is a risk factor for acute kidney injury (AKI). Serum cystatin-C is a more precise test of GFR than serum creatinine level, as serum cystatin-C levels rise earlier than serum creatinine, when GFR decreases.

Objective To assess for a possible correlation between lead poisoning and cystatin-C levels in children.

Methods We conducted a cross-sectional study in children aged 6-11 years with a history of lead poisoning from elementary schools in Talawaan District, North Minahasa Regency from July to October 2013. Cystatin-C and blood lead levels (BLL) were measured in all subjects. Spearman's rho test was used to analyze a potential correlation between BLL and cystatin-C level.

Results This study included 41 children, comprising 21 boys and 20 girls. Their median age was 8.50 (range 6.8-10.7) years. Elevated levels of cystatin-C did not exceed normal values, however, we found a positive correlation between BLL and cystatin C ($r=0.419$, $P=0.006$).

Conclusion There is a positive correlation between BLL and cystatin C level in children with lead poisoning. Regular monitoring of BLL, medical intervention, and an epidemiological study to help find the sources of contamination are needed for children with lead poisoning. **[Paediatr Indones. 2015;55:252-6]**.

Keywords*: lead poisoning, cystatin-C, AKI, children*

Lead is a dangerous substance that can poison the environment and impact many systems in the body. Lead pollution remains a problem in both developed and developing countries.[1] The *American Academy of Pediatrics* (AAP), the *Centers for Disease Control and Prevention* (CDC) and various national and international organizations determined lead levels are elevated (lead poisoning) when exceeding 10 μg/dL.[2,3] Several studies have been conducted to determine the effect of lead on the kidney, but the most recent study has been conducted in adults. A study in Poland concluded that children exposed to lead may exhibit glomerular and tubular renal dysfunction.[4] Serum creatinine is neither a sensitive nor specific examination for diagnosing acute kidney injury (AKI).[5] Many studies have shown serum cystatin-C levels to be a better indicator of GFR compared to serum creatinine levels, making it more sensitive as a marker for changes in renal function.[6-9]

A previous study conducted in the District of North Minahasa Regency, Talawaan reported a

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mean blood lead level that exceeded the threshold of 25.8 μg/dL. The suspected source of pollution was a gold mine possibly affecting villages located downstream from a river along the transportation route for mineral processing.[10] A correlation between lead and cystatin-C, a marker of AKI in children with lead poisoning, has not been previously studied in Indonesia. Therefore, the aim of this study was to assess for a possible correlation between lead poisoning and serum cystatin-C levels in children.

Methods

This was an observational study with a cross-sectional approach implemented in four elementary schools: GMIM 57 Tumbohon, Inpres Patokaan, GMIM 28 Warisa, and Inpres Warisa Elementary Schools in Talawaan District, North Minahasa regency from July to October 2013. The study population was comprised of 6-11-year-old elementary school students. Subjects fulfilled the following inclusion criteria: had lead poisoning (blood lead level ≥10 μg/dL),[3] good nutritional status based on the CDC 2000 Growth Chart, and had parents willing to provide informed consent. We excluded students with comorbidities such as kidney, liver, or chronic infectious diseases (such as tuberculosis), along with malignancy, burns, severe dehydration, or fractures. The minimum required sample size was calculated to be 38 children.

Subjects of this study were taken from a previous study of elementary school students who had high blood lead levels (≥10 μg/dL) one year ago.[10] Subjects underwent history-taking, anthropometric measurements, and physical examinations by researchers. Venous blood specimens were taken for examination of BLL and cystatin C levels. Severity of lead poisoning categorized based on blood lead level as follows: mild (10-40 μg/dL), moderate (40-60 μg/dL), and severe (> 60 μg/dL). Cystatin-C levels are defined as high normal when it is higher than its median and low normal if it its lower than its median.

Characteristics of subjects were reported in distributive tables. Analysis of the correlation between BLL and cystatin-C was done using Spearman's test because the data was not normally distributed, followed by linear regression correlation test. The significance value used in this study was $P<0.05$. All data were processed using *SPSS for Windows version 21*.

This study was approved by the Ethics Committee for Research at Sam Ratulangi University. Informed consent was obtained from parents before the children were examined.

Results

During the study period we identified 64 children. After further sampling, there were 41 children who met the study criteria. Overall, the subjects' median age was 8.5 years, consisting of 21 boys (51.2%) and 20 girls (48.8%). The median weight of subjects' was 23.0 kg (**Table 1**).

Subjects' mean lead level was 37.59 (SD 19.06) μg/dL, of whom 27 (65.9%) children had mild lead poisoning, 9 (22.0%) children had moderate lead poisoning, and 5 (12.1%) children had severe lead poisoning. The median level of cystatin-C was 0.68 mg/L. Six (14.6%) subjects had a high normal level of cystatin-C and 35 (85.4%) subjects had a low normal level of cystatin-C. The levels of blood lead and cystatin-C in the study are presented in **Table 2**.

We used Spearman's rho test to assess for a correlation between BLL and cystatin-C levels in children with lead poisoning. The results showed that higher BLL were associated with higher levels of cystatin C in children with lead poisoning ($r=0.419$, $P=0.006$). This correlation was also estimated by a linear regression equation ($y=0.574 + 0.003x$) (**Figure 1**).

Table 1. Characteristics of children with lead poisoning

Characteristics	(N=41)
Median age (range), years	8.50 (6.80-10.70)
Gender, n (%)	
Female	20 (48.80)
Male	21 (51.20)
Median weight (range), kg	23 (17.0-29.0)
Median height (range), cm	120 (108.0-134.0)

Table 2. Blood lead and cystatin C levels in children with lead poisoning

Variables	(N=41)
Median blood lead level (range), μg/dL	33.0 (14.0-93.0)
Median cystatin C level (range), mg/L	0.68 (0.59-0.96)

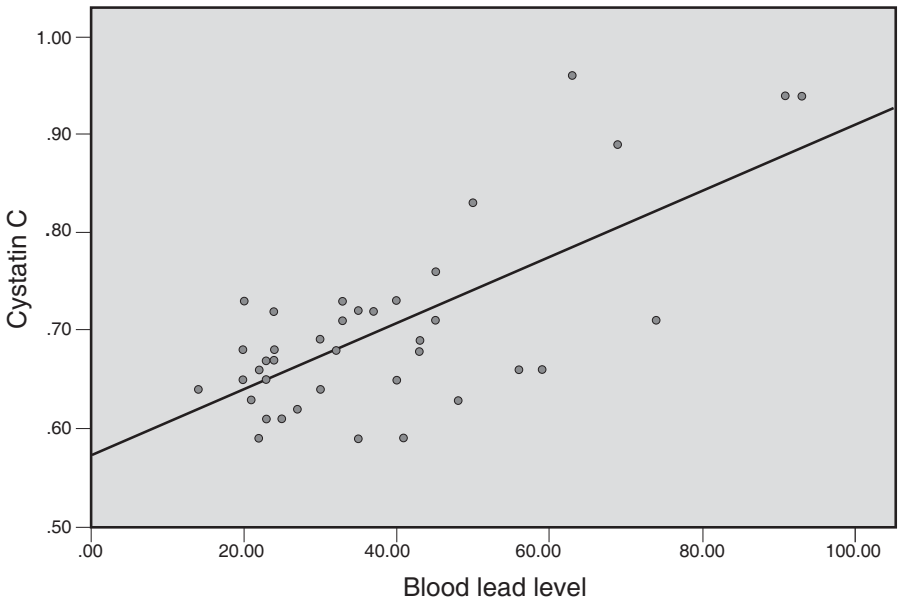

Figure 1. Correlation between blood lead level and cystatin-C level

Discussion

A study of blood lead levels in the District of North Minahasa Regency, Talawaan, had previously been performed on 46 children aged 6-8 years in 2012. The authors found that the average BLL exceeded the threshold of 25.8 μg/dL.[10] In this study, we found an increase in the mean lead level (37.59 μg/dL) compared to that of previous studies, due to chronic exposure and lead accumulation in the blood, as well as the tendency of BLL to increase with age, as older children are more exposed to lead from the environment, their activities, and food. In 1995, the WHO declared that the blood lead levels in children and the effect is persistent.[11] Children are also very sensitive to the effects of lead. They have greater absorption of lead from the air because of their higher respiratory rate, and from the gastrointestinal tract because they ingest more lead.[12-14] As much as 90% of lead in the body is stored in bone, which is released in the blood as children grow and develop.[15]

Blood lead levels in children are affected by potential sources of contamination, such as the location of residence/play area, activities, and parent's work.[16] Environmental factors such as climate and wind direction can cause differences in the risk of lead exposure in towns, villages, or waterfront locations. Absorption of lead is greatest in the respiratory tract, with 90% of inhaled lead absorbed into the body.[17,18]

Further investigation found that the presence of small-scale gold mining in the area was a major source of lead pollution in the environment where these children lived, although gold mining occurred many years prior. The gold mine was located 2 km away from the villages, but trucks hauling rocks for gold processing passed through the main street in the villages, spreading lead-rich dust. Moreover, the widespread use of motorcycles for transportation in the Talawaan District worsened air pollution. These villages also have lead poisoning demographics similar to that of mining sites. A study of 12 gold mines in Brazil in 2009 showed the presence of lead poisoning or contamination that occurs in children living near a gold mine.[16] This is due to the processing of gold by destroying the gold-rich rocks. The gold amalgamation process can release toxic minerals (tailings) including lead, contaminating soil, rivers, and air.[16]

A study on small-scale gold mining in Dimembe showed that acidic mine waste contained heavy metals such as lead and mercury, at thresholds exceeding environmental quality standards. This study also reported a mercury content of the Talawaan river

water to be higher than any other river.[19] The number of dead fish in the pond in Talawaan also suggests possible environmental pollution. The water from the river is used by surrounding communities for rice paddies and freshwater fish farms. The CDC and WHO in 2010 reported deaths caused by lead poisoning, which amounted to 97% of children living near a gold mine in Nigeria who had lead levels ≥45 μg/dL.[20] However, we could not ascertain whether the elevated levels of lead in the area was associated with the presence of gold mines. Future studies to search for the source of lead contamination in the Talawaan District could be crucial in preventing further occurrence of lead poisoning.

In this study, five (12.1%) children had severe lead poisoning. A home visit and search for potential sources of contamination for these 5 children with BLL ≥60 μg/dL in the Talawaan District found no new sources other than those theorized. The CDC recommendations specify that for asymptomatic children with BLL 10-19 μg/dL, treatment or medical intervention is unnecessary. Parents should receive education on the toxic effects of lead on growth and development of children and learn to avoid sources of lead contamination.[3] The effect of lead poisoning in children can be minimized by improving adequate intake of iron and calcium. Lead competes with iron and calcium for cellular metalloprotein-binding sites. As such, adequate levels of iron and calcium reduce the effect of lead in the body.[21] Drug treatment is recommended for children who are symptomatic, or with BLL ≥45 μg/dL.[3] In this study, 11 children had blood lead levels ≥45 μg/dL. Oral iron supplements were given as soon as possible to reduce BLL in accordance with the CDC recommendations.

Cystatin-C is a cytoplasmic protein that functions as an inhibitor of the protease system and is widespread in body fluids. It is constantly produced by all cells with nuclei and eliminated exclusively by glomerular filtration, so it can be used as a good indicator for assessing the glomerular filtration rate (GFR).[22,23] Several studies have shown that levels of serum cystatin-C are a more precise marker of GFR compared to serum creatinine levels, as cystatin-C increases earlier and higher than serum creatinine, with GFR decreases.[8] Cystatin-C is also not affected by obesity, height, gender, body composition, or age (except for under 1 year of age).[24] A study in Poland in 1999 found that lead-exposed children have glomerular and tubular renal dysfunction.[4] Recent study with larger samples in the United States in 2011 concluded that higher BLL was associated with decreased GFR and increased cystatin-C level, and was a risk factor for chronic renal failure.[25]

A correlation between lead and cystatin-C, a marker of early renal damage with lead poisoning, has been widely studied, but the study has been limited to adult subjects.[26] A study in Belgium in 2011 showed minor changes in proximal tubule function in children with BLL >100 μg/dL.[27] Exposure to high lead levels over several years had toxic effects on the kidneys and peritubular interstitial fibrosis, which resulted in atherosclerosis, fibrosis, glomerular atrophy, and hyaline degeneration.[26]

Previous studies on the nephrotoxic effects of lead in children have been conducted in several countries. A Romanian study on children aged 3-6 years who lived near a lead mine reported that they had increased levels of cystatin-C and GFR decline.[26] A Belgian study in children with an average age of 17 years also found that BLL were positively related to cystatin-C levels and urinary β2-microglobulin.[28] Other European study in a population of children who lived in gold mining areas showed that they had increased serum creatinine and cystatin-C.[26]

Spearman rho correlation analysis revealed a correlation between BLL and cystatin-C levels in children with lead poisoning ($r=0.419$, $P=0.006$), suggesting that higher BLL and higher cystatin-C levels increase the risk of AKI. Although a statistically significant correlation was found between BLL and cystatin-C levels in children with lead poisoning, the cystatin-C levels seen were within normal limits, 0.57-0.96 μg/L for children above 1 year of age.

A limitation of our study was that we could not determine the original cause of the lead pollution. The duration of lead exposure affects the BLL in children, but we do not know how long our subjects had increased lead exposure.

In conclusion, BLL is positively correlated to cystatin-C levels in children with lead poisoning, as increased BLL is associated with increased levels of cystatin-C. Routine examination of BLL, therapeutic intervention, and epidemiological study to find the source of contamination are required in children with lead poisoning.

Conflict of interest

None declared.

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