ROLE OF "ATYPICAL" MICROORGANISMS ON THE FORMATION OF BRONCHIAL ASTHMA IN CHILDREN WITH ACUTE AND RECURRENT OBSTRUCTIVE BRONCHITIS

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ABSTRACT

Objective: This study was undertaken to determine the link between the presence of "atypical" infections in patients with acute obstructive and recurrent obstructive bronchitis (AOB/ROB) and bronchial asthma (BA) development based on the concept of risk.

Methods: The materials for the study were the data records of patients hospitalized with AOB or ROB and whose analysis was performed to identify antibodies to "atypical" microflora (796 patients). The study period was 4 years from 2008 to 2011. In the analyzed period, immunosorbent assay for the detection of antibodies to "atypical" microflora (Chlamydophila pneumoniae, Mycoplasma pneumoniae, Mycoplasma hominis) was performed. The concept of risk identification was based on the determination of the absolute risk, attributable risk (ATR), relative risk, population attributable risk, as well as on the definition of the standard errors for each type of risk and the confidence interval.

Results and Conclusion: Methodical aspects of determining the relationship between the presence of "atypical" infections in patients with AOB or ROB and BA development were based on the concept of risk. The analysis showed a direct link between the increase of cases of BA formation against the backdrop of "atypical" infections. Therefore, the performed analysis of atypical pathogens influences on BA occurrence in patients with AOB/ROB which indicates direct dependence increase of BA incidence on atypical infection. In experimental group, Frequency of event is 1.67% in control group. The risk factor increases probability of event by 13.17%, the risk factor increases frequency of event by 1.67% in control group. The risk factor increases probability of event by 13.17%, the presence of atypical infection leads to increase of BA incidence by 8.9 times. Number needed to harm (NNH) is 7.59, i.e., in the presence of atypical infection in patients with AOB/ROB, each eighth exposed person develops BA in addition to background level of BA incidence.

Keywords: Acute obstructive bronchitis, Recurrent obstructive bronchitis, Bronchial asthma, The concept of risk, Risk factor, The absolute risk, Relative risk, Attributable risk, Population attributable risk, Number needed to harm.

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INTRODUCTION

Acute obstructive bronchitis (AOB) is a common disease, which affects 10-15% of child population. AOB incidence is increasing globally. More than 50% of infants may develop recurrent obstructive bronchitis (ROB) in association with acute viral respiratory infection (AVRI) [1]. If bronchitis with bronchial obstructive syndrome (BOS) occurs at least 2-3 times a year, ROB develops. Bronchial asthma (BA) is also the common cause of recurrent incidence of BOS.

Nowadays, continuous increasing incidence and the severity of BA are noted. BA is often evolved in children at an early age, hence it is a considerable problem [2]. Microbe-virus associations were proved, in which one of the infectious agent is intracellular pathogen, for example, Chlamydophila pneumoniae, Mycoplasma pneumoniae, Legionella spp. etc., play an important role in bronchial obstructive disease. In recent years, numerous researches of atypical role of respiratory pathogens in recurrent BOS are performed [3,4].

In epidemiological and clinical researches, often it is necessary to evaluate the power of interaction between impact and outcome (disease, complications, death, etc.) when parameters are paired, i.e., they are alternative outcomes for research subjects. In general, risk concept considers ratio between participants, who is exposed and not exposed of any factor. Hence, risk concept evaluated the effect of smoking on the occurrence of chronic obstructive pulmonary disease exacerbations [5].

The purpose of this research is to reveal the interaction between the presence of atypical infections in patients with AOB, ROB, and BA, according to risk conception.

METHODS

Study site
The study was conducted in a hospital in Nizhny Novgorod.

Study population
The study included stroke patients who underwent treatment.

Study design
The design of the study was of retrospective type.

Period of the study
The study was performed for 4 years (2008-2011).

Inclusion criteria
In the research, we applied medical records of patients, who were hospitalized with AOB/ROB and in whom antibody test for "atypical" microflora (796 patients) was performed.

Over a period of study, enzyme immunoassay for atypical microflora (C. pneumonia, Mycoplasma pneumoniae, and Mycoplasma hominis) antibodies was performed.

IgA antibodies were detected in 256 (32.2%) examined patients.
Methodology of data processing

Detection risk concept was built on absolute risk (AR) detection in exposed group (ARe) and in unexposed group (ARu) (i.e., in patients with concurrent atypical infection and without concurrent atypical infection, respectively), on attributable risk (AtR), relative risk (RR), population AtR (PAR), and also on the detection of standard error for all risk types and confidence interval (CI).

RESULTS

Analysis of risk for occurrence of BA in patients with AOB and ROB begins with the construction of table of conjugate distributions (Table 1). Rows and columns of this table are arranged in certain order. Therefore, parameters that were calculated from this table in the course of research make a sense and may be interpreted correctly. The first row assigns for exposed group, which consists of children having studied risk factor, i.e., patients with BOS and concurrent atypical infection. The second row assigns for values, characterizing of BA risk in patients with BOS, but without atypical infection. The studied risk factor was absent in this group. In summary, the first group is interesting for investigators, i.e., patients in this group were exposed to risk factor. Values in the second row have been received from unexposed group, i.e., from patients without concurrent atypical infection. In the first column, it is recorded how many times the investigated event (risk of BA occurrence) was registered in exposed group (patients with concurrent atypical infection) and in unexposed group (without concurrent atypical infection). In the second column, it is recorded how many times investigated event was absent.

In the beginning, hypothesis is formed that presence of atypical infection in patients with BOS may lead to BA. First of all, AR is calculated, i.e., proportion of ill in the whole group (in exposed and unexposed groups separately). In our case, it means computation of BA risk in group of patients with/without concurrent atypical infection. By Formula (1), we calculate the frequency of BA occurrence in exposed group (with atypical infection), i.e., 14.84%:

\[
ARe = \frac{a}{A}
\]

In other words, 0.1484 or 14.84% of patients in the exposed group have a risk of BA. By Formula (2), we calculate the frequency of BA occurrence in unexposed group (without atypical infection), i.e., 1.67%:

\[
ARu = \frac{c}{B}
\]

As a result, we have the so-called point estimates of BA occurrence frequency in experimental and control groups. Point estimates may have statistical error, hence in the next sample, we may receive different values because we calculate these frequencies not on the base of whole population but on the base of representative parts, which just approximately reflects the features of population. Therefore, it is necessary to calculate the standard error of received AR, i.e., statistical error of each frequency, which indicates the accuracy of estimate. Standard error for AR in the exposed group was calculated by Formula (3) - 0.022:

\[
S = \sqrt{\frac{AR(1-AR)}{n}}
\]

| Atypical infection | Risk of BA | Total |
|--------------------|------------|-------|
|                    | Yes        | No    |
| Present            | 38 (a)     | 218 (b) | 256 (A) |
| Not present        | 9 (c)      | 531 (d) | 540 (B) |
| Total              | 47 (C)     | 749 (D) | 796 (Q) |

BA: Bronchial asthma

Where n - volume of exposed or unexposed group, i.e., A or B.

Standard error for AR in the unexposed group was calculated similarly at 0.005.

The received frequencies may change in case of calculation in other samples. Therefore we need to define how these changes will be significant, and minimal intervals of values involve actual precise values of required frequencies. We define minimal interval, which consists from actual value of required frequency with probability of 95%. In statistics, such interval is named 95% (95% CI). From a practical point of view, 95% CI means that 95% of all potential samples give frequencies that are included in received intervals, but 5% will be out of these intervals. In research, 95% CI or 99% CI is used mostly.

We calculate 95% CI for AR of exposed group at 0.1484±0.0431 or 14.84±4.31% by Formula (4):

\[
CI_{AR} = AR\pm t\times S
\]

Where t - critical value for statistical significance. For 95% CI, t=1.96, S - Standard error of AR.

In other words, minimal value of 95% CI is 10.53%, maximal value is 19.15%, mean ARe is 14.84%, and standard error is 2.20%.

To summarize, the presence of concurrent atypical infections in the studied group led to BA occurrence in 14.84±2.20%, 95% of all possible values of incidence are included in interval at 10.53-19.15%.

Analogically on Formula (4), 95% CI for AR in unexposed group was calculated: 0.0167±0.0098 or 1.67±0.98%.

In other words, without concurrent atypical infection, the risk of BA occurrence in control group is 1.67±0.98%. 95% of all possible values of incidence are included in interval 0.69-2.65%.

Thus, absolute values of morbidity in exposed and unexposed groups were received. Therefore, under the impact, BA occurrence increases. But how significant is the role of risk factor in this increasing? AtR is estimated, which characterizes risk parts that are associated with this risk factor. AtR is calculated by Formula (5) and it is 0.317 or 13.17%.

\[
AtR = ARe - ARu = \frac{a/A}{c/B}
\]

In other words, in experimental group, Frequency of event is 14.84% in experimental group. Frequency of event is 1.67% in control group. The risk factor increases probability of event by 13.17%.

For calculation of standard error of received distinction, it is necessary to compute the combined estimate of the proportion. It is 0.059.

\[
F = \frac{C}{Q}
\]

Then, we determined standard error of AtR by Formula (7). It was 0.0183 or 1.83%.

\[
S_{AR} = \sqrt{F \times (1-F) \times \left(\frac{1}{A} + \frac{1}{B}\right)}
\]

Then, we calculated 95% CI for AtR:0.1317±0.0359 or 13.17%±3.59%.

To summarize, the presence of concurrent atypical infections in patients with AOB or ROB leads to increased risk of BA occurrence by 13.17±3.59%, 95% of possible (true) values of difference of morbidity were included in interval 9.58 - 16.76%. Therefore, possible (true) values, which are included in 95% CI, may indicate about ARe>AR, i.e., atypical infection increases of BA risk.
If $A_{Re}=A_{Ru}$, impact of risk factor does not change the probability of event. If $A_{Re}<A_{Ru}$, impact of risk factor does not change the possibility of event.

Risk estimation methodology is based on statistical parameters (mean, mean error, CI), which are based on probability theory. Therefore, when we calculate any risk, we should talk not about absolute (precision) dependence of outcome from factor but about the probability degree of this dependency. In turn, dependence of the outcome from the factor may be significant. In this case, statistical reliable probability of such dependence may be revealed in small samples. If dependence of the outcome from the factor is insignificant, for detection of statistical reliable probability, big samples are needed, sometimes whole population (e.g., population of certain region).

Analogically considering the features of CI $AtR$, it is necessary to analyze CI for all calculating risks. For example, in $A_{Re}$ and $A_{Rn}$, calculated earlier CI (10.53 and 19.15%, 0.69 and 2.65%, respectively) did not involve 0 or negative values. Consequently, these CIs may be considered statistically significant.

Through $AtR$, it has been demonstrated that presence of atypical infection leads to increase of BA risk by an average of 13.17%.

Through calculation of RR (risk ratio or relative risk), we may demonstrate the power of dependence between impacting risk factor and outcome, i.e., how many times BA morbidity increases in the presence of atypical infection in patients with AOB and ROB. If BA occurred more often in exposed group, ratio of $A_{Re}/A_{Rn}$ is $>1$. If BA morbidity is equal in both groups, $A_{Re}/A_{Rn}$ ratio equals to 1. Thus, according to hypothesis, from mathematical point of view, it is necessary to prove that ratio of BA occurrence in both groups is more than 1.

$RR$ was calculated by Formula (8) and equals to 8.9.

$$RR = \frac{A_{Re}}{A_{Ru}} = \frac{3}{2}$$

In other words, presence of atypical infection leads to increase of BA occurrence by an average of 8.9 times. However, when we are talking about calculation, made on sample, it is necessary to show a statistical significance of received result. For this purpose, standard error of RR was calculated, it equals to 0.3619.

$$S_{RR} = \sqrt{\frac{1-A_{Ps}}{a} + \frac{1-A_{Pn}}{c}}$$

By Formula (10), we calculated 95% CI of RR, received value of 8.9±4.71%.

$$CI_{RR} = RR \pm \text{Exp} \left( \ln \frac{A_{Re}}{A_{Ru}} \pm t \times S \right)$$

The received values of RR are 8.9±0.3619 with 95% CI of 4.19-13.61 (Fig. 1). Analogically to $AtR$ possible (true) values, involving in 95% CI, may indicate that:

- $RR>1$, i.e., atypical microflora influence increases the risk of BA;
- $RR=1$, i.e., atypical microflora influence does not change the risk of BA;
- $RR<1$, i.e., atypical microflora influence decreases the risk of BA.

Therefore, 95% CI values indicate the importance of our hypothesis about atypical microflora influence on BA occurrence.

PAR is absolute difference of values (or risk) in whole population and in the unexposed group. PAR similar to $AtR$. But population component describes the risk component in the whole population. PAR depends upon how widespread risk factors in this population. PAR varies depending on risk factor distribution in population.

By Formula (11), PAR value was calculated, it received 0.042 or 4.2%.

$$PAR = \frac{C Q - c}{Q}$$

In other words, the presence of atypical infection leads to morbidity increase in the whole population by 4.2%.

For calculation of standard error of received difference, it is necessary to compute the combined estimate of the proportion. Standard error of AR in the exposed group was calculated by Formula (6) - 0.059.

By Formula (12), we can calculate mean error, it received 0.0134 or 1.34%.

$$S_{PAR} = \sqrt{F \times (1-F) \times \left( \frac{1}{Q} + \frac{1}{B} \right)}$$

By Formula (13), we can calculate 95% CI PAR. It is 0.042±0.026 or 4.20±2.60%.

$$CI_{PAR} = PAR \pm 1.96 \times S$$

Thus, the presence of atypical infection increases BA morbidity in whole population by 4.20±1.34%, 95% CI equals from 1.6% to 6.8% (Fig. 2).

There is another parameter, which is a derivative from $AtR$, number needed to harm (NNH) or number needed to treat (NNT). If exposure factor presumably caused negative changes in health status, we are speaking about NNH. If exposure factor improves health status (e.g., new treatment method decreases the number of recurrences, prophylactic measures decrease of incidence), we mean NNT. Both parameters are ratio 1 to $AtR$ (14).

$$NNH(NNT) = \frac{1}{AtR}$$

Fig. 1: Corridor fluctuation relative risk values with 95% confidence interval of bronchial asthma by persistent infection with atypical pathogenes

Fig. 2: Corridor fluctuation population attributable risk values with 95% confidence interval of bronchial asthma by persistent infection with atypical pathogens
Diagnosis and treatment of asthma in childhood

Streptococcus Diagnostics and treatment of asthma in childhood and Moraxella (Moraxella: E.C. pneumonia, Moraxella: A)

The frequency of immune response of a child contributing, from one point, to secondary infection, more than half of the examined children suffered from typical bronchitis turns into typical BA. According to the results of long-term follow-up (Yu and Mizernitskiy, 2005), 4-8 years after hospitalization associated with expressed BO with acute respiratory infection, more than half of the examined children suffered from typical BA that had not been diagnosed in the early age.

According to multiple data from literature, the most important aspect concerns studying the role of microbial and viral associations when infection leads to increase of BA incidence by 8.9 times. NNH is 7.59, i.e., in the presence of atypical infection in patients with AOB/ROB, each eighth exposed person develops BA in addition to background level of BA incidence.

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