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Though having steadily fallen over the last decades, linear growth retardation remains a serious problem, with an estimated 170 million children under five years of age being stunted. (A stunted child is too short for its age, having a height below -2 standard deviations of the World Health Organization's reference height for his or her age and sex.) Growth retardation in young children is associated with delays in cognitive development, lower school achievement, and both lower earnings and a higher probability of non-communicable chronic diseases at adulthood. Key then is to make universal improvements to maternal and child health and nutrition in the first 1,000 days (that is, the period from conception to when the child reaches 24 months of life). Providing multiple micronutrient supplementation during pregnancy, improved complementary feeding, and better hygiene would reduce the prevalence of stunting by only an estimated 20.3 percent (Bhutta et al. 2013). Research efforts are therefore focusing on identifying presently unknown causes of growth retardation.

Evidence from human and animal studies and current knowledge of the biological mechanisms of action of aflatoxins suggest that chronic exposure to aflatoxins might lead to stunted growth. This brief summarizes the existing evidence and reviews possible solutions that could be applied if future research confirms the causal relationship between aflatoxin exposure and growth retardation. It begins with an overview of the criteria that must be met to conclude that aflatoxins cause stunting.

Determining causation

To prove a causal relationship between aflatoxin exposure and stunting, four criteria must be met:

1. Aflatoxin exposure and growth retardation must be associated.
2. Exposure to aflatoxins should precede the growth retardation.
3. The effect needs to be biologically plausible.
4. The effect cannot be due to confounding factors.

In terms of the last criterion, one confounding factor particularly challenging to rule out is the socioeconomic status (SES) of the household. Children in poorer households are often fed diets deficient in micro- or macronutrients and suffer from more frequent infections, both of which contribute to growth retardation. If these factors are associated with aflatoxin exposure and are not adequately controlled for in the analysis, the magnitude of the aflatoxin-growth association will be overestimated.

Evidence in humans

While only a small number of observational studies have been carried out, the majority has found strong associations between aflatoxin exposure and stunted fetal, infant, and child growth, thus providing evidence for the first criterion for causality. Some studies

have shown the temporal relationship as per the second criterion. Even though the effect is biologically plausible (criterion 3, see "biological mechanisms" below), the possibility that the association is (at least partially) due to confounding factors, as per the fourth criterion, has not been adequately addressed. Findings from published studies addressing at least two causality criteria are summarized below.

In Ghana, women exhibiting high serum aflatoxin levels at delivery—a marker of having been exposed over the last two to three months—were more likely to have a low-birthweight baby; no association was found with having a baby small for gestational age or with preterm birth (Shuaib et al. 2010). The analysis controlled for SES, but no details were provided on how this was done, making it difficult to evaluate if confounding was adequately controlled for.

A study in The Gambia showed that exposure occurred before the linear growth retardation: serum aflatoxin levels in pregnant women and in infants at 16 weeks of age were strong predictors of linear growth during the first year of life. Cord blood levels were not associated with birth weight or length (Turner et al. 2007). The Gambia study did not control for SES.

A study in Benin and Togo found that the serum aflatoxin level was 30–40 percent higher in stunted children one to five years of age than in non-stunted children, after controlling for confounders including socioeconomic status, child age, and sex. Details on the measure of SES were not provided by the authors (Gong et al. 2002). Finally, the same authors studied the linear growth of 200 Togolese children 16 to 37 months of age over an 8-month period. Children in the highest serum aflatoxin albumin quartile grew 1.7 cm less than children in the lowest quartile, after controlling for age, sex, baseline height, and SES. As in the previous study, the authors did not provide details on the SES measure used (Gong et al. 2004).

Although the findings are generally consistent, none of the studies adequately controlled for factors that could potentially confound the association between aflatoxins and child growth—such as household socioeconomic status, child dietary intake, and child morbidity. Another possible confounding factor is child age. Because growth retardation is a cumulative process, stunting increases with age. Exposure to aflatoxins through the diet is also strongly associated with age; thus if age is not properly controlled for in the analysis, the degree to which aflatoxins and child growth are associated will again be overestimated.

Evidence in animals

A large number of studies conducted with different animal species consistently found that experimental exposure to aflatoxins led to reduced weight gain (brief 5). The evidence suggests that this is at least partially due to reduced feed intake and less-efficient feed conversion. A small number of studies further suggest that in utero exposure negatively affected fetal growth (Khlanguiset, Shephard, and Wu 2011). An important remaining question is to what extent

the weight-gain findings in animals are applicable to linear growth retardation in children.

Biological mechanisms

The known biological mechanisms of aflatoxins make an impact on linear growth plausible. Human and animal studies indicate that aflatoxins cause immunosuppression (which in turn can lead to repeated infections and, consequently, growth retardation in young children), impairs protein synthesis, and changes the hepatic metabolism of micronutrients (Khlanguiset, Shephard, and Wu 2011). It has also been suggested that aflatoxins together with fumonisin and desoxynivalenol (two other mycotoxins commonly found in maize and groundnuts) mediate intestinal damage similar to environmental enteropathy (Smith, Stoltzfus, and Prendergast 2012). Environmental enteropathy is characterized by increased gut permeability, which is a disruption of the tight junctions that allow the membranes of intestinal cells lining the gut to form an impermeable barrier, and villous atrophy, which is erosion of the microscopic, finger-like tentacles that line the wall of the small intestine, reducing the surface area by leaving a virtually flat surface. This condition leads to chronic systemic immune activation and malabsorption of nutrients, which in turn may lead to growth retardation.

Solutions

Human exposure to aflatoxins can be reduced by improved cropping, harvesting, and storage practices and by switching to crops or foods less prone to aflatoxin contamination. The adverse effect of aflatoxins in the body can be mitigated through food additives that bind aflatoxins in the gut and through chemopreventive agents that reduce the toxicity of aflatoxins.

Food additives operate as "enterosorbents" that trap aflatoxins in the gastrointestinal (GI) tract. A well-studied example is calcium montmorillonite clay (marketed as NovaSil), which binds aflatoxins in the GI tract and consequently reduces its bioavailability. A clinical trial in which Ghanaian adults were given a placebo, either a 1.5- or 3-gram clay capsule, daily for three months led to a net reduction in serum aflatoxin levels of 21 percent and 24 percent, respectively, in the low- and high-dose groups (Wang et al. 2008). Whether this reduction is sufficient to result in meaningful improvements in linear growth (should the association between aflatoxin exposure and growth be found to be causal) is unknown. An important

concern is the clay's capacity to bind micronutrients, which might reduce their bioavailability in the gut and hence lead to or aggravate micronutrient deficiencies. The treatment in the Ghana study was not associated with reductions in serum micronutrient levels (Afriyie-Gyawu et al. 2008), but the intervention period was relatively short, which might have allowed homeostatic mechanisms to maintain serum micronutrient levels. NovaSil has not been tested in pregnant women and young children who are particularly prone to micronutrient deficiencies.

Chemopreventive agents such as chlorophyllin (a derivative of chlorophyll) and oltipraz (an antischistosomal drug) have been found to intervene in the biochemical pathway linking liver cancer to aflatoxin exposure. To what extent these chemopreventive agents might be relevant in mitigating the effect of aflatoxins on linear growth retardation is not known.

An important consideration when promoting the use of enterosorbents or chemopreventive agents at scale is to make sure that they are not interpreted as a substitute for good crop husbandry and that they do not unintentionally encourage the use of foods not fit for human consumption.

Conclusion

The current evidence suggests that aflatoxins are a likely cause of linear growth retardation in children. Controlled intervention studies are needed, however, to unambiguously establish the causal relationship and to quantify to what extent the current level of aflatoxin exposure contributes to the global burden of stunting. These studies also need to evaluate if reducing exposure remedies the functional correlates of stunting (such as delays in cognitive development and future economic productivity). Given the known carcinogenicity and acute toxicity of aflatoxins, preventive measures aimed at lowering aflatoxin exposure of children in the womb and of young children should be taken irrespective of the findings of these studies.

FOR FURTHER READING

- Khlanguiset, P., G.S. Shephard, and F. Wu F. 2011. "Aflatoxins and Growth Impairment: A Review." *Critical Reviews in Toxicology* 41 (9): 740–755.
- Smith, L. E., R.J. Stoltzfus, A. Prendergast. 2012. "Food Chain Mycotoxin Exposure, Gut Health, and Impaired Growth: A Conceptual Framework." *Advances in Nutrition* 3: 526–531.

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