Egyptian Journal of Bronchology

Vol. 6, No 2, December, 2012

ORIGINAL ARTICLE

ASSESSMENT OF SUBTLE PULMONARY DYSFUNCTION IN IDIOPATHIC CHILDHOOD EPILEPSY USING IMPULSE OSCILLOMETRY

Hamed A. El Khayat , Maha M. Awadalla, Asmaa A. Al Sharkawy and Heba A. EL Khouly
Pediatrics Department, Ain Shams University, Cairo, Egypt

Correspondence to: Asmaa Al Husseiny Al Sharkawy, E-mail: doctorasma @yahoo.com

Background: *Pulmonary complications were reported in epileptic subjects, and many case reports documents lung injury caused by antiepileptic drugs in adults, but no similar studies were done in children.*

Objective: *was to assess frequency of subtle pulmonary dysfunction in apparently chest free children with idiopathic epilepsy.*

Subjects and methods: *A case control study was done on 50 children with idiopathic epilepsy (10.04±3.641 yrs old) selected from Pediatric Neurology Clinic, Ain Shams University. Spirometry test of forced vital capacity and impulse oscillometry maneuvers were done for patients and compared to 25 healthy matched children.*

Results: *In the studied patients; 16% had evidence of pulmonary dysfunctions. Mean levels of airway resistance (R5% and R20%) were higher in epileptics than healthy (109.1+29.45 & 107.38+26.54 Vs 81.87+16.13 & 87.14+19.42) (p<0.001). FEV1 was significantly lower in uncontrolled epileptics than controlled (85.27+12.70 vs. 97.28+7.08) (p <0.05). Antiepileptic polytherapy reduced FVC than monotherapy (81.86+12.63 vs. 93.82+8.87) (p <0.05). Carbamazepine significantly reduced FEV1/FVC than sodium valproate (95.43+8.89 vs. 111.57+4.64) (p <0.01). FEV1 negatively correlated with duration of disease, frequency of seizures and duration of therapy (p= 0.007, 0.01, 0.02). FVC negatively correlated with frequency of seizures (p= 0.03).*

Conclusion: *There is evidence of subtle pulmonary dysfunction in one fifth of apparently chest free epileptic children.*

Abbreviations: *PFTs: Pulmonary Function Tests, FVC: Forced Vital Capacity, FEV1: Forced Expiratory Volume in 1st second, R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, X5: Reactance at 5 Hz, AEDs: Anti-Epileptic Drugs*

Keywords: *antiepileptic drugs, epilepsy, pulmonary dysfunction, pulmonary function tests.*

INTRODUCTION

The association between pulmonary disorders and epilepsy is bidirectional; Seizures can cause respiratory abnormalities, and primary respiratory dysfunction can cause seizures [1]. Also, many antiepileptic drugs were incriminated in inducing pneumonitis and disturbed PFs. In addition, there are many reasons why pulmonary functions of individuals may be related to their brain function. In other words; lower pulmonary functions are often associated with diseases that may also affect the brain.[2] Antiepileptic drugs were implicated in pulmonary injury; it's worth noting that phenytoin is recognized as causing a combination of pulmonary abnormalities and

lymphadenopathy. Okamoto et al.,[3] reported resistant pneumonia not responding to antibiotics in epileptic women on regular phenytoin. The radiologic studies revealed bilateral ground glass suggestive of acute interstitial pneumonitis. The drug lymphocyte stimulation test (DLST) for phenytoin showed positive results. Lung biopsy specimen by VATS revealed predominant lymphocytic infiltration of lung parenchyma, compatible with drug-induced pneumonitis. Newsome et al.,[4] presented a case of a 9 years old female who developed respiratory failure with poor medical response and after reviewing her medical history and medications; levetiracitam was implicated in the pathogenesis of her diffuse lung disease, suggesting that long term use of levetiracitam could precipitate a diffuse interstitial pneumonitis-like reaction. Furthermore, Nikaido et al.,[5] presented a six month-old female infant who developed dyspnea when she was treated with Valproate sodium (VPA) and zonisamide (ZNS) for epileptic spasms, and concluded that drug-induced interstitial lung disease should be remembered as a possible complication of anticonvulsant treatment, such as VPA and ZNS. So we aimed to assess frequency of subtle pulmonary dysfunction in children with idiopathic epilepsy

SUBJECTS AND METHODS

Study design: A case control study was done on Egyptian children with idiopathic epilepsy who attended Pediatric Neurology Clinic of Ain Shams University Hospital between September 2008 and June 2009. Informed consents of agreement were taken from all participants' parents and the study was approved by Ethics Committees of the Ain Shams University Hospitals.

Subject: Fifty children with idiopathic epilepsy (19 males and 31 females) were enrolled in the study. Their ages ranged from 3 to 17 years (10.04±3.641yr). Patients were diagnosed as idiopathic epilepsy according to Commission on Classification and Terminology of the International League against Epilepsy, 1989.[6] The mean age of disease onset was 4.86+ 3.9 years with a mean duration of illness 5.2+3.7 years and antiepileptic intake for 4.28+3.21 years. Thirty two patients had generalized epilepsy, 18 had partial epilepsy, 22 patients were well controlled with antiepileptic drugs, 28 were uncontrolled, 17 patients were on polytherapy antiepileptic drugs, 17 patients were receiving sodium valproate (VPA) and 16 were receiving carbamazepine (CBZ). Exclusion criteria: Patients with symptomatic epilepsy and patients with chronic chest disease were excluded from the study. The control group comprised 25 age and sex matched apparently healthy children, they were 14 males and 11 females and their age ranged from 4 to 16 years (8.36±3.90).

Methods:

All children were evaluated for pulmonary spirometry (FEV1, FVC, PEF % of the predicted for age and sex) and impulse oscillometry (IOS) techniques (R5, R20, and X5 % of the predicted for age and sex) using VIASYS Healthcare Gmbh, libniz strasse-7.

Oscillation techniques determine breathing mechanics by superimposing small external pressure signals on the spontaneous breathing of the subject without forced respiratory maneuvers. The impulse power spectra of pressure and flow generated by the IOS provide practical assessment of low (5 HZ) as well as high (20 HZ) frequency range.[7] Ninety seconds of spontaneous breathing (tidal breathing) were recorded, graphed, illustrated and automatically analyzed by the system. Test was considered valid only if coherence at 5 Hz (Co5) was ≥ 0.7 and coherence at 20Hz (Co20) was 0.9. Respiratory resistance is referred to as R; R5 is term used to express airway resistance at 5 Hz, R20 is term used to express airway resistance at 20 Hz, R is considered abnormal (increased airway resistance) if exceeded 150% of the expected for age and sex.[8] Lung reactance is expressed as X; X at 5Hz characterizes lung periphery which can be reduced (more negative) in restrictive lung diseases [9]. Abnormal respiratory reactance (reduced lung compliance) is diagnosed if subject's X5- predicted X5 is > 0.15. Spirometry was done using same apparatus. Patient was asked to do the forced breathing maneuver. Three trials was done, the best values were selected to be recorded and graphed. Trials were considered valid only if they met the ATS 2005 criteria.[10] All tests were done in the morning before meal and patient was calmed and put in proper erect standing position after explaining the technique.

Statistics: Standard computer program SPSS for Windows, release 13.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean standard deviation (SD). Comparison of different variables in various groups was done using student t test and Mann Whitney test for normal and nonparametric variables respectively. Probability (p) less than 0.05 was considered significant.

RESULTS

In the studied patients; 16% had abnormalities in PFs; 6 had obstructive pattern of pulmonary disease, one had restrictive pattern and one had mixed pattern. Mean values of R5% and R20% were significantly higher in patients compared to control children ($p< 0.000$, 0.001 respectively) (table 1 & fig 1). Mean values of PFs parameters were similar in patients with generalized epilepsy and those with partial epilepsy. FEV1% was significantly reduced in patients with uncontrolled epilepsy compared to patients with controlled epilepsy ($p<0.05$) (table 2 & fig 2).

FVC% was significantly reduced in patients on AEDs polytherapy compared to patients on AED monotherapy ($p<0.05$) (table 3 & fig 3). FEV1/FVC was significantly reduced in patients on CBZ than in patients on VPA ($p< 0.001$) (table 4 & fig 4).

FEV1 was negatively correlated with duration of disease, frequency of seizures and duration of therapy ($p= 0.007$, 0.01, 0.02). FVC was negatively correlated with frequency of seizures ($p= 0.03$) (table 5).

Table 1. Mean Values Pulmonary Function Tests Among Children with Epilepsy Vs Controls.

	Cases		Control		*t/z*	P	Sig.
	Mean	**±SD**	**Mean**	**±SD**			
R5 %	109.18	±29.45	81.87	±16.13	4.31	0.000	**HS**
R20 %	107.38	±26.54	87.14	±19.42	3.38	0.001	**S**
ΔX	-0.15	±0.15	-0.10	±0.06	-0.83	-0.405	NS
FEV1 %	91.63	±11.57	90.36	±6.97	0.23	0.81	NS
FVC %	90.30	±11.20	82.92	±8.16	1.36	0.18	NS
FEV1/FVC	102.02	±9.87	109.46	±5.19	-1.60	0.12	NS
PEF %	73.59	±17.39	85.58	±14.20	-1.40	0.17	NS

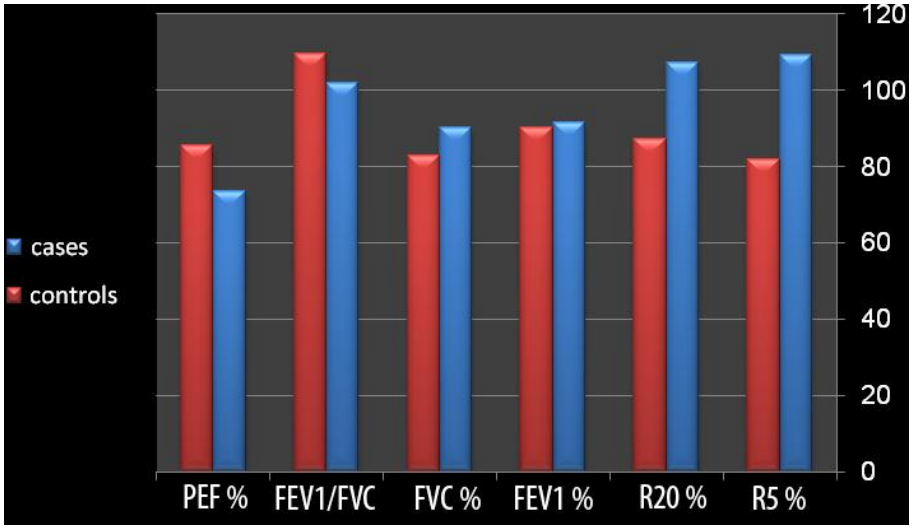

Fig 1. Mean Values of Pulmonary Function Tests Among Children with Epilepsy Vs Controls

Table 2. Mean Values of Pulmonary Function Tests in Controlled Vs Uncontrolled Children with Epilepsy.

	Controlled epilepsy		Uncontrolled epilepsy		*t/z*	P	Sig.
	Mean	±SD	Mean	±SD			
R5 %	111.38	±33.42	107.45	±26.43	-0.46	0.64	NS
R20 %	106.79	±31.83	107.85	±22.13	0.13	0.89	NS
ΔX	-0.14	±0.19	-0.16	±0.11	-1.69	0.91	NS
FEV1 %	97.28	±7.08	85.27	±12.70	-2.44	0.027	**S**
FVC %	93.22	±6.90	87.02	±14.47	-1.14	0.26	NS
FEV1/FVC	104.80	±8.37	98.88	±11.03	-1.25	0.22	NS
PEF %	77.26	±14.63	69.46	±20.24	-0.91	0.37	NS

FEV1% was significantly reduced in patients with uncontrolled epilepsy compared to patients with controlled epilepsy.

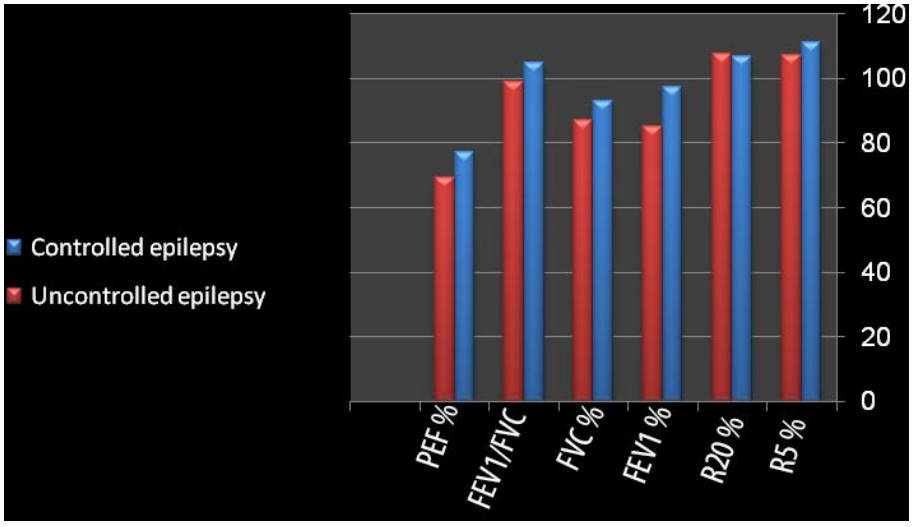

Fig 2. Mean Values of Pulmonary Function Tests in Controlled Vs Uncontrolled Children with Epilepsy

Table 3. Mean Pulmonary Function Tests in Children with Epilepsy on Monotherapy Vs Polytherapy AED.

	Monotherapy		Polytherapy		*t/z*	p	Sig.
	Mean	**±SD**	**Mean**	**±SD**			
R5 %	108.72	±30.72	110.06	±27.69	-0.15	0.88	NS
R20	105.31	±26.50	111.41	±26.96	-0.76	0.44	NS
ΔX	-0.15	±0.17	-0.15	±0.12	-0.49	0.623	NS
FEV1 %	94.18	±11.76	85.52	±9.40	1.45	0.16	NS
FVC %	93.82	±8.87	81.86	±12.63	2.24	0.04	**S**
FEV1/FVC	100.81	±10.92	104.90	±6.87	-0.76	0.45	NS
PEF %	75.23	±14.95	69.66	±23.81	0.59	0.56	NS

FVC % is significantly reduced in patients on AEDs polytherapy compared to patients on AED monotherapy

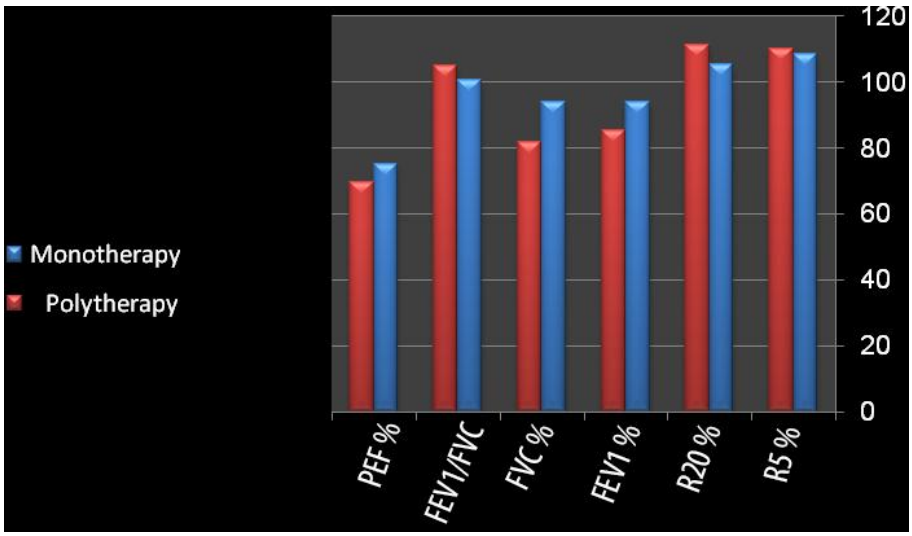

Fig 3. Mean Pulmonary Function Tests in Children with Epilepsy on Monotherapy Vs Polytherapy Antiepileptic Drugs

Table 4. Mean Values of Pulmonary Function Tests in Children with Epilepsy on Carbamazepine Vs Valproate AED.

Tests	Valproate		Carbamazepine		*T*	p	Sig.
	Mean	±SD	Mean	±SD			
R5 %	99.71	±28.97	118.30	±30.47	-1.79	0.08	NS
R20 %	98.55	±29.38	112.50	±21.69	-1.54	0.13	NS
ΔX	-0.18	±0.19	-0.12	±0.13	-0.77	0.43	NS
FEV1 %	97.35	±4.52	92.60	±14.15	0.64	0.53	NS
FVC %	88.42	±6.93	96.52	±8.83	-1.59	0.14	NS
FEV1/FVC	111.57	±4.64	95.43	±8.89	3.35	0.007	**S**
PEF %	85.40	±10.39	70.15	±14.71	1.83	0.096	NS

FEV1/FVC was significantly reduced in patients on carbamazepine compared to patients on valproate

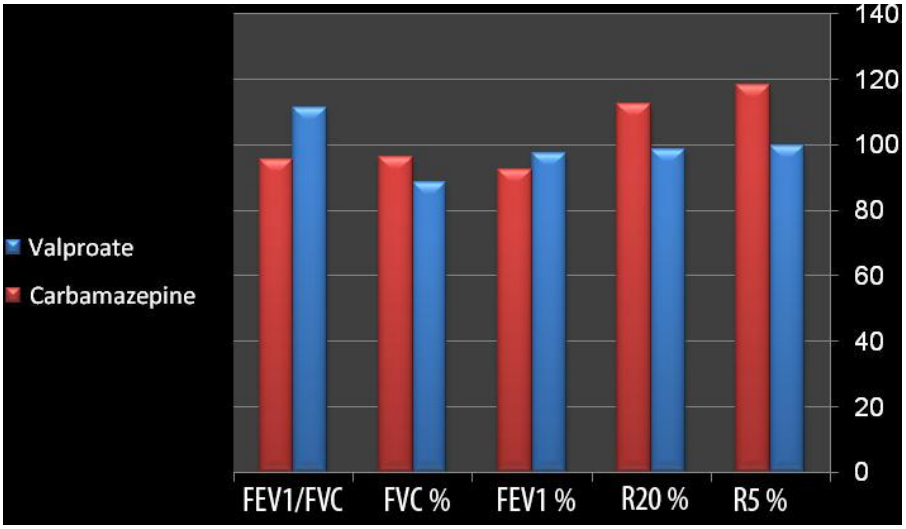

Fig 4. Mean Values of Pulmonary Function Tests in Children with Epilepsy on Carbamazepine Vs Valproate AED

Table 5. Correlation Between Pulmonary Functions and Different Studied Parameters

		R5 %	R20 %	ΔX	FEV1 %	FVC %	FEV1/FVC	PEF %
Age years	***R***	0.10	0.040	0.23	0.316	0.791	-0.474	0.000
	P	0.627	0.851	0.252	0.604	0.11	0.420	1.000
Onset of disease in years	***R***	0.29	0.071	0.159	0.472	0.252	-0.030	0.173
	P	0.842	0.623	0.27	0.056	0.329	0.910	0.507
Duration of disease in years	***R***	0.143	0.16350	0.165	-0.62	-0.35	-0.14	-0.27
	P	0.32	0.258	0.253	**0.007***	0.15	0.58	0.28
Frequency/week	***R***	-0.145	-0.054	-0.22	-0.606	-0.52	-0.21	-0.12
	P	0.31	0.709	0.11	**0.010***	**0.031***	0.419	0.63
Duration of therapy in years	***R***	0.13	0.179	0.134	-0.558	-0.27	-0.19	-0.18
	P	0.33	0.214	0.355	**0.020***	0.291	0.44	0.48
Score of severity	***R***	-0.17	-0.15	-0.15	0.39	0.29	0.55	0.17
	P	0.21	0.27	0.278	0.119	0.24	0.83	0.51

This table shows; there is statistical significant negative correlation between FEV1 and duration of disease, frequency of seizures and duration of therapy. Also there is statistical significant negative correlation between FVC and frequency of seizure.

DISCUSSION

In our study; there was a significant subclinical pulmonary dysfunction in cases with idiopathic epilepsy when compared to healthy controls. This was manifested as significant changes in different parameters of pulmonary functions of epileptic patients (16% of patients had reduced lung functions). In our study; R5% and R20% were elevated in epileptics than non-epileptics. Such findings indicate increased central and peripheral airway resistance (obstructive air way disease). This suggests that epilepsy by some mechanism whether central or peripheral has an association with pulmonary tissues, mechanics, volumes and flow rates. Also, abnormal brain anatomy or electricity may have relation to anatomy or function of lung parenchyma and airways. In agreement with our study is Scorza et al., [11] who found comparable influences of epilepsy on basal respiratory parameters in patients with temporal lobe epilepsy (TLE). Sachdev et al.,[2] designed a study to determine the relationship of lung function to brain anatomical parameters using a random sub-sample of 469 persons from a larger community sample underwent brain magnetic resonance imaging scans and pulmonary function tests (FVC, FEV1) and found out that FEV1 had a significant negative correlation with overall brain atrophy. The FEV1/FVC ratio had a significant correlation with white matter hyperintensity concluding that, decreased lung function is related to poorer cognitive function and increased subcortical atrophy in mid-adult life and that the presence of chronic respiratory disease may be related to deep white matter hyperintensity. [2]

In our study also, uncontrolled epileptics with increased frequency of seizures showed a significant decrease in FEV1 when compared with controlled epileptics. Such finding may raise the question if seizures have a direct mechanical and traumatic effect on airways. The vigorous muscular spasm associated with fits may be accompanied with recurrent severe attacks of bronchiolar spasms or inflammatory changes, which may by time turn into permanent changes. Also, micro aspirations associated with seizures may play a role in airway inflammation. This was similar to Scorza et al., [11] who attributed the absence

of any respiratory affection in his cases for being controlled and stated that increase seizure frequency is a risk factor for respiratory affection.

Drug induced lung disease has been the subject of several recent reviews and classification [2,4,11]. In our study, polytherapy had significantly more grave effect on spirometric values than monotherapy. This seems logic when we imagine that these drugs had additive or synergistic action on lung tissues. Carbamazepine also appeared to be more injurious on lung parenchyma than valproate as evidenced by the significant derangement of FEV1/ FVC. A number of reports have high lightened pulmonary hypersensitivity to CBZ, the drug is being used more frequently for therapy of grand mal and psychomotor seizures. There have been around 10 cases of pulmonary complications previously reported in association with CBZ [12-19].

The mechanism of lung injury by long-term use of CBZ has been suspected to be an immune-mediated hypersensitivity [20,21]. The diagnosis of hypersensitivity to CBZ can be established either by in vivo re-exposure to the drug or by in vitro lymphocyte stimulation tests. In addition, it has been reported that significant lymphocyte stimulation in vitro by CBZ could be demonstrated in all patients on CBZ. [22] Such hypersensitivity may involve type 3 immune complex and type 4 delayed hypersensitivity reaction. Pulmonary toxicity though a rare complication but has been reported previously, it occurs mostly 1-3 months after introduction of the drug [12,13,15,18,23,24,25].

Archibald et al.,[26] described CBZ induced interstitial pneumonitis following one month therapy in 19 years old female with a lung transplant. Bronchoscopy and lung biopsy done for this patient confirmed diagnosis of pneumonitis and discouraged diagnosis of acute transplant rejection. In addition, her symptoms were improved after withdrawal of CBZ.

In our study; FEV1 was negatively correlated with duration of disease, frequency of seizures and duration of therapy. Also FVC was negatively correlated with frequency of seizures. That is to say both epileptic process and antiepileptic medications have an impact on pulmonary functions. However, regression analysis revealed no single independent risk factor for lung injury in epileptic patients.

CONCLUSION

From our study, we can conclude that epileptic children especially those on AEDs polytherapy containing CBZ- may have reduced PFs even during the inter-ictal period. Therefore, we recommend doing initial and regular periodic pulmonary functions to every epileptic child.

ACKNOWLEDGMENTS

The authors are grateful for Professor Magda Yehia El Seify professor of pediatrics, for her valuable support. Authors are also grateful for Doctor Mahitab Morsi, assistant lecturer of pediatric for her help in the practical part.

REFERENCES

1. Steven C. Hematologic and pulmonary disorders. In: Ethinger AB and Devirsky O, eds. Managing epilepsy and Co-existing disorders. Boston: Butterworth-Heinemann. 2002: 209-28.
2. Sachdev PS, Anstey KJ, Parslow RA, et al. Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. Dement Geriatr Cogn Disord. 2006; 21(5-6):300-8.
3. Okamoto H, Ishimaru T, Ohgami N, Furugaki K, Emoto T, Ekimura M. A case of drug-induced interstitial pneumonia due to phenytoin. Nihon Kokyuki Gakkai Zassh 2009; 47(8):758-62.
4. Newsome SD, Xue LY, Jennings T, Castaneda GY. Levetiracitam-Induced Diffuse Interstitial Lung Disease. J Child Neurol. 2007; (22) 628-30.
5. Nikaido K, Kato T, Takayama R, Doi T. Valproate sodium and zonisamide associated interstitial pneumonitis in an infant. No to Hattatsu. 2007; 39 (1): 44-8.
6. Commission on Classification and Terminology of the International League Against Epilepsy Proposal for revised classification of epilepsies and epileptic syndrome. Epilepsia. 1989; 30: 389-99.
7. Komarow HD, Myles IA, Uzzaman A, Metcalfe DD. Impulse oscillometry in the evaluation of diseases of the airways in children. Ann Allergy Asthma Immunol. 2011; 106 (3):191-9. Epub 2011 Jan 6.
8. Oostveen E, MacLeod D, Lorino H. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003; 22(6):1026-41.
9. Delacourt C, Lorino H, Herve-Guillot M, Reinert P, Harf A, Housset B. Use of force oscillation technique to assess airway obstruction and reversibility in children. Am J Respir Crit Care Med. 2000; 161: 730-6.
10. Miller MR, Hankinson J, Brusasco V, et al., 'ATS/ERS task force. Standardisation of spirometry. Eur Respir J. 2005; 26: 319–38.
11. Scorza FA, Abreu AM, Albuquerque M. Quantification of respiratory parameter in patients with temporal lobe epilepsy, Arq Neuropsiquitar. 2007; 65 (2B): 450-3.

12. Cullinan SA, Bower GS. Acute pulmonary hypersensitivity to carbamazepine. Chest. 1975; 68: 580-1.

13. Stephan WC, Parks RD, Tempest B. Acute hypersensitivity pneumonitis associated with carbamazepine. Chest. 1978; 74 (4): 463-4.

14. Schmidt M, Brugger E. Case of carbamazepine induced interstitial pneumonia. Med Klin. 1980; 75: 29-31.

15. Lee T, Cochrane GM, Amlot BR. Pulmonary eosinophilia and asthma associated with carbamazepine. Br Med J. 1981; 282 (6262):440.

16. Lewis IJ, Rosenbloom L. Glandular fever-like syndrome, pulmonary eosinophilia and asthma associated with carbamazepine. Postgrad Med J. 1982; 58: 100-1.

17. Tolmie J, Steer CR, Edmunds AT. Pulmonary eosinophilia associated with carbamazepine. Arch Dis Child. 1983; 58 (10): 833-4.

18. De Swert LF, Ceuppens JL, Teuwen D, Wijndale L, Casaer P, Daele MC. Acute interstitial pneumonitis and carbamazepine therapy. Acta Paediatr Scand. 1984; 73 (2): 285-8.

19. Kitson GE, Wauchob TD. Pulmonary edema following carbamazepine overdose. Anesthesia. 1988; 43 (11): 967-9.

20. Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. J Immunol. 1995; 155(1): 462-72.

21. Wilschut FA, Cobben NA, Thunnissen FB, Lamers RJ, Wouters EF, Drent M. Recurrent respiratory distress associated with carbamazepine overdose. Eur Respir J. 1997; 10(9): 2163-5.

22. Houwerzijl J, De Gast GC, Nater JP, Esselink MT, Nieweg HO. Lymphocyte stimulation tests and patch tests in carbamazepine hypersensitivity. Clin Exp Immunol. 1977; 29 (2): 272.

23. Barreiro B, Manresa F, Valledperas J. Carbamazepine and the lung. Eur Respir J. 1990; 3: 930-1

24. Takahashi N, Aizawa H, Takato S, et al. Acute interstitial pneumonitis induced by a carbamazepine. Eur Respir J. 1993; 6: 1409-11.

25. King GG, Barnes DJ, Hayes MJ. Carbamazepine-induced pneumonitis. Med J Aust. 1994; 160 (3): 126-7.

26. Archibald N, Yates B, Murphy D, et al. Carbamazepine-induced interstitial pneumonitis in a lung transplant patient. Respir Med. 2006; 1660-2. Epub 2006 Mar 2.