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Polymorphisms in DNA Repair Gene *XRCC1* (Arg194Trp) and (Arg399Gln) and their Role in the susceptibility of Bacterial Meningitis

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Abstract

Meningitis is a contagious infectious disease with high rates of mortality. Most pathogenic microbes in humans have the ability to cause bacterial meningitis. However, the most common pathogens are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib). It was found that the susceptibility to this infectious disease may be related to genetic characteristics of the host, such as the occurrence of single nucleotide polymorphisms (SNPs). In our previous work, association of SNPs in DNA repair genes with bacterial meningitis (BM) was demonstrated. In this study we evaluated two non-synonymous SNPs of the repair gene *XRCC1* Arg194Trp (rs 1799782) and Arg399Gln (rs 25487) in patients with BM and health volunteers. The patient genotypes were investigated by PCR-RFLP. DNA damages were quantified using the genomic DNA with formamidopyrimidine DNA-glycosylase (FPG). Cytokines and chemokines were quantified from cerebrospinal fluid samples from BM patients. Concerning the SNP *XRCC1* Arg194Trp, none association was found relation to BM. However, a higher frequency of heterozygous genotype for *XRCC1* Arg399Gln was observed in the control group compared to the BM group (P = 0.043; OR = 0.426). DNA damage and cytokine/chemokines levels were not positively correlated with polymorphic genotypes. In conclusion, there is an indication that the SNP *XRCC1* Arg399Gln could have a possible protective effect against BM.

Keywords: Bacterial meningitis; *Streptococcus Pneumoniae*; *Neisseria Meningitides*; Base excision repair; *XRCC1*; SNPs; Inflammation

Introduction

Bacterial meningitis (BM) is characterized as a severe infection in the central nervous system (CNS), which compromises the meninges. Despite the effectiveness of the vaccination and treatment with antibiotics, negative outcomes are still associated with permanent neurological dysfunctions [1-3].

Most pathogenic microbes in humans are able to cause meningitis. However, the most common pathogens that cause BM are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib) [4]. Although different pathogens involved in the BM evolution are recognized by different toll-like receptors (TLRs), an overlap in the activation of the same inflammatory response which starts with the induction of MyD88 – a dependent pathway of nuclear factor kappa B (NF-κB) has been reported [5]. This finding corroborates the recent studies from our group showing a similar profile of inflammatory modulators during BM caused by *S. pneumoniae* and *N. meningitidis* [6,7].

BM starts with mucosa colonization in nasopharynx by commensal microorganisms. In this step, the immune defense system is important to combat the pathogens, avoiding the disease progression [8,9]. Thus, deficiency in the innate or acquired immune response may cause predisposition to disease [10,11]. Furthermore, strategies have been developed along the evolutionary process to enable some of these pathogens to overcome this natural barrier. The pathogens may invade the bloodstream, and after blood-brain barrier disruption they gained access to subarachnoid space causing the infection.

Several events involving cytokines, chemokines and oxidative stress have been observed during the inflammatory response contributing to brain dysfunction and this is mainly caused by the host immune response rather than by BM pathogen per se [12,13]. Genetic factors, such as single-nucleotide polymorphisms (SNPs) in DNA repair genes and in immune response genes have been shown to be associated with BM occurrence [11,14].

In previous work, polymorphisms in base excision repair (BER) genes, main involved in the repair of oxidized DNA damage, such as *APEX1*, *PARP-1* and *OGG1* have been associated with regulation of immune response in BM [6,15]. However, none study of association between genetic variants in the X-ray repair protein cross-complementing group 1 (*XRCC1*) gene, a key protein from BER which interacts with *APEX1* and *OGG1*, and meningitis inflammation has been performed.

XRCC1 is considered a key protein to interact with several enzymes as *APEX1*and *OGG1*, stimulating their activities. Several variants of *XRCC1* have been described, the most common being located at codon 194 in exon 6, resulting from the substitution of arginine (Arg) with tryptophan (Trp). Another common variant is characterized by the exchange of arginine (Arg) for glutamine (Gln) at codon 399 located in exon 10 into BRCT1 domain [16,17]. The SNPs of *XRCC1*, Arg194Trp and Arg399Gln, have been investigated in several inflammatory diseases and cancer [18,19].

Considering the BER, as the main pathway involved in the repair of oxidative DNA damage in neurons [15], it is important to evaluate the association of genetic polymorphisms of *XRCC1* with BM. In this study, we screened the occurrence of SNPs of *XRCC1* Arg194Trp and Arg399Gln in the individuals with the meningitis disease. To the SNP *XRCC1* Arg194Trp we did not find relation with the disease, but to the SNP *XRCC1* Arg399Gln was found a higher frequency of the heterozygote genotype in the control group, indicating a possible protective effect against BM.

Materials and Methods

Ethics statement

Ethical approval for this study was given by Medical Ethics Committee at Giselda Trigueiro Hospital and by National Committee of Ethics (CONEP) with number 0052.1.051.000-05. In addition, informed consent was obtained from each patient participating in this research or the legal guardian in cases of minors/children.

Study subjects and samples

The study was conducted with a group of patients admitted at Giselda Trigueiro Hospital (HGT), reference for infectious diseases in Natal city, Rio Grande do Norte, state, Brazil. Diagnosis of each case was performed according to clinical signs and hospital routine tests, such as: Kernig's sign and the Brudzinski's sign, fever, headache, nausea and vomiting; cerebrospinal fluid (CSF) bacterial culture; gram staining; latex agglutination test in the CSF or blood; neutrophilic pleocytosis (≥ 500 cells/mm^3) with predominance of polymorphonuclear granulocytes (PMN), evaluation the levels of protein (> 40 mg/dl) and glucose (< 40 mg/dl).

The exclusion criteria for this study were patients undergoing treatment with drugs (i.e. antibiotics) or afflicted with other diseases (i.e. AIDS), which could interfere in the expression of immune and/or inflammatory markers as cytokines. The control group was formed by healthy volunteers and those patients with a negative diagnosis for infectious disease and whose leukocyte levels were within the normal scale. For healthy volunteers a questionnaire was applied in order to assess the history to infectious and inflammatory diseases. In this last group of patients, CSF samples were not collected. The Blood samples were collected to obtain white blood cell counts (WBC) and inflammatory modulators such as cytokines and chemokines were analyzed.

The study involved 160 subjects (86 men and 74 women) split in two groups, BM group (n = 53) and control group (n = 107). From all the individual studied, 31 were less than 18 years old, 124 adults between 18 and 60 years old, 5 individuals aged over 60. In relation to BM group, 53 patients had positive diagnosis: 16 were diagnosed with *S. pneumoniae*, 7 with *N. meningitidis*, 6 with other pathogens, and 24 without specified etiology (Table 1). These data are consistent with other papers published by our group [6,7].

Samples processing

Blood samples were collected and processed by centrifugation at 4000 g for 3 minutes at 4°C in order to separate plasma from cells. Genomic DNA extraction was performed by the salting out procedure following the protocol described by Miller et al. [20]. The DNA integrity was observed on agarose gel 0.7%. Samples of CSF were collected immediately following lumbar puncture and centrifuged at 720 g for 5 min. Supernatants were frozen and stored at -80°C before any further procedure. Blood samples were obtained from all patients and controls, however, CSF were only obtained from patients who were submitted to LP as diagnosis routine once lumbar puncture is an invasive procedure.

Features	Number of cases
BM	53
Age	
0-18	20
19-60	30
>60	3
Gender	
Male	32
Female	21
Pathogen	
S. pneumoniae	16
N. meningitidis	7
Other pathogens	6
Unidentified pathogens	24
Controls	107
Age	
0-18	11
19-60	94
>60	2
Gender	
Male	54
Female	53

Table 1: Clinical features of patients.

XRCC1 **Arg194Trp and Arg399Gln genotyping:** The genotypes of the polymorphisms *XRCC1* Arg194Trp and Arg399Gln were detected from the amplification of DNA by the method of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Primers to each polymorphisms *XRCC1* Arg194Trp (rs1799782) and Arg399Gln (rs25487) were obtained from Wu et al. [18] and Sturgis et al. [21], respectively. Table 2 shows primer sequences. The PCR-RFLP technique was validated after repeated with 20% from samples, beyond the success of genotyping above 80%.

PCR-RFLP products were generated using 100 ng of genomic DNA and 25 µl of PCR reaction containing specific buffer 1X, 10 pM of each primer, 2.0 mM $MgCl_2$, 0.3 mM of each dNTP, and 3.6 U of Taq polymerase. The PCR program had an initial denaturation step of 5 min at 94°C followed by 30 cycles of 1 min at 95°C, annealing of 1 min

and 30 s for codon 194 and of 2 min for codon 399 (temperatures given in Table 2), elongation for 1 min at 72°C and a final extension step of 10 min at 72°C. PCR products were run on a 1% agarose gels and visualized with SYBR green. The amplified fragments were digested with appropriate restriction endonucleases *PvuII* and *NciI* for SNPs *XRCC1* Arg194Trp and Arg399Gln, respectively (Table 2) and the resulting cleavage products were separated by electrophoresis on 8% polyacrylamide gel for 1 h at 100 V and detected with silver staining according to the protocol described by Sanguinetti et al. [22].

Genetic Polymorphism	Exon	Primer sequence	Annealing Temp. (0°C)	Restriction enzyme	Genotype	Fragments (bp)
XRCC1 Arg194Trp (rs1799782)	6	F 5'GTTCCGTGTGAAGGAGGAGGA3' R 5'CGAGTCTAGGTCTCAACCCTACTCACT3' (138 pb)	58.7°C	*PvuII*	Arg/Arg Arg/Trp Trp/Trp	138 138+75+63 75+63
XRCC1 Arg399Gln (rs 25487)	10	F 5'CAGTGGTGCTAACCTAATC3' R 5'AGTAGTCTGCTGGCTCTGG3' (871 pb)	58°C	*NciI*	Arg/Arg Arg/Gln Gln/Gln	461+278+132 593+461+278+132 593+278

Table 2: SNPs in DNA repair genes, primers and conditions used for genotyping.

Detection of FPG sensitive sites

The genomic DNA from patients was submitted to treatment with formamidopyrimidine DNA glycosylase (FPG) (New England Biolabs) as described by da Silva et al. [6]. This enzyme is a functional analog of *OGG1* in bacteria and acts as a bifunctional glycosylase that recognizes oxidized damage as 8-oxodG due to its β-lyase activity [23]. The sensitive sites to FPG were measured by densitometry of DNA, seen after electrophoresis in 1% agarose gel with ImageJ 1.42q software (Wayne Rasband National Institutes of Health, USA). The number of double strand breaks (DSBs) were calculated as described by D'Ambrosio et al. [24], using Poisson distribution. These data were associated with presence or absence of the SNPs in the studied group.

Measurement of inflammatory mediators

The cytokine and chemokine measurements were performed using the CSF of patients with BM. Inflammatory modulators levels were measured by multiplex suspension array using the Bio-Plex 200 suspension array system (Bio-Rad, Hercules, CA, USA) and using microsphere based multiplex assays. Human Cytokine/Chemokine Panel (MPXHCYTO-60k, Millipore) was used including a set of 12 cytokines and chemokines (TNF-α, IL-6, IL-1β, IL-2, INF-γ, IL-10, IL-1Ra, MIP-1α/CCL3, MIP-1β/CCL4, MCP-1/CCL2, G-CSF and IL-8/CXCL8). The samples were processed and measured in duplicates and according to the manufacturer's instructions [6,7]. This assay allowed for the quantification of cytokines and chemokines over a broad range of 3.2–10.000 pg/ml, using Bio-Plex manager 4.01 software. Due to the low quantity of biological material, it was not possible to make the determination in all the patients.

Statistical analysis

Statistical analysis was performed using GraphPad-Prism5 software and STATA software (version 11.0, Stat Corporation, College Station, Texas, USA). First, the allele and genotype frequencies to BM group and control group were determined by direct gene counting. Genotypic distributions in Hardy-Weinberg equilibrium were analyzed by the classical method of X2-test (two-tailed) using Helix SVS program. Logistic regression analyses were used to calculate odds ratios (OR) with 95% confidence interval (CI) and corresponding P-values for the association between the susceptibility to each variant. The effects of sex and age were also evaluated in this analysis.

Differences in the levels of inflammatory modulators and DNA damage level were analyzed using the non-parametric t-test (Mann-Whitney two-tailed). Values of $P \leq 0.05$ were considered statistically significant.

Results

Analysis of genetic polymorphisms

Fifty-three BM patients and 107 control subjects were tested for polymorphisms *XRCC1* Arg399Gln and Arg194Trp. The genotype distribution for both SNPs was in the Hardy-Weinberg equilibrium. For the SNP *XRCC1* Arg399Gln, the frequency of heterozygote (Arg/Gln) was significantly higher in controls ($P = 0.043$) than in BM patients. The frequency of homozygote (Gln/Gln) was more frequent in the control group although the difference was not significant. The frequency of Gln allele was higher in the control group (Table 3). Significant differences between groups were not observed, neither for the genotypes nor the alleles of SNP *XRCC1* Arg194Trp ($P = 0.68$) (Table 4).

Detection of DNA damage

FPG sensitive sites were quantified in genomic DNA obtained from individuals included in this study. The samples were analyzed in relation to the presence or absence of the variant allele. Although there was no significant difference, but a borderline value ($P = 0.056$) was observed for SNP *XRCC1* Arg194Trp, with a small reduction in FPG sensitive sites (Figure 1A).

No statistical difference in the levels of DNA damage was observed for individuals with the variant or wild-type alleles for SNP *XRCC1* Arg399Gln.

Considering no significant difference was observed between cases and control (data not shown), all individuals was grouped and the analysis was done take into consideration the presence or absence of the variant allele.

Measurement of cytokines and chemokines in patients with BM

The main cytokines and chemokines involved in the BM inflammatory response were examined in the CSF samples from patients. BM patients carrying *XRCC1* Gln allele did not showed statistical difference in the cytokines and chemokines levels (Figure 2). For SNP *XRCC1* Arg194Trp, no statistical difference was also observed in the concentration of cytokines and chemokines (data not shown).

Discussion

Bacterial meningitis has been known to be an important cause of mortality and morbidity. The disease evolution is mainly influenced by the host immune response determined by several genes that regulate the intensity of the inflammatory response to infection [8-11].

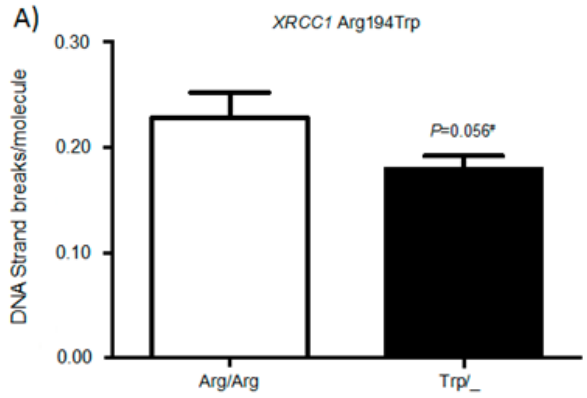

Figure 1A: FPG sensitive sites in genomic DNA in relation to *XRCC1* Arg194Trp and Arg399Gln SNPs. Significant difference was not observed to Arg399Gln SNP. *Statistical significance (P<0.05).

Genotype	Control group n (%)=107	BM group n (%)=51	P_a	OR (95% CI)	Adjusted P_a	Adjusted OR (95% CI)$_a$
XRCC1 Arg399Gln						
Arg/Arg	50 (47.17)	35 (68.63)	0.043*	1	0.048*	1
Arg/Gln	48 (44.34)	14 (24.45)		0.426 (0.204 – 0.889)	0	0.415 (0.196 – 0.878)
Gln/Gln	9 (8.49)	2 (3.92)		0.317 (0.065 – 1.560)		0.356 (0.707 – 1.795)
Gln allele frequency	0.3	0.17				

Table 3: Allelic and genotypic frequencies of BM group compared to control group for *XRCC1* Arg399Gln SNP. BM: bacterial meningitis; OR: odds ratio; CI: confidence interval. Data were analyzed by multivariate logistic regression. *Statistical significance (P<0.05). The reference group in each of the analysis was the most prevalent genotype. A data adjusted for age and gender.

Genotype	Control group n (%)=105	BM group n (%)=53	P_a	OR (95% CI)	Adjusted P_a	Adjusted OR (95% CI)$_a$
XRCC1 Arg194Trp						
Arg/Arg	95 (90.48)	49 (92.45)	0.68	1	0.94	1
Arg/Trp	10 (9.52)	4 (7.55)		0.776 (0.231 – 2.600)		0.954 (0.273 – 3.332)
Trp/Trp	0 (0)	0 (0)				
Trp allele frequency	0.04	0.04				

Table 4: Allelic and genotypic frequencies of BM group compared to control group for *XRCC1* Arg194Trp SNP. BM: bacterial meningitis; OR: odds ratio; CI: confidence interval. Data were analyzed by multivariate logistic regression. *Statistical significance (P<0.05). The reference group in each of the analysis was the most prevalent genotype. A data adjusted for age and gender.

In previous work, we obtained data showing association of the SNPs *APEX1*Asn148Glu, *OGG1* Ser326Cys, and PARP-1 Val762Ala with BM. Furthermore, the SNP in *APEX1*also showed effect on expression of some cytokines as IL-6 and IL-8 [6]. Since *XRCC1* is a key enzyme in BER pathway, being a scaffold protein that is responsible to recruit other proteins as *APEX1*and *OGG1* [16,17], similar data could be expected. However, our data showed that SNP *XRCC1* Arg194Trp is not associated with BM. In addition, for the SNP *XRCC1* Arg399Gln, we found a possible protective effect against BM once the Gln variant allele was more present in the control group, consequently significant

difference in allelic and genotypic frequencies was observed. Although, we used a low number of patients in our work we obtained allele and genotypic frequencies similar to the ones reported in the literature [25-27].

Other authors also found no association of SNP *XRCC1* Arg194Trp with rheumatoid arthritis and Alzheimer's disease [19,28]. The function of this SNP has not been established yet, but studies have suggested a protective role against cancer. Some experimental data indicate that the Arg194Trp variant is associated with increased genomic stability in response to genotoxic agents [29,30]. In agreement with these data, in our work we observed a trend in the reduction of FPG sensitive sites in the genomic DNA from BM patients, which may be associated to the role of *XRCC1* in stimulating the *OGG1* activity [17].

In relation to the SNP *XRCC1* Arg399Gln, the literature data show evidences of its association with rheumatoid arthritis, Parkinson's disease, increased in breast cancer risk, among others [19,31,32]. Some groups have tried to explain their results by ethnic data because populations with different ancestry may cause differences in observed frequencies (Figure 1B). However, the ancestral influence on the current Brazilian population is the result of effects such as, migration and miscegenation, mainly European, African and Amerindian populations and then resulting in a pattern of linkage disequilibrium. So, it is not possible a detailed analysis of the data found in ethnic closed groups for most of the studies conducted in Brazil, which does not have a specific ethnic pattern [33].

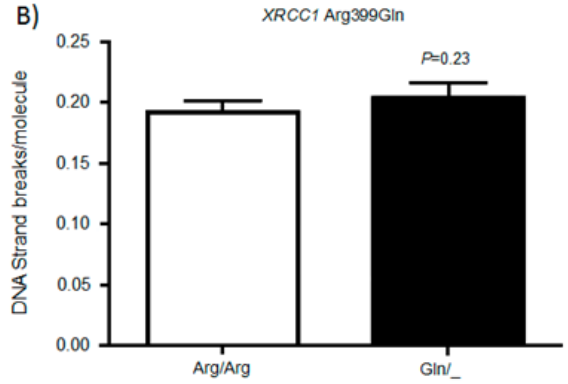

Figure 1B: I was observed a borderline value to XRCC1 Arg194Trp SNP (Mann-Whitney test two-tailed) in relation to the genotypes. *Statistical significance (P<0.05); #Borderline value.

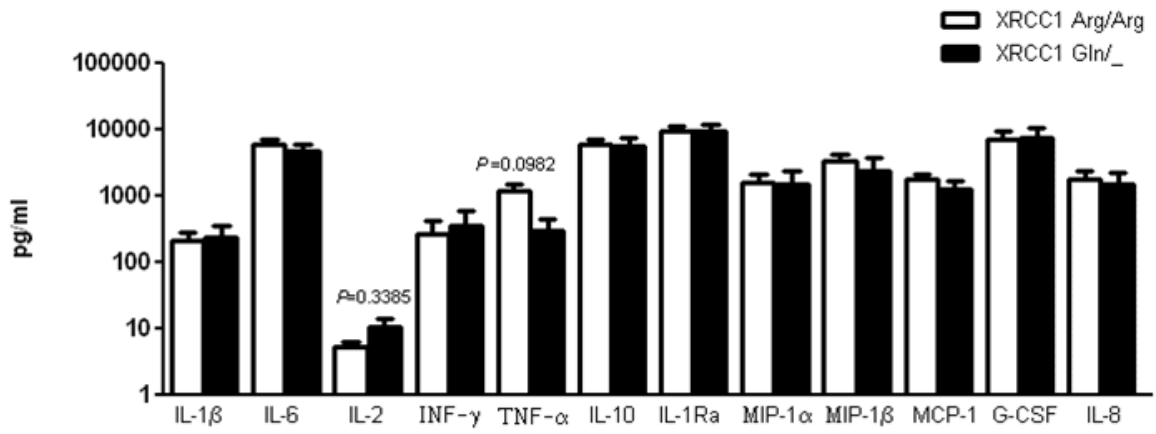

Figure 2: Cytokines and Chemokines levels in cerebrospinal fluid (CSF) of patients with BM for the *XRCC1* Arg399Gln SNP. Significant difference was not observed (Mann-Whitney test two-tailed) in relation to the genotypes. *Statistical significance (P<0.05).

Some authors have obtained evidence that the SNP *XRCC1* Arg399Gln may affect the *XRCC1* functions. The residue 399 is located in *BRCT1* domain of the *XRCC1* protein, which is important for protein-protein interaction. Experimental data indicated that the Gln variant affect the capability of *BRCT1* domain to interact with other proteins, reducing the ability of *XRCC1* to coordinate BER [34]. In cells expressing the *XRCC1* Gln variant, differences in the intra-nuclear localization or in the ability to recruit repair enzymes to the damage sites were not observed in relation to *XRCC1* wild type protein. However, a reduced stability of the repair foci was observed in cells expressing Gln variant. Furthermore, differences in repair profile were observed after treatment of the cells with methyl methanesulfonate (MMS) or hydrogen peroxide, suggesting that this SNP may affect the repair under stress conditions [35]. Corroborating these data, in non-small cell lung cancer patients with polymorphism to Arg399Gln a lower 8-oxoG incision activity was observed in lung tissues, but not in leukocytes. This suggests that this SNP may influence the *OGG1* activity in tissues exposed to stress [36].

Despite *XRCC1* interacting with *OGG1* which stimulates its activity 2 to 3-fold and being important in the repair of 8-oxoG [17], we did not observe differences in the occurrence of DNA damage in relation to *XRCC1* genotypes in our work. Since BM is a localized infection in CNS, and the genomic DNA was obtained from blood samples, our data corroborate with previous researches who propose that the SNP Arg399Gln may affect the repair function mainly in cells under stress [35,36]. In contrast to the commitment of the DNA repair functions, the SNP Arg399Gln has also been associated with a reduced risk of

some types of cancer, showing a protective role [37]. To explain this contradictory data, Stern et al. proposed the hypothesis that the reduced repair activity of Gln variant could predispose cells to increased apoptosis or senescence, thus preventing the tumor progression.

In the context of BM, it is not clear how the Gln variant could be associated to the protection of the disease. It was demonstrated that monocytes are highly sensitive to oxidative stress due to a reduced level of *XRCC1*, PARP-1 and LigIII proteins. After the differentiation in macrophages and dendritic cells, the repair proteins levels are restored. The authors proposed that the deficiency in repair of monocytes may be important to the regulation of inflammatory response, since the selective killing of monocytes during oxidative stress induced by macrophage may act as a negative regulatory feedback, reducing the macrophage differentiation and avoiding the excess of oxidative stress during inflammation [38]. In this scenario, it could be important to investigate the effect of the *XRCC1* Gln variant in monocytes/macrophage differentiation process.

Cytokines have an important role in controlling infection. Their deficiency may cause predisposition to diseases but in excess or in the wrong tissues can cause serious complications as observed in BM [8-11]. Some BER enzymes as *APEX1*, *OGG1* and *PARP-1* were implicated in the regulation of expression of some cytokines [6]. However, in this work we did not find any association between SNPs in *XRCC1* with cytokines and chemokines expression. Despite this, the hypothesis that *XRCC1* plays an important role in inflammation should not be ruled out, since a possible protective role of Gln allele was observed in our study. Considering that BM is a complex disease, the interaction between *XRCC1* with other important proteins in modulating inflammatory response should also be evaluated, since *XRCC1* is a scaffold protein important not only for BER, but also in nucleotide excision repair (NER) and non-homologous end joining (NHEJ) [39,40].

Conclusion

In conclusion, we found no association of the SNP *XRCC1* Arg194Trp with the disease and an indication that the Gln *XRCC1* allele of the SNP *XRCC1* Arg399Gln may play a protective role for BM. However, the low frequency of cases of meningitis and the poor conditions of the public health system in Natal (Brazil) did not allow for a more precise stratification of patients. With this, our results are preliminary and which will be necessary to extend this study to a larger cohort in the future to confirm this finding to understand the mechanisms involved in this protection.

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