Dysnatraemia in malaria

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Abstract – Malaria is often associated with hyponatraemia, but neither the extent nor the probability of hyponatraemia has been estimated and it is not clear whether they depend on the infective species. Analysis of reports of hyponatraemia shows that it tends to be less severe in non-falciparum malaria than it is in falciparum malaria. However, the probability of observing serum sodium concentrations of less than 130 mM decreases in the sequence cerebral falciparum > severe falciparum > vivax > non-severe falciparum > knowlesi and falciparum > non-falciparum. In addition to a greater probability of hyponatraemia in severe falciparum malaria than in non-severe falciparum malaria, the probability of hypernatraemia in falciparum malaria is slightly greater than it is for healthy individuals.

Keywords – hyponatraemia, malaria, Plasmodium spp., serum sodium

1. Introduction

Five Plasmodium spp are associated with malaria in humans. Of these, more than 2 billion people are exposed to P. falciparum [4] and it has been estimated that there were more than 500 million clinical episodes of falciparum malaria in 2002 [6]. The non-falciparum species are P. vivax, P. ovale, P. malariae and P. knowlesi, of which P. vivax is even more widespread than P. falciparum [10, 11], P. ovale has recently been shown to comprise two species [14] and P. knowlesi has been recognised as a concern only recently [15]. The World Health Organization [16] defines severe and cerebral forms of falciparum malaria and, while non-falciparum malaria may also have severe or cerebral forms [17-21], they are not necessarily explicitly acknowledged in non-falciparum malaria and some authors explicitly discount the possibility [22, 23].

Hyponatraemia has often been associated with malaria, but it is common in hospitals [24-27] and is not infrequently associated with mortality [28]. Reports of serum sodium concentrations in non-falciparum malaria are not common, but they are more numerous in cases involving P. falciparum. Of the latter, hyponatraemia may be reported frequently in severe falciparum malaria than other forms of falciparum malaria. It has been suggested [29] that the extent of hyponatraemia depends on the infective species, but this remains to be substantiated [30], as does the species-dependence of the probability of observing hyponatraemia in malaria.

There is considerable variation in what is considered to be hyponatraemia. The usual reference range for serum sodium concentration is 135-145 mM [31], although the lower limit is sometimes set at 130 mM [32, 33] and in some instances it is greater than 135 mM [34]. It has been suggested [35] the number of false positive results in routine health evaluations would be limited by a 99.9% reference range (corresponding to 131.6-148.4 mM in this case). Howanitz and Howanitz [31] suggest a critical lower value (120 mM) below which and a critical upper value (155 mM) above which the patient should be regarded as being in imminent danger unless treatment is initiated. In the reports surveyed here, the serum sodium concentration below which an individual is said to be hyponatraemic has been taken to be 135 mM [7, 23, 36, 37], 132 mM [38], 130 mM [1, 39-44], 125 mM [5, 45] or 120 mM [46]. Of course, whether a value is simply slightly lower than normal or indicative of hyponatraemia is a clinical judgement [47], but where an arbitrary criterion is required, 130 mM, which is close to the lower limit of the 99.9% range, is useful and, where necessary, I take values below this to be indicative of hyponatraemia.

Here, I analyse systematically reports of hyponatraemia in non-falciparum and falciparum malaria. I show that (i) the extent and (ii) the probability of hyponatraemia is related to the type of malaria, but that (iii) the data do not appear to substantiate a significant relationship between mortality associated with malaria and hyponatraemia.

2. Methods

2.1. Data sources

Data were obtained from the literature identified from searches of Pubmed and Web of Science using (malaria OR plasmodium) AND (“serum sodium” OR hyponatraemia OR hyponatremia). These were supplemented by manual scanning of the reference lists of the reports identified and of selected journals not included in the databases. Only those reports clearly stating either or both of (a) the relative frequency of a clearly defined hyponatraemia, and (b) serum sodium levels with a standard deviation (s), a clearly defined confidence interval or a range [l, h] were included.

2.2. Statistical analyses

In several reports a median (m) rather than a mean (l+h) was given and l+h was estimated from the range [l, h] using

\[
\langle x \rangle \approx \begin{cases} \frac{1}{4} (l + 2m + h + (l - 2m + h) n) & n \leq 25 \\ m & n > 25 \end{cases}
\]

(1)
[48]. Where the standard deviation (s) was not provided, it was estimated using

\[
s \equiv \begin{cases} 
\frac{1}{n-1} \left( \frac{(l-2m+h)^2}{4} + (h-l)^2 \right) & n \leq 15 \\
\frac{h-l}{4} & 15 < n \leq 70 \\
\frac{h-l}{6} & n > 70 
\end{cases}
\]  

(2)

as recommended by Hozo et al. [48]. In those instances where data were reported for k separate groups (for example severe and non-severe), the composite mean was determined using

\[
\bar{x} = \frac{\sum_{i=1}^{k} n_i \bar{x}_i}{\sum_{i=1}^{k} n_i} 
\]

(3)

the pooled standard deviation was calculated from the \( s_i \) using

\[
s = \frac{\sum_{i=1}^{k} (n_i - 1) s_i}{\sum_{i=1}^{k} (n_i - 1)} 
\]

(4)

and the composite range was taken to be \([\min(l_i), \max(h_i)]\) of the constituent ranges. Odds ratios and the associated confidence intervals were calculated using Fisher’s exact test as implemented in the exact2x2 package [2] in R [49].

3. Results

Instances of hyponatraemia ([Na\(^+\)\text{serum} < 130 mM]) have been reported in all forms of falciparum malaria and in non-falciparum malaria (Fig. 1). However, the mean reported values lie within the reference range for non-severe falciparum and non-falciparum malaria, but are slightly lower than 135 mM in severe and cerebral falciparum malaria (Fig. 1). Only in falciparum malaria are there reports of serum sodium concentrations below the lower critical value (120 mM) identified by Howanitz and Howanitz [31].

The literature also includes reports of serum sodium concentrations of 145 mM or more for all forms of malaria (Fig. 1). If hypernatraemia can be taken as [Na\(^+\)\text{serum} > 145 mM], the extent of hypernatraemia reported is small in non-severe falciparum and non-falciparum malaria. However, the extent of hypernatraemia it is much greater in severe and cerebral falciparum malaria, in which values in excess of the upper critical value (155 mM [31]) have been reported.

3.1. Probability of dysnatraemia

While the ranges of serum sodium concentrations shown in Fig. 1 are informative, they do not provide an explicit indication of the likelihood of dysnatraemia. Some reports provide data from which the probability of dysnatraemia can be calculated. These estimates indicate that the probability of hyponatraemia does vary between species and with the form of falciparum malaria. Moreover, the few data available also provide some indication of the probability of hypernatraemia.

Hyponatraemia is more common in falciparum malaria than in non-falciparum malaria, and is more likely in the cerebral and severe forms than in the non-severe forms of falciparum malaria (Fig. 2). However, suitable reports of cerebral falciparum and non-falciparum malaria are rare.
indications that more data have been collected. For example, Kochar et al. [19] studied 456 severe cases of vivax malaria and, despite measuring serum electrolytes, did not report the data, and Prakash et al. [72] reported hyponatraemia in 3 of 19 cases of vivax malaria, but did not indicate how they defined hyponatraemia and did not give any serum sodium concentration data. Despite this limitation it is possible to infer from the odds ratios that the sequence of relative probability of hyponatraemia is cerebral falciparum = severe falciparum > vivax > non-severe falciparum > knowlesi and falciparum > non-falciparum (Table 1).

The number of reports in which it is possible to identify the number of cases of hypernatraemia ([Na+]serum > 145 mM) is small, in fact the odds ratio of hyper- and hyponatraemia for severe falciparum malaria is 0.09 (95% CI: [0.04, 0.17], p < 0.001) for those reports including definite numbers for both states [8, 9, 23, 36, 40, 42]. In several reports it is clear that hyponatraemia was observed [9, 23, 36], and in others it can only be inferred from the range of serum sodium concentrations reported [1, 7]. This ambiguity makes it difficult to assess the relative probability of hypernatraemia in non-falciparum and falciparum malaria. The odds ratio calculated from the available data is 0.31 (95% CI: [0.03, 1.87], p = 0.330), indicating that there is no significant difference in the probability of hypernatraemia in non-falciparum and falciparum malaria. However, this should be regarded only as a guide because of the unreported data.

3.2. Estimates of serum sodium distributions

The relatively large number of reports of the probability of hyponatraemia in non-severe and severe falciparum malaria provides a means of estimating the cumulative distribution of hyponatraemia (Fig. 3A). Data were obtained from the reported probabilities of (i) hyponatraemia and the wide range of definitions of what constitutes hyponatraemia (upper limits ranged from 135 mM to 120 mM), (ii) serum sodium concentrations in particular ranges and (iii) hypernatraemia. A relatively small number of reports for healthy individuals were employed to construct the corresponding cumulative distribution for comparison (Fig. 3A). The approximate distributions obtained using this approach are remarkably consistent despite the wide range of reports employed (only one outlier, indicated in Fig. 3A, was apparent in the data for non-severe falciparum malaria).

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds ratio [95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-severe falciparum vs non-falciparum</td>
<td>5.71 [2.27, 15.18]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>non-severe falciparum vs severe falciparum</td>
<td>0.23 [0.17, 0.32]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cerebral falciparum vs severe falciparum</td>
<td>1.25 [0.89, 1.75]</td>
<td>0.179</td>
</tr>
<tr>
<td>non-falciparum vs falciparum</td>
<td>0.26 [0.17, 0.40]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>non-severe falciparum vs vivax</td>
<td>0.46 [0.26, 0.85]</td>
<td>0.011</td>
</tr>
<tr>
<td>severe falciparum vs vivax</td>
<td>1.78 [1.06, 3.00]</td>
<td>0.027</td>
</tr>
<tr>
<td>knowlesi vs non-severe falciparum</td>
<td>0 [0.0, 0.3]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The values were calculated using Fisher’s exact test as implemented in the exact2x2 package [2].

The cumulative distribution of hyponatraemia in severe falciparum malaria clearly differs from that of non-severe falciparum malaria which is, in turn, somewhat different from that of healthy individuals (Fig. 3A). Specifically, the mean serum sodium concentrations decrease and the apparent variances increase in the sequence healthy to non-severe falciparum malaria to severe falciparum malaria. The estimated probability density functions overlap considerably, but the increased probability of hyponatraemia and a small increase in the probability of hypernatraemia in falciparum malaria is very clear (Fig. 3B).

Figure 3. Cumulative distribution of serum sodium concentration in the general population (○) and non-severe (●) and severe (■) falciparum malaria (A) and the corresponding probability density functions (B). Estimates for the general population [24, 31, 33, 73-75] and non-severe [37, 44, 62, 63, 76] and severe falciparum [1, 5, 7, 9, 23, 36, 38, 42, 45, 62, 67, 76] malaria were obtained from the literature. The curves in (A) are fits of the cumulative normal distribution to the data, although one datum (▲) was not included in fitting the non-severe falciparum curve, and those in (B) are normal density functions with the same means and variances as in (A).
Table 2. Summary of reports of serum sodium concentrations and mortality

<table>
<thead>
<tr>
<th>Country</th>
<th>Serum sodium concentration (mM)</th>
<th>P</th>
<th>survived</th>
<th>died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papua New Guinea [1]</td>
<td>133 [110-151; 237]</td>
<td>0.91</td>
<td>132</td>
<td>15</td>
</tr>
<tr>
<td>Kenya [3]</td>
<td>134 [127-142; 50]</td>
<td>0.12</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Senegal [5]</td>
<td>131 [128-133; 33]</td>
<td>0.48</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Bangladesh [7]</td>
<td>132 [130-133; 102]</td>
<td>0.01</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Malaysia [8]</td>
<td>131.4 [125-139; 18]</td>
<td>0.149</td>
<td>127.7</td>
<td></td>
</tr>
<tr>
<td>Kenya [9]</td>
<td>134 ± 1 [nr; 42]</td>
<td>&lt;0.001</td>
<td>141 ± 1</td>
<td></td>
</tr>
<tr>
<td>South Africa [12]</td>
<td>133.28 ± 5.613 [nr; 99]</td>
<td>ns</td>
<td>133.07 ± 11.91 [nr; 14]</td>
<td></td>
</tr>
<tr>
<td>Pakistan [13]</td>
<td>133.89 ± 9.23 [nr; 35]</td>
<td>0.082</td>
<td>127.81 ± 11.15 [nr; 11]</td>
<td></td>
</tr>
</tbody>
</table>

Where no range was reported this is indicated by nr.

The interquartile range is reported.

3.3. Mortality and serum sodium concentration

There appears to be no particular association between hyponatraemia and mortality in *falciparum* malaria. In six of eight reports the serum sodium concentration of survivors was not significantly different from that of those who died (Table 2). In the other two reports [7, 9], the serum sodium concentration of those who died was significantly greater than that of survivors (Table 2). Overall, the serum sodium concentrations of 616 survivors ranged from 110 mM to 151 mM (mean value 132.4 [131.9, 132.9] mM) and the 190 individuals who died had values ranging from 117 mM to 156 mM (mean value 133.1 [132.2, 134.0] mM). In one report of 100 *falciparum* malaria patients [77], hyponatraemia was more likely among those who died than those who survived (the odds ratio was 5.78 (95% CI: [2.05, 17.53], p < 0.001)).

4. Discussion

Dysnatraemia is often observed in malaria. Hyponatraemia is common in *falciparum* malaria, but is less frequently reported in non-*falciparum* malaria (Fig. 2). Moreover, cerebral and severe forms of *falciparum* malaria are more often associated with hyponatraemia than is non-severe *falciparum* malaria (Figs 2 and 3A). The extent of hyponatraemia is also more extreme in *falciparum* malaria than in non-*falciparum* malaria (Fig. 1). In non-*falciparum* and in all forms of *falciparum* malaria there are some reports of hypernatraemia (Figs 1 and 3B). Despite this, there is no clear association between hyponatraemia and mortality in malaria (Table 2).

There are at least two deficiencies in the analysis reported here, both are due to the relatively limited data available. The first deficiency is that no attempt has been made to consider the contribution of age, comorbidity and other factors. The second is that only one serum sodium concentration has been used to define hyponatraemia, despite ethnic and geographic differences in reference ranges [33, 34, 78, 79] and serum sodium concentration changes with diet [80] and season [81, 82].

Despite any deficiencies, it is clear that dysnatraemia is more likely and tends to be more severe in *falciparum* malaria than in non-*falciparum* malaria. It is also apparent that while there is some evidence to support the suggestion that the probability of hyponatraemia varies with species (*falciparum* ≥ vivax > knowlesi), there are insufficient data to determine the position of *malariae* and ovale malaria in this sequence. However, the data do indicate that hyponatraemia is more likely in *falciparum* malaria than in non-*falciparum*. Moreover, there are insufficient data to substantiate the suggestion [29] that the extent of hyponatraemia depends on the infective species except to the extent that hyponatraemia may tend to be more severe in *falciparum* malaria than it is in non-*falciparum* malaria.

References


