CASE REPORT

Severe parainfluenza pneumonia in a case of transient hypogammaglobulinemia of infancy

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SUMMARY

Human parainfluenza viruses (HPIVs) infection, largely known to cause self-limiting bronchiolitis and pneumonia in immune competent patients, can lead to severe to fatal pulmonary disease in immune disorders, such as primary or acquired-immune deficiencies. We report the case of a 1-year-old child who developed an acute respiratory distress syndrome. Because of a progressive respiratory failure unresponsive to conventional treatment extracorporeal membrane oxygenation (ECMO) was rapidly started. HPIV-3 infection was diagnosed on the rhinopharyngeal fluid and immunological examinations revealed a hypogammaglobulinemia. A combination therapy with ribavirin, intravenous immunoglobulin (IVIG) and steroid under ECMO support was started with considerable improvement. Subsequent analysis and more specific immunological assessment resulted normal confirming the diagnosis of transient hypogammaglobulinemia of infancy (THI). This case highlights the importance of prompt therapy with early ECMO support in combination with ribavirin, IVIG and steroids in patients affected by severe HPIV-3 pneumonia and THI.

BACKGROUND

We report the case of a severe HPIV-3 pneumonia in a patient affected by transient hypogammaglobulinemia of infancy (THI), successfully treated with a therapeutic combination strategy including extracorporeal membrane oxygenation (ECMO), in association with systemic ribavirin, corticosteroids and intravenous immunoglobulins (IVIG). Treatment of uncommon viral pneumonia in childhood is debated and poor therapeutic tools are available,¹ particularly for rapid progressive cases.²

This case highlights the importance of combine different treatment strategies. Specifically in cases of severe rapidly progressive HPIV-3-related pneumonia, any drug available risk to be ineffective, with a consequent fatal outcome, if an early lung rest, provided by ECMO, is not given.

Moreover, this case shows that in children affected by severe and rapidly progressive pneumonia caused by opportunistic pathogens, an immune disorder should be suspected and ruled out. To our knowledge, this is the first report of a paediatric patient with THI and HPIV3 pneumonia successfully managed with ECMO.

CASE PRESENTATION

A 1-year-old child was admitted to our paediatric intensive care unit because of a moderate dyspnoea. Familial and physiological history was silent. The child presented cyanosis (SpO₂ 85%), tachypnoea with intercostal retractions and bilateral inspiratory crackles. Chest X-ray showed bilateral patchy consolidations in the right middle and left upper lung fields, with prominent perihilar and peribronchial thickening (figure 1A).

Continuous positive airways pressure delivered by helmet (H-CPAP)³ with a FiO₂ of 45% and a positive end expiratory pressure of 5 cm H₂O was suddenly started.

Despite the use of H-CPAP, the child did not show any improvement requiring oral intubation and mechanical ventilation.

A chest CT showed bilateral, multiple, non-cavitating nodules with irregular margins, bilateral upper lobes collapsed and bilateral pleural effusion (figure 2).

Pneumocystis carinii, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, adenovirus, RSV, human herpes virus 6, Ebstein-Barr virus and cytomegalovirus infection were ruled out. PCR examination on nasopharyngeal swab specimens resulted positive for HPIV-3.

The initial complete blood count showed normal haemoglobin level (11.5 g/dL), leucocytosis (37 000/μL, >90th percentiles), normal lymphocytes (5470/μL, 14.8%), normal chemistry profile and elevated platelet count (684 000/μL). Immunological findings revealed age-related mild CD4+penia (27.3%, <10th percentiles) and CD8+penia (9.9%, <10th percentiles), normal IgM (80 mg/dL) and IgA (21 mg/dL) levels but low age-related IgG values (189 mg/dL). Parents referred that previous routine blood tests performed at 5 month of age already showed hypogammaglobulinaemia (176 mg/dL).

On the third day of hospitalisation, despite medical treatment with endovenous wide-spectrum antimicrobial therapy and steroids her clinical condition and gas-exchange worsened and a venovenous (VV)-ECMO was initiated. We used a surgical approach from the internal jugular vein, inserting a 16F-Bi-caval dual lumen cannula. ECMO was instituted using a centrifugal pump (Pedivas, THORATEC PEDIVAS). Oxygenation was given with a blood flow of 700 mL/min and ventilator settings were adjusted to provide lung rest. Blood flow/gas flow ratio was approximately 1:1.

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Figure 1 Chest radiography: on admission (A), after 3 days from the beginning of extracorporeal membrane oxygenation support (B) and at discharge (C).

Oral therapy, via nasogastric tube, with ribavirin (120 mg/die) for 10 days was started during ECMO support. The child also received intravenous γ globulin (IVIG 400 mg/kg/daily for 5 days) in combination with bolus of steroids (methylprednisolone 30 mg/kg/die for 3 days). After 6 days of ECMO, the child showed a marked clinical and radiological improvement (figure 1B) and in the following 3 days the patient was weaned off from the extracorporeal support.

Six days after the end of ECMO the patient was extubated and transferred to the paediatric ward.

Owing to the hypogammaglobulinaemia, CD4+ penia and CD8+ penia, a deeper immunological evaluation was performed, in order to exclude primary immune deficiency.

Following analysis of CD40-ligand expression, in vitro production of immunoglobulin after CpG stimulation of B cells⁴

and titration of specific antibodies to haemophilus and pneumococcus excluded congenital immune deficiencies. Analysis of cytotoxic function by CD107+ expression on CD8+ T cell and lymphoproliferation to mitogens did not reveal impaired T-cell function.

The improvement of the general conditions in association with the normalisation of laboratory examinations confirmed the transitory nature of the immune disorder. The patient was discharged from the hospital on the 26th day of hospitalisation.

Six months after discharge, a CT angiography was performed and resulted negative, excluding vascular anomalies and showing the complete resolution of pulmonary lesions. The patient over the last 8 months of follow-up remained in good health condition achieving and maintaining normal levels of immunoglobulin, confirming the diagnosis of THI.

Figure 2 High-resolution chest CT scan performed on admission: sagittal cut of upper lobes (A), middle lobes (B), basal lobes (C) and coronal cut of the chest (D).

TREATMENT

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OUTCOME AND FOLLOW-UP

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DISCUSSION

HPIV-3 infection is a common cause of pneumonia and bronchiolitis among children younger than 1-year-old,^{2 5 6} however, extremely severe manifestations such as giant cell pneumonia have been described only in immune compromised patients affected by SCID or in haematopoietic stem cell transplant recipients under immune suppressive therapy.^{1 7-9} Although HPIV-3 infects two-thirds of children within the first year of life, most of them do not show any symptom. This is probably due to the fact that most children are born with neutralising antibody to all four types of HPIV, but these titres quickly fall during the first 6 months of life.¹⁰ Host defence against HPIV is mediated largely by humoral immunity; however, cytotoxic T-lymphocyte responses appear to be important in the clearance of virus from the lower respiratory tract directly acting on HN, P and NP HPIV-3 proteins.¹¹

In our case hypogammaglobulinemia supports the hypothesis that a suboptimal immune response contributed to the rapid deterioration of the clinical conditions caused by the virus. The subsequent progressive normalisation of the immunoglobulin level confirmed the diagnosis of THI.

This self-limiting disorder is characterised by an abnormal delay in the onset of IgG production with normal circulating B lymphocytes and normal capacity to synthesize specific antibodies in response to protein antigens. Although THI remain asymptomatic in many patients, it may be associated with recurrent infections, including sinusitis, otitis media and pneumonia.^{12 13} In this case is still unclear whether the virus itself could have had an additional impact on the transitory immune defect. In fact, it has been shown that HPV-3 is able to reduce the cytotoxic activity against the infection thus hampering an effective immune response. In fact HPV-3 possess two accessory proteins (V and C proteins) which are involved in the viral transcription and interferon (IFN) signalling.^{14 15} More specifically the HPIV-3 C protein is capable of counteracting the IFN signalling pathway by specifically inhibiting the activation of Signal Transducer and Activating of Transcription 1 (STAT-1) thus eluding the IFN-induced antiviral activity.¹⁴

Regarding the therapeutic approach, clinical evidences about ribavirin efficacy are discordant^{2 16 17} and at present, there are no licensed antiviral agents for the treatment of HPIVs infection.

In our case, the early initiation of ECMO support radically changed the course of illness allowing the combination treatment to be effective in the long run. This suggests that drugs would have been probably ineffective with a consequent fatal outcome, if an early lung rest provided by ECMO was not given.

ECMO originally applied to support the respiratory function of neonatal patients improved survival rates in patients with

severe acute respiratory distress syndrome not responding to other ventilation strategies.¹⁸ Moreover, it has been shown that viral pneumonia has a better outcome in terms of survival rates compared to other causes of respiratory failure.¹⁹ Although neurological sequelae such as intracranial haemorrhage or infarction still remains the major adverse event related to ECMO support,²⁰ our patient did not show any side effects. Our patient did not show any side effect. This positive outcome is likely to be due to the limited duration and to the short runs of the ECMO support. In conclusion our report suggest that in cases of severe rapidly progressive HPIV-3-related pneumonia, ECMO ventilation should be rapidly considered in order to permit the efficacy of a combination therapy with IVIG, ribavirin and steroids.

Learning points

- ▶ In cases of severe and rapidly progressive HPIV-3-related pneumonia extracorporeal membrane oxygenation ventilation should be rapidly considered in order to permit the efficacy of a combination therapy with intravenous immunoglobulin, ribavirin and steroids.
- ▶ Although transient hypogammaglobulinaemia of infancy remain asymptomatic in the majority of children, it may be associated with severe infectious diseases.
- ▶ In children affected by severe and rapidly progressive pneumonia caused by opportunistic pathogens, an immune disorder should always be suspected and ruled out.

Contributors NC, ECM, PDA, PP wrote the first draft of the manuscript. FS, MM and MDN attended the patient in the intensive care unit. AI provided ribavirin oral formulation. SC performed the immunological analysis. All authors revised and accepted the final version of the manuscript.

Competing interests None.

Patient consent Obtained.

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