



The Spectrum of Viruses Causing Hepatitis

Authors: Evan Kimber, EMJ, London, UK

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VIRAL hepatitis presents one of the most diverse challenges currently perplexing experts within the field of hepatology. An insightful session at the European Association for Study of the Liver (EASL) Congress 2023 collated vital new information in this area for clinicians to take away and incorporate into their practice. Presenting at this meeting, held in Vienna, Austria, between the 21st–24th June, Tassos Grammatikopoulos, King's College Hospital NHS Trust, London, UK, gave an update on the interaction of adenoviruses with hepatitis. Meanwhile Gonzalo Crespo, University of Barcelona, Spain, spoke about post-liver transplant viruses.

ADENOVIRUSES CAUSING HEPATITIS

Grammatikopoulos began by discussing viruses causing acute severe hepatitis in paediatric populations, and presented data that crossed over with the COVID-19 pandemic. Looking back to 2014, Grammatikopoulos referenced the low figure of 33% for unexplained cases of hepatitis in the UK and Ireland, and that 1 in 39 children presented with non-A or B hepatitis-related acute liver failure that required a transplant, before comparing these with far higher figures from 2022. Grammatikopoulos also presented retrospective data from between 2017–2021 and 2021–2022, as well as data from 2022.

In 2022, paediatric hepatologists saw the annual number of patients they would usually treat with acute liver failure who needed transplant within the first trimester rise to a significantly higher incidence than expected. "Hepatitis in itself really evolved hand-in-hand with the cases of adenovirus that were identified in the general population, [and] in children's faecal material," was the description Grammatikopoulos gave, reflecting on this association during the pandemic. Moving on to outline virology and liver histology, Grammatikopoulos described that close to 70% of their study cohort presented

with adenovirus, stressing the variable degree of fibrosis uncovered in these patients, along with the difficulty clinicians experience calculating this because of extensive hepatocellular necrosis.

Grammatikopoulos acknowledged that a higher incidence of human adenovirus led to a stronger association with paediatric acute liver failure in the 2022 epidemic. Interestingly, this relationship was found not to be a novel phenomenon, and up to 75% of a similar cohort experienced positivity for adenoviraemia but did not experience as much liver failure between the years 2017–2019. Jaundice was highlighted as a key feature for identifying hepatitis, showing agreement in European and American branches of study.

Finishing with treatment options for clinicians to consider in their practice, Grammatikopoulos focused on the use of ribavirin, ganciclovir, Ig, and cidofovir, which they flagged as the medicine of choice. Despite receiving a high dose of cidofovir 5 mg/kg, intervention in the discussed cohort failed to halt the clinical progression of disease, which was not changed in about 70% of patients, who consequently required a transplant. What is clear from this is that adenoviraemia remains a complex issue that is linked with liver disease, there is a significant but not clearly defined crossover with COVID-19, and further research is needed



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to guide advances in practice, and build on the currently limited treatment options.

POST-LIVER TRANSPLANT VIRUSES

Recognising that times have changed, and that significant advances have been made in the field, Crespo chose to focus much of their talk on hepatitis E, cytomegalovirus, herpes, and torque teno virus instead of hepatitis B, C, and D, which might have dominated a presentation of this nature previously.

After liver transplant, hepatitis E virus remains a common cause of acute hepatitis in endemic countries, such as Mexico, as well as much of Asia and Africa. Crespo provided data from a study from Southern France, showing that this infection may evolve into chronic hepatitis, and stating that this is often due to a third genotype of zoonotic infection and ingestion of undercooked meat.

Discussing the prevalence of IgG and IgM in recipients of transplant, Crespo acknowledged that using serology to define hepatitis E infection is not as accurate as researchers would like, and they briefly spoke about the challenges associated with this in patients who are immunocompromised. Crespo explained the importance of using hepatitis E virus RNA molecular testing as the standard of care in defining recipients who are suitable for liver transplant to overcome this. Clinicians observing this presentation would note the following key actions after diagnosing hepatitis E virus infection: a decrease in immunosuppression, and then a 3-month wait to see if the infection evolves to a chronic state, and intervening with ribavirin treatment, which has an admirable 80% success profile. Crespo mentioned the vaccine for hepatitis E virus, which is currently approved for use in China, stating that it may be useful, but requires further confirmation and study in other areas.

Moving on to discuss the characteristically latent herpesvirus, Crespo clarified the recent confusion and disagreement among experts when classifying the subgroup cytomegalovirus, defining this as any detectable viraemia, regardless of symptoms. Answering one of the key questions clinicians are faced with in their treatment of cytomegalovirus, Crespo discussed the pros and cons of prophylactic and pre-emptive approaches. For patients of high-risk liver transplant, 3 months of prophylaxis with (val)ganciclovir is recommended. Meanwhile, in low- and mid-risk cases, a pre-emptive approach should be employed, using weekly or bi-weekly cytomegalovirus PCR to monitor viral load, and beginning treatment when this reaches a predetermined threshold. In the patients who experience side effects, are refractory to these drugs, or present with resistant disease, alternative interventions are recommended. This should involve a higher dose of ganciclovir for the latter two. Alternatively, foscarnet and maribavir provide good treatment options to clear cytomegalovirus viraemia.

Bringing their presentation to a close, Crespo spoke about torque teno virus from transfusion

transmission, highlighting that this reflects immune status after liver transplant. More research is needed in this field to investigate if this may be used as a biomarker to guide immunosuppression, an integral part of dealing with all the discussed branches of hepatitis in this section of the session.

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CONCLUDING REMARKS

This symposium was governed by chairs Jane Hartley, University of Birmingham, UK, and Ralf Bartenschlager, Heidelberg University, Germany, who reflected on the information provided by both speakers. Hartley described it as "very, very informative." Both presentations furthered understanding, and gave a new perspective on different aspects of hepatitis, helping to shape the practice of onlooking clinicians, and guide next steps for researchers. ●

