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Original article

Comparing imported malaria in adults and children presenting to an Italian teaching hospital: A 10-year retrospective study

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ABSTRACT

Background: Malaria is not endemic in Italy, but it still represents an important threat to the travelers' health. With this study we wanted to compare the characteristics of imported malaria between adults and children.

Method: This retrospective observational study includes all patients admitted to the Infectious Diseases Unit and in the Pediatric Department of Padua (Italy), and discharged with a diagnosis of malaria from 2005 to 2015. The variables considered are epidemiological and clinical.

Results: 172 cases of imported malaria were studied (124 adults and 48 children), *P. falciparum* was responsible for 90,7% of the cases, and was contracted mostly in Africa (96,5%), especially by foreigners visiting friends and relatives (VFR). Chemoprophylaxis was adopted only by few patients.

93% of all the patients developed the uncomplicated malaria, but pediatric patients had severe malaria significantly more often than adults (OR = 4,06, p = 0,015). Children also had significantly lower hemoglobin levels and higher parasitemia. The drugs used to treat the two groups were substantially different, but both had a good overall outcome.

Conclusions: In order to reduce the risk of imported malaria, educational actions should target potential VFR travelers, and they should underline the different risk of severe malaria in adults and children. A further implementation of the recommended therapies could improve the patients' outcome.

1. Introduction

Malaria represents a serious global health threat: according to World Health Organization (WHO), this arthropod-borne parasitic disease is endemic in 95 countries, and an estimated 3.2 billion people are at risk of infection. The global number of cases has been constantly decreasing since 2000, and it was around 214 million in 2015, with around 438 000 deaths. The burden was heaviest in Africa, where an estimated 90% of all malaria deaths occurred, two thirds of which were children under 5 years [1].

In Europe malaria is not endemic anymore, but it is continuously imported by travelers coming from endemic areas, especially by foreigners who travel to visit their friends and relatives (VFR) [2–9]. In Italy, the notification of malaria cases is mandatory, and Ministero della Sanità (Italian Ministry of Health) and Istituto Superiore di Sanità (ISS), are in charge of its surveillance. According to these authorities, the number of confirmed cases has been decreasing from the year 2000 to the year 2007 and it is now stable around 600–700 per year, with a prevalence of 1/100 000 inhabitants [2,4,10]. Almost all the reported cases are classified as "imported", even if in some rare cases autochthonous vector-borne transmission was reported [11]. Italian travelers account only for one third of the national cases, and all the others are settled foreigners who contract the disease while traveling to their native countries (mainly in Africa), to visit their friends and relatives (VFR) [2,4,5].

Even if children represent a special population, and even if they are worldwide more vulnerable to malaria, no specific database has been created for them, and to our knowledge, only one study

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describes their specific characteristics in Italy [9].

2. Material and methods

This observational, retrospective study includes all hospitalized patients with malaria from January 1, 2005 to December 31, 2015 in the University Hospital of Padua, Italy. In this tertiary care center (catchment area: 400 000 people) adults affected by malaria are hospitalized in the Infectious Disease Unit, while the children are hospitalized in the Pediatric Department.

All the patients included in this study had laboratory confirmed diagnosis of malaria. The laboratory techniques performed to identify the parasites were peripheral blood smear observation and PCR, which was used especially to identify patients with low parasitemia. All laboratory analyses were carried out in the microbiology department of Padua University hospital.

2.1. Data collection and classification

All discharge diagnoses with "malaria" as ICD-9 code were caught electronically through Qlik software, and data were collected by detailed chart review, using a standardized care report form (CRF). Recorded data included the following parameters: age, sex, nationality, travel history, clinical signs and symptoms, baseline laboratory values (complete blood cells count, hemoglobin, CRP, creatinine, bilirubine, AST, ALT), microbiology details (plasmodium species and parasitemia), treatment and outcome.

The collected cases were then classified according to the Italian Minister of Health's [12] and World Health Organization's [13] classifications as follows:

1) Origin of infection [12]: imported malaria, autochthonous malaria, recurrence/relapse.
2) Patients' classification: Italians living in Italy, Italians living abroad, foreigners settled since more than 6 months, foreigners in Italy since less than 6 months and foreign tourists visiting Italy.
3) Reason for traveling to endemic areas [12]: visit friends and relatives (VFR), immigration, tourism, work and study (including voluntary and religious activities).
4) Plasmodium species, identified through thin peripheral blood smear observation.
5) Chemoprophylaxis was categorized as follows:
   - "Adequate" if extended to the whole period recommended by the Italian guidelines [12], that is:
     - for mefloquine and chloroquine: from one week before the arrival to a risk area, to four weeks after the departure from it;
     - for proguanil and doxycycline: from 24 h before the arrival to a risk area, to four weeks after the departure from it;
     - for atovaquone/proguanil: from 24 h before the arrival to a risk area to 1 week after the departure from it.
   - "Inadequate" if limited to a shorter time than recommended, or if the drug was used in an area where malaria is resistant to that drug (this criterion applies in particular to chloroquine [12]).
   - "No" if no drug was taken for prophylaxis. This also includes foreigners arriving for the first time from endemic countries, like immigrants and tourists visiting Italy.
   - "Not known", if information about it was not available in the record.
6) Severity of disease [13]: uncomplicated malaria, severe malaria, including cerebral malaria.

2.2. Statistics

For the statistical analysis, categorical variables were described as absolute frequencies and proportions, and compared by Chi square test. Continuous variables were assessed for normal distribution and their means were compared with Students *t*-test. Statistical descriptive analysis was carried out with *Microsoft Office Excel (2007)* spreadsheet.

3. Results

172 patients were included in the dataset, their main characteristics are presented in Table 1. 74.5% (124/172) were adults and 25,5% (48/172) children. The median annual prevalence was 2.45% for the Infectious Diseases Unit and 0.49% for the Pediatric Department. The median age was 39 (range: 17–72) years for the adults and 4 (range: 0–13) years for children.

No autochthonous transmission was reported: 97.5% (168/172) were imported cases, while the remaining were recurrences or relapses of previous infections. Most of the patients were settled foreigners (75.6% of the total, 87.4% of the pediatric cases). Italians only accounted for a limited amount of cases, especially among the pediatric group, where only 6.3% (3/48) of the patients were Italian children.

The annual distribution shows no significant increase nor decrease in the number of cases, neither among Italians nor among foreigners, both among adults and children (Fig. 1), and the cumulative seasonal distribution shows that there is a peak of diagnoses in September (Fig. 2).

Most of patients, in both groups (166/172, 96.5%) had been infected in Africa, especially in the central-western countries such as Nigeria, where most of them come from. The reason for traveling is different between foreigners and Italians, as shown in Table 2. Among the foreigners, 88.9% (128/144) traveled to visit relatives and friends, 7.6% (11/144) were foreigners arriving to Italy, and 3.5% (5/144) traveled for tourism. Among the Italians 46.4% (13/28) traveled for tourism, while the remaining 53.6% (15/28) traveled for work or study.

P. falciparum was identified in 90.7% (156/172) cases, while *P. vivax* was found only in 3.5% (6/172), *P. malariae* in 1.7% (3/172), *P. ovale* in 1.2% (2/172). In two cases (1.2%) both *P. falciparum* and *P. ovale* were found. In four patients the identification of the species was not performed.

Only 3.5% of patients (6/172) took an adequate chemoprophylaxis. The drugs used were: mefloquine (three cases), doxycycline (one case) and in two cases the drug used was unknown. In one case the prophylaxis was considered inadequate because, even if the patient took chloroquine for the recommended time, she visited an area of endemic chloroquine-resistant malaria (Burkina Faso). The remaining patients didn't take any prophylaxis at all (66.3%), or took it just for a limited period (7.6%) (inadequate). In 38 cases (22.1%) information about the prophylaxis was not available (Table 1).

According to the World Health Organization's classification [13], 6.9% (12/172) patients had severe malaria, and among those, five (two adults and three children) had cerebral complications, but no death occurred. Severe cases were significantly more frequent among children than among adults (OR = 4,06, $p = 0{,}015$).

When they were admitted at the hospital, almost all the patients had fever (95.6%), together with migrane, nausea and other less specific (Table 3). The most common baseline laboratory findings were: increased CRP levels (99.4%), thrombocytopenia (80.6%), and anemia (80.4%).

Thrombocytopenia was significantly more common and more severe among adults ($p < 0{,}002$), with a mean count of