Acute lipid profile changes in malaria patients - a gateway towards novel antimalarial drug class identification?

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON44881

Source
ToetsingOnline

Brief title
Lipomal

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
jungle fever, Tropical fever

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: International Society of Travel Medicine

Intervention

Keyword: Hemozoin, Lipid prolife, Malaria

Outcome measures

Primary outcome

The primary outcome measure is the plasma lipid profile. Full plasma lipid analyses (total cholesterol, HDL, apolipoprotein A1, LDL, VLDL and triglycerides) will be conducted in both maparia patient and control groups.

Secondary outcome

The secondary outcome measures in the patient group are hemozoin quantity proxies as outlined above, in correlation with parasite density, and clinical characteristics as obtained in the framework of routine clinical care.

Study description

Background summary

In industrialized countries, malaria remains the most important, potentially live-threatening infectious disease imported by travelers from endemic regions. From 2001 to 2011, it accounted for an estimated 6,000-16,000 imported cases in Europe annually [1-6]. Recently, progress in malaria control has been made and elimination, if not eradication, appears again on the international agenda as a long-term goal seriously to be considered [7]. However, there is still a long way to go, from better understanding of malaria patho-physiology to the identification and exploitation of routes towards new and improved control tools, including novel drugs. Alterations in plasma lipid profiles in the acute phase of infectious diseases are well-known since long and possibly owed to a whole range of at least in part disease-specific mechanisms. With regard to malaria, a characteristic pattern consisting of low overall cholesterol, high-density lipoprotein cholesterol (HDL), apolipoprotein a, low-density lipoprotein cholesterol (LDL), very low-density lipoprotein (VLDL) and high triglycerides has been reported before in returned travelers by various groups [8-11], and a correlation with parasitaemia [9] but not with overall disease severity [10] was noted. However, apart from a suggestion made that these transient changes related to the parasitaemic phase may be a potential adjuvant

diagnostic tool [9,10], little attention has been paid up to date to exploit this phenomenon any further.
Hemozoin (Hz; *malaria pigment*) is the plasmodial end product of haem metabolism and detoxification, and interference with its intraplasmodial formation and storage in one way or another is the prime target of most of our antimalarial drugs to date [12]. Its detection is utilized as adjuvant diagnostic and prognostic tool, and its role as influential host immunity modulator has been recognized clearly [12], yet the underlying mechanisms are still to be fully elucidated. Host plasma lipids have been found to be implicated in hemozoin formation in vivo [13,14]. It has been shown that hemozoin is formed at the interface of the aequeous medium of the parasite*s food vacuole and lipid nanospheres [15]; and the *lipid hypothesis* postulates that hemozoin formation occurs most rapidly at lipid-water interfaces [16]. Moreover, not only does the Hz production requires host lipids, but it appears also that the inhibition of host monocyte functions as one of the eminent immune-modulating Hz effects are hydroxy fatty acids, generated by plasmodia in large amounts in the human host .
If a link between human host serum lipid alterations and the above outlined mechanisms can be demonstrated, further studies to elucidate the precise pathways are thinkable - moreover - novel treatment approaches could be explored (first in vitro, and e.g. by experiments subjecting P. falciparum to lipid metabolism-regulating drugs).

Hypotheses:
(i) The lipid profile of acute malaria exhibits characteristic changes, including low overall cholesterol, low HDL and apolipoprotein a, low LDL and VLDL and high triglycerides.
(ii) These changes are characteristic for the malaria-specific pathogen-host interplay and are directly proportional to the amount of hemozoin produced by human-pathogenic plasmodia, thus opening up avenues to explore novel antiparasitic interventions.

Study objective

In order to confirm previous observations and to increase our understanding of the patho-physiologic mechanism of the plasma lipid changes; in this study, we will prospectively measure the blood lipid profile of approx. 120 malaria patients and an equal number of matched healthy controls over time during acute disease and following recovery. This is best done in travelers representing a wide range of strains and hosts rather than one particular strain group and a homogenous human ethnicity, as typical for field studies:
(A) To test hypothesis (i) the plasma lipid spectrum (total cholesterol, HDL, apolipoprotein A1, LDL, VLDL and triglycerides) in 120 acute malaria cases will be assessed.
(B) To test hypothesis (ii) the amount of circulating malaria pigment in parasites and macrophages will be quantified and correlated both with light

microscopy and laser flow-cytometric detection.

Study design

We propose a prospective observational cohort study including suitable controls and malaria patients

Study burden and risks

In this study, 12 mL of blood shall be drawn for study purposes from each participant at three time points (additional volume, yet only one additional venipuncture required as blood draws at least at D0, D3 will be obtained for routine care in any case). In volunteers, one single blood draw of 12 mL is required. To that end, risk of study-related physical harm will be limited, yet personal risks and benefits for participating in the study shall be explained in detail.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1100 DD
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1100 DD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients > 18 jaar gedianosticeerd met malaria
Controls > 18 jaar with acute symptoms

Exclusion criteria

chronic lipid metabolic disorder
chronic use of medication

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO

Date:	06-01-2014
Application type:	First submission

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44993.018.13