Pulmonary Function and Exercise Stress Tests in Children Following Acute Influenza Lower Respiratory Tract Infection: Follow-Up after 1 Year

Suchada Sritippayawan MD*, Thanyarat Ratanawongkosol MD*,
Jitladda Deerojanawong MD*, Nuanchan Prapphal MD*

** Division of Pulmonology and Critical Care, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Objective: *To evaluate long-term pulmonary function and airway hyperresponsiveness (AHR) in children following acute influenza lower respiratory tract infection (LRI).*

Material and Method: *Children aged 8 to 18 years who had no underlying disease and were discharged from the hospital for acute influenza LRI at least one year ago were studied. Pulmonary function tests (PFT) (spirometry, body plethysmography) and exercise stress tests were undertaken. Exercise-induced AHR was evaluated by serial spirometries after the maximal exercise.*

Results: *Eighteen children (mean age 12.2±2.6 years, 67% male) were studied. The meantime interval after recovery from acute influenza LRI was 2.5±1.0 years. Fifty-six percent had acute influenza LRI at least two years ago. Abnormal PFT compatible with mild restrictive defect was found in one child who had H1N1-2009 influenza pneumonia 3.2 years ago. Maximal exercise was achieved in 15 children. Exercise-induced AHR was demonstrated in three (20%). All of them had acute influenza LRI more than two years ago.*

Conclusion: *Residual lung function defect and AHR could be found in normal children who had acute influenza LRI more than one year ago. Monitoring of pulmonary function and AHR would be helpful for appropriate respiratory care in otherwise asymptomatic children previously hospitalized with acute influenza LRI.*

Keywords: *Children, Airway hyperresponsiveness, Influenza, Lung function, Exercise stress test, Pneumonia*

J Med Assoc Thai 2017; 100 (8): 876-80
Full text. e-Journal: *http://www.jmatonline.com*

Influenza is a common viral etiologic agent of acute lower respiratory tract infection (LRI) in children. Lung function abnormalities and airway hyperresponsiveness (AHR) following influenza virus infections have been reported in adults and children[1-8]. However, most of the studies followed the patients for a period of less than one year. Long-term pulmonary sequelae following influenza virus infection longer than one year ago have rarely been reported, especially in children. The authors were interested in investigating lung function and AHR in children who had history of acute influenza LRI and recovered from the illness at least one year ago.

Material and Method

Children aged 8 to 18 years who had no coexisting diseases and were hospitalized with acute influenza LRI between 2009 and 2012 were enrolled. Influenza virus was isolated from nasopharyngeal aspirates during the acute LRI episodes by reverse transcriptase polymerase chain reaction (RT-PCR) technique. Exclusion criteria included those who had any underlying diseases, recurrent pneumonia, recent respiratory tract infection within two weeks prior to the study, and poor compliance with pulmonary function and cardiopulmonary exercise tests (CPET). The study protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University. Informed consent and assent (when applicable) were obtained from study participants and/or their legal guardians before being enrolled in the study.

Correspondence to:
Sritippayawan S, Division of Pulmonology and Critical Care, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Rama IV Road, Bangkok 10330, Thailand.
Phone: +66-2-2564951, Fax: +66-2-2564911
E-mail: Suchada.Sr@chula.ac.th

Pulmonary function study

Spirometry and lung volumes (measured by body plethysmography) were evaluated by a diagnostic system Vmax 6200 Autobox (SensorMedics, Yorba Linda, CA) when the participant was in a resting stage. Pulmonary function test (PFT) parameters

included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, forced expiratory flow rate between 25 and 75% of vital capacity ($FEF_{25-75\%}$), total lung capacity (TLC), residual volume (RV), and RV/TLC ratio. All PFT parameters except for FEV_1/FVC and RV/TLC ratio were expressed as the percentage of predicted value calculated from the normal value for Asian population (European Respiratory Society 1993, Update). Obstructive defect was defined if the FEV_1 was less than 80% predicted value (and/or $FEF_{25-75\%}$ was less than 70% predicted value) with the FEV_1/FVC ratio lower than 0.85[9]. Restrictive defect was defined if the TLC was less than 80% predicted value while hyperinflation was defined if the RV was greater than 135% predicted value and RV/TLC ratio was greater than 0.35[9,10]. Severity of lung function defect was graded in accordance to the American Thoracic Society and European Respiratory Society (ATS/ERS) criteria[11].

Cardiopulmonary exercise test (CPET)

AHR was evaluated by exercise challenge test. The CPET was carried out on a motor driven, electronically controlled treadmill. Exercise capacity was evaluated by using a portable ergospirometry system (Oxycon mobile with Integrated 3-lead ECG®, Viasys Healthcare, Yorba Linda, CA). Half Bruce protocol was applied[12]. Treadmill velocity was started at 2.7 km/hour with 10% elevation. The velocity was increased to 3.4, 4, 4.7, 5.4, 6, 6.7, 7.3, 8, 8.4, 8.8, and 9.2 km/hour, every 1.5 minutes. The elevation was increased 1% together with the increase of the velocity. The exercise was performed until the criteria for exercise termination was met. Recovery period included standard 3-minute duration (2.7 km/hour and 0% elevation).

Throughout the CPET, the participant was allowed to breath through a fitting face mask connected to a pneumotachometer used for tidal volume and minute ventilation (VE) measurement. Inspired and expired gases were sampled and analyzed breath-by-breath by using a computerized system (Oxygen Lab manager system, Viasys Healthcare, Yorba Linda, CA). The data were averaged every 30 seconds and calculated for oxygen consumption (VO_2) and carbon dioxide production (VCO_2). The respiratory exchange ratio (RER) was calculated by dividing the VCO_2 with VO_2. The system was calibrated before each test with gases of known concentration. Heart rate was continuously monitored by electrocardiography (Oxycon mobile with Integrated 3-lead ECG®; Viasys Healthcare, Yorba Linda, CA). Oxygen saturation (SpO_2) was recorded by using a pulse oximeter (Oxycon mobile with Integrated 3-lead ECG®; Viasys Healthcare, Yorba Linda, CA). The participant was allowed to exercise until reaching the maximum exercise (heart rate 85% or greater of maximum heart rate [HR_{max}]; HR_{max} = 200 - 0.7 x age [years] and RER 1.1 or greater) or at least one of the following criteria was met: the participant requested to stop, significant desaturation (decreased SpO_2 4% or greater from baseline), cyanosis, cardiac arrhythmia, or confusion[13,14].

Spirometry was performed at 5, 10, 15, 20, and 30 minutes, respectively after achieving the maximal exercise to determine AHR. Exercise-induced AHR was defined if the participant demonstrated at least 12% declination of FEV_1 or 26% decrease of $FEF_{25-75\%}$ from the pre-exercise values[15,16].

Collected data included age, sex, time interval after acute influenza LRI, type of isolated influenza virus, family history of atopy, history of tobacco exposure, PFT, and CPET parameters.

Results

Eighteen children (mean age 12.2±2.6 years, 67% male) who were discharged from the hospital after recovering from acute influenza LRI at least one year ago and had no underlying diseases were studied. The diagnoses of acute LRI were pneumonia (14 cases, 77.8%) and acute bronchitis (4 cases, 22.2%). All participants had no respiratory symptoms and signs at the time of the enrollment. The time interval after acute influenza LRI was 2.5±1.0 years (range 1.0 to 4.2 years). Ten children (56%) had acute influenza LRI more than two year ago. Types of isolated influenza viruses were influenza A [H1N1-2009] 10 cases (56%), influenza A [H3N2] four cases (22%), and influenza B four cases (22%). Initial mean SpO_2 at room air during the illness was 98% (range 96 to 100%). Oxygen therapy was required in three cases (17%). No patients required assisted mechanical ventilation. The mean duration of hospitalization was 2.8±1.1 days (range 1 to 6 days). All children were completely recovered without complications and never had had recurrent LRI thereafter.

PFT parameters were showed in Table 1. Abnormal PFT compatible with mild restrictive defect (TLC 75% predicted value) was found in only one child who had H1N1-2009 influenza pneumonia 3.2 years ago. Her chest X-ray at that time showed patchy opacity over the right lung. She required oxygen therapy for

Table 1. Pulmonary function test (PFT) parameters of the study children

PFT parameters	Mean ± SD
FVC (% predicted)*	96.1±11.3
FEV_1 (% predicted)*	97.8±10.2
FEV_1/FVC (%)	90.3±6.8
$FEF_{25-75\%}$ (% predicted)*	93.8±19.1
TLC (% predicted)*	94.9±12.1
RV (% predicted)*	94.2±35.6
RV/TLC (%)	22.6±6.1

$FEF_{25-75\%}$ = forced expiratory flow rate between 25 and 75% of vital capacity; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity

* % predicted was calculated in accordance to the normal value for Asian population (European Respiratory Society 1993, Update) stored in the database of the diagnostic system Vmax 6200 Autobox (SensorMedics, Yorba Linda, CA)

three days without any complications and completely recovered from the illness and had been doing well since then.

Of the 18 children, three could not achieve the maximal exercise due to poor condition. Among 15 children who achieved the maximal exercise, three demonstrated exercised-induced AHR. All of them had acute influenza LRI more than two years ago (2.8, 3.6, and 4.2 years, respectively). They had normal resting PFT and had never been treated with either bronchodilator or inhaled corticosteroid. One of them had family history of atopy, while none had history of tobacco exposure.

Discussion

In the present study, the authors investigated long-term pulmonary sequelae in 18 children previously hospitalized with acute influenza LRI and had fully recovered from the illness at least one year ago. The majority of the cases had mild influenza LRI and did not require oxygen therapy. Mild restrictive defect and AHR were found in one and three patients, respectively. All of them had mild influenza LRI more than two years ago and had been doing well since then. Previous studies reported various lung function abnormalities including obstructive, restrictive, diffusion defects, and AHR in adults and children following acute influenza infections[1-8]. However, most of the defects were transient and disappeared within three to six months[6-8]. Some studies followed the patients for one year after the infection and still found abnormal lung functions[1,17]. The residual lung function defects occurred after either mild or severe influenza infections. Whether the persistence of lung functions abnormalities was correlated with the severity of influenza infection or not have never been established.

Currently, there have been very few reports of pulmonary function assessment in children following acute influenza infection at the time period of longer than one year after the infection. Laraya-Cuasay et al[4] reported pulmonary functions and histopathologic findings of three children who had chronic respiratory symptoms occurring after having influenza infections during their first year of life. Various degrees of bronchiolitis obliterans and interstitial fibrosis were found in lung biopsies at day 51 to 166 of the illness in all children. Moreover, pulmonary functions evaluated at three to six years after the acute influenza infections still demonstrated peripheral airway obstruction and AHR[4]. All of them had persistent pulmonary symptoms. In the present study, the authors demonstrated mild restrictive defect and AHR in asymptomatic children who had acute episode of influenza pneumonia more than two years ago. All of them had never had significant respiratory illness after the acute episode of influenza LRI. These findings suggested that asymptomatic residual lung functions defect could occur for several years even after mild influenza LRI. Lung function monitoring would be helpful in these children to plan for the appropriate rehabilitation program.

In the present study, the authors were not able to recruit a large number of participants since most of the children who had influenza LRI and required hospitalization had some underlying diseases such as hematologic malignancies, chronic lung diseases and were excluded from the study. In addition, pulmonary function and exercise challenge tests were undertaken at only one time point, not serially monitored since after the recovery of influenza infections. Therefore, it would be difficult to verify whether these lung function defects and AHR were associated with influenza infection in the past. However, since these children had no other coexisting pulmonary diseases and never had recurrent pulmonary infections since after the episode of acute influenza LRI, it could be possible that these residual lung function defect and AHR were the consequence of previous influenza LRI.

In conclusion, the present study reported residual lung function abnormality and AHR in normal children who had acute influenza LRI more than one year ago. Pulmonary function and AHR should be

carefully monitored in otherwise asymptomatic children who were previously hospitalized with acute influenza LRI.

What is already known on this topic?

Transient abnormal lung function and AHR after acute influenza infection has been reported in children and adults.

What this study adds?

This cross sectional study reported long-term residual lung function abnormalities and exercise-induced AHR in otherwise healthy children who had been hospitalized with acute influenza LRI.

Acknowledgement

We would like to thank Chulalongkorn University for the funding support (Ratchadapisek-sompotch Research Fund).

Potential conflicts of interest

None.

References

1. Liu W, Peng L, Liu H, Hua S. Pulmonary function and clinical manifestations of patients infected with mild influenza A virus subtype H1N1: a one-year follow-up. PLoS One 2015; 10: e0133698.
2. Edgeworth D, Brohan J, O'Neill S, Maher M, Breen D, Murphy D. Pulmonary sequelae of severe H1N1 infection treated with high frequency oscillatory ventilation. Ir Med J 2013; 106: 249-52.
3. Luyt CE, Combes A, Becquemin MH, Beigelman-Aubry C, Hatem S, Brun AL, et al. Long-term outcomes of pandemic 2009 influenza A(H1N1)-associated severe ARDS. Chest 2012; 142: 583-92.
4. Laraya-Cuasay LR, DeForest A, Huff D, Lischner H, Huang NN. Chronic pulmonary complications of early influenza virus infection in children. Am Rev Respir Dis 1977; 116: 617-25.
5. Udomittipong K, Chokephaibulkit K, Susiva C, Nithipunyathumrong S, Mahoran K. Clinical presentation and lung function of children hospitalized with 2009 pandemic influenza A (H1N1) pneumonia. Southeast Asian J Trop Med Public Health 2011; 42: 824-30.
6. Little JW, Hall WJ, Douglas RG Jr, Mudholkar GS, Speers DM, Patel K. Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. Am Rev Respir Dis 1978; 118: 295-303.
7. Zarogoulidis P, Kouliatsis G, Papanas N, Spyratos D, Constantinidis TC, Kouroumichakis I, et al. Long-term respiratory follow-up of H1N1 infection. Virol J 2011; 8: 319.
8. Hall WJ, Douglas RG Jr, Hyde RW, Roth FK, Cross AS, Speers DM. Pulmonary mechanics after uncomplicated influenza A infection. Am Rev Respir Dis 1976; 113: 141-8.
9. Mueller GA, Eigen H. Pediatric pulmonary function testing in asthma. Pediatr Clin North Am 1992; 39: 1243-58.
10. Ruppel GL. Manual of pulmonary function testing. 9th ed. St Louis: Mosby; 2009.
11. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26: 948-68.
12. van der Cammen-van Zijp MH, Ijsselstijn H, Takken T, Willemsen SP, Tibboel D, Stam HJ, et al. Exercise testing of pre-school children using the Bruce treadmill protocol: new reference values. Eur J Appl Physiol 2010; 108: 393-9.
13. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. Eur Respir J 1997; 10: 2662-89.
14. Mahon AD, Marjerrison AD, Lee JD, Woodruff ME, Hanna LE. Evaluating the prediction of maximal heart rate in children and adolescents. Res Q Exerc Sport 2010; 81: 466-71.
15. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000; 161: 309-29.
16. Carlsen KH, Carlsen KC. Exercise-induced asthma. Paediatr Respir Rev 2002; 3: 154-60.
17. Winterbauer RH, Ludwig WR, Hammar SP. Clinical course, management, and long-term sequelae of respiratory failure due to influenza viral pneumonia. Johns Hopkins Med J 1977; 141: 148-55.

สมรรถภาพปอดและความสามารถในการออกกำลังกายในผู้ป่วยเด็กภายหลังการติดเชื้อไวรัสไข้หวัดใหญ่ในระบบทางเดินหายใจส่วนล่าง: ผลการติดตามผู้ป่วยภายหลังการการติดเชื้อมากกว่า 1 ปี

สุชาดา ศรีทิพยวรรณ, ธัญรัตน์ รัตนวงษ์โกศล, จิตลัดดา ดีโรจนวงศ์, นวลจันทร์ ปราบพาล

วัตถุประสงค์: *เพื่อประเมินการเปลี่ยนแปลงของสมรรถภาพปอดในระยะยาวและภาวะหลอดลมไวเกินในผู้ป่วยเด็กที่เคยมีประวัติเข้ารับการรักษาในโรงพยาบาลด้วยโรคติดเชื้อเฉียบพลันในระบบทางเดินหายใจส่วนล่างจากเชื้อไวรัสไข้หวัดใหญ่*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงวิเคราะห์ ณ จุดใดจุดหนึ่งของเวลา ทำในผู้ป่วยเด็กอายุ 8-18 ปี ที่เคยเข้ารับการรักษาในโรงพยาบาลด้วยโรคติดเชื้อเฉียบพลันในระบบทางเดินหายใจส่วนล่างจากเชื้อไวรัสไข้หวัดใหญ่ ระหว่าง พ.ศ. 2552 ถึง พ.ศ. 2555 อาสาสมัครทุกรายได้รับการตรวจสมรรถภาพปอด (spirometry และ body plethysmography) และประเมินภาวะหลอดลมไวเกินโดยวิธี exercise challenge test*

ผลการศึกษา: *มีผู้ป่วยเข้าร่วมในการศึกษา 18 ราย อายุเฉลี่ย 12.2±2.6 ปี เป็นเพศชายร้อยละ 67 ทุกรายหายจากการติดเชื้อไวรัสไข้หวัดใหญ่เป็นเวลานานอย่างน้อย 1 ปีขึ้นไป ก่อนเข้าร่วมการศึกษาครั้งนี้ (ระยะเวลาเฉลี่ย 2.5±1.0 ปี) ร้อยละ 56 เคยมีการติดเชื้อไวรัสไข้หวัดใหญ่ในอดีตนานตั้งแต่ 2 ปีขึ้นไป) และไม่มีอาการผิดปกติทางระบบหายใจภายหลังจากนั้นอีก ผู้ป่วย 1 ราย ตรวจพบสมรรถภาพปอดผิดปกติแบบ restrictive ภายหลังการติดเชื้อไวรัสไข้หวัดใหญ่สายพันธุ์ H1N1-2009 เมื่อ 3.2 ปีที่แล้ว ผลการทดสอบสมรรถภาพในการออกกำลังกายพบว่า ผู้ป่วย 15 ราย ออกกำลังกายได้จนถึงจุดสูงสุด ในจำนวนนี้ 3 ราย (ร้อยละ 20) ตรวจพบภาวะหลอดลมไวเกิน ทุกรายเคยมีประวัติติดเชื้อไวรัสไข้หวัดใหญ่ในระบบทางเดินหายใจส่วนล่างตั้งแต่เมื่อนานมากกว่า 2 ปีที่แล้ว*

สรุป: *พบความผิดปกติของสมรรถภาพปอดและภาวะหลอดลมไวเกินในเด็กที่เคยมีประวัติติดเชื้อเฉียบพลันในระบบทางเดินหายใจส่วนล่างจากเชื้อไวรัสไข้หวัดใหญ่ แม้จะเป็นระยะเวลานานมากกว่า 1 ปีขึ้นไปแล้วก็ตาม การตรวจสมรรถภาพปอดและทดสอบการออกกำลังกายเพื่อวินิจฉัยภาวะหลอดลมไวเกินเป็นระยะ ๆ ในเด็กกลุ่มนี้อาจมีประโยชน์ในการวินิจฉัยและเฝ้าระวังภาวะผิดปกติเหล่านี้ เพื่อวางแผนการดูแลรักษาทางระบบหายใจที่เหมาะสมต่อไป*