Anales de Pediatría 100 (2024) 465–474

analesdepediatría

www.analesdepediatria.org

SCIENTIFIC LETTER

Severe adenovirus infection: presentation of 3 cases

Infección grave por adenovirus: descripción de 3 casos

Dear Editor:

In children, infection by adenovirus is a frequent cause of self-limiting, mild to moderate febrile and/or respiratory illness, but in some instances it can cause severe disease followed by chronic sequelae. We present 3 cases of severe adenovirus infection that illustrate the broad clinical spectrum of this pathogen and the short- and long-term impact of the infection.

A boy aged 22 months with acute bronchitis of 2 day's duration was transported to the emergency department in an ambulance due to hypoxaemia with an oxygen saturation (SaO_2) of 87%, tachypnoea with 58 bpm, generalized retractions and bilateral expiratory wheezing. The patient experienced cardiac arrest requiring orotracheal intubation and mechanical ventilation in the intensive care unit for 8 days. Testing by polymerase chain reaction of a throat swab specimen turned out positive for adenovirus and respiratory syncytial virus. After extubation, inspiratory and expiratory rhonchi, bilateral coarse crackles and the need for oxygen therapy persisted for three weeks, prompting performance of a lung CT scan that revealed a bilateral mosaic attenuation pattern compatible with postinfectious bronchiolitis obliterans (PiBO[1] (Fig. 1A). Treatment of PiBO was initiated with intravenous high-dose methylprednisolone, azithromycin, montelukast and acetylcysteine.[2] As a complication, the patient developed tracheal stenosis of 60%–70% secondary to intubation, diagnosed by a chest TC scan and flexible bronchoscopy that allowed visualization of tracheal granuloma (Fig. 1B) and treated with repeated balloon dilations and nebulised budesonide, leaving residual stenosis of 20%–30% (Fig. 1C). The respiratory manifestations improved gradually, and the patient was discharged 60 days after admission without need of oxygen therapy. The outcome at 1 year is satisfactory, with no signs of respiratory distress, although the lung sounds continue to be abnormal with bilateral coarse crackles. The patient experiences acute episodes of infectious bronchitis that are managed with inhaled salbutamol and oral corticosteroids.

A boy aged 3 years presented with increased work of breathing in the context of febrile acute bronchitis. The salient findings of the physical examination were increased work of breathing with generalized retractions, tachypnoea with 70 bmp, bilateral expiratory wheezing with hypoventilation in the left hemithorax and an SaO_2 of 84%. The plain chest radiograph showed complete opacification of the left hemithorax with tracheal shift toward the involved lung and hyperinflation of the contralateral lung, all of which was compatible with complete atelectasis of the left lung (Fig. 2A). A few hours later, a flexible bronchoscopy examination revealed mucus plugging in the left main bronchus occluding the entire bronchial lumen. Aspiration achieved full clearance of the plugging, with removal of bronchial casts (Fig. 2B), and full re-expansion of the left lung with rapid improvement of the respiratory symptoms. Testing of a bronchoalveolar lavage sample detected adenovirus, confirming the diagnosis of plastic bronchitis secondary to adenovirus infection, an association that is rare in our region.[3,4] The patient was then discharged, at which time the physical examination was normal, and has since experienced recurrent episodes of mild bronchitis.

A girl aged 2 years presented with malaise, vomiting and high fever of 4 days' duration. The physical examination evinced poor general health, palpable hepatomegaly of 2–3 finger widths and a Glasgow score of 12–13 points. The blood glucose level as 26 mg/dL with a ketone body concentration of 1.3 mg/dL and metabolic acidosis with a lactate level of 11.7 mmol/L. Further blood tests revealed an ammonia level of 528 μmol/L, hypertransaminasaemia (gamma-glutamyl transferase 98 U/L; aspartate aminotransferase 16 658 U/L and alanine aminotransferase 7384 U/L), C-reactive protein level of 3.95 mg/dL and severe coagulopathy with a prothrombin time percent activity of 9% and an international normalized ratio of 7.95. The abdominal ultrasound scan found hepatomegaly and gallbladder oedema. These findings, suggestive of acute liver failure, prompted transfer of the patient to a reference centre, where she underwent liver transplantation for management of fulminant hepatic failure. Adenovirus was detected in the bloodstream, leading to diagnosis of acute liver failure due to adenovirus infection in the context of an outbreak of severe acute hepatitis that affected 1010 children from 35 countries across the world in the first half of 2022 and associated with infection by serotype 41.[5] During the post-transplantation follow-up, there has been no evidence of complications or acute transplant rejection. The patient remains in treatment with tacrolimus, which she tolerates well.

DOI of original article: https://doi.org/10.1016/j.anpedi.2024.03.008

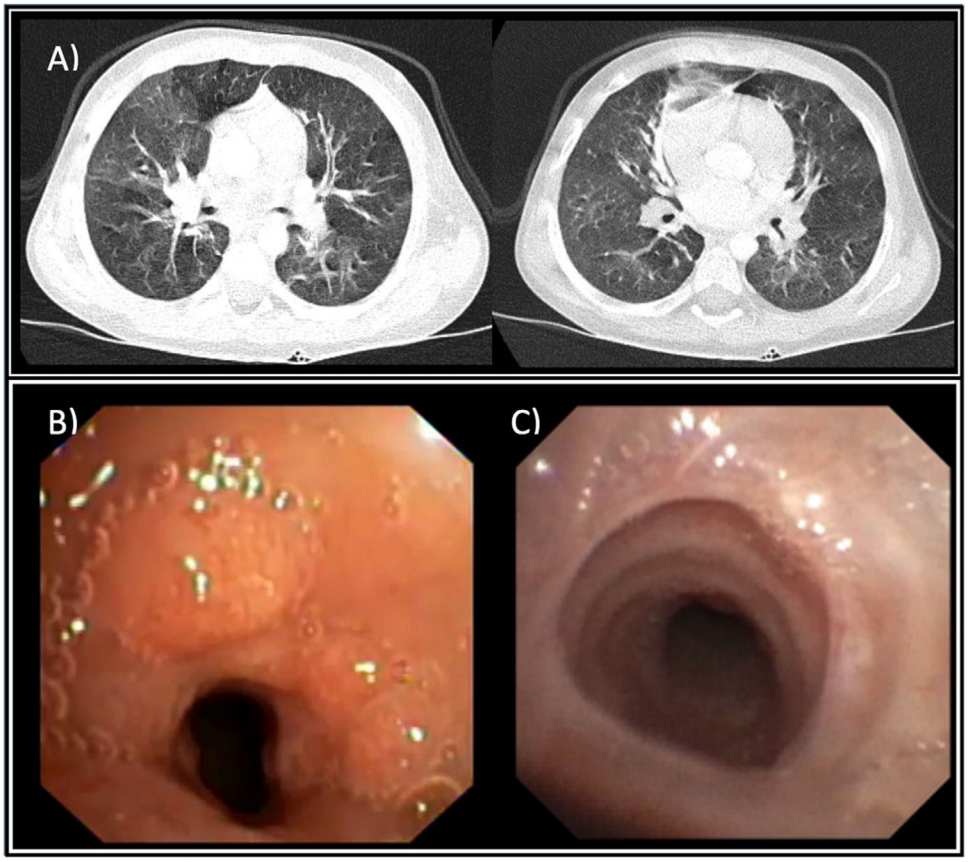

Figure 1 (A) Lung computed tomography scan: bilateral mosaic attenuation pattern compatible with bronchiolitis obliterans. (B) Flexible bronchoscopy: tracheal stenosis with reduction of 60% to 70% of the tracheal lumen due to granuloma. (C) Flexible bronchoscopy, 3 months after image B: residual membrane after steroid therapy and dilations.

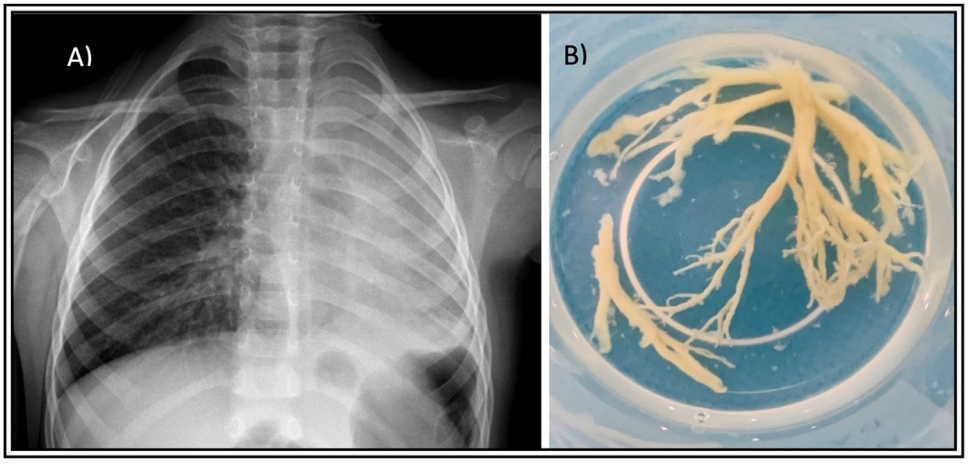

Figure 2 (A) Complete opacification of left hemithorax due to massive lung atelectasis with hyperinflation of the contralateral lung. (B) Bronchial casts removed during flexible bronchoscopy.

We consider that the cases presented are examples of the phenomenon known as ''immunity debt'',[6] which we have been experiencing since 2022 after the lifting of the restrictions imposed to fight SARS-CoV-2 and is characterised by an increase incidence and virulence of classical pathogens due to the reduction in herd immunity resulting from prolonged periods of decreased exposure, as was the case during the recent COVID-19 pandemic.

References

1. Teper A, Colom AJ, Schubert R, Jerkic PS. Update in postinfectious bronchiolitis obliterans. Pediatr Pulmonol. 2023, http://dx.doi.org/10.1002/ppul.26570. Online ahead of print.
2. Weng T, Lin X, Wang L, Lv J, Dong L. Follow-up on the therapeutic effects of a budesonide, azithromycin, montelukast, and acetylcysteine (BAMA) regimen in children with post-infectious bronchiolitis obliterans. J Thorac Dis. 2021;13:4775–84.

3. Zeng L, Wei J, Tang Y. Clinical characteristics of human adenovirus plastic bronchitis in 10 pediatric cases: a retrospective study of seven years. Virol Sin. 2021;36:550–4.
4. Yuan L, Huang JJ, Zhu QG, Li MZ, Zhuo ZQ. Plastic bronchitis associated with adenovirus serotype 7 in children. BMC Pediatr. 2020;20:268.
5. Phan J, Eslick GD, Elliott EJ. Demystifying the global outbreak of severe acute hepatitis of unknown aetiology in children: a systematic review and meta-analysis. J Infect. 2023;S0163-4453(23):00580–7.
6. Calvo C. Changes in the epidemiology of infections in children. Is there an immune debt? Only for respiratory viruses? An Pediatr. 2023;98:155–6.

Ana Cristina Galindo García[a,*], Inés Teresa Bolsa Ferrer[a], Paula Casajús Pelegay[a], Ruth García Romero[b], Carlos Martín de Vicente[c]

[a] *Servicio de Pediatría, Hospital Universitario Miguel Servet, Zaragoza, Spain*
[b] *Unidad de Gastroenterología Pediátrica, Hospital Universitario Miguel Servet, Zaragoza, Spain*
[c] *Unidad de Neumología Pediátrica, Hospital Universitario Miguel Servet, Zaragoza, Spain*

* Corresponding author.
E-mail address: acgalindog@salud.aragon.es (A.C. Galindo García).

https://doi.org/10.1016/j.anpede.2024.05.005

The clinical complexity of *PKHD1* gene: from neonatal lethality to casual diagnosis in late pediatric stages

La complejidad clínica del gen *PKHD1*: de la letalidad perinatal al diagnóstico casual en etapas pediátricas tardías

Dear Editor,

Autosomal recessive polycystic kidney disease (ARPKD), a rare inherited ciliopathy primarily involving the kidney and liver, is in most cases caused by pathogenic variants of the *PKHD1* gene (locus 6p21.1-p12) encoding the fibrocystin protein.[1] Historically, it has been considered a heterogeneous disease in terms of its presentation and outcomes, and a clear genotype-phenotype correlation has not been established.[1]

Focusing on the clinical presentation at onset and the course of disease during the paediatric age range, we reviewed the health records of 7 patients with a diagnosis of ARPKD, all with pathogenic variants of *PKHD1*, to describe the phenotype of the disease and attempt to contribute data on clinical aspects that have yet to be fully elucidated.

Genetic testing was carried out with a gene panel that included several genes contemplated in the differential diagnosis of ARPKD (*PKD1, PKD2, PKHD1, UMOD, MUC1, REN, HNF1B, OFD1, TSC1, TSC2, COL4A3, COL4A4, COL4A5*) with the Ion Torrent (IG S5 Sequencer, Thermo Fisher Scientific, Waltham, MA, USA) next generation sequencing (NGS) platform. Variants were identified with the Variant Caller version 5 software (Thermo Fisher Scientific, Waltham, MA, USA). All genetic findings were corroborated by means of Sanger sequencing.

The study was approved by the Research Ethics Committee of the Principality of Asturias.

Table 1 presents the clinical characteristics at baseline and during the follow-up and presents the pathogenic variants of the *PKHD1* gene detected in the 7 patients. As would be expected in a sample including recently diagnosed cases, most patients (5/7) received the diagnosis antenatally, although only 2 cases were diagnosed as early as the second trimester of gestation, the period when diagnosis is most common at the time of this writing. The clinical manifestations in patients in our case series reflected the substantial phenotypic heterogeneity of ARPKD, including late termination of pregnancy, severe or even fatal respiratory and renal complications that required complex treatment approaches in the early postnatal period, mild and slowly progressing impairment of renal function and even chance diagnosis during childhood.

When it came to diagnosis, in agreement with the previous literature, the presence of bilateral enlarged echogenic kidneys and oligohydramnios was the presentation most frequently leading to prenatal detection of ARPKD.[2] However, we ought to highlight two clinically relevant aspects deduced from the features observed in our patients, on one hand, while kidney enlargement is found in nearly every case, the presence of normally sized kidneys does not rule out the disease (patient 5 had kidneys of normal size at age 8 years); on the other, the presence of renal cysts detectable by ultrasound is not a common feature in cases diagnosed in the perinatal period, which may give rise to diagnostic uncertainty if the clinician and/or radiologists are not acquainted with the disease.

Our findings also corroborated the strong association between prenatal nephromegaly and oligohydramnios and greater postnatal disease severity. Along with other renal and nutritional problems, this association also seems to be closely related to respiratory complications,[2] secondary to pulmonary hypoplasia, pneumothorax or abdominal distention itself, which may be fatal in up to 30% of cases,[3] as occurred in patient 6 in our series.

Among the less frequently described clinical aspects of ARPKD, although they are not rare, given their presence in this case series, we ought to highlight the low frequency of surgical management with nephrectomy, an approach that is usually indicated due to the negative impact of

DOI of refers to article: https://doi.org/10.1016/j.anpedi.2024.04.001