Paratuberculosis and Crohn's disease: Premises and open questions

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Mycobacteria and some other bacteria are sources of peptidoglycans, the parent compounds for muramyldipeptide (MDP), a potent immunomodulator.

N-glycolyl-MDP (derived from mycobacteria) has a greater NOD2-stimulating activity than N-acetyl MDP (derived from other bacterial species).

The participation of MDPs in immunomodulation (Freund adjuvans), in inflammatory processes and autoimmune and autoinflammatory diseases is well documented.

Paratuberculosis in ruminants differs from similar diseases in non-ruminants, omnivores and primates by virtue of its extraordinarily potent production of huge numbers of mycobacteria. A speculative reason may lie in differing metabolisms, different immunological pathways or different microbioms.

The pathogenesis of both paratuberculosis in ruminants and Crohn's disease can be triggered by several different pathways in different species and in individuals of the same species. Genetic factors, innate and adaptive immunity are well described; the participation of mycobacteria is hypothesized, with good grounds, but cannot be experimentally proven in humans.

Some other factors may play a role in Crohn's disease etiology:

- exposure to mycobacteria at different stages of life
- exposure to different species of mycobacteria
- exposure to differing numbers of mycobacteria for differing time spans
- exposure to live or dead mycobacteria
- interval between successive exposures
- coincidence of exposure with other diseases or factors like stress, starvation, gravidity
- differing modes of exposure (ingestion or inspiration) or a combination of different modes

Crohn's disease can likely be triggered by other bacteria or viruses which interact with the relevant pathogen recognition or NOD-like receptors. Crohn's disease is hypothesized to be linked with several infectious diseases, in the course of which high numbers of cells can be replicated.

Non-tuberculous mycobacteria including causal agent of paratuberculosis in milk and dairy products, in meat, in water from household plumbing, in bottled table and mineral water, in indoor and open swimming pools, in rivers and lakes, in aerosols inspired during showering, baby swimming or bathing, or in the vicinity of polluted rivers are not yet considered to be a risk. Thus, no legal limits for mycobacteria exist which could at least enable the removal of highly contaminated foods from distribution.

The number of mycobacterial cells in milk, meat, dairy and beef products and in tap water can be in the order of 10^4 per gram. Eight million cells in one package consumed by a baby over the course of one week, sometimes augmented by mycobacteria from tap water, represent a heavy load of triggers.

A premise of the importance of both live and dead cells as possible triggers of Crohn's disease does not run counter to prevailing hypotheses regarding the etiology of Crohn's disease:

- infectious, caused by different pathogens
- hygiene hypothesis, with the availability of hot water from communal distribution
- cold chain hypothesis
- the protective effect of breast feeding as an opposite to formula feeding
- the resistance of some ethnic groups (Canadian Indians, Maoris in New Zealand, Gypsies in Hungary and Palestinians in Israel) or social groups with higher dispositions (city residents, those from higher social strata, immigrants to western countries from countries with a low prevalence) also chimes with the above, given that these groups have different approaches to breast and formula feeding of babies, to burger consumption, to showering and bathing using household plumbing.

Many authors have noted the parallel increase in the incidence of Crohn's disease and paratuberculosis. The exact data on Crohn´s disease sufferers are available in the Czech Republic. The index 2011/1995 is 5.0, 4.9 and 11.6 for age categories 0-19, 20-64 and 65+, respectively. Irrespective of age the total number of Crohn's disease patients has increased 5.3 fold over the course of 16 years. Unfortunately, similarly exact data for paratuberculosis in cattle are not available. However, until 1990 paratuberculosis was unknown due to the near complete isolation of the country from the world animal market. Subsequently, the borders were suddenly opened both for the import of heifers from highly infected western countries and for the import of dairy and meat products including baby foods and dried milk for formula feeding. The paratuberculosis prevalence is now estimated to be similar to western countries.

Paratuberculosis in cattle is in many parameters different from other infectious or emerging diseases:

- Several years can pass from the first contact with an agent which causes either latent infection or some sensitization or immunomodulation, and clinical signs of the disease.
- Shedding of mycobacteria or antibodies in serum is not in direct relation with clinical signs of the disease.
- Paratuberculosis is not thought by farmers and veterinary authorities to be very important despite the economical losses calculated.
- A possible zoonotic link is ignored despite the well documented and published data including meta-analyses on microbial triggers of chronic human illnesses.
- Culture of mycobacteria requires four to six or more months; some strains of causal agents of paratuberculosis are uncultivable in vitro as well. The diagnosis can be shortened using sophisticated expensive instrumentation or molecular methods, which are able not only to detect, but also quantify some mycobacterial species including causal agents of paratuberculosis and avian mycobacteriosis; but they are also rather expensive. Unfortunately, most methods are not sensitive or diagnosis fails due to the irregular shedding of mycobacteria or their ability to lose their cell wall.

Control and eradication of paratuberculosis is possible, but requires a heavy investment of both time and money. The herd must be closed, individual faecal or pooled samples periodically checked and shedders including progenies immediately culled. Alternatively ELISA of milk or blood serum, analysis of milk filters, bulk tank milk, environmental samples or liquid dung can be evaluated.

Complete eradication of mycobacteria from the environment, water and food is not a realistic aim. However, the following should be required:

- To consider paratuberculosis and mycobacteria as real public health threat.
- To develop methods for simple determination of mycobacteria in water, milk, and meat in concentration over the limit and to remove foods contaminated over the limit from distribution.
- To preferentially use milk and beef free from causal agent of paratuberculosis (or contaminated less than some lower than general limit) for the production of baby foods or foods for people at the highest risk (suffering from Crohn's disease or relatives of such patients).
- To explain the importance of breast feeding for four to six months (mothers suffering from Crohn's disease should be sure that their milk is mycobacteria-free).
- To widely introduce a method for the determination of mycobacteria in household plumbing and shower heads. If tap water is contaminated a suitable alternative (bottled or filtered water) should be available.
- To prepare legal measures for mycobacterial control of water in bottling plants, in food producing plants and in public swimming pools, especially those also used for babies.

All these issues are very sensitive for public including farmers, producers and market. Well prepared information must be available and public panic should be avoided. Unfortunately, general support from state budgets cannot be expected. Some measures require global understanding and realization, e.g., in baby food production. Producers should be aware that the solving of these problems is also in their own interest and not only in the interest of consumers.

PDF document can be downloaded for printing.

Comments and questions will be appreciated.
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