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LETTER TO EDITOR (Journal of Hepatology)

Could the paediatric acute hepatitis of unknown origin be related to a new autoimmune disease?

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In relation to recent articles from Okamoto et al.¹ and Jagadisan et al.² published in the Journal of Hepatology.

Okamoto et al. studied the HLA association in children who underwent liver transplantation due to severe pediatric acute hepatitis of unknown origin (PAHUO) (defined as A-to E- negative hepatitis, lack of autoantibodies, and drug-induced or toxic liver injury discarded). This group described firstly that HLA-B*52:01, HLA-C*12:02, and HLA-DQB1*06:01 alleles have a protective role in this disease and secondly the lack of association in their cohort with HLA-DRB1*04:01. These associations could be due to the different distribution of HLA alleles according to the population studied (Oriental vs Caucasian), which limits the comparison between the results.¹ The presence of HLA-DRB1*04:01 had been described previously by Ho et al.³ as associated to the 93% of PAHUO 2022 cases in Scotland outbreak, compared to healthy blood donors. With the exception of these authors, the PAHUO were studied mainly under the microbiological point of view with adenovirus (ADV) and/or adeno-associated virus (AAV) infections as potentially associated findings^{2,4} in the outbreaks of UK and USA.

This study aims to investigate the association of HLA in PAHUO 2022 Spanish outbreak. For this purpose, the HLA-DRB1 four-digit alleles were determined in 40 affected individuals (37 Caucasoids and 3 Amerindians). Control HLA populations from Spanish Caucasoids and Amerindians (Mayans/ Bolivian-Quechuas) were used.^{5,6}

A total of 61 cases were reported in 2022 under the PAHUO Health Ministry alert.⁷ Among them, total-blood samples were available in 40 for HLA analysis, 37 Caucasoid origin (Table 1). From them, 13 (35.1%) were DRB1*04 (two of them with two copies). After the analysis of the four-digit subtypes of DRB1*04, no association was found with any of them including DRB1*04:01. However, the sum of DRB1*04:01, *04:03 and *04:07 alleles reached the 84.61% of DRB1*04s PAHUO patients versus the 34% in healthy individuals ($p=0.0008$, pc (p corrected) = 0.072). Consequently, although DRB1*04 was not associated to PAHUO, alleles DRB1*04:01, *04:03 and *04:07 seemed to be more present than in general population. On the other hand, and interestingly, the combinations in which there was at least one copy of the HLA-DRB1*01, *04, *10 or *15 alleles, amounted 89.9% in PAHUO compared to 59.27% in the general population ($p=0.0004$; $pc=0.006$). Additionally, the cohort included a minor number of Amerindian individuals ($n=3$), all having DRB1*14:02, only found in the Amerindians of the south of North America and South America, but considered not frequent. (from 8,3% in Mayans to 16,3% in Bolivian Quechuas healthy population). Interestingly, in PAHUO cases reached 100% being significant higher than general population (Mayans $p=0.0000003$, $pc=0.000008$; Bolivian Quechua: $p=0.0003$; $pc=0.009$).⁶ Although the number of patients of Amerindian origin is very scarce in this study, both the high DRB1*14:02 allele frequency and the fact that it shares the same epitope than alleles DRB1*01, *04, and *10 suggest that this exclusive shared epitope could be under the pathogenesis of the disease in these two different populations.⁶

The association of the DRB1*01, *04, and *10 alleles has been described as related to rheumatoid arthritis in adults and specifically constituting the “shared epitope” theory, where positions 70 and 74 are shared between these alleles in the beta chain of the DR protein.⁸ Additionally not sharing this epitope, but harbouring an exclusive one different to the others, DRB1*15 is associated with other several autoimmune diseases such as

systemic lupus erythematosus, multiple sclerosis, or Goodpasture syndrome.⁹ Autoimmune hepatitis (AIH) has been described as a chronic inflammatory liver disease with two different subtypes defined according to the serum autoantibody profile present: AIH-1 with the presence of anti-smooth muscle (SMA), α -actinin and/or antinuclear antibodies (ANA) and associated with the DRB1*03:01 and DQB1*02 alleles and AIH-2 characterized by the presence of anti-LKM-1 antibodies and associated with DRB1* 07 in European children.¹⁰

In conclusion, children with PAHOU in general, without considering other factors, are associated with a set of characteristic HLA alleles associated with autoimmune diseases such as DRB1*01, *04, *10, *15, and 14:02 (in Amerindians), all having epitopes, non-present in the other alleles, which would suggest the possibility of an autoimmune aetiology of PAHOU. The relationship of this findings with the microbiological results is yet to be determined. In the 42 Spanish cases included in the report by the Ministry of Health⁹, were detected CMV (14,3%), HHV6 (2,4%), HHV7 (4,8%), EBV 4,8%), HSV (2,3%), EV (7,1%), ADV (42,8%), AAV (19,0%) among others. The hypothesis is that one or some of these infections could have triggered the PAHOU with the generation of an autoimmune response of the immune system. More studies are needed in order to support these results, including the possible correlation of HLA alleles with different infections, the study of hepatitis of unknown origin in adults and the expanded study to other different populations, due to the different specific frequencies of the HLA alleles in different parts of the world.

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Authors contributions: Ana Avellón designed the study and was the principal investigator of the study. Jorge Martinez-Laso developed the HLA study and interpreted its results. Isabel Cervera and Milagros Muñoz provided technical assistance. Inmaculada Casas was responsible of storage of total blood samples. Jorge Martinez-Laso and Ana Avellón wrote the manuscript.

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Author names in bold designate shared co-first authorship

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