

Summaries

Weber/Protzer (eds): Comparative Hepatitis

Summary

Michael P. Manns and Katja Deterding

Hepatitis in the clinics – Treatment options

Hepatitis is an inflammation of the liver based on different aetiologies. Clinicians distinguish acute from chronic hepatitis. Pathophysiological changes lead to damage and hepatocellular degeneration. The causes for hepatocellular injury are heterogeneous, such as viruses, toxins, drugs, autoimmunity, cryptogenic. The latest official classification of chronic hepatitis by the International Association the Study of the Liver (IASL) [1] is still valid and is based on:

1. Aetiology
2. Inflammatory activity (Grading)
3. Fibrosis stage (Staging)

This classification has become very relevant since we nowadays not only diagnose the different liver diseases according to their aetiology but also have developed specific treatments that are targeting specific aetiologies of chronic liver disease. Overlap syndromes with primary biliary cirrhosis and primary sclerosing cholangitis and genetic liver diseases add to the clinical spectrum of this syndrome.

In this chapter we will describe the different causes of hepatitis, their treatment options and differential diagnosis.

Summary

Martin F. Sprinzl and Peter R. Galle

Differential diagnosis of human hepatitis

There is a variety of differential diagnoses of acute and chronic human hepatitis regularly seen in clinical praxis. Risk factor assessment for specific entities provides important information and should guide individual diagnostic procedures. Liver screening tests often remain the first indicator for hepatic pathologies and should include quantification of liver enzymes, liver function parameters and cholestatic parameters. Nevertheless, virus serology should always be done during further laboratory evaluation. To estimate the parenchymal liver damage and to exclude biliary obstruction or hepatic lesions an abdominal ultrasound scan is essential. A liver biopsy may complete the diagnostic approach, if either the underlying hepatic pathology remains obscure or parenchymal liver damage needs to be defined.

Summary

Thomas Longerich and Peter Schirmacher

Comparative pathology

Hepatitis is defined as a necroinflammation of the liver displaying liver cell damage, inflammatory cell infiltrates, and regeneration to a variable extent. In contrast to acute hepatitis, which is characterised by a self-limiting damage of the acinar parenchyma, chronic hepatitis is pathomorphologically defined by the persistence of necroinflammation, portal predominance of mononuclear inflammatory infiltrates, and the development of fibrosis. Whereas HAV and HEV do not cause chronic hepatitis in humans, HBV (alone or in

combination with HDV) and HCV infection may result in chronic liver disease in humans, which may progress to liver cirrhosis and HCC. Initial animal models for the study of viral hepatitis belonged to the group of nonhuman primates, especially chimpanzees, which can be infected by human hepatitis viruses. These models develop a milder acute hepatitis compared to humans and although chronic hepatitis may also develop, progressive liver disease and liver cirrhosis are generally absent. In the case of HBV, several mammalian and avian HBV-related viruses are known. The most intensively characterised model is the Eastern woodchuck infected with WHV. This example is the only model in which chronic liver disease and HCC frequently develop. Recently, the tree shrew (*Tupaia belangeri*) has become an interesting model since it can be infected with human hepatitis viruses, it can be handled more easily compared to chimpanzees, and it can be used in transplantation models. Additionally, several transgenic mice and human mouse chimera have been developed, which allow for the studying of viral replication and novel therapeutic approaches *in vivo*.

Summary

Stephan Urban and Ulrike Protzer

Hepatitis B virus: lessons learned from the virus life cycle

The human hepatitis B virus (HBV) is the prototype member of the family of hepadnaviridae, small enveloped viruses which replicate their compact and highly organized DNA genome *via* reverse transcription. In humans, HBV may cause inflammatory liver disease, hepatitis B. With more than 350 million chronically infected people at high risk to develop liver cirrhosis or hepatocellular carcinoma, HBV is one of the most important human pathogens. In recent years, the viral life cycle has been characterised in considerable detail, our understanding of immunology and pathogenesis of hepatitis B has largely improved, and nucleos(t)ide analogues have been established as antivirals. However, current treatment options are still limited because they only rarely eliminate the virus, and thus long-term treatment is required. Following a general introduction, we therefore discuss which steps in the viral life cycle may serve as targets for novel therapeutic strategies.

Summary

Ralf Bartenschlager, Gang Long and Darius Moradpour

Chronic hepatitis C: Portrait of a silent epidemic and the etiologic agent

Chronic liver disease caused by infection with the hepatitis C virus (HCV) is an important medical problem. Although primary infection usually is mild, and often asymptomatic, in the vast majority of cases HCV establishes persistence that in the course of one or several decades may result in chronic liver diseases including liver cirrhosis and hepatocellular carcinoma. Therapeutic options are limited and a vaccine to prevent HCV infection is not in sight. Diagnostic tests to detect HCV-containing blood products have become available after the first molecular cloning of the viral genome. This achievement also opened the field for studies of the viral replication cycle as well as the development of selective antiviral drugs. HCV is a hepatotropic flavivirus which has several remarkable properties. Among these are the potent inhibition of the induction phase of the innate antiviral response, the high genomic plasticity and the unusual strategy of virus particle assembly that occurs in close association with lipid droplets and the very-low-density lipoprotein production pathway. This chapter will briefly summarise some old and new aspects of chronic hepatitis C and of the pathogen responsible for this disease.

Summary

Manfred H. Wolff and Axel Schmidt

Hepatitis A infection

Hepatitis A is a ubiquitous disease of man with acute, self-limiting liver inflammation and a low mortality rate, also known as ‘traveller’s hepatitis’, ‘hepatitis epidemica’, and ‘infectious hepatitis’. The causative infectious agent is the hepatitis A virus belonging to the family of the *Picornaviridae*, genus *Hepatovirus*. The route of transmission is mainly faecal-oral. Hepatitis A is an acute hepatitis that does not become chronic like hepatitis B and C, and it is no risk factor for the development of hepatocellular malignancies. The severity of clinical manifestation is often age related with predominantly inapparent infection in young individuals to more severe courses of infection in the adults and elderly. Hepatitis A is most predominant in countries with poor hygienic conditions and is therefore sometimes attributed as ‘traveller’s hepatitis’. Potent vaccines for protection and disease prevention are available and the ambitious medical aim – eradicating HAV by aggressive vaccination strategies – appears realistic.

Summary

Axel Schmidt and Manfred H. Wolff

Hepatitis E infection

Hepatitis E – formerly called ‘enterically transmitted non-A non-B hepatitis’ – is transmitted by the faecal-oral route. The Hepatitis E Virus (HEV) is a positive-sense single-stranded RNA virus and has great similarities to the caliciviruses. Virus replication appears to be limited to the hepatocyte. The disease is especially endemic and/or epidemic on the Indian sub-continent. Epidemics are mostly waterborne infections. Also in other ‘developing regions’ outbreaks of HEV infection are observed. In industrialised countries this disease only plays a minor role in hepatitis infections. HEV causes epidemics, endemics and sporadic cases of acute hepatitis. The incubation period for hepatitis E varies from 2–9 weeks. The course of disease is usually mild and self-limiting and resolves within a 2 weeks period. Fulminant cases of infection are rare. HEV infection does not induce chronic courses of hepatitis or liver disease. In clinically apparent cases of infection jaundice, pruritus, clay-coloured faeces and generalised lymphadenopathia may be observed. Fatal infections of fulminant hepatitis E are rare. Pregnant women appear to be exceptionally susceptible to severe disease forms, with an excessive mortality of infected mothers of about 20% in this group. HEV infections appearingly induce mostly life-long immunity to re-infection. To date there is no therapy against HEV infection available. The attempts in generating a vaccine against HEV infections are promising. Improving the socioeconomic situation including hygienic conditions is the most effective measure of disease prevention.

Summary

Hilmar Wisplinghoff and Darryn L. Appleton

Bacterial infections of the liver

Bacterial infections of the liver can be categorised into three entities: acute bacterial hepatitis, bacterial liver abscesses and granulomatous liver disease caused by bacteria. A broad spectrum of bacteria has been implicated in different forms of hepatic infections, and a wide variety of systemic bacterial infections affect the liver during the course of infection. Clinical

symptoms, causative pathogens and therapeutic approaches overlap widely. Most bacterial infections that affect the liver cause secondary hepatitis with only discrete clinical and laboratory findings. Standard diagnostic procedures including physical examination, imaging and microbiological cultures will usually be sufficient to detect and ascertain the bacterial causes of hepatitis. Therapy of bacterial infections of the liver usually includes antimicrobial chemotherapy according to standard guidelines for the underlying disease and the identified pathogen as well as additional invasive therapy which may be required for certain manifestations.

Summary

Achim Harder and Heinz Mehlhorn

Comparative hepatitis: Diseases caused by adult parasites or their distinct life cycle stages

There are a variety of parasites – protozoans, cestodes, trematodes, nematodes or pentastomides – which reside in the liver or invade this organ and are responsible for inflammation resulting in hepatitis. Among the Protozoa *Entamoeba histolytica* is of high importance. In the cyst fluid of the liver abscess purulent components are visible, but also some amoeba, so-called magna forms. Furthermore the amastigote stages of *Trypanosoma cruzi* and *Leishmania donovani* – both are Protozoa which possess a kinetoplast – and the schizonts of *Plasmodium* spp, which are the causative pathogens of malaria, have to be mentioned as a putative cause of parasite-induced hepatitis. Among cestodes *Echinococcus granulosus* and *E. multilocularis* preferentially reside in the liver. Within the trematodes *Schistosoma* spp, *Clonorchis sinensis*, *Opisthorchis viverrini*, *Dicrocoelium dendriticum* and the juvenile stages of *Fasciola hepatica* have to be considered. Among the large group of human nematodes, only *Capillaria hepatica*, migrating nematode larvae (such as larva 2) and the adults of *Ascaris lumbricoides*, larvae of *Strongyloides stercoralis*, hookworms, *Toxocara canis* and microfilariae of different filariae play a role in inducing liver inflammation.

Summary

Stefan Lüth and Ansgar W. Lohse

Autoimmune hepatitis in humans

Autoimmune hepatitis (AIH) can occur in all age groups from earliest childhood up until the 8th decade. AIH affects women more commonly than men (3:1). Clinical presentation may be an acute hepatitis up to fulminant liver failure, but can also be asymptomatic.

AIH is characterised by lympho-plasmacellular infiltrates on liver biopsy, elevated liver enzymes in serum and association with the HLA haplotypes B8, DR3 and DR4 in the absence of active viral markers. Patients characteristically present with hypergammaglobulinemia, elevated serum levels of IgG and autoantibodies, such as antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antibodies to soluble liver antigen/liver pancreas (SLA/LP) or to liver-kidney microsomes (LKM).

Corticosteroids are the drug of choice for remission induction, azathioprine the drug of choice for maintenance of remission. The rapid response to immunosuppressive treatment supports the diagnosis of AIH and leads to a good long-term prognosis. Treatment duration remains controversial and can be discussed after resolution of all clinical, laboratory and histological manifestations of disease activity. Treatment should be maintained for a minimum of 3 years.

Summary
Jan Rothuizen
Hepatitis in dogs

Liver diseases are a major focus of research in the Faculty of Veterinary Medicine. In a clinical population 1% of the dogs has a form of hepatitis. There are several aspects of canine hepatitis which make comparison with human hepatitis very useful. As a whole, liver diseases and especially different forms of hepatitis in dogs develop highly similar to human hepatitis (fulminant, acute, chronic). This makes dog diseases interesting to study important aspects in the pathogenesis of the disease. We have shown that in humans and dogs identical processes with respect to formation of fibrosis, regeneration, stem cell activation, and oxidative damage occur. In most aspects identical pathogenesis and pathophysiology of canine and human hepatitis make these spontaneous dog diseases ideal models to study the effect of new modes of intervention to stimulate regeneration and reduce or prevent cirrhosis.

Summary
Andy E. Durham
Hepatitis in horses

The main causes of hepatitis in horses include serum hepatitis, cholangiohepatitis and chronic active hepatitis with occasional cases of haematogenous bacterial hepatitis (e.g., Tyzzer's disease in foals), abscesses, viral hepatitis, parasitism and chronic infiltrative inflammatory disease. Not all cases of hepatitis will be clinically apparent due to the large reserve capacity of the liver. However, signs of marked hepatic insufficiency and hepatic encephalopathy reduce the likelihood of a successful outcome. Serum enzymes including alkaline phosphatase, aspartate aminotransferase, gamma glutamyltransferase and glutamate dehydrogenase offer an approximate reflection of hepatic damage whereas functional indicators such as bile acids, bilirubin, albumin, globulins, urea and ammonia may provide more prognostically useful information. Nevertheless all serum biochemical parameters have significant limitation in terms of sensitivity or specificity. Liver biopsy, when guided by ultrasonographic images, offers the optimal safe and effective means of investigating suspected hepatitis in horses and will provide useful diagnostic and prognostic information in addition to aiding selection of therapeutic choice.

General and supportive care for equine hepatitis cases includes fluid therapy, antipyretics and dietary management comprising small frequent feeds of low fat, good quality protein and cereal based feeds such as grass, good grass hay, dried proprietary chaffs, alfalfa, processed wheat/maize and B vitamin supplements. Care should be taken to ensure that supplements do not contain potential hepatotoxins (e.g., iron). Specific therapy is usually selected on the basis of biopsy findings and may comprise antibacterials, anthelmintics, glucocorticoids and lactulose.

Summary
Bud C. Tennant, William E. Hornbuckle and John L. Gerin
The woodchuck model of hepadnavirus infection

Since discovery of the hepatitis B virus (HBV), closely related viruses have been described in several animal species. The first of these was the woodchuck hepatitis virus (WHV),

identified in woodchucks (*Marmota monax*) that were maintained at the Philadelphia Zoological Garden and which had experienced a high prevalence of chronic hepatitis and hepatocellular carcinoma (HCC). On the basis of morphological and molecular analyses, it was concluded that WHV was closely related to HBV. Since description of WHV, infection with viruses that belong to the family Hepadnaviridae have been described in the California ground squirrel (*Spermophilus beecheyi*) and the Arctic ground squirrel (*Spermophilus parryi*), two species closely related phylogenetically to woodchucks, and in six avian species. A total of four well characterized, mammalian hepadnaviruses now have been associated with development of HCC. These observations on naturally acquired hepadnavirus infections combined with the development of HCC in woodchucks following experimental infection with WHV or with the California ground squirrel virus (GSHV) provides, by analogy, convincing comparative medical evidence for the hepatocarcinogenicity of HBV. The woodchuck has become useful as an experimental animal model for research on the pathogenesis of HBV infection and for investigation of the molecular mechanisms of hepatocarcinogenesis. The woodchuck also has been useful in the discovery and preclinical development of antiviral drugs for treatment of HBV infection and for testing new forms of immunotherapy using cytokines and therapeutic vaccination. In particular, the woodchuck has been valuable for determining the impact of long-term antiviral treatment on the outcome of chronic hepadnavirus infection in placebo controlled, lifetime survival studies which have been predictive of the results of subsequent clinical trials.

Summary

Kai Dallmeier and Michael Nassal

Hepadnaviruses have a narrow host range – do they?

Host range describes the range of species that a virus can infect to productively propagate itself. Productive infection requires compatibility between virus and host molecules. Thus host range may be restricted by lack of appropriate permissivity factors; alternatively, hosts may actively counteract infection using restriction factors. Incompatibility between virus and host can manifest on the level of individual cells, of tissues or organs, and of the entire organism. All hepatitis B viruses are hepatotropic, but individual viruses infect the livers of only selected mammalian (orthohepadnaviruses) and avian (avihepadnaviruses) hosts. Hence a narrow host range is thought to be a salient feature of hepadnaviruses. Here we briefly review general mechanisms of host range restriction, and summarise older as well as recent data pertaining to hepadnaviral host range. Clearly, the term species-specific is inadequate for many hepadnaviruses because they can infect different species from one genus, and even species from different genera. For a few others, only a single species, or genus, has been identified that supports efficient infection; however, this could as well relate to the restricted number of experimentally addressable test species. Together with the uncertainty about quantitative phylogenetic relationships between species, still largely based on morphological rather than molecular criteria, this leaves the term narrow open to interpretation. Finally, few if any of the host molecules enabling productive infection by a hepadnavirus have unambiguously been identified, the role of restriction factors has not yet been assessed, and even on the virus side the so-called host determining regions in the PreS domains of the large envelope proteins appear to be relevant only under specialised experimental conditions. Hence this important aspect of hepadnavirus biology is still far from being understood.

Summary

Percy A. Knolle and Dirk Stabenow

The liver as immune escape site for pathogens

Besides its important function for protein, lipid and glucose metabolism the liver exerts scavenger function in order to clear the blood from degradation products. It is becoming increasingly clear that this scavenger function is closely linked to the liver's immune function, which favours induction of immune tolerance rather than immunity. The cell population most actively involved in scavenging of blood-borne macromolecules is an organ-resident cell population, the liver sinusoidal endothelial cells (LSEC). LSEC also have prominent immune-regulatory function as they bear the capacity to prime naive CD4 and CD8 T-cells after presentation of exogenous antigens on MHC Class II or MHC Class I molecules, respectively. The outcome of such T-cell priming by antigen-presenting LSEC is induction of T-cell tolerance. Here, we also discuss the other mechanisms and cell populations involved in mediation of hepatic immune tolerance. We describe the mechanisms of how a virus may get across cell barriers, in particular the endothelial cell barrier. Importantly, blood-borne virus is scavenged by LSEC. Here we discuss the experimental evidence in the literature that virus uptake by LSEC does not necessarily lead to lysosomal destruction but rather results in transcytotic transport of the virus to hepatocytes. Thus, LSEC may play a pivotal role in hepatocellular infection by blood-borne virus: (i) retrieval from the bloodstream and transcytotic transport for infection of the target cell, the hepatocyte, and (ii) prevention of virus-specific CD8 T-cell immunity by skewing antigen-specific T-cell responses by presentation of viral antigens at the very early stage of infection.

Summary

Olaf Weber

Drug candidates for the treatment of viral hepatitis

While progress has been made in treating viral hepatitis some problems are not adequately addressed with current therapies. This includes the challenge of treating both chronic as well as fulminant infections. This chapter provides an overview about current activities in the development of novel therapies for viral hepatitis. The activities in this area are very competitive and dynamic and, therefore, the list of projects and compounds might not be complete or reflect the very latest status of certain projects. However, it is clear that the medical need is being addressed and that novel approaches can be expected that might hopefully strengthen the antiviral armamentarium in the future.

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