DOI: 10.4274/tpa.46.75

The management of an adenovirus epidemic in a neonatal intensive care unit

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Summary

Aim: Epidemic conjunctivitis caused by adenovirus frequently spreads by direct contact during ophtalmologic examination. This report is written to share our experience of an adenovirus epidemic in our neonatal intensive care unit.

Material and Method: The detailed medical and infection control committee records of the newborns cared in Ege University neonatal intensive care unit and the personnel together in the period between 09.14.2009-10.17.2009 were used in this report. Conjunctiva, nasopharynx and stool samples were collected from 15 patients hospitalized in the service (9 girls, 6 boys) and from 25 personnel. Weekly samples were collected from infants during the epidemic. Direct fluorescence antibody test and "shell vial" cell culture method were conducted synchronously in all samples. Adenovirus conjunctivitis was diagnosed according to clinical evidence and/or detection of adenovirus in direct fluorescence antibody test and cell cultures. SPSS 13.0 statistics programme was used for analysis.

Results: Severe conjunctivitis occurred within 3 days of fundus examination for screening of retinopathy of prematurity in 5 newborns who were examined in the same day, in the ophtalmologist who examined the infants and in 2 newborns who were not examined. Ten of 15 infants who were cared in the neonatal intensive care unit during this epidemic had conjunctivitis. Five of these patients had also gastroenteritis. Five nurses had conjunctivitis and had a leave for therapy and isolation. Adenovrus was detected in direct fluorescence antibody test and cell culture in one nurse. Adenovirus antigen was detected in 3 conjunctival swabs and 1 tracheal aspirate in symptomatic infants. The diagnosis was confirmed with tissue cultures. In addition to standard precautions droplet precautions were also taken with the recommendation of Infection Control Committee.

Conclusions: The meticulous infection control measures including closing the unit to new admissions, detailed cleaning and decontamination of neonatal intensive care unit prevented the epidemic to spread further and limited the duration of the epidemic. A second epidemic did not occur and all patients recovered. *(Turk Arch Ped 2011; 46: 194-8)*

Key words: Newborn, perinatal care, regionalization, transport

Introduction

Adenovirus (AV) is a DNA virus with double spiral without an envelope and can lead to infections in humans with 52 different serotypes gathered under seven subspecies (from A to G) (1,2). In infants, the causative agent in 5-11% of acute respiratory infections is AV. In addition, it also causes to pharyngoconjuntival fever, follicular conjunctivitis, epidemic keratoconjunctivitis, myocarditis, hemorrhagic cystitis, acute diarrhea, invagination and encephalomyelitis. It is the most common cause of follicular conjunctivitis and keratoconjunctivitis. Specifically, AV types 4, 8, 19 and 37 have been shown to be related to epidemic keratoconjunctivitis (3).

Adenovirus infections are frequently observed in individuals with immune deficiency, T or B cell dysfunction and hypogammaglobulinemia. In newborns, the cytotoxic activity of T lymphocytes and natural killer cells is decreased. In addition, B lymphocytes produce limited numbers of antibodies in newborns and maternal antibodies are not sufficient in premature infants. Therefore, newborns are more sensitive against AV infections (1,4).

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E-mail: betulsiyah@yahoo.com **Received:** 04.09.2010 **Accepted:** 14.04.2011

Turkish Archives of Pediatrics, published by Galenos Publishing.

Adenovirus is transmitted by direct contact, aerosols and objects. It is rather resistant against the external enviroment. Epidemic keratoconjunctivitis has been shown to generally occur after examination by an ophtalmologist (2).

In this report, the management of an epidemic of AV infection in an NICU is described.

Material and Method

The AV epidemic which occured in the NICU between 09.14.2009 and 10.17.2009 was examined retrospectively. In this report, the data of medical records and the infection control committee were used. During the epidemic, lower palpebral swab samples were obtained from the infants with conjunctivitis. Stool sample was taken, if diarrhea was present and nasopharyngeal swab sample was obtained from asymptomatic infants. In symptomatic employees, lower palpebral swab samples were obtained, if conjunctivitis was present and throat swab sample was obtained, if upper respiratory infection was present. Throat swab samples were obtained also from asymptomatic employees. Swab samples were obtained from 15 patients (9 female, 6 male) and 25 physicians, nurses and employees and were immediately sent to the laboratory in viral transport medium (Universal transport medium (UTM) kit, Copan Diagnostics, Brescia, Italy) abiding by cold chain rules. Direct fluorescent antibody (DFA) test (sensitivity 86%, specificity 100%) and "shell vial" cell culture method were simultaneously applied in all samples. The diagnosis of adenoviral conjunctivitis was made with clinical findings and/or positive DFA and cell cultures (5). Throughout the epidemic, samples were obtained weekly from all infants. Weekly samples were obtained until findings of conjunctivitis disappeared in all infants and serologic tests and culture results became negative (33 days). Values were given as mean±standard deviation. Fisher test was used for comparison of ratios between groups and Mann Whitney U test was used for comparison of mean values. A p value of <0.05 was considered to be statistically significant. SPSS 13.0 statistical program was used for analysis.

Results

10 of 15 infants who were cared in the NICU during the epidemic had conjunctivitis and 5 had diarrhea and conjunctivitis simultaneously. In 5 of the infants who developed conjunctivits, ophtalmological examination was performed 3 days ago for follow-up of retinopathy of prematurity.

Mean birth weight of 10 infants who developed conjunctivitis was 1090 g (600-1990 g); gestational age ranged between 26 weeks and 33 weeks (mean 28,5±2 weeks) and the age at the beginning of the epidemic ranged between 3 and 104 days (mean 60±37 days). 3 infants among 10 infants with conjunctivits were male and 7 were female. AV was demonstrated by positive DFA and cell cultures in 3 infants in eye swabs and in one infant in the transtracheal aspiration.

Symptomatic and asymptomatic infants were compared in terms of birth weight, gender, ventilator monitoring, ophtalmological examination, number of ophtalmological examinations, age during the epidemic, bronchopulmonary dysplasia (BPD) and corticosteroid therapy. In symptomatic infants, age during the epidemic, the presence of ophtalmological examination just before the epidemic, higher number of ophtalmological examinations, use of corticosteroid before the epidemic and presence of BPD was found statistically significantly higher compared to asymptomatic infants. There was no statistically significant difference between the two groups in terms of birth weight, gender and presence of ventilatory care (Table 1). Two groups with conjunctivitis in whom AV could be demonstrated and could not be demonstrated in laboratory investigations were compared in terms of birth weight, gender, ventilator monitoring, opthalmological examination, number of ophtalmological examinations, age at the time of epidemic, diagnosis of BPD and corticosteroid therapy and no statistically significant difference was found (Table 2). When the epidemic started, there was no subject who was receiving corticosteroid therapy.

For treatment of conjunctivitis, non-steroid antiinflammatory collyria and antibiotic collyria were used in symptomatic subjects. AV was not found in weekly follow-up swabs in symptomatic infants. During the epidemic, no infant was lost.

Table 1. Comparison of the characteristics of 10 infants who were symptomatic (conjunctivitis-gastroenteritis) and 5 infants who were asymptomatic during the epidemic

Characteristics	Symptomatic	Asymptomatic	p
Birth weight (g)	1090 (±426)	1248 (±355)	0.32
Gender (male)	3(30%)	3 (60%)	0.32
Gestational age (weeks)	28.3(±2.3)	29 (±1.8)	0.53
Ventilator treatment at the time of infection	7 (70%)	2 (40%)	0.32
Age at the time of infection (gün)	58.2 (±37)	11 (±11)	0.014
Number of opthalmological examinations	2.8 (±2,4)	0	0.020
Bronchopulmonary displasia (%)	8 (80%)	0	0.007
Use of corticosteroid (%)	8 (80%)	0	0.007
Opthalmological examination	7 (70%)	0	0.026

In addition, conjunctivitis developed in the ophtalmologist and five nurses and AV was evaluated to be positive by DFA method in one of them. Others were found to be negative. In screening of the employees, AV was found by DFA in nasophryngeal swabs in three individuals.

Epidemiology and management of the epidemic

At the time of the epidemic, a total of 15 infants were cared for in the NICU in three rooms. In one of the infants, conjunctivitis was observed three days after ophtalmological examination was performed for retinopathy of prematurity. It was learned that the opthalmologist took a sick report because of conjunctivits three days later.

On the 3rd day of the epidemic, an urgent meeting with the infection control committee was held since conjunctivitis was observed in a total of seven infants and five nurses and decisions on the preventive measures were made. In accordance with the recommendations of the infection control committee, eye swab samples were sent from symptomatic infants, if conjunctivitis was present and stool samples were sent, if diarrhea was present. Only nasopharyngeal swab samples were sent from asymptomatic infants and employees. In addition, in symptomatic employees, eye swab samples were sent, if conjunctivitis was present and nasopharyngeal swab samples were sent, if upper respiratory infection was present. DFA test and "shell vial" cell culture were applied in all samples simultaneously.

Table 2. Comparison of four infants with conjunctivitis in whom AV could be demonstrated and in 6 infants with conjunctivitis in whom AV could not be demonstrated

Characteristics	Serology (+)	Serology (-)	p
Birth weight (gr)	1030 (±476)	1130 (±433)	0.454
Gender (male)	1(25%)	2 (33%)	1
Gestational age (weeks)	28.5 (±2.4)	28.5 (±2.3)	0.91
Ventilatory treatment at the time of infection	4 (100,)	3 (50%)	0.20
Age at the time of infection (days)	83 (±16)	45 (±39)	0.20
Number of opthalmological examinations	3.7 (±1)	1.7 (±2.4)	0.12
Bronchopulmonary dysplasia (%)	4 (100%)	4 (66%)	0.46
Use of corticosteroid (%)	4 (100%)	4 (66%)	0.47
Ophtalmological examination	4 (100%)	3 (50%)	0.20

Table 3. Droplet and contact isolation precautions

1. Hands should be definetely washed and/or hygiene should be provided by alcohol-based hand disinfectant before contact with the patient.
2. To prevent cross-infection hands should be definetely washed and hygiene should be provided by alcohol-based hand disinfectant before passing form one patient to another.
3. Before contact with the patient gloves, mask, protective gown and protective eyeglasses should be worn (Picture 1). Protective eyeglasses should be disinfected with 70% alcohol after use.
4. Before passing to different parts during body care, hands should be washed and gloves should be changed.
5. Laundry washed in the unit should be washed at at least 71°C and for 25 minutes. Clean and dirty laundry should be kept in different places.
6. Laundry which will go to the laundry room should be transferred in a red bag.

Table 4. Cleaning and disinfection of incubators for isolation of adenovirus

1. The inside and outside of incubators should be cleaned with acid-based disinfectant daily.
2. Cleaning should be done twice a day and additionally whenever contamination is observed.
3. Separate cleaning cloths should be used for each incubator.
4. Cleaning should be directed from the lower part to the superior part in incubators.
5. Outer lids and cushions and arms surrounding these lids which are the most common contamination regions should be wiped with a disinfectant (preferably 70% alcohol) twice a day.
6. If the surfaces of the beds have lost integrity, they should be changed with new beds. Damage to the matresses of the patient beds prevents efficient disinfection and sterilization.
7. After use and after each infant exchange cleaning and disinfection of incubators and open beds should be performed.
8. If the infants are being monitored for long-term their incubators are disinfected at least once a week (for infants lower than 1000 g every five days). Firstly all separable parts of the incubator should be removed, washed by brushing and cleaned by rubbing with detergent. All parts of the incubator should be disinfected with 5000 ppm chlorine solution.
9. Incubators should be ventilated before reusing. If the incubators will not be used, complete drying should be provided by heating for 24 hours after disinfection without putting water in the moisturizer part.
10. Containers into which water is placed should be sterilized once a week or before each infant exchange and filled with distilled water or sterile water every 24 hours.
11. If a fan is present, it should be cleaned and disinfected.

In accordance with the infection control committee, contact and droplet isolation precautions were taken in addition to known precautions during the AV epidemic and information tables related to these precautions were placed in the enterance of the unit and in different parts of the service (Table 3).

For adenovirus isolation cleaning and disinfection of incubators were defined in writing, described to the personnel and controlled (Table 4).

Symptomatic infants were placed in the same room and their nurses were separated. Patients who could be discharged were rapidly discharged. Five nurses who had conjunctivitis were not allowed to work. No more patients were admitted to the unit. The patients were taken to a transient intensive care service in order to perform general hygienic cleaning and disinfection of the service and airconditioning system of the whole service was reviewed, cleaning was performed and the walls of the service were painted again.

On the 6th day of the epidemic, cojunctivitis developed in three more infants in the room where asymptomatic infants were placed and they were taken to the room of symptomatic infants. These infants had not been screened for retinopathy. Contact and isolation precautions were taken for all symptomatic and asymptomatic infants. After the 6th day of the epidemic no new case of conjunctivitis was observed. All infants were checked with weekly swab samples for 33 days. Since adenoviral diagnositic tests became negative in all infants and the signs of conjunctivitis disappeared in all infants, the infants were transferred from the transient intensive care service to the NICU on the 33rd day of the epidemic. Infection control precautions were ended 27 days after the last case was observed (on the 33rd day of the epidemic) (Figure 1).

Since the virus was thought to have entered into the unit during opthalmological examination, a meeting with the opthalmologists was held and decisions on precautions which should be taken during the evaluation of retinopathy of prematurity were made in accordance with the decisions of the American Ophtalmology Academy (Table 5).

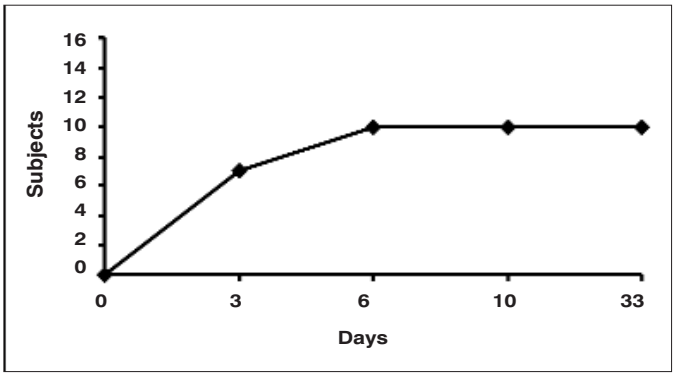

Figure 1: Time graphics of the development of the epidemic

On the 0th day, ophtalmological examination was performed in 5 infants. On the 3rd day, conjuntivitis developed in five infants who were undergone opthalmological examination and in 2 infants who were not undergone opthalmological exmination. On the 3rd day, contact and droplet isolation precautions were taken. Symptomatic and asymptomatic infants were taken to separate rooms and their nurses were isolated. On the 6th day, conjunctivitis developed in 3 infants in the room where asymptomatic infants were cared for and these infants were transferred to the room where symptomatic infants were cared for. No new patient was hospitalized in the service and no vizitors were allowed. Infants who had no urgent problems any more were discharged and families were informed about precautions. Conjunctivitis developed in the father of one of the symptomatic infants after discharge. On the 10th day, patients were transferred to a transient intensive care unit. The whole service was disinfected. No other cases were found. Swab samples obtained were found to be negative. On the 33rd day of the epidemic, patients were transferred back to the NICU. Contact and droplet isolation precautions were ended, since all infants were asymptomatic and AV could not be demonstrated by weekly DFA and cell culture.

Discussion

Adenoviruses have long been associated with nasocomial infections and many epidemics have been reported especially in intensive care units. Epidemics have commonly been reported in NICUs. The mortality rate of the epidemics were demonstrated to be lower with AV type 8 and higher with type 30 and type 7 due to respiratory failure caused by pneumoniae (4,6,7). Therefore, it has been thought that the severity of the epidemics may be related to the serotype of the virus. No infant was lost in the epidemic in our unit. Adenovirus typing could not be done, since there is no center which can perform this investigation in our country. Samples were kept for later evaluation. Since no infant was lost during the epidemic in our unit, pneumonia was not observed and the most common agent of viral conjunctivitis was found to be AV type 8 in a study performed in our country, it was thought that the agent might be AV type 8 (8).

In some studies, it was suggested that corticosteroids might cause the clinical state to detoriorate in premature infants infected with AV or even lead to mortality (7). Since

Table 5. Rules which ophtalmologists should abide by in the neonatal intensive care unit

1. Ophtalmologists should wear gowns and masks before entering the unit.
2. During ophtalmological examination glowes should be used and changed for each patient.
3. Instruments used should be kept in 70% alcohol liquid for 10 minutes and this liquid should be changed twice a day.
4. A separate blepharostate should be used for each patient.

conjunctivitis was the finding at the time of the epidemic, no other risk factor was found except for ophtalmological examination. When symptomatic and asymtomatic patients were compared in terms of the presence of BPD before the epidemic and use of corticosteroid because of BDP, BDP and use of corticosteroid were significantly found to be more common in infants with conjunctivitis. However, no patient was using corticosteroid during the epidemic. We thought that this prevented severe symptoms and mortality in these infants.

Since retinopathy examination was performed at 4-6 months of age and every 1-2 weeks until the retina matured in symptomatic infants, their ages were statistically significantly older compared to asymptomatic infants and their number of retinopathy examinations was higher.

Various therapies have been tried during adenovirus epidemics and different results have been found. It has been thought that intravenous immunglobulin (IVIG) might prevent viral infection, since it includes antiviral antibodies. However, in a contrary study, IVIG used to prevent viral infections was shown to cause AV epidemics (9). In addition, commercial IVIGs are not expected to include sufficient antibodies against rarely seen AV serotypes. The benefit of ribavirin or recently sidovir has also been demonstrated (10). Since no systemic symptoms were observed in our patients during the epidemics, IVIG, ribavirin or sidovir treatment was not administered. Only non-steroid antiinflammatory collyria and antibiotic collyria were used for treatment of conjunctivitis.

As far as the literature reveals, in three of AV epidemics observed in NICUs, the AV epidemic was demonstrated to have occured after opthalmological examination. The causative agent was commonly reported to be adenovirus type 8 (4,7,11).

It was thought that our patients were contaminated by adenovirus during opthalmological examinations and became infected, because conjunctivits was observed in the patients 3 days after ophtalomological examination and the opthalmologist also developed conjunctivitis simultaneously. When infants with and without conjunctivits were compared, the number of opthalmological examinations was found to be statistically significantly higher in infants with conjunctivitis. When retrospective evaluation was made, it was found that masks and gloves were not used during ophtalmological examinations at that time and instruments were found to be insufficient and not disinfected. It was thought that these defects were involved in spreading of the epidemic.

Adenovirus keeps its activity on plastic and metal surfaces for 49 days and on clothes and paper for 10 days and it is excreted in stool for long-term (2,11). AV was not found in stools examined during the epidemic and later. When the epidemic was started, admission of patients to the unit was stopped (for 33 days) until AV was found to be negative in DFA test and cell culture. Early recognition of the epidemic, performing necessary isolation precautions meticulously, stopping of admission of patients to the unit, transferring the unit and detailed cleaning prevented the spread of the epidemic and lengthening its duration.

Meetings were held with ophtalmologists and opthalmological examinations which will be performed in the unit were provided to be performed in accordance with written standards. As a result of all precautions a second epidemic did not occur and no patient was lost.

Adenovirus epidemics require the services in NICUs to be closed and very serious precautions to be taken and the risk of recurrence is high. Continuous education is the main component for protection from infections.

Conflict of interest: None declared.

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