□ CASE REPORT □

Successful Treatment of Heart Failure in an Adult Patient with Prader-Willi Syndrome

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Abstract

Prader-Willi Syndrome (PWS) is a rare genetic disorder characterized by physical, psychological and physiological abnormalities. Obesity and related cardiovascular diseases are a common problem in adult patients with PWS. This report describes a case of adult PWS with heart failure associated with marked obesity and sleep-disordered breathing that was successfully treated with oxygen therapy, adaptive servoventilation, medications, diet therapy and rehabilitation.

Key words: obstructive sleep apnea, central sleep apnea, obesity hypoventilation syndrome, rehabilitation, noninvasive positive pressure ventilation

Introduction

Prader-Willi syndrome (PWS), first described by Prader, Willi and Labhart in 1956, is a rare genetic disease with an estimated prevalence of 1 in 8,000 to 50,000 live births (1). It is characterized by hypotonia, developmental delays, hypogonadism, a short stature, small extremities, hyperphagia leading to obesity, dysfunction of several hypothalamic centers, learning disabilities, cognitive impairments and other behavioral problems (1-3). The diagnosis is based on clinical criteria (2) and confirmed with genetic studies, including a deletion in chromosome 15 involving bands 15q11.2-q13 (3, 4). In adult patients with PWS, marked obesity is the most serious and most common complication, contributing significantly to morbidity and mortality (5-7). Such obesity also leads to sleep-disordered breathing (SDB) (1, 7), which is associated with heart failure. The present report describes the case of an adult patient with heart failure due to marked obesity and SDB associated with PWS whose condition was improved with oxygen therapy and adaptive servoventilation (ASV) in addition to medical treatment and rehabilitation for heart failure and diet therapy for obesity.

Case Report

A 37-year-old Japanese woman presented to an emergency room in our hospital with dyspnea, edema, cyanosis and excessive daytime sleepiness (EDS). Her history was notable in that after birth she was unable to take in milk due to muscle weakness, and tube feeding was administered for nutritional support. She had been clinically diagnosed with Prader-Willi syndrome at 5 years of age. Her childhood period was notable for obesity but no other medical conditions. She was able to speak, although she could not read or write due to cognitive impairment and learning disabilities, which are a characteristic feature of PWS. Her father had died from a cerebral hemorrhage several years previously, and there was no family history of hypertension. After presentation to the emergency room, she was admitted to the hospital with a diagnosis of congestive heart failure with hypoxia and hypercapnia.

On examination, the patient's height was 135 cm and her body weight was 114 kg (body mass index: 62.6 kg/m^2). Her heart rate was 57 beats/min, her blood pressure was 196/80 mmHg and her respiratory rate was 22 breaths/min.

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LVDD 55mm, LVDS 41mm
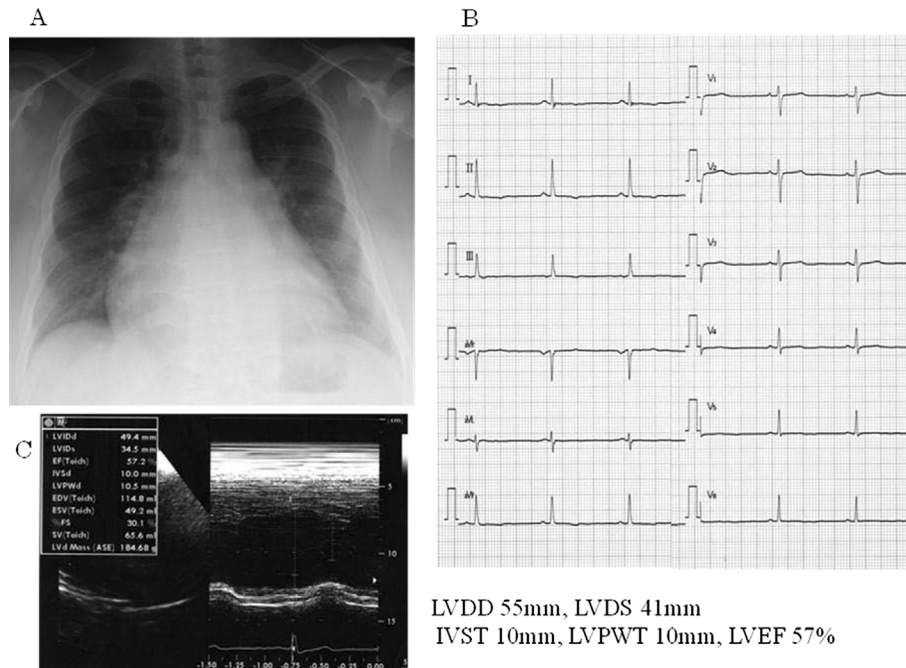IVST 10mm, LVPWT 10mm, LVEF 57%

Figure 1. **A. Chest radiography showed mild cardiomegaly. B. Initial electrocardiogram showed a sinus rhythm with flat T waves in the I, aVL and V_{4-6} leads and mild inverted T waves in the II, III and aVF leads. C. Echocardiography showed an almost normal left ventricular ejection fraction without LV dilatation or hypertrophy. LVDD: left ventricular end-diastolic diameter, LVDS: left ventricular end-systolic diameter, IVS: interventricular septal wall thickness, LVPWT: left ventricular posterior wall thickness, LVEF: left ventricular ejection fraction**

She had generalized edema. Chest radiography showed cardiomegaly (Fig. 1A). Initial electrocardiogram (ECG) showed a sinus rhythm with flat T waves in I, aVL and V_{4-6} and mild inverted T waves in II, III and aVF (Fig. 1B). Echocardiography showed an almost normal (57%) left ventricular (LV) ejection fraction without LV dilatation or hypertrophy (Fig. 1C) with diastolic dysfunction (E/A 2.2, deceleration time 157.5 ms, E/e' 13). Her serum lactate dehydrogenase level was slightly increased (278 mEq/L) and other laboratory parameters were as follows: blood urea nitrogen, 23.4 mg/dL; creatinine, 0.49 mg/dL; aspartate amino transferase, 33 IU/L; alanine amino transferase, 36 IU/L; fasting plasma glucose (FPG), 121 mg/dL; hemoglobin A1c, 5.7%; immunoreactive insulin, 6.3 μU/mL; and homeostasis model assessment insulin resistance (HOMA-R), 1.9. The serum levels of creatine kinase and serum cardiac troponin I were normal, while the serum level of brain natriuretic peptide (BNP) was increased (540.6 pg/mL) (Table). Furthermore, the laboratory data showed a normal thyroid function and normal lipid profile (Table). The results of a blood gas analysis were as follows: pH, 7.341; pCO_2, 63.3 torr; pO_2, 57.7 torr; sPO_2, 87.1%; HCO_3-, 33.3 mmol/L, base excess (BE): 6.1 mmol/L.

Laboratory screening for secondary hypertension was performed due to the patient's hypertension, although it did not show any abnormalities (Table).

Chest computed tomography (CT) showed no lung diseases that could cause hypoxia or hypercapnia (Fig. 2). The patient had no neuromuscular diseases. She was not able to perform respiratory function testing due to her cognitive impairment. Based on these data, we diagnosed her with obesity hypoventilation syndrome (OHS). OHS is a combination of hypercapnia and obesity (body mass index >30 kg/m^2) in the absence of other causes for hypoventilation, such as hypothyroidism or neuromuscular disease (8). Cardiac catheterization was not performed because there was no chest pain or ischemic changes on ECG monitoring while walking during rehabilitation. Furthermore, the patient was not able to understand the examination of cardiac catheterization and her family decline to proceed with it.

Due to the patient's obesity and heart failure (HF), the presence of SDB was examined using portable polysomnography with the Sleeptester LS-300 (FUKUDA DENSHI, Japan). It showed SDB with obstructive sleep apnea (OSA) and central sleep apnea (CSA) based on the following data: apnea hypopnea index (AHI): 54.2/hour (h), OSA: 217/7h, CSA: 101/7h, oxygen desaturation index (ODI): 311/7h (39.1/h), sPO_2: 59-100%, mean sPO_2: 93%.

A fluorescence *in situ* hybridization (FISH) analysis using probes for small nuclear ribonucleoprotein polypeptide N (SNRPN), which map inside the chromosomal region 15q11-15q13, confirmed the presence of the 15q11-15q13 deletion of paternal chromosome 15, the predominant genetic defect in PWS (Fig. 3).

Based on these data and the patient's clinical signs and symptoms, we diagnosed her with heart failure with a pre-

Table.   Laboratory Data

WBC: 6,210 /µL	Na: 144 mEq/L	UA: 6.0 mg/dL	**Blood gas analysis**
RBC: 486×10^4/µL	K: 4.5 mEq/L	FPG: 121 mg/dL	pH: 7.341
Hb: 13.2 g/dL	Cl: 105 mEq/L	LDL-C: 68 mg/dL	pCO_2: 63.3 torr
Hct: 44.5%	BUN: 23.4 mEq/L	HDL-C: 56 mg/dL	pO_2: 57.7 torr
PLT: 9.5×10^4/µL	Cre: 0.49 mEq/L	TG: 59 mg/dL	sPO_2: 87.1 %
PT(INR): 1.08	T P: 6.2g/dL	HbA1c: 5.7 %	HCO_3^-: 33.3 mmol/L
HBsAg (-)	T bil : 0.7 mg/dL	CRP: 0.37 mg/dL	BE: 6.1 mmol/L
HCVAb (-)	AST: 33 IU/L	Troponin I: 0.039 ng/mL	
Serological test	ALT: 36 IU/L	BNP: 540.6 pg/mL	E: >100 pg/mL
for syphilis	LDH: 278 IU/L	TSH: 2.05 µIU/mL	NE: 90 pg/mL
RPR (-)	ALP: 281 IU/L	free T3: 2.13 pg/mL	DA: >20 pg/mL
TPHA (-)	γ-GTP: 45 IU/L	free T4: 1.23 pg/mL	PAC: 11.3 pg/mL
	AMY: 25 IU/L	HOMA-IR: 1.9	PRA: 0.7 ng/mL/hour
	CH-E: 199 IU/L	IRI: 6.3 mU/mL	Cortisol: 12.4 µg/dL
	CK: 78 IU/L		

WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, Hct: hematocrit
PLT: platelet, PT: prothrombin time, BUN: blood urea nitrogen, Cr: creatinine, TP: total protein
T bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase
LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltransferase
AMY: amylase, Ch-E: cholinesterase, CK: creatine kinase, UA: uric acid
FPG: fasting plasma glucose, LDL-C: low-density lipoprotein cholesterol
HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, CRP: c-reactive protein,
BNP: brain natriuretic peptide, TSH: thyroid stimulating hormone
HOMA-IR: homeostasis model assessment insulin resistance, IRI: immunoreactive insulin
BE: base excess
E: epinephrine, NE: norepinephrine, DA: dopamine, PAC: plasma aldosterone concentration
PRA: plasma renin activity

served ejection fraction (HFPEF), i.e., diastolic dysfunction with SDB associated with obesity due to Prader-Willi syndrome. She was treated with oral administration of 20 mg of furosemide and 25 mg of spironolactone per day, 1 L/min of nasal oxygen supplementation, adaptive servoventilation (ASV) using variable positive airway pressure adaptive servoventilation, VPAP Adapt SV™ (ResMed Limited, Australia), calorie restriction (1,000 cal/day), salt restriction (<6 g/day of NaCl) and rehabilitation for obesity, heart failure and hypertension.

After treatment with ASV with oxygen at 1 L/min, her condition dramatically improved (AHI: 5.7, reported by the ResScan™ software program of VPAP Adapt SV™ (ResMed Limited, Australia)). After the administration of ASV at nighttime, a blood gas on room air in the daytime analysis showed persistent hypoxia with resolution of hypercapnia (pH, 7.441; pCO_2, 41.1 torr; pO_2, 58.9 torr; sPO_2, 92.0%; HCO_3^-, 27.5 mmol/L; and BE, 3.5 mmol/L). Therefore, oxygen therapy of 1 L/min was initiated, and a blood gas analysis (BGA) showed increased oxygenation (pH, 7.341; pCO_2, 52.8 torr; pO_2, 78.2 torr; sPO_2, 93.7%; HCO_3^-, 31.7 mmol/L; BE, 5.8 mmol/L). Although the pCO_2 level was mildly high, we did not decrease the amount of oxygen because we thought that rehabilitation was needed to improve the patient's condition in association with obesity.

Rehabilitation was started two days after admission. However, the sPO_2 level decreased from 96% to 85% after a 100 m-walk, and oxygen therapy of 2 L/min was needed to maintain an sPO_2 level greater than 90% after a 100 m-walk. Therefore, we instituted oxygen therapy with exertion in ad-

dition to 1 L/min at rest. Moreover, the patient's heart rate (HR) increased from 60 beats/min to 140 beats/min after a 100 m-walk with oxygen therapy at 2 L/min. Due to her marked obesity and muscle weakness, we decided to decrease the rehabilitation to a 70 m-walk with oxygen therapy. This resulted in a change in her HR to 120 beats/min. Elastic band resistance training (muscle strength training) of the shoulder muscles, elbow muscles, quadriceps femoral muscles and iliopsoas muscles was conducted with two sets of 10 repetitions daily.

Approximately 40 days after admission, the patient was discharged with a body weight of 94 kg, a blood pressure of 113/83 mmHg and a serum BNP level of 21.2 pg/mL (Fig. 4). Echocardiography performed before discharge showed improvement in the diastolic function (E/A 1.46, deceleration time 206.6 ms, E/e' 10). At discharge, we prescribed furosemide and spironolactone, which improved the patient's heart failure. We did not add other medicines for heart failure, including beta-blockers and angiotensin converting enzyme (ACE) inhibitors and so on, for the following reasons: 1) primarily in order to facilitate adherence due to the patient's cognitive impairment, 2) bronchial asthma was not neglected because the patient was not able to perform respiratory function testing, 3) it would be serious if ACE inhibitors induce upper airway angioedema in addition to upper airway narrowing due to severe obesity, and 4) spironolactone was prescribed as a renin-angiotensin-aldosterone inhibitor instead of an ACE inhibitor and angiotensin receptor blocker.

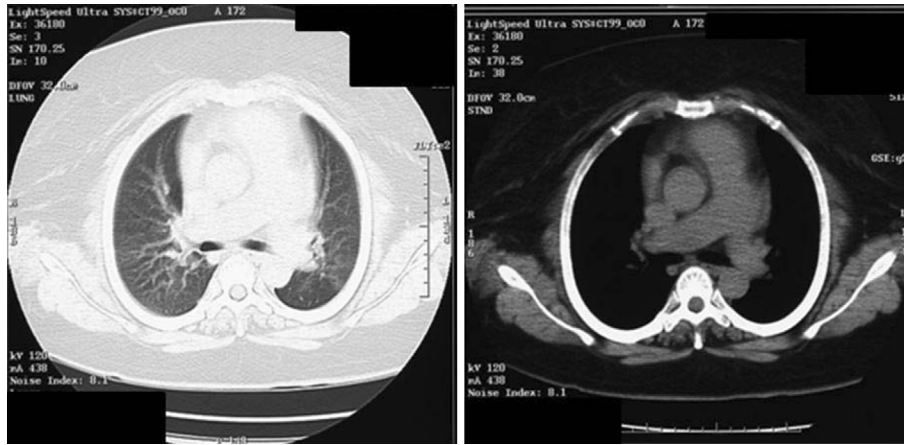Before discharge, we educated the patient and her mother

Figure 2.   Chest computed tomography showed no lung diseases or dilatation of the pulmonary artery.
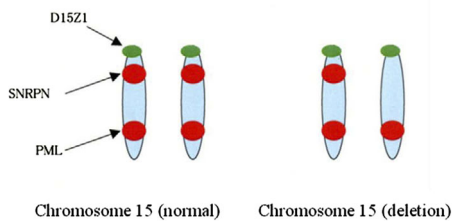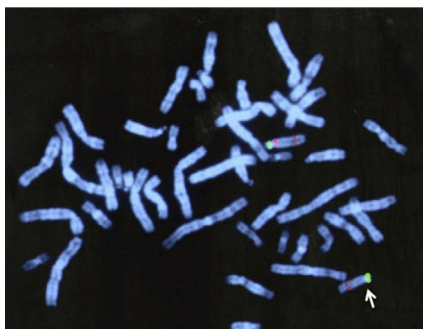

Figure 3.   A fluorescence _in situ_ hybridization analysis using probes for small nuclear ribonucleoprotein polypeptide N (SNRPN), which map inside the chromosomal region 15q11-15q13, confirmed the presence of the 15q11-15q13 deletion of paternal chromosome 15. (PML and D15Z1 are control markers of chromosome 15.)

Figure 4.   Time course of the present patient.

regarding drug adherence, diet, oxygen therapy with ASV and exercise training.

At the first follow-up visit one month after discharge, the patient was found to be noncompliant with medications and the prescribed diet, although she had continued oxygen therapy and ASV. Her body weight had increased from 94 kg to 98 kg, mild edema was present, her serum BNP level was 129.5 pg/mL, her FPG level was 103 mg/dL, her hemoglobin A1c level was 5.8% and her triglyceride level was 98 mg/dL. The AHI was 1.7/h on ASV, as calculated by the ResScan™ software program. Therefore, we provided supplementary education regarding the need for diuretics for the treatment of heart failure and the importance of diet. Approximately one month after the first outpatient visit, the patient's body weight had decreased from 98 kg to 92 kg, her
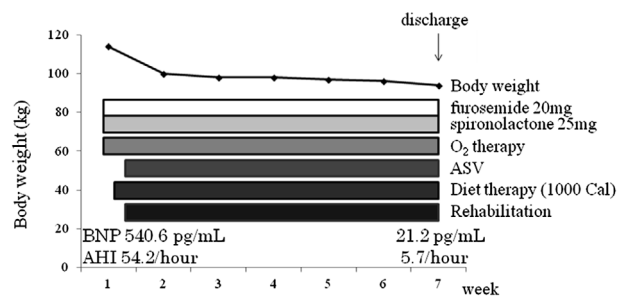
serum BNP level decreased to 28 pg/mL, her FPG level was 90 mg/dL and her hemoglobin A1c level was 5.4%, thus suggesting a resolution of the acute heart failure.

Discussion

Respiratory and other febrile illnesses are the most frequent causes of death in children with PWS, while obesity-related cardiovascular problems, cor pulmonale exacerbated by obstructive and central apnea and septicemia due to skin infections are the most frequent causes of morbidity in adult patients with PWS (9-12). Previous studies also have demonstrated that PWS patients are at a high risk for obesity-related health problems such as hypertension, type 2 diabetes mellitus and dyslipidemia (13-15).

The present case involved a 37-year-old patient with PWS who had HF associated with severe obesity and SDB. On admission, she had hypertension, which resolved after the institution of diuretics, salt restriction and oxygen therapy with ASV. This indicated that the hypertension was likely related to the obesity and SDB. The patient did not have any apparent diabetes mellitus or dyslipidemia. Moreover, her insulin level was normal, although she had marked obesity. A previous study using magnetic resonance imaging reported selective relative reductions in visceral adiposity in nondiabetic PWS adults, which may be distinct from the metabolic syndrome seen in obese patients (16). Therefore,

SDB, heart failure and obesity were important targets for treatment in the present case.

There are three major types of SDB with respect to prevalence and health consequences: OSA syndrome (OSAS), Cheyne-Stokes respiration (CSR) and CSA in chronic heart failure (CHF) and OHS (17). CSA is also related to PWS itself, and it has also been demonstrated that nonobese PWS children have CSA (18). A variety of SDB types have been reported in PWS (1). The present patient had these three types of SDB: OSA, CSA and OHS with HF. HF patients with SDB are characterized by a reduced left ventricular function, an increased incidence of malignant arrhythmia and a poor prognosis (19). Either type of SDB worsens the prognosis of patients with HF (20, 21). Therefore, in the present case, the causes of HF seemed to be related to SDB and obesity and a vicious cycle among these factors.

A previous report showed that the use of continuous positive air pressure (CPAP) and nasal intermittent positive pressure ventilation may be beneficial for patients with PWS (1). In ordinary cases, CPAP should be the first choice for OHS, as recommended in the Japanese guidelines for the diagnosis and treatment of sleep-disordered breathing in cardiovascular disease. If CO_2 retention is worsened in spite of CPAP therapy, then bilevel-PAP can be used to replace CPAP. However, ASV using variable positive air way pressure adaptive servoventilation, VPAP Adapt SV™ (ResMed Limited, Australia) was used for the treatment of SDB in the present case because we thought that the patient's cognitive impairment made it difficult for her to complain about the unfitness of CPAP when CPAP was tried and titrated and because the patient had severe HF and seemed to also have CSA related to severe HF or Prader-Willi syndrome, as well as OSA and OHS, as already reported (18). Recently, ASV therapy has been reported to be more effective than CPAP for treating HF patients with OSA and Cheyne-Stokes respirations, although CSA was dominant in these cases (22). In addition, ASV seemed to be effective for SDB and HF in the present case to stop the vicious cycle of SDB and HF, although the patient was receiving other therapies, including minimal medications for heart failure and rehabilitation. Therefore, ASV may be more beneficial in HF and SDB patients with Prader-Willi syndrome than OHS patients without HF. Further study is needed to evaluate this issue.

PWS patients may also demonstrate a range of abnormalities in sleep architecture and breathing during sleep as well as excessive daytime sleepiness (EDS). In the general population, EDS is associated with OSAS. In PWS, by contrast, OSAS is unlikely to fully explain EDS. Instead, other factors, including hypothalamic dysfunction, are likely to contribute to EDS (23). In the present case, EDS disappeared after the resolution of acute HF. Therefore, heart failure may be one of the causes of EDS in PWS patients.

Weight reduction and physical activity seem to be effective for treating HF as well as for reversing the respiratory complications of obesity (24).

The level of physical activity in PWS patients is significantly reduced, which is likely related to obesity, hypersomnolence and persistent poor muscle tone (25). Body composition studies show both increased body fat and reduced muscle in PWS patients from infancy to adulthood (26). Moreover, in adult life, although hypotonia does not progress, the progressive effects of obesity on joints produce an abnormal gait (27), while muscle weakness reduces balance in PWS patients (28). These factors may make it difficult to perform advance rehabilitation in patients with PWS, especially in those with HF. However, no previous studies have so far investigated the utility of rehabilitation for HF in patients with PWS.

In the present case, rehabilitation included repeat short-distance walking, resistance training and diet therapy for the management of marked obesity and muscle weakness. A 100 m-walk was too strenuous for this patient due to her abnormal gait and imbalance, both of which were also the result of marked obesity and muscle weakness. Therefore, more frequent walks with shorter walking distances were used, and resistance training was performed to strengthen the muscles related to walking and balance. This strategy resulted in weight loss and increased physical activity, which contributed to the therapeutic effects on HF in combination with medications, ASV and oxygen therapy.

The altered body composition observed in PWS patients resembles that seen in subjects with growth hormone (GH) deficiency, in which a reduction of lean body mass is observed. Recently, it was reported that GH therapy exerts beneficial effects on physical activity and agility as well as on body composition in adult patients with PWS (29).

We did not use GH therapy in the present case because it is not a definitively established treatment for PWS.

Cognitive impairment was another important problem for this patient. As a result, we limited medical therapy to furosemide and spironolactone in order to facilitate adherence. Therefore, conventional therapies for HF, including angiotensin converting enzyme inhibitors and beta-blockers, were not used. Despite efforts to simplify her medical regimen, the patient was initially noncompliant with therapy, resulting in the recurrence of HF despite an AHI of 1.7/h on ASV. This indicates that ASV and oxygen therapy alone were not sufficient to treat HF in this case.

The precise mechanisms underlying heart failure in Prader-Willi syndrome are unknown. In the present case, the type of HF was HFPEF related to SDB and obesity. Recent studies have demonstrated that obesity and hypertension are more frequent in HFPEF patients, although these patients are older, more frequently female and have higher blood pressures (30, 31). Moreover, the recurrent nocturnal hypoxia observed in several diseases, including OHS, increases sympathetic activity and alters peripheral vascular tone (32). Therefore, these factors may contribute to the mechanisms underlying HF in patients with Prader-Willi syndrome.

In conclusion, these observations suggest that simultaneous management of SDB, obesity and muscle weakness is needed to treat HF in adult patients with PWS.

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