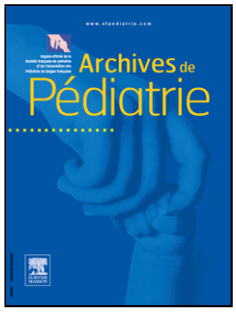
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



Child with liver transplant recovers from COVID-19 infection. A case report

A. Morand MD PhD B. Roquelaure P. Colson S. Amrane E. Bosdure D. Raoult J-C Lagier A Fabre

PII: S0929-693X(20)30110-X

DOI: https://doi.org/doi:10.1016/j.arcped.2020.05.004

Reference: ARCPED 4823

To appear in: *Archives de pédiatrie*

Received Date: 15 April 2020

Revised Date: 27 April 2020

Accepted Date: 2 May 2020

Please cite this article as: Morand A, Roquelaure B, Colson P, Amrane S, Bosdure E, Raoult D, Lagier J-C, Fabre A, Child with liver transplant recovers from COVID-19 infection. A case report, *Archives de pédiatrie* (2020), doi: https://doi.org/10.1016/j.arcped.2020.05.004

Child with liver transplant recovers from COVID-19 infection. A case report

Short title: A child with liver transplant recovers from COVID-19 infection

A. Morand [1,2*], B. Roquelaure[3], P. Colson[2,4], S. Amrane [2,4], E. Bosdure[1], D. Raoult [2,4], J-C Lagier[2,4], A Fabre[3,5].

1. Department of Infant Medicine and Specialized Pediatrics, La Timone Children Hospital, Aix Marseille University, APHM, 13005 Marseille, France

2. Aix Marseille University, IRD, APHM, MEPHI, 13005 Marseille, France

3. Department of Pediatric Gastroenterology and Hepatology, Multidisciplinary pediatric, La Timone Children Hospital, Aix Marseille University, APHM, 13005 Marseille, France

4. IHU-Méditerranée Infection, 13005 Marseille, France

5. Aix Marseille Univ, INSERM, MMG, 13005 Marseille, France

*__Corresponding Author:__

Doctor Aurélie Morand, MD-PhD

Department of Infant Medicine and Specialized Pediatrics, La Timone children hospital, 278 Rue Saint-Pierre, 13005 Marseille, France - Tel: +33 (0)4 91 38 68 17 - Fax: +33 (0)4 91 38 68 09 - E-mail: aurelie.morand@ap-hm.fr

***Declaration of interest**: None*

***Financial disclosure**: None*

Abstract:

We present the case of a 55-month-old girl who recovered from coronavirus disease 2019 (COVID-19) infection 5 months after undergoing liver transplantation; she had a co-infection with Epstein–Barr virus (EBV). To the best of our knowledge, this is the first case report of a COVID-19 infection in a pediatric patient with liver transplantation. Additionally, this is also the first report of confirmed co-infection between COVID-19 and EBV. On the basis of this case, we suggest that liver transplantation is not associated with COVID-19

symptom severity and development. Moreover, COVID-19 and EBV co-infections do not seem to aggravate the clinical outcome.

Keywords: COVID-19; children; liver graft; biliary atresia

We herein present the case of a 55-month-old girl who was infected with coronavirus disease 2019 (COVID-19) 5 months after undergoing liver transplantation. After an uneventful birth at term, she was diagnosed with congenital cholestasis due to biliary atresia and underwent Kasai portoenterostomy (KPE) at 53 days of age. KPE was partially successful, but in the following years she developed portal hypertension with refractory ascites and angiocholitis. Liver transplantation (from her father) was performed without major complications at the age of 50 months. The patient was discharged 20 days after the procedure on tacrolimus immunosuppression therapy and with no immunization against Epstein–Barr virus (EBV) before the transplantation. She had mildly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (approx. 1.5 of upper limit of normal [ULN]) levels, but normal bilirubin and gamma glutamyl transferase (GGT) levels. A mild increase in the GGT level (approx. 2 ULN) after 96 days of transplantation prompted magnetic resonance imaging (MRI) and ultrasound (US) examinations, which showed a mild dilatation of the intrahepatic biliary tract possibly linked to an anastomotic stenosis. Moreover, the girl presented with an asymptomatic EBV primary infection linked to the transplantation (the father was EBV positive) with a high viral load in the blood. A radiological angioplasty procedure was planned. She weighed approximately 15 kg and her usual treatment consisted of tacrolimus (0.07 mg/kg b.i.d.), acetylsalicylic acid (4.7 mg/kg qd), and ursodeoxycholic acid (10 mg/kg b.i.d.).

A few days before the child's presentation, the mother, a 29-year-old woman with no medical history, presented with rhinopharyngitis. She felt progressively tired and had a fever, cough, polypnea, thoracic pain, and headache. She was referred to the Méditerranée Infection University Hospital Institute where she was diagnosed with COVID-19 by RT-PCR of a nasopharyngeal swab [1]. She was hospitalized in the Contagious Infections Diseases Department. Low-dose computed tomography showed bilateral, asymmetrical, peripheral frosted-glass images and two alveolar condensation foci in two different segments of the right

lung. This was compatible with COVID-19 pneumonia. The mother was treated with oral hydroxychloroquine and oral azithromycin[2]. On the fourth day of treatment, the results of her nasopharyngeal samples were negative and within 8 days she was discharged from hospital and followed up as an outpatient.

The young liver transplant girl had rhinitis starting from mid-March, 2020, shortly after the onset of her mother's symptoms. Two days later, she suffered from fever, cough, and polypnea, and 3 days later she was referred to the Méditerranée Infection University Hospital Institute at the same time as her mother, where she was also diagnosed with COVID-19 after a nasopharyngeal swab test. At the time of admission, the girl had only polypnea but no fever or other signs of respiratory distress. Her blood pressure was 130/90 mmHg, her pulse was 130/min, and her oxygen saturation (breathing in ambient air) was 99%. She had no inflammatory syndrome (C-reactive protein [CRP], 3.2 mg/L), and her chest radiography showed a focal alveolar condensation of the lingula and a stable mediastinal enlargement. The results of her liver function tests were worse when compared with the results during her last hospitalization in February. The girl showed signs of anicteric cholestasis (GGT approx. 5 ULN) and cytolysis (AST approx. 4 ULN, ALT approx. 3 ULN). US of the liver showed an aggravation of the transplanted biliary tract stenosis and an elevated EBV blood viral load (1,560,000 copies/mL). She was not subjected to COVID-19-specific treatment. The girl’s health improved by treating the symptoms using 15 mg/kg of paracetamol every 6 h. Her nasopharyngeal swab samples came back negative 11 days after the first positive test. She recovered from COVID-19 despite the high level of immunosuppression caused by her tacrolimus treatment (T0 8.8 ng/mL). We reduced the dose of tacrolimus to 0.04 mg/kg b.i.d. Management of the liver transplant was organized 1 week after this acute event.

To the best of our knowledge, this is the first case report of a liver transplantation patient with COVID-19. Although children seem to have a less severe reaction to COVID-19 than

adults [3], even when they have significant health complications [4], there have been some doubts regarding immunosuppression therapy and the risk of severe infections as they are usually negatively correlated. An immunocompromised state has been associated with increased risk of severe lower respiratory tract disease in patients with coronavirus [5]. Contrary to other viruses, during the COVID-19 infection, the host's innate immune response seems to be the main cause of lung tissue damage [6]. It should be noted that the most important factors in adult patients are age, sex, and a history of hypertension [7]. A report of the successful recovery of 52-year-old renal transplantation patient was recently published [8].

Additionally, this is also the first report of confirmed co-infection between COVID-19 and EBV. Two studies reported patients having a positive serology result for EBV at the same time as a COVID-19 infection, but EBV DNA was not assessed [9,10]. A single study conducted in China aimed to assess the role of EBV co-infection during COVID-19. In all, 35 out of 62 COVID-19 patients (56.5%) were seropositive for EBV viral capsid antigen (VCA) IgM antibody, which reflects an acute EBV infection or reactivation [10]. EBV was reported to be correlated with a more severe course of COVID-19. The authors noted that EBV-positive COVID-19 patients had a 3.64-fold higher risk of presenting with fever (95% CI: 1.26–10.5; p=0.02), higher CRP levels (p=0.01), and a lower proportion of CD8+ and CD4/CD8 lymphocytes (p=0.048 and =0.046, respectively) than EBV-negative patients. The median recovery time for EBV-seropositive COVID-19 patients was higher than for EBV-negative patients, without being statistically significant (p=0.07) [10]. These authors hypothesized that EBV infection and COVID-19 share some pathogenic characteristics such as an overactivation of T cells, which can lead to severe immune injury [11]. In fact, even if EBV infection is often asymptomatic [12], some people present with fever, asthenia, myalgia, sore throat, anorexia, skin rash, and the disease can be fatal, especially in immunocompromised individuals [13].

Therefore, the clinical case of our young immunocompromised patient recovering from EBV infection at the same time as COVID-19 is particularly interesting.

The hepatic anicteric cholestasis and cytolysis of our patient was probably due to her transplant state, as no hepatitis during COVID-19 infection was described in the literature [14].

On the basis of this case, we suggest that liver transplantation is not associated with COVID-19 symptom severity and development, even when there is a high level of immunosuppression under tacrolimus treatment. Moreover, COVID-19 and EBV co-infections do not seem to aggravate the clinical outcome.

Acknowledgments: We thank the family for allowing us to publish this case report.

References:

1.Amrane S, Tissot-Dupont H, Doudier B, et al. Rapid viral diagnosis and ambulatory management of suspected COVID-19 cases presenting at the infectious diseases referral hospital in Marseille, France, - January 31st to March 1st, 2020: A respiratory virus snapshot. Travel Med Infect Dis 2020:101632. doi: 10.1016/j.tmaid.2020.101632. [Epub ahead of print]
2. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 20:105949. doi: 10.1016/j.ijantimicag.2020.105949.
3. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Engl J Med 2020 ; 382:1663-5.
4. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020 Mar 16. pii: e20200702. doi: 10.1542/peds.2020-0702. [Epub ahead of print]
5. Ogimi C, Englund JA, Bradford MC, et al. Characteristics and Outcomes of Coronavirus Infection in Children: The Role of Viral Factors and an Immunocompromised State. J Pediatric Infect Dis Soc 2019 28;8:21-8
6. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl 2020 doi: 10.1002/lt.25756. [Epub ahead of print]
7 Shi Y, Yu X, Zhao H, et al. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care 2020;24:108.
8. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant 2020 doi: 10.1111/ajt.15869. [Epub ahead of print]
9. Wang Y, Liu Y, Liu L, et al. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. J Infect Dis. 2020： pii: jiaa119. doi: 10.1093/infdis/jiaa119. [Epub ahead of print]
10. Chen T, Song J, Liu H, et al. Positive Epstein-Barr Virus Detection in Corona Virus Disease 2019 (COVID-19) Patients. Research Square 2020. DOI: 10.21203/rs.3.rs-21580/v1
11. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.
12. Sousa H, Silva J, Azevedo L, et al. Epstein-Barr virus in healthy individuals from Portugal. Acta Med Port 2011;24:707-12.

13. He H, Wang Y, Wu M, et al. Positive Epstein-Barr virus detection and mortality in respiratory failure patients admitted to the intensive care unit. Clin Respir J 2017;11:895-900.
14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 28;395:1054-62.