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CASO CLÍNICO

Acute Hepatitis of Unknown Origin in Children: Two Cases in a Portuguese Hospital

Hepatite Aguda de Origem Desconhecida em Crianças: Dois Casos num Hospital Português

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ABSTRACT

Several cases of paediatric acute hepatitis of an unknown aetiology have been described in these last few months and in several countries worldwide. We present two patients, a 7-month-old girl and an 8-year-old boy, with gastrointestinal symptoms and lethargy, associated with elevation of transaminase levels. Serologies for hepatitis A-E virus and PCR test to SARS-CoV-2 were all negative. In the first case, an adenovirus serotype C could be isolated in a respiratory sample as well as cytomegalovirus (CMV) in the blood (100 copies/mL). In both children, there was a progressive decrease in the hepatic markers and symptomatic resolution, compatible with a good prognosis, also seen globally in most cases. To date, infection remains the most plausible cause to consider, especially when it is presumed to be linked to adenovirus. Other potential agents and causes are still being evaluated, thus emphasizing the importance of continuous epidemiological surveillance, notification, and detailed study of all hepatitis cases.
Keywords: Acute Disease; Child; Disease Outbreaks; Hepatitis; Portugal

RESUMO

Casos de hepatite aguda de origem desconhecida têm sido descritos em idade pediátrica nos últimos meses e em vários países por todo o mundo. Apresentamos dois casos, uma lactente de sete meses e uma criança de oito anos, com sintomas gastrointestinais e prostração, associados a elevação das transaminases. As serologias para vírus da hepatite A-E e a pesquisa por PCR de SARS-CoV-2 foram negativas. Na lactente isolou-se adenovírus serotipo C nas secreções respiratórias e citomegalovírus (CMV) no sangue (100 cópias/mL). Em ambos houve uma descida progressiva dos marcadores hepáticos e resolução sintomática, compatível com o bom prognóstico que se tem verificado globalmente na maioria dos casos. A etiologia infeciosa é a hipótese mais plausível, sobretudo a infeção por adenovírus, mas outras causas têm também sido propostas, realçando a importância da vigilância epidemiológica, notificação e estudo detalhado de todos os casos de hepatite.
Palavras-chave: Criança; Doença Aguda; Hepatite; Portugal; Surtos de Doenças

INTRODUCTION

By the end of March 2022, the Scottish National Health Service raised concerns about a large number of children under 16 years old presenting with symptoms compatible with acute hepatitis (AH) not caused by the usual viral suspects.[1] Several hypotheses are still being considered to justify this strange rise in paediatric AH incidence,[2,3] with the infectious cause being quite appealing to the scientific community as an adenovirus (41F) has been identified in a large proportion of patients.[4] Other studies also suggested a potential role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or even other toxic agents, but no research has yet brought complete light on the matter.[4-6] The current proposed case definitions also require high transaminase levels (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 500 UI/L),[2-4] which may suggest that milder cases are not being reported, probably underestimating the real number of affected children.

The most common clinical presentation consists of jaundice preceded or accompanied by vomiting.[4,7] However, other gastrointestinal (GI) symptoms have also been commonly reported, such as diarrhoea, pale stools, nausea and abdominal pain.[4,7] Severe lethargy is also a frequent complaint[4] and, in some cases, respiratory symptoms are also reported.[4,7]

As of 26th May 2022, the World Health Organisation had reported 650 probable cases of AH in 33 countries worldwide, 34% of these located in the United Kingdom (UK).[2] In the UK, most cases were children under five years of age (75.4%), around 60% were positive for an adenovirus (110 of the 181 tested),[2] 180 children required hospitalisation and 11 of those cases required liver transplantation.[4] There were no deaths recorded over one month of follow-up.[4]

Until the 3rd June 2022, in Portugal, 15 children remained under investigation and surveillance.[8]

We present two cases, whose initial symptoms report back to the 31st March and the 2nd April, 2022, respectively, making them possibly some of the first cases notified in our country.

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CLINICAL CASES

A previously healthy 7-month-old girl presented to our paediatric emergency department (PED) on the 6th April 2022, with a six-day history of diarrhoea and vomiting, and also with persistent fever and lethargy for the previous four days. There were no changes in the physical examination apart from mild dehydration. She was anicteric and there was no reported coluria or faecal acolia. There was also no recent significant epidemiological context and she had had coronavirus disease 2019 (COVID-19) in January 2022. Serial blood workup over a three-week period showed elevated ALT (maximum level 1386 U/L), AST (maximum level 1059 U/L), and gamma glutamyl transpeptidase (gamma-GT) (maximum level 168 U/L). Prothrombin time (PT), activated partial thromboplastin time (aPTT) and total bilirubin levels were normal (Table 1). The respiratory viral panel was positive for adenovirus and coronavirus HKU1. Serologies were negative for hepatitis A-E virus and Epstein-Barr virus (EBV), only showing a positive IgG for cytomegalovirus (CMV), with negative IgM. Complementary investigation performed by Instituto Ricardo Jorge (INSA) on blood, serum and faecal samples revealed: positive C serotype adenovirus desoxyribonucleic acid (DNA) detected by polymerase chain reaction (PCR) method on a faeces sample (but negative in the blood), with positive IgG and negative IgM on serology; positive DNA PCR for CMV in the blood (100 copies/mL); negative DNA PCR for EBV in the blood; and positive IgG-anti-nucleoprotein and anti-S protein for SARS-CoV-2.

Around the same time, a previously healthy 8-year-old boy was also brought to our PED with complaints of anorexia and severe lethargy with seven days duration, accompanied by diffuse abdominal pain, vomiting, cough and rhinorrhoea, which had started a few days earlier. There was no fever, diarrhoea or reported changes in faeces or urine. According to his parents, there had been no relevant epidemiological link, including previous COVID-19, and the boy had not been vaccinated for SARS-CoV-2. His blood work-up was relevant for elevation of transaminases (AST max. of 1081 U/L, ALT max. of 1999 U/L), and elevated lactate dehydrogenase (LDH) of 651 U/L. There were no other relevant changes, including bilirubin, albumin and coagulation studies (Table 2). The virus panel testing was negative for hepatitis A-E virus, EBV, CMV, SARS-CoV-2 and additional investigation performed at INSA revealed inconclusive IgG with negative IgM, and negative DNA PCR for adenovirus; negative DNA PCR for CMV and EBV; negative RNA PCR for enterovirus; negative IgG anti-nucleoprotein but positive IgG anti-S protein for SARS-CoV-2.

Over a two-month follow-up, both children normalized their transaminase levels and have fully recovered from their symptoms.

DISCUSSION

So far, an infectious agent remains the most plausible cause as it is shown in one of the presented cases.[4-7] Both children had GI symptoms at presentation and both had frank elevation on hepatic markers, although none presented with jaundice or pale stools, which are a common feature in other case series.[2-4,7] Our first patient had fever, a sign present in about 30% of the previously described cases,[4,7] and the second patient also had respiratory symptoms, as seen in around 19% of those reported, so far, in the literature.[4,7]

As in the majority of cases in the UK,[4,5] an adenovirus was also detected in our first case (in the respiratory panel and stools), although the revealed serotype in our case was not the one being currently considered as the most likely culprit by the international scientific community (the 41F serotype, not previously known to cause severe AH).[4,9] Besides, in the UK, this adenovirus is being more easily detected in the blood or serum than in stool or respiratory samples,[4] contrary to what happened in our case, where no adenoviral DNA could be detected in blood PCR.

Although the adenovirus hypothesis is a substantial focus of investigation, there are some questions about its true role, since it is a frequent infection in children and can be only an incidental finding. Moreover, between November 2021 and April 2022, England's health surveillance system registered more positive tests for adenoviral infection in 1- to 4-year-old-children, than in comparable periods in the previous five years, which could suggest a post-pandemic peak, unrelated to the surge of new AH cases.[4]

Additionally, in our first case, CMV was detected by PCR method on the blood which could have had justified the whole clinical picture. But since there were negative IgM antibodies and the detected viral load detected by the PCR method was low, at around 100 copies/mL, we consider this virus an unlikely aetiology for the AH. The detection of low levels of CMV by the PCR method could be explained by a reactivation of previous infections, in a context of a probable immunocompromised state, similar to the reactivation of EBV seen in patients who go through stem cell transplantation.[5] There are reports of positive EBV by PCR testing with negative EBV IgM antibodies in the context of some these unexplained hepatitis cases, and even other agents such as CMV have also been identified in some cases, although in lower frequency.[5-7,9]

Another possible theory is that all these newly identified AH cases can be due to acute COVID-19 (with perhaps a new variant and incidental isolation of other viruses) or that we could be looking at yet another form of a post infectious

SARS-CoV-2 syndrome.[4,6,7,9]

Weeks after the SARS-CoV-2 delta variant outbreak, there were reports in India of 37 children with mild hepatitis with preserved synthetic liver function and no jaundice.[7,10] Although these seem to be less severe than the newly reported AH cases, it cannot be ruled out that they can still represent a more severe end of spectrum of the same condition.[7] However, this seems to be unlikely, since most children with AH in the UK and other countries have, so far, tested negative for SARS-CoV-2 acute infection on admission.[4,6,7,9] Nevertheless, it is logical that most of these children had had a previous COVID-19 infection and serological testing has been supportive of this fact.[9]

Another prominent hypothesis to consider is the possibility of a shared role between SARS-CoV-2 and other viruses (such as adenovirus), in the pathophysiology of these unexplained hepatitis cases.[4] Investigations on how SARS-CoV-2 could alter the immune response to infection, allowing for a more severe adenoviral infection are ongoing.[4,6,7,9] There are current theories that infection with SARS-CoV-2 can lead to the establishment of a viral reservoir persisting in the GI tract, and progressively releasing viral proteins across the epithelium, leading to constant non-specific T-cell activation.[6] This unceasing activation is most likely due to a superantigen motif in the spike protein that resembles staphylococcal enterotoxin B.[6] It is known that, in mice models, infection with adenovirus makes them more susceptible to subsequent staphylococcal enterotoxin B-mediated toxic shock, which leads to liver failure and death, so extrapolating the data to an *in vivo* scenario allows us to speculate that a child with previous SARS-CoV-2 infection and possible persistence of viral reservoir, infected with an adenovirus with GI-trophism (such as F41), could suffer from an immune deregulatory state that could culminate in severe AH and eventual liver failure.[6]

Basal immune dysregulation or suppression is thought to contribute in some part to explain these cases, but evidence is still lacking.[4-7,9] Physical isolation during the pandemic gave rise to a lack of exposure to common pathogens, resulting in an immunodeficiency state-like, with higher susceptibility to other viruses after relaxation of the pandemic restrictions, which therefore allowed for rarer outcomes of common infections to be detected.[4,7]

Concerning SARS-CoV-2, in our first case, the positive IgG anti-nucleoprotein and anti-S protein for SARS-CoV-2, indicates a previous infection corroborated by the clinical history. In the second case, negative IgG anti-nucleoprotein but positive IgG anti-S protein for SARS-CoV-2 remains a mystery as the child's mother denies any previous (at least symptomatic with laboratory evidence) infection and the boy had not been vaccinated, but we speculate it may also suggest previous infection not diagnosed in the acute state by nasopharyngeal swab PCR or other similar method. As is internationally reported, our two cases have not been vaccinated which makes a post-vaccine reaction an unlikely scenario.[4-7]

Both of our cases had a favourable outcome, like most literature reports, and neither child had synthetic liver failure, with coagulation issues, or need of transplant.

As the origin of these severe AH cases remains overall still a mystery for the scientific and medical community, it is important to notify them according to regional and national protocols.

These cases should make us wonder about these children's basal immune status, the role SARS-CoV-2 may play in a possible upregulation and explore other potential underlying causes, besides considering adenovirus upfront as the most likely suspect.

The prognosis appears to be good in most cases, even though there is a non negligible risk of acute hepatic failure and need of transplant. As such, prompt identification and close follow-up are required.

AUTHOR CONTRIBUTIONS

RCC: Draft of the article, data acquisition and analysis.

CSE: Critical review of the manuscript, contribution to data analysis and interpretation.

PF, LV: Design of the article, critical review of the manuscript, final approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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Table 1 – Laboratorial evaluation of patient 1 (7-month-old girl)

	2022/04/06	2022/04/10	2022/04/13	2022/04/27	Reference values*
Hb (g/dL)	10.9	11.4	11.2	11.3	10.5 – 14.0
Leuc (cel/uL)	9900	7600	10100	8700	6000 – 14 000
Plat (cel/uL)	**173 000**	**84 000&**	321 000	334 000	150 000 – 400 000
PT (sec)		12.43	12.73	11.2	10.3 – 12.8
INR		1.16	1.19	1.06	
aPTT (sec)		23.48	**34.46**	27.70	21.6 – 28.7
pCr (mg/dL)	**4.38**	0.36	0.17		0.08 – 1.12
AST (U/L)	**758**	**1059**	**782**	**219#**	22 – 63
ALT (U/L)	**838**	**1386**	**677**	**259#**	8 – 32
GGT (U/L)	25	**168**	**107**	29	5 – 32
LDH (U/L)		**970**	**715**	385	150 – 580
Total bilirubin (mg/dL)		0.4		0.38	< 1.00
Direct bilirubin (mg/dL)		**0.21**		0.12	0.00 – 0.20
Indirect bilirubin (mg/dL)		0.19		0.26	0.20 – 0.80

ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Hb: haemoglobin; INR: international normalized ratio; LDH: lactate dehydrogenase; Leuc.: leucocyte count; Plat: platelet count; PT: prothrombin time; sec: seconds

* Normal range reference values for age stated on Nelson's Textbook of Pediatrics (Chapter 748, 21st Edition, published in 2020) were considered. Reference values not present in this chapter were substituted for those considered by the laboratory at our institution.

By May 24th 2022, AST was of 47 U/L and ALT was of 37 U/L (values obtained in outpatient work-up).

& No pseudo-thrombocytopenia was detected by our laboratory and a double confirmatory essay was performed in the same sample; the patient was not submitted to any platelet transfusion.

Table 2 – Laboratorial evaluation of patient 2 (8-year-old boy)

	2022/04/09	2022/04/10	2022/04/11	Reference values*
Hb (g/dL)	13.8	12.4		11.5 – 14.5
Leuc (cel/uL)	11500	5500		4000 – 12 000
Plat (cel/uL)	22300	215 000		150 000 – 400 000
PT (sec)	12.38	**12.97**		10.3 – 12.8
INR	1.16	1.21		
aPTT (sec)	23.18	25.80		23.0 – 31.9
pCr (mg/dL)	0.22	0.14	0.13	0.06 – 0.79
AST (U/L)	**1081**	**651**	**391#**	15 – 50
ALT (U/L)	**1999**	**1656**	**1408#**	5 – 45
GGT (U/L)	26	29	**42**	5 – 32
LDH (U/L)	**651**	426		150 – 500
Total bilirubin (mg/dL)	0.9	**1.0**		< 1.00
Direct bilirubin (mg/dL)	**0.29**	**0.39**		0.0 – 0.20
Indirect bilirubin (mg/dL)	0.61	0.70		0.20 – 0.80

ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Hb: haemoglobin; INR: international normalized ratio; LDH: lactate dehydrogenase; Leuc.: leucocyte count; Plat: platelet count; PT: prothrombin time; sec. seconds

* Normal range reference values for age stated on Nelson's Textbook of Pediatrics (Chapter 748, 21st Edition, published in 2020) were considered. Reference values not present in this chapter were substituted for those considered by the laboratory at our institution.

By May 17th 2022, AST was of 26 U/L and ALT was of 22 U/L (values obtained in outpatient work-up).