Haematology in the Tropics: A Review

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Abstract

Tropical Haematology in current usage in medical literature and practice is understood to mean haematological manifestations of either primary or secondary haematological diseases/disorders which have been influenced or driven by infectious agents and poor nutrition and their sequelae. In this communication, the common examples of infectious agents with serious impact on human haematological manifestations discussed are malaria parasite and HIV. Malaria has contributed greatly to shaping the human genome and driven our evolutionary history. The roles of hookworm and schistoma parasites in relation to the prevalence of iron deficiency anaemia-a component of nutritional anaemia, in the tropics, are mentioned. Poor nutrition itself constitutes a common cause of nutritional anaemia, a common cause of morbidity and deaths in the tropics.

Primary haematological malignancies such as the leukaemias and lymphomas [including lymphomas secondary to HIV infection], are also considered. Similarly, common inherited disorders believed to be the consequences of malaria infections in the past, i.e. the haemoglobinopathies e.g. Sickle Cell diseases/anaemia, and the enzymopathies, eg Glucose-6-phosphate dehydrogenase deficiency [G6Pd], are also mentioned, as are inherited disorders of haemostasis eg the less common inherited disorder, the Haemophilias.

The impact of Genomics, the most recent and far-reaching development in molecular biological research is bound to have profound impact on Tropical Haematology as it already has been in other knowledge areas of human medicine. These early findings in genomics clearly emphasize the need for all haematologists in the Tropics to acquire adequate knowledge, and many, the expertise in Genomics, and for some specialized Centres/Institutes in Genomics to be established in different countries in the Region as a matter of utmost urgency.

Introduction

The Tropics constitute a portion of the planet earth that lies between latitudes 23° 27[1] North and South of the Equator. The weather in the region is characterised by an average temperature of 15.5°Celsus and average heavy rainfall greater than 50cm annually. These weather conditions favour the growth and proliferation of most forms of life, unicellular

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and multi-cellular as animals and plants that are mutually beneficial or harmful to each other. This latter group includes organisms such as the malaria parasite, the human species that is harmful to the human being is the *Plasmodium[P]* species, the most harmful in this group being *P falciparum*. Other human plasmodium parasites are *P.vivax, P. ovale and P malariae.* Other parasitic organisms of importance to humans are viruses, a current important example is the Human Immunodeficiency Virus [HIV] that causes the pandemic Acquired Immunodeficiency Syndrome [AIDS], or past epidemics for example the influenza virus that caused the epidemic of 1918. There is also endemic human poverty in most of the region.

Development of the modern era of Haematology

The modern era of Haematology started as Descriptive Haematology about 1926. It was then, as now, closely associated with developments in other aspects of the sciences. For instance, the seminal contributions of William Hewson [1734-1774] variously regarded as the "father of Haematology"[1] were made during the scientifically turbulent period of his short life of only 35 years from infection acquired in the course of his research. Similar contributions were made by Georges Hayem [1841-1935], another "father of Haematology" and Paul Erlich [1854-1915]. Erlich applied the burgeoning knowledge of chemistry in Germany at the time to develop differential as well as vital staining of different tissues and cells including blood cells. Other cells such as those of Hodgkin's Lymphoma, non-Hodgkin Lymphoma and "leukaemia" cells were described by Rudolf Virchow [1821-1902] in 1845, and John Hughes Bennet [1812-1875] who called them "leucocythaemia" also in 1845.

Much of the above seminal developments depended on the expertise of Antoni van Leeuwenhoek [1632-1723] who developed lens grinding to perfection. He produced the best lenses and assembled his own efficient prototype compound microscope which he and others used to describe accurately and produced the best pictures of blood cells [and other cells] available at the time[1]. The point of emphasis being made here is that van Leeuwenhoek although an uneducated but very talented, curious labourer developed a very keen interest in grinding lenses and produced the best product at the time. He used it to demonstrate the best pictures of blood cells available at the time. The best biologists who wanted to see nature clearly learnt and copied from him.

Early investigations of Tropical diseases

In 1874, Africanus Horton, a West African freed slave in Sierra Leone but of Nigerian origin published a book titled, "Diseases of Tropical Climates and their treatment" [Africanus Horton 1874]. In addition to other diseases described, the clinical features of an illness which later workers found to be manifestations of sickle cell anaemia are detailed. He might on this basis, be justifiably considered as a pioneer of Tropical Haematology. The earlier foreign medical scientific investigators in the Tropics were directed by their home authorities to concentrate on, and find solutions to, the cause[s] of the fever which was invariably fatal among the Caucasian and other foreign nationals who came to Tropical Africa either for exploration, trade or missionary activities. The commonest cause identified was malaria caused by infection acquired when a female Anopheles gambiae mosquito that had previously been infected with malaria parasite, bit the victim during its blood meal. During such feeding process, the mosquito usually transmitted the parasite to the victim. Such infected Caucasian explorers, traders or missionaries invariably developed malaria fever and almost always died as at the time, no cure had been found. Since Nigeria and other Tropical countries of West Africa were, and have remained holo-endemic areas for malaria, the clinical features of diseases observed, whether of infectious or non-infectious causes [communicable and non-communicable

diseases], were routinely attributed to malaria or other infectious agents. These others included small pox or yellow fever viruses that were later recognized. The conclusions were made despite contrary evidence.

Results of some early Investigations in Tropical haematology

Although the Tropics as already stated spans a very wide geographic area, human populations, activities and problems, significant research output in Tropical Haematology was limited to only a few centres such as the University of Ibadan, Nigeria, Makarere University, Kampala, Uganda, the University in Harare, Zimbabwe [then known as Salisbury, Rhodesia], those in Mozambique and some in South Africa [61], all in Africa. There were other centres within the Tropics in India, South America and the Carribean islands etc. Some examples of achievements in the African centres include the discovery of Lactate dehydrogenase sub-unit variants in human blood (1963)[2] and Haemoglobin D^{Ibadan} [beta 87 Threonine to Lysine] which did not sickle with Haemoglobin S[2], South American trypanosomiasis [Chaga's disease] in South America.

Other examples of relevance were those on Glucose-6-Phosphate Dehydrogenase[3] [G6PD] earlier described by Beutler, some of its variants in the local population [31, 41].

Haematology associated with nutritional disorders

Anaemia is the commonest haematological disorder worldwide, including the Tropics and poor nutrition is the commonest cause of this category known as Nutritional Anaemia[5, 6, 7]. Studies in Nigeria and elsewhere revealed the commonest deficient nutrients to be Iron and Folic acid[2, 3, 8, 9]. Despite definitive knowledge on the issue, the problem of malnutrition has remained a serious challenge because of the issue of prevalent poverty. It is difficult to give a reliable figure on the prevalence of either Iron or Folic acid deficiency because of the many confounding factors that are involved such as age, sex, economic status, cultural habits and beliefs that often render such figures almost meaningless[7]. For instance, with respect to Folic acid, the traditional methods of preparing meals in many communities in Nigeria are such that only minimum to zero concentration of the vitamin may remain in the meals consumed after such preparation. However, despite the limitations outlined above, the prevalence of iron deficiency is stated to be 30% in general though lower in informed segments of affluent societies[5, 7, 9]; it is 45% among some communities in the South- South zone of Nigeria[10].

Some common genetic diseases and disorders in the Tropics

Several disorders and diseases are common in the Tropics as a result of the tropical environment. These include the Haemoglobinopaties such as Sickle Cell Diseases whose highly suggestive clinical features had earlier been described by Africanus Horton 1874 [see above] and definitively later 1962 [16, 17, 22, 19]. This has, and continues to be, well reviewed [11, 12,18]. Other abnormal haemoglobins such as the Thalassaemias have also been intensively studied[20]. Another example investigated intensively is the red blood cell enzyme, Glucose-6-phosphate dehydrogenase [G6PD][23, 24, 26, 14, 13,].

Sickle cell anaemia [and disease] was shown to be the result of a point mutation in the haemoglobin molecule [GAG to GTG] in the 6th codon of its beta chain[17]. These studies of sickle cell and other haemoglobinopathies provided insight into the link between haematology, human genetics and the role of malaria in their occurrence[22, 18, 20, 21, 12].

Comments on some uncommon hereditary haematological disorders in the Tropics

Haemophilia is a relatively uncommon inherited bleeding disorder that exists in all human populations. However, for some curious reasons, this inherited disease was thought inconcievable among peoples of

African descent in the USA[1]. If any was found among Africans on the continent, it was thought to be a different type of inherited disease from that which occurred among Caucasians including those in Apartheid South Africa[1,27]. The definitive studies of haemophilia in Nigeria[28] ended such unhelpful views.

The 10/90 phenomenon and Tropical haematology

The trend of intensive study was and still is, understandably devoted to problems commonest among the population that is usually most able and ready to pay for such research, services and facilities. This issue was highlighted in the 10/90 Report [2000]. The Report addressed the problem in which 90% of the available resources world wide were [are] devoted to research into diseases that affect 10% of the world's human populations, while only 10% of such resources are devoted to address diseases [including Tropical Haematology-my emphasis] that affect 90% of the world's populations [The 10/90 Report on Health Research, 2000].

What is Tropical haematology?

The question raised in the context of this communication is whether the Tropical environment as here conceptualized to exclude more than minimal infectious agents, poor nutrition as integral components but inclusive of genetic influences, does exert effects on, and define normal haematology in the healthy population of the region. The studies of Ezeilo[29, 30, 31, 32, 33] on granulocytes, Essien and associates on platelets on haematological parameters strengthen the need to investigate the question more fully utilising all the scientific knowledge and tools including expertise in Genomics, Some workers do suggest such in relation to malaria research[21].

In the mean time, it is here recommended that Tropical Haematology should be understood to mean the manifestations of normal Haematological parameters as defined in the healthy population of the Tropics as well as the manifestations of different blood diseases be they primary or secondary haematological disorders, or manifestations that are due exclusively to infections. It should also include interactions among these different categories. The roles of genetics and nutrition in haematological diseases are already well known [34].

Malaria

The malaria parasite of the species *Plasmodium[P]*, with the human species comprising *P falciparum, P.vivax, P. ovale and P malariae,* is the most important human parasite, and the most malignant member of the group to humans is *P falciparum*[35, 36]*. P knowlesi* that primarily infects monkeys is also infectious to humans[37]. It is estimated that these parasites infect about 40%, [approximately 515million] of the world's human population accounting for about 3 million deaths annually especially among children aged under five years, and pregnant women[9,38]. It is responsible for the high maternal mortality observed in the region[39], and contributes very significantly to the poverty level prevalent in the affected countries. The latter effect is through its debilitating impact that it exerts on adult victims that leaves them much weakened and unable to work hard enough to contribute meaningfully to the economic development of their countries[35, 36]. Most significantly, there is good evidence which supports the view that the malaria parasite had contributed to shaping the human genome and has driven our evolutionary history[21].

Two of many relevant examples support this latter view. They are firstly, the existence of sickle cell haemoglobin and its health impact [16, 17, 22, 19, 11, 12, 18]. Other abnormal haemoglobins such as the Thalassaemias have also been intensively studied[20].

The second example of this impact on human development is manifested in the enzyme, Glucose-6-phosphate dehydrogenase [G6PD],

primarily a red blood cell enzyme but also present in other cells and tissues [23, 26, 14, 13].

The spectrum of diseases usually associated with *P. falciparum*, infection initially focused on its impact on the red blood cell and resultant anaemia, its most common complication[39, 35]. Other complications apart from its most serious one, cerebral malaria, include hyperimmune malarial splenomegaly [HMS], a massive splenomegaly complication which occurs in addition to the usual, mild splenomegaly in the infection, Burkitt's lymphoma, glomerulonephritis among others. Other interactions involve leucocytes and include phagocytosis, cytokine production and cytotoxicity, and changes in leucocyte count. This latter effect varies depending on the age of the patient, the species of the parasite involved and disease severity. It also depends on whether the infection is acute, acute- on-chronic or chronic, as well as on co-infection with bacteria[40]. Other white cell changes include lymphopenia which may be transient, and monocyte hyperplasia[40].

The mechanisms in these changes include up-regulation and effects of interferon-gamma, tumour necrosis factor-alpha [TNF-a], nitric oxide [NO] and of reactive oxygen intermediates on the tissues and organs[41, 40].

More recently following the publication of the human genome in 2000 and subsequent explosive development of Genomics, sequencing of the genomes of *P falciparum*[42], *P vivax* and of the non-human parasite, *P knowlesi* [43] have been published. It is expected that sequencing of the other malaria parasites will soon be accomplished as well as developments of new drugs, and new diagnostic strategies.

Despite the progress indicated above, the negative impact of malaria both in haematology, other clinical aspects as well as in economic and development spheres remain. For instance, the problem of early diagnosis of cerebral malaria and thus improving its outcome remains a challenge to Tropical Haematology. It is hoped that further developments in malarial genomics will help sort out the situation. The struggle for the real hope of malaria conquest however, lies in a total commitment to vaccine development and its vigorous, whole-hearted pursuit[44].

Platelet changes in acute malaria

With respect to platelet changes, thrombocytopenia has been demonstrated in human and animal infections since Maslova's first report *[Maslova 1924]* and by others since then. The controversies on this topic concern the prevalence, severity, variations in degree of thrombocytopenia, duration after treatment[32] and prognostic value. Platelet activation has been demonstrated in mild, moderately severe and severe human infections with *P. falciparum, P.vivax*[31] and in the animal models: Syrian golden hamsters, Swiss albino mice and suckling rats experimentally infected with *P. bergei* bergei[31, 32, 33,]. It has more recently been suggested that activated platelets are involved in promoting cerebral malaria[45, 46]. The demonstrated mechanisms of the platelet activation were enhanced response to the agonists, Adenosine diphosphate [ADP], Thromboxane A2, and an as yet unidentified agonist. Interestingly, it was observed that platelet refractoriness to sub-optimal concentration of ADP as agonist was abolished [31, 32, 33]. Other platelet changes reported include enhanced loss of platelet total membrane sialic acid, elevated plasma concentrations of platelet factor 4 [PF4] and adenosine triphosphate [ATP], changes that could also contribute to enhanced response to the agonists. Details of the mechanism[s] of platelet activation by ADP are still to be clarified. The clinical applications of the above platelet changes in acute malaria infection include the observation that clinically bleeding symptoms are rare even in cases of severe thrombocytopenia[31, 32]. It has also recently been reported that activated platelets are involved in promoting cerebral malaria complication[45, 46].

Malignant and pre-malignant haematological diseases in the Tropics

Primary Haematological malignancies such as the leukaemias which are either acute or chronic, the lymphomas- Hodgkin and non-Hodkin's, and the eminently treatable Burkitt's lymphoma[47, 48] and pre-malignant disease states including myelodysplastic syndrome [MDS] are commonly encountered in the Tropical environment. Other difficult problems that are frequently encountered include hypoplastic and aplastic states. The difficulties that complicate these problems in the tropical environment include scarce resources, inadequately trained personnel, inadequate infrastructures and frequently, a generally non-challenging intellectual working environment.

Human Immunodeficiency Virus [HIV] infection and Acquired Immunodeficiency syndrome [AIDS]

Much progress has been made in our knowledge and understanding of the problems which are profound, of HIV and AIDS including the haematology associated with the diseases. HIV-1 is the commoner of the two main RNA viruses in the Lentivirinae sub-family of Retrovirus that caused and has been driving the current HIV pandemic since it was first reported in 1981. The haematological diseases associated with HIV infection involve blood or bone marrow and manifest either as anaemia, neutropenia or thrombocytopenia. These occur either singly or, more commonly, in combinations. Malignancies commonly associated with HIV/AIDS include lymphoma, Kaposi sarcoma and cervical cancer.

Anaemia: This is reported to be the commonest of the complications of HIV infection or AIDS. It is reported to occur in 3% of asymptomatic, HIV-infected persons, in up to 30% of symptomatic persons depending on the seriousness of the symptoms, rising to between 70-80% in the course of the infection progressing to AIDS. Among 558 Nigerian patients at presentation, anaemia [PCV< 30%] occurred in 35% in the course of the disease[32].

Neutopenia: This has been reported in 10% of asymptomatic patients and in greater than 40% in AIDS patients. Aetiologic factors responsible for this complication include opportunistic infections, other chronic infections, depression of G-CSF, HIV-associated malignancies such as Kaposi's sarcoma, drugs used in treating the infections as well as HAART drugs used in treating the HIV

Thrombocytopenia: It has been reported in 1.7% of HIV-infected patients at presentation, in 3.1% of patients with CD4 count of < 200/ul and 8.7% among AIDS patients [Nardi *et al* 2007] In a study of 725 Nigerian AIDS patients, thrombocytopenia was observed among 3.9% of the patients of which 2.1% was categorized as mild, 1.1% moderately severe and 0.7% severe[21]. In the context of an African population, these terms have been defined as 60-99 X 10^9/L, 30-59 X 10^9/L and <30 X 10^9/L respectively[31, 32, 33].

The results of platelet counts of Africans and Afro-Carribean peoples, all of whom had lived in Britain for several years, some for decades, and who might be assumed to have escaped the devastating effects of different infections prevalent in the Tropics, raises the important question about defining Tropical Haematology only in relation to the combination of infective agents and poor nutrition. There are urban slums in the inner cities of industrialized countries; the grindingly poor of these societies who live in these slum areas are exposed to similar degrees of pernicious infections and poor nutrition as the general poor citizens in the Tropics. The difference between the poor in the industrialized countries those in most Tropical countries is the environmental temperature, the parasites and other infectious organisms prevalent in these temperate countries, and their accessibility to health facilities if they can pay for the services provided.

Conclusion

The contents of Medicine taught in Medical Schools and medical practice worldwide are rapidly moving into the era of Genomics and its implications to healthcare such as personalized medicine are compelling. This new field of knowledge has defined the challenge for Tropical Haematology and Haematologists in the Tropics.

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