BRIEF REPORT

α-Thalassaemia trait is associated with Antibody prevalence against Malaria Antigens AMA-1 and MSP-1

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SUMMARY

A longitudinal study was conducted in a low endemic area in northern Tanzania to examine the influence of the α-thalassaemia trait on malaria incidence and antibody responses to malaria apical membrane antigen-1 (AMA-1) and merozoite surface protein-1-19 (MSP-1). Out of 394 children genotyped for α-thalassaemia trait, 4.1% (16 of 394) and 30.7% (121 of 394) were homozygous and heterozygous, respectively. During the 1 year follow-up, four incidents of malaria cases were detected without an evident association with α-thalassaemia. Being heterozygous or homozygous for α-thalassaemia was associated with increased antibody responses to AMA-1 (odds ratio [OR]: 1.83, 95% confidence interval [CI]: 1.07–3.12, p = 0.027) and MSP-1 (OR: 2.04, 95% CI: 1.16–3.60, p = 0.013) after adjustment for age and reported bednet use. The observed association between α-thalassaemia and malaria antibody responses may reflect longer-term differences in antigen exposure or differences in antibody acquisition upon exposure in this low endemic setting.

KEYWORDS: malaria, immunity, thalassaemia.

INTRODUCTION

Several human genetic traits have been associated with protection against malaria or malaria mortality [1–3]. α-Thalassaemia is associated with protection against malaria-associated anaemia [4], severe malaria but not against asymptomatic infection [5] and probably not against uncomplicated disease [6]. The precise mechanisms by which α-thalassaemia
influences malaria risk is not well understood and may involve impaired growth or an immunological component [7]. It has been hypothesized that thalassaemic red blood cells have enhanced antibody binding and faster clearance of parasitized red blood cells by the spleen [8, 9]. Improved antigen presentation in the spleen may also result in a more efficient acquisition of immune responses [8]. In this study, we describe the associations between \(\alpha\)-thalassaemia trait, protection against clinical malaria and malaria-specific antibody responses in children living in an area of low malaria endemicity in Tanzania.

**MATERIALS AND METHODS**

The study was conducted in Magugu in the Northern Rift Valley in Tanzania in 2008–09. A total of 394 children aged 6 months–15 years were recruited and followed for 12 months for malaria incidence. Passive and active case detection was performed. Every 3 months, children were invited for cross-sectional sampling during which a slide and rapid diagnostic test (RDT) were taken. At enrolment, 2 ml of blood was collected by venipuncture from children for slide, and filter paper blood spot. The prevalence of \(\alpha\)-thalassaemia was determined by detection of the African \(\alpha\)-globin deletion, \(\alpha 3.7\), by polymerase chain reaction [10]; antibodies to apical membrane antigen-1 (AMA-1) and merozoite surface protein-1 (MSP-1\(_{19}\)) were detected by Enzyme Linked Immunosorbent Assay [11]. Ethical clearance was given by the Kilimanjaro Christians Medical Center Research Ethics Committee and the Tanzanian National Institute for Medical Research (NIMR/HQ/ R.8a / Vol.IX / 759). Data were analysed using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) and Stata version 12 (Statacorp, College Station, TX, USA).

**RESULTS AND DISCUSSION**

After adjustment for age, mean haemoglobin concentrations were significantly lower in individuals who were heterozygous \([\beta = -0.43, \text{SE}(\beta) = 0.14,\ p = 0.002]\) and homozygous for \(\alpha\)-thalassaemia \([\beta = -1.04, \text{SE}(\beta) = 0.32,\ p = 0.001]\) compared with wildtype individuals. Mild anaemia (Hb < 11 g/dL) was diagnosed in 9.0% (23 of 257) of the wildtype, 14.1% (17 of 121) of the heterozygous and 25.0% (4 of 16) of the homozygous individuals for \(\alpha\)-thalassaemia \((p = 0.025)\). Anaemia and lower Hb values in malaria-free individuals have previously been associated with \(\alpha\)-thalassaemia [4, 12]. During the 1 year of follow-up, four clinical malaria episodes were recorded, defined as a positive Lactate Deshydrogenase-based RDT in the presence of fever. The incidence of clinical malaria \((\sim 1\%)\) and asymptomatic parasite prevalence \((<5\%)\) were not significantly different between groups.

![Fig. 1. Age- and \(\alpha\) thalassemia dependent prevalence of antibodies against AMA-1 and MSP-1. Heterozygous and homozygous individuals for \(\alpha\)-thalassaemia are combined in the category \(\alpha\)-thalassaemia. An asterisk indicates statistical significance between thalassaemic and non-thalassaemic individuals of this age group \((p < 0.05)\).](https://academic.oup.com/tropej/article-abstract/61/2/139/1728368)
possibly because malaria burden was too low to allow meaningful analysis. Being heterozygous or homozygous for α-thalassaemia was associated with an increased prevalence of antibodies to AMA-1 [odds ratio (OR): 1.83, 95% confidence interval (CI): 1.07–3.12, \( p = 0.027 \)] and MSP-1 (OR: 2.04, 95% CI: 1.16–3.60, \( p = 0.013 \)) after adjustment for age and reported bednet use. When antibody prevalence was compared between wildtype individuals and hetero- and homozygous individuals in different age groups, the elevated antibody prevalence in hetero- and homozygous individuals was most evident in older age groups (Fig. 1). The occurrence of clinical malaria episodes during follow-up, plausibly reflecting previous malaria exposure, did not confound these associations. For HbAS (hemoglobin type AS) and HbAC (hemoglobin type AC), several studies have reported higher antibody prevalences against Plasmodium falciparum antigens [13–15] that suggest that differences in antibody responses may play a role in the conferred protection against malaria. For α-thalassaemia, the same association has not been established [12]. In our study, malaria infections were too uncommon to allow the formation of meaningful cohorts with differential exposure to malaria to study antibody acquisition in relation to malaria exposure. We can therefore only speculate on the reasons for the positive association between antibody responses and α-thalassaemia trait, which may reflect a more efficient acquisition of antibody responses upon malaria infection or a higher exposure to malaria infection in α-thalassaemic individuals. This would explain our finding that the difference between thalassaemic and wildtype individuals becomes larger with increasing age [16, 17].

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### Table 1. Associations between α-thalassaemia and haemoglobin concentration, antibody prevalence and malaria incidence and prevalence

<table>
<thead>
<tr>
<th>Variables</th>
<th>a-Thalassaemia</th>
<th></th>
<th></th>
<th></th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of study population (n/N)</td>
<td>65.2 (257/394)</td>
<td>30.7 (121/394)</td>
<td>4.1 (16/394)</td>
<td></td>
<td></td>
<td>-</td>
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<tr>
<td>Age, median (IQR)</td>
<td>4 (3–7)</td>
<td>4 (3–6)</td>
<td>4 (3–9)</td>
<td>0.66</td>
<td></td>
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<tr>
<td>Haemoglobin concentratons, mean (SD)</td>
<td>12.5 (1.3)</td>
<td>12.1 (1.3)</td>
<td>11.6 (1.4)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Enrolment anaemia, % Hb &lt; 11 g/dL (n/N)</td>
<td>9.0 (23/257)</td>
<td>14.1 (17/121)</td>
<td>25.0 (4/16)</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolment AMA-1 antibody prevalence</td>
<td>27.7 (71/256)</td>
<td>34.7 (42/121)</td>
<td>43.8 (7/16)</td>
<td>0.073</td>
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<tr>
<td>Enrolment MSP-1, antibody prevalence</td>
<td>18.7 (48/256)</td>
<td>25.6 (31/121)</td>
<td>43.8 (7/16)</td>
<td>0.014</td>
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<tr>
<td>Malaria incidence, % of children with clinical malaria episode (n/N)</td>
<td>0.8 (2/257)</td>
<td>1.6 (2/121)</td>
<td>0.0 (0/16)</td>
<td>0.47</td>
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<tr>
<td>Parasite prevalence in all surveys combined, % (n/N)</td>
<td>4.7 (12/257)</td>
<td>5.0 (6/121)</td>
<td>0 (0/16)</td>
<td>0.66</td>
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IQR = interquartile range.
REFERENCES


