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| |  | | --- | | HAEMOCHROMATOSIS |  |  | | --- | | Haemochromatosis is a condition in which the amount of total body iron is increased; the excess iron is deposited in and causes damage to several organs including the liver. It may be primary or secondary to other diseases ([Box 23.53](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023053#B023053)). |  |  | | --- | | HEREDITARY (PRIMARY) HAEMOCHROMATOSIS |  |  | | --- | | 23.53 CAUSES OF HAEMOCHROMATOSIS |      |  | | --- | | **Primary haemochromatosis** |  |  | | --- | | * Heriditary haemochromatosis * Congenital acaeruloplasminaemia * Congenital atransferrinaemia |  |  | | --- | |  | |
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| **Secondary iron overload** |

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| * Parenteral iron-loading (e.g. repeated blood transfusion) * Iron-loading anaemia (thalassaemia, sideroblastic anaemia, pyruvate kinase deficiency) * Liver disease * Dietary iron overload (prolonged oral iron therapy) |

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**Complex iron overload**

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| * Juvenile haemochromatosis * Neonatal haemochromatosis * Alcoholic liver disease * Porphyria cutanea tarda * African iron overload (Bantu siderosis) |

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| In this disease iron is deposited throughout the body and total body iron may reach 20-60 g (normally 4 g). The important organs involved are the liver, pancreatic islets, endocrine glands and heart. In the liver, iron deposition occurs first in the periportal hepatocytes, extending later to all hepatocytes. The gradual development of fibrous septa leads to the formation of irregular nodules, and finally regeneration results in macronodular cirrhosis. An excess of liver iron can occur in alcoholic cirrhosis but this is mild by comparison with haemochromatosis. |

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| Aetiology |

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| Hereditary haemochromatosis (HHC) is caused by increased absorption of dietary iron and is inherited as an autosomal recessive gene located on chromosome 6. Approximately 90% of patients have a single-point mutation resulting in a cysteine to tyrosine substitution at position 282 (C282Y) in a protein (HFE) with structural and functional similarity to the human leucocyte antigen (HLA) proteins. The exact function of the HFE protein in regulating iron absorption is not known. However, it is believed that HFE is absent from the basolateral membrane of intestinal epithelial cells, where it normally interacts with the transferrin receptor. This defect in uptake of transferrin-associated iron may lead to up-regulation of enterocyte iron-specific divalent metal transporters and excessive iron absorption. A histidine to aspartic acid mutation at position 63 (H63D) in HFE causes a less severe form of haemochromatosis that is most commonly found in patients who are compound heterozygotes also carrying a C282Y mutated allele. Fewer than 50% of C282Y homozygotes will develop clinical features of haemochromatosis; therefore other factors must also be important. Iron loss in menstruation and pregnancy may protect females, as 90% of patients are male. |

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| Clinical features |

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| Symptomatic disease usually presents in men aged 40 years or over with features of hepatic cirrhosis (especially hepatomegaly), diabetes mellitus or heart failure. Tiredness, fatigue and arthropathy are early symptoms. Leaden-grey skin pigmentation due to excess melanin occurs, especially in exposed parts, axillae, groins and genitalia; hence the term 'bronzed diabetes'. Impotence, loss of libido, testicular atrophy and arthritis with chondrocalcinosis secondary to calcium pyrophosphate deposition are also common. Cardiac failure or cardiac dysrhythmia may complicate heart muscle disease. |

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| Investigations |

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| The serum ferritin is greatly increased; the plasma iron is also increased, with a highly saturated plasma iron-binding capacity. CT may show features suggesting excess hepatic iron. The diagnosis is confirmed by liver biopsy, which shows heavy iron deposition and hepatic fibrosis which may have progressed to cirrhosis ([Fig. 23.32](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@id=hc023183.htm)). The iron content of the liver can be measured directly. Both the C282Y and H63D mutations can be identified by genetic testing. |

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| Management |

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| Treatment consists of weekly venesection of 500 ml blood (250 mg iron) until the serum iron is normal; this may take 2 years or more. Thereafter, venesection is continued as required to keep the serum ferritin normal. Liver and cardiac problems improve after iron removal, but joint pain is less predictable and can improve or worsen after iron removal. Diabetes mellitus does not resolve after venesection. Other therapy includes that for cirrhosis and diabetes mellitus. First-degree family members should be investigated, preferably by genetic screening and also by checking the plasma ferritin and iron-binding saturation. Liver biopsy is only indicated in asymptomatic relatives if the LFTs are abnormal and/or the serum ferritin is greater than 1000 μg/l because these features are associated with significant fibrosis or cirrhosis. Asymptomatic disease should also be treated by venesection until the serum ferritin is normal. |

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| Prognosis |

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| Pre-cirrhotic patients with HHC have a normal life expectancy; even cirrhotic patients have a relatively good prognosis, compared with other forms of cirrhosis (three-quarters of patients are alive 5 years after diagnosis). This is probably because liver function is usually well preserved at diagnosis and improves with therapy. Screening for hepatocellular carcinoma ([p. 984](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=p0984#P0984)) is mandatory because this is the main cause of death, affecting about one-third of patients with cirrhosis irrespective of therapy. |

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| ACQUIRED IRON OVERLOAD (SECONDARY HAEMOCHROMATOSIS) |

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| Many conditions, including chronic haemolytic disorders, sideroblastic anaemia, other conditions requiring multiple blood transfusion (generally over 50 litres), porphyria cutanea tarda, dietary iron overload and occasionally alcoholic cirrhosis, are associated with widespread secondary siderosis. The features are similar to primary haemochromatosis, but the history and clinical findings point to the true diagnosis. Some patients are heterozygotes for the primary haemochromatosis gene and this may contribute to the development of iron overload. |
| WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION) |

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| Wilson's disease is a rare but important autosomal recessive disorder of copper metabolism that is caused by a variety of mutations in the gene ATP7B on chromosome 13. Total body copper is increased, with excess copper deposited in, and causing damage to, several organs. |

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| Aetiology and pathology |

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| Normally dietary copper is absorbed from the stomach and proximal small intestine and is rapidly taken into the liver, where it is stored and incorporated into caeruloplasmin, which is secreted into the blood. The accumulation of excessive copper in the body is ultimately prevented by its excretion, the most important route being via the bile. In Wilson's disease, there is almost always a failure of synthesis of caeruloplasmin; however, some 5% of patients have a normal circulating caeruloplasmin concentration and this is not the primary pathogenic defect. The amount of copper in the body at birth is normal, but thereafter it increases steadily; the organs most affected are the liver, basal ganglia of the brain, eyes, kidneys and skeleton. |

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| The gene responsible for Wilson's disease (ATP7B, chromosome 13) encodes a member of the copper-transporting P-type adenosine triphosphatase family, which functions to export copper from the various cell types. At least 200 different mutations have been described. Although most of the mutations are rare, their relative frequency varies in different populations. The histidine to glucine single-base mutation at position 1069 is most common in Polish and Austrian patients, but rare in India, other Asian countries and Sardinia. In contrast, approximately 60% of Sardinian patients have a 15 nucleotide deletion in the 5' untranslated region of the Wilson's gene. Most cases are compound heterozygotes with two different mutations in the Wilson's gene. Attempts to correlate the genotype with the mode of presentation and clinical course have not shown any consistent patterns. |

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| Clinical features |

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| Symptoms usually arise between the ages of 5 and 45 years. Hepatic disease occurs predominantly in childhood and early adolescence, although it can present in adults in their fifties. Neurological damage causes basal ganglion syndromes and dementia which tends to present in later adolescence. These features can occur alone or simultaneously. Other manifestations include renal tubular damage and osteoporosis, but these are virtually never presenting features. |

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| Liver disease |

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| This can manifest in many ways which are not specific. Episodes of acute hepatitis, sometimes recurrent, can occur, especially in children, and may progress to acute fulminant liver failure. The latter is characterised by the liberation of free copper into the blood stream, causing massive haemolysis and renal tubulopathy. Chronic hepatitis can also develop insidiously and eventually present with established cirrhosis; liver failure and portal hypertension may supervene. Recurrent acute hepatitis of unknown cause, especially when accompanied by haemolysis, or chronic liver disease of unknown cause in a patient under 40 years old suggests Wilson's disease. |

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| Neurological disease |

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| Clinical features include a variety of extrapyramidal features, particularly tremor, choreoathetosis, dystonia, parkinsonism and dementia ([p. 1216](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=p1216#P1216)). Unusual clumsiness for age may be an early symptom. |

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| Kayser-Fleischer rings |

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| These are the most important single clinical clue to the diagnosis and can be seen in 60% of adults with Wilson's disease (less often in children but almost always in neurological Wilson's disease), albeit sometimes only by slit-lamp examination. Kayser-Fleischer rings are characterised by greenish-brown discoloration of the corneal margin appearing first at the upper periphery ([Fig. 23.33](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@id=hc023192.htm)). They eventually disappear with treatment. |

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| Investigations |

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| A low serum caeruloplasmin is the best single laboratory clue to the diagnosis. However, advanced liver failure from any cause can reduce the serum caeruloplasmin, and occasionally it is normal in Wilson's disease. Other features of disordered copper metabolism should therefore be sought; these include a high free serum copper concentration, a high urine copper excretion of greater than 0.6 μmol/24 hrs and a very high hepatic copper content. Measuring 24-hour urinary copper excretion whilst giving D-penicillamine is a useful confirmatory test; more than 25 μmol/24 hrs is considered diagnostic of Wilson's disease. |

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| Genetic testing is limited by the existence of multiple genetic defects, but may be useful in screening families once the abnormality has been identified in an affected individual. |

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| Management |

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| The copper-binding agent penicillamine is the drug of choice. The dose given must be sufficient to produce cupriuresis and most patients require 1.5 g/day (range 1-4 g). The dose can be reduced once the disease is in remission but treatment must continue for life, even through pregnancy. Care must be taken to ensure that reaccumulation of copper does not occur. Abrupt discontinuation of treatment must be avoided because this may precipitate acute liver failure. Toxic effects of penicillamine occur in one-third of patients and include rashes, protein-losing nephropathy, lupus-like syndrome and bone marrow depression. If these do occur, trientine dihydrochloride (1.2-2.4 g/day) and zinc (50 mg 8-hourly) are alternative effective therapies. |

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| Liver transplantation is indicated for fulminant liver failure or for advanced cirrhosis with liver failure. The value of liver transplantation in severe neurological Wilson's disease is highly controversial. |

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| Prognosis |

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| The prognosis is excellent, provided treatment is started before there is irreversible damage. Siblings and children of patients with Wilson's disease must be investigated and treatment should be given to all infected individuals, even if they are asymptomatic |

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| ALPHA1-ANTITRYPSIN DEFICIENCY |

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| Alpha1-antitrypsin (α1-AT) is a serine protease inhibitor (Pi) produced by the liver. The form of α1-AT is genetically determined, and one of these forms (PiZ) cannot be secreted into the blood by liver cells because it is polymerised within the endoplasmic reticulum of the hepatocyte. Homozygous individuals (PiZZ) have low plasma α1-AT concentrations, although globules containing α1-AT are found in the liver, and they may develop hepatic and pulmonary disease ([p. 678](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=p0678#P0678)). Liver disease includes cholestatic jaundice in the neonatal period (neonatal hepatitis) which can resolve spontaneously, chronic hepatitis and cirrhosis in adults, and in the long term hepatocellular carcinoma. There are no clinical features distinguishing liver disease due to α1-AT deficiency from other causes of liver disease, and the diagnosis is made from the low plasma α1-AT concentration and the PiZZ genotype. Alpha1-AT-containing globules can be demonstrated in the liver ([Fig. 23.34](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@id=hc023202.htm)) but this is not necessary to make the diagnosis. Occasionally, patients with liver disease and minor reductions of plasma α1-AT concentrations have α1-AT phenotypes other than PiZZ, such as PiMZ or PiSZ, but the relationship of these genotypes to liver disease is uncertain. No specific treatment is available; the concurrent risk of severe and early-onset emphysema means that all patients should be advised to abandon cigarette smoking. |

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| |  | | --- | | AUTOIMMUNE LIVER DISEASES |  |  | | --- | | AUTOIMMUNE HEPATITIS |  |  | | --- | | Autoimmune hepatitis is a liver disease of unknown aetiology characterised by a strong association with other autoimmune diseases ([Box 23.54](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023054#B023054)), high levels of serum immunoglobulins (hypergammaglobulinaemia) and autoantibodies in the serum. It occurs most often in women, particularly in the second and third decades of life, but may develop in either sex at any age |  |  | | --- | | Aetiology and pathology |  |  | | --- | | 23.54 CONDITIONS ASSOCIATED WITH AUTOIMMUNE HEPATITIS |  |  | | --- | | * Migrating polyarthritis * Urticarial rashes * Lymphadenopathy * Hashimoto's thyroiditis * Thyrotoxicosis * Myxoedema * Coombs-positive haemolytic anaemia * Pleurisy * Transient pulmonary infiltrates * Ulcerative colitis * Glomerulonephritis * Nephrotic syndrome |  |  | | --- | |  |  |  | | --- | | 23.55 FREQUENCY OF AUTOANTIBODIES IN CHRONIC NON-VIRAL LIVER DISEASES AND IN HEALTHY PEOPLE |      |  |  |  |  | | --- | --- | --- | --- | | **Disease** | **Antinuclear antibody (%)** | **Antismooth muscle antibody (%)** | **Antimitochondrial antibody\*** **(%)** | | **Healthy controls** | 5 | 1.5 | 0.01 | | **Autoimmune hepatitis** | 80 | 70 | 15 | | **Primary biliary cirrhosis** | 25 | 35 | 95 | | **Cryptogenic cirrhosis** | 40 | 30 | 15 |  |  | | --- | | \* Patients with antimitochondrial antibody frequently have cholestatic LFTs and may have primary biliary cirrhosis (see text). |  |  | | --- | | Several subtypes of this disorder have been proposed which have differing immunological markers. Classical (type I) autoimmune hepatitis is characterised by a high frequency of other autoimmune disorders such as Graves' disease. Type I autoimmune hepatitis is associated with HLA-DR3 and DR4, particularly HLA-DRB3\*0101 and HLA-DRB1\*0401. These patients have high titres of antinuclear and anti-smooth muscle antibodies but none of these antibodies is cytotoxic. A suggested hypothesis for the development of type I autoimmune hepatitis is the aberrant expression on the hepatocyte of HLA antigen, influenced by viral, genetic and environmental factors. Type II autoimmune hepatitis is characterised by the presence of anti-LKM (liver-kidney microsomal) antibodies and lack of antinuclear and anti-smooth muscle antibodies. Anti-LKM antibodies recognise cytochrome P450-IID6, which is expressed on the hepatocyte membrane. In Type III, serum immunoglobulin levels are elevated whilst the antibodies described above are absent, and antibodies against soluble liver antigen are present. The histopathological features of all forms of autoimmune hepatitis are similar. |  |  | | --- | | Clinical features |  |  | | --- | | The onset is usually insidious, with fatigue, anorexia and jaundice. In about one-quarter of patients the onset is acute, resembling viral hepatitis, but resolution does not occur. This acute presentation can lead to extensive liver necrosis and liver failure. Other features include fever, arthralgia, vitiligo and epistaxis. Amenorrhoea is the rule but general health may be good. Jaundice is mild to moderate or occasionally absent, but signs of chronic liver disease, especially spider naevi and hepatosplenomegaly, are usually present. Some patients have a 'Cushingoid' face with acne, hirsutism and pink cutaneous striae, especially on the thighs and abdomen. |  |  | | --- | | Approximately two-thirds of patients have associated autoimmune disease such as Hashimoto's thyroiditis, renal tubular acidosis and rheumatoid arthritis. |  |  | | --- | | Diagnosis and investigations |  |  | | --- | |  | |  | |  |  |  | | --- | | 23.56 IMMUNOSUPPRESSION IN AUTOIMMUNE HEPATITIS |      |  | | --- | | 'In autoimmune hepatitis treatment with prednisolone ± azathioprine improves serum biochemistry and hepatic histology. It also improves survival at 10 years from 27% to 63% (NNTB 2.7).'   'In patients who have been in remission for more than 1 year, increasing the dose of azathioprine (from 1 to 2 mg/kg) and withdrawing prednisolone reduces steroid side-effects and does not increase the risk of relapse.' |  |  | | --- | | * Kirk AP, et al. Gut 1980; 21:78-83. * Johnson PJ, et al. N Engl J Med 1995; 333:958-963. |  |  | | --- | |  | | | |
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| Serological testing for specific autoantibodies may suggest autoimmune hepatitis ([Box 23.55](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023055#B023055)). However, low titres of these antibodies occur in some healthy people. Antinuclear antibodies also occur in connective tissue diseases and other autoimmune diseases, including various thyroid disorders and pernicious anaemia, while anti-smooth muscle antibody has been reported in infectious mononucleosis and a variety of malignant diseases. Antimicrosomal antibodies (anti-LKM) occur particularly in children and adolescents. Elevated levels of serum IgG immunoglobulins are invariable and are an important diagnostic feature. Liver biopsy typically shows interface hepatitis, with or without cirrhosis. |

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| Management |

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| Treatment with corticosteroids is life-saving in autoimmune hepatitis, particularly during exacerbations of active and symptomatic disease. Initially, prednisolone 40 mg/day is given orally; the dose is then gradually reduced as the patient and LFTs improve. Maintenance therapy is required for at least 2 years after LFTs have returned to normal, and withdrawal of treatment should not be considered unless a liver biopsy is also normal. Azathioprine 1.0-1.5 mg/kg/day orally may allow the dose of prednisolone to be reduced ([Box 23.56](mk:@MSITStore:C:\aDavidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023056#B023056)). Azathioprine can also be used as the sole maintenance immunosuppressive agent. Corticosteroids treat acute exacerbations and do not prevent cirrhosis; they are therefore less important in mild asymptomatic autoimmune hepatitis. |

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| Prognosis |

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| The disease is characterised by exacerbations and remissions, but most patients eventually develop cirrhosis and its complications. Hepatocellular carcinoma is uncommon. Approximately 50% of symptomatic patients will die of liver failure within 5 years if no treatment is given, but this falls to about 10% with therapy. |