Immunogenetic Mechanisms of Black Water Fever: Review Article

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ABSTRACT

The authors systematically reviewed the literature on mechanisms of Black Water Fever 'BWF) on immunology and genetics point of view to determine whether immunity and genetics are involved in the occurrence of Acute Intravascular haemolysis in malaria, leading to BWF.. All original reports of BWF were retrieved from Embase, Medline from 1935 to December 2018. Information extracted from each article included study design, definitions of BWF, pathogeny and risk factors of the disease. Descriptive, Prospective cohort, cross sectional, and case-control studies were assessed. Malaria IgG1 antibodies were measured. MBL2 gene were amplified and sequenced. BWF was associated to high level of malaria IgG1 antibodies. The geometric mean of antibodies in patients with BWF was high [1,95mg/l (IC95% :1,55-2,44) compared to [1,19 mg/l (IC95%: 0,98–1,43)] in children with uncomplicated malaria. High malaria IgG1 were statistically significantly associated with increased risk to develop BWF Children with MBL2 gene variants were less susceptible to develop BWF compared to children with normal MBL2 gene. Genotypes MBL2 AB&AC (AO) were more frequent in the control children group compared to the BWF cases: [OR: 0,21 (0,06-0,78) avec p=0,019] suggesting a protection conferred by gene mutations. Because of high level of MBL protein in MBL2AA genotypes patients; complement activation do to this protein can increase risk to acute intravascular hemolysis, the major mechanism of BWF Malaria .High level IgG1 and the MBL2 AA genotypes seem to the risk factors incriminated in the occurrence of BWF.

Keywords: Blackwaterfever; Malaria; IgG1; MBL2gene polymorphism

INTRODUCTION

According to WHO 2018, there were an estimated 228 million cases compared to 231 million in 2017.The global incidence rate of malaria (number of cases per 1000 population) fell from 71 in 2010 to 57 in 2014 and remained at similar levels through. Estimated deaths due to malaria fell globally from 585 000 in 2010 to 405 000 in 2018. However, the rate of reduction of malaria mortality was slower in the period 2016–2018 than in the period 2010–2015. Children under the age of 5 years accounted for two thirds (67%) of global malaria deaths in 2018.. More than half of all cases were in six countries: Nigeria (25% of cases); Democratic Republic of the Congo (12%); Uganda (5%); Côte d'Ivoire, Mozambique and Niger (4% each). About 3.4% of all malaria cases were in the WHO South-East Asia Region and 2% in the WHO Eastern Mediterranean Region [1].

In Democratic Republic of Congo; Falciparum specie is the most frequent [2]. Black Water Fever is one of the severe threatening malaria clinical form described in non-immune Europeans expatriates who stayed in malaria endemic area and used irregularly auto medication to Quinine to prevent malaria [3-9]. First of all; BWF was considered as non- immune Europeans expatriates disease until description of cases was done in autochthone population supposed to have malaria protection immunity [5,10-17].

Many factors seem to be involved in the occurrence of bwf

- *Falciparum. plasmodium:* It causing severe hemolysis by the invasion of Red Blood cells, the enzymatic activity deviated by plasmodium and oxidative stress caused by malaria infection.

- **Malaria immunity:** Malaria immunity should be involved because BWF was described firstly in none-immune population of European expatriates. Autochthone populations who develop BWF have probably malaria immune deficiency exposing them to develop massive intravascular hemolysis as expatriate individuals. Measure of malaria IgG is necessary to explore this issue.

- **Genetics:** All European expatriates who used Quinine in prevention and treatment of malaria did not develop BWF. Genetic factor should be involved. MBL gene can be analyzed because many studies showed the involvement of this gene in malaria occurrence.

- **Quinine:** This drug was incriminated in the occurrence of BFW since the first case described whether in none immune expatriate

population than in autochthone inhabitants.

IMMUNOLOGY PATHOGENESIS OF BWF

Pathogenesis of BWF is complex. Malaria immune deficiency observed in expatriate population and the use of Quinine are incriminated [4,6,8,9].

ACTION OF *P. FALCIPARUM* ON RED BLOOD CELLS (RBC)

Basically, Red Blood Cells are protected by many mechanisms like NADPH [18,19]. Those protective mechanisms based on enzymatic system as glutathione reductase, peroxidase, dismutase and catalase, can be deviated by plasmodium parasites profit. Study *in vitro* performed on the activity reduction of glutathione, glutathione peroxidase and the quantity of peroxidation products of RBC membrane lipids showed moderate increasing of glutathione only mature schizontes compared to other stage of RBC invaded by Plasmodium where Glutathione activation was low. The products of RBC membrane lipid peroxidation as malonic aldehyde were four times increased in schizontes than none parasite RBC. This parasite aggression leads to alteration of RBC membrane and his destruction [18,19]. It is clear that parasite plays an important role in the occurrence of BWF [20]. Interaction between parasite, RBC. Immune activated cells and products of activation can cause important damages on RBC even none parasite RBC which become more susceptible to hemolysis showing the toxic effect of parasite products [18,19].

ACTION OF QUININE ON RED BLOOD CELLS (RBC)

Quinine salts highly concentrated causes hemolytic action on Red blood cells. The association of Quinine administration and the occurrence of BWF was reported in many studies. The frequency of BWF decrease when Quinine was replaced by other malaria drugs in the treatment of malaria [10,19,21-30].

The action of Quinine and parasite can be combined. In fact, the contact of RBC with plasmodium and antimalarial metabolite produce a neo-antigen. The contact of neo-antigen and the immune system leads to the synthesis of an auto-antibodies named hemolysin. This contact with the fraction C1q of complement cause hemolysis [3, 31]. The liver is the site of hemolysin production [22].

Combined action of *P. falciparum* and quinine on the immune system

The auto-antibodies will react against quinine and *Plasmodium falciparum* during new episodes of the disease causing acute intravscularis hemolysis [11, 13-16, 29-31]

Pathogenesis of acute intravascular hemolysis in BWF

Pathogenesis of acute massive intravascular hemolysis in

Blackwater Fever (BWF) is recognized to be very complex.

Deficiency in malaria immunity often observed in the European expatriate population, Quinine treatment and *Plasmodium falciparum* parasite are the most commonly incriminated factors [4,8,12]. Malaria Antibodies increase gradually with age in autochthone population living in malaria endemic areas due to

sustained contacts with the vector and malaria parasite [32-47]. This malaria antibodies elevation is a complex process .It is divided in 3steps.

Children aged below 6 months, children between 6 months and 5 years and children more than 5 years Children under 6 months are under protection provided by maternally antibodies transmitted, fetal hemoglobin, the low concentration of Para Amino Benzoic Acid contained in maternal breast milk, and the use of the Insecticide Treated Net (ITN). Later, children between 6 months and 5 years lose most of the protective factors and become exposed to malaria this vulnerability is confirmed by the occurrence of about 90% of malaria gross mortality during this time window [48]. Finally after 5 years of age, children develop acquired protective malaria immunity and clinical malaria episodes decrease both in frequency and severity [48-50].Regarding the specific aspects of this malaria immunity, IgG1 directed against Apical Membrane 1 (AMA1) and the carboxyl-terminal region of the Merozoite Surface Protein 1(MSP1-19), are predominant in malaria immunity protection during the first 2 years of life [45,51].From the 3rd year of the life, malaria IgG3, directed against MSP2, increase [45,51]. Basically, the role of these Antibodies is to protect against malaria episodes. Surprisingly, the majority of children with BWF are above 5 years old, an age where children are expected to have already acquired protective immunity against malaria in the stable endemic area [15, 52-54]. To date, Results of study of immunity during BWF episode shows that IgG1 were highly elevated in BWF patients compared to children with uncomplicated malaria episode [55].These data suggest that patients with BWF did not realize a good immune transition. In fact non-immunes malaria travelers coming back in France after a stay in malaria endemic area have exclusively malaria sub-class IgG1 antibodies against MSP2 antigen and not IgG3 [56] According to this results, we can assume that autochthone children with BWF have the same immune profile like non- immunes Europeans expatriates. These observations were noted in prospective longitudinal studies about susceptibility to develop malaria in children between 3 and 8 years. Studies show a high prevalence of IgG3 in malaria asymptomatic patients whereas patients with symptomatic malaria have a high elevated level of IgG1 [57,58].

During some studies, malaria IgG1 directed against AMA1 and MSP1-19 antigen were predominant in young age and present all other age, whereas malaria IgG3 to MSP2 depended strongly to the age. IgG1 antibodies were observed in the young children, but IgG3 were observed in old children and adults. We can conclude that the premonition is mostly linked to IgG3 directed to MSP-2 and not IgG1 directed to AMA1 and MSP-19 which are more antiparasitemia [59,60] These results are supported by those of Taylor [51-61].

Children with high malaria IgG1 develop BWF. This result suggests the role played by these antibodies in the occurrence of the disease. BWF shows realty the role played by malaria IgG1 in the occurrence of acute massive intravascular hemolysis leading to disease. There is evidence that acute massive intravascular hemolysis which occurs in expatriates population arriving recently in malaria endemic area is due to low concentration of malaria antibodies [4-9]. Autochthone children more than 5 years old who develop BWF have high concentration of malaria antibodies [55]. These facts depend to immunology mechanisms. It should be the same mechanism between expatriates and autochthones. It is probably a hyper sensibility reaction type III according to Gel and Coombs

due to toxicity of antigen-antibodies complex. In expatriate population, this reaction occurs in the presence of high malaria antigen (*Plasmodium falciparum*) whereas in malaria autochthone children population the same reaction occurs in the presence of high concentration of malaria antibodies (IgG1) [55,62].

Hyper sensibility reaction type II due to reaction of quinine antibodies directed to quinine metabolite fixed on RBC is possible also. Unfortunately, we did not yet measure quinine antibodies.

GENETICS AND BWF

Host genetics influence the malaria outcome especially in children. [63-69]. Host genetic factors can determine the occurrence, the clinic features and the evolution of the disease [70]. Among the gene which influence malaria outcome, we have the MCH (Major Complex Histocompatibility), the gene of Complement Receptor-1: CR1), the genes of sickle cell disease, the Tumor Necrosis (TNF-α), the G6PD, Interleukin-10 and 12, thalassemia and mannose binding lectin 2 [68,71]. We focus our research on MBL2 gene because we fund opportunity to amplify and sequence this gene in immuno-genetic laboratory of Nagasaki University in Japan.

### Description of Mannose Binding Lectin 2 gene (MBL2)

MBL2 gene has 969 base pairs with 4 exons and code for the synthesis of Mannose Binding Lectin protein (MBL protein), which belongs to C-lectin, family playing a capital role in innate immunity. The gene is located at chromosome 10, [10,11,2-21]. Each exon has a function in the synthesis of MBL protein. .Exon 1 codes for the synthesis of N-terminal protein part of the protein and a portion of " collagen-like ",part, exon 2 codes for the synthesis of the other portion of "collagen-like" of the protein, exon 3 codes for the alpha-helical of the protein and exon 4 codes for C-terminal part with the domain of recognition: Carboxylate Recognition Domain (CRD). The region of promotor of the gene of Mannose Binding Lectin 2 (MBL2)

Carries the sites bind of transcription factors involved in the response to the acute phase of malaria infection or any other infection [72-77].

The next figure shows MBL2 gene with the region of promotor and the 4 exons .It presents polymorphism positions in the region of promotor in positions -550, -221, -70 and at exon 1. At exon 1, there are different polymorphism sites, +4, +223, +230, +239. The figure shows also the alleles at different positions (Figure 1).

Figure 1: Gene MBL2, promotor region and the 4 exons Described by Vandana, et al. [76].
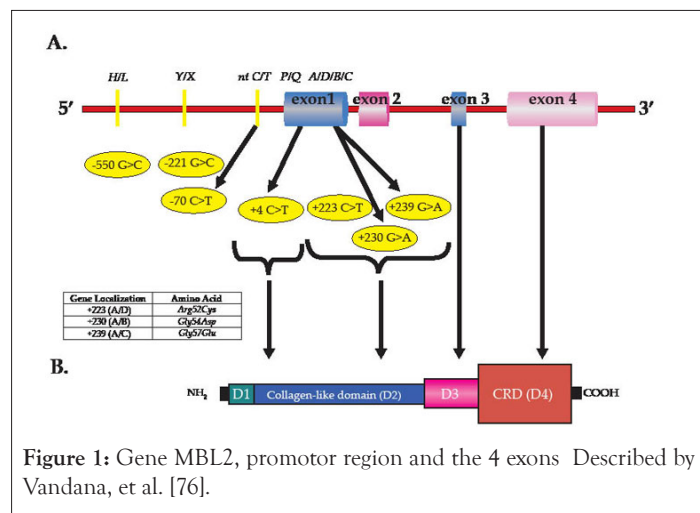
The follow figure is illustration of MBL2 gene according to Juliger S with the polymorphic sites at region of promotor (-550, -427, -349, -338 et-221) and codons 54, 57 of exon1. Position +4 and codon 52 are not represented in this scheme (Figure 2).

**Figure 2:** MBL2 gene with the region of promotor and exon 1) Described by Juliger [77].
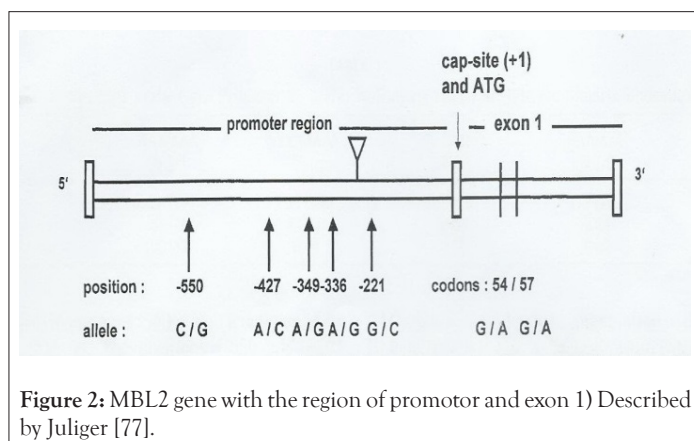
The three polymorphic sites at exon 1, identified at codons [52,54,57] of MBL2 Gene by Sum iya et al., Lipsombe et al and Madsen et al. [78-80] are conventionally represented by the letters D, B, and C respectively whereas the normal gene is represented by A [78,81-82]. Codons [52,54,57] can also be designed by g (+223, +230, +239). When variants MBL2 Gene structure is described, many authors adopt the nomenclature A/A for homozygotes individuals for the normal allele, A/O for heterozygotes and O/O for homozygotes in variants [56]. Other variants couples made by Single Nucleotide Polymorphism (SNP), are also described and represented by conventional symbols either at promoter region of gene (H/ L at position -550 and Y/X at position-221) or at position +4(P/Q). Other diverse combinations of different variants are described on whole gene, Seven haplotypes were first of all described: HYPA, LYPA, LYQA, LXPA, HYPD, LYPB, LYQC), which are accompanied with decreasing concentration of MBL protein in circulation, with a consequence on the alteration of complement activation pathway [82-85]. The variants (H, L, X, and Y) located at promoter region have drastic effects in the MBL protein concentration. Different frequencies of variants reflect inter-racial differences in the serum concentration of MBL protein [86-88]. Initially; three haplotypes were investigated (HY, LY, LX) [86]. However, many other haplotypes are possible if we consider polymorphisms at position +4 (P/Q) and those of exon 1 [89].

World distribution of MBL haplotypes

Studies were performed worldwide [90] about the distribution of some haplotypes of MBL2 gene. Those studies reported haplotypes distribution in different autochthone populations from Africa autochthones [82-83], Europe [71, 83], Asia [91,92], Australia [93], Greenland [82-83] South America [83].

Haplotypes presented in below have frequency more than 5%. Haplotypes who carry mutations at exon 1 (B, C, or D) are presented with color and deficient functional halophytes (LXPA) is in italic. Haplotype LYQC is typically observed in Sub-Saharan Africa, HYPD is frequently met in Caucasian population and LYPB is spreader in Europe until American natives via Asian populations following population's historic migrations. The three haplotypes miss in Australian population [92]. (Figure 3).
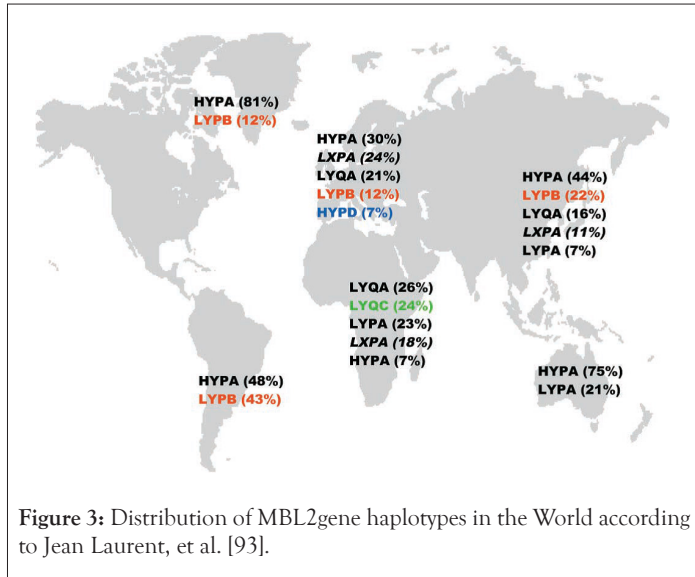
Figure 3: Distribution of MBL2gene haplotypes in the World according to Jean Laurent, et al. [93].
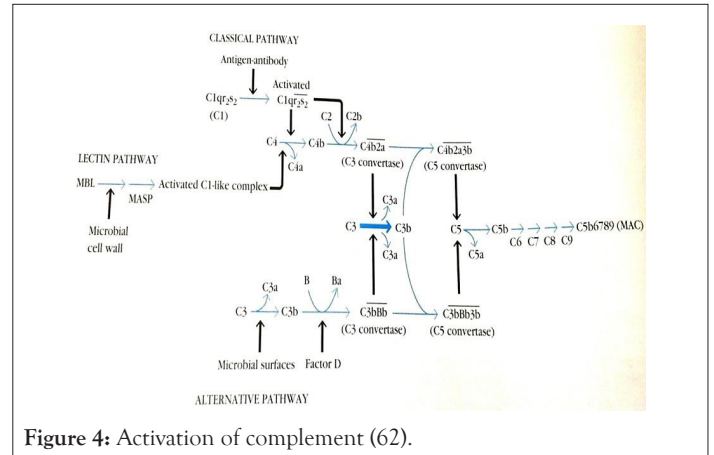
ROLE OF MBL2 GENE IN MALARIA

The results about the role of MBL2gene in malaria is somewhat contradictory [78,94] Bellamy et al. studied polymorphism of MBL2 gene in Gambian children with severe malaria, uncomplicated malaria and health children considered as group control. Authors did not observe significant differences in different groups [94]. Garred et al. did not observe differences in Ghanaians children [85]

In opposite, other studies reported significant differences between children in different groups'. Luty et al. [72] observe that mutations at the region of promoter of MBL2 gene influence the clinic evolution of the disease. Other studies showed the evidence of association between the evolutions of malaria in regard of concentration [77]. Studies performed in Gabon revealed 14 new haplotypes and authors have found significant association between a new mutation (g797 C>A) and severe malaria [75].

Protein Mbl

Definition: Mannose Binding Protein called also mannan binding lectin protein is a protein of C-lectin family protein. The protein is produced in the liver and is linked to residue of Carbone hydrate like mannose, glucosamine in the presence of calcium. His molecular weight is 96 KDa by monomeric unit.

Functions of MBL protein: MBL protein plays important role in immunity:

• MBL protein is linked by his collagen- like part to collecting receptor of phagocytes cells [92] ;

• MBL Protein recognize residues of Carbone hydrates (mannose and N-acetyl glucosamine) at the surface of bacteria, champignons, virus, and parasites like plasmodium [95-103].

• MBL protein plays an important role during opsonisation process of pathogen micro-organisms [102,104-110].

• MBL protein is associated to serines proteases 1, 2 and 3. His function in the activation of complement with serines proteases 1 et 2 acting on the fractions C1 et C3 of complement (105-110). MBL protein is the 3e pathway of complement activation, an independent pathway of antigen-antibodies presence (Ag-Ab), but which is near by the activation of C4 and C2 complement fractions

[62,72,81,82,111,112]. Deficiency in MBL protein is not rare and seems to predispose to severe infections [113] (Figure 4).

**Figure 4:** Activation of complement (62).

MBL protein is a protein of acute phase of inflammation [78]. The level of his synthesis is linked to the normal allele and haplotypes of MBL2 gene MBL2 and also the evolution of the disease.In case of normal gene; the concentration of the protein is 50-5000ng/L according to many authors. In the allelic forms and haplotypes of gene, diminution of MBL protein concentration was reported [114-118].

The diminution of MBL protein concentration was linked to the occurrence of sepsis and severe features of many bacteria and parasite infections because this diminution increases susceptibility to infection especially during childhood period [74,83,115-120].

Punctual mutations at codon 52 (Arg → cys), 54 (gly → Asp) et 57(gly → glu) at exon 1 play an importatn role in the synthesis of MBL protein [78-80,85].

Structure of MBL protein: MBL protein is a macromolecular complex containing 6 structural molecules united by disulfures bonds. Each structural molecule is monomer molecule and the molecular weight is 96 KDa and is composed of 3 polypeptide chains or sub-units of 32 KDa. Each chain has 228 amino acid and 4 domains which reflect the structure of MBL2 gene [121]:

• The rich-cystein domain located at N- terminal extremity and has 20 amino acids;

• The collagen-like domain containing tandems in repetitions of 18 to 20 amino acids;

• The domain of alpha helice or flexible domain named neck

• The recognition domain of Carbone hydrate on the surface of pathogen agents at C-terminal extremity (Figure 5).

Figure 5: Structure of MB protein [119].
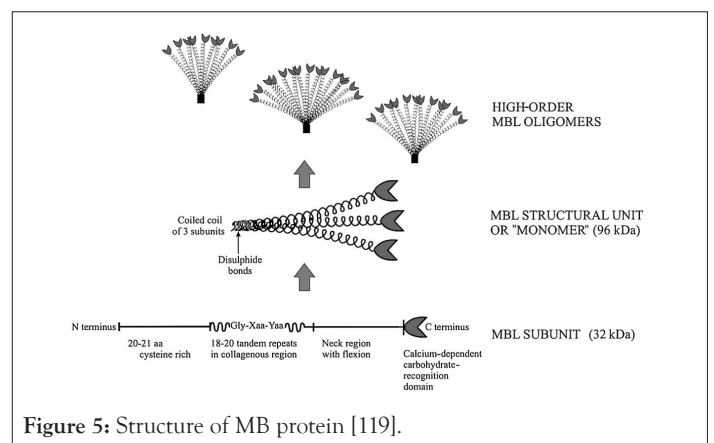
In a case- control study carried out at Kinshasa, capital town of RDC about exploring association between MBL2 gene polymorphisms and the occurrence of clinical Blackwater fever in Congolese children, authors observed that heterozygotes genotypes MBL2 A/B&A/C (A/O) were more frequent in the control group with uncomplicated malaria whereas most of children with clinical Blackwater fever have the normal genotypes A/ A (72%) (1122).

Previous studies reported that carriers of variant allele and genotypes * B, *C and *D represented by O (O/O) for the homozygotes and A/O for the heterozygotes, are more susceptible to develop infections especially malaria. Individual's carrier of normal allele A (A/A) were resistant to develop malaria [78,114-115-117].

Surprisingly for Blackwater fever, patients with genotype MBL2 A/B or A/C who are heterozygotes A/O with genotype MBL2 A/B or A/C were protected to develop BWF compared genotype homozygote MBL2 A/A [122]

In genetic point of view of BWF pathogenesis, MBL protein should be involved in the occurrence of acute massive intravascular hemolysis, the major mechanism of BWF by Complement activation pathway by MBL protein .In fact, heterozygotes for MBL2 gene have a reduced concentration of MBL protein. Decreasing concentration of MBL protein is known to hamper phagocytosis of intracellular bacteria and parasites [83,115,123,124-126].

However, this diminution of MBL protein concentration reduce also excessive complement activation which is deleterious for the host. This mechanism can explain the protection of heterozygotes and variants against acute massive intravascular hemolysis. Mutations at exon 1 offer protection to develop acute massive intravascular hemolysis the major mechanism of BWF. [79,123,126].

As known, MBL protein is the 3e pathway of complement activation, an independent pathway of antigen-antibodies presence (Ag-Ab), but which is near by the activation of C4 and C2 complement fractions [78,81-82,112,119]. Deficiency MBL protein is not rare and seems to predispose to severe infections [113].

Majority of children with normal genotypes A/A(72%) develop BWF [122]. We assume that excessive complement activation by normal concentration of MBL protein is the main mechanism causing acute massive hemolysis and BWF in those patients with normal genotypes known to have high MBL protein.

CONCLUSION

Pathogenesis of BWF is really complex. Immune activation and genetics mechanisms are really involved in the occurrence of BWF especially malaria immune complex antigen-antibody, MBL protein and excessive complement activation. Future studies are needed to explore those mechanisms to get more evidence by the measure of IgG3 antibodies, MBL protein; complement activity and quinine antibodies.

LIMITATIONS OF STUDY

We did not measure quinine anti-bodies, malaria IgG3, MBL protein and complement activation.

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