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Case of Nonalcoholic Steatohepatitis Occurring in Combination with Sleep Apnea Syndrome, Who Showed Improvement of Liver Function by Continuous Positive Airway Pressure

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Abstract

We present a case of Nonalcoholic Steatohepatitis (NASH) occurring in combination with sleep apnea syndrome (SAS) in a 35-year-old man whose liver function improved on introduction of continuous positive airway pressure (CPAP). The patient had been steadily gaining body weight since the age of 20, and liver dysfunction had been frequently highlighted during regular health checks. He had a history of snoring, nasal obstruction, and lethargy and was admitted to our hospital for evaluation and diagnosis of these symptoms. Following Polysomnography (PSG), he was diagnosed with SAS on the basis of an apnea and hypopnea index (AHI) score of 34.7/hour. Following CPAP treatment, his symptoms gradually improved and his AHI score reduced to 3.8/hour. However, despite CPAP contributed to the improvement of Alanine Aminotransferase (ALT) and aspartate aminotransferase (AST) these levels remained elevated, and he showed sustained liver dysfunction. Therefore, we were consulted for evaluation and diagnosis of the sustained liver dysfunction. On admission, his body mass index (BMI) was 34.5 kg/m^2 and abdominal Ultrasonography (US) and Computed Tomography (CT) indicated the presence of severe fatty liver. A liver biopsy was performed and the patient was diagnosed with NASH, grade 1/stage 2 and steatosis grade 3.

Keywords: Sleep apnea syndrome; Nonalcoholic steatohepatitis; Continuous positive airway pressure

Introduction

The abundant availability of food in the developed world has coincided with an increasing incidence of obesity and metabolic syndrome. Similarly, the number of patients diagnosed with Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH) is also on the rise. At present, there are 10 million estimated cases of NAFLD in Japan, with approximately more than 10% of these patients going on to develop NASH [1]. Obesity is a significant risk factor for the development of both NASH and Sleep Apnea Syndrome (SAS) [2,3]. Sleep apnea is defined by total cessation of airflow for at least 10 seconds. Hypopnea in adults is defined as a 10-second event during which there is continued breathing, but with ventilation reduced by at least 50% from baseline. The diagnosis of SAS is based on at least 5 obstructed breathing events per hour or 30 events per 7 hours of sleep [4]. We encountered a case of NASH occurring in combination with SAS, and here, we discuss the relationship between SAS and NASH with bibliographic consideration.

Case Report

The patient was a 35-year-old Japanese man with a history of obesity, hyperuricemia, hypercholesterolemia, and liver dysfunction since youth. He had experienced nasal obstruction and was prone to snoring and lethargy since 2005. The patient underwent Polysomnography (PSG) on July 4, 2007. The findings of PSG indicated that his apnea and hypopnea index (AHI) was 34.7/hour, and he was diagnosed with SAS. He was treated with continuous positive airway pressure (CPAP) from July 27, 2007, and his symptoms, such as nasal obstruction, snoring and lethargy, gradually improved and eventually disappeared. The follow-up AHI using PSG was 3.8/hour on October 26. However, despite CPAP contributed to the improvement of ALT and AST, he showed persistently high aminotranferase levels. Therefore, we were consulted for evaluation and diagnosis of sustained liver dysfunction in February 2008. He was admitted to our division on May 28, 2008.

The patient had no family history of liver disease and no history of alcohol abuse or blood transfusion. Physical examinations conducted on the first day of admission to our department showed that the patient's abdominal girth was 90.0 cm, height was 168.0 cm, body weight was 97.4 kg, and Body Mass Index (BMI) was 34.5 kg/m^2. His blood pressure was 117/70 mmHg. Biochemical analysis showed elevated serum levels of AST and ALT (47 IU/L and 116 IU/L, respectively). Examinations for Hepatitis B surface antigen (HBsAg), Hepatitis B antibody to core antigen (HBcAb), and Hepatitis C Virus (HCV) antibody yielded negative results. Furthermore, autoimmune antibodies were not detected (Table 1). Ultrasound examinations indicated deep-echo attenuation and enhancement of hepatorenal contrast (Figure 1), while CT revealed a low liver: spleen ratio (Figure 2). Results of a percutaneous liver biopsy suggested that there was extensive macrovesicular steatosis with minimal inflammation and hepatocyte ballooning degeneration (Masson trichrome stain, Hematoxylin and eosin stain). On the basis of these findings, the patient was diagnosed with NASH Stage1/Grade1 (Brunt's criteria).

After introduction of CPAP, his subjective symptoms improved. Moreover, follow-up PSG indicated his AHI was 3.8/hour, and his SAS had also improved.

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Hematology			Biochemistry					
WBC	6600	/μl	AST	47	IU/l	Ferritin	190	ng/dl
Seg	64.5	%	ALT	116	IU/l	Insulin	8.4	μU/ml
Lympho	1.5	%	γ-GTP	65	IU/l	CRP	0.15	mg/dl
mono	27.2	%	ALP	167	IU/l			
Eosino	6.5	%	LDH	195	IU/l			
Baso	0.3	%	T.Bil	0.7	mg/dl	Serology		
RBC	5.07×10^4	/μl	D.Bil	0.3	mg/dl	ANA	<40	×
Hb	15.8	g/dl	ChE	549	IU/l	AMA	<40	×
Hct	46	%	T.P	7.0	g/dl	IgG	1184	mg/dl
Plt	28.9×10^4	/μl	Alb	4.7	g/dl	IgA	180	mg/dl
ESR	2	mm/hr	Cr	0.92	mg/dl	IgM	111	mg/dl
			BUN	7.8	mg/dl	HBsAg	(-)	
			T.Chol	205	mg/dl	HBcAb	(-)	
			LDL-C	157	mg/dl	HCV 2nd Ab	(-)	
Coagulation			HDL-C	48	mg/dl	TSH	0.628	μU/ml
P.T	102%	%	T.G	78	mg/dl	FT3	3.4	pg/ml
APTT	28.7	sec	HbA1c	5.3	%	FT4	1.3	ng/ml
Fib	217	mg/dl	FPG	90	mg/dl	Hyaluronic acid	34	ng/ml

Table 1: Laboratory data on admission.

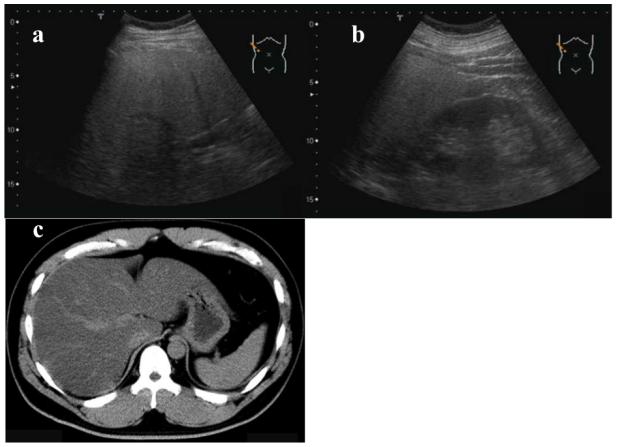

Figure 1: Ultrasound and Computed Tomgraphy on Admission.

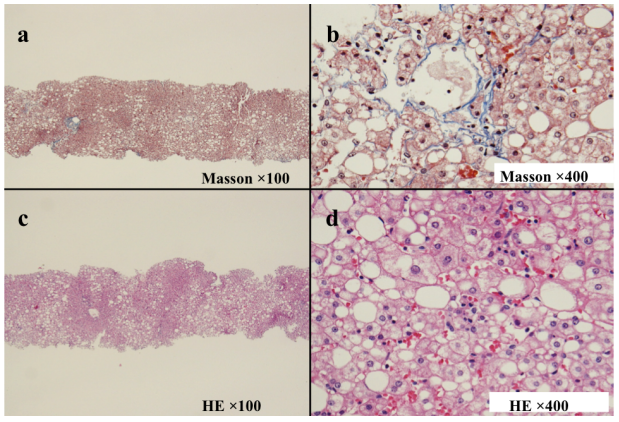

Figure 2: Liver Biopsy.

Serum ALT level slowly decreased from 156 to 116IU/L before and after CPAP therapy (Table 2). And the same time, his weight lost from 99 to 97 kg. Both CPAP therapy and weight loss of 2 kg contributed to the improvement of serum ALT level and normalization

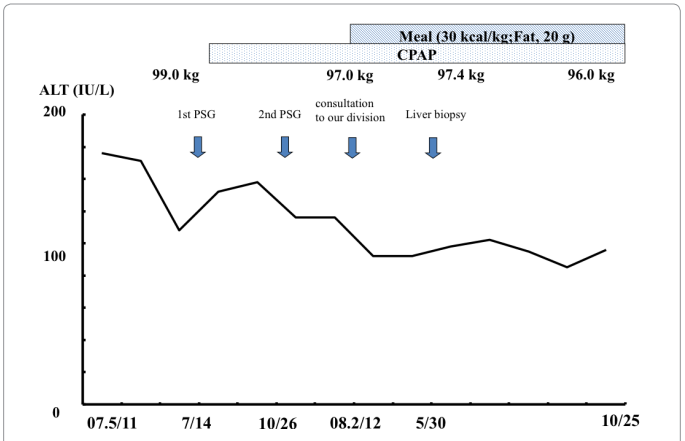

Figure 3: Clinical Course.

		Before CPAP	3 months after CPAP	4 months after CPAP+diet therapy	8 months after CPAP+diet therapy
		07.5.11	07.10.26	08.6.28	08.10.25
AST	IU/L	64	48	46	51
ALT	IU/L	156	116	98	96
γ-GTP	IU/L	97	65	56	61
T.Chol	mg/dL	201	224	198	165
T.G	mg/dL	221	114	85	96
LDL-C	mg/dL	101	-	139	108
HDL-C	mg/dL	45	-	42	43
FPG	mg/dL	93	104	93	98
HbA1c	% (JDS)	5.2	5.3	5.1	-

Table 2: Chronological change of laboratory data.

of hypertriglycemia. However inspite of CPAP therapy and weight loss, serum ALT level had sustained high level which was around 120 IU/L. After strict diet therapy (30 kcal/day with 20 g fat/day), serum ALT level furthermore decreased from 116 to 98 IU/L (Table 2). In addition to CPAP therapy and weight loss, strict diet therapy contributed to the improvement of serum ALT level. However in spite of those therapies, serum ALT level had sustained high level which was around 90 IU/L. Further weight loss and some medication, such as vitamin E and angiotensin II receptor antagonist, and so on, are required in order that transaminase may improve much further. However unfortunately, after this initial follow-up period, we were unable to further observe the patient's clinical course as he was no longer able to attend our hospital because of a personal matter (Figure 3).

Discussion

Recently, several articles have reported cases of concurrent SAS and NASH and highlighted an important relationship between the diseases [5-10]. It is suggested that SAS is an independent risk factor for NASH aside from BMI [5,6]. NASH was originally proposed by Ludwig et al. [11] in 1980. Despite a lack of alcohol intake (<20 g/day), patients had steatohepatitis similar to alcoholic liver disease. Recently, the number of patients with NASH has gradually increased in proportion to the number of patients with obesity or metabolic syndrome.

The patient in the current case was diagnosed with NASH on the basis of Brunt's classification [12]. In patients with SAS, it is suggested that SAS-induced hepatocyte ischemia with hypoxia [13-16], insulin resistance, and oxidant stress are involved in the development of liver dysfunction. Chin et al. reported that the results obtained after

a single night of nasal CPAP treatment suggest that recurrent apnea and hypopnea with hypoxemia may aggravate hepatic dysfunction in these patients, which manifests by release of AST, a well-established marker of hepatocellular injury after ischemia and reperfusion [17]. Similarly, our patient's symptoms and PSG findings definitely improved after introduction of CPAP (AHI 34.7/hour → 3.8/hour). Additionally, the ALT and AST levels also improved after introduction of CPAP. Therefore, we suggest that SAS might partially contribute to the pathogenesis of NASH.

It is suggested that the improvement of hepatic ischemia by SAS-induced hypoxia can contribute to a decrease in aminotransferase levels. However serum ALT level had sustained high level in spite of treatment, such as strict diet therapy, weight loss and CPAP therapy. This fact supports that various factors can contribute to pathogenesis of NASH and it can be difficult to normalize serum ALT level if we can't deal with every contributing factor which patients have. NASH is often linked with disorders that are clearly associated with insulin resistance (IR) [18,19]. Additionally, it is reported that SAS leads to IR, which can contribute to pathogenesis and development of NASH [20-22]. CPAP leads to an improvement in SAS-induced IR [20], and may therefore have the potential to improve NASH that occurs in combination with SAS.

Although the pathogenesis of NASH is poorly understood, the "two hit theory" has been widely accepted [23]. The "first hit" is steatosis following dyslipidemia based on IR, while the "second hit" have not been established yet and the mechanism is still debatable. In addition to IR, several reports suggest that the levels of oxidative stress, inflammatory cytokines, and inflammatory markers are elevated in patients with SAS [24-26]. Since SAS is associated with oxidative stress, it may potentiate the "second hit." It is widely recognized that obesity is a risk factor that aggravates both NASH and SAS. We hope that further loss of body weight through dietary restriction and exercise will improve the patient's condition [27].

With the increasing incidence of obesity and related disorders, it is thought that the number of patients with NASH will increase further and more patients with these conditions will be encountered in daily medical practice. At present, the association between SAS and NASH remains poorly understood, and further evaluation and accumulation of cases are required. As the number of patients with metabolic syndrome increases, the number of patients with both NASH and SAS will also increase. In the future, cross-sectional studies and collaboration with related departments will be required to analyze this phenomenon in greater detail.

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