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First reported cases of human adenovirus serotype 14p1 infection, Ireland, October 2009 to July 2010

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We report the first nine confirmed cases of human adenovirus 14p1 infection (HAdV-14p1), identified at different locations in Ireland between October 2009 and July 2010. These were the first notifications in Ireland and all were sporadic cases. Following these notifications, the Health Protection Surveillance Centre set up an enhanced surveillance system for HAdV-14p1 infection. Seven cases were male and five were aged less than one year. Three patients died, giving a case fatality rate of 33%. It should be noted that cases presented here were diagnosed on presentation to hospital and may represent the severe end of the spectrum of HAdV 14 disease in Ireland.

Introduction

Between October 2009 and July 2010, nine cases of human adenovirus 14p1 (HAdV-14p1) infections were identified at different locations in Ireland. Human adenoviruses (HAdVs) are a common cause of infection and are associated with sporadic infection and community and institutional outbreaks, particularly among military recruits. Infection with HAdV occurs all year round but may be more common in temperate regions from late winter to early summer. The viruses are predominantly transmitted by the respiratory and faecal-oral routes [1]. They rarely cause serious or fatal illness in otherwise healthy individuals, but can cause severe disease in newborn or elderly patients and immunocompromised persons, particularly transplant recipients. The clinical spectrum of disease in humans can vary substantially depending on the infecting serotype and can include asymptomatic infection, fever, colds, pharyngitis (sore throat), conjunctivitis, gastroenteritis, bronchitis, pneumonia, acute haemorrhagic cystitis, meningoencephalitis, hepatitis, myocarditis and life-threatening disseminated disease [1]. There are 51 recognised HAdV serotypes, which are assigned to six subgroups (A–F) on the basis of biophysical, biochemical and genetic characteristics [1].

The epidemiological characteristics of HAdV infection vary by viral serotype. Compared with other adenoviruses, infection with HAdV-14p1 serotype appears to result in a higher rate of severe illness [2]. However,

in general, information on severe adenovirus disease in healthy individuals is limited and severe manifestations (including sepsis and pneumonia) are typically limited to newborns, immunocompromised persons and persons with underlying respiratory or cardiac disease [3]. This serotype was first discovered in 1955 during an outbreak of acute respiratory disease (ARD) at a military recruit training facility in the Netherlands [4]. It was subsequently identified during similar outbreaks of ARD among young adults in Great Britain in 1955 [5], Uzbekistan in 1962 [6] and the former Czechoslovakia in 1963 [6]. Reports of clusters of cases of HAdV-14 infection are unusual, with most reported infections being sporadic cases.

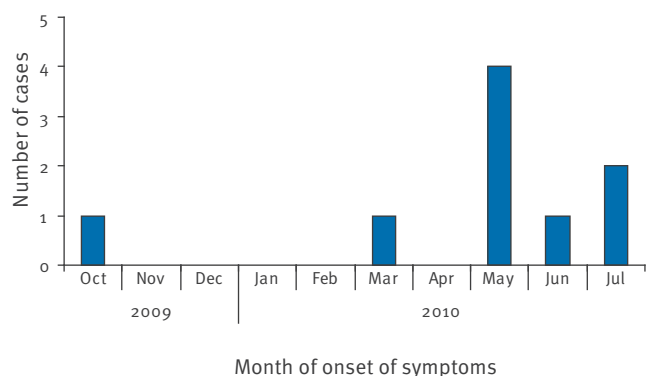
In 2008, Louie *et al.* described a severe pneumonia in the United States (US) associated with a newly emergent HAdV-14 strain, designated HAdV-14a, now called HAdV-14p1, which displayed some genetic differences from the strain detected in the 1950s [7]. Outbreaks of HAdV-14-associated ARD of variable severity were subsequently detected in US military bases [8,9] and in civilian populations in Washington [10], Oregon [11], Alaska [2], Wisconsin and Pennsylvania [6]. The community outbreak in Oregon resulted in 29 hospitalisations and seven deaths [11], while an outbreak in a military base in the US described by Tate *et al.* involved high rates of transmission of HAdV-14 infection sustained over five months and was associated with 23 hospitalisations and one death [9]. The Alaskan outbreak in 2008 involved 46 confirmed and probable cases of HAdV-14 infection, of whom 11 were hospitalised and one died [2]. In 2010, an article by Kajon *et al.* described how retrospectively molecular analysis was undertaken on 99 isolates (between 2003 and 2009) in the US, from military and civilian populations from different geographic locations and circulation periods. Civilian populations included those from Alaska, Oregon, Pennsylvania and Wisconsin. All examined viruses were identical and belonged to the new genome type designated HAdV-14p1 [6].

Cases of HAdV-14p1 infection are statutorily notifiable in Ireland under the Infectious Disease Regulations

2004 (S.I. 865) which came into effect on 1 January 2005. These regulations require that clinicians and directors of laboratories report any unusual clusters or changing pattern of any illness or individual cases thereof that may be of public health concern to the

FIGURE 1

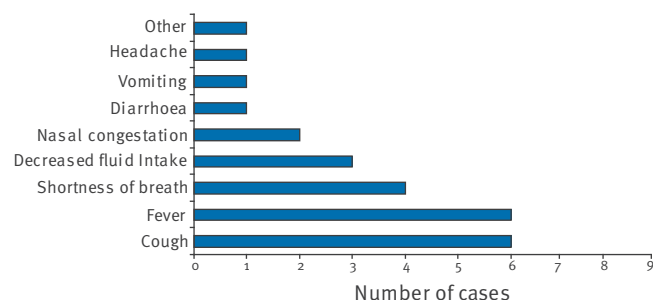
Cases of HAdV-14p1 infection by month of symptom onset, Ireland, October 2009–July 2010 (n=9)



HAdV-14p1: human adenovirus 14p1.

FIGURE 2

Symptoms reported for cases of HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)^a



HAdV-14p1: human adenovirus 14p1.

^a Some cases may have had more than one symptom.

TABLE 1

Signs reported for cases of HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)^a

Sign	Number of cases
Fever ($\geq 38^{\circ}\text{C}$)	7
Tachypnoea ^b	7
Decreased systolic blood pressure ^b	2
Hypoxaemia documented ^c	7

HAdV-14p1: human adenovirus 14p1.

^a Some cases may have had more than one sign of clinical infection.

^b Tachypnoea (elevated respiratory rate) is defined as > 60 , > 40 , > 30 , > 25 and > 20 breaths per minute for individuals aged under 6 weeks, 6 weeks to < 6 months, 6 months to < 3 years, 3 years to 6 years, and > 6 years, respectively.

^c Decreased systolic blood pressure is defined as < 50 , < 70 , < 80 and < 90 mmHg for individuals aged under 6 weeks, 6 weeks to < 6 months, 6 months to < 3 years, 3 years to 6 years, and > 6 years, respectively.

^d Hypoxaemia (decreased oxygen saturation) is defined as less than 93%, for all age groups.

Medical Officer of Health. In August 2010, the National Virus Reference Laboratory (NVRL) in Ireland notified the Health Protection Surveillance Centre of HAdV-14p1 infection in nine patients whose specimens were sent to the NVRL between November 2009 and July 2010. These were the first notifications of HAdV-14p1 infection in Ireland and all were sporadic cases. Following these notifications, the Health Protection Surveillance Centre set up an enhanced surveillance system for HAdV-14p1 infection in Ireland. In this article, we report the characteristics of these initial Irish cases of HAdV-14p1 infection.

Microbiological investigation

Specimens from the nine patients with HAdV-14p1 infection [12] were analysed at the molecular level by

TABLE 2

Laboratory and radiological investigations for cases of HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)

Investigation	Result	Number of cases
White blood cell count	Low	1
	Normal	6
	Elevated	2
Lymphocyte count	Low	4
	Normal	4
	Elevated	1
Neutrophil count	Low	1
	Normal	6
	Elevated	3
Creatinine levels	Elevated	2
Lung infiltrates	Single-lobe	1
	Multi-lobe	4
	Interstitial	0
Normal chest X-ray	Yes	2
	No	7

HAdV-14p1: human adenovirus 14p1.

TABLE 3

Treatment given to patients with HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)

Treatment	Number
Antiviral treatment	3
Antibiotic therapy	9
Mechanical ventilation	6
Renal replacement therapy	2
Bronchodilator therapy	5
Supplemental oxygen	6
Corticosteroid therapy	2
Vasopressor therapy	4
Extra corporeal membrane oxygenation (ECMO)	2

HAdV-14p1: human adenovirus 14p1.

the NVRL. The HAdV-14 infections were detected by immunofluorescence (IF) and/or a generic HAdV hexon real-time polymerase chain reaction (PCR) for detection of all serotypes. HAdV positives were then typed by HAdV-14-specific real-time PCR, HAdV-14-specific end-point PCRs and DNA sequencing from a range of clinical specimens (serum, plasma, urine, nasopharyngeal aspirates, bronchoalveolar lavages and a lung biopsy). The molecular characterisation of these cases as HAdV-14p1 will be published elsewhere (Carr *et al.*, submitted). A virology screen for influenza A, influenza B, respiratory syncytial virus and parainfluenza 1, 2 and 3 viruses was also undertaken on patients' specimens.

Epidemiological investigation

A case definition for HAdV-14p1 infection was developed. A confirmed case was defined as a person hospitalised with HAdV-14p1 who meets the clinical description of one or more of the following: respiratory infection, pneumonia, pharyngitis, gastroenteritis, conjunctivitis, cystitis, meningoencephalitis and disseminated disease.

The Health Protection Surveillance Centre wrote to all consultant microbiologists, infectious disease consultants, intensive care unit (ICU) directors, respiratory physicians and consultant paediatricians in August 2010 to alert them to the situation. They were requested to report all cases of HAdV-14p1 infection, including unusual clusters of severe adenoviral respiratory disease or clusters of pneumonia of unknown aetiology to the local Director of Public Health, who would subsequently notify the Surveillance Centre.

As previously stated, an enhanced surveillance system was initiated. The objectives of the system were to describe: (i) the incidence of the disease (based on the number of cases meeting the case definition); (ii) the symptoms and signs on hospital admission and results of initial investigations; (iii) the treatment provided; (iv) the complications associated with the infection; (v) the outcome at 30 days after the start of treatment; and (vi) the presence of known predisposing risk factors.

Enhanced surveillance data were collected on the nine reported cases and included demographic details, clinical details, medical complications, risk factors (e.g. immunosuppression, chronic respiratory disease, post solid-organ transplant and smoking status), investigations on admission, treatment and outcome at 30 days.

Details of the cases of HAdV-14p1 infection

Of the nine cases, two were female and seven were male. Five cases were less than one year of age, of whom two were less than one month old, and the remaining three were aged between two and seven months. One case was in the 5–9-year age group, one in the 30–39-year age group and the remaining two were in the 40–49-year age group. All nine cases were Irish. The majority of the cases (n=8) lived in eastern

Ireland. No cases resided in institutional settings. Two of the three adults were smokers.

Clinical details

The date of onset of symptoms ranged from October 2009 to July 2010. For seven cases, symptom onset occurred between May and July 2010 (Figure 1). All nine cases were hospitalised. The length of stay in hospital was known for six cases, ranging from four to 36 days, with a median of 10 days. Five cases were admitted to an intensive care unit. The most commonly reported symptoms were cough (n=6), fever (n=6) and shortness of breath (n=4) (Figure 2). The signs are detailed in Table 1.

All patients aged over one year had underlying medical conditions, which included developmental delay, immunosuppression, chronic pulmonary disease, hypertension and congenital genetic disorder. Of those aged less than one year of age, one was premature and one had intrauterine growth retardation. Three of the nine patients died, giving a case fatality rate of 33%.

Of the nine cases, six developed pneumonia, two had disseminated infection, one had acute respiratory distress syndrome, one had hepatitis and one had meningoencephalitis. Other reported complications included bronchiolitis and seizures. Complications were not mutually exclusive. Table 2 outlines the results of laboratory and radiological investigations. Seven patients had abnormal chest X-ray findings, with four having multi-lobe infiltrations and one having single-lobe infiltrates and right mid-zone consolidation. A sixth case had mild pulmonary oedema. Chest X-ray findings were not provided for the seventh case. Of those with multi-lobe infiltrations, two had pleural effusions and one had bilateral pneumonia.

A summary of treatment interventions is provided in Table 3. Three of the nine patients had received antiviral therapy with cidofovir (n=1) and acyclovir (n=2). All patients received antibiotic therapy. Two thirds of patients were mechanically ventilated and two, both aged less than one year, were on extracorporeal membrane oxygenation (ECMO).

Discussion

Of the nine cases of newly emergent HAdV-14p1 infection described in this report, the majority were male and more than half of cases were aged less than one year. This compares with the Alaskan and Oregon outbreaks, where 70% (32 of 46) and 66% (25 of 38) of cases, respectively, were male. In our series, five cases were neonates or infants, which contrasts with the Alaskan outbreak, where 91% (29 of 32) cases were older than 19 years, and the Oregon outbreak, where 61% (23 of 38) patients were aged over 40 years [2,11]. Six of the nine (67%) Irish cases had underlying medical conditions including immunosuppression, developmental delay, chronic lung disease, hypertension, intrauterine growth restriction and prematurity.

Previous publications suggest that underlying chronic illness may predispose individuals with HAdV-14p1 infection to severe illness [10,11]. However, other respiratory adenoviruses are also known to be associated with higher fatality rates among immunocompromised individuals [13]. In the Oregon outbreak, 47% (18 of 38) of cases had one or more underlying medical condition while the Alaskan outbreak reported 61% of cases (28 of 46) had an underlying medical conditions including chronic heart and lung disease, diabetes mellitus and asthma [2,11].

An outbreak investigation in Alaska in 2008 identified that smoking may have facilitated transmission of the virus [14]. Smoking was also observed in a high proportion of patients in the Oregon outbreak, with 60% (18 of 30) adult cases reporting having smoked in the previous 30 days. The Alaskan outbreak investigation also suggested that the spread of the HAdV-14p1 virus was more likely to occur in situations leading to close person-to-person contact such as sustained household contact or contact among members of a tight social network. It also indicated that spread is less likely to occur during most normal social contact situations in the community. This is also supported by the reporting of outbreaks of HAdV-14p1 infections in military bases in the US, where recruits live in close proximity [9]. Adenoviruses spread from person to person via coughing or sneezing. People may also become infected by touching something with adenovirus on it and then touching their mouth, nose or eyes [15]. In order to prevent spread of the infection, it is important to advise patients to follow respiratory precautions [16].

Healthcare professionals should follow standard contact and droplet precautions when caring for people hospitalised with adenoviral infections. Environmental decontamination should also be implemented in the rooms occupied by such patients. Patients with symptoms of severe viral respiratory infections and those diagnosed with adenovirus infection should be placed in a single room or share a room with other patients with the same infection, to help control the spread of infections [17].

Management of adenoviral infections is largely supportive using antibiotics, steroids, bronchodilators, mechanical ventilation and ECMO. A number of antiviral drugs including ribavirin, vidarabine and cidofovir have been used to treat adenoviral infections such as those caused by HAdV-14p1 and may be beneficial [10]. A retrospective review of a community outbreak of HAdV-14p1 infection in Oregon did not provide any conclusions about the efficacy of cidofovir, the antiviral drug used by clinicians for critically ill patients, except that its use was associated with worsening renal function [11]. In our study, six of the nine patients required mechanical ventilation and two patients aged less than one year required ECMO, highlighting the severity of illness and also the intensity of interventions required. Cases presented here were diagnosed on presentation

to hospital and may represent the severe end of the spectrum of HAdV 14 disease in Ireland. Information on asymptomatic or mild cases of HAdV-14 disease in the community is lacking at this time.

Currently no licensed vaccine for HAdV-14p1 virus exists. Safety and efficacy trials are currently in progress in the US for HAdV-4 and HAdV-7 vaccines and vaccines for these adenovirus serotypes may provide cross immunity to HAdV-14 [4,18]. Rapid diagnosis and improved surveillance, with serotyping and molecular characterisation to identify emerging adenovirus variants, may assist with the targeted development of antiviral agents or type-specific vaccines.

Infections with HAdV-14p1 are not commonly reported and most are not thought to be serious. However, clinicians should consider this infection in the differential diagnosis of severe acute respiratory disease or pneumonia and of clusters of respiratory disease. This especially relates to patients who are immunosuppressed (including transplant recipients), those who have underlying respiratory or cardiac disease as well as children aged one year and under (particularly neonates) and those aged 65 years or older. Clinicians should liaise with a virus reference laboratory for guidance on testing patients with a possible diagnosis of HAdV-14p1 infection. It is recommended that clinicians and laboratories should endeavour to report all cases of HAdV-14p1, including unusual clusters of severe adenoviral respiratory disease, to their local Public Health Authority. Public health surveillance of this re-emerging pathogen is also recommended in order to improve our knowledge of the pathogenesis associated with species B adenovirus infections.

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