

Pleural effusion adenosine deaminase is not accurate in diagnosis of pediatric tuberculous pleural effusion: a retrospective study

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Abstract. – OBJECTIVE: Pleural effusion (PE) adenosine deaminase (ADA) has good performance in detection of tuberculous pleural effusion (TPE). However, few study was conducted for its value in pediatric patients. To evaluate PE ADA in diagnosis of pediatric TPE, a retrospective study was performed.

PATIENTS AND METHODS: 204 pediatric PE patients were enrolled, and then were grouped into TPE group (77 cases, aged 11.51 ± 0.40 years) and non-TPE group (127 cases, aged 6.39 ± 0.35 years). Man-Whitney U test was used to compare difference in pleural ADA between the two groups. The correlation between age and ADA activity was analyzed by Spearman's correlation coefficient analysis.

RESULTS: In our study, there was no difference in pleural ADA between TPE (62.1 ± 4.2 U/L) and non-TPE patients (87.7 ± 10.0 U/L). Compared with empyema patients (183.8 ± 30.0 U/L), pleural ADA was lower in parapneumonic effusion (PPE) patients (63.4 ± 3.8 , $p < 0.01$), or TPE patients ($p < 0.01$). Correlation analysis showed that there were no correlation between age and pleural ADA within TPE, PPE or both patients (all $p > 0.05$). Meanwhile, there was no significant difference in PE ADA level between genders.

CONCLUSIONS: Considering the fact that the majority of pediatric PEs is TPE and PPE, our study suggests that PE ADA isn't accurate in detection of pediatric TPE. Meanwhile, an extremely high ADA activity should raise suspicion of empyema or lymphoma.

Key Words:

Adenosine deaminase, Tuberculosis; Pleural effusion; Child.

Introduction

Pleural tuberculosis (TB) is the most common presentation of extra-pulmonary tuberculosis and the most common cause of pleural effusion (PE)

worldwide^{1,2}. In children, 4%-22% of tuberculosis patients presented with pleural TB^{3,4}. The diagnosis of pleural TB in children is based on compatible history, clinical findings, medical thoracoscopy, chest x ray, tuberculin skin test (TST), microbiological tests (acid-fast bacilli (AFBs) in smear or mycobacterial culture), PE biochemical analysis and response to anti-TB treatment⁵⁻⁹. Due to the paucibacillary nature of pediatric TB, the AFB positivity was low and culture was a moderate diagnostic test, which takes 6-12 weeks¹⁰⁻¹².

PE adenosine deaminase (ADA) was evaluated as a good biomarker in the diagnosis of tuberculous pleurisy and had been evaluated in many reports¹³⁻¹⁶. A meta analysis showed that PE ADA had sensitivity 0.92 and specificity 0.90 in the diagnosis of tuberculous pleurisy¹⁷. PE ADA usually was higher in the tuberculous pleural effusion (TPE) patients compared to non-TPE patients, but sometimes may elevate in some patients. For example, more than 40% of parapneumonics and half of lymphomatous effusions exceeded the cutoff set for pleural TB¹⁸. Pleural ADA was also elevated in empyema, legionnaires' disease, pleural brucellosis, and mycoplasma pneumoniae pneumonia¹⁸⁻²¹. As many as 9% of patients with lung cancer and 15% of those with mesothelioma showed high ADA activity and were false-positive with ADA cutoff setting²². A recent study demonstrated that PE ADA was affected by age and there was significant correlation between PE ADA and age ($r = -0.621$)²³.

In a Turkish retrospective analysis for etiologies of 492 pediatric pleural effusions²⁴, parapneumonic effusions (PPEs) were the most common cause and made up 77.4% of whole group, TPEs, as the second cause, made up 12.6%. Based on above problems, ADA activity may ele-

vate in pediatric PPE patients and in children because of negative correlation between ADA activity and age. There would be limited value of ADA activity in detection of pediatric TPE. In this retrospective study, we aimed to evaluate the usefulness of ADA activity for the diagnosis of TPE in children.

Patients and Methods

This was a retrospective study of the medical records of pediatric patients investigated for pleural effusion in our hospital from January 2006 to November 2013. The protocol was approved by the Ethical Committee of Shandong Provincial Chest Hospital, written informed consent was not required because of the retrospective nature of the investigation. Patient records/information were anonymized and de-identified prior to analysis.

Based on laboratory records, a list of consecutive pediatric patients who aged ≤ 15 years old with PE ADA sent was obtained. The ADA activity was measured in PE by kinetic method employing xanthine oxidase peroxidase²⁵ on automated clinical chemistry analyzer using commercially available kits (Maker, Sichuan, China), intra-assay and inter-assay coefficient of variability were $\leq 5\%$ and $\leq 10\%$. 211 pediatric PE patients were enrolled, 7 were excluded due to uncertain diagnosis. 77 patients with TPE were identified, 106 patients were diagnosed as PPE patients, 18 were empyema., Tthe remaining 3 patients were diagnosed as malignant pleural effusion (MPE).

TPE patients were diagnosed based on compatible history (contact with a pulmonary TB patient), clinical findings (pleuritic chest pain, chest pressure, dyspneadyspnoea, and cough), chest *x* ray, TST, microbiological tests (AFB smear and mycobacterial culture), PE biochemical analysis and response to anti-TB treatment. PPE was defined as any exudative effusion (criteria established by Light et al²⁶ associated with bacterial pneumonia, lung abscess or bronchiectasis²⁷. MPEs were confirmed by positive pleural fluid cytology or pleural biopsy histology (closed biopsy or medical thoracoscopic biopsy).

Statistical Analysis

Statistical analysis was carried out using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Data were expressed as mean \pm standard error of

the mean (SEM). Non-Parametric tests were used since ADA data was skewed distributed as determined by the Kolmogorov-Smirnov test. Comparisons of data between TPE patients and non-TPE patients were performed using Mann-Whitney U test. Association between ADA activity and age was assessed with Spearman's correlation coefficient analysis. A *p* value < 0.05 was considered statistically significant.

Results

Pediatric patients were grouped into two groups: TPE patients, non-TPE patients (empyema, MPEs and PPEs). Among 3 MPE patients, 1 had lymphoma, 1 had mediastinal teratoma, and another had pleural mesothelioma. Of 77 pediatric pleural TB patients, 22 were culture confirmed, 2 were confirmed by histological examination and the remaining was clinical diagnosis. Table I presents the mean age, sex and other characteristics of every evaluated group, including age-subgroups. All patients were hospitalized.

The study population had a mean age of 8.32 ± 0.32 years (range 1 day to 15 years), and 61.7% were male. The mean age of the 77 TPE patients was 11.51 ± 0.40 years, and 66.2% of these patients were men. 127 non-TPE patients (aged 6.39 ± 0.35 years, 59.1% were male) were divided into three subgroups: (1) empyema group, 18 pediatric patients, 27.8% were male, aged 5.77 ± 1.23 years; (2) PPE group, 106 patients, 66.0% were male, aged 6.40 ± 3.51 years; (3) MPE group, 3 pediatric patients, aged 9.67 ± 3.93 years, all were female.

For TPE patients, pleural ADA activities were 55.96 ± 15.00 U/L (≤ 5 years, 3.20 ± 0.58 years old, 5 cases), 69.68 ± 10.38 U/L (6-10 years, 8.33 ± 0.30 years old, 21 cases) and 59.66 ± 4.43 U/L (11-15 years, 13.63 ± 0.18 years old, 51 cases) respectively. For PPE patients, pleural ADA activities were 62.53 ± 4.16 U/L (≤ 5 years, 3.20 ± 0.24 years old, 47 cases), 68.70 ± 7.84 U/L (6-10 years, 7.63 ± 0.20 years old, 43 cases) and 51.78 ± 7.00 U/L (11-15 years, 12.50 ± 0.38 years old, 16 cases) respectively. No significant differences in PE ADA could be found between TPE age-subgroups and PPE age-matched subgroups. For empyema patients, pleural ADA activity was 183.8 ± 30.0 (5.77 ± 1.23 years old, 18 cases). Compared with TPE patients (6-10 years subgroup), empyema patients had a higher level of PE ADA (*p* < 0.01).

Table 1. Characteristics of pediatric PE patients.

Group		Subgroup	Number	Age (years)	Sex (male)	ADA activity (U/L)
TPE patients		≤ 5 years	5	3.20 ± 0.58	4	55.96 ± 15.00
		6-10 years	21	8.33 ± 0.30	16	69.68 ± 10.38
		11-15 years	51	13.63 ± 0.18	31	59.66 ± 4.43
Total			77	11.51 ± 0.4	51	62.1 ± 4.2
Non-TPE patients	Empyema MPE		18	5.77 ± 1.23	5	183.8 ± 30.0
			3	9.67 ± 3.93	0	367.5 ± 344.0
	PPE	≤ 5 years	47	3.20 ± 0.24	27	62.53 ± 4.16
		6-10 years	43	7.63 ± 0.20	35	68.70 ± 7.84
		11-15 years	16	12.50 ± 0.38	8	51.78 ± 7.00
	Total		106	6.40 ± 3.51	70	63.4 ± 3.8
			127	6.39 ± 0.35	75	87.7 ± 10.0

Data were expressed as mean ± standard error of the mean (SEM); ADA: adenosine deaminase; TPE: tuberculous pleural effusion; PPE: parapneumonic effusion; MPE: malignant pleural effusion.

Among non-TPE patients, PE ADA was significantly higher in the empyema group compared to PPE group (183.8 ± 30.0 U/L vs 63.4 ± 3.8 U/L, $p < 0.01$). PE ADA in empyema patients was also higher than TPE patients (62.1 ± 4.2 U/L, $p < 0.01$). There was no statistically significant difference in PE ADA level between TPE patients (62.1 ± 4.2 U/L) and non-TPE patients (87.7 ± 10.0 U/L, $p > 0.05$), and PPE patients (63.4 ± 3.8 U/L, $p > 0.05$). A patient diagnosed as lymphoma had a very high PE ADA increasing to 1056 U/L. Correlation analysis was performed and showed a low negative correlation between age and pleural ADA among non-TPE patients ($r = -0.223$, $p < 0.05$), but there were no correlation between age and pleural ADA within TPE, PPE or both patients (all $p > 0.05$). Meanwhile, there was no significant difference in PE ADA level between genders.

Discussion

PE ADA has good performance in detection of tuberculous pleural effusion (TPE). However, few studies were conducted for its value in pediatric patients. To evaluate PE ADA in diagnosis of pediatric TPE, a retrospective study was performed. This is also, to the best of our knowledge, one of the first few studies to determine the

ADA level in pediatric pleural effusions. Our report suggests that PE ADA isn't accurate in detection of pediatric TPE as it increases in PPEs or empyema.

Several factors can affect the level of PE ADA, such as, causes of pleural effusions, age, pleural fluid protein^{18,23}. In this investigation, we didn't find the correlation between age and pleural ADA within TPE, PPE or both patients, this may contribute to subject difference between our study and other report (pediatric vs adult patients)²³. However, because of empyema groups with low age, there was a low correlation between age and pleural ADA among non-TPE patients. PE ADA usually was higher in the TPE patients compared to non-TPE patients, but sometimes pleural effusion had elevated levels of ADA activity in some diseases (parapneumonics, empyema, lymphoma, and mycoplasma pneumoniae pneumonia)¹⁸⁻²¹. In the study, for diagnosis of TPE, PE ADA also met these problems. Levels of PE ADA in empyema were higher than in TPE or PPE. Meanwhile, a patient diagnosed as lymphoma had a highest PE ADA among whole population. PE ADA levels in 13 patients were greater than 180 U/L, 84.6% (10 cases) were empyema patients. So ADA activity in PE > 180 U/L is highly suggestive of empyema or lymphoma rather than TB.

Few researches have looked at the diagnostic value of pleural ADA in detection of TPE.

Mishra et al²⁸ evaluated the utility of ADA activity for the diagnosis of tuberculous effusions in children. The mean fluid ADA was significantly higher in tuberculous effusions than in non-tuberculous effusions ($p < 0.001$). The sensitivity and specificity of ADA (≥ 38 U/L) were 81% and 75%, in diagnosing tuberculous effusions. In our work, there was no statistical difference between TPE and non-TPE pediatric patients in pleural ADA. One possible explanation for the paradox results in PE ADA between TPE and non-TPE patients is that, in our study, the non-tuberculous group included patients with effusions was mainly PPE and empyema, but in that by Mishra et al²⁸, causes of effusions were due to other causes (10 transudative ascites, 8 empyema thoracis, 3 malignant pleural and 3 pyopericardium).

The Turkish retrospective analysis for etiologies of pediatric pleural effusions showed that parapneumonic effusions were the most common cause, followed by tuberculous effusions²⁴. In our study, since China was the second high burden-TB country, TPE made up 37.2% of whole group. PPEs and TPEs also made up about 90% of all patients, being similar to the Turkish results. These implied that our findings were more useful in clinical practice. Although ADA had good performance in detection of tuberculous effusion, pleural ADA isn't accurate in diagnosis of pediatric TPE, considering the majority of pleural effusions were was PPE and TPE.

The mean age of TPE patients was 11.51 years old, age distribution showed that the incidence rate of pediatric TPE patients increased with age. Usually Chinese newborn received BCG vaccination that had found a protective effect (reduction in incidence of tuberculosis in the children). Meanwhile, age was positively correlated with TB exposure time, so the chance to get TB infection in high TB burden countries increase with age²⁹. The mean age of non-TPE patients was 6.39 years old and lower than TPE patients, the incidence rate of pediatric PPE patients decreased with age, similar results were reported^{30,31}. Although there was age difference between TPE group and non-TPE group, considering the fact that no correlation between age and pleural ADA and comparison results of age-matched subgroups between TPE and PPE patients, there should be no significant differences in PE ADA between TPE group and non-TPE group.

Conclusions

PE ADA isn't accurate in detection of pediatric TPE as it increases in PPEs (especially in empyema). An extremely high ADA activity should raise suspicion of empyema or lymphoma.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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