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Review Article

Adenovirus infections in paediatrics: Understanding the symptoms, diagnosis and treatment

Pooja Doddikoppad[1], Bhaskar Shenoy[1]

[1]Department of Paediatrics, Manipal Hospitals, Bengaluru, Karnataka, India.

***Corresponding author:**
Pooja Doddikoppad,
Department of Paediatrics,
Manipal Hospitals, Bengaluru,
Karnataka, India.

pujanarendra86@gmail.com

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ABSTRACT

Adenovirus infections in paediatrics present a significant health burden, causing various respiratory, gastrointestinal and ocular illnesses. Diagnosing adenovirus infections in pediatric patients can be challenging due to overlapping symptoms with other viral and bacterial infections. Molecular techniques, such as polymerase chain reaction, are highly sensitive and specific for adenovirus detection. Enhanced surveillance, accurate diagnosis, supportive management and preventive measures are crucial for reducing the morbidity and mortality associated with adenovirus infections in pediatric populations. Further research is needed to advance our understanding of adenovirus pathogenesis, develop effective antiviral therapies and improve vaccine strategies.

Keywords: Adenovirus, Symptoms, Diagnosis

INTRODUCTION

Adenoviruses are a common cause of respiratory, gastrointestinal, and ocular infections in paediatric populations. These viruses were first isolated from adenoid tissue.[1] They belong to the Adenoviridae family, which are small, non enveloped double stranded DNA viruses. They are responsible for a wide range of clinical manifestations, ranging from mild common cold-like symptoms to severe respiratory and systemic illnesses. This article aims to provide an overview of adenovirus infections in paediatrics, including their symptoms, diagnosis, and treatment options.

CHARACTERISTICS OF ADENOVIRUSES

Adenoviruses exhibit several distinctive features that set them apart from other viral pathogens. They possess an icosahedral capsid composed of 252 capsomeres, encapsulating their DNA genome. With a diameter of approximately 70–90 nanometres, these viruses are relatively large compared to other common viral pathogens. There are over 50 known serotypes of adenoviruses, classified into seven species (A–G), each exhibiting tropism for different host tissues and causing distinct clinical manifestations.[2]

EPIDEMIOLOGY

Transmission

Adenoviruses are highly contagious and can be transmitted through respiratory droplets, close personal contact, faecal-oral route, or contact with contaminated objects and surfaces (e.g.,

linens, pillows, and lockers,) or reactivation from a previous infection. The incidence of infection appears greatest.

In lower socioeconomic groups and situations of crowding, there is a higher incidence of infection. Epidemic disease commonly occurs in military recruits. Outbreaks, especially of pharyngoconjunctival fever, have followed exposure at swimming pools, summer camps, and childcare centres and in health-care settings.[2]

Populations at risk

Adenoviruses can affect individuals of all ages, but young children are more susceptible, usually from age 6 months to 2 years of age, and can occur as well in 5–9-year-old children and immunocompromised individuals.

Seasonality: Adenoviral infections can occur throughout the year, but some serotypes exhibit seasonal patterns, with increased incidence during late winter and early spring.

CLASSIFICATION

Serotypes

Adenoviruses are classified into different serotypes based on their surface antigens. At present, there are seven species (A–G) of human adenoviruses and each species contains multiple serotypes. For example, species C includes serotypes C1–C5, and species D includes serotypes D1–D89. Serotypes within a species may share certain biological properties but can also cause distinct clinical manifestations. Adenoviruses in subgroups B and C, predominantly Group C, have the ability to cause latent infections in lymphoid cells.[2]

Here is a breakdown of the species and some notable types within each species:

- Species A: Includes types 12, 18, and 31, among others
- Species B: Includes types 3, 7, 11 and 14, among others
- Species C: Includes types 1, 2, 5 and 6, among others. Type 5 (HAdV-5) is the most extensively studied and commonly used in research
- Species D: Includes types 8, 9, 17, 19, and 37, among others. Type 8 (HAdV-8) is associated with epidemic keratoconjunctivitis (EKC)
- Species E: Includes types 4, 29, and 35, among others. Type 4 (HAdV-4) causes acute respiratory disease in military recruits
- Species F: Includes types 40 and 41, among others. These types are primarily associated with gastroenteritis, especially in children
- Species G: Includes types 52, 53 and 54, among others.

CLINICAL SIGNIFICANCE

Different adenovirus serotypes are associated with specific clinical syndromes. For instance, adenovirus serotype 1 through 7 and 21 is commonly associated with respiratory infections; types 8, 19, and 37 are most commonly associated with EKC, while serotypes 32, 40 and 41 are known to cause gastroenteritis. Disseminated adenovirus disease in immunocompromised children can be associated with several serotypes including 1–3, 5, 7, 11, 31, 34 and 35.[3]

CLINICAL MANIFESTATIONS

Adenovirus infections can cause a range of clinical manifestations, depending on the specific strain of the virus and the affected individual's immune system. The most common clinical manifestations of adenovirus infection include:

Adenoviruses commonly cause respiratory tract infections, leading to symptoms such as fever, sore throat, cough, nasal congestion, runny nose and sneezing. These symptoms are similar to those of the common cold or flu. Adenovirus is also known to cause bronchitis, laryngotracheobronchitis, pertussis-like syndrome, bronchiolitis, pneumonia, pleural effusions, necrotising pneumonia, and hyperlucent lung syndrome.

Adenoviral pneumonia is more serious in infants than older children often associated with lethargy, diarrhoea, and vomiting. On radiological examination, it reveals diffuse bilateral pulmonary infiltrates and is often associated with complications such as necrotising bronchitis, bronchiolitis and can be associated with long-term sequalae such as bronchiectasis and bronchiolitis obliterans. Pneumococcal vaccination has been associated with a reduction in the incidence of pneumonia in infants with adenovirus and other respiratory virus infections.[3]

Conjunctivitis

Adenovirus can cause acute follicular conjunctivitis without any long-term sequelae, also known as pink eye. This condition involves redness, irritation, and discharge in one or both eyes. The constellation of symptoms of conjunctivitis, fever, pharyngitis, and cervical or preauricular lymphadenopathy is called as adenoviral pharyngoconjunctival fever.

Gastrointestinal symptoms

It can cause gastroenteritis, resulting in symptoms such as diarrhoea, abdominal pain, nausea and vomiting. These gastrointestinal symptoms are more common in infants and young children. Adenoviruses can also be associated with mesenteric lymphadenitis, appendicitis and intussusception. Fulminant hepatic necrosis can occur in patients with disseminated adenoviral disease and in immunosuppressed patients.

Febrile illness

Adenovirus infections can lead to a febrile illness, characterised by a high fever (above 100.4°F or 38°C). Fever is a common symptom of many viral infections, including adenovirus and is also associated with febrile seizures.

Skin rash

Certain adenoviral infections can lead to a viral exanthem, which is a widespread rash on the skin. The rash is typically non-itchy and can appear in various patterns.

Enlarged lymph nodes

Adenoviral infections may cause swollen or tender lymph nodes, particularly in the neck region.

Pharyngitis and tonsillitis

Infections with adenoviruses can cause inflammation of the throat and tonsils, leading to symptoms such as sore throat, difficulty swallowing and swollen tonsils.

Otitis media

Adenoviral infections can sometimes result in middle ear infections, leading to symptoms such as ear pain, fluid drainage from the ear and temporary hearing loss.

Urinary tract infections

In children can result in acute haemorrhagic cystitis in both healthy and immunocompromised patients. The infection has been associated with nephritis, orchitis and haemolytic uremic syndrome. Children who have undergone bone marrow transplant are particularly at risk of developing haemorrhagic cystitis with systemic disease, leading to an increase in the incidence of mortality coinfection and morbidity.[4]

Adenoviruses can cause acute myocarditis and pericarditis associated with disseminated disease.

Skin infections

In rare cases, adenovirus can cause skin infections, resulting in symptoms such as a rash, blisters or ulcers. These skin manifestations are more commonly seen in immunocompromised individuals.

Neurologic manifestations

Although uncommon, adenovirus infections can occasionally affect the central nervous system, leading to symptoms such as headache, aseptic meningitis (inflammation of the membranes covering the brain and spinal cord) and encephalitis (inflammation of the brain), and transverse myelitis occurs rarely.

Adenovirus has been associated with infectious mononucleosis-like syndrome as well as Kawasaki disease-like syndrome.[3]

Good hygiene practices

Teach your child proper hand hygiene, including regular handwashing with soap and water for at least 20 seconds. Encourage them to cover their mouth and nose with a tissue or elbow when coughing or sneezing to prevent the spread of the virus.

Isolation and preventing spread

Adenoviruses are highly contagious, so it is important to keep infected children away from others, especially those who have weakened immune systems. Follow the guidance of your health-care provider regarding the duration of isolation and when it is safe for your child to return to school or day-care.

DIAGNOSIS

Clinical presentation plays an essential role in suspecting an adenoviral infection. Symptoms can vary depending on the site of infection and the serotype involved. Common clinical presentations include respiratory symptoms such as cough, sore throat and fever, as well as conjunctivitis, gastroenteritis and urinary tract infections. Epidemiological factors, such as exposure to affected individuals or outbreaks, also aid in suspecting an adenoviral infection.

Inflammatory markers

In contrast to other viral infections, adenoviral infections are associated with markedly elevated C-reactive protein.[5] Interleukin-6 concentration and erythrocyte sedimentation rate are associated with severity of adenoviral respiratory infections and are markedly elevated in children with severe fatal adenoviral infections.[6]

Viral culture

Viral culture involves inoculating patient samples, such as respiratory secretions, onto susceptible cell lines. Adenoviruses cause characteristic cytopathic effects in infected cells, allowing for their identification. However, viral culture is time-consuming, requiring several days to obtain results, and it may lack sensitivity compared to newer techniques.

Polymerase chain reaction (PCR)

It enables the detection and quantification of viral DNA/RNA in patient samples. Adenoviral PCR assays have been developed to target conserved regions of the viral genome,

ensuring broad coverage across different serotypes. PCR offers high sensitivity and specificity and can provide results within a few hours, making it an invaluable tool for rapid diagnosis.[7,8]

PCR is a highly sensitive and specific assay that can be used to detect adenovirus DNA from a variety of sterile specimens such as blood, cerebrospinal fluid and tissues. A positive result from upper respiratory tract or stool samples is more difficult to interpret as it may represent virus shedding rather than symptomatic infection. Therefore, PCR results must be interpreted in the context of the clinical findings of adenovirus disease.[9]

Serology

Serological testing plays a supportive role in diagnosing adenoviral infections. Serological assays detect specific antibodies (Immunoglobulin M and Immunoglobulin G) produced in response to adenovirus infection. Enzyme immunoassays and complement fixation assays measure adenovirus-specific anti-heron antibodies but do not provide information about the serotype. Detection of haemagglutination inhibition antibodies or neutralising antibodies is more sensitive and is serotype specific. A rise in antibody titres between acute and convalescent serum samples suggests a recent infection. Serology is particularly useful for epidemiological studies, determining the seroprevalence of adenovirus in a population and differentiating between primary and secondary infections.[10]

Antigen detection

Rapid antigen detection tests (RADTs) use monoclonal antibodies to detect viral antigens in patient samples, such as respiratory secretions or conjunctival swabs. RADTs are relatively quick, providing results within minutes to a few hours. However, they may have lower sensitivity compared to PCR and false negatives can occur, necessitating confirmation with other methods.

Next-generation sequencing (NGS)

NGS technologies have emerged as powerful tools for viral genome sequencing and characterisation. NGS enables the identification of adenovirus serotypes, the detection of novel or recombinant strains, and the analysis of viral genetic diversity. Whole-genome sequencing using NGS can provide valuable insights into adenovirus epidemiology, transmission patterns and drug resistance. However, NGS is still primarily used in research and surveillance settings due to its cost and technical complexity.

MANAGEMENT

It involves supportive care to alleviate symptoms and prevent complications. Here are some general guidelines for managing adenoviral infections

Rest and fluids

Adequate rest helps the body fight off the infection, while fluids prevent dehydration.

Fever control

Administer acetaminophen or ibuprofen to manage fever and alleviate discomfort.

Nasal congestion and cough

Use saline nasal drops or sprays to relieve nasal congestion. A cool-mist humidifier in the child's room can also help alleviate symptoms.

Eye infections

For conjunctivitis (pink eye), clean the eyes with warm water and use saline eye drops to relieve irritation. Avoid touching or rubbing the eyes and wash hands frequently to prevent spreading the infection.

Antiviral therapy

It is generally reserved for patients with severe adenovirus disease, the majority of whom are immunocompromised, Cidofovir is a commonly used antiviral agent with a major side effect of severe dose limiting nephrotoxicity and Fanconi type syndrome, the dose of 5 mg/kg once weekly for three weeks then every two weeks is being under trial. However, more guidelines and studies are needed for the management of adenoviral infections in children.[9]

Immunotherapy

There is an increased evidence regarding the use of pooled intravenous immunoglobulins in severe adenoviral infections in immunocompromised children.[10]

PREVENTION

Adenoviruses are non-enveloped viruses, being resistant to disinfection from alcohol and chlorhexidine that are known to cause increased mortality and morbidity in neonatal intensive care units and immunocompromised children.

Instruments contaminated with adenoviruses can be disinfected by immersion in a 1% solution of sodium hypochlorite for 10 min 22 or by steam autoclaving. Adenoviruses can persist on hands despite handwashing for 10 seconds; therefore, disposable gloves that are changed between contacts with patients should be used to help control institutional outbreaks.

The use of gowns and masks is recommended for tracheostomy care. Other measures to control adenovirus nosocomial infections are isolation and charting of ill patients.

Good hygiene practices

Proper hand hygiene, including regular handwashing with soap and water for at least 20 seconds. Encouraging them to cover their mouth and nose with a tissue or elbow when coughing or sneezing to prevent the spread of the virus.

Isolation and preventing spread

Adenoviruses are highly contagious, so it is important to keep infected children away from others, especially those who have weakened immune systems.

Emerging research and potential applications

Despite their pathogenic nature, adenoviruses have garnered interest in the field of gene therapy and vaccine development. Their ability to efficiently transduce mammalian cells and deliver foreign genes into the host genome has made them attractive vectors for gene therapy applications. Researchers have explored adenoviral vectors for various conditions, including cancer, genetic disorders and infectious diseases, utilising their ability to elicit robust immune responses.

Moreover, adenoviral vectors have played a pivotal role in the development of COVID-19 vaccines, including those by Oxford-AstraZeneca and Johnson and Johnson. These vaccines employ modified adenoviruses to deliver the genetic instructions to produce the spike protein of the SARS-CoV-2 virus, triggering an immune response and conferring protection against COVID-19.

CONCLUSION

Adenovirus infections in children can present with-respiratory, ocular, and gastrointestinal symptoms. Diagnosis often involves a combination of clinical evaluation and laboratory tests, considering the specific symptoms and medical history of the child. Effective treatment strategies include providing supportive care, including fever and pain relief, hydration, and good hygiene practices to prevent further transmission. However, in immunocompromised patients, various drugs, including cidofovir, ribavirin, ganciclovir, and vidarabine, have been employed to manage adenovirus infections. It's important to note that most of these medications are virostatic, they may lead to the development of drug resistance and carry significant risks of toxicities. The decision to use specific therapy for adenovirus infection in immunocompromised individuals should be carefully considered on a case-by-case basis.

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Declaration of patient consent

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Conflicts of interest

Bhaskar Shenoy is the member of the editorial board of the journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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