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SUDDEN SPIKE IN ADENOVIRAL INFECTION TO CHILDREN IN INDIA: THE INNOCENT TO THE PERNICIOUS

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Abstract: At present, India is witnessing a sudden spike in adenovirus cases, specifically from Mumbai, Pune and Jaipur and the situation is concerning in West Bengal, where hospitals are seeing an influx of patients aged six months to two years. Health officials are reporting that at least 30 per cent of samples sent to the National Institute of Cholera and Enteric Diseases (ICMR-NICED) in Kolkata since January have tested positive for the virus. Adenovirus is an important cause of respiratory infections in infants and children. There are a total of 88 serotypes of adenovirus. Out of them, type 3, 4 and type 7 are notorious and have been linked to cause severe epidemics and acute respiratory illness.Studies found a new strain of adenovirus that is more transmissible and has immune escape properties was behind the surge in cases in our country. Most of the mutations don't change the properties of the virus. But sometimes, the mutations can make the virus more contagious and make it evade previously acquired immunity. This is what happened with adenovirus this time. The symptoms are prolonged and not just limited to a day or two and we are seeing mostly severe cases in children.Genomic sequencing has revealed that the adenovirus serotype 3, 7 as well as a new 7/3 recombinant strain were found in most cases in Bengal.

Keywords: Adenovirus, Disease severity in children, HAdV-3, HAdV-7, Recombinant adenovirus

Introduction

Acute respiratory infections (ARIs) are a significant cause of childhood mortality and morbidity worldwide [1].Several respiratory pathogens have been identified as causative agents for respiratory symptoms including the human Adenovirus (HAdV). This pathogen belongs to*Adenoviridae* family and genus classified as *Mastadenovirus*. It is a ubiquitous nonenveloped virus of medium-sized containing double-stranded-DNA ranging from 34kb to more than 37kb, which encodes around 40 genes [2].

Currently, there are 103differentHAdV types (HAdV-1 to HAdV-51 were serotypes and HAdV-52 to HAdV-103 were genotypes) known, which have been classified into seven species (A to G)based on a biological criteria and DNA homology and new adenovirus types continue to emerge [3].The distribution of HAdV genotypes is variable, depending on geographical, environmental, and meteorological characteristics. Some strains may have a higher epidemic potential [4]. The majority of HAdV types belong to species HAdV-D (57 types) followed by species HAdV-B (16 types) (http://hadvwg.gmu.edu/). Homologous recombination among capsid genes (hexon, penton and fibre) is crucial for contributing to the high diversity of species HAdV-D types. On the other hand, rapid selection of novel capsid gene sequences is the major factor for diversity in species HAdV-B [5-8], although a few recombinantsHAdV types of species B have also been described [9].Several species were found to be associated with different clinical profiles. Those most common genotypes implicated in ARIs belong to HAdV-C (types 1, 2, 5, and 6), HAdV-B (types 3 and 7), and HAdV-E (a single type 4) species [10]. Actually, recombination in genes of capsid protein may diversify the tissue tropism of novel HAdV types and thus enhance the pathogenicity and virulence of the new viruses [11-12].Adenoviruses, being a diverse group,are found naturally in the upper respiratory tracts and gastrointestinal systems of humans, other mammals, and avian species. In humans, transmission of adenovirus infection and associated clinical diseases can be sporadic or epidemic. The pattern often

correlates with the HAdV type and the age of the susceptible population. Serologic surveys have provided estimates of the prevalence of HAdV infections. From global collections of epidemiological data, different types of HAdV appear to manifest different pathogenic properties and cause diverse diseases, suggesting tissue tropism varies among HAdVs [Figure 1].HAdVs are fond of pediatric population younger than 5 years as at that age they spend a significant portion of their days in closed environments, such as daycare centers, schools, orphanages, or other institutions. Study shows that respiratory infections are the most common disease caused by HAdVs in children. HAdVs are estimated to account for 7% to 8% of viral respiratory illnesses in children less than 5 years [13-14]. In addition to respiratory system,HAdVs have been associated withclinical diseases in other systems, asillustrated in Figure 1.

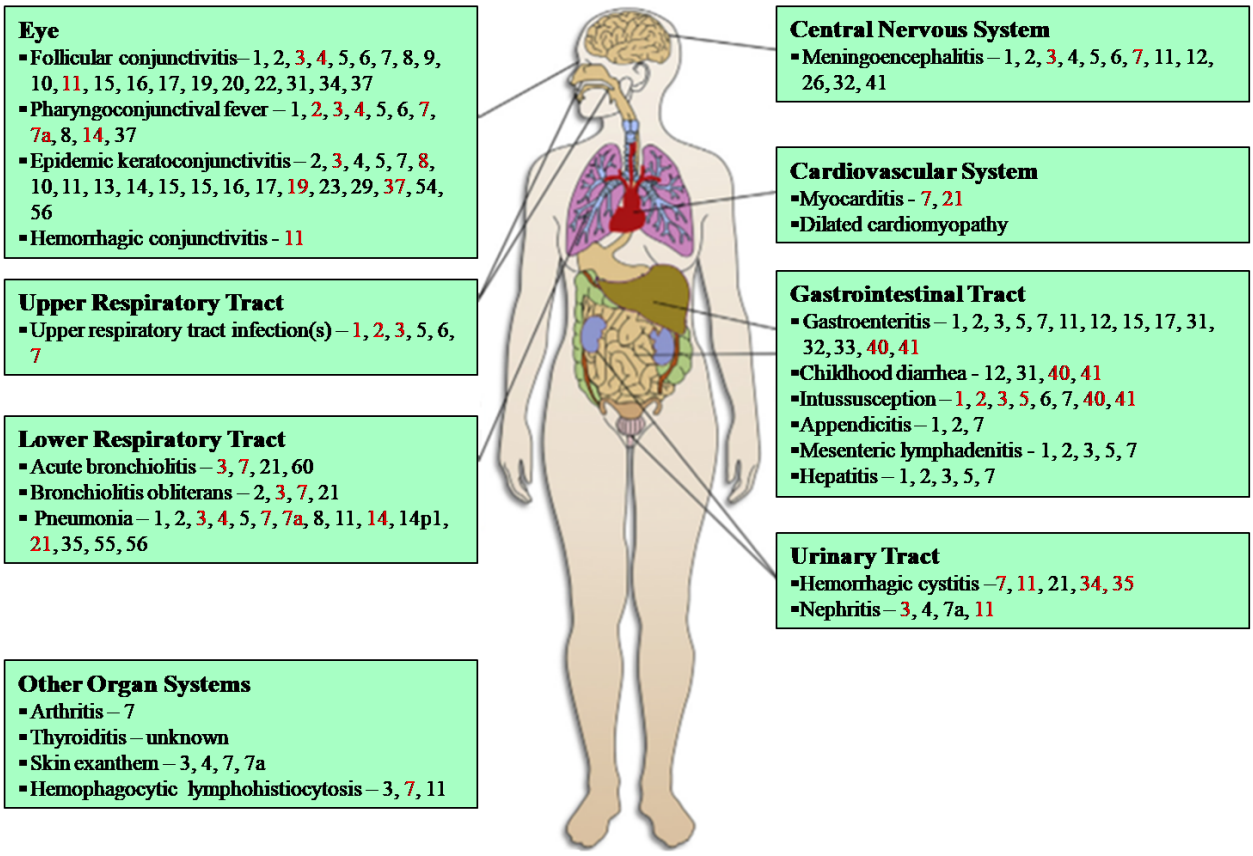

Figure1 Tropism of human adenoviruses with associated clinical diseases in various organ systems. The numbers indicate HAdV types; the numbers in red are the more common types.

Adenovirus infections may in fact result in high morbidity and mortality in children, and fatality rates for untreated severe HAdV pneumonia or disseminated disease may exceed 50% [15]. Severe adenovirus infection in children can be complicated with pleural effusions [16], acute respiratory distress syndrome (ARDS) [17], respiratory failure [18],myocarditis [19], and central nervous system dysfunction [20], leading to either mechanical ventilation or extracorporeal life support, even death. Unfortunately, effective adenoviral vaccine for children and specific antiviral drugs against human adenoviruses are currently not available.

Probable Reasons for Severity of Adenoviral Infection Presently in Various States in India:

This year India has been experiencing a surge of dangerous adenoviral infection in children.Since January, adenovirus infected cases have been reported from Mumbai, Pune and Jaipur, while the

situation is concerning in West Bengal, where hospitals are seeing an influx of patients aged six months to two years.According to latest news, more than 12,000 cases of adenovirus were recorded in West Bengal, where19 children died so far this year after suffering from acute respiratory infections, and thousands remain hospitalized as the nation fights an adenovirus outbreak. But, the Association of Health Service Doctors warned that there are chances of the number of cases anddeaths turning out to be much higher than official statistics. Some local media have reported the death toll to be more than 100 children.

The consequences of human adenovirus (HAdV) infections are generally mild. However, despite the perception that HAdVs are harmless, infections can cause severe disease. A number of adenoviral infection outbreaks are reported in different countries all over the world. In 2018, United States confronted an adenovirus outbreak in which an unusual number of adenovirus cases were reported at two locations, one in Maryland and one in New Jersey, resulting in deaths in both states.

Studies showed that HAdV accounts for 5–10% of all childhood respiratory tract infections, which are commonly caused by HAdV types 1–7 [21-23]. HAdV-B3 and -B7 are two of the most common genotypes associated with acute respiratory disease (ARD) and hospitalization in pediatric cases [21-23]. More severe disease and enhanced cytotoxicity in cell culture were recently associated with HAdV-B7 infection compared with HAdV-B3 [24]. HAdV-B7 also displayed more robust replication in cell culture and induced higher levels of inflammatory cytokines combined with more severe airway inflammation in infected mice compared with HAdV-B3 [24]. This provides potential insight into the enhanced pathogenicity of HAdV-B7 in humans [24]. Besides, recent emergence of more pathogenic genomic variants of various genotypes is one of the culprits. And it has been well reflected in the cases of recent outbreak of adenovirus in India. According to Dr. Prabhas Prasun Giri, associate professor and PICU (paediatric ICU) in-charge at Institute of Child Health in Kolkata, who has been dealing with adenovirus cases in the past 3-4 months, gave the statement that type 3, 4 and type 7 are notorious and have been linked to cause severe epidemics and acute respiratory illness. Among them adenovirus 7 is the most dangerous. And also said genomic sequencing has revealed that the adenovirus serotype 3, 7 as well as a new 7/3 recombinant strain were found in most cases in Bengal and e outcome is severe and causing so many ICU admissions and fatalities [25]. There are some other reasons behind the journey to be an innocent virus to notorious one, such as, zoonotic transmission, interspecies recombination, and the lack of approved AdV antivirals or widely available vaccines, HAdVs remain a threat to public health.

Moreover, there is evidence that coinfection of *Mycoplasma pneumoniae* (*M. pneumoniae*) with adenovirus appears to have more severe impact on child health. *M. pneumoniae*is an important pathogen of community-acquired pneumonia (CAP) in children. Gao *et al.* showed that human adenovirus coinfection aggravates the severity of *Mycoplasma pneumoniae* pneumonia in children. Compared with *M. pneumoniae* mono-infection, patients co-infected with HAdV had a longer hospital stay and fever duration and a higher rate of dyspnea, which led to a higher rate of oxygen therapy and noninvasive continuous positive airway pressure (NCPAP) use, as well as a higher proportion of extremely severe pneumonia and severe disease defined by the clinical score system [26]

Who are in Risk Zone?

Human adenoviruses can cause infections at any age but most commonly in pediatric population, especially in young children and infants. By the time of 10 years old, most children have had at least one episode of adenovirus infection. Adenoviruses can cause many symptoms similar to common cold, including rhinorrhea, fever, cough, and sore throat. Lower respiratory infections such as bronchitis, bronchiolitis, and pneumonia can be severe and even fatal. Other diseases such as conjunctivitis, gastroenteritis, cystitis, myocarditis, cardiomyopathy, and meningoencephalitis can also be associated with adenovirus infections.

Infections in immunocompetent individuals typically resolve within 7–10 days without treatment or hospitalization [27]. By contrast, immunocompromised individuals and children are at risk for more severe disease [28]. Immunocompromised populations at risk for HAdV infection include recipients of hematopoietic stem cell and solid organ transplants, orindividuals with primary

immunodeficiencies, such as severe combined immunodeficiency syndrome, HIV infection, or those undergoing immunosuppressive therapies [27]. Clinical manifestations of HAdV infection, such as pneumonia and hepatitis, can prove fatal in immunocompromised patients and occasionally even in the immunocompetent, as observed historically in military recruits [29-31].

Treatment: Where We are Today?

Clinically, immunosuppressed transplant recipients have significant risk for HAdV infection. In these cases, the most effective strategy to control HAdV infections is to reduce immunosuppressivetreatment, restoring the natural ability to combat infection [32]. Unfortunately, there are no clinically approved treatments for HAdV. Broad-spectrum antivirals, such as ganciclovir, ribavirin, and cidofovir, have all been reported to have varying degrees of efficacy at controlling HAdV infections, but cidofovir is the most commonly used, despite concern for significantnephrotoxicity[33]. Supplementing cidofovir treatment with intravenous immunoglobulin (IVIG) from pooled donors may exhibit some efficacy, but it is not considered standard therapy [34].

Routine monitoring for HAdV infection is often used in individuals at high risk for severe disease, particularly patients receiving HSCTs (HAdV-infected pediatric hematopoietic stem cell transplant recipients). Forethoughtfulmonitoring for HAdV viremia is performed using quantitative PCR-based detection of viral DNA in blood samples [32].

Many clinically approved compounds for the treatment of other pathologies have been investigated for anti-HAdV activity. These compounds interrupt the HAdV replicative cycle at different points to exert their antiviral activity. While there are promising*in vitro*and*in vivo*data supporting the efficacy of these drugs, none have been approved for treatment of HAdV infection in humans [33].

There is growing interest in, and experience with, the use of HAdV-specific $CD8^{+}$T cells as a therapy. Clinical trials using this T cell therapy report good efficacy, low toxicity, and protection against a broad range of HAdV types, making them increasingly attractive as an off-the-shelf therapeutic, especially for emerging HAdV outbreaks [35-36].

Another potential therapeutic strategy is the use of engineered, antiviral monoclonal antibodies. Of the four classes of human IgG, anti-hexon IgG3 demonstrated enhanced TRIM21 activity and complement C1/C4-mediated neutralization in an IgG3 hinge-dependent manner [37]. Overall, IgG3 delivered the most potent neutralization of HAdV-C5, providing novel insights that can be exploited to guide antibody engineering [37].

Regarding vaccine development, an oral, live virus vaccine against HAdV-E4 and HAdV-B7 is used in the US military, but no HAdV-specific vaccine is available to the general population.

Conclusion:

As the frequency and breadth of viral disease outbreaks appear to increase, understanding and combating disease emergence is important. The self-limited nature of HAdV infections, accompanied by recombination events, evolutionary gain- or loss-of-function mutations, and gaps in knowledge about zoonotic potential, complicates the detection of emerging HAdVs. Current surveillance efforts are often region specific and may rely on voluntary reporting or provide insufficient HAdV-genotyping data. There is still much to learn about the many different facets of HAdV pathogenesis. There is a need for improved understanding of how individual genetic variations and co-infections can affect transmission, replication, and host response, along with continued research into prevention and treatment of HAdV infection. Moreover, this is an exciting era for HAdV virology because the output of decades of seminal research has allowed these viruses to be harnessed for their therapeutic potential as our partners for gene therapy and vaccine development [38-39]. Nevertheless, while HAdV may be an innocuous pathogen to many, to some it may become a formidable predator.

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