Possible mechanisms for the hypothesis that acute hepatitis of unknown origin in children is caused by adeno-associated virus type 2

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I have postulated the hypothesis that acute hepatitis of unknown origin in children is caused by adeno-associated virus (AAV) type 2[1].

The liver injury seen with intravenous injection of high-dose AAV vectors for gene therapy purposes is likely not dependent on the transgene or transgene product. This is because hepatotoxicity has occurred in humans with AAV vectors for several types of genetic disorders[2]. AAV vectors that have caused severe liver damage in humans at high doses in gene therapy clinical trials are of nonhuman primate origin, such as types 8 and 9, and not type 2. However, asymptomatic transaminase elevation was seen with a decrease in transgene product after 2-3 weeks of administration of medium or high doses of AAV type 2 vector to humans[6,9]. In these cases, analysis of peripheral blood mononuclear cells by interferon-γ enzyme-linked immunospot (IFN-γ ELISPOT) showed a response to AAV type 2 capsid but not to transgene product[6,9]. This measurement suggested the destruction of transduced hepatocytes by CD8+ Tcells. If hepatitis occurs with AAV, hepatitis may be delayed from adenovirus or AAV infection, which may affect viral detection.

Prevalence for neutralizing antibodies in French adults was significantly lower for AAV8 (38%) than for AAV type 2 (72%), and even when positive for AAV type 8, titers are mostly low[8,10].

AAV type 2 shares 83% homology with AAV type 8 [3]. Immune responses to mice were not very different between AAV type 2 and AAV type 8 [11]. AAV type 2 may have the potential to cause severe liver damage in humans if present in the blood in large quantities with poor immunity to AAV2.

Some studies suggest that AAVs are sensed by Toll-like receptor 2 (TLR2) and TLR9 innate immune receptors in mice and humans[5,6,11]. The capsid of AAV type 2 may interact with the innate immune system via TLR2 and has recently been shown to be present in nonparenchymal cells of the human liver (Kupffer cells and hepatic sinusoidal endothelial cells) [7].

Besides T cell involvement[6,9], complement played a role in the adaptive immune response to AAV[12].

SARS-CoV-2 infection can enhance broad and non-specific immune activation including hyperactivation of the complement[13]. Co-occurrence of SARS-CoV-2 infection may be an exacerbating factor and may be the reason for the high rate of SARS-CoV-2 co-infection

Corticosteroids have been reported to be effective in the treatment of liver injury with AAV vectors. Since all of the current candidate causes are unlikely to be seriously aggravated by short-term corticosteroid administration, a single, short-acting corticosteroid administration and observation of response may be considered at an early stage of diagnosis, given the risk of progression to severe hepatitis. AAV type 2 is difficult to test for in the general hospital setting, and guidelines should be urgently developed for tests that should be performed on acute hepatitis of unknown origin in children. Polymerase Chain Reaction testing

for AAV should be performed in both blood and stool, along with adenovirus. In addition, analysis of AAV type 2 capsid-specific T cells by ELISPOT in patients may be the key to elucidating the cause

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