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Adenovirus infection in families

O RUUSKANEN, J MERTSOLA, AND O MEURMAN*

*Departments of Paediatrics and *Virology, University of Turku, Finland*

SUMMARY Eighteen families were followed up for four to six weeks after one member of each family was diagnosed as having an adenovirus infection. In 17 of 18 index cases the diagnosis was based on the rapid detection of adenovirus hexon antigen in the nasopharyngeal mucus specimens and in one case (the only adult index case) on isolation of the virus. All index cases had high temperatures associated most commonly with tonsillitis, acute otitis media, gastroenteritis, or febrile convulsions. In 14 of the 16 families with symptomatic contacts the index case was the first symptomatic case, or one of the first symptomatic cases, in that family. Fifteen (94%) of the siblings and 20 (56%) of the parents had signs and symptoms of acute infection during the follow up period. In 10 (63%) and eight (20%) of these cases, respectively, adenovirus was confirmed. The mean (SD) incubation period of confirmed adenovirus infections was 10 (3) days. The observations show that adenovirus infection spreads actively to other siblings in the family. Rapid diagnosis permits parents to be informed prospectively about the expected spread and clinical picture of the illness in the family.

Adenoviruses are a common cause of febrile infections in children. Because the infection often lasts a long time and may be difficult to distinguish from bacterial infection, rapid diagnosis is important.[1–4] Detection of adenovirus hexon antigen with immunoassay has been developed in our laboratory by Halonen *et al*[5 6] and used in routine diagnostic work since 1981. During these seven years the clinical value of this test has been proved[4 7 8] and about 700 cases of adenovirus illness have been diagnosed. We report that rapid diagnosis of a primary case in a family is clinically important, because the infection spreads actively to siblings.

Patients and methods

The study was carried out between September 1984 and February 1985. During that period 974 specimens of nasopharyngeal mucus were taken for rapid virus diagnosis (NPS test) from febrile children at Turku University Hospital (622 samples) and at a private paediatric clinic (352 samples). Adenovirus antigen was isolated from 65 samples and the information was available to investigators 24–48 hours after the sample of mucus had been taken. Twenty families were contacted within five days of diagnosis of the index case. Three families refused to enter the study and 17 gave informed consent. In addition, the NPS test was negative in one adult index case (house officer of the department of paediatrics) but the virus was isolated. Eleven index cases were diagnosed at Turku University Hospital and seven in a private paediatric clinic.

Follow up questionnaires were given to parents, and samples of blood were taken for viral studies. After four to six weeks, follow up questionnaires were returned and samples of blood were again taken for serological tests. Forty six paired serum samples and seven single serum samples were obtained from 53 contacts. Specimens for the NPS test and for virus isolation during the follow up period were collected from 40 and 22 of the contacts, respectively. Haematological tests were done using routine techniques.

EZYME IMMUNOASSAY (ELISA) FOR ADENOVIRUS ANTIGEN

Nasopharyngeal specimens were collected by suction through the nostrils with a disposable mucus extractor (Vygon, Ecouen, France) and diluted 1:5 in phosphate buffered saline. The indirect ELISA used to detect adenovirus antigen has previously been described in detail.[6] The assay detects a true infection in children.[7] The specimens were tested in parallel for respiratory syncytial virus, influenza A and B virus, and parainfluenza virus types 1, 2, and 3 antigens by analogous assays.

ELISA FOR ADENOVIRUS ANTIBODY

The ELISA for IgG and IgM antibodies to adenovirus hexon antigen has previously been described.[7] A fourfold or greater increase in the concentration of IgG in paired serum samples, or the detection of IgM antibodies, indicated a recent infection.

VIRUS ISOLATION

Adenovirus isolation from throat swabs were carried out in HeLa cells using routine laboratory methods.

Results

At the time of the diagnosis of adenovirus disease 10 of 18 index cases were the only symptomatic cases in the family—that is, primary cases. In four cases the symptoms of the index case began at the same time as those of other family members. In two cases febrile infection had already occurred in other family members, in both cases in parents. In two cases insufficient information was obtained concerning the family history at the time of the diagnosis of the index case. Serological tests from paired serum samples were carried out from 14 of 17 index patients in whom the NPS test was positive, and these indicated recent infection in 13 cases. The one index patient in whom the NPS test was negative but from whom the virus was isolated also had a considerable increase in IgG antibodies to adenovirus.

Tables 1 and 2 shows the main characteristics of the 18 index cases. With one exception, all were children with a mean age of 2·2 years. There were 10 girls and eight boys. All index cases had high fevers, and the most common signs and symptoms were tonsillitis, otitis media, febrile convulsions, and gastroenteritis.

During the four to six week follow up period, symptoms and signs of acute respiratory infection were recorded in non-index family members of 16 of the 18 families studied (table 3). With one exception, all other 16 siblings in the study families developed symptoms. Evidence of adenovirus infection was found in 10 of 17 siblings; in four the NPS test was positive (serological response was studied in three of them and was positive in all) and in six the NPS test was negative, but they had considerable seroresponses, one of them having the virus isolated from serum. One sibling had a parainfluenza type 1 infection (by the NPS test) that began 20 days after the onset of the adenovirus infection in the index case. Twenty (56%) of the parents became symptomatic. All 23 NPS tests from parent contacts were negative as were all virus isolation studies. Serological evidence of adenovirus infection was obtained in four cases. In addition, four parents showed considerable increases in adenovirus IgG antibody titres, but were asymptomatic. Two symptomatic parents had high adenovirus IgG antibody titres but no significant increase was found. In six cases the timing of taking the blood samples for serology was not optimal for detection of the virus because the first sample was taken too late after the onset of symptoms. The mean (SD) incubation period calculated from the first symptomatic day of the primary case (calculated reliably in 17 cases) was 13 (6) days for the whole group and 10 (3) days for serologically confirmed cases (n=9).

The clinical picture in contact siblings was characterised by high fever, rhinitis, and cough. Half the

Table 1 *Main characteristics of 18 index cases with adenoviral infection*

	Mean (range)
Age (years)*	2·2 (0·5–7·8)
Duration of fever of the time of diagnosis (days)	3·3 (0–10)
Highest temperature (°C)	39·6 (38·2–40·7)
Erythrocyte sedimentation rate (mm in the first hour) (n=5)	62 (16–85)
C reactive protein (mg/l) (n=12)	49 (0–180)
White cell count $\times 10^9$/l (n=11)	15·8 (5·4–23·9)

*One adult (aged 32 years) excluded.

Table 2 *Diagnoses**

	No
Tonsillitis	7
Otitis media	6
Febrile convulsion	3
Gastroenteritis	3
Fever without focus of infection	2
Upper respiratory tract infection	2
Conjunctivitis	1
Urticaria	1

*Some patients have more than one diagnosis.

Table 3 *Symptoms of infection in family contacts of a patient with adenoviral disease*

	Siblings (n=16) No (%)	*Parents (n=36) No (%)*
Total signs and symptoms of infections	15† (94)	20† (56)
Fever ≥37·5°C	10 (63)	8 (22)
Pain in swallowing	4 (25)	17 (47)
Hoarseness	1 (6)	10 (28)
Upper respiratory tract infection	11 (69)	16 (44)
Exanthema	2 (13)	3 (8)
Gastroenteritis	8 (50)	5 (14)
Conjunctivitis	3 (19)	3 (8)

*One sibling in whom the nasopharyngeal mucus test was positive for parainfluenza type 1 infection excluded; †adenovirus infection was confirmed in 10 siblings and in four parents.

patients had gastrointestinal symptoms (table 2). Three of the sibling contacts were treated with antibiotics, two because of otitis media, and one because of an upper respiratory tract infection with fever. In the parents the major symptoms were pain on swallowing, rhinitis, and cough. Additionally many of the adult contacts had symptoms of laryngitis—for example, hoarseness. Only one (3%) of the parents had temperatures exceeding 39·0°C whereas the corresponding number in siblings was seven (41%). Vomiting, diarrhoea, and abdominal pains were more common among siblings than among parents. Four parents were treated with antibiotics for upper respiratory tract infections.

Discussion

This study confirms our earlier experience that rapid diagnosis of adenovirus infection is of great clinical value.[4 8] Adenovirus often causes a more serious illness than other respiratory viruses.[9] In addition, adenovirus infections are commonly associated with a high white cell count ($>15\times10^9$/l), increased erythrocyte sedimentation rate (>30 mm in the first hour), and increased serum C reactive protein concentration (>40 mg/l). These also differentiate them from other respiratory virus infections and make the clinical management more difficult.[4 8 10]

The rapid diagnostic test we used is simple and inexpensive and can be carried out in any modern virus laboratory. Quick fluoroimmunoassay technology had recently been applied to the detection of the adenovirus antigen permitting the diagnosis in 30 minutes.[11 12] We are currently testing this assay in clinical practice. It has been clearly shown that the NPS test detects a true infection,[7] and our study confirms this. Its sensitivity compared with virus isolation, however, has not been systematically studied. During this study we found two patients in whom the NPS test was negative but from whom the virus was subsequently isolated. We also found 10 symptomatic patients in whom the NPS test was negative but who developed considerable serological responses. This can be explained in some patients from whom the mucus sample could not be aspirated within the first five days of the onset of illness, because this is the optimal time for the diagnosis.[7] The results of this study (and of our earlier studies) suggest that the NPS test should be used as a primary diagnostic test. If it is negative and diagnosis is still needed, virus isolation and IgG antibody assay should be done.

Adenovirus infection is highly contagious. Several outbreaks of adenovirus induced pharyngoconjuctival fever in hospitals,[13 14] schools,[15] and day nurseries[16] have been described. In the Seattle virus watch study a large number of contacts were monitored, and 32 to 100% of the susceptible contacts became infected.[1] Our observations confirm these studies. In this family study a total of 94% of the siblings and 56% of the parents had signs and symptoms of acute infection during the follow up period of 4 to 6 weeks. Adenovirus disease was confirmed in 63% and 20% of these cases, respectively. This finding is consistent with the observations of Sterner *et al*[17] who confirmed the infection serologically in only 38% of their family contacts, but adenovirus was isolated from 85% of the cases and all had symptoms of adenovirus infection.

To see if patients had any other virus infections we did NPS tests and attempted virus isolation for many symptomatic contacts, but found only parainfluenza virus type 1 in one sibling. In addition to adenoviruses, parainfluenza virus was the only other respiratory virus detected in the community during the first four months of the study when 16 of the 18 index cases were diagnosed. This supports the idea that in most of the symptomatic contacts the illness was caused by adenovirus. It is further supported by the fact that the incubation periods of the laboratory confirmed, and the clinically diagnosed, cases did not differ significantly.

The important clinical observation that we made was that in 88% of the families with symptomatic contacts the index case was the first symptomatic case, or one of the first symptomatic cases, in the family. Adenovirus usually results in so fulminant an infection that the first symptomatic child is taken to a physician.[4] The rapid detection of adenovirus hexon antigen in nasopharyngeal mucus permitted us to diagnose the illness usually within 24 hours. The practical implication of these observations is that by using rapid virus diagnosis parents can be informed prospectively about the expected spread and clinical picture of the illness in the family. This information is especially important in adenovirus infections because they may be difficult to distinguish from bacterial infections.[4 8] In this study 11 of the 18 index cases were treated with antibiotics, whereas only seven of 35 symptomatic family members (three siblings and four parents) were treated when it was known that one family member had an adenovirus infection.

In the children in this study adenoviruses most commonly caused febrile exudative tonsillitis, acute otitis media, and gastroenteritis. This confirms our previous study of 105 hospital patients.[4] In parents the major symptoms were pharyngitis, cough, and rhinitis; high fever (39·0°C), however, was recorded in only one adult. The degree of contagion and the fulminant clinical manifestations of adenoviral infection emphasise the need for rapid diagnosis. In the

Turku area the extensive use of rapid diagnostic procedures for viral infections during the last seven years has resulted in increased awareness and clinical recognition of the signs and symptoms of adenovirus infection. Consequently in the present study most of the index cases were first suspected clinically as adenovirus infections.

In conclusion, this study stresses the need for generalised use of rapid diagnostic methods of adenovirus infections; not only does it help families, but it will be useful in nursery and school epidemics, especially those of severe illness induced by adenovirus type 7.[18] Rapid virus diagnosis will permit studies of antiviral drugs[19] and should have a pronouced influence on the proper use of antibiotics.

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Correspondence to Dr O Ruuskanen, Turku University Hospital, 20520 Turku, Finland.

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