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Role of Intestinal Parasitic Infection in Stunting

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Mini-review Article

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ABSTRACT

Aim: To review recent findings in the context of the relation between intestinal parasitic infection (IPI) induce the host's chronic immune activation and systemic inflammation that contributes to stunting.
Discussion: To some extent, based on the parasite species (with the account of the condition of co-infections), combined with its timing (when was the initial infection took place), the duration of the disease, its intensity, and also must be considered the patho-physiology effects, can cause serious effect to their host. Prolonged IPI contributes to the formation of stunting. Active IPI can cause direct dysregulation of growth factors which are important for prenatal and postnatal growth. Furthermore, IPI opens the door for the entry of secondary infections, bacterial and viral, and allowed them to established definite co-infection which can cause prolonged inflammation, locally and systematically. Several potential interrelated mechanistic routes also could be connected through the host's imbalanced nutritional status, possible environmental enteric dysfunction (EED) due to persistent IPI and prolonged inflammation, hormonal derangement and perhaps also due to metabolic disturbances, immune dynamics, the consequences of definite anaemia, changed microbiota composition, and also changes in epigenetic signature.
Conclusion: Persistent and prolonged IPI induced both chronic immune activation and systemic inflammation that contributes to the formation of stunting, directly and indirectly.

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Keywords: Helminths; protozoan; co-infection; children; nutrition; environmental enteric dysfunction; microbiota composition.

1. INTRODUCTION

Intestinal parasitic infection (IPI) can contribute to the formation of stunting, with Ascaris lumbricoides and hookworms contributed the most notable to stunting [1]. Individuals who experienced childhood stunting are more likely to encounter higher risk of morbidity [2], mortality [3], and its unnoticed consequences, such as less optimal cognitive function [4] and serious delay in motoric advancement [5]. According to The UNICEF-WHO-World Bank Joint Child Malnutrition Estimates (JME) Working Group, in the year of 2020, 149.2 million children under 5 years of age were too short for their age (stunting) [6].

Unfortunately, the progression to eliminate stunting is not as expected, even reduction in prevalence are still uneven and still shows wide gap of differences in many countries [7]. Fortunately, because reduction of stunting is part of the MDG's targets, global research and networking has been established and has produced a lot of thought-provoking products for stunting alleviation [8]. Understanding is developed regarding the causes of stunting, one of them is that enormous fraction of stunting is not caused by just diarrhea or inappropriate diet [9], it remains that other factors must explain continued growth faltering [9,10]. Persistent IPI contributes to the origination of stunting.

The pathognomonic esplanade by which IPI lead to stunting must always be considered multi-factorial [1] and milieu-specific, [11] and dependent on various interrelated factors such as parasite species, personal hygiene practice, geographic location, and a multitude of other circumstantial elements. The aim of this mini-review is to re-visit and refresh knowledge about how IPI contributes to the genesis of stunting.

2. THE VICIOUS CYCLE OF STUNTING

Until nowadays, the most globally accepted pathway to stunting is a theory named 'vicious cycle' [12]. Stunting is a result of continuous cyclical process based on women who were themselves stunted in childhood, in the future tend to have stunted offspring; this generating an intergenerational cycle of poverty and diminished human capital that is almost impossible to break by themselves, unless there is assistance from outside parties in power (the government) in breaking the chain of this cycle.

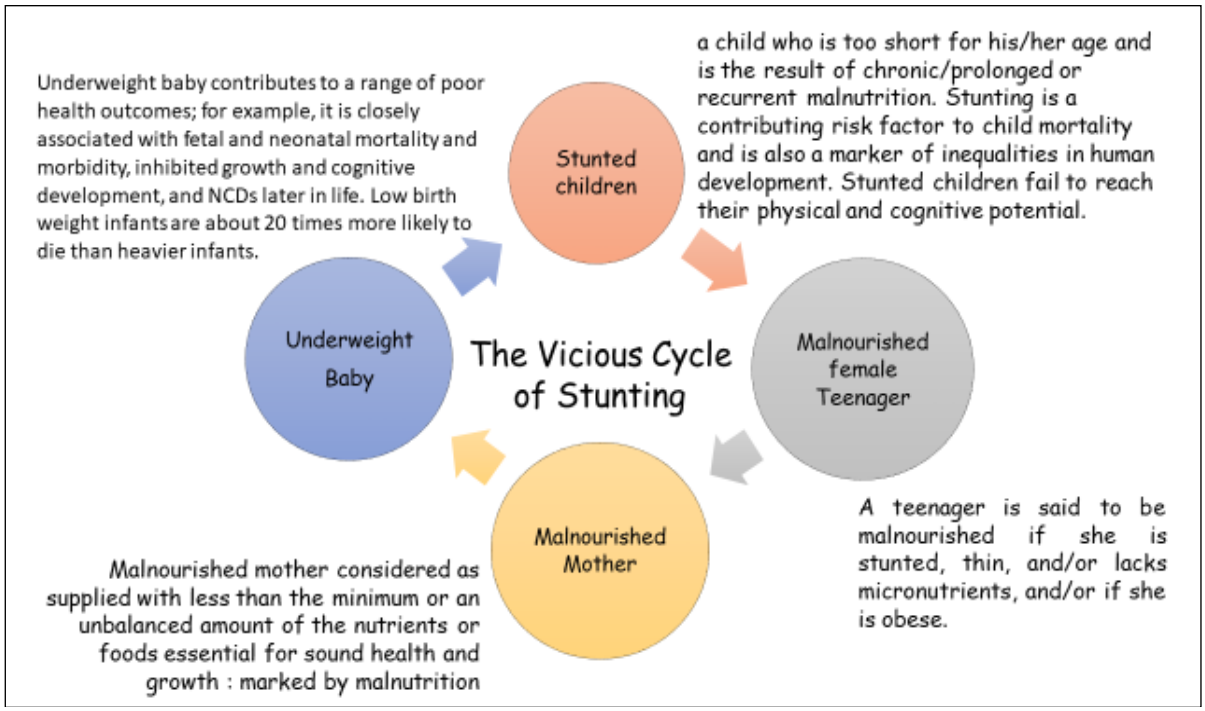

Fig. 1. The vicious cycle of stunting

Stunting vicious cycle revealed the connection between double burden of deteriorating nutritional status and infection [13] which is in turn progresses to into the following:

(i) Encompass dysbiosis of the intestinal normal microbiota [14,15]. The vertebrate intestine be overflowing with a huge, miscellaneous, and vigorous inhabitants microbiota community [15] that has ubiquitous outcomes on overall intestine function, physiologically, biochemically, and last but not least immunity [14,15]. In normal situations, these inhabitants microbiota dividend their habitation with a correspondingly spirited neighborhood of eukaryotes organisms (e.g., helminths, protozoans, and also fungi), many of which are well-known parasites. This sudden combo group of the existing prokaryotic microbiota and the 'new comer' parasites can fiercely convert the actual physical and immune topography of the intestine, and fabricating tolerable possibilities for both parties (normal microbiota and parasites) to merge or at least to interact [16]. Such an unique relationship may substantially affect the infection courses and outcomes and definitely influenced the condition of host's health and disease, comprehensively. For example, sudden parasite invasion can alter normal host association with its normal bacterial flora, [15] either compelling or guarding against the condition of dysbiosis and inflammatory disease [17,18]. Conversely, the microbiota can alter a parasite's colonization success, replication, and virulence, shifting it along the parasitism-mutualism spectrum [14,16,17].

(ii) Initiating locally intestinal restricted inflammation [19,20] Helminth parasites are the classic perverters of Th2 responses. Immunologically, the Th2-polarized T cell response driven by helminth infection has been linked to the attenuation of some damaging Th1 driven inflammatory feedback, definitely blocking several Th1-mediated autoimmune conditions in the host, including experimentally induced colitis [21]. Scientifically, there is an antithetical interdependence between the amount of revelation to the eukaryotes intestinal helminths and the occurrence of unequivocal immune-mediated conditions, including inflammatory bowel diseases (IBD). intestinal helminth infection can prevent the outgrowth of a common intestinal bacterium that causes IBD in genetically susceptible mice [20]. However, recent studies have provided evidence indicating the exacerbating effects of helminths on bacterial as well as non-infectious colitis in animal models [18,19]. According to study conducted by Brosschot et al, [22] intestinal helminth infection can impair host resistance to co-infection with enteric bacterial pathogens Salmonella and the administration of anthelmintic regiment prior to Salmonella challenge is adequate to reestablish host initial resistance to Salmonella.

(iii) Initiating systemic inflammation [18,23]. Intestinal helminths can manage deleterious inflammatory reactions and in the same time keeping homeostasis by way of stimulating systemic immune responses. The induction of distinct elements of immunity awakened by the existence of certain helminths, which includes Type 2 and immune regulatory responses, that can both contribute toward the reduction in harmful Type 1 immune responses that drive certain inflammatory diseases. Regardless of inducing type 2 responses, IPI may also down regulate harmful Type 2 immune responses including allergic responses. We consider the possibility that intestinal helminth infection may indirectly affect inflammation by influencing the composition of the intestinal microbiome [25]. Some previous study analyzed the effect of intestinal parasite to their host's systemic inflammation. According to Caudet et al, [24] enteric eukaryotic unicellular intestinal parasites may play an important role in modulating the antioxidant defenses of an obese host, thus could have beneficial effects with respect to the development of systemic metabolic disorders. While other study by Rajamanickam et al [23] revealed that helminth infection is associated with attenuation of systemic inflammation and microbial translocation in Type 2 Diabetes Mellitus and its reversal following anthelmintic therapy.

(iv) The loss of energy due to hormonal and metabolic consequences of IPI [26,27]. A variety of helminths spend some part of their life cycle in the gastrointestinal tract and even entirely enteral nematode infections exert beneficial effects on

glucose and lipid metabolism. Parasitic nematodes can impact metabolism including effects gastrointestinal hormones, altering epithelial function, and changing the number and/or phenotype of immune cells in metabolic tissues. Nematodes can also exert their beneficial effects through Th2 cytokines that activate the transcription factor STAT6, which upregulates genes that regulate glucose and lipid metabolism. Parasitic infections, even those restricted to the intestine, increase circulating levels of IL-4, IL-5, and IL-13 which may act to blunt or reverse the Th1-induced inflammation in metabolic tissues. In the context of hormonal consequences, many parasites produce ecdysteroids, but restricted evidence is convenient on sex steroid and corticosteroid amalgamation. In most, but not all cases of parasite infection, the host's hormonal milieu regulates the susceptibility, the course, and severity of parasite infections [28]. In most cases, parasitic infection disturbs the normal existing host immune environment, [15] and actually triggers immune reactions that become stirring the host's endocrine armamentarium. In addition, sex steroids and corticosteroids may also straightly reshape the parasite reproductive ability and its molting [29]. Available information stipulates that living parasitizing organisms synthesize some steroid hormones, e.g., ecdysteroids and sex steroids, and the presence and activity of related enzymes have been studied elsewhere [27].

3. THE MECHANISM BY WHICH PARASITIC INFECTION CONTRIBUTES TO STUNTING FORMATION

The human GI tract accommodate diverse but dynamic normal microbiota population since very early of life. These organisms contributes positively on its host's well-being, biochemically and physiologically, in terms of local milieu and also systemic function. Whenever there is invading parasitic eukaryotes, these normal microbiota must share their milieu with one main goal, namely to maintain homeostasis, whatever the cost. The bidirectional relationship between intestinal parasites and the existing microbiota [15] if happens very early (childhood early life), and their combined effects, [15,30] could play a key role in stunting. Intestinal parasite infection may contribute to stunting formation by way of:

a. Directly induce prolonged and persistent sub clinical systemic inflammation [1,2] and having an immunomodulatory properties that interfere with all features of the host immune response to ensure their persistence within the host [3] which has a detrimental effect on the individual who experiences it, or
b. Indirectly by triggering persistent local gut inflammation as a result of Environmental enteric dysfunction (EED), [31,32] an uninterrupted inflammatory state, persistently, derived via the adaptive immune reaction, which also has a serious impact on the digestive and absorptive process. The presence of persistent yet active sub-clinically intestinal parasitic infections was unquestionably linked with stunting but not with wasting. [11] Intestinal parasites can also collaborate with normal gut microbiota (and it can alter each other's pathogenicity), and this interaction also leading to malnutrition [5].

The condition of EED, even though initially it only took place locally and causing subclinical condition in term of disease progression, but we must realize that the condition of this intestinal inflammation, can occur since infants-age, most common found across underdeveloped countries, and is proposed as an immediate causal factor connecting poor sanitation and stunting [31]. A result of long term pathogen exposure (often found in types of infection by multicellular parasites that inhabited organs for a very long time), EED presents multiple causal pathways [33]. Although the definite pathogenesis of EED and the mechanism by which stunting occurs are yet to be defined, but evidence regarding contribution of intestinal parasitic infection cannot be ignored.

4. HOW CALORIES AND NUTRIENTS ARE LOST DUE TO THE COMBINATION OF IPI AND STUNTING?

One consideration governing immune-metabolic interactions includes sharing versus competition for energetic resources [34]. Immune activation cannot be denied responsible for the lost of calorie intake and vital nutrients, that normally should be used for other routine non-immune activity (e.g., study, exercise etc).

Unfortunately, active immune armamentarium is actually high priced, in terms of both energetically and metabolically; and this may

directly (or indirectly via other pathway) divert calories and nutrients away from other normal and routine physiological processes such as linear growth, in an energetic trade-off.[35,36] A study conducted by Urlacher et al in Amazonian youngster found out that substantial increased in total IgE level, antibody against parasite as an adaptive immune reactions, was correlated with definite growth inhibitions [35].

The sequence of events can overlap and occur simultaneously. These chains of events can exacerbate the course of the disease. note that short-term effects can occur immediately and quickly, but if not handled adequately they can continue to become serious long-term effects and may be irreversible clinically

Energetic tradeoffs implying human immune armamentarium activation are to be expected to arise since the very early of life, [37] based on exposure to outside world, that shape the way humans respond efficiently to energy needs while synchronizing with resilience to stimuli and even promote tolerance (e.g. to extreme heat) [38]. The more active the immune system, the higher the energy needed [39]. This is a characterization in human evolution by considerable controlled energy allotment. [40] To some extent, physical development during growth spur phase is predicted to be exceptionally subtle to immune-related tradeoffs at this occasion [36,37,40]. It is not surprising that ordinary people also know that children who are often sick usually do not have good physical growth.

The direct consequences of IPI is that it may increase gut permeability, local (gut) inflammation, and systemic inflammation [18-21]. Parasites not inhabiting in the gastrointestinal tract may still cause systemic inflammation directly via activation of the immune response [17]. Changes in the gut microbiome and epigenetic signature of the host may also be implicated in the pathway to stunting, via the gut and/or systemic inflammatory response [41,42]. Gut permeability and inflammation (associated with environmental enteric dysfunction) and systemic inflammation may be causative in the pathway to stunting [31,32].

Furthermore, any multicellular parasites may manipulate amino acids, essentials substance needed for the host's growth, by way of:

1) Competing with their host and utilize them up for their own benefit, [43] or
2) Via sudden and escalating requirement by the immune system during infection; usually bacterial based that it is usually a bacterial-based type of infection that occurs as a secondary infection or co-infection with the primary IPI [44].

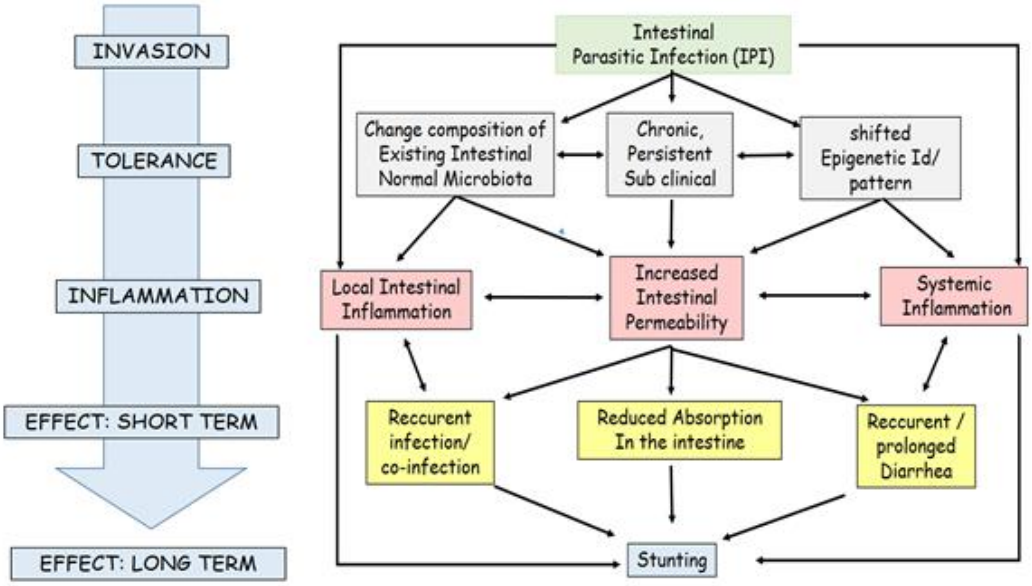

Fig. 2. Possible mechanistic pathway of stunting that begins with intestinal parasitic infection in the very early phase of life

5. LOSS OF ESSENTIAL AMINO ACIDS AND ITS CONSEQUENCES

Essential amino acids are critical for nucleic acid and hormone biosynthesis and cellular replication, [45] and in turn for the long term, amino acids, especially that comes from animal [46], are very good for child development and growth, Anatomically and Neuro-cognitively.

According to Parikh et al, [45] the high incidence of growth faltering among children under 5 years of age, even if those kids are lucky enough not to be stunted, but still they underwent the condition of unable to outstretch their maximum growth potential. The time between conception and 2 years of age is critical for development [47]. It is often found, especially among mothers who are having children for the first time, at the age of 6-23 months is actually a critical period for inhibiting child growth due to the initial introduction and administration of complementary foods for their children, but unfortunately it concur mostly with the initial formation of growth faltering and accompanied with postponed neurocognitive developments; two most common condition found which could have preceded the stunting event [48]. Fortunately, this is also the time period of which diet exercises is familiarized, culturally [49].

According to Semba et al, [50] child stunting is associated with definite poor circulating essential amino acids., systematically Furthermore they stated that unfortunate children with a high possibility of developing stunting may not be obtaining sufficient daily dietary intake that consist of essential amino acids and choline, an important nutrient for the synthesis of sphingolipids and glycerophospholipids.

Unfortunate children who grow up in a poor milieu, with a constant long-term deficient and inappropriate dietary intake, as typically seen in poor countries, inhibits growth and development of children and prevents them from achieving their maximum potential developmental and economic future potential [51]. The availability of adequate nutrient, in the context of quality and quantity, and its main implementation which is to make sure child's growth and development, especially in the post- breastfeeding period [52]. Children from poor country, although it is possible that children consuming sufficient total protein, but unfortunately it might fail to fulfill their essentials amino acids requirements [53]. The underlying condition for that perhaps as a consequences of poor diet heterogeneity and under-quality dietary protein; conditions that are very likely to be found in low level socio-economic society with low purchasing power and almost non-existent bargaining power in the community; it is a very good example of a marginalized poor society.

Amino acids deficiencies that took place in a very early life can cause limitations in linear growth-spur and neuro-cognitive advancement [36]. Assuring the availability and adequacy of amino acids in daily foods for children, especially through incorporation of nutrient-dense animal source foods for children aged 6 to 23 months, is forcibly reassured in order to reimburse for previously less than optimal growth during complementary feeding.

Parasites may also utilize host amino acids; for example, intestinal protozoan Giardia lamblia directly consumes arginine as an energy source, and by doing so they showed their competitiveness and interactivity [30]. Furthermore, amino acids are also contributes significantly for intestinal barrier function, with its shortage likely intensifying the EED cycle by way of diminishing the ability of intestinal cells to repair injury [54]. Amino acids ameliorate the (a) functions of intestinal barrier and expressions of anti-inflammatory cytokines and (b) tight junction proteins. Besides that, amino acids actively reduce (a) oxidative stress and (b) the apoptosis of enterocytes as well as (c) the expressions of proinflammatory cytokines in the intestinal inflammation.

Active IPI can cause direct dysregulation of growth factors which are important for prenatal and postnatal growth [55]. The consequences of immune activation upregulates acute-phase proteins, which prevent IGF-1 in the liver, directing to the condition of growth hormone (GH) resistance and inhibition of longitudinal bone growth via direct effects on the growth plate, potentially reducing optimal linear growth [56]. According to Maleta et al, that conducted a study among Malawian and children, infection caused by protozoan named Cryptosporidium spp. was correlated indirectly with lower length-for-age; a condition obtain by way of developed systemic inflammation and diminished plasma IGF-1 concentrations, [57] Another study conducted in Gambia also traversing these previously mentioned theories [58]. Mbuya et al [58] found that repeatedly appraised EED and its immune markers (representing normal gut

microbiota translocation, intestinal permeability, and inflammatory reaction), together the three of them as a mechanism, forecasted of growth faltering condition up to 55%.

This condition can also occur in other types of parasitic infections, depending on the species, location, number and severity of the disease. Further exploration is needed to increase awareness, prevent fatalities and most importantly break the chain of infection so that stunting can be prevented.

6. CONCLUSION

Intestinal parasitic infection definitely contributes to the formation of stunting. The definite underlying mechanism is still being explore extensively. But in general speaking, the condition of EED and its successive inflammation trigger by IPI, these three together may be an underappreciated contributor to stunting, at least until recently. Fortunately, findings and achievements in the fields of nutrition, immunology, Internal Medicine, Public Health and clinical Parasitology/Microbiology contributes significantly to the understanding of the course of the disease with their consequences for stunting, and all of these has shed light on the global effort to prevent IPI and eliminate stunting,

COMPETING INTERESTS

Author has declared that no competing interests exist.

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