in the antigen presenting cell affect the differentiation of the T-helper cell Th1/Th2 cytokine response.[12]

Improvement in GSH status could result in augmented lung function through several mechanisms. Within lung epithelial cells, augmented GSH may block the activation of nuclear factor κB by tumor necrosis factor-α,[13–15] and so limit the production and release of proinflammatory cytokines. Augmented intracellular GSH may reduce the need to recycle GSH from the lung lining fluid, and thus maintain extracellular levels.[16] Alternatively, increased intracellular GSH levels may lead to extracellular transport to buttress lung lining levels. In the lung lining fluid, augmented GSH may prevent oxidative damage to antiproteases.[17,18] Improvement in skeletal muscle function due to augmented GSH stores[7] may also partially account for our results, as the baseline FEV_1/FVC ratio did not change between times 7 and 8 (66% and 62%, respectively).

The ELF GSH pool has been the target of direct administration of nebulized GSH, although success has been limited by GSH-induced bronchospasm.[5] Trials of systemic N-acetyl cysteine, acting as both a cysteine donor and an ROS scavenger, for the treatment of chronic obstructive airway disease have met with limited success, because of N-acetyl cysteine toxicity and limited clinical effect.[2,19]

The relationship between whole blood GSH, lung epithelial cell GSH levels, ELF GSH, and peripheral blood GSH-Px activity is poorly defined. There are several possible mechanisms by which GSH could improve obstructive airway disease, either via immunologic modulation or by improving antioxidant defenses. More work needs to be done to further define the specific abnormalities of antioxidant function, as well as the relative contribution of such abnormalities to the pathophysiology observed in obstructive airway disease. Nevertheless, the modulation of GSH and antioxidant defenses in obstructive airway disease (and many other diseases) represents an intriguing potential modality for anti-inflammatory therapy.

References

1 Powell CV, Nash AA, Powers HJ, et al. Antioxidant status in asthma. Pediatr Pulmonol 1994; 18:34–38
2 Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease: Oxidative Stress Study Group. Am J Respir Crit Care Med 1997; 156:341–357
3 Anderson ME. Glutathione and glutathione delivery compounds. Adv Pharmacol 1997; 38:65–78
4 Meister A. Metabolism and function of glutathione. In: Dolphin D, Poulsen R, Avramovic O, eds. Glutathione: chemical, biochemical, and medical aspects. New York, NY: John Wiley and Sons, 1989; 367–474
5 Marrades RM, Roca J, Barbera JA, et al. Nebulized glutathione induces bronchoconstriction in patients with mild asthma. Am J Respir Crit Care Med 1997; 156:425–430
6 Lands LC, Grey VL, Smountas AA, et al. Lymphocyte glutathione levels in children with cystic fibrosis. Chest 1999; 116:201–205
7 Lands LC, Grey VL, Smountas AA. Effect of supplementation with a cysteine donor on muscular performance. J Appl Physiol 1999; 87:1381–1385
8 Anderson ME, Meister A. Transport and direct utilization of gamma-glutamylcyst(e)ine for glutathione synthesis. Proc Natl Acad Sci USA 1983; 80:707–711
9 Richie JP Jr, Abraham P, Leutzinger Y. Long-term stability of blood glutathione and cysteine in humans. Clin Chem 1996; 42:1100–1105
10 Heffner JE, Repine JE. Pulmonary strategies of antioxidant defense. Am Rev Respir Dis 1989; 140:531–547
11 Cantin A, North S, Hubbard R, et al. Normal epithelial lining fluid contains high levels of glutathione. J Appl Physiol 1987; 63:152–157
12 Peterson JD, Herzenberg LA, Vasquez K, et al. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. Proc Natl Acad Sci USA 1998; 95:3071–3076
13 Flohe L, Brigelius-Flohe R, Saliou C, et al. Redox regulation of NF-kappa B activation. Free Radic Biol Med 1997; 22:1115–1126
14 Palombella VJ, Rando OJ, Goldberg AL, et al. The ubiquitin-proteasome pathway is required for processing the NF-kappa B1 precursor protein and the activation of NF-kappa B. Cell 1994; 78:773–785
15 Rahman I, Macnee W. Role of transcription factors in inflammatory lung diseases. Thorax 1998; 53:601–612
16 Hull J, Vervaart P, Grimwood K, et al. Pulmonary oxidative stress response in young children with cystic fibrosis. Thorax 1997; 52:557–560
17 Hubbard RC, Ogushi F, Fells GA, et al. Oxidants spontaneously released by alveolar macrophages of cigarette smokers can inactivate the active site of alpha 1-antitrypsin, rendering it ineffective as an inhibitor of neutrophil elastase. J Clin Invest 1987; 80:1289–1295
18 Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 1989; 320:365–376
19 Koch SM, Leis AA, Stokic DS, et al. Side effects of intravenous N-acetylcysteine [abstract]. Am J Respir Crit Care Med 1994; 149:A321

An Unreported Risk in the Use of Home Nasal Continuous Positive Airway Pressure and Home Nasal Ventilation in Children*

Mid-Face Hypoplasia

Kasey K. Li, DDS, MD; Robert W. Riley, DDS, MD; and Christian Guilleminault, MD

We report the case of a 15-year-old boy with obstructive sleep apnea and obesity who was treated since the age of 5 with nasal continuous positive airway pressure. Due to the long-term use of a nasal mask, the child developed a mid-face hypoplasia. Chronic use of a nasal mask for home ventilation in children should always be associated with regular evaluations of maxillomandibular growth.

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Key words: apnea; children; complication; craniofacial; growth; nasal continuous positive airway pressure; risk; sleep apnea

Abbreviations: CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea

Nasal continuous positive airway pressure (CPAP) has been widely used as a home treatment in adults since a good response to treatment was initially reported in 1981.[1] We have shown that nasal CPAP can be used without difficulties in children[2] and in infants.[3] Several large studies have confirmed that CPAP therapy is safe and clinically effective in adults[4] and in children,[5,6] with only minor side effects, such as nasal symptoms and symptoms related to poor mask fit (air leak and skin irritation). Clinical observations over time, however, have led to new questions. The question of long-term compliance has been studied using CPAP devices that measure frequency of use.[7,8] Not surprisingly, as in any chronic illness, compliance with treatment was shown to be variable. Another issue that has not been investigated is the possible impact of long-term use of a nasal mask on craniofacial structures. We report here a case of mid-face hypoplasia in a child secondary to long-term nasal CPAP therapy.

Case Report

A 15-year-old African-American boy with obstructive sleep apnea (OSA) and morbid obesity was referred for evaluation to assess the present CPAP level. The patient was the product of a normal birth without evidence of any craniofacial or developmental anomalies. He has had a history of significant weight gain since 3 years of age. At age five, obesity and OSA at polygraphic recording were diagnosed. At that time, his height was normal for his age and he had normal craniofacial features. He had a nasal CPAP titration, and nasal CPAP therapy was begun via face mask, set at 7.5 cm H_2O.

The patient was followed by his pediatrician. At age eight, his CPAP pressure was adjusted to 9 cm H_2O. He was not seen again in a sleep clinic until he was 15 years old, primarily because he lived far from any sleep clinic, lacked clinical symptoms, and had limited health insurance coverage. When he was seen again at the sleep clinic, his nasal CPAP was still set at 9 cm H_2O, as recommended 7 years earlier. Although several attempts had been made at weight loss, including enrollment in weight loss programs, he had continued to gain weight. His OSA, however, had been well controlled by CPAP therapy, and he reported that he had been a nightly CPAP user for the past 10 years without problems.

On examination, the patient was found to be morbidly obese (body mass index, 44.1 kg/m^2). Although he had no history of craniofacial syndromes, the mid-face region appeared severely depressed, especially in the perinasal region. When the child was seen by a maxillofacial specialist, the maxilla was recognized as being hypoplastic. The patient has a skeletal class III relationship. Lateral cephalometric radiograph confirmed the clinical findings (Fig 1). Fitting of the CPAP mask matched the most severely affected perinasal region. Airway evaluation demonstrated adenotonsillar hypertrophy. The patient subsequently underwent nocturnal polysomnographic recording and retitration of his CPAP with good results. The respiratory disturbance index was 1.2 events/h of sleep, with oxygen saturation nadir at 90% at a CPAP pressure of 9 cm H_2O. He elected to continue CPAP therapy. He has also enrolled in a weight loss program. The mid-face hypoplasia has not yet been addressed.

*From the Center of Excellence in Sleep Disorders Medicine, Stanford University, Palo Alto, CA.
Manuscript received June 29, 1999; revision accepted September 14, 1999.
Correspondence to: Kasey K. Li, DDS, MD, 750 Welch Rd, Suite 317, Palo Alto, CA 94304

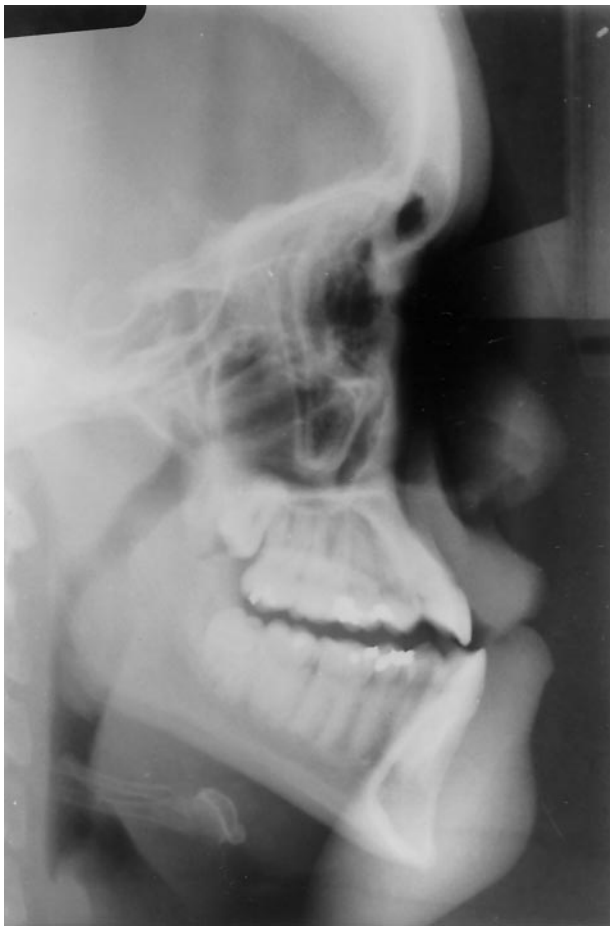

Figure 1. Lateral cephalometric radiograph.

Discussion

To the best of our knowledge, this is the first reported case of mid-face hypoplasia secondary to prolonged nasal CPAP therapy by face mask. It is well known that craniofacial development occurs primarily during the prepubertal years. By 4 years of age, about 60% of the adult face is developed. At age five, when nasal CPAP treatment was initiated in this child, facial development was normal. Due to the positive pressure exerted by the face mask, a counteracting force with a headgear is necessary to maintain the mask in position and prevent leaks. Long-term application of the tight-fitting headgear and face mask has resulted in the retardation of facial skeletal development in this growing child. Indeed, the application of headgear and face mask to manipulate facial growth has been applied in orthodontics for years, and craniofacial modifications are well documented in orthodontic literature.[9–11]

It is difficult to estimate the duration of CPAP therapy that could lead to adverse effects on facial growth, but it is logical to assume that it correlates directly with the length of therapy as well as the amount of pressure applied. What may be even more important, however, is the timing of therapy as it relates to the timing of facial growth. Since approximately 90% of the facial growth is completed by

age 12, it seems reasonable to suggest that long-term use of a nasal mask (whether it be nasal CPAP, nasal bilevel, or nasal intermittent positive pressure ventilation) prior to age 12 may affect the development of the facial skeleton. Whether long-term use of a nasal mask can have a similar impact in adults is unknown. It is possible that there may be some impact on the vascular bed irrigating the upper region, particularly in the elderly, but our information is only anecdotal.

The majority of children with OSA have adenotonsillar hypertrophy and are successfully treated with adenoidectomy and tonsillectomy.[12] Nasal CPAP is primarily used in children with craniofacial anomalies, trisomy 21, obesity, neuromuscular weakness, surgical failures, or as an interim treatment prior to surgery.[2–6] Because most children do not require long-term CPAP or nasal ventilation therapy,[13] and treatment beyond 4 to 6 years is uncommon,[2,3,5,6] retardation of midface development may be less likely to occur. In addition, children who require long-term nasal ventilation therapy may have preexisting craniofacial deformity, which makes the diagnosis difficult. It must be cautioned, however, that the prolonged application of an orthopedic force (CPAP headgear/face mask unit) on the malleable and developing facial skeleton can result in deleterious effects on growth and may worsen an already existing problem. Individuals at risk should have regular (at least yearly) maxillomandibular evaluations, and more data should be accumulated on problems associated with long-term use of any type of face mask in children, adults, and the elderly.

References

1 Sullivan CE, Berthon-Jones M, Issa FG, et al. Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nose. Lancet 1981; 1:862–863

2 Guilleminault C, Nino-Murcia G, Heldt G, et al. Alternative treatment to tracheostomy in obstructive sleep apnea syndrome: nasal continuous positive airway pressure in young children. Pediatrics 1986; 78:797–802

3 Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995; 127:905–912

4 Sullivan CE, Issa FG, Berthon-Jones M, et al. Home treatment of obstructive sleep apnea with continuous positive airway pressure applied through a nose mask. Bull Eur Pathophysiol Respir 1984; 20:49–54

5 Waters KA, Everett FM, Bruderer JW, et al. Obstructive sleep apnea: the use of nasal CPAP in 80 children. Am J Respir Crit Care Med 1995; 152:780–785

6 Marcus CL, Davidson Ward SL, Mallory GB, et al. Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. J Pediatr 1995; 127: 88–94

7 Kribbs BN, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993; 147:887–895

8 Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. Am J Respir Crit Care Med 1994; 149:149–154

9 Cooke MS, Wreakes G. The face mask: a new form of reverse head-gear. Br J Orthod 1977; 4:163–168

10 Cooke MS, Wreakes G. Fabrication of the face mask reverse headgear: clinical and technical procedures. Br J Orthod 1979; 6:49–51

11 Bowden DE. Theoretical considerations of headgear therapy: a literature review. Br J Orthod 1978; 5:145–152

12 Brouillette RT, Fernbach SK, Hunt CE. Obstructive sleep apnea in infants and children. J Pediatr 1982; 100:31–40

13 Ellis ER, Bye PTB, Bruderer JW, et al. Treatment of respiratory failure during sleep in patients with neuromuscular disease. Am Rev Respir Dis 1987; 135:148–152