Adenovirus Infection in Immunocompetent Children: Not Always as Innocent as Assumed

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Abstract

Adenovirus infection of respiratory or gastro-intestinal epithelial tissues is a common disease, frequently occurring in childhood. These infections mostly cause mild febrile respiratory and/or gastro-intestinal disease. Specific adenoviral subtypes may cause sepsis-like disease or central nervous system infections with severe symptoms and sequelae.

The goal of this paper is to describe the clinical presentation of different adenoviral infections in children and to stress that these often assumed innocent infections of childhood may also present as severe disease even in immunocompetent children.

We present four different clinical presentations in relation to adenovirus types and summarize the relevant literature on species-specific clinical presentation in immunocompetent children.

We conclude that clinical presentation of adenovirus infection in childhood is often species-specific and might present with severe symptoms mimicking serious bacterial infection. Viral diagnostic testing is important to differentiate between bacterial and viral disease in terms of disease progression and prognosis and may diminish unnecessary or prolonged antibiotic treatment. The use of semi quantitative molecular diagnostic methods (i.e. polymerase chain reaction and genotyping) may be used to discriminate between colonization and infection.

ABBREVIATIONS

BOOP: Bronchiolitis Obliterans with Organizing Pneumonia; CNS: Central Nervous System; CRP: C-Reactive Protein; CSF: Cerebrospinal Fluid; Ct-value: Cycle Threshold Value; HAdV: Human Adenovirus; HR-CT: High Resolution Computer Tomography; ORS: Oral Rehydration Solution; PICU: Pediatric Intensive Care Unit; PCR: Polymerase Chain Reaction

INTRODUCTION

Human adenovirus (HAdV) is a double-stranded DNA virus belonging to the family of Adenoviridae and the genus of Mastadenovirus. There are currently 70 described types of HAdV, divided over 7 species (A-G) [1-3]. Some studies on HAdV respiratory infections show seasonal variation with a peak in early winter [4,5]. While other studies however, describe peaks in the summer period or different peaks every year [6,7]. For gastrointestinal infections seasonal variation is not clear, with one study showing a peak in winter months and other studies showing a year round infection [8,6]. Transmission of the virus occurs by inhalation of aerosols from infected individuals, via the fecal-oral route and by direct conjunctival inoculation [1]. HAdV infection establishes an immune response of the innate and adaptive immune system. Eventually HAdV specific T-cells are produced, which show cross-reactivity with different HAdV species. This leads to a wide HAdV immunity in the course of life [1]. After primary infection HAdV persists in a latent state in lymphoid, intestinal and respiratory tissue [1]. In immunocompromised children, latency frequently leads to reactivation causing severe systemic disease [9]. In immunocompromised children prolonged asymptomatic shedding has been reported [8]. Risk groups for (severe) adenovirus infections are children, elderly and immunocompromised individuals. In children, HAdV mainly affects young children under the age of five [10,11]. In upper respiratory tract infections, HAdV accounts for up to 15% of known causative agents and in lower respiratory tract infections...
HAdV infection usually causes mild respiratory and/or gastro-intestinal disease. Children often present with fever, cough, rhinorhoea, conjunctivitis, diarrhea and/or vomiting. Less common presentations are lower respiratory tract infection, encephalitis, meningitis, hepatitis, nephritis and myocarditis [19]. More severe clinical presentations usually occur in immunocompromised children or children with an extensive medical history [20]. In rare cases, HAdV can cause sepsis-like disease leading to multiple organ failure with high morbidity and mortality rates, also in children with a normal immune status [10,21].

In one study on immunocompetent children, presenting with adenoviral infection 44% of children received antibiotics from their primary care physician prior to admission in hospital and 30% of admitted patients were empirically treated with antibiotics [6]. A study in the Netherlands, where antibiotic prescription generally is low, showed that in 57.4% of children who received antibiotics prescribed by their primary care physician for fever and respiratory symptoms, a virus was diagnosed in their nasopharyngeal swab [22]. Critical clinical assessment and awareness combined with sensitive molecular diagnostic techniques could potentially avoid unnecessary prescription of antibiotics, which could possibly influence the ongoing development of antibiotic resistance.

In this paper we describe four cases with different clinical presentations of HAdV infection in immunocompetent children. We put these different cases in perspective of what is studied on subtype specific clinical presentations and summarize what is reported on the relation between HAdV species and different clinical presentations in children with a normal immune status. Diagnostic methods are based on either cell culture and serotyping in the older cases and molecular diagnostic methods and genotyping in the more recent cases. HAdV infections in immunocompromised patients are well studied [1,23] and beyond the scope of this article.

CASES

Case 1

A 10-month-old girl, without a relevant medical history was admitted to the pediatric ward with fever and dehydration due to persisting diarrhea and vomiting. Upon admission she was treated with ORS administered by a nasogastric tube. After three days she improved and was no longer suffering from ongoing gastro-intestinal fluid losses and was discharged. PCR tested positive for HAdV species F DNA in a fecal sample, with a Ct-value of 26.

Case 2

A 7-month-old, previously healthy girl presented at the emergency department with fever, purulent conjunctivitis, cough and respiratory distress. She also developed diarrhea. The days before presentation she experienced symptoms of rhinorhoea. Her oxygen saturation in room air was 84% and oxygen therapy was started with good effect. Laboratory analysis revealed a C-reactive protein (CRP) level of 40 mg/L and leukocyte count of 16.5 10^9/L. Cultures of blood, conjunctivital secretions and nasopharyngeal swabs did not show growth of pathogenic bacteria. All the specimens were then tested for HAdV with viral culture and immunofluorescence techniques and returned positive for HAdV type 3, now known to belong to species B. With supportive care, consisting of oxygen therapy and nasogastric tube feeding during one week she recovered without any sequelae.

Case 3

A boy, two years of age and known with episodes of viral induced wheezing was admitted to a general hospital with signs of respiratory tract infection and diarrhea. He quickly deteriorated and developed respiratory insufficiency, despite the fact that both antibiotic and corticosteroid therapy were started. After intubation and stabilization he was transported to the nearest pediatric intensive care unit (PICU). He was mechanically ventilated with high pressures. Because of severe bronchospastic episodes, endotracheal and intravenously salbutamol was administered. Laboratory analyses showed a remarkably high CRP of 218 mg/L and signs of hepatitis (alanine aminotransferase 78 E/L, aspartate aminotransferase 48 E/L, gamma-glutamyl transferase 141 E/L and alkaline phosphatase 157 E/L). Chest X-ray examination showed bilateral infiltrative changes. Cultures of blood, feces and sputum returned negative for pathogenic bacteria. Viral culture of sputum, conjunctival secretions and feces was positive for HAdV type 3, belonging to species B, and viremia was confirmed with a positive HAdV PCR of 6,5 10^4 copies/mL in blood. Ventilatory support could gradually be decreased and after 10 days of mechanical ventilation the patient was successfully extubated. He remained in need of high oxygen levels and even after discharge he chronically remained in need of 1-3L/min O_2 via a nose tube and later non-invasive mechanical ventilation. Because the prolonged severity of his pulmonary disease was not fully understood a HR-CT was performed on day 11 after onset of symptoms. This showed severe bronchiectasis. Underlying pre-existing causes were excluded. Follow-up showed progressive lung disease because of bronchiolitis obliterans with organizing pneumonia (BOOP). We concluded that this severe sequela was caused by the HAdV infection.

Case 4

An 18-month-old boy was admitted to the PICU after febrile convulsions and subsequent respiratory insufficiency. He had a history of diarrhea, vomiting and high fever since 2 days. He was intubated and ventilated mechanically for 2 days and was also in need of inotropic therapy for 2 days, because of low blood pressures and oliguria, which was not anticipated. The chest X-ray showed consolidation of the right lung. The CRP level was 134 mg/L with a leukocyte count of 5.6 10^9/L. Cultures...
of blood, CSF, sputum and feces where negative for pathogenic bacteria. Sputum from the endotracheal tube showed a positive viral culture and by immunofluorescence technique HAdV type 2, belonging to species C was identified. All other body specimens, including CSF tested negative for HAdV. Antibiotics were continued for 7 days. He recovered without neurological or pulmonary sequelae.

**OVERVIEW AND DISCUSSION**

This paper describes four immunocompetent children with HAdV infection presenting with different clinical characteristics. These cases illustrate that HAdV may present on a spectrum varying from mild to severe and even life threatening disease, mimicking serious bacterial infection. In the literature many similar cases have been described in immunocompromised children [23]. We will discuss and summarize the recent literature and present what is known on the relation between HAdV species and their clinical presentation in immunocompetent children. For gastro-intestinal- and respiratory tract infections we will discuss the diagnostic challenges and make the point of the importance of differentiating between colonization and infection when using highly sensitive molecular diagnostic techniques.

**Clinical features of different adenovirus types**

Currently 70 HAdV types have been described, based on serology for neutralizing antibodies [2,13]. They are divided over 7 phylogenetic species. Species A (type 12,18, 31 and 61), F (type 40 and 41) and G (type 52) mainly cause gastroenteritis. Species B (type 3, 7, 11, 14, 16, 21, 34, 35, 50, 55 and 66), C (type 1, 2, 5, 6 and 57) and E (type 4) usually infect the respiratory system and species D (type 8, 9, 10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, 56, 58-60, 63-67,69 and 70) more specifically causes conjunctivitis [24,1,25,2,3]. The exact association between species or type and clinical expression is however not completely differential, and overlap in clinical presentation does occur.

**Gastroenteritis**

As presented in case one; HAdV is frequently detected in feces of children presenting with vomiting, diarrhea and fever. This mainly occurs in children between the ages of 6 to 24 months [18]. Up to 20% of young children admitted to hospital with symptoms of gastroenteritis tested positive for HAdV [14-18]. Most common HAdV types causing gastroenteritis are 40 and 41 belonging to species F [15,17,26,18]. Type 52, belonging to species G, was recently discovered to also specifically cause gastroenteritis [24]. HAdV types 1,2 (species C), 7 (species B), 19 (species D),18 and 31 (species A) however are also frequently detected in children with gastroenteritis, but are less specific [15,18]. Another study also detected type 3 (species B), type 5 (species C) and type 12 (species A) HAdV, in children with gastroenteritis [17]. These latter types are mainly known to cause respiratory disease and are nevertheless frequently detected in feces of children with gastroenteritis [14,17]. This might reflect prolonged gastro-intestinal shedding of HAdV after initial respiratory infection. Moreover, using PCR, HAdV has also been detected in up to 41.7% of fecal samples of asymptomatic children [8]. Is this primary infection, post-infectious shedding or colonization? The interpretation of these findings is difficult and further studies are needed to help improve the clinical relevance of these results. In case one the Ct-value of 26 makes the diagnosis of HAdV gastroenteritis likely, however not certain. Distinction between colonization or viral shedding and infection might be possible by establishing clinical cut-off values using semi-quantitative molecular methods, as described before in rotavirus gastroenteritis [14].

**Respiratory tract infections**

Adenoviral upper and lower respiratory tract infections are common in young children. HAdV is isolated in up to 18% of children with fever and respiratory symptoms [4,13]. In a longitudinal study 27% of upper respiratory tract infection episodes were caused by HAdV [27]. As shown in case two, common clinical presentation of HAdV respiratory tract infection consists of fever, rhinorrhea, cough and respiratory distress, often accompanied with conjunctivitis, known as pharyngoconjunctivitis [6,11].

One study performed in Hong Kong found that HAdV types 2, 3, 5 and 7, belonging to species B and C, are most prevalent in adenoviral upper respiratory tract infections in children [6]. Concomitant involvement of the gastro-intestinal tract is however not uncommon [6,12]. Tonsillitis is a common finding on physical examination. Up to 52% of adenoviral tonsillitis patients present with an exudative form mimicking bacterial infection [28,29].

In hospitalized children with a lower respiratory tract infection HAdV was detected in 15.7% to 30% of children [5,4,30]. One study showed 50% of co-infections with other viruses when detecting HAdV [4]. In lower respiratory tract infections respiratory distress with tachypnea is often observed and may be severe. As shown in case three, this may even lead to respiratory failure with need for mechanical ventilation. Moreover, lower respiratory tract infections caused by HAdV sometimes result in severe chronic pulmonary sequelae, such as BOOP, illustrated by case three. HAdV types isolated from children with lower respiratory tract infection belong to species C (1,2,5, and 6) and B (3,7, and 21) [31,6,32,13,11]. One study determined that HAdV bronchiolitis in young children in Hong Kong was mainly caused by type 2 and pneumonia in older children (3-5 years of age) by type 3 [6]. HAdV type 3 and 7 (species B) are specifically associated with the development of BOOP, a rather severe pulmonary complication of adenoviral lower respiratory tract infection [33,6,34].

Finding HAdV in respiratory specimens by highly sensitive molecular methods should always be interpreted in relation to clinical symptoms. HAdV may cause severe illness, but may also cause asymptomatic infections. In fact, in the study of Singleton et al. HAdV was detected in up to 16% of the samples from asymptomatic children [30]. This emphasizes the need for a method to improve clinical interpretation of these results, preferably quantitatively.

**CNS infection and CNS involvement in HAdV infections with other origin**

It is not common for HAdV to cause CNS infections. However, cases are described showing severe infections with neurological involvement in young immunocompetent children [21]. The most
common presentation of adenoviral CNS infection is encephalitis, followed by encephalopathy, meningitis, meningoencephalitis and cerebellitis [21]. In one case with encephalitis HAdV type 5 belonging to species C was isolated from post-mortem acquired brain tissue [35]. Another paper described a case of sudden death in a child, who turned out to have suffered from adenoviral meningitis [36]. A case series detected HAdV type 6 (species C), 7 (species B) and 12 (species A) in CSF from children presenting with meningoencephalitis [37].

Besides primary CNS infections, 3.3% of all HAdV respiratory infections present with signs of CNS involvement [19]. In almost one quarter of those children a lumbar puncture was performed, but HAdV was not detected in CSF [19]. This might explain the severe presentation of case four with a febrile seizure without proven CNS infection. Studies evaluating all children presenting with febrile seizures, demonstrated the presence of HAdV in 3.4 to 18.4% of the cases [38,39]. A relative risk of 4.3 was calculated for developing a febrile seizure following febrile illness by HAdV [38]. HAdV, detected in the isolates of these children, mainly showed type 3, 2 and 1 (in order of detected frequency, species B and C respectively). Another case series described encephalopathy caused by HAdV type 7 (species B) in children presenting with symptoms of gastro-intestinal or respiratory infection [40].

**Sepsis-like disease**

In immunocompetent children, HAdV type 3, 7 and 21 (species B) have been described as the cause of severe clinical disseminated disease involving liver (in case three), kidney and heart [10]. Moreover, HAdV can also present with sepsis-like disease, including petechiae [41], or a diffuse erythematous rash with edema [42], mimicking severe bacterial illness. Type 3, 7 (species B) and 5 (species C) are known to cause severe disseminated disease with a sepsis-like presentation in immunocompetent children [43,44,10], as also shown in the patient in case four, who was in need of inotropic support.

Systemic treatment of HAdV with cidofovir is still under discussion because of the often severe adverse effects, especially on kidney function, and is currently only indicated for severe infections in immunocompromised children [23].

**Mimicking bacterial disease**

HAdV is known to present with prolonged high fever with an average of 5 days [6,45]. HAdV not only mimics bacterial disease by its clinical presentation. Other markers that usually guide us in the direction of bacterial infection such as high CRP and high erythrocyte sedimentation rate (ESR) can also be markedly elevated in HAdV infection. Up to 56% of all HAdV positive children had CRP levels higher than 40 mg/L [19,11]. HAdV has been known to cause significantly higher CRP levels than other viral respiratory infections [46]. Concomitant with our cases, with a maximum CRP level of 218 mg/L in case three, another case series showed CRP elevation of up to 191 mg/L [45]. ESR was shown to be elevated >30 mm/h in 62.5% of type 1 (species C), 80.6% of type 2 (species C) and 33.3% of type 3 (species B) HAdV infection [11]. In this study mean ESR was higher in type 1 and 2 compared to type 3 infections. HAdV commonly presents with a persistent high neutrophil count [6].

All these markers make discrimination from bacterial disease very hard. Molecular testing could provide rapid results thereby making distinction easier.

**CONCLUSION**

Although not frequent, HAdV infection in immunocompetent children may present with severe clinical symptoms, thereby mimicking severe bacterial disease. Besides awareness for the often species-specific disease presentation, testing for HAdV could also decrease prescription or cessation of antibiotic therapy in an early stage of disease. Currently, molecular diagnostic techniques (e.g. PCR) are the preferred method of testing and will provide rapid results with a high sensitivity. Positive test results for HAdV in CSF and blood are confirmatory for disease, although this is not so clear for positive results of feces and respiratory tract specimens. In these specimens positive HAdV PCR results may also be found due to asymptomatic shedding or prolonged shedding after infection because of increased analytical sensitivity of molecular techniques. By using semi-quantitative real-time PCR results for these samples, we should be able to determine clinically relevant cut-off values in future research. This will improve distinction between colonization and infection and therefore enhance interpretation of molecular findings in critically ill children.

We conclude that clinical presentation of adenovirus infection in childhood is often species-specific and might present with severe symptoms mimicking serious bacterial infection. Viral diagnostic testing is important to differentiate between bacterial and viral disease in terms of disease progression and prognosis and may diminish unnecessary or prolonged antibiotic treatment. The use of semi-quantitative molecular diagnostic methods and genotyping may be used to discriminate between colonization and infection.

**REFERENCES**


