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Association of Asthma and Epilepsy

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Abstract: Acute exacerbation of asthma can induce respiratory alkalosis, which not only decreases serum level of ionized calcium but also results in cerebral vasoconstriction. Several studies have cleared that respiratory alkalosis and decreased CO_2-pressure in blood (hypocapnia) can increase neuronal excitability and its epileptogenic activity. This situation may also increase CNS dopamine level and risk of convulsion, therefore we planned this study to assess the association of asthma and epilepsy. In a cross-sectional and analytical study, 800 asthmatic children, who were referred to Specialists' Clinic of Tabriz University of Medical Sciences (TUMS) from January 2004-2008 underwent surveillance for epilepsy; then resultant data analyzed by Z-test for a ratio. About 26/800 children found to be affected simultaneously by asthma and epilepsy, including 15 males and 11 females whose age average was 6±2.1 years (95% CI = 3.5-6.7). The prevalence of epilepsy in asthmatic patients was higher than general population and this difference was statistically meaningful ($p<0.05$). According to prevalence of epilepsy, which is about 1% in general population and 3.25% in our asthmatic patients and because of possible hypocapnia and resultant respiratory alkalosis during asthma exacerbations, the probability of recurrent convulsive attacks in those, who have simultaneous asthma and epilepsy will be much higher and needs special care and treatment.

Key words: Asthma, epilepsy, respiratory alkalosis, Hypocapnia

INTRODUCTION

The theory of Hidden Hyperventilation to explain the etiology of asthma. However, since several decades ago many medical researchers have dealt with hypocapnia as a result of hyperventilation during acute exacerbation of asthma (Bruton and Stephe, 2005). Hombery *et al.* (1988) studied the respiratory pattern of asthmatic patients and found that they have a lower End-Tidal CO_2 (ET-CO_2) level in comparison with control group: 37 versus 41 mmHg. Similar, results were declared by Van den Elshout *et al.* (1991) (ET-CO_2 of 36 versus 40 mmHg in asthmatics versus non-asthmatics, respectively). Osborne *et al.* (1988) similarly revealed that ET-CO_2 and CO_2-pressure of arterial blood ($PaCO_2$) in asthmatic patients are meaningfully lower than control group. According to Mountain *et al.* (1990), respiratory alkalosis is the most common acid-base disturbance in asthmatic patients, which can be detected in 48% of asthmatic attacks. Hypocapnia is a constant finding in asthma and a common constituent of many acute diseases, but its importance is usually underestimated. Hypocapnia can induce cerebral ischemia by several mechanisms, including: Vasoconstriction causing cerebral hypoperfusion, diminished oxygen delivery by hemoglobin, increased neuronal excitability and probable release of cytotoxins such as glutamate. Hypocapnia can increase neuronal dopamine and therefore, risk of seizure as well (Laffey and Kavanagh, 2002). Hypoxic effects of hypocapnia can be aggravated by alkalosis and shifting the hemoglobin-oxygen dissociation curve to the left. In other words, not only the available oxygen in hemoglobin is decreased, but also its release into tissues slows down. The final results of these processes will be: Less cerebral blood flow, lesser oxygen transport and least oxygen delivery to brain (Lum, 1975). It has been supposed that each 1 mmHg decrease of $PaCO_2$ can diminish cerebral blood flow by 2%. Moreover, alkalosis enhances calcium bonding to plasma albumin and may induce paresthesia, tetany and convulsion by lowering plasma ionized-

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calcium level (Geeenbaum, 2004). Beside the general complications of hypocapnia caused by hyperventilation in asthmatic patients, decreased CO_2 level has a significant role in temporal lobe epilepsy, as in these patients the risk of symptom presentation during hyperventilation is 10 times higher than in resting or sleep states. Hyperventilation is a method of activation, which can induce slowness of cerebral physiologic rhythm, seizure and interictal discharges especially in idiopathic generalized epilepsy. In a study on 97 patients, 24 participants showed seizure activation, although stimulation of temporal lobe was prior to frontal lobe, but there was no difference between characters of spontaneous and induced seizure activities. According to the study of Guranha *et al.* (2005) hyperventilation-induced activation is about 30% in temporal lobe and 17% in other foci. The study of Yamatani *et al.* (1994) revealed that active hyperventilation can induce slowing in EEG. This effect has been known as an inducing factor for absence seizure; the same was mentioned in the study of Lainec *et al.* (1996) that hyperventilation caused symptoms in 68% of their patients.

MATERIALS AND METHODS

In a cross-sectional and analytical study on 800 children with different stages of asthma from mild intermittent to severe persistent, who were referred to Specialists' Clinic of Tabriz University of Medical Sciences (TUMS) from January 2004-2008 all were assessed for seizure disorders. The patients with disorders mimicking signs and symptoms of asthma such as bronchiectasis and recurrent aspiration pneumonia due to cerebral palsy were excluded from study. Finally, all collected data were analyzed by Z-test for a ratio.

RESULTS

There were 26 children with concomitant asthma and epilepsy, including 15 males and 11 females whose age average was 6±2.1 years (95% CI = 3.5-6.7). The prevalence of epilepsy in asthmatic patients was 3.25%, while it is 1% in general population and this difference is statistically meaningful ($p<0.05$). We compared the prevalence of epilepsy in various stages of asthma (from the aspect of severity) and found no meaningful difference. From 26 epileptic patients, 21 had generalized tonic-clonic and 5 absence seizure.

DISCUSSION

This study was planned to evaluate the association of asthma and epilepsy. Although, many previous studies have discussed this association, but few related epidemiologic evidences have been published. In the study of Castaneda *et al.* (1998), 3 from 400 asthmatic patients (0.75%) had idiopathic epilepsy and 12 out of 201 patients with idiopathic epilepsy (5.97%) had asthma.

In this study the prevalence of both asthma and epilepsy was similar to general pediatric population, but the possible aggravating effect of asthma on epilepsy (by mechanism of hyperventilation) has not been mentioned. We had 12 epileptic patients in 400 asthmatic children (3%); this makes a significant difference with general pediatric population ($p<0.05$), which declares that asthma is a risk factor for recurrent seizure attacks. Similarly, Czubkowska *et al.* (1994) reported the prevalence of epilepsy in asthmatic patients to be as high as 7.5% (9 epileptics among 120 asthmatics). They believed that attacks during chronic asthma are stimulating factors for epilepsy and proper treatment of asthma in these children is the best preventive factor for recurrent seizure attacks. Although, in comparison to our study, this study has showed a higher prevalence of epilepsy in asthmatics, but its results especially about stimulating effects of asthma on generating recurrent seizure attacks resembles those of our study. Barr *et al.* (1998) also reported that epilepsy form activities were detected in 6 out of 24 asthmatic patients (25%), who had no previous history of neurological disorders, while this event was seen in 1patient in 24 control-group participants (4.2%); but whether hyperventilation in these patients underlies EEG abnormalities or not, is yet obscured. The effects of hyperventilation in induction of seizure has been also evaluated in other studies, in an animal study by Schuchmann *et al.* (2006) on rats, it was declared that increased PH of brain can induce hyper-excitability in neurons, besides, hyperthermia can result in respiratory alkalosis but its suppression by 5% CO_2-inhalation can stop convulsion in 20 sec. De wet *et al.* (2003) also evaluated the association of asthma and pesudoseizure and found that asthma acts as a risk factor by ($p = 0.003$) for presentation of epilepsy in which the role of hyperventilation must be emphasized). From 12 epileptic patients in our study, 10 had generalized tonic-clonic and 2 absence seizure, this result is similar to that of Czubkowska *et al.* (1994).

Moreover, various studies have showed a correlation between epilepsy and asthma; as Hoang Bax *et al.* (2006) supposed a probable epileptic-like state in bronchial tree (mentioned as bronchopulmonary hyper-excitability), which may play some role in pathogenesis of asthma, they finally named it as bronchial epilepsy.

CONCLUSION

The role of asthma-induced hyperventilation in production of symptomatic epilepsy must be deeply considered in approach to these patients and this necessitates preventive measures for seizure attacks in them.

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