Para tuberculosis and its Link to Human Disease

Burhan Nabi and Sanober Rasool
Department of Veterinary Clinical Complex, KCVAS, Amritsar, Punjab
Department of Veterinary and Animal Husbandry Extension Education, KCVAS, Amritsar,Punjab

Introduction

Paratuberculosis, also known as Johne's disease, is a chronic infectious disease affecting domestic and wild ruminants. It is caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), a slow-growing, acid-fast bacterium that primarily infects the intestines of affected animals (Nabi et al., 2024). The disease leads to significant economic losses in the livestock industry due to reduced milk production, weight loss, and premature culling (Feller et al., 2007).

In addition to its effects on animal health, Johne's disease has been related to Crohn's disease in humans (Behr & Kapur, 2008, Nabi et al., 2024). Concerns regarding the zoonotic potential of MAP have been raised by multiple investigations that found it in the intestinal tissues, blood, and breast milk of individuals with Crohn's disease (Whittington & Marshall, 2021). However, there is still debate over the exact involvement of MAP in Crohn's disease, necessitating further research (Feller et al., 2007).

Causative Agent and Pathogenesis

MAP is a hardy bacterium that can persist in soil and water for extended periods, making it difficult to eradicate from contaminated environments (Grant, 2017). Infection occurs primarily through ingestion of MAP-contaminated feed, water, or milk, with young animals being the most susceptible (Behr & Kapur, 2008). Once inside the host, MAP invades the intestinal mucosa, replicates within macrophages, and induces a chronic granulomatous enteritis, leading to progressive tissue damage (Chiodini, 1989, Whittington & Marshall, 2021).

Clinical Signs in Ruminants

- Chronic diarrhea that is often watery but lacks blood or mucus (Grant, 2017).
- Progressive weight loss despite a normal appetite, leading to emaciation (Feller et al., 2007).
- Reduced milk production in dairy cattle, leading to economic losses (Whittington & Marshall, 2021).
- Poor growth and infertility in affected breeding animals (Behr & Kapur, 2008).

Johne's disease has no effective treatment, making prevention and control measures

crucial for limiting its spread in livestock populations (Feller et al., 2007).

MAP and Human Health: The Crohn's Disease Connection

Crohn's disease is a chronic inflammatory bowel disorder characterized by relapsing intestinal inflammation, diarrhoea, abdominal pain, and weight loss (Chiodini, 1989). Its pathology shares striking similarities with Johne's disease in cattle, prompting researchers to investigate MAP as a potential causative agent (Behr & Kapur, 2008).

Several key findings support a possible association between MAP and Crohn's disease:

1. **Detection of MAP in Crohn's Disease Patients**

MAP DNA and viable bacteria have been isolated from intestinal tissues, blood, and breast milk of Crohn's patients (Grant, 2017).

Higher MAP detection rates in Crohn's disease patients compared to non-IBD individuals suggest an association (Feller et al., 2007).

2. **Transmission Pathways to Humans**

Dairy and Meat Consumption: MAP has been detected in raw and pasteurized milk, suggesting potential foodborne exposure (Whittington & Marshall, 2021).

Waterborne Transmission: MAP is highly resistant to chlorination and can persist in water supplies, posing a public health risk (Grant, 2017).

Occupational Exposure: Farmers, veterinarians, and dairy workers who handle infected animals may be at an increased risk of MAP infection (Behr & Kapur, 2008).

3. **Immune Response and Genetic Susceptibility**

Crohn's patients exhibit an immune response to MAP, supporting the hypothesis that the bacterium may contribute to disease progression (Feller et al., 2007).

Genetic susceptibility factors may play a role, as not all Crohn's patients test positive for MAP (Chiodini, 1989).

Controversy and Research Gaps

The potential link between *Mycobacterium avium* subsp. *paratuberculosis* (MAP) and Crohn's disease in humans remains one of the most debated topics in medical and veterinary research. While several studies have identified MAP in Crohn's patients, significant scientific uncertainties, conflicting findings, and methodological challenges prevent the establishment of a definitive causal relationship. The key areas of controversy and research gaps include:

1. **Incomplete Fulfilment of Koch's Postulates**

Koch's postulates are a set of criteria used to determine whether a microorganism is the cause of a specific disease. For MAP to be confirmed as the causative agent of

Crohn's disease, it must:

a) Be present in all cases of the disease.
b) Be isolated from diseased individuals and grown in pure culture.
c) Cause the disease when introduced into a healthy host.
d) Be re-isolated from the experimentally infected host.

Although MAP has been detected in Crohn's disease patients, it is not found in all cases, nor does every individual carrying MAP develop Crohn's disease. Additionally, experimentally infecting animal models with MAP does not always replicate Crohn's disease pathology, failing to fully satisfy Koch's postulates (Grant, 2017).

2. Inconsistent Detection of MAP in Crohn's Patients

One of the major issues in proving MAP's role in Crohn's disease is the inconsistent detection of the bacterium in affected individuals. While some studies report MAP presence in 40-90% of Crohn's patients, others find little or no association (Feller et al., 2007). Variability in detection rates can be attributed to:

- Differences in diagnostic techniques (PCR, culture, histopathology).
- Challenges in culturing MAP, as it is a slow-growing bacterium requiring months to isolate.
- Variability in study populations, with geographic and genetic differences potentially influencing MAP prevalence.
- Furthermore, MAP has also been found in healthy individuals and patients with ulcerative colitis (another inflammatory bowel disease), suggesting that its presence alone may not be sufficient to cause disease (Whittington & Marshall, 2021).

3. Genetic and Immune System Variability

Not all individuals exposed to MAP develop Crohn's disease, suggesting that host factors, including genetics and immune responses, play a crucial role. Specific genetic mutations, such as those in the NOD2 gene, have been associated with increased susceptibility to Crohn's disease (Behr & Kapur, 2008). However, this genetic predisposition does not explain why some genetically susceptible individuals do not develop the disease, even when exposed to MAP.

Additionally, differences in immune system responses may influence whether MAP infection leads to chronic inflammation. Some researchers argue that Crohn's disease may result from an abnormal immune reaction to gut microbiota, where MAP is only a secondary player rather than a primary cause (Feller et al., 2007).

4. Alternative Causes of Crohn's Disease

Crohn's disease is a multifactorial condition, with several potential triggers beyond MAP, including:

- Dysbiosis of gut microbiota: Altered composition of gut bacteria has been implicated in Crohn's disease, independent of MAP infection (Grant, 2017).

- Dietary and environmental factors: Processed foods, Western diets, and urban lifestyles have been linked to increased Crohn's disease incidence.
- Autoimmune mechanisms: Some researchers propose that Crohn's disease is an autoimmune disorder where the body mistakenly attacks the gut lining (Behr & Kapur, 2008).
- The complexity of Crohn's disease etiology makes it difficult to isolate MAP as the primary cause, further complicating the debate.

5. Lack of Effective MAP-targeted Treatments for Crohn's Disease

If MAP were the causative agent of Crohn's disease, antibiotics targeting mycobacteria (such as clarithromycin, rifabutin, and clofazimine) should lead to significant improvement or cure. However, while some patients respond well to anti-MAP therapy, others show little or no benefit (Whittington & Marshall, 2021). The variability in treatment responses raises doubts about whether MAP is truly driving the disease or simply present as an opportunistic pathogen.

6. Need for Large-scale, Longitudinal Studies

Most studies investigating MAP and Crohn's disease are retrospective (analysing past cases) rather than prospective (tracking individuals over time to establish causation). Large-scale longitudinal studies tracking individuals from early life, monitoring MAP exposure, and assessing Crohn's disease development would provide stronger evidence for or against a causal link. However, such studies require significant time, funding, and coordination (Feller et al., 2007).

7. Future Research Directions

To resolve these controversies, future research should focus on:

1. Standardizing diagnostic methods to improve MAP detection accuracy.
2. Conducting large-scale epidemiological studies to assess MAP's role in Crohn's disease more conclusively.
3. Investigating host immune responses to determine whether MAP is a trigger or merely a bystander in Crohn's disease pathogenesis.
4. Developing MAP-targeted therapies and vaccines to assess whether preventing MAP infection reduces Crohn's disease incidence.
5. Potential vaccine research to control MAP infection in livestock and reduce the risk of human exposure (Behr & Kapur, 2008).

Public Health Implications and Future Directions

Given the potential zoonotic risk of MAP, precautionary measures are warranted (Whittington & Marshall, 2021).

1. Control Strategies in Livestock

Herd Testing and Culling: Regular screening of livestock for MAP infection to prevent its spread (Behr & Kapur, 2008).

2. Pasteurization of Milk

Although MAP can survive standard

pasteurization, ensuring optimal heat treatment can reduce exposure risks (Grant, 2017).

3. **Improved Biosecurity Measures**

Proper manure management and hygiene practices can minimize environmental contamination (Feller et al., 2007).

Conclusion

The link between animal paratuberculosis and human Crohn's disease remains an area of active investigation. While MAP has been detected in Crohn's patients and various food sources, conclusive proof of its role in disease causation is still lacking. Given the potential risks, continued efforts in MAP control, food safety, and research are essential for protecting both animal and human health. Until further research provides clearer answers, the debate over MAP's role in Crohn's disease will continue.

References

1. Behr, M. A., & Kapur, V. (2008). The evidence for Mycobacterium avium subsp. paratuberculosis in Crohn's disease. Current Opinion in Gastroenterology, 24(1), 17-21.
2. Chiodini, R. J. (1989). Crohn's disease and the mycobacterioses: a review and comparison of two disease entities. Clinical Microbiology Reviews, 2(1), 90-117.
3. Feller, M., Huwiler, K., Stephan, R., et al. (2007). Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. The Lancet Infectious Diseases, 7(9), 607-613.
4. Grant, I. R. (2017). Zoonotic potential of Mycobacterium avium subsp. paratuberculosis: the current position. Journal of Applied Microbiology, 123(3), 632-657.
5. Nabi B, Upadhyay SR, Singh SV, Rasool S, Najar AA, Singh R, Yousuf J, Yousuf R and Lone IM, 2024. Haemato-biochemical and oxidative stress evaluation in Beetal goats naturally infected with Mycobacterium avium subsp. paratuberculosis in Sub-Himalayan region of India. Indian J Anim Health, 63(2): 298-302.
6. Whittington, R. J., & Marshall, D. J. (2021). Mycobacterium avium subsp. Para tuberculosis—A food borne pathogen? Microorganisms, 9(9), 1847.