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MIGRATION TOWARD A CHAOTIC KINSHASA MEGACITY: EFFECTS OF METAL TOXICITY, EROSIONS, FLOODS, WASTES, GARAGE STATIONS, WORKING IN INDUSTRIES, AND THE OCCURRENCE OF CASES WITH HEMATOLOGIC MALIGNANCY

Mireille Solange Nganga Nkanga[1], Benjamin Longo-Mbenza[2], Jacques Bikaula Ngwidiwo[1], Antoine Lufimbo Katawandja[1], Cécile Roth Laure Mapapa Miakassissa[3], Paul Roger Beia Kazadi[4], Solo Kuanda Thomas[5], Jimmy Yuma Ilemba[1], Blady Mpibi Mpiana[1], Mokondjimobe Etienne[6], Aurore Cecilia Orphée Beia Mbombo[1], Victor Nzuzi Babeki[7]

[1]Department of Medical Biology, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo, [2]Department of Research in Health Sciences Walter Sisulu University, South Africa, [3]Department of Medical Biology, Service of Pediatry, University Hospital of Brazzaville, Democratic Republic of the Congo, [4]Department of Medicine, OVD Hospital Center, Democratic Republic of the Congo, [5]Department of Laboratory Medicine , Regional Center of Nuclear Studies of Kinshasa, University of Kinshasa, Kinshasa, Democratic Republic of the Congo, [6]Department of Medical Biology, School of Masters and Doctors in Sciences, Faculty of Health Sciences, Marien Ngouabi University, Brazzaville, Democratic Republic of the Congo, [7]Department of General Medicine, Lomo Medical Clinic, Kinshasa, Democratic Republic of the Congo

Corresponding Authors : Mireille Solange Nganga Nkanga, E-mail: mnganga2002@yahoo.fr

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ABSTRACT

Background: Kinshasa is a megacity, capital of Democratic Republic of the Congo, with uncontrolled urbanization, demographic transition, migration, and heavy pollution. **Objectives:** The objective of this study is to classify hematologic malignancy (HM) cases by levels of environmental pollution using discriminant and factor analyses. **Methods:** The case series study design was undertaken. Adult patients aged ≥20 years were enrolled. The study was conducted in the Department of Chemical Pathology of Kinshasa University Clinics between 2015 and 2016. **Results:** In total, 114 HM cases (93 leukemia and 21 multiple myeloma) were diagnosed from patients residing within Kinshasa areas. There was a significant difference in the occurrence of HM cases between participants residing in areas located away from erosions-floods-wastes-cars and participants residing in areas located closer to erosion-floods-wastes-traffic gem-stations/garages-industry ($P < 0.0001$). After adjusting for confounding factors, only age, white cell count, serum nickel, serum mercury, and serum gamma-glutamyltransferase (GGT) were identified as the most important and significant markers able to discriminate participants with or without HM by levels of environmental pollution. Seven uncorrelated factors were identified as follows: Manganese-iron-nickel, copper, arsenic, and GGT elevation (Factor 1); increase in bromium, mercury, and depletion of iodine (Factor 2); depletion of selenium and increase in uric acid (Factor 3); increase in molybdenum and direct bilirubin (Factor 4); increase in chromium and total bilirubin (Factor 5); increase in total bilirubin (Factor 6); and increase in zinc and lead (Factor 7). There was a significant interaction between the degree of

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urbanization and geotype origin among cases of HM. **Conclusion:** This study demonstrates the impact of micronutrient deficiency and oxidative stress as the result of liver's involvement, aging, macronutrient, and metal toxicity on the occurrence of HM cases among different residents in Kinshasa megacity. Hence, these variates can be described as risk factors contributing in the pathophysiology of HM as a result of pollution in the Kinshasa megacity.

Key words: Central Africa, Environment pollution, Hematologic malignancy, Oxidative stress

INTRODUCTION

Kinshasa, capital of Democratic Republic of the Congo (DRC), is now probably the second megacity with respect to rapid urban growth and largest population size after Lagos (Nigeria) (1). Unfortunately, in Kinshasa, there are erodible sandy hills, unstable types of buildings, degradation of infrastructures, absence of well-made roads for vehicles and floods as well as the absence of waste management. There are also petrol stations and industries located even in residential areas (1).

These environmental and social changes (overcrowding from rural to urban uncontrolled migration and development of poor and informal settlements) might no doubt have serious health consequence. The previous studies have shown the presence of toxic metal among pre-eclamptic women (2) and toxic heavy metals in ambient air in Kinshasa town (3). Outdoor and indoor air pollutions and waste accumulation were shown to be associated with elevated levels of in trace elements in Kinshasa's ambient air (4,5); and these were higher than those reported from American, Canadian, French, and German populations (6-9). Sadly, there are no published data on the effect of environmental pollution on hematologic malignancy (HM), in the Kinshasa megacity, DRC – a developing country; whereas there are valid scientific information about heavy metal, toxicity, and HM in both developed (10-13) and other developing (14,15) countries.

Therefore, the primary objective of this study was to determine the distribution of proportions of HM by remote residence far from erosions, floods, wastes, and cars; residence closed to traffic and closed to erosions-floods-wastes-traffic gem-stations-industries; and interaction between urbanization and geotype origin after rural-urban migration in Kinshasa megacity, DRC. The secondary objective of this study was to discriminate residence types by hematologic, metabolic, and heavy metal markers from participants (HM patients and healthy control with normal bone marrow) as well as to characterize HM patients by such markers using factor analysis.

MATERIALS AND METHODS

The case-control study was undertaken with adult patients aged ≥20 years with HM who were matched for sex and age with participants without HM. Cytologic aspect of normal myelogram and HM cases was confirmed in the Department of Chemical Pathology of Kinshasa University Clinics (KUC) between 2015 and 2016. FISH was performed at KU Leuven Hospitals, Belgium. The markers of interest were hematologic (hemoglobin, white cell, platelet, and ERS), metabolic (total bilirubin, indirect bilirubin, GGT, uric acid, and albumin), and metal toxicity (Cr, Mn, Zn, Cu, As, Se, Br, Mo, Cd, I, Hg, Pb, and Ni).

The study was approved by the Ethics Committee of the School of Public Health in Kinshasa at the Faculty of Medicine (ESP/CE/108/15).

The present study was undertaken in compliance with the Helsinki Declaration (59th WMA General Assembly, Seoul, South Korea, October 2008. http://www.wma.net/en/10 policies/b3/index.html).

Procedures

Peripheral blood sample were obtained into ethylenediamintetraacetic acid tubes for the hemogram and into citrate-containing tubes for the erythrocyte sedimentation. Three smears of peripheral blood were performed.

Bone marrow aspiration was done from the sternal bone or posterior iliac spine. Ten smears were used for the morphological study (staining by routine May Grünwald Giemsa; and special staining by Sudan black B, Periodic acid Schiff, Perls).

Toxicology data (Cr, Mn, Zn, Cu, As, Se, Br, Mo, Cd, I, Hg, Pb, and Ni) were performed and analyzed at the 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.

Operational definition

Resident and/or occupation closed to traffic roads (exposure to gasoline), petrol stations/garages, dusts, smoke, batteries, and industries - all those are well-defined pollutants for the environments from the toxic air. Thus, we had three types of residence such as follows: (1) Remote rural residence - far

from erosions-floods-wastes-cars; (2) semi-rural informal settlements and precolonial cities closed to traffic gem; and (3) westernized urban cities closed to erosion-floods-wastes-traffic gem-stations/garages-industry. This urbanization's degree was either cosmopolitan (metropolitan), planned, and administrative areas (new rich cities) with a regular supply of potable water and electricity or made of old and colonial cities characterized by irregular supply of potable water/electricity and chaotic urbanization.

Indeed, both rural, semi-rural, and urban areas of Kinshasa megacity are exposed to high levels of metal toxicity (3-4,16). Central Kinshasa areas (Kalamu, Lemba, and Makala municipalities) are well known as high-risk zones for lead and mercury emissions: Urban environment next to many mechanical workshops and other former battery manufacturing factories, old water drainage systems and road networks as a source of car combustion gases containing lead, decomposition of lead-containing paints, house dust (residual contaminants), consumption of vegetables grown along the main roads (16), and fish (Jack mackerels or Trachurus, rich in mercury) (17). The use of cosmetics with hydroquinone and mercury (17) is well prevalent in Kinshasa rural areas (Nsele, Maluku, Mont Ngafula, Selembao, Kisenso, and Ngaliema municipalities). Far away from these industrial sites, main roads and with a non-westernized lifestyle were defined as an environment, not high in metal pollution risk (WHO, 1996) (18).

DRC Center provinces (Kasai Oriental, Lomami, Sankuru, and Kasai Central), DRC East provinces (Tsopo, Bas Uele, Haut Uele, Ituri, Nord Kivu, Sud Kivu, Maniema, Tanganyika, Haut Lomami, Haut Katanga, and Lualaba), and DRC West provinces (Kongo Central, Kinshasa, Kwango, Kiulu, Mai Ndombe, Equateur, Tshuapa, Mongala, Nord Ubangi, and Ubangi) were used to determine geotype origin of the study participants (Figure 1).

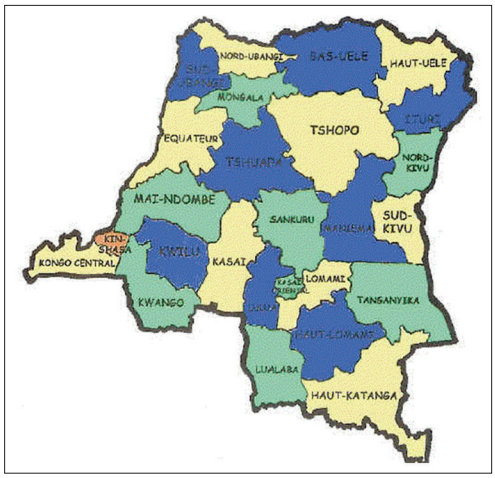

Figure 1: Map of Kinshasa

Multiple myeloma, a subtype of HM, was defined according to the French-American-British (FAB) classification and supplemented by the WHO criteria for hematologic cancers (2008) (20,21).

MM is also a malignancy of plasma cells that result from an overproduction of light and heavy chain monoclonal immunoglobulins (22-28).

Leukemia, another subtype of HM, was defined according to the FAB classification and supplemented by the WHO criteria for hematologic cancers (2008).

Statistical analysis

Continuous variables were normally distributed and presented as means ± standard deviation (SD), while categorical variables were presented as frequency (count = n) and proportions (%).

In univariate analysis, Student's t-test was calculated to assess differences between 2 groups and analysis of variance to compare means between ≥3 groups. Multiple comparisons of means were computed using *post hoc* Bonferroni pair means at considering Type I error rate of 0.05. Chi-square test was used to compare percentages at categorical variables between groups.

In multivariate analysis, DA was used as the model of the conventional classification techniques at discriminating a single categorical variable using multiple attributers such as normal myelogram and different subtypes of hematological cancers. DA used canonical variables that would maximally differentiate (classify) group membership within patients with anemia. The important underlying assumptions of DA were stated as follows: (i) Each predictive variable was normally distributed; (ii) there must be homogeneity of covariance between subtypes and normal myelogram; (iii) there must be at least two groups with each subgroup belonging to only one group so that the groups were mutually exclusive and collectively exhaustive; (iv) the groups should be characterized before collecting the data; (v) the predictive variables considered to separate the groups should classify quite clearly between the groups so that each category overlap was clearly non-existent or minimal; and (vi) group sizes of the dependents should not be grossly different and should be at least 5 times the number of independent variables.

The Box's test of equality for covariance matrices was considered to check the assumption for homogeneity of covariance across the categories.

Mahalanobis distances were computed at supporting the classification of canonical variables into distinct subtypes and

normal myelogram among groups' centroids at determining the degree of segregation with each Wilk's Lambda value closer to zero being the evidence for well-separated groups.

Factor analysis is a multivariate model for investigating variable relationships for the complex concept, is originated in psychometrics, and is used in behavioral sciences, social sciences, dietary sciences, nutrition sciences, marketing, product management, operational research, and other applied sciences that deal with large quantities of data.

Therefore, orthogonal matrix was hold for being factors and factor loadings. Thus, common factor analysis or principal factor analysis, the squared factor loading is term of the percent of variance in variable explained by the factor, the Eigenvalue for a given factor measured the variance in all the variables, and extraction sums of squared loadings were also used. According to the Kaiser criterion, the Eigenvalue was a measure of how much of the variance of the observed variables a factor explains. Any factor with an Eigenvalue ≥1 explains more variance than a single observed variable.

The Cattell scree test has plotted the factors or components as the X-axis and the corresponding Eigenvalues as the Y-axis toward the right with later components, and the Eigenvalues drop with the curve at an elbow toward less steep decline.

Varimax rotation was used to obtain the output more understandable and facilitated the interpretation of factors. Indeed, this orthogonal rotation of the factor axes served to maximize the variance of the squared loadings of a factor (column) on all the variables (rows) in a factor matrix that has the effect of differentiating the original variables by extracted with a single factor. Varimax rotation proceeded for results, which make it as easy possible to identify each variable with a single factor.

A $P < 0.05$ was considered as statistically significant. All analyses were performed using the Statistical Package for Social Sciences (IBM* SPSS, New York, MD, USA) for Windows version 23.0.

RESULTS

In total, 114 HM cases (93 leukemia, and 21 multiple myeloma) were residing within Kinshasa areas. There was a significant difference in the occurrence of HM cases between participants residing in areas located away from erosions-floods-wastes-cars and participants residing in areas located closer to erosion-floods-wastes-traffic gem-stations/garages-industry ($P < 0.0001$) (Figure 2).

Table 1 summarizes univariate comparisons of mean values of variables of interest among all participants across selected

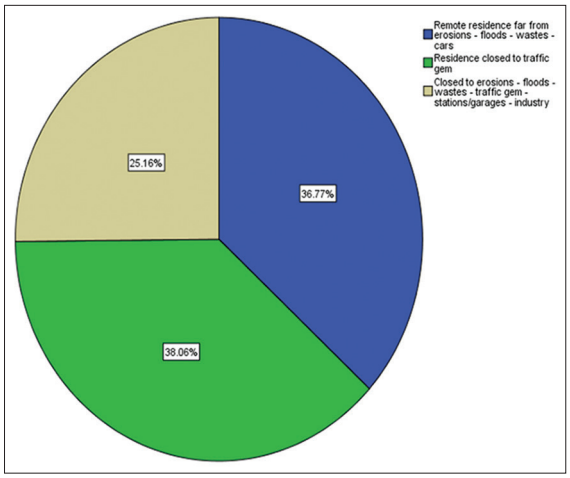

Figure 2: Repartition of population study by environment pollution

residence types in Kinshasa. The mean levels of platelets, total bilirubin, direct bilirubin, and serum molybdenum did not vary ($P > 0.05$) across residence types. However, the rest of mean levels of hematologic profiles, liver function, kidney function, inflammation, and heavy metals did significantly ($P < 0.05$) vary across selected residence types. These mean concentrations were increasing from remote residence far from erosions-floods-wastes-cars through residence closed to traffic gem till closed to erosion-floods-wastes-traffic gem-stations/garages-industry. Moreover, the lowest levels of serum lead, selenium, copper, iodine, and albumin were observed among HM patients from closed to erosions-floods-wastes-traffic gem-stations/garages-industry in comparison with the levels of those nutrients among HM patients from residence closed to traffic gem and remote residence far from erosions-floods-wastes-cars, respectively.

In multivariate DA, tests of equality group means with Wilks Lambda, Box's test of equality of covariance matrices, summary of canonical discriminant functions, canonical discriminant functions, and classification function coefficients are displayed in Table 2a and b. For caution, first 3 canonical discriminant functions were used. After adjusting for such confounding factors, only age, white cell count serum nickel, serum mercury, and serum GGT were identified as the most important and significant markers to discriminate environments with different scales of pollution (Table 2a and b).

Age, serum nickel, serum mercury, and serum GGT were characterized by highest, intermediate, and lowest mean levels at closed, residence closed to traffic gem, and remote residence from erosions, floods, wastes, cars, respectively.

However, highest levels of white cell count were concurrent at residence closed to traffic gem, whereas lowest of white cell count were concurrent at both remote residence far from

Table 1: Univariate comparisons of means values of interest

Variables	Mean±SD (95% confidence interval for Mean)			
	Remote residence far from erosions-floods-wastes-cars	Residence closed to traffic gem	Closed to erosions-floods-wastes-traffic gem-stations/garages-industry	*P* value
Age years	36.89±17.259 (32.32-41.47)	44.08±16.937 (39.67-48.50)	65.82±10.993 (62.26-69.38)	0.0001
Transfusion number	1.632±1.7991 (1.154-2.109)	2.559±1.9588 (2.049-3.070)	2.410±2.520 (1.593-3.227)	0.041
Hemoglobin g/dL	8.136±2.177 (7.5590-8.7146)	7.869±2.185 (7.3000-8.4390)	6.871±1.837 (6.2762-7.4674)	0.013
White cell count/mm^3	17442.368±30534.235 (9340.545-25544.192)	87622.542±140512.080 (51004.895-124240.190)	31391.974±34245.643 (20290.821-42493.128)	0.0001
Platelet/mm^3	215123.193±110615.075 (185773.0628-244473.3231)	270747.457±252293.806 (204999.3337-336495.5816)	242400.641±87171.263 (214142.9865-270658.2956)	0.235
ESR/1st h	55.912±44.160 (44.195-67.630)	80.492±33.966 (71.640-89.343)	80.385±37.367 (68.271-92.498)	0.001
Serum chromium mg/L	1.59±1.567 (1.09-2.08)	2.61±1.182 (2.28-2.93)	3.59±0.788 (3.32-3.86)	0.0001
Serum manganese mg/L	1.270±0.515 (1.0572-1.4828)	1.696±0.855 (1.4605-1.9320)	2.995±1.744 (2.4057-3.5860)	0.0001
Serum iron mg/L	5.160±2.278 (4.2195-6.1005)	5.109±2.058 (4.5421-5.6767)	6.744±2.429 (5.9223-7.5666)	0.002
Serum nickel mg/L	2.332±0.840 (1.9849-2.6791)	3.487±1.147 (3.1714-3.8041)	5.347±0.860 (5.0561-5.6383)	0.0001
Serum copper mg/L	3.576±1.163 (3.1070-4.0469)	3.593±0.998 (3.3177-3.8684)	4.105±0.865 (3.8126-4.3985)	0.040
Serum zinc mg/L	0.604±0.515 (0.3966-0.8127)	0.539±0.416 (0.4251-0.6545)	0.371±0.224 (0.2954-0.4474)	0.049
Serum arsenic mg/L	0.007±0.009 (0.0047-0.0097)	0.003±0.008 (0.0498-0.1573)	0.103±0.165 (0.0153-0.0450)	0.0001
Serum selenium mg/L	0.359±0.133 (0.3042-0.4142)	0.341±0.152 (0.2999-0.3839)	0.235±0.054 (0.2168-0.2537)	0.0001
Serum bromium mg/L	3.788±2.336 (2.8234-4.7526)	3.509±1.598 (3.0687-3.9501)	6.044±2.380 (5.2389-6.8500)	0.0001
Serum molybdemun mg/L	2.882±1.581 (2.2290-3.5350)	3.481±1.382 (3.1000-3.8623)	3.000±1.420 (2.5193-3.4807)	0.145
Serum cadmium mg/L	1.515±1.326 (1.0372-1.9940)	2.794±1.899 (2.2708-3.3179)	3.688±1.881 (3.0521-4.3256)	0.0001
Serum iodine mg/L	0.532±0.340 (0.4076-0.6576)	0.415±0.129 (0.3802-0.4506)	0.303±0.111 (0.2660-0.3413)	0.0001
Serum mercury mg/L	0.066±0.223 (-0.0690-0.2013)	0.252±0.417 (0.0911-0.4146)	1.170±0.344 (1.0250-1.3158)	0.0001
Serum lead mg/L	0.200±0.424 (-0.0262-0.4262)	0.783±0.399 (0.6398-0.9277)	1.022±0.157 (0.9560-1.0890)	0.0001
Serum albumin mg/L	3.543±1.084 (3.2559-3.8314)	2.707±1.267 (2.3774-3.0382)	2.165±1.020 (1.8346-2.4962)	0.0001
Serum total bilirubin mg/dL	1.336±1.194 (0.0831-2.5903)	0.810±0.550 (0.4782-1.1434)	0.663±0.404 (0.3257-1.0018)	0.204
Serum direct bilirubin mg/L	1.208±0.735 (0.8643-1.5527)	1.020±0.589 (0.8513-1.1900)	1.099±0.643 (0.8785-1.3203)	0.532
Serum indirect bilirubin mg/dL	0.588±0.501 (0.3812-0.7956)	0.484±0.469 (0.3548-0.6135)	0.257±0.320 (0.1494-0.3662)	0.009
Serum uric acid mg/dL	6.585±4.445 (5.4063-7.7653)	9.723±4.787 (8.4763-109715)	11.163±3.274 (10.1020-12.2247)	0.0001
Serum GGT UI/L	266.850±317.853 (42.10071-182.5130)	397.845±290.461 (37.81485-322.1513)	702.942±288.093 (609.5534-796.3317)	0.0001

SD: Standard deviation, GGT: Gamma-glutamyl transferase, ESR: Erythrocyte sedimentation rate

Table 2a: Classification function coefficients in discriminant analysis

Variables	Remote residence far from erosions-floods-wastes-cars	Residence closed to traffic gem	Closed to erosions-floods-wastes-traffic gem-stations/garages-industry
Age years	0.28	0.396	0.617
White cell count/mm^3	−1.272E-6	3.889E-6	−1.880E-5
Serum nickel mg/L	1.535	6.113	9.792
Serum mercury mg/L	5.252	7.601	18.152
Serum GGT UI/L	0.011	−0.016	−0.22
(Constant)	−7.697	−17.868	−48.29
Fisher's linear discriminant functions			

GGT: Gamma-glutamyltransferase

Table 2b: Variables of discriminant analysis

Variables	Environment pollution		
	Remote residence far from erosions-floods-wastes-cars	Residence closed to traffic gem	Closed to erosions-floods-wastes-traffic gem stations/garages-industry
Age years	0.028	0.396	0.617
White cell/mm^3	−1.272E-6	3.889E-6	−1.880E-5
Serum nickel mg/L	1.535	6.113	9.792
Serum mercury mg/L	5.252	7.601	18.152
Serum GGT UI/L	0.011	−0.016	−0.022
Constant	−7.697	−17.868	−48.929

GGT: Gamma-glutamyltransferase

erosions-floods-wastes-cars and closed to erosion-floods-wastes-traffic gem-stations/garages-industry.

Figure 3 describes canonical discriminant environment functions at discriminating with pollution.

Factor analysis revealed 7 uncorrelated factors (components) which cumulative and individual explained variances among all HM. Figure 4 presents the number of those 7 factors using the Scree plot according to the Eigenvalues. Thus, both 7 factors could be identified as manganese-iron-nickel, copper, arsenic, and GGT elevation (Factor 1), increase in bromium, mercury, and depletion of iodine (Factor 2), depletion of selenium and increase in uric acid (Factor 3), increase in molybdenum and direct bilirubin (Factor 4), increase in chromium and total bilirubin (Factor 5); increase in bilirubin total (Factor 6), and increase in zinc and lead (Factor 7) (Figure 4).

There was a significant interaction between urbanization degree and geotype origin on cases of HM: The highest, intermediate, and lowest number of HM in interaction between chaotic urbanization and DRC West provinces, interactions between all new cities and DRC West provinces and westernized and administrative centrum, and DRC East-Center provinces, respectively.

DISCUSSION

The study discriminated also residence types by hematologic, metabolic, and heavy metal markers from participant (HM patients) as well as to characterize HM patients by such markers using factor analysis.

Sadly, all serum heavy metals in these Congolese HM patients were reflecting metal toxicity with levels higher than ranges recommended by the WHO (18) and were also reflecting air pollutant environment among patients (2,4,19) and dwellers from Kinshasa community (29), and in participants from other Sub-Saharan African megacities such as Johannesburg, Nigeria (30,31). In Kinshasa megacity, the following heavy metals are the most incriminated: Lead, mercury, copper, arsenic, zinc, manganese, chrome, vanadium, and selenium (3,4).

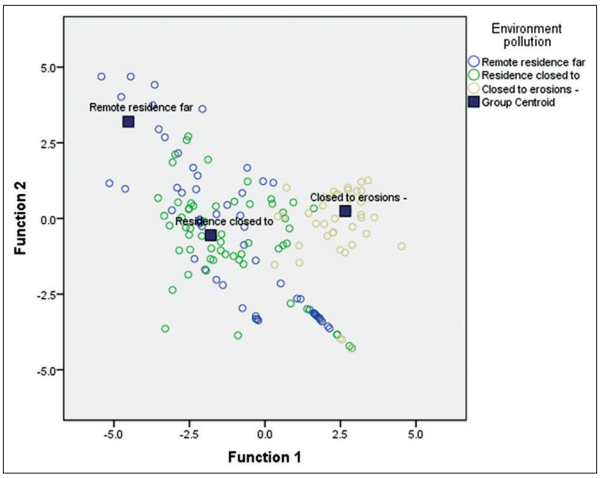

Figure 3: Canonical discriminant functions

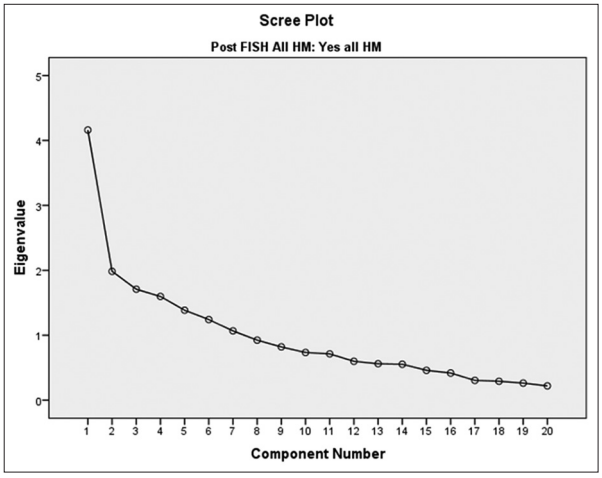

Figure 4: Scree plot for component number in factor analysis

Proportions of HM

In this study, HM was recognized as a heterogeneous nosological entity with 8 leukemia patients to 10 HM patients versus emerging 2 MM cases to 10 HM patients at KUC. These findings confirmed epidemiological studies related to HM in general and both leukemia and MM from developed countries (26,32) and from Sub-Saharan Africa.

Aging was associated with these Congolese HM patients as it is well reported (33-35).

Classification of HM patients according to residence and pollution

Except platelet count, molybdenum, direct bilirubin, and total bilirubin, the rest of continuous markers were able to distinguish univariately the present HM patients across remote residence far from erosions-floods-waste-cars, residence closed to traffic gem, and closed to erosions-floods-wastes-stations/garages-industry. However, the multivariate discriminate analysis identified increasing level of age, serum nickel, mercury, and GGT were the most independent markers to discriminate HM according to remote residence far from erosions-floods-waste-cars, residence closed to traffic gem, and closed to erosions-floods-wastes-stations/garages-industry from Kinshasa megacity. The present study, therefore, reported that HM residences closed to Kinshasa megacity erosions-floods-wastes-traffic gem-stations/garages-industry were more vulnerable for metal toxicity than their HM counterparts did from residence closed to traffic gem and remote residence far from erosions-floods-wastes-cars, respectively.

Physiopathogenic mechanism for HM

In this study, factor analysis produced 7 factors which were identified as manganese-iron-nickel, copper, arsenic, and GGT elevation (Factor 1); increase in bromium, mercury, and depletion of iodine (Factor 2); depletion of selenium and increase in uric acid (Factor 3); increase in molybdenum and direct bilirubin (Factor 4), increase in chromium and total bilirubin (Factor 5); increase in bilirubin total (Factor 6), and increase in zinc and lead (Factor 7).

Interaction between urbanization degree and geotype after migration

These present findings demonstrated that the highest proportion of HM patients was observed in the concurrent actions of DRC West provinces and chaotic urbanization-old and colonial-westernized new cities in comparison of proportions of HM patients with interaction between DRC West provinces and westernized and administrative Center, DRC East provinces, DRC Center provinces, and the rest of Kinshasa megacity residences. These findings from DRC West provinces and chaotic urbanization-old and colonial-westernized new cities may be explained by longer exposure to fish (Jack mackerels or Trachurus, rich in mercury), cosmetics/soaps use, deforestation, lifestyle changes (tobacco, excessive alcohol), and petrochemical refinery (1,19,36). In total, Kinshasa megacity is characterized by historical, demographic, and chaotic extension from 1923 to 2005 (37-39). Past and recent migrations are due to repeated violence reactions/wars from peripheral provinces to Kinshasa megacity [40] and poor and vulnerable to pollutant environment.

The present findings produced knowledge to understand the mechanism of clustering of inflammation/allergy-oxidative stress markers of aging, urbanization levels-rural migration from peripheral provinces, micronutrient (depletion of iodine, selenium, zinc, and copper), macronutrient protein energy (depletion of serum albumin), liver function (increase in GGT), kidney function (increase in uric acid), and metal toxicity (increase in nickel, lead, iron, molybdenum, arsenic, mercury, bromium, chromium, and cadmium).

In total, these disturbances were reflecting important antioxidant/oxidant imbalances which are incriminated in cancers in general (References) and HM in particular (41-43) across Kinshasa areas plenty of dust (allergy), smoke (hypoxia), psychological stress/Immunity decline (migration, erosions), and pollution (metal toxicity).

These patients from Kinshasa megacity are facing demographic transition (elderly HM patients from residence closed to erosions-floods-wastes-traffic gem-stations/garages-industry).

Aging and HM

These findings outlined the incidence of HM including multiple myeloma elderly as confirmed in the literature (27,32,34). However, the present analysis revealed younger age in leukemia patients, whereas aging is associated with leukemia patients from rich countries (44,45).

Indeed, aging process is well known as a biologic complex entity mediated by genetic and epigenetic factors and environmental factors (36,46) across aging; the hematologic stem cells do experience DNA damage, telomerase shortening, oxidative stress, and poor homing efficiency (47,48).

Micronutrient deficiency, loss of antioxidant properties, and HM

Depletion of serum selenium concentration in these HM patients might explain the higher risk of cancer in general and in HM in particular (41,49).

Depletion of serum iodine in these HM patients might also explain higher risk for other cancers such as thyroid neoplasm (50). Furthermore, iodine depletion does increase H_2O_2-mediated, reactive oxygen species generation, which can damage DNA and result in mutations (51).

Zinc deficiency induces immune dysfunction in Belgium patients with HM (49). Zinc deficiency also may enhance DNA damage through impairments of DNA repair mechanism (43).

Macronutrient deficiency

Serum albumin deficiency, kwashiorkor or disease of migrant in Ghana, is a condition of antioxidant capacity loss (42).

Biochemical markers for liver dysfunction and purine metabolism

Increase in GGT, among these HM patients, is a very strong enzyme to catalyze 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) (52,53). Indeed, GGT plays an important key in the gamma-glutamyl cycle for the synthesis and the degradation of glutathione, drug, and xenobiotic detoxication (54). Excessive intake of alcohol with elevated GGT and free radicals, metals, and antioxidants in oxidative stress is well known to induce cancer (43).

Moreover, different studies have demonstrated that levels of serum uric acid, an antioxidant defendant against age related free radicals and scavenger of singlet Oxygen, were previously reported to be associated with incident cases of cancer (55,56). Uric acid is also a weak organic acid which is a metabolic and product of purine degradation, as inconsistence and conflicting impact on mortality, heart disease, and certain cancers (57,58).

Heavy metal toxicity and HM

The majority of heavy metal was dramatically elevated and clustering in this study. Different studies report that cadmium is a human carcinogen and occupational exposure to it has been associated with cancers (43).

Other studies revealed that copper is well-known pro-oxidant and may participate in metal-catalyzed peroxidation of lipids. Copper is also an essential component of several endogenous antioxidant enzymes, and that free radicals have been proposed to play a role in the process of carcinogenesis (59).

Indeed, nickel is a common carcinogen that can alter gene expression by enhanced DNA methylation, rather than through mutagenic mechanisms. Nickel may interfere with DNA repair.

Indeed, several metals such bromium-mediated formation of free radicals across a Fenton reaction (60).

Indeed, iron-induced free radical damage to DNA appears to be important for the development of cancer, and cancer cell are known grow rapidly in response to iron (43,61-64).

However, manganese and molybdenum are essential micronutrients involved in anti-oxidant defense (64-67).

CLINICAL IMPLICATIONS

The present results will impact on the management of HM in Kinshasa megacity. Indeed, biochemical, oxidative stress, and metal toxicity markers will serve for early prevention, diagnosis, and treatment of HM.

These results will be also used for training of biologist, perspective public health in terms of educational of persons, and high awareness about emerging HM among these Congolese people who are facing epidemiologic, demographic, and nutrition health transitions.

CONCLUSION

This study demonstrated the significant discrimination of classification of HM patients from remote residence far from erosions-floods-wastes-cars, residence closed to traffic gem, and residence closed to erosions-floods-wastes-stations/garages-industry in Kinshasa megacity, DRC.

The pathophysiology of HM might be explain by clustering of micronutrient, macronutrient, biochemical, oxidative stress, and metal toxicity biomarkers after rural migration and living in at Kinshasa megacity.

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REFERENCES

1. INS, UNDP (Institut National de la Statistique and United Nations Development Programme). Un Aperçu Démographique. Vol. 255. Zaïre: Résultats du Recensement Scientifique de la Population En 1984, Zaïre-Afrique; 1991. p. 227-61.
2. Elongi Moyene JP, Scheers H, Tandu-Umba B, Haufroid V, Buassa-Bu-Tsumbu B, Verdonck F, et al. Preeclampsia and toxic metals: A case-control study in Kinshasa, DR Congo. Environ Health. 2016;15:48.
3. Kabamba M, Basosila N, Mulaji C, Mata H, Tuakuila J. Toxic heavy metals in ambient air of Kinshasa, democratic republic Congo. J Environ Anal Chem. 2016;3:178.
4. Tuakuila J, Lison D, Lantin AC, Mbuyi F, Deumer G, Haufroid V, et al. Worrying exposure to trace elements in the population of Kinshasa, Democratic Republic of Congo (DRC). Int Arch Occup Environ Health. 2012;85:927-39.
5. Tuakuila J, Lison D, Mbuyi F, Haufroid V, Hoet P Elevated blood lead levels and sources of exposure in the population of Kinshasa, the capital of the Democratic Republic of Congo. J Expo Sci Environ Epidemiol. 2013;23:81-7.
6. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19:59-68.
7. Health Canada. Report on Human Biomonitoring of Environmental Chemicals in Canada, Results of the Canadian Health Measures Survey Cycle 1 (2007-2009); 2010. Available from: http://www.healthcanada.gc.ca. [Last accessed on 2017 Aug 22].
8. Fréry N, Saoudi A, Garnier R, Zeghnoun A, Falq G. Exposition de la Population Française Aux Substances Chimiques de L'Environnement, Institut de Veille Sanitaire, Saint-Maurice; 2011. Available from: http://www.invs.sante.fr. [Last accessed on 2017 Aug 22].
9. GeRES. GeRES-Health and Environmental Hygiene-German Environmental Survey 1998 (GerES III), German Environmental Survey 1990-1992 (GerES II). Available from: http://www.umweltbundesamt.de/gesundheit-e/survey/index.htm. [Last accessed on 2017 Aug 22].
10. Winters N, Goldberg MS, Hystad P, Villeneuve PJ, Johnson KC; Canadian Cancer Registries Epidemiology Group. Exposure to ambient air pollution in Canada and the risk of adult leukemia. Sci Total Environ. 2015;526:153-76.
11. Yu CL, Wang SF, Pan PC, Wu MT, Ho CK, Smith TJ, et al. Residential exposure to petrochemicals and the risk of leukemia: Using geographic information system tools to estimate individual-level residential exposure. Am J Epidemiol. 2006;164:200-7.
12. Barregard L, Holmberg E, Sallsten G. Leukaemia incidence in people living close to an oil refinery. Environ Res. 2009;109:985-90.
13. Micheli A, Meneghini E, Mariottini M, Baldini M, Baili P, Di Salvo F, et al. Risk of death for hematological malignancies for residents close to an Italian petrochemical refinery: A population-based case-control study. Cancer Causes Control. 2014;25:1635-44.
14. Weng HH, Tsai SS, Chiu HF, Wu TN, Yang CY. Association of childhood leukemia with residential exposure to petrochemical air pollution in Taiwan. Inhal Toxicol. 2008;20:31-6.
15. Jude AL, Salikala K, Kumar RA, Sudha S, Rachel J. Haematological and cytogenetic studies in workers occupationally exposed to cement dust. Int J Genet. 2002;2:95-9.
16. Masiala TC. Toxiques alimentaires. In: Tandu-Umba NF, editor. Nutrition: De la Théorie à La Pratique. Kinshasa: Nutrition: De la Théorie à la Pratique, PUK; 2001. p. 110-27.
17. Masiala TC, Moyogo M. Evaluation par activation neutronique des teneurs de mercure dans *Trachurus trachurus et Heterotis niloticus*, deux poissons couramment consommés à Kinshasa. Kinshasa: Université de Kinshasa; 1995.
18. WHO, FAO, IAEA, World Health Organization. Trace Elements in Human Nutrition and Health. Switzerland, Geneva: WHO; 1996.
19. Masiala CT, Masamba SW, Mbodo M, Longo-Mbenza B, Mbungu SF, Vangu DN. Lead and Mercury pollution in breast milk in Kinshasa: Mother and child health risks. J Innov Res Health Sci Biotech. 2015;1:49-55.
20. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002;100:2292-302.
21. Sabattini E, Bacci F, Sagramoso C, Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: An overview. Pathologica. 2010;102:83-7.
22. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. Br J Haematol. 2003;121:749-57.
23. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351:1860-73.
24. Hideshima T, Bergsagel PL, Kuehl WM, Anderson KC. Advances in biology of multiple myeloma: Clinical applications. Blood. 2004;104:607-18.
25. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. Nat Rev Cancer. 2002;2:175-87.
26. Becker N. Epidemiology of multiple myeloma. In: Moehler T, Goldschmidt H, editors. Multiple Myeloma, 25 Recent Results in Cancer Research. Vol. 183. Berlin, Heidelberg: Springer-Verlag; 2011.
27. Willan J, Eyre TA, Sharpley F, Watson C, King AJ, Ramasamy K. Multiple myeloma in the very elderly patient: Challenges and solutions. Clin Interv Aging. 2016;11:423-35.
28. Hong J, Lee JH. Recent advances in multiple myeloma: A Korean perspective. Korean J Intern Med. 2016;31:820-34.
29. Nsokimieno MM, Chen S, Zhang IQ. Sustainable urbanization's challenge in democratic republic of Congo. J Sustain Dev. 2010;3:242-54.
30. Naicker K, Cukrowska E, McCarthy TS. Acid mine drainage arising from gold mining activity in Johannesburg, South Africa and environs. Environ Pollut. 2003;122:29-40.
31. Olife IC, Okaka AN, Dioka CE, Meludu SC, Orisakwe OE. Iodine status and the effect of soil erosion on trace elements in Nanka and Oba towns of Anambra State, Nigeria. Ann Chim. 2007;97:895-903.
32. Alexander DD, Mink PJ, Adami HO, Cole P, Mandel JS, Oken MM, et al. Multiple myeloma: A review of the epidemiologic literature. Int J Cancer. 2007;120:40-61.
33. Huang MD, Yao M, Tang JL, Lee WC, Tsay W, Cheng AL, et al. Cancer epidemiology of multiple myeloma in Taiwan. Cancer. 2007;110:896-905.
34. Errahhali ME, Errahhali ME, Boulouiz R, Ourzame M, Bellaoui M. Distribution and features of hematological malignancies in Eastern

Morocco: A retrospective multicenter study over 5 years. BMC Cancer. 2016;159. DOI: 10.1186/s12885-016-2205-5.
35. Bron D, Ades L, Fulop T, Goede V, Stauder R; Elderly task force in hematology EHA SWG. aging and blood disorders: New perspectives, new challenges. Haematologica. 2015;100:415-7.
36. Haefliger P, Mathieu-Nolf M, Lociciro S, Ndiaye C, Coly M, Diouf A, et al. Mass lead intoxication from informal used lead-acid battery recycling in Dakar, Senegal. Environ Health Perspect. 2009;117:1535-40.
37. Pain M. Kinshasa, symbole d'une Afrique urbain. Cah O M. 1985;38:25-51.
38. Matthieu KW, de Maeyer M, Wolff E. The mapping of the urban. In: Escalante B, editor. Growth of Kinshasa (DRC) Through High Resolution Remote Sensing Between 1995 and 2005, Remote Sensing-Applications; 2012.
39. Unzola EB. Urbanisation de Kinshasa: La Politique de la Partie Extrême Orientale, Mémoire en Urbanisme et Aménagement. Kinshasa: Université Libre de Bruxelles; 1997. p. 85.
40. Martin M. Human Security in the Democratic Republic of Congo: The European Union as a Force for Good? Kinshasa: IPG; 2008.
41. Ringstad J, Jacobsen BK, Tretli S, Thomassen Y. Serum selenium concentration associated with risk of cancer. J Clin Pathol. 1988;41:454-7.
42. Buijsse B, Fesses EJ, Moschandreas J, Jansen EH, Jacobs DR. Oxidative stress, and iron and antioxidant status in elderly men: Differences between the Mediterranean South (Crete) and Northern Europe (Zutphen). Eur J Cardiovasc Prev Rehabil. 2007;4:495-500.
43. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006;160:1-40.
44. Mauritzson N, Johansson B, Albin M, Billström R, Ahlgren T, Mikoczy Z, et al. A single-center population-based consecutive series of 1500 cytogenetically investigated adult hematological malignancies: Karyotypic features in relation to morphology, age and gender. Eur J Haematol. 1999;62:95-102.
45. Oguma S, Takatsuki K, Uchino H, Kamada N, Oguma N, Kuramoto A. Factors influencing survival in Philadelphia chromosome positive chronic myelocytic leukemia. Cancer. 1982;50:2928-34.
46. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153:1194-217.
47. Kamminga LM, de Haan G. Cellular memory and hematopoietic stem cell aging. Stem Cells. 2006;24:1143-9.
48. André T, Meuleman N, Stamatopoulos B, De Bruyn C, Pieters K, Bron D, et al. Evidences of early senescence in multiple myeloma bone marrow mesenchymal stromal cells. PLoS One. 2013;8:e59756.
49. Beguin Y, Bours V, Delbrouck JM, Robaye G, Roelandts I, Fillet G, et al. Use of PIXE to mesure serum copper, zinc, selenium, and bromine in patients with hematologic malignancies. Nucl Instrum Method Phys Res B Beam Interact Mater Atoms. 1990;49:202-4.
50. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: A comprehensive review of animal and human studies. Thyroid Res. 2015;8:8.
51. Krohn K, Maier J, Paschke R. Mechanisms of disease: Hydrogen peroxide, DNA damage and mutagenesis in the development of thyroid tumors. Nat Clin Pract Endocrinol Metab. 2007;3:713-20.
52. Tate SS, Meister A. gamma-Glutamyl transpeptidase from kidney. Methods Enzymol. 1985;113:400-19.
53. Whitfield JB. Gamma-glutamyl transferase. Crit Rev Clin Lab Sci. 2001;38:263-355.
54. Courtay C, Oster T, Michelet F, Visvikis A, Diederich M, Wellman M, et al. Gamma-glutamyl transferase: Nucleotide sequence of the human pancreatic cDNA. Evidence of a ubiquitous gamma-glutamyl transferase polypeptide in human tissues. Biochem Pharmacol. 1992;43:2527-33.
55. Kolonel LN, Yoshizawa C, Nomura AM, Stemmermann GN. Relationship of serum uric acid to cancer occurrence in a prospective male cohort. Cancer Epidemiol Biomarkers Prev. 1994;3:225-8.
56. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. Proc Natl Acad Sci U S A. 1981;78:6858-62.
57. Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler I. Serum uric acid and 11.5-years mortality of middle-aged women: findings of the Chicago Heart Association detection project in industry. J Clin Epidemiol. 1989;42:257-67.
58. Bengtsson C, Lapidus L, Stendahl C, Waldenström J. Hyperuricaemia and risk of cardiovascular disease and overall death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Acta Med Scand. 1988;224:549-55.
59. Daniel KG, Harbach RH, Guida WC, Dou QP. Copper storage diseases: Menkes, Wilson's, and cancer. Front Biosci. 2004;9:652-2662.
60. Ercal N, Gurer-Orhan H, Aykin-Burns N. Toxic metals and oxidative stress Part I: Mechanisms involved in metal-induced oxidative damage. Curr Top Med Chem. 2001;1:529-39.
61. Berg D, Gerlach M, Youdim MB, Double KL, Zecca L, Riederer P, et al. Brain iron pathways and their relevance to Parkinson's disease. J Neurochem. 2001;79:225-36.
62. Siah CW, Trinder D, Olynyk JK. Iron overload. Clin Chim Acta. 2005;358:24-36.
63. Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology. 2004;127 5 Suppl 1:S79-86.
64. Deugnier Y, Turlin B. Iron and hepatocellular carcinoma. J Gastroenterol Hepatol. 2001;16:491-4.
65. Mistry HD, Broughton Pipkin F, Redman CW, Poston L. Selenium in reproductive health. Am J Obstet Gynecol. 2012;206:21-30.
66. Mistry HD, Williams PJ. The importance of antioxidant micronutrients in pregnancy. Oxid Med Cell Longev. 2011;2011:841749.
67. Hovdenak N, Haram K. Influence of mineral and vitamin supplements on pregnancy outcome. Eur J Obstet Gynecol Reprod Biol. 2012;164:127-32.