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URINARY ANTIGEN SCREENING IN PNEUMOCOCCAL INFECTIONS IN CHILDREN

ÇOCUKLARDA PNÖMOKOK ENFEKSİYONLARINDA ÜRİNER ANTİJEN TARAMASI

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ABSTRACT

Streptococcus pneumoniae is a leading cause of meningitis, bacteremia, pneumonia and otitis media in childhood. The diagnosis of pneumococcal infections still remains problematic. Binax NOW® is a rapid immunochromatographic test (ICT) that detects S. pneumoniae C-polysaccharide antigen in the urine.

We evaluated the usefulness of ICT in the diagnosis of pneumococcal infections in children in our study. Fifty children with sepsis, pneumonia, otitis or meningitis (patient group) and 50 healthy children (control group) were enrolled in the study. Urine samples and nasopharyngeal cultures were obtained from all cases. Blood, transtracheal aspirate, urine and CSF (cerebrospinal fluid) cultures were also taken from the patient group when possible.

We found urinary antigen positivity in 7 cases in the control group and 10 cases in the patient group. All the children who carried S. pneumoniae in their nasopharynx (1 in the control group and 2 in the patient group for a total of 3 cases) had positive ICT. We detected S. pneumoniae in 3 patients (1 blood culture and 2 CSF cultures) and ICT was positive in all. There was no effect of antimicrobial treatment, vaccination and acute phase reactant levels on the urinary antigen detection test.

We concluded that this test is not useful in the diagnosis of pneumococcal infections in children as high carrier rates cause false positivity. This test can only be used with other conventional microbiological tests as a supplementary method.

Key words: Streptococcus pneumoniae, urinary antigen, children

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ÖZET

Streptococcus pneumoniae çocukluk çağındaki menenjit, bakteriyemi, pnömoni ve otitlerin en önemli nedenidir**.** Pnömokokkal enfeksiyonların tanısı halen problemdir. Binax NOW, idrarda *S.* pneumoniae C- polisakkarit antijenini tarayan hızlı bir immunkromotografik testtir (İKT) .

Biz çalışmamızda, çocuklardaki pnömokok enfeksiyonlarının tanısında İKT in kullanılabilirliğini araştırdık. Çalışmamıza 50 sağlıklı çocuk (kontrol grubu) ile sepsis, pnömoni, otit ve menenjit tanılı 50 çocuk (hasta grubu) alındı. Tüm olgulardan idrar örnekleri ve nasofaringeal kültürler elde edildi. Ayrıca hasta grubunda uygun olan olgulardan kan, transtrekeal aspirat, idrar ve BOS (beyin omurilik sıvısı) örnekleri alındı.

Kontrol grubunda 7 olguda ve hasta grubunda da 10 olguda üriner antijen pozitifliği bulduk. Nazofarinkslerinde S. pneumoniae taşıyan 3 çocuktan (1 kontrol grubunda, 2 hasta grubunda) hepsinde IKT pozitifti. Biz 1 kan kültüründe, 2 BOS kültüründe olmak üzere 3 olguda pnömokok saptadık. Hepsinde İKT pozitifti. Antimikrobial tedavinin, aşılamanın ve akut faz reaktan düzeylerinin üriner antijen tarama testi üzerine etkisi yoktu.

Biz, çocuklardaki pnömokoksik enfeksiyonların tanısında yüksek taşıyıcılık oranlarının yanlış pozitifliğe yol açması nedeniyle bu testin kullanılabilir olmadığı sonucuna vardık. Bu test, sadece diğer geleneksel mikrobiyolojik yöntemlerle birlikte destekleyici yöntem olarak denenebilir.

Anahtar kelimeler: Streptokokus pnömonia, üriner antijen, çocuk

INTRODUCTION

S. pneumoniae is the most common cause of community-acquired pneumonia (CAP), acute otitis media (AOM), sinusitis and bacteremia in children. Pneumococcal infections still cause high rates of morbidity and mortality worldwide (1). The diagnosis of pneumococcal infections continues to be difficult (2,3). Inadequate sensitivity of blood culture isolation, difficulty in obtaining sputum, high sputum sample contamination rates and the rare use of pulmonary aspiration samples due to the invasiveness of the method are some of the reasons for this difficulty (3).

Binax NOW® has been approved by the FDA (US Food and Drug Administration) as a screening method for pneumococcal infections in 1999 (4). This kit looks for the C-polysaccharide antigen found in the S. pneumoniae cell wall in the CSF and urine. The system covers common pneumococcus serotypes together with the 23 serotypes that cause more than 90% of pneumococcal infections It is a convenient choice for screening as it is not affected by contamination with respiratory tract flora and can be used on easily available urine (5,6). When traditional microbiological methods are used as reference, the test sensitivity is 60-75.9% and the specificity is 89.7-100% (2,5,7-11). Ishida et al. have demonstrated that using the urinary antigen screening test together with classical microbiological methods increases the efficacy in the diagnosis of pneumococcal pneumonia 38.9% (8). There have been only a limited number of studies in children due to their high pneumococcal carrier rate and the related false positivity. The use of the test in children is controversial. However, Homer et al. have shown a specificity of 96% in non-carrier children in their study (12). Problems persist with the treatment of pneumococcal infections as with the diagnosis. Antibiotic resistance is increasing in pneumococcal infections due to incorrect and unnecessary antibiotic usage. Various studies have

reported less change/higher rate of success with initial beta-lactam monotherapy in cases with a positive urinary antigen screening test (9).

The aim of this study was to evaluate the usefulness of the urinary antigen screening test in children thought to have a pneumococcal infections. Demonstrating the diagnostic value of this method in children would increase treatment success and decrease antibiotic resistance with the selection of the proper antibiotics possessing a narrower spectrum.

MATERIAL AND METHOD

This study was performed on patients followed-up at the Ege University Department of Pediatrics between June 2008 and April 2009. Consent was obtained from the local ethics committee before the study and written consent was signed by the parents of the subjects.

The study was performed on 50 patients aged 1 month to 17 years and another 50 subjects as the control group to determine the effect of carrier status, for a total of 100 children. The patient group included cases presenting at our clinic with high fever (≥38 ºC) and suffering from sepsis, central nervous system (CNS) infection, pneumonia or AOM where S. pnonomoniae was suspected as the infectious agent. The control group included cases being followed-up for reasons other than infection. Patients who had been vaccinated for pneumococcus within the last 5 days or had underlying chronic pulmonary disease were not included in the study.

Surveys that included information on the participant's vaccination history, presentation complaint and antibiotic usage were completed. Throat cultures and urine samples were obtained from all patients while blood, CSF and urine cultures and blood C-reactive protein (CRP) values were also evaluated from suitable cases. Throat swab samples were inoculated on 5% sheep blood agar media. The plates were kept at 36°C in a 5% CO2 environment for 18-24 hours. Gram staining and the catalase test were performed on suspect (mucoid, shiny, with a depressed center) alpha-hemolytic colonies. Colonies that formed doublets or chains, with a morphology of Gram-positive cocci, catalase (-), optokin-sensitive (showing an inhibition zone ≥14 mm with a 6 mm disc containing 5 micrograms of optokin or a positive bile liquidation test if the zone diameter was not adequate with optokin) were defined as S. pneumoniae.

The urine samples were promptly evaluated according to the manufacturer's recommendations with the Binax NOW S. pneumonia® (Inverness Medical International, Cranfield, U.S.A.) kit. The test strip was dipped into the urine and put on the assembly consisting of a nitrocellulose membrane covered with rabbit anti-pneumococcus antibody. The assembly was closed after a drop of citrate/phosphate solution was placed. The test was interpreted 15 minutes later as negative if only the control strip was stained and positive if both the sample and control strips were stained.

The data were statistically evaluated with SPSS version 15.0. Pearson Chi-square, Fisher's exact test and the Mann-Whitney U test were used to analyze the variables. A p value < 0.05 was accepted as significant.

RESULTS

A total of 100 subjects consisting of 50 patients and 50 control group members were included in the study. The mean age of all cases was 50.44 months (1 month-16.2 years). The throat carrier rate for pneumococcus was 3%. Urinary antigen was positive in 17/100 cases. Table 1 presents the general features of the cases.

A total of 50 children aged 2 to 143 months were evaluated in the control group. The urinary antigen screening test was positive in 7 out of 50 children. S. pneumoniae grew in throat culture from one patient and this case was among the antigen test positive group. The effect of being a throat carrier of pneumonia on positive antigen screening test results was found to be statistically significant. There was no statistically significant relationship between the urinary antigen positivity and gender, age or history of pneumococcal vaccination in the control group (Table 2).

A total of 50 children aged 1 to 195 months were included in the patient group. Table 3 provides the general features of the group. The diagnosis was pneumonia in 27, CNS infection in 10, sepsis in 9 and AOM in 4. We found no statistically significant difference between the type of infection, CRP values and the urinary antigen screening test. Throat culture was obtained from all children while 9 CSF cultures, 20 blood cultures, 4 transtracheal aspirate (TTA) cultures and 9 urine cultures were evaluated from the suitable patients. Staphylococcus aureus and Pseudomonas aeruginosa grew respectively in two TTA

Table 1: General features of study participants

	Patient Group	Control Group	Total
Number of cases	50	50	100
Gender	19 F/ 31 M	24 F/ 26 M	43 F/ 57 M
Mean age (months)	58.2	43	50.4
Antigen secreening positivity	10	7	17
Vaccination history positivity	12/50	18/50	30/100
Pneumococcal carrier state	2/50	1/50	3/100

(F: female, M: male)

Table 2 : Evaluation of the control group according to urinary antigen screening test results

	Antigen screening(-)	Antigen secreening (+)	P
Mean age (months)	45.4	28.1	0.293
Gender	21 F/ 22 M	3 F / 4 M	0.769
Vaccination history (+)	16/43	2/7	0.659
Throat pneumococcus (+)	0/43	1/7	*0.044*

(F: female, M: male)

Table 3: Evaluation of the patient group according to the urinary antigen screening results

		Antigen screening (-)	Antigen screening (+)	P
Mean age (months)		61.3	46.1	0.416
Gender		15 F / 25 M	4 F / 6 M	0.884
Antibiotic usage (+)		18 / 40	5 / 10	0.732
Antibiotic usage duration	**0-3 days**	10 / 40	3 / 10	0.787
	4-7 days	6 / 40	1/ 10	
	7 days <	2 / 40	1 / 10	
Vaccination history (+)		8 / 40	4 / 10	0.225
Throat pneumococcus (+)		0 / 40	2 / 10	*0.037*
CRP elevation (+)		28/ 34	7/ 10	0.156

(F: female, M: male)

cultures while there was no growth in the two others. The antigen screening test was not positive in any patient from whom a TTA sample had been obtained. There was growth in 3 of the 9 CSF samples obtained from children with a diagnosis of CNS infection. One grew enterovirus and the other two S. pneumoniae. The urinary antigen was positive in both the cases that grew pneumococci. No antigen positivity was found among children from whom CSF samples had been obtained except these two cases. The antigen screening test was negative in another case that had received antibiotics for over a week and where pneumococcal meningitis had been found according to the CSF sample obtained before treatment (there was no growth in the last CSF culture of this patient at the time the urine sample was taken). Evaluation of the 20 cases from whom a blood culture had been obtained revealed growth in one case with a diagnosis of pulmonary infection + sepsis. The urinary antigen screening test of this case with growth in the blood culture was positive. The urinary antigen test was positive in 4 of the other

Table 4: Relationship between culture results and the antigen screening test

Culture obtained			Urinary Antigen (-)	Urinary Antigen (+)
TTA	Pneumococcus (+)	Throat pneumococcus (+)	0	0
		Throat pneumococcus (-)	0	0
	Pneumococcus (-)	Throat pneumococcus (-)	4	0
		Throat pneumococcus (+)	0	0
Blood	Pneumococcus (+)	Throat pneumococcus (-)	0	1
		Throat pneumococcus (+)	0	0
	Pneumococcus (-)	Throat pneumococcus (-)	15	3
		Throat pneumococcus (+)	0	1
CSF	Pneumococcus (-)	Throat pneumococcus (+)	0	0
		Throat pneumococcus (-)	7	0
	Pneumococcus (+)	Throat pneumococcus (+)	0	1
		Throat pneumococcus (-)	0	1

19 cases with no demonstrable growth in blood culture. Escherichia coli grew in one of the 9 urine cultures. This patient's diagnosis was urosepsis and the antigen screening test was positive. The patient had also been vaccinated for pneumococcus 8 days previously. Table 4 presents the relationship between cultures and the urinary antigen screening.

There was no relationship between age and gender in the patient group and the antigen screening test (Table 3). Evaluating the pneumococcal vaccine status revealed no significant effect of pneumococcal vaccination, vaccine type and number of doses administered on antigen screening in the patient group . Evaluation of antibiotic usage showed that 23 of the 50 patients had a history of prior treatment. One of the two patients with a diagnosis of pneumococcal meningitis and positive urinary antigen screening had received treatment for less than three days and the other for more than a week. The child with pneumococcal bacteremia had received 4 days of antibiotics. We did not find a statistically significant relationship between antibiotic usage duration, antibiotic type and urinary antigen test positivity (Table 3).

Evaluation of all the children included in the study together revealed no statistically significant difference between the antigen screening test positive and negative cases for age, gender, antibiotic usage, vaccination history. The carrier rate was significantly higher in the group with positive urinary screening test results (*P*: 0.04)

DISCUSSION

Various studies with Binax NOW (immunochromatographic test-ICT) in adults have shown that the test can be used for screening in this group. The advantages of this test are; No influence of antibiotic usage, rapid result, non-invasiveness, possibility of bedside use, high sensitivity and specificity, and the possibility to use when microbiological methods are inadequate (8). This test has been shown to increase the rate of diagnosis especially when used in CAP's together with other microbiological methods (5,6,8). Various studies have reported a sensitivity of 55-82% and specificity of 67-100% for the test (9). High nasopharyngeal carrier rates in children make it difficult to differentiate between infection and healthy carriers. There are therefore only a few studies on ICT use in children. The throat carrier rates for pneumococcus in various studies are 21-52.1% in Europe, 30-50% in the USA, 85-87.2% in Africa, and 22.3% in Asia (4,13-17). Our rate of colonization in throat cultures was 3%. The pneumococcal carrier rate in our country is 13.9- 22.5% and our low rate may be due to the low number of participants and antimicrobial treatments used in the patient group which would have decreased the colonization rate

(17-19). Adegbola et al. reported from their study in Gambia a sensitivity of 55% and specificity of 85% for ICT for detecting carrier status in children (1). When assessed for our control group, our sensitivity was 10% and specificity 100%, taking throat cultures as reference. We found a significant relationship between throat pneumococcus colonization and ICT positivity, as reported in the literature (1,4,12,20). This shows that the test has a high rate of providing incorrect results in showing pneumococcus as the causative agent.

We did not find a relationship between the type of infection and ICT positivity in our study. However, it was noteworthy that the urinary antigen screening was positive in all cases where pneumococcus had grown in the blood and CSF cultures at the time the samples were taken. Sakata has reported the antigen screening sensitivity as 73.1% and the specificity as 96% in children with meningitis and suggested its use (21). Watanuki et al. have shown that antigen screening is positive at higher rates in severe pneumococcal infections (22). Fuse et al. have not found a relationship between the severity of the infection and ICT positivity (11). The Binax NOW ® kit has only been studied in meningitis and pneumonia cases as regards pneumococcal infections in children (20-22). The diagnostic benefit in AOM or other pneumococcal infections has never been studied previously. It is necessary to investigate the usefulness of this test in other pneumococcal infections as well, taking into account its simplicity, non-invasiveness and the demonstrated benefit for adult cases.

We did not find a significant effect of antibiotic usage on the ICT result in this study. Other articles also report continuing urinary antigen positivity despite antibiotic usage. It has been demonstrated that antigen positivity can continue for about one month despite antibiotic usage (8,9,23). The important advantage of the test as regards the lack of any influence of treatments administered before the diagnosis was also noted in our study. We did not find a relationship between the type of antibiotic and ICT results in the patient group and there are no other studies on this subject. Other studies are required to evaluate the influence of effective and ineffective treatments on the test.

When we evaluated the vaccination history, we did not find a statistically significant effect of vaccination on the antigen screening test. Navarro et al. have reported a higher ICT positivity rate in children vaccinated for pneumococcus then children with chronic pulmonary disease and no active infection and stated that vaccination may affect the screening test by causing antigen excretion (20). The manufacturer also suggests that testing should not be done in the 5 days after vaccination. The positive urine result in the patient with a diagnosis of sepsis without any growth on blood culture may be due the vaccination done 8 days ago. More studies with more subjects are required to determine the effect of vaccination on test positivity. Pneumococcal vaccination has now been included in the routine program in many countries including Turkey and the effect of vaccination will therefore become even more important in the future.

Kobayashi et al. and Hashikita et al. have found much higher rates of acute phase reactants in the ICT positive group in their respective studies on adult pneumonia patients (24,25). We did not find such a relationship. The reason may be the use of antibiotics by a large proportion (46%) of the children in the patient group and the related post-treatment decrease in acute phase reactants.

The most important limitation of our study was that we were unable to use comparison with microbiological methods in all the patient group members. Performing tympanocentesis in otitis cases, or obtaining samples with bronchoscopy or transtracheal aspiration in pneumonia cases are quite invasive. One must also take into account the difficulty of obtaining adequate sputum samples in children. It is also known that growing S. pneumoniae in culture can be difficult even with traditional microbiological methods. We did not evaluate the weak positive and strong positive cases separately in our study. We were unable to clarify whether these results were false positive or actual positive as we were unable to perform a full comparison with microbiological methods. Another limiting factor was the low number of cases included in the study. Studies with larger number of cases are required to determine the effect of carrier status in children on the test. We evaluated patients with various diagnoses together in the patient group in this study. Other studies where the usefulness of the test in the four diagnostic groups ascertained in our study and other pneumococcal infections is evaluated separately are needed.

In conclusion, the urinary pneumococcal antigen screening test is affected by the carrier state and cannot be used a gold standard method in the diagnosis of child-

hood pneumococcal infections while it can be used as an ancillary screening method.

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