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Plasmodium infections and fluctuating asymmetry among children and teenagers from Senegal

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ABSTRACT

Although fluctuating asymmetry is a sensitive indicator of stress, its links with health remains controversial, especially in humans. Here, we explored for the first time the association between fluctuating asymmetry and malaria infections in humans, from 107 participants involved in a long term medical survey in Senegal. No clear relationship was detected. Depending on traits considered, associations were not significant, or (marginally) significant but not in the same directions. We discuss the possible reasons for the global weakness of the signals detected in this study.

1. Introduction

Fluctuating asymmetry (FA) refers to the non-pathological left–right asymmetry of body traits that are usually left–right symmetrical, i.e. deviations in either direction from perfect bilateral symmetry (Palmer, 1994; Van Valen, 1962; Palmer and Strobeck, 1986). It is classified as a non-directional asymmetry (NDA) because, in spite of individual asymmetries, the average values of left and right sides are not statistically different in the population. At the individual level, for a trait showing FA, both the amount and the direction of bilateral differences are randomly distributed. Antisymmetry is another kind of NDA, where the amount of bilateral difference is more or less constant among individuals. FA is considered as a marker of developmental stability – i.e. the ability to withstand developmental perturbations (and consequently a putative indicator of underlying genetic quality (Møller, 1997). This imprecise expression in the developmental design occurs in most individuals from a large range of species of both plants and animals (see Møller and Swaddle, 1997 for review). Although the nature and amplitude of FA can vary considerably between taxa, traits, and/or types of stress, it has been shown to increase with exposure during ontogeny to genetic perturbations (e.g. inbreeding, deleterious recessives, homozygosity…) and/or to various environmental insults including pollutants, radiation and parasitism (see review by Møller and Swaddle, 1997). FA is thus frequently used as a monitoring tool to reveal environmental stress experienced by organisms (Parsons, 1990, 1992), being sometimes a more sensitive indicator of stress than traditional measures such as mortality, growth rate, fecundity or population density (Leary and Allendorf, 1989; Thornhill and Møller, 1997).

Linking FA and health in humans has been considered as a promising avenue but yielded inconsistent results (see Van Dongen, 2006; Livshits and Kobyliansky, 1991; Van Dongen and Gangestad, 2011 for review), associations being sometimes positive (see Møller, 1999, 2006; Thornhill and Møller, 1997 for review), negative (Gangestad and Thornhill, 1997) or not significant (e.g. Hume and Montgomerie, 2001; Tomkinson and Olds, 2000). For instance, in a recent study Pound et al. (2014) investigated relationships between facial fluctuating FA and detailed individual health histories in a large sample of 4732 individuals

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from a large longitudinal study in South West England and did not support the idea that facial symmetry acts as a reliable cue to physiological health. Conversely, Thornhill and Gangestad (2006) found significant, positive associations between FA and the number of respiratory infections/antibiotic use, suggesting that developmental stability covaries positively with disease resistance. Human health, however, represents a huge and diversified field (e.g. mental and physiological disorders, cardio vascular diseases, ageing, cancers, infectious diseases, etc.), suggesting that despite the considerable amount of study conducted to date, more work is undoubtedly needed to provide a full understanding of the relationships between FA, health and fitness in humans (Penton-Voak et al., 2001; Honekopp et al., 2004; Holtzman et al., 2011; Van Dongen and Gangestad, 2011; Munoz-Reyes et al., 2012).

As far as infectious diseases are concerned, the literature currently suggests that infection in both animals and humans can be a cause of FA, as well as an indicator of susceptibility to pathogens (see Møller, 1999, 2006 for review). Indeed, high levels of developmental instability may make individuals more susceptible to various diseases, including infectious ones, and/or this can also be the outcome of parasite attacks during development, if for instance the activation of the immune system causes increased FA in developing individuals.Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans of the genus Plasmodium. It is one of the most severe public *health problems* in tropical and sub-tropical areas, being a leading cause of severe disease and death in many developing countries, where young children and pregnant women are the groups most affected (Breman, 2001). In this study, we explored whether infection with *Plasmodium* parasites is associated with increased FA among children and teenagers from Senegal. In tropical Africa, malaria differs from all other regions of the world, having a particular ferocity due to the exceptional vectorial capacity of the three anopheline species (*Anopheles gambiae* s.s., *Anopheles arabiensis* and *Anopheles funestus*) which are endemic in this region of the world (Trape et al., 2014). Although the pattern of illness varies according to the species of *Plasmodium*, patients with malaria usually exhibit high fever and anemia, and can also develop several more or less serious complications (e.g. respiratory distress, pulmonary oedema, encephalopathy, convulsions, splenomegaly, hypoglycemia...) (Bartoloni and Zammarchi, 2012; Mackintosh et al., 2004). Because relapses (especially with *Plasmodium vivax* and *Plasmodium ovale*) and reinfections may occur, frequency of illness at the individual level is elevated in tropical and subtropical African regions, at least until the host develops immunity. For all these reasons, malaria appears as a disease with a high potential to alter developmental stability when it occurs during an organism's development. To explore this avenue, we focused our FA study on young persons because they are both vulnerable to malaria due to an absence of immunity to the parasite, and also because they are predicted to have higher FA levels than adults because rapid growth may make it difficult to maintain symmetry (Mitton, 1993; Wilson and Manning, 1996). This is to our knowledge the first study exploring the links between FA and malaria infection in humans.

2. Materials and methods

2.1. Participants

We conducted our study with 171 participants (77 males and 94 females) aged from 1 to 20 years. All were resident from Dielmo (13°45′N, 16°25′W), Senegal, a village 280 km south east of Dakar and about 15 km north of the Gambian border. Between 1990 and 2012, a prospective longitudinal study of the Dielmo population has been performed to identify all episodes of fever and investigate the host/vector/parasite association of malaria (see Trape et al., 2014 for details). This survey included daily medical surveillance with systematic parasite detection for individuals with fever. This project was initially approved by the Ministry of Health of Senegal and the assembled village population. Approval was then renewed on a yearly basis with written informed consent for individuals enrolled in the project and parents (or adoptive parents, child custodian) for children. Audits were performed regularly by the National Ethics Committee of Senegal and ad-hoc committees of the Ministry of Health, The Pasteur Institutes (Dakar and Paris), and the Institut de Recherche pour le Développement (IRD, formerly ORSTOM).

3. Procedures

3.1. Fever frequency and Plasmodium infections

All households were visited daily from 1990 to 2012, except on Sunday, and nominative information was recorded including the presence of fever or other symptoms. Body temperature was systematically recorded at home three times a week (every other day) in children younger than 5 years of age, and in older children and adults in cases of history of fever or fever-related symptoms (hot body, asthenia, headache, vomiting, diarrhoea, abdominal pain, cough). Blood testing was done for all suspected or confirmed cases of fever, and we provided detailed medical examination, prompt diagnosis and specific treatment for malaria and other diseases, applying the national guidelines of the Extended Programme of Immunization (EPI). With this protocol we could then measure malaria prevalence and density (see below) for each *Plasmodium* species at least quarterly from 1990 to 2012 for all participants. Blood was taken using a finger prick and we examined 200 oil-immersion fields (approximately 0.5 μl of blood). We applied similar procedures when examining thick blood films from patients. We measured the incidence rates of malaria episodes and other causes of fevers as the ratio of the number of fever episodes recorded during a given period divided by the number of followed up person-days under survey during the corresponding period. We counted separately two episodes of fever (including history of fever) if they occurred 15 or more days apart. We attributed fever to malaria when parasite density was higher than an age-dependent threshold calculated for each *Plasmodium* species during the corresponding period according to methods described in Roucher et al. (2012). Maximum threshold values in young children for *P. ovale* and *malariae* clinical attacks ranged from 3800/μl to 2000/μl according to study periods and decreased to 350–300/μl in older adults (Roucher et al., 2014). For *Plasmodium falciparum*, maximum threshold values in young children ranged from 21,500/μl to 10,000/μl and minimum values in older adults from 2000/μl to 500/μl (Roucher et al., 2012, 2014). For infants, thick blood films were taken twice a month up to six months and we attributed fever episodes to malaria when the onset of fever corresponded either to the onset of patent parasitaemia and/or to peaks of high parasitaemia.

3.2. Photographs

Asymmetry was assessed by taking two facial photographs for each individual with a digital camera (Olympus) from a constant distance of 1.5 m at a resolution of 1600 × 1200 pixels. Before being photographed, subjects' hair was removed from the face and glasses were removed. Participants were asked to look straight into the camera and maintain a neutral facial expression with their