Patient

View this article online at: patient.info/doctor/whipples-disease

Whipple's disease

What is Whipple's disease?

A chronic, relapsing multisystem disease first described in 1907 by George Hoyt Whipple, an American pathologist.[1] He described the disease as an intestinal lipodystrophy characterised by:

- Weight loss.
- Chronic cough.
- Fat accumulation in the intestine, mesenteric lymph nodes and stool.

Whipple hypothesised that the condition was due to an infectious agent, but this was only fully identified in 1992. It is now thought to be due to infection with the actinomycete *Tropheryma whipplei,* combined with defective cell-mediated immunity.[2] It is probably acquired as an enteric infection as this organism is commonly found in sewage effluent. It has also been detected in soil and is presumed to be ubiquitous.[3] [4]

Traditionally, Whipple's disease has presented a diagnostic challenge, both to clinicians and to pathologists.[5] [6]

How common is Whipple's disease? (Epidemiology)

Whipple's disease is an extremely rare condition. Incidence is estimated as between 1 to 6 cases per 1,000,000 people, per annum, globally. Its prevalence is estimated as 1.1 per million.[7]

Risk factors[7]

Upon infection with *T whipplei*, most people clear the infection completely, a small number become asymptomatic carriers, and only a discrete group of people go on to develop Whipple's disease. Whipple's disease is more common in:

- Middle-age and older individuals (mean age at diagnosis is 55 years).
- Men (85% of cases are in men).
- White people.
- Family clusters (suggesting an immunogenetic component).
- Certain geographic locations: most cases of Whipple's disease are diagnosed in Western Europe and North America.
- HLA-B27 antigen; HLA-DRB1*13 and DQB1*06 alleles.[8]
- Sewage plant workers, farmers and agricultural workers.

Symptoms of Whipple's disease (presentation)[5] [9] [7]

Not everyone with infection develops symptoms, supporting the thought that a defect in cellular immune response may predispose certain individuals.[3]

Whipple's disease may cause many different issues, due to the involvement of several organs. These include:

- Polyarthralgia - transient and episodic (often a prodromal symptom).
- Gastrointestinal symptoms - resembling other malabsorption syndromes:
    - Abdominal pain.
    - Diarrhoea.
    - Anorexia and weight loss.
    - Distension.
    - Flatulence.
    - Steatorrhea (due to malabsorption).
    - Gastrointestinal bleeding.

- Intermittent low-grade fever.
- Chronic cough.
- Hyperpigmentation (occurs in 50%).

There may also be:

- Generalised lymphadenopathy.
- Anaemia and, more rarely, clotting abnormalities.
- Cardiac involvement - pericarditis, myocarditis, valve lesions.
- Central nervous system (CNS) involvement in 10% - headache, confusion, dementia, ophthalmoplegia, myoclonus, oculomasticatory movements (convergent eye movements with simultaneous chewing movements), gait abnormalities, seizures, coma.
- Ocular involvement - uveitis, vitritis, keratitis, retinitis, retinal haemorrhages.
- Pulmonary involvement - pleural effusion, mediastinal widening (due to lymphadenopathy).
- Protein-losing enteropathy with hypoalbuminaemia and oedema (due to protein loss).
- Skin involvement - very rare; may be due to malnutrition or an immune reaction to *T. whipplei* leading to conditions including eczematous plaques, psoriasis and erythema nodosum.[10]

Differential diagnosis[11]

- AIDS with *Mycobacterium avium* complex infection of the small intestine.
- Coeliac disease.
- Sarcoidosis.
- Reactive arthritis.
- Familial Mediterranean fever.
- Behçet's disease.

- Intestinal lymphoma.
- Inflammatory bowel disease.
- Tuberculosis.

Investigations [7] [12]

Given its rarity, wide spectrum of symptoms, and an absence of pathognomic clinical signs, diagnosis is very challenging, and requires a high index of clinical suspicion:

- Routine blood and malabsorption tests are nonspecific.
- Imaging will confirm involvement of different organs but is not diagnostic.
- Biopsy of affected tissue, usually the duodenum, shows infiltration of the lamina propria with periodic acid-Schiff stain (PAS)-positive macrophages with intracellular clumps of *T. whipplei*. Supplementary staining with anti-*T whipplei* antibodies or Ziehl-Neelsen staining is recommended, as other bacteria, such as *Mycobacterium avium*, also stain PAS-positive.
- PCR of bacterial RNA (unique 16s rRNA sequence) is increasingly used in diagnosis and can be done from peripheral blood, CSF and other tissue samples. [13]

Management of Whipple's disease [9]

- Antibiotics are the main treatment. [14] Expert microbiological advice will be needed. Prolonged treatment for 1-2 years is usually advised.
- Repeat PCR at the end of treatment.

Prognosis

- Insidious progression and fatal if untreated.
- Locomotor and gastrointestinal symptoms may improve very rapidly with treatment but histological and microbiological remission can take several years.

- Follow up closely for signs of recurrence - there is relapse in about 40%.[9]

References

1. Fenollar F, Puechal X, Raoult D; Whipple's disease. N Engl J Med. 2007 Jan 4;356(1):55-66.
2. Desnues B, Ihrig M, Raoult D, et al; Whipple's disease: a macrophage disease.; Clin Vaccine Immunol. 2006 Feb;13(2):170-8.
3. Deriban G, Marth T; Current concepts of immunopathogenesis, diagnosis and therapy in Whipple's Curr Med Chem. 2006;13(24):2921-6.
4. Schneider T, Moos V, Loddenkemper C, et al; Whipple's disease: new aspects of pathogenesis and treatment. Lancet Infect Dis. 2008 Mar;8(3):179-90.
5. Rakshit RC, Mackay JD; A diagnostic conundrum.; Postgrad Med J. 2003 Sep;79(935):540, 545-6.
6. Mahnel R, Marth T; Progress, problems, and perspectives in diagnosis and treatment of Whipple's disease.; Clin Exp Med. 2004 Sep;4(1):39-43.
7. Boumaza A, Ben Azzouz E, Arrindell J, et al; Whipple's disease and Tropheryma whipplei infections: from bench to bedside. Lancet Infect Dis. 2022 Oct;22(10):e280-e291. doi: 10.1016/S1473-3099(22)00128-1. Epub 2022 Apr 12.
8. Martinetti M, Biagi F, Badulli C, et al; The HLA alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. Gastroenterology. 2009 Jun;136(7):2289-94. Epub 2009 Jan 27.
9. Amendolara M, Barbarino C, Bucca D, et al; Whipple's disease infection surgical treatment: presentation of a rare case and literature review. G Chir. 2013 Apr;34(4):117-21.
10. Schaller J, Carlson JA; Erythema nodosum-like lesions in treated Whipple's disease: signs of immune J Am Acad Dermatol. 2009 Feb;60(2):277-88.
11. Murray JA, Rubio-Tapia A; Diarrhoea due to small bowel diseases. Best Pract Res Clin Gastroenterol. 2012 Oct;26(5):581-600. doi: 10.1016/j.bpg.2012.11.013.
12. Manufacturer's PIL, Calcichew® 500 mg Chewable Tablets; Manufacturer's PIL, Calcichew® 500 mg Chewable Tablets, Shire Pharmaceuticals Limited, electronic Medicines Compendium. Dated January 2009, accessed February 2010.
13. Yajima N, Wada R, Kimura S, et al; Whipple disease diagnosed with PCR using formalin-fixed paraffin-embedded specimens of the intestinal mucosa. Intern Med. 2013;52(2):219-22. Epub 2013 Jan 15.
14. Basagiannis CS, Panagoulias GS, Tentolouris N, et al; Whipple disease. South Med J. 2010 Apr;103(4):353-6.

Last updated by: Dr Doug McKechnie, MRCGP 22/05/2023	
Peer reviewed by: Dr Colin Tidy, MRCGP 22/05/2023	**Next review date:** 12/05/2028

View this article online at: patient.info/doctor/whipples-disease

Discuss Whipple's disease and find more trusted resources at Patient.