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Research Article

Correlations between Aging, Oxidative Stress, Micronutrient Deficiencies, Pollutant Metal-Toxicity and Increased Serum Gamma-Glutamyl Transferase (GGT) among Chronic myeloid Leukemia Congolese

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Abstract

Background: Hematologic Malignancy (HM) including Chronic Myeloid Leukemia (CML) is well established as a leading cause of morbidity and mortality worldwide in general and developing countries such as sub-Saharan African environment.

However, there is no understanding on hematologic malignancy from Central African clinics in Democratic Republic of Congo (DRC). The objective of this study was to determine the level independent association between aging, oxidative stress, micronutrient deficiencies, pollutant metal-toxicity and increased serum GGT among CML Congolese.

Methods: The present study was designed as a retrospective analysis for adult patients aged ≥ 20 years with anemia classified into confirmed cytologic aspects such as normal myelogram and CML between 2009 and 2015 at KUC, Department of chemical pathology.

Results: In total, 38 Black Bantu CML were examined with 16 men vs. 22 women: sex ratio 1 Man: 1 Woman, and mean age of 53.5 ± 20.6 years. After adjusted for confounding factors (transfusion number, plasmocytes, blast and lymphocytes, serum manganese, iodine, copper, arsenic, bromium, molybdenum, albumin, uric acid) using multiple linear regression model, only increase in age (oxidative stress), and metal toxicity related to cadmium and nickel were significant and independently and positively correlate with increase in serum GGT, whereas antioxidant capacity loss defined by decrease in serum iodine, selenium, and indirect bilirubin, was significantly and independently correlated with increase.

Conclusion: The present findings support a significant role of aging, and persistent imbalance between exaggerated prooxidant metal toxicity-urban pollution and loss of antioxidant ability to repair cellular damage in Bantu adults CML in Kinshasa. Serum GGT might be considered as a cheap proxy of expensive and unavailable, early, precise and efficient pathological-cytogenetical tools for diagnose treatment of CML from poor Kinshasa megacity DRC.

Keywords: Aging; Chronic myeloid leukemia; Gamma glutamyl transferase; Oxidative stress

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Introduction

Hematologic Malignancy (HM) including Chronic Myeloid Leukemia (CML) is well established as a leading cause of morbidity and mortality worldwide in general [1-3] and developing countries such as sub-Saharan African environment [3-5].

In the literature and in Central Africa including Rwanda and our Congolese experience the management of CML is feasible despite it challenging early and precise diagnose as well as the threat of epidemiologic-demographic-nutrition transitions [6-12]. Furthermore, oxidative damage and cell signaling transduction and treatment in general and in CML in particular [13,14].

Epidemiological studies supports a fundamental role of Gamma-Glutamyl Transferase (GGT/γ-GT) in oxidative stress conditions [15,16], metabolic syndrome, alcohol addiction, chronic liver disease and tuberculosis drug toxicity, and as well as cancers such as lymphoid and hematopoietic cancers [11-16]. Indeed, GGT is a strong enzyme at catalyzing the transfer of gamma-glutamyl functional group from molecules such as glutathione to an acceptor that may be an amino acid, a peptide or water (forming glutamate) [17]. GGT thus play an important key in the gamma-glutamyl cycle for the synthesis and the degradation of glutathione, drug, and xenobiotic detoxication [18]. Free radicals, metals, and antioxidant in oxidative stress are well known to induce cancer [19]. Aging is a real oxidative stress

conditions and is also a risk factor of cancers in general and HM in particular [20].

Different metals such as iron, copper, lead, mercury, chromium, cobalt, cadmium, arsenic and nickel generate structural, chemical, and biochemical of free radical (oxidative stress, cancer and DNA mutation) [21-24]. Although evidence of high level of lead, chromium, cobalt, copper, nickel, cadmium reported in breast milk in mother and children from Kinshasa, Democratic Republic of Congo (DRC) and among pre eclamptic women from Kinshasa, DRC there is data about variations of serum GGT in Kinshasa DRC patients with CML [25,26]. Moreover, there is insufficient and inaccurate diagnosis as well as other information of incident CML from African literature in general and from DRC in particular [27-29]. Therefore, the aim of this study was to determine the level independent association between aging, oxidative stress, micronutrient deficiencies, pollutant meta-toxicity, and increased serum GGT among CML Congolese.

Materials and Methods

The present study was designed as a retrospective analysis for CML adult patients aged ≥ 20 years well clinically, pathologically, cytogenetically, digitally and according to discriminante analysis in different previous scientific articles (publications mireille) classified into confirmed cytologic aspects such as normal myelogram and CML between 2009 and 2015 at KUC, Department of chemical pathology.

The variables of interest were gender, age, transfusion number, serum manganese, iron, copper, arsenic, selenium, bromium, molybdenum, cadmium, iodine, albumin, indirect bilirubin, uric acid, plasmocytes, blast, lymphocytes, colonial provinces, and HM form Albumin, total bilirubin, direct bilirubin, uric acid, γGT were performed at Lomo Medical using Photometer DNT-410 DIALAB, Wiener Neudorf, Austria 2012 by the enzymatic method.

Toxicology data (chromium, bromium, copper, mercury, lead, manganese, selenium, iron, zinc, nickel, arsenic, molybdenum, cadmium) were proceeded and analyzed at Research Center of Nuclear Energy of Kinshasa (CRENK) using the X-ray Fluorescence Spectrometer, Dispersive Energy, trademark AMETEK XEPOS, Model XEPOS IIIn with Mini PX Anode RX Generator CML, was define using WHO criteria for hematologic cancers (2008) Oxidative stress was specifically defined in Congolese patients including serum uric acid or decrease in levels of serum albumin indirect bilirubin (migration), selenium and iodine [4,19,30-32]. Metal toxicity was defined by increasing serum iron, manganese, copper, arsenic, bromium, molybdenum, cadmium, bromium [30]. The declines in concentrations serum selenium, iodine was also characterized for micronutrients deficiencies [30,32].

Statistical analysis

Descriptive statistics was used for count (frequency = n) and proportions (%) for gender whereas means ± Standard Deviation (SD) to describe continuous variables of interest. Bivariate analysis was used to calculate correlation simple Pearson's r-coefficient between serum GGT and the rest of continuous variables. In multivariate linear multiple regression model, variations (R^2) adjusted for potential confounding factors was obtained for independent association between serum GGT as a dependent variable and most important and significant independent determinant. Thus, unstandardized coefficients (B and Standard Error), standardized coefficients (Beta and 95% confident of interval/ CI), regression standardized Residual, observed cumulative (Com Prob), studentized deleted (Press) residual, and partial regression plot for each significant independent variable, were presented. The value of P < 0.05 was considered for significant difference. Statistical Package of Social Science (SPSS) version 23.0 for Windows (IBM/SPSS Inc., New York, USA) was used. Tables and figures were for messages as well as Box Plots for the variability of GGT.

Results

In total, 38 Black Bantu CML were examined with 16 men vs. 22 women: sex ratio (sex ratio 1 Man: 1 Woman, and mean age of 53.5 ± 20.6 years. Table 1 Summarized mean values of correlate and significant bivariate correlations between variables of interest among all CML patients. Indeed, there was significant POSITIVE bivariate association between aging, transfusion number and positive serum manganese, iron, nickel, copper, bromium, molybdenum, cadmium, uric acid, plasmocytes, lymphocytes, arsenic and serum GGT. However, there was a significant negative correlation between serum selenium, iodine, albumin, serum indirect bilirubin, blast and serum GGT.

Correlates	Mean ± SD	GGT/r coefficient	P-value
Serum GGT UI/L	430 ± 255	0.852	< 0.0001
Transfusion number	2.106 ± 1.7027	0.24	< 0.01
Hemoglobin g/dL	8.9465 ± 1.7027		< 0.0001
Serum manganese mg/L	2.0181 ± 1.35111	0.483	< 0.0001
Serum iron mg/L	6.1858 ± 1.8504	0.22	0.019
Serum nickel mg/L	3.8491 ± 1.47044	0.698	< 0.0001
Serum copper mg/L	3.8374 ± 0.81288	0.236	0.012
Serum selenium mg/L	0.3447 ± 0.11918	-0.392	< 0.0001
Serum bromium mg/L	4.489 ± 2.30424	0.211	0.024
Serum molybdenum mg/L	3.1907 ± 1.45658	0.229	0.014
Serum cadmium mg/L	3.7301 ± 1.14797	0.612	< 0.0001
Serum iodine mg/L	0.6076 ± 0.43211	-0.297	< 0.001
Serum albumin g/dL	3.1734 ± 1.25420	-0.479	< 0.0001
Serum indirect bilirubin mg/dL	0.4305 ± 0.44928	-0.359	< 0.0001
Serum uric acid mg/dL	9.5942 ± 3.80366	0.492	< 0.0001
Plasmocytes %	12.0566 ± 20.37370	0.529	< 0.001
Blasts	18.6425 ± 33.38051	-0.253	0.007
Lymphocytes	39.3628 ± 23.35864	0.411	< 0.0001
Serum arsenic mg/L	0.1037 ± 0.18047	0.45	< 0.0001

Table 1: Mean value of correlates and bivariate correlations between of interest among all CML patients.

After adjusted for confounding factors (transfusion number, plasmocytes, blast and lymphocytes, serum manganese, iodine, copper, arsenic, bromium, molybdenum, albumin, uric acid using multiple linear regression model, only increase in age (oxidative stress), and metal toxicity related to cadmium and nickel were significant and independently and positively correlate with increase in serum GGT, whereas antioxidant capacity loss defined by decrease in serum iodine, selenium, and indirect bilirubin, was significantly and independently correlated with increase in GGT (Table 2). Indeed the variation of serum GGT adjusted was R2 = 80.1%. This multivariate linear regression excluded clinical, protein energy nutrition (albuminemia)

hematological heavy metal parameters, unable to explain independent variations of serum GGT in all adult CML. However, exaggerated prooxidant markers such as aging, increasing of both cadmium and nickel explained independently increasing concentration of serum GGT. Whereas loss of antioxidant properties in terms of important decline in serum iodine, selenium and indirect bilirubin were significantly and independently associated with increased concentration of serum GGT in those adult CML.

	Unstandardized Coefficients		Standardized Coefficients	P-value
	B	Standard Error	Beta	
Age years	9.45	0.979	0.591	< 0.0001
Serum Cadmium mg/L	32.873	15.49	0.117	0.036
Serum Nickel mg/L	39.15	13.142	0.178	0.004
Serum Iodine mg/L	-66.704	33.463	-0.089	0.049
Serum Selenium mg/L	-343.383	130.605	-0.127	0.01
Serum Indirect bilirubin mg/L	-70.043	32.92	-0.097	0.036

Table 2: Most important determinants of Serum GGT among all cases of hematologic Malignancies.

Discussion

The present study characterized Black Bantu CML patients according to demographics (gender and age), treatment (transfusions number), hematologic profile (plasmocytes, blast, lymphocyte), cytogenetical profile (Philadelphia chromosome) oxidative stress markers (serum albumin, uric acid, indirect bilirubin, iodine, selenium), and metal toxicity (serum cadmium, molybdenum, bromium, arsenic, copper, manganese). The levels of serum GGT were compared according to CML, while univariate (bivariate) correlates and independent determinants of variations of serum GGT were identified in these CML patients.

This study did not reveal any sex predominance among CML cases. Sex did not influence the concentration of GGT. In general, these Black Bantu CML patients were young old adult, whereas CML patients in developed countries are elderly [23,33]. Markedly elevated serum GGT in CML patients, might be considered as the most sensitive and prognostic marker of hematologic cell proliferation and oncogenesis among these Black Bantu Congolese patients. Furthermore, there was a significant positive correlation between plasmocytes, blasts, lymphocytes and increasing level of serum GGT in this study.

In this study, oxidative stress was demonstrated by imbalance between the production of prooxidant (reactive oxygen species) and the decline of antioxidant properties in leukemia cancers in general and in CML in particular [18,19,22,34,35]. The present adult CML are often exposed to megacity Kinshasa pollution with metal toxicity underlying oxidative stress [11,30].

Both bivariate (univariate) and multivariate analysis confirmed that serum GGT augmentation is the marker of oxidative stress induced by aging, micronutrient deficiencies, and pollutant metal-toxicity [23,30]. Indeed, there was univariate and highly significant association between age, serum manganese, iron, nickel, copper, arsenic, selenium, bromium, molybdenum, cadmium, iodine, albumin, indirect bilirubin, uric acid and increased serum GGT. However, only six independent variables such as aging, metal toxicity (serum cadmium and serum nickel), and loss of antioxidant capacities of serum selenium, iodine, and indirect bilirubin were identified as the most important independent and significant determinants of increasing in serum GGT among these Black Bantu CML patients. This multiple linear model was fitted after adjusting for the majority of confounding factors with almost 100% of predicted cumulative probability.

This study showed. 80% of the variance of serum GGT after adjusted confounders using multiple linear analysis globally and there was a great differential influence of partial variances (R2) of serum GGT predicted individually by age, serum cadmium, nickel, iodine, selenium, and indirect bilirubin. Moreover, the present study demonstrated that increase in age was identified as the most important independent determinant of the increase in serum GGT with individual variations R2 = 47% in comparison with respective lowest individual variations R2 = 9% for serum nickel, 6% for serum selenium, 4% for serum cadmium, 4% for serum iodine and 4% for serum indirect bilirubin.

The understanding of the Pathophysiology of serum GGT will impact on the medical biology for Black and Bantu CML patients from DRCongo and among CML cases from others countries. Further studies on GGT and glutathione homeostasis and antioxidant defense, GGT gene could be performed in DRCongo [15,36]. In terms of perspectives for CML, aging, and longer exposure to carcinogens such heavy metal, and chronic loss of antioxidant capacity (micronutrient deficiencies) will be an emerging challenges of CML in DRCongo soon as well predicted to almost tripe around 2060 among [23]. Indeed aging is well-established as a biologic complex process mediated by genetic factors and environmental factors [37]. During aging, the Hematologic Stem Cells (HSC) will experience DNA damage, telomerase shortening, oxidative stress and poor homing efficiency [38, 39]. Therefore, genetic and epigenetic damage research is needed in CML patients over 65 years [23].

Limitations and Strength

This is the first study to characterize the clustering of several markers of oxidative and metal-toxicity and micronutrient deficiencies among Black Bantu CML patients. Despite this strength, the study was limited by each cross-sectional design without causal association only demonstrated by cohort studies (longitudinal cohort). Another limitation in this study was observed in the multiple linear analysis with 20% of unknown factors.

Conclusion

The present findings support a significant role of aging oxidative stress), and persistent unbalance between exaggerated prooxidant metal toxicity-urban pollution and loss of antioxidant ability to repair cellular damage in Bantu adults CML in Kinshasa. Serum GGT might be considered as a cheap proxy of expensive and unavailable, early, precise and efficient pathological-cytogenetical tools for diagnose treatment of CML from poor Kinshasa megacity DRC.

Conflit of Interest

There is no competing financial interest in relation to the work described.

Acknowledgments

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