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Prevalence of Interleukin-6-174 *G/C* and Interleukin-6-190 *C/T* Polymorphisms in Malnourished Children Aged 0-59 Months in Senegal

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Abstract: Malnutrition, which is one of the main causes of morbidity and mortality in children under five years of age worldwide, especially in developing and middle-income countries, constitutes a problem about which we have only minimal genetic comprehension. Interleukin 6 (IL6), a cytokine that regulates cell proliferation and differentiation as well as balance between the pro- and anti-inflammatory pathways, is reportedly associated with certain diseases in children, such as malnutrition, asthma, and obesity. The aim of this study was to evaluate the prevalence and distribution of *IL6*-174 *G/C* and *IL6*-190 *C/T* gene polymorphisms in malnourished children in Senegal. We analyzed polymorphisms *IL6*-174 *G/C* and *IL6*-190 *C/T* in 57 malnourished and 10 healthy children (age 0-59 months), using the polymerase chain reaction-restriction fragment length polymorphism assay. Z-score values were obtained using WHO Anthro® version 3.2.2 software. All data were entered into Excel spreadsheets and analyzed using R Studio version 4.2.2 software. Hardy Weinberg equilibrium, genotypic, and allelic frequencies were generated using GenePop version 4.3 software. Univariate logistic regression analysis was applied to determine the associations of the polymorphisms with malnutrition and anthropometry. The *GG* genotype was more frequent in the malnourished (84.44%) and healthy children (100%) for the IL6-174 polymorphism; whereas for IL6-190, the *CC* genotype was present in all healthy children (100%) and 89.47% malnourished children. The *IL6*-174 CC and *IL6*-190 TT genotypes were present only in 15.56% and 10.53% respectively in malnourished children. No heterozygous genotypes were found for either gene polymorphism. For the malnourished children, logistic regression analysis showed no significant associations between the *IL6*-174 and *IL6*-190 genotypes and the anthropometric measurements, whereas it did show significant associations ($P < 0.05$) of the *IL6*-174 *GC* and *GG* and *IL6*-190 *CC* genotypes with the female gender. It was concluded that *IL6*-174 *G/C* and *IL6*-190 *C/T* polymorphisms are not significantly associated with childhood malnutrition or anthropometric measurements.

Keywords: Malnutrition, Children, *IL6*-174, *IL6*-190, Polymorphism

1. Introduction

Child Malnutrition is defined as an imbalance between nutrient requirements and intake, resulting in cumulative deficits in energy, protein, or micronutrients, which can negatively affect the growth and development of children [1]. It is one of the main causes of morbidity and mortality in children under five years of age worldwide, especially in developing and middle-income countries [2], such as Senegal [3]. The latest Continuous Demographic and Health Survey (EDS-Continue) report in Senegal revealed that 18% of children suffer from chronic malnutrition and 8% are acutely malnourished [4]. Factors that lead to child malnutrition in this African country include socioeconomic and political determinants, poor complementary feeding practices, infections and diseases, and limited access to healthcare [4].

However, despite the scourge of this global problem on children's health, knowledge about child malnutrition remains limited. The study of genetic variations in nutrient metabolism and diet-related diseases is named nutrigenetics [5]. Current methods for assessing the nutritional status of children include anthropometric measurements, biochemical and immunological assays, and the investigation of genetic polymorphisms [6]. Cytokines play an important role in malnutrition [6, 7]. It has been shown that *in vitro*-stimulated blood cells from malnourished children exhibited low levels of tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL6) production and interleukin-like activity [8]. IL6 is a cytokine that regulates cell proliferation and differentiation and balance between the pro- and anti-inflammatory pathways [9, 10]. The gene encoding the IL6 protein is located on chromosome 7p21 and comprises five exons and four introns [11]. It has five known promoter polymorphisms: -174 *G/C*, -190 *C/T*, -572 *C/G*, -597 *G/A*, and -634 *C/G* [7]. Given those polymorphisms of the *IL6* gene have been frequently associated with certain childhood diseases, such as malnutrition [6], asthma [12], and obesity [13], the aim of our study is to evaluate the prevalence and distribution of *IL-6* 174 *G/C* and *IL-6*-190 *C/T* polymorphisms in malnourished children aged 0-59 Months in Senegal.

2. Methodology

2.1. Study Population

Our study included 67 children (aged 0-59 months) who had been admitted to the pediatric wards of the National Hospital Center of Pikine (C. H. N. P), Pediatric Social Institute of Pikine/Guediawaye, and Roi Baudoin Hospital Center of Guediawaye in the suburbs of Dakar, Senegal. Informed consent for study recruitment was signed by a legal tutor. This study was approved by the UCAD Research Ethics Committee (Protocol N°: 0340/2018/CER/UCAD).

The criteria for inclusion in the study were as follows:

For the malnourished group: any child with moderate or severe malnutrition (z-score <-2) who was being followed up at the above-mentioned facilities. In total, 57 children were introduced into this group.

For the control group: any child of 0-59 months of age with a normal nutritional status with respect to anthropometric indicators (Z-score> -2) and without chronic diseases that could affect the individual's nutritional status. In total, 10 children were introduced into this group.

2.2. Anthropometric Measurements and Indices

The anthropometric parameters measured were weight, height, head circumference, chest circumference, and mid-upper arm circumference. The height in centimeters (cm) was obtained using a centimeter tape, with the measurements taken in the lying position for children under two years of age and in the standing position for those over two years of age. The weight in kilograms (kg) was determined using an electronic scale (on the grams setting). A millimeter tape was used to measure mid-upper arm circumference, while a metric tape was used for chest and head circumferences (cm). Three anthropometric indices (weight-for-height Z-score, weight-for-age Z-score, and height-for-age Z-score) were also determined by the software WHO Anthro® version 3.2.2 [14]. Children with an anthropometric Z-score indicator of less than -2 were considered malnourished.

2.3. Blood Sampling

Blood samples were drawn from all children at admission into tubes of 2 ml containing ethylenediaminetetraacetic (EDTA) for genomic DNA extraction.

2.4. DNA Extraction

Genomic DNA was extracted from the leukocytes in a 200 µl sample of whole blood, using the Zymo Research blood DNA extraction kit according to the manufacturer's instructions. The extracted samples were stored at - 20°C until further use.

2.5. Polymerase Chain Reaction-Restriction Fragment Length Polymorphism Assay

Genotyping of the *IL6-174 G/C* and *IL6-190 C/T* polymorphisms was performed using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) assay. The primers used for the amplification of the two genes are listed in Table 1. These primers allowed us to amplify 190 bp fragments with specific restriction sites to determine the different alleles *IL6*-174 *G/C* and *IL6*-190 *C/T*.

The amplification of *IL6*-174 *G/C* was performed in a 25 µl reaction volume containing 2 µl of genomic DNA, 2.5 µl of 10× buffer, 0.5 µl of dNTP, 1.5 µl of $MgCl_2$, 0.1 µl of Taq polymerase, 1.25 µl of each primer (forward and reverse), and 15.9 µl of PCR-grade water. The PCR was performed in an Eppendorf thermal cycler under the following conditions: initial denaturation at 95°C for 5 min; 35 cycles of denaturation at 95°C for 30 s, hybridization at 63°C for 30 s, and elongation at 72°C for 30 s; and final elongation at 72°C for 10 min. The PCR was finally looped with a HOLD at 10°C. Visualization of primer attachment to the gene was achieved by electrophoresis of the PCR products on a 2% agarose gel.

Digestion of the gene was performed in a final volume of 20 µl containing 15 µl of PCR product, 2 µl of buffer, 0.5 µl of NlaIII, and 2.5 µl of PCR-grade water, with incubation at 37°C for 120 min. After electrophoresis on a 3% agarose gel, the resultant products were visualized in the presence of SafeView (an alternative of ethidium bromide) using a UV transillumination apparatus. A single band at 163 bp indicated *GG* homozygosity; two bands at 111 and 52 bp, respectively, indicated *CC* homozygosity; and three bands at 163, 111, and 52 bp, respectively, indicated *GC* heterozygosity.

The PCR for *IL6*-190 *C/T* amplification was performed (in the absence of $MgCl_2$) in a 25 µl volume in each well of a microplate and consisted of 2 µl of genomic DNA, 12.5 µl of Master Mix, 9.5 µl of PCR-grade water, and 0.5 µl of each primer (forward and reverse). The PCR conditions were as follows: initial denaturation at 95°C for 5 min; 35 cycles of denaturation at 95°C for 30 s, hybridization at 52°C for 30 s, and elongation at 72°C for 45 s; and final elongation at 72°C for 5 min, followed by a HOLD at 10°C. After verifying the PCR products using 2% agarose gel electrophoresis, they were digested with 5 U of MnlI (Promega) at 37°C for 180 min. Then, the digested fragments were visualized on a 3% agarose gel stained with SafeView. The products resulting from 113 and 85 bp demonstrated the C allele, and 113, 56, and 29 bp demonstrated the T allele.

Table 1. *Primer sequences used for the amplification of IL6-174 and IL6-190.*

Genes		Primers
IL6-190 C/T	Forward	5′-TGACTTCAGCTTTACTCTTTGT-3′
	Reverse	5′-CTGATTGGAAACCTTATTAAG-3′
IL6-174 G/C	Forward	5′-GCCTCAATGACGACCTAAGC-3′
	Reverse	5′-TCATGGGAAAATCCCACATT-3′

2.6. Statistical Analysis

All data were entered into an Excel spreadsheet and analyzed using R Studio version 4.2.2 software. Hardy-Weinberg equilibrium, genotypic and allelic frequencies were determined using GenePop version 4.3 software. All anthropometric measures are presented as the mean and standard deviation. Proportion calculations were performed for categorical variables, the distributions of which were compared using Fisher's exact test. For the comparison of means, the normality of the variables was first verified using the Shapiro-Wilk test. The nonparametric Wilcoxon test was used to determine the significance of the quantitative variables. Univariate logistic regression analysis was used to determine the associations of the polymorphisms with malnutrition and anthropometry. These associations were expressed as odds ratios, confidence intervals (CIs), and significance (P-value). The significance of the odds ratios was assessed using the Chi-squared test, with the threshold set at 5%.

3. Results

3.1. Global Characteristics of the Study Population

The means and standard deviations of the anthropometric measurements and indices of the healthy and malnourished children are shown in Table 2. Malnourished children had significantly lower weight and birth weight than healthy children. Additionally, significant differences were observed between the healthy and malnourished children for all anthropometric indices examined (weight-for-height Z-score, weight-for-age Z-score, and height-for-age Z-score).

Table 2. *Anthropometric measurements and indices of the overall study population.*

Variable	Healthy children	Malnourished children	P-value
Age (months)	13.90 ± 6.52	14.35 ± 8.10	0.73
Sex			
Female	6 (8.96%)	34 (35.82%)	
Male	4 (5.97%)	23 (34.33%)	1
Weight (kg)	9.08 ± 1.50	6.18 ± 1.87	<0.0001
Height (cm)	75.68 ± 6.81	69.71 ± 9.95	0.07
HC (cm)	44.8 ± 3.29	43.16 ± 3.95	0.88
MUAC (cm)	13.16 ± 0.91	11.75 ± 1.33	0.002
CC (cm)	43.99 ± 3.88	42.26 ± 3.66	0.3
WHZ	-0.48 ± 1.19	-3.37 ± 1.77	<0.0001
WAZ	-0.47 ± 0.99	-3.63 ± 1.26	<0.0001
HAZ	-0.19 ± 1.09	-2.41 ± 1.79	0.0001
Birth weight (kg)	3.04 ± 0.38	2.40 ± 0.54	0.0003

HC = Head circumference; MUAC = Mid-upper arm circumference; CC = Chest circumference; WHZ = Weight-for-height Z-score; WAZ = Weight-for-age Z-score; HAZ = Height-for-age Z-score.

3.2. Hardy-Weinberg Equilibrium

As shown in Table 3, the genotype distribution of IL6-174 and IL6-190 within each study group differed from those expected in Hardy-Weinberg equilibrium (P-value ≤ 0.05). The coefficient of consanguinity of all populations tended toward 1, suggesting an excess of homozygosity.

Table 1. *Hardy-Weinberg equilibrium analysis in malnourished and healthy children.*

Genotype	Malnourished children		Healthy children	
	Observed	Excepted	Observed	Excepted
IL6-174				
GG	38	32.02	5	5
GC	0	11.96	0	0
CC	7	1.02	0	0
P-value	≤0.05		≤0.05	
IL6-190				
CC	51	45.6	10	10
CT	0	10.83	0	0
TT	6	0.59	0	0
P-value	≤0.05		≤0.05	

3.3. Genotypic Distribution of the IL6-174 and IL6-190 Gene Polymorphisms in Malnourished and Healthy Children

Table 4 shows the frequencies of the *IL6* genotypes in healthy and malnourished children. The frequencies of the *IL-6* 174 *GG* and *CC* genotypes were 84.44% and 15.56%, respectively, in malnourished children. Only the *IL6*-174 *GG* genotype was recorded in healthy children at a frequency of 100%. No heterozygous *GC* genotype was observed in our study.

For *IL-6*-190 *C/T* gene polymorphism, the *CC* genotype was found in both healthy (100%) and malnourished children (89.47%). The homozygous *TT* genotype was observed in 10.53% of the malnourished children but was not found in the healthy children. None of the children carried the *CT* genotype. Overall, no statistically significant difference was found between the malnourished and healthy children to concerning the *IL6*-174 *G/C* and *IL6*-190 *C/T* genotypes (P-value> 0.05).

Table 2. *Genotypic frequencies of the IL6-174 and IL6-190 polymorphisms in malnourished and healthy children.*

Gene polymorphism	Genotype	Malnourished children (n = 45)	Healthy children (n = 5)	P-value
IL6-174	*GG*	38 (84.44%)	5 (100%)	1
	CC	7 (15.56%)	0	
	GC	0	0	

Gene polymorphism	Genotype	Malnourished children (n = 57)	Healthy children (n = 10)	P-value
IL6-190	*CC*	51 (89.47%)	10 (100%)	0.58
	TT	6 (10.53%)	0	
	CT	0	0	

3.4. Allelic Distribution of the IL6-174 and IL6-190 Gene Polymorphisms in Malnourished and Healthy Children

For *IL6*-174, the *G* allele was the most represented in both groups. This allele was identified in all healthy children and 84.44% of the malnourished children. The *C* allele was present only in the malnourished children, at a frequency of 15.56%.

For *IL6*-190, the allelic frequencies of *C* and *T* were respectively 89.47% and 10.53% in the malnourished children. The C allele was found in all the healthy children (100%) whereas the *T* allele was not observed in the healthy children (Table **3**).

Table 3. *Allelic frequencies of the IL6-174 and IL6-190 polymorphisms in malnourished and healthy children.*

		Healthy children	Malnourished children	P-value
IL6-174	*G*	76 (84.44%)	10 (100%)	0.34
	C	14 (15.56%)	0	
IL6-190	*C*	102 (89.47%)	20 (100%)	0.21
	T	12 (10.53%)	0	

3.5. Associations of the Anthropometric Measurements of Malnourished Children with IL-6 Gene Polymorphisms

logistic regression analysis showed no significant association between the different IL6-174 and IL6-190 genotypes and the various anthropometric measurements of the malnourished children (Table 6). Only the female gender showed a significant association (P <0.05) with the different genotypes; that is, genotypes *IL6*-174 *GG* (OR=8, 95% CI: 2.80-33.66) and *IL6*-190 CC (OR=10.33, 95% CI: 3.69-43.05) are frequently associated with the risk of malnutrition in girls carrying these genotypes. Whereas, *IL-6* 174 CC (OR=0.13, 95% CI: 0.03-0.36) and *IL-6*-190 TT (OR=0.10, 95% CI: 0.02-0.27) are protective factors against the development of malnutrition in the female gender.

Table 6. *Logistic regression tests of IL6-190 and IL6-174 in the malnourished group.*

	IL6-174				**IL6-190**			
	GG		***CC***		***CC***		***TT***	
	OR	**P-value**	**OR**	**P-value**	**OR**	**P-value**	**OR**	**P-value**
Age	1.07 (0.96-1.24)	0.32	0.94 (0.81-1.04)	0.32	0.93 (0.85-1.03)	0.14	1.07 (0.97-1.17)	0.14
Weight	1.04 (0.65-1.68)	0.86	0.96 (0.60-1.53)	0.86	1.04 (0.65-1.61)	0.87	0.96 (0.62-1.54)	0.87
Gender								
Female	8 (2.80-33.66)	0.001	0.13 (0.03-0.36)	0.001	10.33 (3.69-43.05)	0.0001	0.10 (0.02-0.27)	0.0001
Male	0.44 (0.08-2.26)	0.32	2.29 (0.44-13.07)	0.32	0.65 (0.11-3.79)	0.61	1.55 (0.26-9.11)	0.61
Height	1.01 (0.92-1.11)	0.88	0.99 (0.90-1.09)	0.88	0.96 (0.87-1.05)	0.43	1.04 (0.95-1.14)	0.43
MUAC	1.20 (0.57-2.44)	0.62	0.84 (0.41-1.77)	0.62	1.15 (0.59-2.10)	0.65	0.87 (0.48-1.68)	0.65
HC	0.90 (0.62-1.18)	0.53	1.11 (0.85-1.62)	0.53	0.94 (0.67-1.16)	0.66	1.06 (0.86-1.48)	0.66
CC	0.99 (0.72-1.29)	0.94	1.01 (0.77-1.39)	0.94	0.96 (0.70-1.19)	0.77	1.04 (0.84-1.43)	0.77
WHZ	1.08 (0.67-1.64)	0.74	0.93 (0.61-1.49)	0.74	1.41 (0.91-2.23)	0.11	0.71 (0.45-1.09)	0.11
WAZ	0.94 (0.43-1.70)	0.86	1.06 (0.59-2.32)	0.86	1.56 (0.85-2.82)	0.13	0.64 (0.36-1.17)	0.13
HAZ	0.84 (0.46-1.36)	0.53	1.19 (0.73-2.18)	0.53	1.04 (0.62-1.62)	0.85	0.96 (0.62-1.61)	0.85

OR = Odds ratio; MUAC = Mid-upper arm circumference; HC = Head circumference; CC = Thoracic circumference; WHZ = Weight-for-height Z-score; WAZ = Weight-for-age Z-score; HAZ = Height-for-age Z-score.

4. Discussion

Despite that malnutrition remains a real burden on public health worldwide, few studies have focused on the role that genetics plays in childhood malnutrition, particularly in Africa. The study by Marginean *et al.* [6] is the most recent one to correlate genetic polymorphisms with childhood malnutrition. Thus, in this present study, we evaluated the prevalence and the association of the *IL6*-190 *C/T* and *IL6*-174 *G/C* polymorphisms in Senegalese malnourished children aged 0-59 months.

Our results showed that the frequency of the *GG* genotype in the *IL6*-174 polymorphism was the highest in both the malnourished (84.44%) and healthy children (100%). A study conducted in Egypt [13] showed a lower prevalence of the *GG* genotype (28.2%) in obese children than in their non-obese counterparts (71.8%), and it was also noted that none of the children carried the *CC* genotype. Other studies carried out on African populations [15, 16] have recorded an absence of the *CC* genotype in their cohorts, which differs from our findings, where the *CC* genotype was found in 15.56% of the malnourished children. We observed the absence of the heterozygous *GC* genotype in both groups, which differs from the result obtained in Romania [6], where 41% of malnourished children had *GC* genotype. In our study, no significant association was found between the *IL6*-174 genotypes and anthropometric parameters in malnourished children. By contrast, in the previously mentioned Romanian [6] study, significant associations were noted between malnutrition and the *IL6*-174 *GG* and *GC* genotypes. In our study, the *IL6*-174 G was present in 84.4% of malnourished children, while the *IL6*-174 C allele was found in only 15.56% of malnourished children. Indeed, the presence of the *IL-6* 174 G allele was reported in 82.7% of patients, being a characteristic of undernutrition and frequently associated with malnutrition [6] while the *IL6*-174 C allele was associated with indices of obesity [17].

For the *IL6*-190 *C/T* polymorphism, the *CC* genotype was observed in 89.47% of the malnourished children and 100% of the healthy children in our study, whereas the *TT* genotype was only identified with the malnourished children with a frequency of 10.53%. We found no significant associations between the gene polymorphisms and anthropometric indices in malnourished children. Our results differ from those of the Romanian study, where a significant association was noted between malnutrition and the heterozygous *IL6*-190 *CT* genotype [6]. In that study, the *IL6*-190 *TT* genotype was found to be a protective factor against malnutrition [6]. Additionally, the levels of serum IL6 (615 pg/mL) were found to be higher in the malnourished children than in the control children. The *IL6*-190 C allele was observed in 89.47% of malnourished children and the *IL6*-190 T allele in 10.53%. A study of cachexia has found only homozygous patients to the *IL6*-190 C allele. No significant differences were found in *IL-6*-190 C distributions between the cachexia and non-cachexia groups [7].

A limitation of our present study is its small sample size. Thus, a more in-depth study of a larger population would allow us to better identify the genetic causes of malnutrition. The greatest strength of this study is that it is the first to correlate genetic polymorphisms with child malnutrition in Senegal. As such, it provides a crucial foundation for gaining insights and understanding the significance of this relationship.

5. Conclusion

In this study, we found no significant associations of the *IL6*-174 *G/C* and *IL6*-190 *C/T* polymorphisms with child malnutrition or anthropometric measurements. The most frequent genotypes in the malnourished children were *GG* for *IL6*-174 and *CC* for *IL6*-190. Only the female gender was significantly associated with the *IL6*-174 *GG* and *IL6*-190 *CC* genotypes. These findings deserve great attention and deeper evaluation in a large sample, because they will facilitate the readjustment of the methods used to manage malnutrition in Senegal. Thus, previous studies could highlight other polymorphisms of interleukin 6 or other cytokines, and integrate other biological factors. This would provide a better understanding of the role of genetics in childhood malnutrition in Senegal.

Conflicts of Interest and Funding

The authors declare no conflicts of interest. This study did not benefit from the funding reform.

Ethics Committee Statement

This study was approved by the UCAD Research Ethics Board (reference number: 0340/2018/CER/UCAD).

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