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Sleep Apnea in Obese People Can Lead to Sensory Neuropathy

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INTRODUCTION:

Obesity is frequently acquainting as an abnormal accumulation of body fat to the degree that may cause serious health consequences. (Yanovski *et al.*, 2014). One of the most common complication of obesity is obstructive sleep apnea(OSA). Obstructive Sleep Apnea is a widespread complaint that is closely associated with global obesity epidemics, and it is described as frequent complete or partial flop of the upper airway during sleep leading to gaseous exchange impairment and disturbance of sleep. It is the commonest category of sleep disordered breathing (SDB) in the world as reported in different epidemiological studies. (McNicholas *et al*., 2007).

Central sleep apnea : is described as decreased respiratory effort leading to decrease or absence of ventilation .While in mixed apnea it is categorized by starting centrally and ending with obstructive events.In obstructive sleep apnea: the effort of respiration is preserved but ventilation decrement or absence due to partial or total obstruction in the upper airway; apnea is well-defined as the total airflow cessation lasting 10 sec. or more , There are three types of apneas :obstructive, central and mixed . A hypopnea: is defined as a reduction in airflow (30-50%) that is followed by an arousal from sleep or a decrease in oxyhaemoglobin saturation (3-4%)(The Report of an American Academy of Sleep Medicine Task Force, 1999 and Kushida *et al*.,2005).

The severity of sleep apnea is evaluated with apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour of sleep.

According to the American Academy of sleep Medicine recommendations , OSA is defined with AHI>5., and it is classified as mild OSA with AHI of 5 to 15;moderate OSA with AHI of 16 to 30;and severe OSA with AHI > 30.(The Report of an American Academy of Sleep Medicine Task Force, 1999).

The Apnea–Hypopnea Index or Apnoea–Hypopnoea Index (AHI) is an index used to determine sleep apnea severity. It is characterized by the number of apnea and hypopnea events per hour of sleep. The apneas (pauses in breathing) must last for at least 10 seconds and associated with a decrease in blood oxygenation. Combining AHI and oxygen desaturation measurement gives a complete sleep apnea severity score that assesses the number of sleep disruptions and degree of oxygen desaturation. (Ruehland *et al*.,2009).

The AHI is calculated by dividing the number of apnea events by the number of hours of sleep. AHI values are categorized as

Normal: 0-4;Mild Sleep Apnea: 5-14;Moderate Sleep Apnea: 15-29; Severe Sleep Apnea: 30 or more.(Ruehland *et al*., 2009).

Prevalence of Obstructed Sleep Apnea:

Worldwide , it is about 2-5 per cent for adult females and 3-7 per cent for adult males in the general population. (Punjabi, 2008). Therefore, OSA it's prevalence in men much more than in women, approximately 2 to 3 times that of women. In addition, OSA prevalence is the same in Caucasians and Asians, and it is noticed that OSA is not only common in developed but also in developing countries. Nevertheless, the prevalence of OSA is greater in overweight or obese elderly people and those of different ethnic origins . And these results were explained mainly by the increased obesity indices (Villaneuva *et al*., 2005).

Diagnosis of Obstructive sleep apnea:

The novel test for diagnosis of OSA is the in-laboratory overnight polysomnography. (The Report of an American Academy of Sleep Medicine Task Force., 1999 and Kushida *et al.,* 2005).Another option for diagnosis of OSA is polysomnography at Home (unattended)is a feasible choice for detecting patients with moderate to high clinical suspicion for sleep-disordered breathing ,However ,subjects with un successful or non-conclusive studies or with negative studies but still suffering from symptoms should go through standardized polysomnography .(Boyer and Kapur, 2003 and Collop , 2008).

Since the access to polysomnography is not possible we use Berline Questionnaire to assess the patients with OSA.

Nerve conduction studies :Nerve conduction studies are the most informative portion of the electrodiagnostic evaluation for a peripheral neuropathy. It is preferable to design a nerve conduction study for each patient to answer specific questions. The plan of the examination is as important as interpretation of the results (Shin, 2001).

Nerve conduction studies is used in diagnosis of neuropathy at sensitivity of about 90% in utmost ;if the right test is chosen ; focal and diffuse neuropathies (Shin, 2001and Yasuda *et al*.,2007).

The NCS can precisely measures the peripheral nerves ability to transmit electrical signals and shows

atypical results if pathology are exist in the nerve. Studying both sensory and motor fibers function of upper and lower limbs ideally illustrate the presence, severity and distribution, of peripheral nerve disease (Albers *et al.*, 1995 and Costa *et al*., 2006). As extension of the clinical neurological examination the NCS is used to examine peripheral nerve functions as it is accurate, most reliable, , informative and sensitive measure. Moreover, these tests had always been considered as the gold standard for diagnosis of all neuropathies (Kimura, 2013).The NCS results relate with clinical endpoints, and the amplitudes of the nerve reveal the degree of nerve fiber loss which characterizes the pathological hallmark of Diabetic Peripheral Neuropathy. Standardized methods improve the reliability of testing such that NCS have the lowest degree of variance of all tests for Diabetic Peripheral Neuropathy (Perkins and Brill, 2003). The accuracy of NCS in diagnosis can be increased by examining other parameters such as F-wave testing, ratio of sural-to-radial sensory nerve potential amplitudes, conduction studies for the planter sensory nerve, and combination of anthropomorphic factors such as height and weight (Kikawa *et al*., 2005 and Uluc *et al*., 2008).

1-Motor nerve conduction study (MNCS):

Different aspects of peripheral motor nerves that innervate a somatic muscle can be evaluated by MNCS. Compound muscle action potential (CMAP), is the electrical response obtained by stimulation of motor nerve is called which represents summated electrical activity of the muscle fibers that are in the region of recording electrode and that are innervated by that particular nerve (Aminoff, 2012).

The latency or distal motor latency (DML) of the motor response is the time in millisecond from the giving the stimulus to the early deflection from the baseline, could be positive or negative. It represents the time required for the action potential in the fastest conducting fibers to reach the nerve terminals and activate the muscle fibers. The amplitude is the elevation in millivolt from the baseline to the peak of the negative phase and it signifies the number of muscle fibers activated and offers an estimation of the sum of functioning nerve and muscle fibers. The conduction velocity (CV) is the speed of conduction in nerve fibers that is measured in meter/second . (Uluc *et al*.,2008).

2-Sensory nerve conduction study (SNCS):

The sensory nerve action potential (SNAP) signifies the summation of the single nerve fiber action potentials that is recorded from a sensory nerve and reveals the dorsal root ganglion cells integrity with their peripheral axons (Kimura, 2013).The latency, amplitude and conduction velocity are measured for sensory nerve fibers as are for motor nerve fibers and usually reflect same principles (Aminoff, 2012).

MATERIALS AND METHODS:

One hundred fifty female were included in this study (75female were classified as overweight or obese) & (75 female with normal BMI).Their age range from 18-60 Years.

All participants subjected to the same clinical, biochemical and neurophysiological tests.

1- Sensory Nerve Conduction Studies

The stimulus intensity was 20-30% above the current necessary to arouse a maximal sensory nerve action potential. The supra maximal stimulating current was kept below threshold for motor fibers especially in the mixed nerves, since sensory fibers generally, had lower threshold of stimulation than that of motor fibers (Aminoff, 2012).

The sites of the electrodes for sensory nerve conduction studies for the tested nerves were as the follow:

Median Nerve

Stimulation: Stimulation was applied with electrode at the plantar aspect of forearm near the wrist joint between the tendons of palmaris longus and flexor carpi radials

Recording: the recording electrode was placed over the median nerve at the index finger (Imada *et al.,* 2007).

Ulnar Nerve

Stimulation: stimulation was applied with surface electrodes at the wrist, just radial to the flexor carpi ulnaris.

Recording: the recording electrode was placed over the ulnar nerve around the fifth digit (Aminoff, 2012).

Sural Nerve

Stimulation: stimulation electrodes was placed lateral to the mid-line of the calf 12cm proximal to the recording electrode.

Recording: the recording needle was inserted posterior and below the lateral malleolus of the fibula (uluc *et al*., 2008).

RESULT

Peripheral Neuropathy in Study Groups among Sensory Nerves

Variable	Study groups		Total	X^2	Odds Ratio (95% C.I.)	P value
	Case (%)	Control (%)				
LT Median Sensory						
Normal	64(85.3)	75 (100.0)	139 (92.7%)	**11.871**	2.17 (1.81-2.60)	**<0.001***
Abnormal	11(14.7)	0 (0.0)	11 (7.3%)			
LT Ulnar sensory						
Normal	69(92.0)	73(97.3) 2	142(94.7%)	2.113	3.17 (1.62-16.26)	0.146
Abnormal	6 (8.0)	(2.7)	8 (5.3%)			
RT Median Sensory						
Normal	62(82.7)	69(92.0)	131(87.3%)	2.953	2.41 (0.86-6.73)	0.086
Abnormal	13(17.3)	6 (8.0)	19 (12.7%)			
RT Ulnar sensory						
Normal	72(96.0) 3	75 (100.0)	147 (98.0%)	3.061	0.49 (0.41-0.58)	0.080
Abnormal	(4.0)	0 (0.0)	3 (2.0%)			
LT Sural sensory			139			
Normal	64(85.3)	75 (100.0)	(92.7%)	**11.871**	2.17 (1.81-2.60)	**0.001***
Abnormal	11(14.7)	0 (0.0)	11 (7.3%)			
RT Sural sensory						
Normal	57(76.0)	72 (96.0)	129 (86.0%)	**12.458**	7.57 (2.13-27.01)	**0.001***
Abnormal	18(24.0)	3 (4.0)	21 (14.0%)			

Association of Obstructive Sleep Apnea risk with Nerve Conduction Study Findings

Variable	Obstructive Sleep Apnea		X^2	P value
	High (%)	Low (%)		
LT. Median Sensory				
Normal	29 (82.9)	35 (87.5)	0.322	0.571
Abnormal	6 (17.1)	5 (12.5)		
LT Ulnar sensory				
Normal	31 (88.6)	38 (95.0)	1.048	0.409[a]
Abnormal	4 (11.4)	2 (5.0)		
RT Median Sensory				
Normal	26 (74.3)	36 (90.0)	3.217	0.073
Abnormal	9 (25.7)	4 (10.0)		
RT Ulnar sensory				
Normal	33 (94.3)	39 (97.5)	0.502	0.596[a]
Abnormal	2 (5.7)	1 (2.5)		
LT Sural sensory				
Normal	30 (85.7)	34 (85.0)	0.008	0.930[a]
Abnormal	5 (14.3)	6 (15.0)		
RT Sural sensory				
Normal	25 (71.4)	32 (80.0)	0.752	0.386[a]
Abnormal	10 (28.6)	8 (20.0)		

Mean Difference of Apnea Hypopnea Index by Nerve Conduction Study Findings

Variable	AHI Mean ± SD	t-test	P value
LT Median Sensory			
Normal (64)	8.22±5.64	0.610	0.544
Abnormal (11)	9.36±6.41		
LT Ulnar sensory			
Normal (69)	7.93±5.16	2.431	0.018*
Abnormal (6)	13.67±9.35		
RT Median Sensory			
Normal (62)	8.08±5.83	1.011	0.316
Abnormal (13)	9.85±5.16		
RT Ulnar sensory			
Normal (72)	8.07±5.25	2.426	0.018*
Abnormal (3)	16.00±12.00		
LT Sural sensory			
Normal (64)	8.28±5.93	0.382	0.703
Abnormal (11)	9.00±4.58		
RT Sural sensory			
Normal (57)	8.02±5.87	0.993	0.324
Abnormal (18)	9.55±5.24		

Association of Apnea Hypopnea Index Categories with Nerve Conduction Study Findings

Variable	AHI Categories			X^2	P value
	Normal (%)	Mild (%)	Moderate (%)		
LT Median Sensory					
Normal	27 (84.4)	31 (91.2)	6 (66.7)	3.367[a]	0.183
Abnormal	5 (15.6)	3 (8.8)	3 (33.3)		
LT Ulnar sensory					
Normal	30 (93.8)	33 (97.1)	6 (66.7)	**6.584[a]**	**0.031***
Abnormal	2 (6.3)	1 (2.9)	3 (33.3)		
RT Median Sensory					
Normal	28 (87.5)	27 (79.4)	7 (77.8)	0.923	0.630
Abnormal	4 (12.5)	7 (20.6)	2 (22.2)		
RT Ulnar sensory					
Normal	31 (96.9)	34 (100.0)	7 (77.8)	**6.114[a]**	**0.018***
Abnormal	1 (3.1)	0 (0.0)	2 (22.2)		
LT Sural sensory					
Normal	28 (87.5)	28 (82.4)	8 (88.9)	0.450	0.897
Abnormal	4 (12.5)	6 (17.6)	1 (11.1)		
RTSural sensory					
Normal	25 (78.1)	26(76.5)	6 (66.7)	0.513	0.774
Abnormal	7 (21.9)	8 (23.5)	3 (33.3)		

Correlation of Apnea Hypopnea Index with Sensory and Motors Nerves' Latency, Amplitude and Conduction Velocity

Nerves	Nerve (Mean± SD)	AHI (Mean± SD)	r	P value
LT Median Sensory		8.38±5.73		
Latency (ms)	2.44±0.48	8.38±5.73	0.091	0.250
Amplitude (µV)	36.47±19.26		**-0.393**	**0.001***
LT Ulnar sensory		8.38±5.73		
Latency (ms)	2.05± 0.22	8.38±5.73	0.028	0.735
Amplitude (µV)	38.03± 18.69		**-0.304**	**0.001***
RT Median Sensory		8.38±5.73		
Latency (ms)	2.42± 0.52	8.38±5.73	0.042	0.609
Amplitude (µV)	33.21± 19.08		**-0.279**	**0.001***
RT Ulnar sensory		8.38±5.73		
Latency (ms)	2.07± 0.27	8.38±5.73	-0.079	0.339
Amplitude (µV)	36.44± 18.71		**-0.300**	**0.001***
LT. Sural sensory				
Latency (ms)	2.27±0.39	8.38±5.73	0.003	0.974
Amplitude (µV)	17.70±9.90	8.38±5.73	**-0.294**	**0.001***
RT. Sural sensory				
Latency (ms)	2.29±0.39	8.38±5.73	0.028	0.735
Amplitude (µV)	16.19±7.43	8.38±5.73	**-0.331**	**0.001***

DISCUSSION

It is well known that one of the complication of obesity is sleep apnea . And sleep apnea which disturb the sleep leading to obesity ,therefore sleep apnea can affect nerve function by different mechanisms . Severity of sleep apnea is evaluated by apnea –hypopnea index(AHI).As AHI is increased that mean more frequent the patient stop breathing and more hypoxia and this hypoxia leads to more deterioration of nerve function.

Low and his co-workers, (1986)and Ludemann and his co-workers ,(2001) showed that chronic hypoxaemia decelerate the nerve conduction velocity and Studies of the oxygen consumption in the microenvironment of the peripheral nerve under conditions of nerve oedema and experimental diabetic neuropathy show that the peripheral nerve function is oxygen dependent. Axonal transport is an energy requiring process and its impairment by hypoxaemia can enhance axonal degeneration.

There are many explanations by which hypoxia can disturb nerve function:

(Mayer *et al*.,1999) demonstrated that Hypoxic neuropathies causing hyperplasia and hypertrophy of the capillary endothelial cell of the nerve ,and this hypertrophy and hyperplasia, prompting luminal occlusion this may inhibit the transport of oxygen and nutrients. This explanation appear to be valid to peripheral nerve dysfunction and lesions, resulting from impaired axonal transport and causing axonal degeneration .And this is consistent with the finding demonstrated in table (4.10) that reveal strong negative correlation between the AHI and the amplitude of some nerves that indicate axonal injury and degeneration.

Meanwhile Lim and his co-workers, (2010) had revealed that the patterns of sleep apnea oxygenation have been influential in explaining the injury mechanisms. The hypoxia/re-oxygenation events result in inflammatory, oxidative, and endoplasmic reticulum stress responses in susceptible groups of nerves.

For the time being Paiva and Attarian said that OSA creates a proinflammatory state with high levels of TNF-α and other cytokines. If left untreated, OSA can cause significant neurological problems including peripheral neuropathy ,stroke, headaches, cognitive decline, depression, and non-arteritic ischemic optic neuropathy as these literature stated by the scientist Paiva and Attarian ,(2014).

The cardinal feature that is associated with sleep apnea is intermittent hypoxia and it will lead to endothelial dysfunction, systemic inflammation , oxidative stress, metabolic abnormalities Relationships between Intermittent Hypoxia and nerve conductance abnormalities have been explored (Valencia-Flores *et al*.,2015).

Some studies pointed precisely to the correlation between the hypoxemia degree and severity of peripheral neuropathy. All former studies noticed that peripheral neuropathy encompassing the sensory nerves in these patients (Kayacan *et al*.,2001 and Ozge *et al*.,2001).

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