PERPETUAL SUCCOUR HOSPITAL
Department of Internal Medicine
Section of Pulmonology

Activity	Interhospital Conference
Topic	Late Onset – Congenital Central Hypoventilation Syndrome
Discussant	Pulmonary Fellows, Perpetual Succour Hospital
Venue	Nathan Hall, CETA Building, GSK, Inc., Makati City
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Our case starts when a 40 y.o man was seen in the ER after a drinking spreee with officemates for the holidays. He was seen 20 minutes prior by his officemates sleeping in a room but was cyanotic with irregular breathing. Attempts to wake him failed thus was brought to PSH for management.

At the ER, he was seen gasping with deep rapid breathing and use of accessory muscles of respiration was prominent. He also had cyanotic lips and digits. His vital signs showed tachycardia, tachypnea, hypertension and desaturation to as low as 60%. An ABG was taken and revealed an acute respiratory acidosis with a pH of 7.2 and PCO2 of 101 but with more than adequate oxygenation at 222 with 60% fiO2. He patient was in acute ventilatory failure and Intubation was done.

At the end of the conference, we will have:

1. Discussed a case of an adult who was intubated due to acute respiratory failure Type 2.
2. Enumerated the cases associated with this Chronic Hypoventilation and their management.

After initial management, his case was reviewed. ST is a 40y.o male who is non-diabetic. He was diagnosed with hypertension and bronchial asthma last 2005 and was given maintenenace medications but with poor compliance. He is a nonsmoker but an occassional alcoholic beverage drinker. He has no food and drug allergies and has not used prohibited drugs. Chemical exposure at work is negligible. Hypertension runs on his paternal side.

In 1994, he underwent CTT insertion and pleurodesis for primary spontaneous pneumothorax. In 2003, he was also treated for Pulmonary TB. In July2005, he complained of gradual onset dyspnea with moderate exertion. This was associated with chest pain and occassional night awakenings which spontaneously resolved. A weeks after, Consult was done and was diagnosed clinically with bronchial asthma and prescribed medications which he temporarily complied. Follow-up after a month noted improvement of symptoms but was seen to have elevated blood pressure of 180/100mmHg. Anti-hypertensive medications were started. 3 months after, dyspnea recurred and gradually progressed. It was now associated with Paroxysmal Nocturnal Dyspnea and 2 pillow orthopnea. He often complained of body malaise and excessive daytime sleepiness causing 2 motor vehicular accidents. These symptoms gradually worsened and bipedal edema was noted thus prompting follow-up. CBC revealed erythrocytosis of 67%, impaired fasting glucose of 103mg/dL, sinus tachycardia on Electrocardiogram and Concentric LVH with adequate Systolic function and diastolic function was seen on 2D-echocardiogram. Admission was advisedfor further work-up. Considerations were cardiac disease caused by hypertension or an intracardiac shunt. Hematologic disease was also considered. Transesophageal Echocardiogram was ordered as well as an ultrasound of the whole abdomen.
During the TEE, Midazolam 1mg IV was given for the procedure however caused ventilatory arrest. He was immediately given Flumazenil to counter the effects of the sedative. His ABG taken after Midazolam was acute ventilatory failure with adequate oxygenation and ABG after reversal using Flumazenil showed significant improvement when he was already awake. This prompted the attending physician to refer the patient to a sleep specialist. After a review of patients history with physical exam, the sleep specialist entertained a possible chronic hypoventilation syndrome versus a possible sleep apnea. Pulmonary workup was done and confirmed that he has chronic hypoventilation of unknown origin. He was discharged with BiPAP and Theophylline.

After the effects of alcohol had worn off, he was extubated and discharged after a day of observation. Present follow-up noted good compliance to BiPAP and he is apparently. He still enjoys a bottle or more of alcoholic drinks however avoids intoxication.

Good Evening!

The importance of breathing need hardly be stressed. It literally supports the fires of life. We live in an ocean of air like fish in a body of water. By our breathing, we are attuned to our atmosphere. If we inhibit our breathing, we isolate ourselves from the medium in which we exist. In all oriental and mystic philosophies, the breath holds the secret to the highest bliss. To breath is to live. Imagine your existence if you lose this most precious ability you so often take for granted.

Our story begins when a 40 year old man was seen in the Emergency room after a drinking spree with officemates for the holidays.

Twenty minutes prior to admission, He was discovered by his officemates cyanotic and unresponsive to vigorous stimuli. He was then rushed to our institution for management. Pertinent findings during a fast and focused physical examination revealed a patient who was already cyanotic and gasping. The arterial blood gas shows an acute respiratory acidosis with more than adequate oxygenation. A diagnosis of acute ventilatory failure was made hence, intubation and mechanical ventilation were immediately instituted.

At so so high blood alcohol levels, the respiration might be depressed but normally one passes out due to intoxication before this happens. An apparently healthy young adult does not just crash into ventilatory failure even when inebriated. You have to consume more than 4 L of beer to go into a state of coma.

At the end of this conference, we will have presented the case of an adult male who was intubated due to acute respiratory failure Type 2 and discussed the diagnosis and management of patients presenting with hypoventilation.
After initial ER management, in the hopes of fully understanding why this happened, we reviewed the patient's history. ST is a 40y.o male who leads a moderately active lifestyle and had an unremarkable medical history until 1994 when he underwent Closed tube thoracostomy and chemical pleurodesis for a primary spontaneous pneumothorax. In 2003, he was treated for Pulmonary Tuberculosis.

The history became interesting about eight years ago, when he noted difficulty of breathing, which gradually worsened such that around july 2005, moderate exertion like carrying boxes at work was already associated with dyspnea. This was accompanied by a vague chest pain and occassional night awakenings. On medical consultation a diagnosis of bronchial asthma was made but he was non-compliant to his regimen after improvement of symptoms within one month. He was also noted to have elevated Blood pressure and amlodipine was started. 3 months after, dyspnea recurred and this time it was progressively becoming more severe until he was breathless even at rest. This was already associated with more frequent awakenings due to shortness of breath and 2 pillow orthopnea then later swelling of the legs. He also complained of body malaise and excessive daytime sleepiness, the latter causing 2 accidents because he fell asleep while driving. After consulting with his doctor who is a cardiologist, he was advised confinement for a more comprehensive work-up upon suspicion of a possible cardiac problem due to the initial findings of erythrocytosis on CBC, cardiomegaly on chest radiograph and LVH on 2D-Echo. Cardiovascular disease was entertained due to an underlying hypertension. However, the possibility of an intracardiac shunt was considered due to his hypoxemia. A Primary cause of Erythrocytosis also prompted consult with a hematologist. An arterial blood gas taken during admission showed chronic respiratory acidosis with moderate hypoxemia at room air. To afford a better window for a suspected intracardiac shunt, a transesophageal echocardiogram was performed. During the procedure, he was given 1mg of midazolam for sedation. Immediately thereafter, he can no longer be roused and became cyanotic. Flumazenil was given which promptly reversed the effects of the benzodiazepine. High flow oxygen supplementation was also given. Arterial blood gas during the event noted acute on top of chronic respiratory acidosis with more than adequate oxygenation. While benzodiazepines can cause respiratory failure, the dose given was just small. Nonetheless, this necessitated further investigation.

ST was then referred to a pulmonary sleep specialist who considered a hypoventilation syndrome on the basis of cyanosis, stupor and hypercarbia immediately after sedation. However, Erythrocytosis, high serum bicarbonate levels, hypertension, cardiomegaly and somnolence point to a chronic cause.
Reviewing the patient's history, he scored 24 on the Epworth sleepiness scale suggesting a high risk for sleep disordered breathing. Polysomnography showed no episodes of hypopnea or apnea however

frequent desaturations to as low as 50% despite oxygen supplementation was documented. These desaturations were most prominent during REM sleep. Sleep apnea was then ruled out. Hypoventilation syndromes are caused by disorders affecting the metabolic control and neuromuscular control of breathing and the ventilatory apparatus. As a quick test to rule out neuromuscular and chest wall abnormalities, voluntary hyperventilation maneuver as done resulting in a significant decrease in hypercarbia with correction of hypoxemia after 3 minutes. The capacity to voluntarily blow off carbon dioxide thru hyperventilation eliminates chest wall and neuromuscular etiology of hypoventilation.

To further strenghten our impression of a metabolic control defect, we asked the patient to hold his breath to assess appropriateness of response to hypoxia and hypercapnea. This video shows that the patient can hold his breath to the point of desaturation to as low as 81% without any perceived symptoms. We terminated the maneuver after 1 minute 15 seconds due to profound desaturation.. Please watch closely as this event occurs very abruptly. His response to hypoxia and hypercarbia are clearly blunted.

Both hyperventilation and breath holding maneuvers strengthen the impression of a defect in metabolic control of breathing. However, we are still tasked to rule out chest wall and neuromuscular etiologies of hypoventilation thus additional tests were conducted.

To determine any Neuromuscular causes of hypoventilation, EMG-NCV and ultrasound of the diaphragm was done. Negative results ruled out a Neuromuscular defect. A chest CT scan demonstrated patchy consolidation in the right upper and lower lobes which are compatible with a prior Pulmonary TB and pleural thickening which can be explained by the pleurodesis done for his pneumothorax. Physiologically, these findings are compatible with spirometric results of severely restrictive ventilatory defect. These results are not compatible and cannot explain the patients symptoms. Thus a chest wall etiology is also ruled out. Disorders in the metabolic control of breathing can either be organic or idiopathic. A Brain MRI was done to rule out any central organic lesions that can cause hypoventilation. Results were negative.

Having crossed out the other possible causes of hypoventilation, we are now left with a defect in the metabolic control of breathing without a central organic cause. Could the patient have primary alveolar hypoventilation? Or does he have an adult manifestation of a congenital disaease? Could he be cursed?

While the route we took was long and circuitous, it is nonetheless mandatory and fruitful as eventually we were able to demonstrate this is really a case of congenital central hypoventilation syndrome. Is this something acquired? Or Congenital? Or is he just an unfortunate victim of the whims of the Gods as they rolled the dice of fate and condemned him to a life where man is bereft of the gift of breathing. But to know better is to do better. Dr. Adrian Lu will help u understand better the intricacies of this disease. So that in the end, we will be wiser and know better what to do when we are confronted by a similar case.

Hypoventilation is defined as a reduction in the level of alveolar ventilation, resulting in an increase in alveolar PCO2 and therefore in arterial PCO2. Because there is an inverse relationship between alveolar PCO2 and PaO2, this rise in alveolar PCO2 produces an obligatory decrease in alveolar PO2 resulting in hypoxemia.[1]

The initial consequence of hypoventilation leads to an increase in PCO2 thereby reducing blood pH and later reflecting increased bicarbonate levels the consequent hypoxemic event will lead to haemoglobin desaturations and erythrocytosis presenting as cyanosis and polycythemia as with our patient. In the pulmonary circulation vasoconstriction occurs also as a result of hypoxemia this state will eventually lead to increase in pulmonary arterial pressure, right ventricular dysfunction and later on heart failure this event can be contributed if hypopneas or apneas are present as well consequential cerebral vasodilation, as a result of hypoxemia as well as impaired sleep quality would eventually result in excessive sleepiness or somnolence. All these findings were present with our patient.

Primary alveolar hypoventilation and congenital central hypoventilation syndrome arise from defects of the metabolic control system of ventilation. Both these diseases may clinically present the same pathophysiologic features. The difference is simply a genetic mutation.

The classic disease called Ondine's curse, now being discouraged as a misnomer, is properly called Congenital Central Hypoventilation syndrome.[2] This condition classically presents in newborns as an

apparent hypoventilation with monotonous respiratory rates and shallow breathing either during sleep only or both while awake and asleep along with manifestations of autonomic nervous system dysregulation, and in some individuals, altered development of neural crest-derived structures and/or tumors of neural crest origin. This disease has been implicated with sudden-infant death syndrome, poor neurocognitive developmental sequela and grave cardiopulmonary compromise if left undiagnosed. A milder, later onset of the disease may present in toddlers, children, and adults termed: Late-onset Congenital Central Hypoventilation syndrome (LO-CCHS). Reported Individuals with mild manifestations of LO-CCHS may remain undiagnosed until their 3rd, or even up to their 5th decades of life. In this subset of patients, the condition should be considered in cases of centrally mediated alveolar hypoventilation and/or cyanosis or seizures noted during treatment of obstructive sleep apnea, recent severe pulmonic infection or after administration of anesthetics or CNS depressants (which occurred with our index case - twice).[2] There should be the absence of a primary pulmonary, cardiac, neuromuscular, or a causative brain stem disease that can account for the entire phenotype – all were ruled out in our patient.

Central to the diagnosis of CCHS is the identification of mutations in the PHOX2b gene – a gene necessary for promoting neuronal differentiation and expression of motor neuron necessary for the development of the autonomic nervous system. The fate of these early neuronal cells could lead to imbalance between the sympathetic and parasympathetic nervous system as well as dysfunction in the enteric nervous system seen in children with CCHS.[3]

The PHOX2B gene is encodes a highly conserved homeodomain transcription factor and is transmitted by autosomal dominance. The main defect lies in exon 3 where variable Polyalanine repeat expansion mutations commonly occur. The remaining 10% are non-polyalanine repeat expansion mutations. Emphasis on identifying these genotypes will subsequently ascertain phenotypic formats.

This graph will demonstrate the number of ANSD symptoms among different genotype of CCHS. What is observed is that there is a significant association between Polyalanine repeat mutation length and number of symptoms of ANSD.[4] As seen the green box, these patient will have lesser repeats by only 24 and 25. Contrast to what is seen in the red box where a higher number of autonomic symptoms are present. These repeats are these one seen in classic CCHS while those with lesser repeats of 24 and 25 are LO-CCHS manifesting as either mild symptoms of autonomic nervous system dysfunction or none at all – a consistent finding with our patient.

In short: PHOX2B gene mutation is disease-defining for CCHS. The usual mutation is dependent on the number of polyalanine repeats. The more the repeats, the more the symptoms of ANSD and in patients with LO-CCHS, having lesser repeats, they have lesser symptoms (or none at all).

These are some of the documented associated disorder in patients with CCHS which are typically seen in classic CCHS and not manifested in LO-CCHS as well as with our patient.
So how rare is rare? Before the identification of the PHOX2B gene, the condition was thought to be extremely rare. But with increasing disease awareness and utilization of genetic screening, a rising number of cases have been reported. Since 2010, more than a thousand cases have been confirmed having CCHS.[1] Rand et.al. reported back in 2011 that there is an roughly around 25 confirmed cases per year.[5] This census, however still remains an underestimate since most patients with LO-CCHS remain well under the radar while most genetic testing are usually done among Caucasians.[1] There are currently no sex or ethnic epidemiological prospective studies for this disease.

If Spirometry is to COPD then PHOX2B mutation testing is mandatory to diagnose CCHS.[1] It should be founded on a background of clinical suspicion for a centrally mediated alveolar hypoventilation as mentioned previously. Screening by targeted mutation analysis identifies 95% of the cases. A follow-through Sequence analysis then Deletion/duplication analysis can be done if initial screening result is negative. If testing does not confirm the diagnosis, patient can be labelled as primary/idiopathic alveolar hypoventilation.

Although it would be mandatory to do genetic testing for our patient, practicality dictates otherwise as therapeutic measures are the same for primary alveolar hypoventilation and CCHS.

CCHS does not resolve spontaneously, nor does it appear to respond to pharmacologic stimulants, or improve with age. Based on the official statement on CCHS by the American Thoracic Society (ATS),[1] chronic ventilatory support remains the best option for maintaining longevity among these patients (as well as those with primary alveolar hypoventilation syndrome). Although oxygen administration without

artificial ventilation improves the PaO2 and relieves cyanosis, this treatment is inadequate as hypoventilation persists and pulmonary hypertension ensues.

Although there are some controversies about the optimal modality of ventilatory support, the ATS recommends positive pressure ventilation via tracheostomy in the first several years of life when brain growth and development requiring normal oxygen levels occurs.[1] Use of Passy-Muir speaking valve can aid in speech development. During late childhood, patients may be shifted to diaphragm pacers during waking hours to participate in age-appropriate activities – freeing them from the ventilator use at daytime.

Bilevel positive airway pressure ventilation by mask or nasal prongs are more compatible for patients with LO-CCHS or milder forms of PAH.[1] There are no current guidelines for pressure support/adjustment in this population but it is recommended that treatment should still be individually prescribed. Avoidance of alcohol or substance abuse is imperative to cardiovascular complications or premature death. Counselling will play an important role especially among teenagers.Pregnant women with CCHS may require increasing respiratory load as the uterus enlarges. Therefore, these women will require frequent monitoring of adequacy of gas exchange in both asleep and awake cycles. And since transmission is autosomal dominant, prenatal Genetic testing and genetic counselling is recommended.

There are currently no roles for pharmacologic treatment in patient with LO-CCHS. Generally, these respiratory stimulants have not been shown to improve ventilation status of patients with CCHS.

It can never be overemphasized that patients with CCHS may suffer from complete respiratory arrest or sleep hypoventilation at sleep onset. They, therefore, require continuous and frequent monitoring so that adequate ventilatory support can be given. Likewise, the ATS recommends biannual then annual in-hospital comprehensive physiologic studies during awake and sleep cycles. For those with late-onset CCHS annual 72-hour holter recording and ECG to detect asystoles or heart rate variability is recommended. Other Surveillance of affected systems including respiratory inductance plethysmography, ECG, haemoglobin levels, pulse waveforms, end tidal carbon dioxide, sleep state staging, blood pressure and temperature monitoring are necessary. The remaining recommendations should be done among those with classic CCHS. Evaluation of Hirschsprung disease and tumors of the neural crest is also essential in affected patients.

Patients with LO-CCHS, with their mild symptoms, have a favourable prognosis. In fact, there have case reports of patient diagnosed with LO-CCHS not requiring ventilatory support at all. This is simply reflects the variance of phenotypic expression of the PHOX2B gene mutation. With proper vigilance, aggressive management and increasing awareness of the disease, patients with classic CCHS may attain normal lifespan.

Now, let's go back to our patient. He regained consciousness almost immediately after mechanical ventilatory support. Vital signs remained stable with adequate oxygenation on the next day. ABG showed normalization of acid-base status with more than adequate oxygenation. He was eventually extubated and discharged after 24 hours and advised to continue BiPAP. So how does the patient fare?

Dr. Raymund Bontol will present his follow-ups.

During his last consult, he claimed to have no daytime sleepiness or fatigue. He is able to swim regularly as part of his weekly exercise routine. He also claims good compliance to his BiPAP during sleep. Laboratory workup showed Cardiomegaly on repeat chest radiograph while a repeat arterial blood gas at room air demonstrated chronic respiratory acidosis with moderate hypoxemia. An appropriate responses to exercise with a functional capacity of 7-8 mets was seen on Exercise Stress test confirming the absence of a cardiac autonomic dysfunction. A repeat sleep study with BiPAP showed episodes of hypoventilation and desaturation despite oxygen supplementation. Compared to prior sleep study, no changes were observed and end tidal CO2 recorded during the procedure and was in range of 58-62 mmHg. A repeat 3 minute Hyperventilation maneuver was done and noted correction of hypercarbia and hypoxia consistent with prior test done last 2005. While prior breath hold test showed that he can hold his breath for more than a minute without any symptoms of desaturation, a repeat test done showed that he can no longer hold his breath for more than 30 secs and that no desaturations were observed during the test. His response to hypoxia and hypercapnea were no longer blunted and were appropriate. According to anecdotal reports cited in the 2010 American thoracic Society clinical policy statement, improvement of CCHS symptoms are possible with advancing age.

We have just presented proof that this is unarguably a case of central hypoventilation syndrome. While we cannot overemphasize the necessity of pursuing genetic testing to differentiate between congenital and idiopathic causes, we realized that the management and prognosis for both are the same. We therefore argue that from a practical point of view, we may forego with genetic studies for now in favor of allocating the patient's limited resources to treatment.

Conclusion

As we wind down this presentation, we have just presented to you a case of central hypoventilation syndrome. That CCHS should be a differential for type 2 Acute respiratory failure. And we showed facts that will draw the line between mythology and science. That Palemon was not a victim of a curse from the jilted Ondine but was an inevitable product of genetics. Thank you.

References:

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REACTORS

Ethel Cabrera (PHC) – Good evening, we were presented a case of a 40 year old man,who became a cyanotic while asleep after drinking spree. When it countered with such patient during our training or in the near future in our private practice, we must take in consideration the reason why our patient like the one presented to us is not breathing adequately. Could this be due to a central obstructive,or due to a hypoventilation hypopnea syndrome? To arrived at such definite diagnosis, we must be able to do a term history to be able to request for the diagnostic test like what was done to the patient presented. We were able to do a serious of test, including psg and MRI .Among the diagnostics done, for me ABG is the most definitive test that can help us with the identification of the syndrome. you have to do a blood gas when the patient is awake during daytime and at night when the patient is asleep. With this procedure, congenital central hypoventilation can be documented with that increase in pcO2 when the patient is sleeping and even when awake. So doing a genetic analysis such as in this case is warranted in concluding that such disease entity is truly a congenital central hypoventilation syndrome,if negative then primarily of lower hyperventilation is the diagnosis. In this case, intake of alcoholic beverage like what happen to our patient can trigger more severe hypoventilation by suppressing the activity of the upper airway dilator muscle. I am grateful that Perpetual Succour was able to present this case for us to be aware that the simple lose of consciousness could be at first sign of ondine's curse. Thank you.

Evan Mendoza- Good evening..First of all, I would like to congratulate the presentors that they give their homework very well, an organize, a very nice presentation and of course I think they are in good luck because not only that it is difficult to find a case like this but it is also very difficult to undergo so many many test like this to come up with the diagnosis of the ondines syndrome. It is quite unfortunate sometimes when we are presented with this cases and we will just end up with trying to be dues what diagnosis are we dealing with and all we do is we try to support,the usual thing that you do when you come up with your patient who is hypoventilating and hypoxemic but then, after that episode what would you do? If you did not have this kind of work-up you will never know what are we facing it and what can we tell our patients, what can advice to patients but one thing for sure we can advice them not to follow the footsteps of Palemon . And I think there's not much I can really talk about this case although this case started before as a spontaneous pneumothorax patient rather thus an ondine case that was the time when I saw this patient. And although this patient had been diagnos already for

ondine's case but sometimes he comes to me for follow up. But so far as I've seen him in the out-patient clinic he was ok and the latest work-up for just to find out how he is and we've all the work-ups we do with this years how he'd fear and so far he is doing well and I think he had broken from the cursed sparkly may with lot of prayers do. Thank you.

Albert Rafanan- First of all, I would like to congratulate the two first year fellows of Perpetual Succour for an excellent presentation. This was a good learning case for everybody and I think they did it very well as I said was very classy, interesting and very educational for all. When I first started this case was in 2005, I was then a young consultant and sleep lab is one year old then. It is easier to call a young consultant to come in, I was called by the cardiologist after he gave the midazolam and the patient stop breathing, became cyanotic. And when we saw him he had revived, he was still hypoxemic and the first thing that struck me was the blood gas. The blood gas showed hypoxemia but the A-a gradient was close to normal even with that abnormal X-ray so that means to us that it's either hypoventilation or increase altitude. So, in this case the hypoventilation was a cause of the hypoxemia. Now, we don't have a lot of diagnostic test. One of the ways we did was we had the patient hyperventilate. When we hyperventilated, the hypoxemia is enough to knock down. So it wasn't clearly the fact,that the patient was not responding to the hypoxemia or to hypercarbia so we had to look this case, so actually it's a little bit funny now but it was a little bit scary then the patient would stop breathing. He would go to sleep and sit at bedside to wake the patient up anytime he sleeps especially at that time we had a bipap, we didn't have the critical care ventilators or NIV then. When we had the MRI done, their was an intern by his side waking him up every now and then to make him breathe. So we had the bipap, and then the MRI because we cannot put the bipap in the MRI so we had to wake him up every now and soon often.The lucky thing about him is he was just regularly employee but he had an owner he works in a company Dr. Mendoza mention, his owner paid for everything but we had the limitation of funds so actually we just did the first part the sleep study and when we prescribe the bipap we just ruled to made an settings and asked him to come back to have repeat sleep study. Apparently when he came back initially followed to the closely but he got better and subsequently thus to follow.And then the last time I heard,I heard from doctor Bontol ,he drunk himself and he was found cyanotic.And that's when I came back and we had him repeated sleep study. He doesn't have apnea so in sleep the reason why medicine so involve in sleep medicine its because there's a lot breathing disorders that happen during sleep.By the way,we had two sleep fellowship programs available right now and it's open. Two sleep fellows are currently in lung center now two sleep fellows are in heart center.And I heard that, St.Luke's and Medical City will be opening so that's another point of interest for our young pulmonary fellows who wants to go into sleep medicine. It's a young field and we just starting our first sleep board exam this year. So in sleep, pulmonologists are wasting sub-out obstructive sleep apnea syndrome. But there are actually 4 categories under the international classsifications of sleep disorder. The first one is obstructive sleep apnea syndrome, the second one is central sleep apnea syndrome which you had your change talk perspiration and high altitude, the third one is sleep related hypoventilation/hypoxemia related to medical conditions like COPD, this 4th one which is presented is primarily sleep related alveolar hypoventilation syndrome. Now in this case, I think about this sleep study it's interesting instead and most of the events happen during grand sleep and then took occur in during adolescence so I think it's apparently normal primary alveolar hypoventilation syndrome though the only way to be to differentiate is Unfortunately I think they'd ask how expensive it is. But it's fairly common I think in children but in the adults actually this is the first case I've seen and I was very excited 1962 2005.So things are evolving, maybe in the future primary alveolar hypoventilation syndrome would come out with different lesson why we had them…So this is a learning case for all of us and as medicine progresses maybe ten years from now this would come out for a different name. Thank you