Hepatitis A virus

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THE MICROORGANISM AND ITS CLINICAL PRESENTATION

Hepatitis A virus (HAV) is a non-enveloped, positive-strand RNA virus, which belongs to the family of picornaviruses genus Hepatovirus. There is one single serotype but there are six genotypes, of which three genotypes infect humans (I, II and III) [Costa-Mattioli 2002, Robertson 1992].

HAV will give an acute infection of the liver, is usually self-limiting and is typically symptomatic with jaundice. The mean incubation period is approximately 28 (range 14-49) days [LCI 2019]. The presence and severity of illness is age-dependent [Shin 2018]. In children HAV infection is usually asymptomatic (>70%), but in adults 70-80% is symptomatic. The onset is often abrupt and characteristic prodromal symptoms are followed, within a few days to a week, by dark urine and jaundice. The case definition for Hepatitis A is: acute illness with jaundice and elevated transaminase levels and a positive anti-hepatitis A virus IgM [Brundage 2006]. Mild to moderate tenderness over an enlarged liver is usually detected. Extrahepatic signs such as splenomegaly, rash or arthralgias may occur [Koff 1992, LCI 2019, Shin 2018].

COMPLICATIONS

Fulminant HAV infection is rare (less than 1%) in symptomatic patients and has a high mortality [LCI 2019, Shin 2020]. More severe disease is seen in old-age, immunocompromised patients, and patients with preexisting chronic liver disease. Atypical clinical manifestations with relapses and prolonged cholestasis (6-10%) and extrahepatic disease occur [Lai M 2019, Koenig 2017, Shin 2018], but even in these circumstances, recovery is the rule and chronic hepatitis is not seen [Koff 1992, LCI 2019]. Case-fatality rate increases with age, being 0.3-0.6% <50 and 1,8% >50 years of age.

EPIDEMIOLOGY

HAV is transmitted from person to person (human reservoir) via the faecal-oral route. Primarily transmitted by faecal-oral route, HAV can

also be transmitted by sexual contact in MSM and outbreaks may also be associated with IV drug use [Gowland 2004, LCI 2019, Ponde 2017]. Populations at risk are among others second and third generation migrants, travellers, MSM or employees who come into contact with faecal excretion. Seroprevalence in the Netherlands depends mainly on age, with lower seroprevalence (~25%) in non-HAV vaccinated persons born after the second World War [LCI 2019]. In the Netherlands numbers have decreased to 164 countrywide infections in 2019, from which 40% were contracted abroad, 19% MSM (men who have sex with men), 23% secondary cases, 5% contaminated food/water and 13% of unknown origin (personal communication RIVM). The number decreased further down to 50-60 in 2020. Infections in preschool children in low-income countries with poor sanitation can cause severe hepatitis with high rates of acute liver failure (ALF) [Yeung 2009]. Good sanitation and hygienic practices result in a low incidence. Exposure to contaminated food or water nowadays can cause common-source outbreaks and cases of HAV infection. Vaccination since 1995 has led to dramatic decrease in HAV infections in western countries, almost eradicating the disease [Jacobson 2010, Carillo-Santisteve 2017, Koenig 2017], though the low immune rates allow for numerous outbreaks to happen [CarilloSantisteve 2017], with increasing mortality, because the infection occurs in older persons.

DIAGNOSTIC TESTING

The clinical, viral and serological course are depicted in figure 1.

Techniques

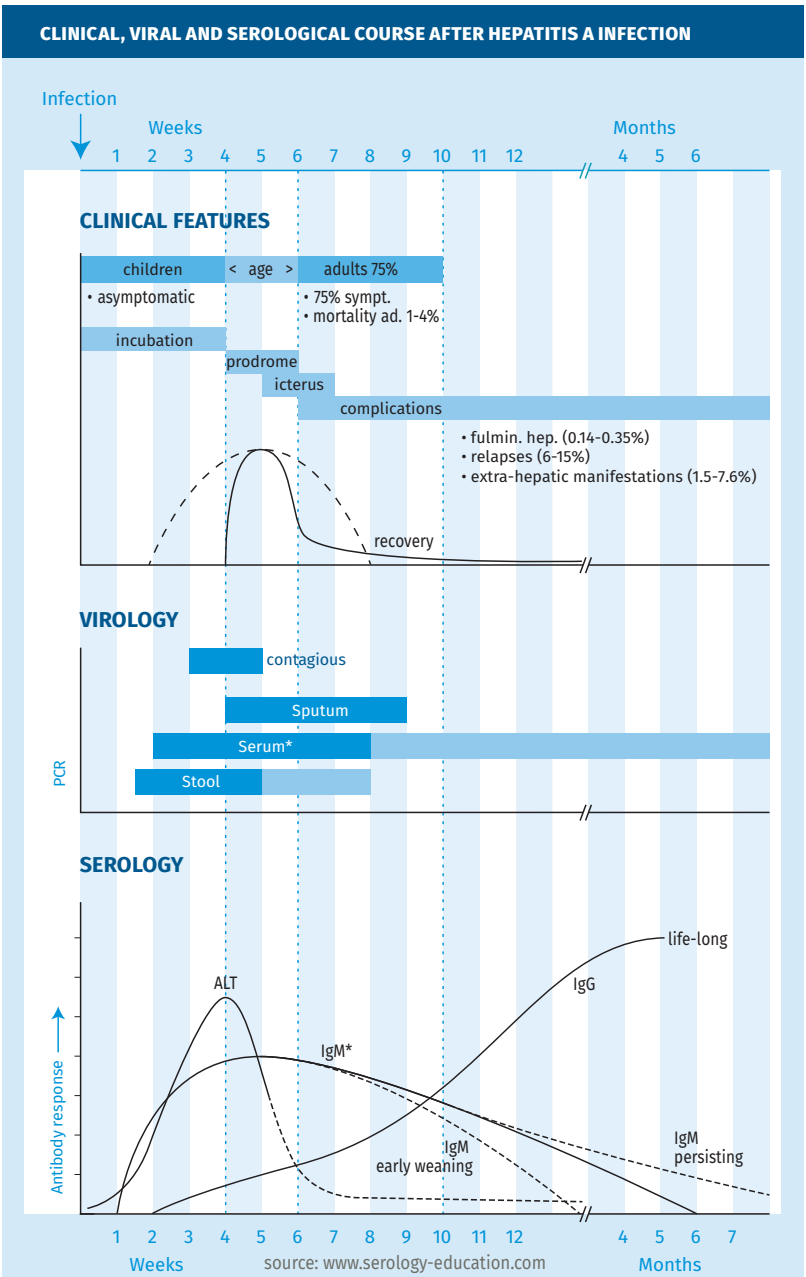
1. Enzyme Immuno Assay (EIA) IgM, IgG or total Ig [Ponde 2017, Arcangeletti 2011, Park 2013].
2. Confirmation and genotyping (in outbreaks) by PCR for HAV RNA in faeces.

PRACTICAL USE OF SEROLOGY

Screening

Testing for specific immunity, for example in immunocompromised persons or risk groups, with IgG anti-HAV or total Ig anti-HAV. Optional: Travellers born or raised in HAV-endemic countries before HAV vaccination. Immunity for Hepatitis A correlates with a positive IgG anti- HAV or total Ig anti-HAV in serum [NSW 2019].

FIGURE 1.



***** Decreasing IgM-titer tends to occur with decreasing amounts of HAV genome equivalents, and vice versa.

[Koff 1992, LCI2019, Oba 2000, Joshi 2002, Tjon 2006, Bower 2000, Brundage 2006, NSW 2019, Dollberg 1990, Kao 1984, Liaw 1986, Lai 2019, Shin 2018, Cuthbert 2001, Jung 2010].

Suspected infection in immunocompetent child or adult

Diagnosis of recent infection in immunocompetent adults and children with typical symptoms: IgM anti-HAV in serum. Following an incubation period, IgM anti-HAV usually becomes positive several days before the onset of symptoms and usually remains positive for approximately 3-6 months after the onset of illness [Ponde 2017, MMWR 1999]. In a minority of patients IgM antibodies may persist even for years after infection [Sikuler 1987, MMWR 2005, Castrodale 2005, Shin 2018, Liaw 1986, Dollberg 1990, Kao 1984], or do not show in symptomatic patients at all (6-11%) [Jung 2010, Lee 2013].

Suspected Infection in an immunocompromised child or adult

Diagnosis of recent infection: IgM anti-HAV in serum. In case of severely immunocompromised patients with decreased antibody production, PCR HAV in faeces or serum/plasma should be considered [NSW 2019].

INTERPRETATION OF SEROLOGY

The interpretation of IgM and IgG results in an immunocompetent person is depicted in table 1.

TABLE 1.

IgM	IgG/total Ig	Interpretation	
Negative	Negative	No infection	
Negative	Positive	Past infection or vaccinated; Immune	
Positive	Positive	Recent infection	!
Positive	Negative	Recent infection or false-positivity IgM	!!

! Low level positive IgM with a positive or negative IgG: beware of false-positive IgM (see chapter "Pitfalls of serological testing").

!! Can be confirmed with PCR HAV on faeces or serum/plasma or second serum for seroconversion of IgG/total Ig

- In case of symptoms the current standardized assay to use is an IgM antibody capture system for anti-HAV IgM tests, or a total Ig anti-HAV test with a high sensitivity and specificity (table 2) [Ponde 2017, Arcangeletti 2011, Park 2013].
- The presence of serum IgM anti-HAV in a patient with typical symptoms of HAV infection indicates acute HAV infection.
- The presence of IgG-antibodies against HAV correlates with immunity against HAV. No difference can be made serologically whether immunity is due to infection or vaccination.

SENSITIVITY, SPECIFICITY

TABLE 2.

	Sensitivity	Specificity	PPV**
ELIA-IgM*	93.8-99%	91-95%	88%
HAV-Multiplex	99%	95%	

* Cuthbert 2001, Ye 2017, Bohm 2017, Hess 1995

** With a population prevalence of <1% this means that 1 of every 4 positives would be "false positive".

PITFALLS

- Recent hepatitis A vaccination can give a positive IgM anti-HAV test result (8-20%) [MMWR 1999, Sjogren 1991, Shouval 1993], which can be differentiated from a recent HAV infection by PCR HAV on faeces or serum/plasma.
- A small proportion of immunocompetent patients (6.4%-10.9%) is IgM negative at initial presentation with clinical symptoms, retesting in a couple of days or PCR can confirm the diagnosis of HAV infection. This proportion is higher in outbreak settings, when patients have not developed clinical illness (yet) [Lee 2013, Jung 2010, Hyun 2012].
- Do not test asymptomatic persons with IgM due to the relatively high rate of false positive results in low prevalence populations [Alatoom 2013, NSW 2019].

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KEYWORDS

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