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[Authors section](#)
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Plasma levels of IL-12, IL-18 and TGF-beta in Plasmodium falciparum malaria



Abstract

The interaction between pro- and anti-inflammatory cytokines such as interleukin 12 (IL-12), interleukin 18 (IL-18) and transforming growth factor beta (TGF- β) may play an important role in malaria pathogenesis and outcome. IL-18 cooperates with IL-12 in the IFN- γ production by T, B, and NK cells, and synergizes with IL-12 for IFN- γ production by Th1 cells. Recently it has been demonstrated that these cytokines modulate the immunoresponse in *Plasmodium falciparum* malaria. The aim of this study was to measure the plasma levels of IL-12, IL-18 and TGF- β in 105 African children with various degrees of malaria, and correlate the production of these cytokines with the severity of the disease. IL-12, IL-18 and TGF- β levels were determined using enzyme-linked immunosorbent assay. The severity of malaria was established by parasitemia, clinical symptoms and haematological parameters. The levels of IL-12, IL-18 and TGF- β were found to be significantly elevated (15.6 ± 12.3 , 22.7 ± 13.8 pg/ml and 25.14 ± 13.22 pg/ml respectively) in all of the children. IL-12 and IL-18 levels were significantly lower (13.2 ± 5.53 and 21.5 ± 10 pg/ml pg/ml) in children with severe disease, whereas the level of TGF- β was higher (28.09 ± 12.39 pg/ml). In contrast, IL-12 and IL-18 levels were found to be higher (17.32 ± 7.8 pg/ml and 25.7 ± 7.6 pg/ml) in patients with mild disease, whereas the level of TGF- β was lower (20.92 ± 12.76 pg/ml) compared to the severe malaria group. The correlation between IL-12 and IL-18 demonstrated a progressive relationship up to a value of IL-12 < 25 pg/ml, while IL-18 remained stable at higher levels of IL-12. An inverse correlation was found between IL-12 and TGF- β up to a value of IL-12 < 30 , after which the level of TGF- β remained stable. This finding suggests that fine mechanisms regulate the interaction between IL-12, IL-18 and TGF- β in the immune response to *Plasmodium falciparum*.

Full text

Malaria is one of the major causes of morbidity and mortality in sub-Saharan Africa [1]. Severe anemia and cerebral malaria constitute the major cause of death, and mostly in children under the age of 5 years [2]. Recent evidence indicates that the balance between type 1 and type 2 immune responses, and between proinflammatory and antiinflammatory cytokines is important in determining the level of malaria parasitemia, disease outcome and rate of recovery [3]. It has been shown that IFN- γ , followed by IL-10 production, promotes a favourable outcome, limits the initial phase of parasite replication [3], but also contributes to acute symptoms of malaria through the induction of TNF- α and IL-1 [4]. Thus, overproduction of either pro-inflammatory or anti-inflammatory cytokines may be associated with disease severity and mortality [5, 6]. In addition to IL-6 and TNF- α , IL-12 and IL-18 could also have a critical role in the adaptive immune response to malaria through macrophage activation, directly related to the effects of hemozoin (HE) on phagocytic cells [7]. The hemozoin (HE), an

insoluble polymer of haemoglobin, is produced by monocytes and resident macrophages after ingestion of erythrocytes containing parasites, and represents for them an enormous stimulus [8]. IL-18 has a wide range of immunoregulatory functions, inducing gene expression and synthesis of TNF- α , IFN- γ and IL-1 by macrophages, induction of natural killer cell cytotoxicity and an increase in Th1 differentiation [9, 10]. Torre *et al.* [11] have shown that interleukin 18 (IL-18) may have a proinflammatory role in patients with uncomplicated *Plasmodium falciparum*, but it is not known whether IL-18 correlates with disease severity.

IL-12 and IL-18 act synergistically on CD4⁺ cells for IFN- γ production by Th1 cells [12], and it has been hypothesized that IL-12 is needed for IL-18-induced IFN- γ production, and that IL-18 induces IFN- γ , but only when its receptor is upregulated by IL-12 [13, 14]. Also, transforming growth factor (TGF- β) is an important regulator of inflammation since it possesses both pro-inflammatory and anti-inflammatory functions depending on the plasma concentration [15]. Perkins *et al.* suggest that the inflammatory cascade in severe malaria is characterized by suppression of the protective effects of TGF- β 1 and IL-12, and that overproduction of TNF- α may promote deleterious effects such as severe anemia [16].

The main goal of this study was to measure the plasma levels of IL-8, IL-12, and TGF- β to assess the relationships between pro-inflammatory and anti-inflammatory cytokines and the relationships among them in various degrees of malaria severity.

Patients and methods

The study was conducted in the city of Ouagadougou (Burkina Faso), which is situated at the center of the country, in a mesendemic area for *Plasmodium falciparum* malaria, peaking between July and October, and was carried out in collaboration with local Medical Centre Saint Camille (CMSC). The institutional review board of the centre obtained ethical approval for the study. The patients were evaluated and enrolled at the Pediatric Dispensary. Informed consent for participation in this study was obtained, from parents or guardian of each individual prior to inclusion.

Diagnosis and classification of cases

To perform this study, 105 children (55 males and 50 females) affected by acute malaria, median age 19.5 months (range 2–144), were observed during the month of October, 2000 at the Medical Centre St Camille of Ouagadougou (Burkina Faso). Inclusion and classification of each case were based on the symptoms, physical signs and laboratory findings of malaria at the onset of the disease. On the basis of hematological parameters, hyperparasitemia and evidence of neurological involvement, two different level of severity were classified as A and B.

(A) "Severe malaria" (complicated) was established by microscopic confirmation of asexual *Plasmodium falciparum* parasites in the peripheral blood and at least one of the following clinical and physical sign, according the WHO criteria: evidence of neurological compromise (prostration, lethargy), gastrointestinal symptoms, severe anemia (Ht < 20 %, Hb < 6 g/dl), hyperparasitemia corresponding to $E_p > 5 \times 10^5$ or > 5 %, hypoglycemia (serum glucose less than 2.2 mmol /L corresponding to 40 mg/dl), acidosis with respiratory distress, oliguria, cardiovascular shock, jaundice, diffuse hemorrhages.

(B) "Mild malaria" (uncomplicated) was established by microscopically confirmed parasitemia of $E_p < 5 \times 10^5$ or < 5 % with fever, headache, and myalgia, without any findings of severe malaria.

Patients with "uncomplicated malaria" and parasitemia $E_p < 5 \times 10^5$ were treated with chloroquine at a dosage of 10 mg/kg for 2 days, then 5 mg/kg for another day. Patients with severe malaria or parasitemia $E_p > 5 \times 10^5$ received intravenous treatment with glucose 5 %, and quinine dichlorhydrate, according to the official therapeutic protocol of the local Programme National de Lutte contre le Paludisme (PNLP). The PNLPP protocol was followed by treatment with quinine for seven days or chloroquine for three days.

As the control group for the cytokine determination, 40, healthy black children of the same range of age (median 22 months, range 10 – 100) were also included in the study. All children enrolled as part of the control group were negative at the thick-smear examination for *Plasmodium falciparum*, had not suffered from any febrile episodes during the previous 6 months and had no signs of anaemia (Hb > 10 g/dl).

Detection of parasitemia and plasma sample collection

Standard hematological parameters were determined in each patient. For detection of parasitemia, a calibrated, thick-smear technique was used, with standard Giemsa staining. The blood samples were collected for immunological assessment in sterile tubes containing EDTA. All the samples were centrifuged and the serum was frozen at -40°C and were sent to the Laboratory of the Department of Biomedical Sciences, University of Catania, Italy, for the determination of IL-12, IL-18 and TGF- β .

Cytokine assays

Serum samples were analysed for IL-12, IL-18 and TGF- β using enzyme-linked immunosorbent assay (ELISA) obtained commercially (R&D Systems - Milan, Italy). The assays were performed according to the manufacturer's protocol. Each plate included a standard curve and known positive and negative controls. Absorbance was read against a blank at 450 nm using a microtiter ELISA reader. The coefficient variation intra-assay ranged from 1.1 to 1.4 pg/ml, from 3.4 to 6.9 pg/ml and from 2.7 to 5.9 pg/ml respectively for IL-12, IL-18 and TGF- β .

Statistical analysis

Within these experiments, statistical significance was analyzed using the Student's two-tailed t distribution test for parametric data. The level of significance was set at a two-tailed p of < 0.05 . The correlations and regression lines were made using an SPSS-10 program.

Results

In Table 1, the mean values of the more important hematological parameters are reported according to severity of the disease. The 77 children affected by severe malaria were younger, with mean a Hb level of 3.72 ± 1.26 gr/dl and platelet count of 157.76 ± 84.55 , while the Hb level and platelet count were higher in 28 children with less severe disease (8.28 ± 1.57 and 234.84 ± 150.67 respectively). The leukocyte count did not show any significant variation. A significant correlation was found between hemoglobin concentration and platelet count in all children with malaria ($R^2 = 0.173$). IL-12, IL-18 levels were found to be significantly lower (13.2 ± 5.53 pg/ml) and (21.5 ± 10 pg/ml) respectively, in all children with severe disease ($p < 0.001$), whereas TGF- β was higher (28.09 ± 12.39 pg/ml). The levels of IL-12 and IL-18 were significantly higher (17.1 ± 7.8) and (25.7 ± 7.6 pg/ml) in children with less severe disease ($p = 0.044$), they were older and showed less severe anemia (Hb 8.28 ± 1.57 g/dl), a higher platelet count ($234.84 \pm 150.67/\text{mm}^3$) and did not show signs of neurological involvement. In these children, TGF- β was lower (20.92 ± 12.76 pg/ml). The parasite density was higher ($E_p > 5 \times 10^5$) in patients with severe malaria but IL-12 and IL-18 levels were lower. From these results it can be seen that the level of IL-18 increases up to a corresponding level of IL-12 < 25 pg/ml (Figure 1). The correlations between IL-12 and TGF- β and IL-18 and TGF- β showed an inverse relationship, up to a level of IL-12 and IL-18 > 25 -30 pg/ml (Figures 2 and 3).

Discussion

In our study, the IL-12, IL-18 and TGF- β levels were elevated in all children with malaria, as an expression of immune activation in response to the presence of parasites. However, by distinguishing two groups according to the different levels of hemoglobin concentration, platelet count and level of parasitemia, it is possible to understand the role of these cytokines and their relationship in the pathogenesis of malaria infection. A large body of evidence indicates that cytokines are determinants of malaria severity and outcome [3-6, 17] and can represent potential targets for therapeutic intervention. Several studies suggest that the balance between pro-inflammatory cytokines such as TNF- α , IFN- γ , IL-6 and anti-inflammatory cytokines, such as IL-4 and IL-10, determines the degree of malaria parasitemia, level of anemia and clinical severity [18, 19]. Other evidence suggests that malaria outcome depends on cytokines overproduction and not on the balance between them, since high levels of anti-inflammatory as well as pro-inflammatory cytokines may be associated with disease severity and mortality [5].

Our results in children with malaria suggest that a fine regulation mechanism modulates the production of IL-12, IL-18 and TGF- β , since the production of IL-12 seems open the way to IL-18 for the IFN- γ production, an important mediator of the immune response to *Plasmodium falciparum*. In contrast, the production of TGF- β is downregulated more by IL-12 than IL-18. Moreover, the synthesis of IFN- γ , a direct consequence of CD4^+ and CD8^+ T cells activation, is followed by the production of IL-12, which in turn induces IFN- γ production by NK cells in a positive feed-back loop that represents an important amplifying mechanism of the immune response [20]. Reduced IL-12 concentrations in children with severe *Plasmodium falciparum* malaria may be related to the reduced T-cell-mediated IFN- γ activity [21]. Evidence from our recent results establishes a

critical role for IL-12 in the adaptive immune response to malaria, and confirms the association between the levels of IL-12 and macrophage activation, with production of IFN-g, directly related to the effects of hemozoin on phagocytic cells [22].

The IFN-g produced by CD4⁺ T cells *via* signal transducers associated with transcription, activates iNos (inducible nitric oxide synthase), inducing the L-arginine-dependent NO pathway, and participates in the elimination of the hepatic schizonts within the infected hepatocytes [23]. In this mechanism of removal of intracellular parasites, IL-12 and IL-18 are cofactors for the development of the Th1 response [17], which stimulates the production of IFN-g. Our results confirm that, in a very early phase of *Plasmodium falciparum* infection, when the production of IL-12 is uncontrolled, IL-18 production is not synchronous with the variation of IL-12 (Figure 2).

In *Plasmodium falciparum* malaria the involvement of TGF-b becomes necessary since it inhibits IFN-g and TNF-a production up-regulating IL-10 and down-regulating the expression of adhesion molecules [24, 25]. In fact, the attachment of parasitized erythrocytes to the endothelial adhesion molecules of brain vessels is responsible for the evolution to severe malaria [26]. Studies in murine models have shown that low levels of TGF-b production were associated with lethal outcome, whereas sustained production of TGF-b was associated with resolving infection [26]. Thus, levels of TGF-b are inversely correlated with the severity of the malaria infection, and TGF-b appears to play an essential role in down-regulating the production of pathogenic pro-inflammatory cytokines. Moreover, levels of TGF-b inversely correlate with rates of parasite replication; neutralization of TGF-b led to more rapid parasite growth, while conversely, treatment with optimal doses of rTGF-b slowed the rate of parasite replication [27]. Thus TGF-b plays two important roles in malaria infection, which vary depending on the phase of infection. Early in the infection, TGF-b promotes Th-1-mediated mechanisms that control parasite growth. Later in infection, TGF-b down-regulates Th-1-like response to limit inflammation-associated pathology [28].

Our results confirm that TGF-b counteracts the production of IL-12 and IL18, modulating the immune response to the *Plasmodium falciparum* parasite. The susceptibility to severe anemia and other aspects of malarial pathophysiology (such as anemia and cerebral malaria) could result the response of host macrophages to parasite products and consequently from unbalanced cytokines production. The synchronised IL-12 and IL-18 production and the early production of TGF-b may play an important role in the outcome of malaria, reducing the systemic damage induced by the presence of *Plasmodium falciparum*. Recently, the use of IL-12 has been proved to be effective in experimental malaria [29], but the dose appears to be critical, given the potential toxic effects of this cytokine [30, 31]. Our results on the synchronised of IL-12 and IL-18 production during the disease suggest further investigation to optimize the combination of these two cytokines for the treatment of severe *Plasmodium falciparum* malaria. The rapid escalation of parasitemia can be repressed by TGF-b administration in the early phase of the disease, promoting Th1 cell-mediated immunity.

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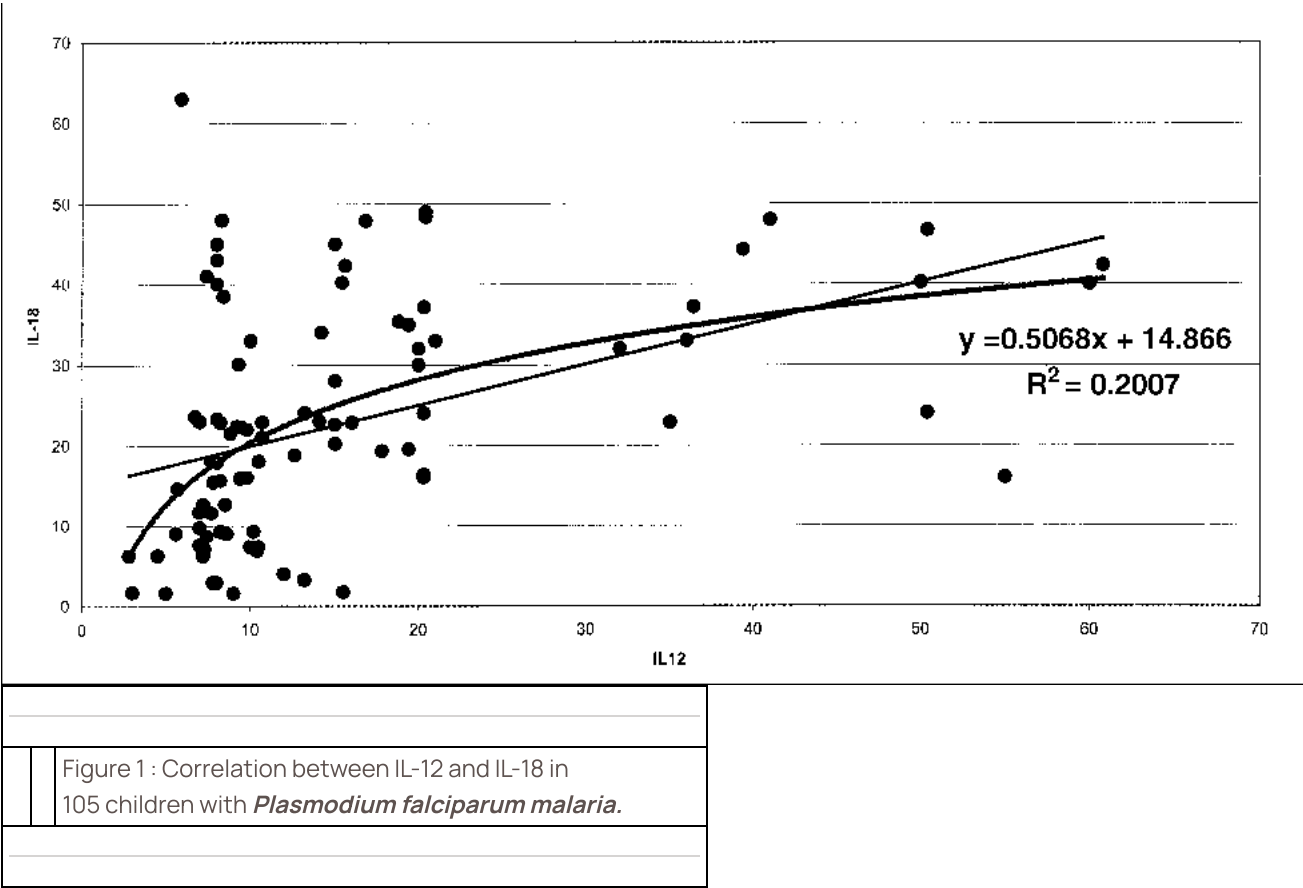
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Figures



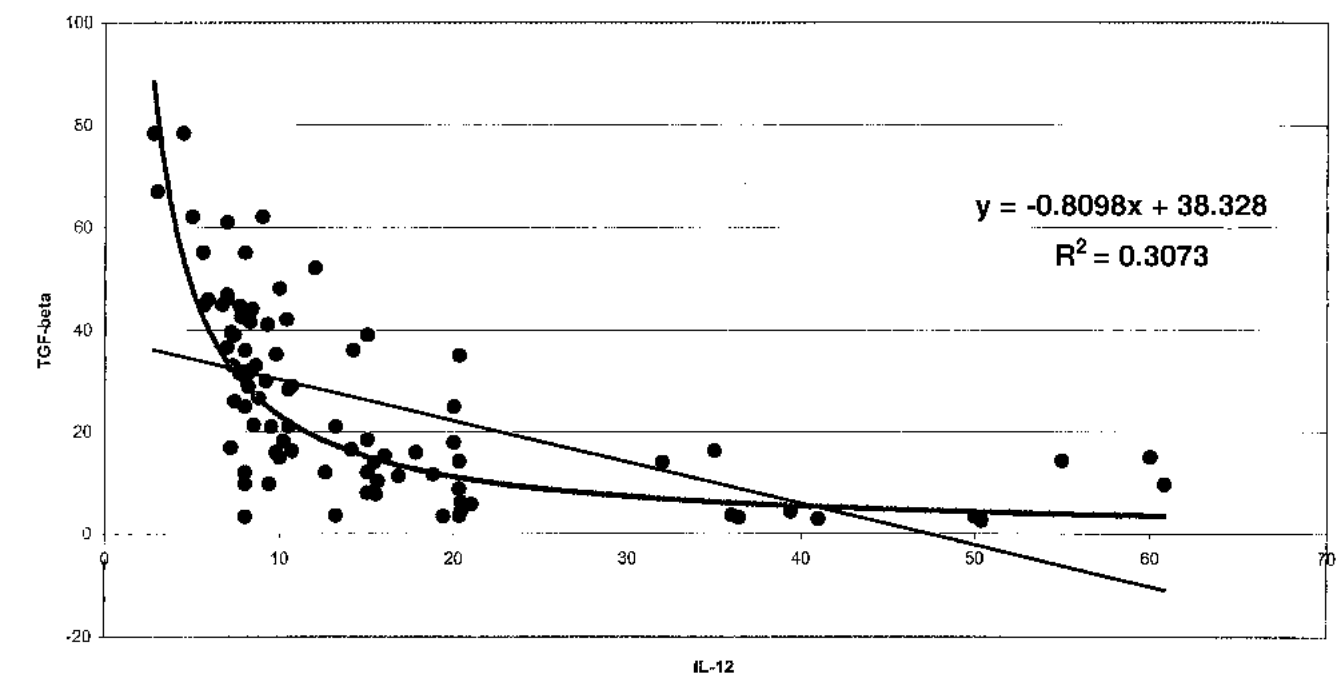


Figure 2 : Correlation between TGF-beta and IL-12 in 105 children with *Plasmodium falciparum* malaria.

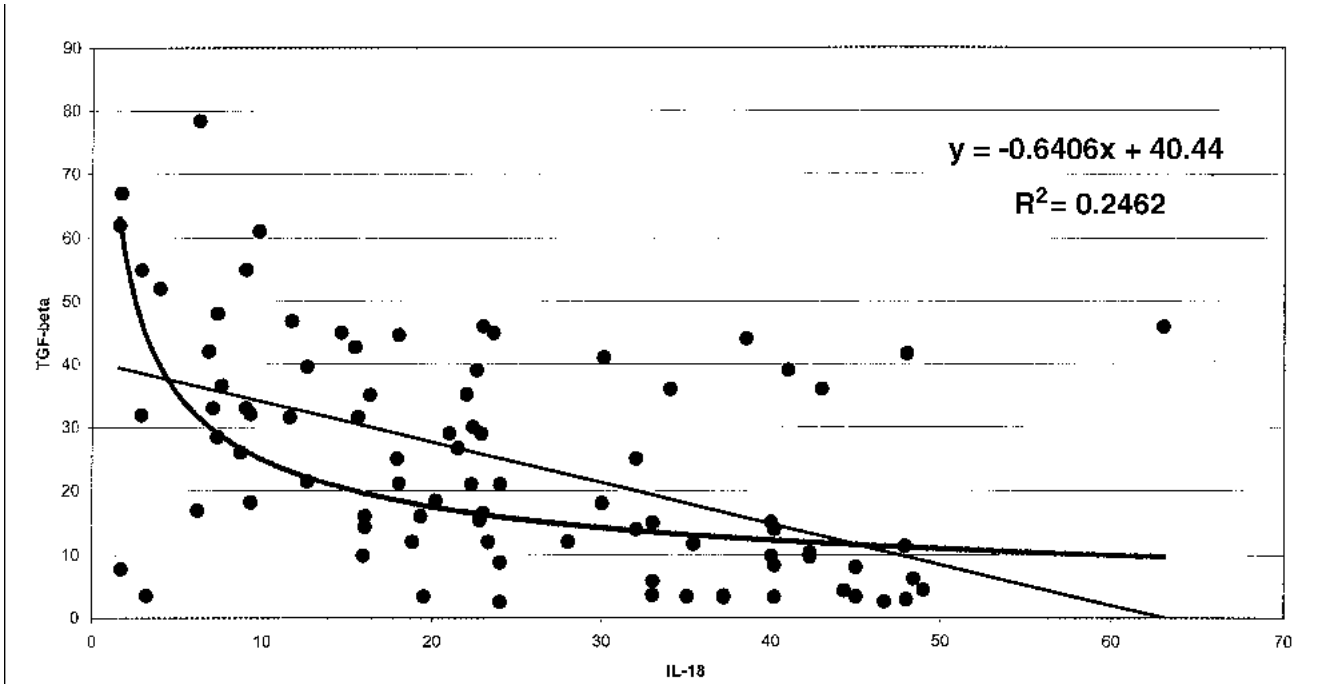


figure 3 : Correlation between TGF-beta and IL-18 in 105 children with *Plasmodium falciparum* malaria.

Patient Numbers	Age (months)	Leukocytes (mm ³)	Red cells (mil/mm ³)	Hb (g/dl)	Ht (%)	MCV (u ³)	MCH (YY)	MCHC (%)	Platelets (mi
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N. 77 (A)	13 (2 - 72)	17.3 ± 12.5*	1.43 ± 0.64*	3.72 ± 1.26*	11.6 ± 3.9*	84.1 ± 18.7	27.8 ± 6.04**	32.56 ± 4.31*	157.76 ± 84.6
N. 28 (B)	24 (9 - 144)	17.8 ± 7.97*	3.23 ± 0.74*	8.28 ± 1.57*	24.9 ± 5.09	73.7 ± 13.3**	25.8 ± 4.63	33.28 ± 3.43**	234.84 ± 150
Healthy Controls N. 40	22 (10 - 100)	8.53 ± 2.74	3.95 ± 0.78	9.6 ± 2.28	26.4 ± 4.38	81.55 ± 11.48	24.52 ± 4.40	30.21 ± 2.66	324.12 ± 102.1

Patients versus healthy controls * p < 0.001; ** p < 0.01 (A) & rarr; (B) IL-12 p = 0.005; IL-18 p = 0.044; TGF-b p = 0.0106.

In the control group, the values of IL-12, IL-18 and TGF-b were 7.6 ± 2.5 pg/ml, 9.3 ± 3.5 pg/ml and 6.4 ± 2.0 pg/ml respectively.

	Table 1: Haematological data for 105 children with <i>Plasmodium falciparum malaria according to the clinical severity</i>

Authors

Lucia Malaguarnera, Salvatore Pignatelli, Jacques Simporè, Mariano Malaguarnera and Salvatore Musumeco

Department of Pediatrics, Viale San Pietro n. 12, 07100 Sassari, Italy.

In this issue

- European Cytokine Society president’s address

Josef van Damme
- Losing balance : cytokine signaling and cell death in the context of hepatocyte injury and hepatic failure

Tom Luedde, Christian Liedtke, Michael P Manns, Christian Trautwein

liver failure, apoptosis, tumor necrosis factor, NF-KB, interleukin-6, Fas
- Presented at the 4th symposium on Cytokines and apoptosis in the cardiovascular system, Halle, Germany, June 6-7, 2002
- Activated STAT-1 pathway in the myocardium as a novel therapeutic target in ischaemia/reperfusion injury

Anastasis Stephanou

STAT, heart, ischaemia/reperfusion, apoptosis
- A subset of caspase substrates functions as the Jekyll and Hyde of apoptosis

Jian-Yan Yang, Christian Widmann

RasGAP, MEKK1, caspase substrates, apoptosis, survival

○ Compromised IFN-gamma production in the elderly leads to both acute and latent viral antigen stimulation: contribution to the immune risk phenotype?

Qin Ouyang, Wolfgang M Wagner, Anders Wikby, Ed Remarque, Graham Pawelec
Aging, T-cell, IFN-g, CMV, EBV, immune risk phenotype, longitudinal study

○ Cytokines in chronic heart failure: possible involvement in the neurohormonal and the cytokine systems at the cAMP level?

Claudia Werner, Harald Loppnow, Mathias Rauchhaus, Armin Wessel, Karl Werdan, Reiner Buchhorn
Adult, b-blocker, children, chronic heart failure, cyclic AMP, cytokine, infant, interleukin, soluble TNF receptor, tumor necrosis factor

○ Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations

Helle Bruunsgaard
TNF-a, IL-6, aging, mortality, inflammation

○ Energetic depression caused by mitochondrial dysfunction

Frank Norbert Gellerich, Sonata Trumbeckaite, Ying Chen, Marcus Deschauer, Tobias Müller, Stephan Zierz
Mitochondria, outer membrane, inner membrane, mitochondrial disease, sepsis, phosphorylation potential

○ Senescence: the cost of being young and healthy?

Graham Pawelec

○ The regulation of death-associated protein (DAP) kinase in apoptosis

Galit Shohat, Taly Spivak-Kroizman, Miriam Eisenstein, Adi Kimchi
apoptosis, DAPk, autophosphorylation, negative regulation

○ Neisseria meningitidis can induce pro-inflammatory cytokine production via pathways independent from CD14 and toll-like receptor 4

Tom Sprong, Peter van der Ley, Liana Steeghs, Will J Taw, Trees JW Verver-Janssen, Mihai G Netea, Jos WM van der Meer, Marcel van Deuren
Neisseria meningitidis, lipopolysaccharide, endotoxin, cytokines, CD14, TLR4

○ Evaluation of tumor necrosis factor alpha production in ex vivo short term culture whole blood from women with polycystic ovary syndrome

A Veronica Araya, Adam Aguirre, Carmen Romero, Cristian Miranda, Maria Carmen Molina, Arturo Ferreira
LPS, polycystic ovary syndrome, TNF-a, whole blood cell culture

○ Plasma levels of IL-12, IL-18 and TGF-beta in Plasmodium falciparum malaria

Lucia Malaguarnera, Salvatore Pignatelli, Jacques Simportè, Mariano Malaguarnera and Salvatore Musumeco
IL-12, IL-18, TGF-b, Plasmodium falciparum

○ In vitro analysis of IFN-gamma and IL-12 production and their effects in ileal Crohn's disease

Stefaan Colpaert, Kathleen Vastraelen, Zhanju Liu, Philippe Maerten, Chong Shen, Freddy Penninckx, Karel Geboes, Paul Rutgeerts, Jan L Ceuppens
IL-12, IFN-g, anti-IL-12/ anti-IFN-g, in vitro, Crohn's disease

○ Differential modulation of IL-2- and IL-4-mediated early activation of normal human B lymphocytes by the caspase inhibitor zVAD-fmk

Shahul Mouhamad, Damien Arnoult, Marie-Thérèse Auffredou, Jérôme Estaquier, Aimé Vazquez
IL-2, IL-4, B lymphocyte, caspase, proliferation, cell cycle entry

○ Prolactin-cytokine network in the defence against Acanthamoeba castellanii in murine microglia

Nunzia Benedetto, Claude Auriault
Prolactin, cytokine, A. castellanii, MGC.

○ CINC-1 mediates the sympathetic component of inflammatory mechanical hypersensitivity in rats

Berenice B Lorenzetti, Fabiane H Veiga, Claudio A Canetti, Stephen Poole, Fernando Q Cunha, Sergio H Ferreira
Inflammatory hyperalgesia, CINC-1, tumour necrosis factor alpha, interleukin-1b, interleukin-8, sympathetic mediators, prostaglandin E2

○ A CXC chemokine sequence isolated from the rainbow trout *Oncorhynchus mykiss* resembles the closely related interferon-gamma-inducible chemokines CXCL9, CXCL10 and CXCL11

Kerry J Laing, Niels Bols, Christopher J Secombes
Chemokine, rainbow trout, IP10, I-TAC, Mig

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