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Complex therapeutic approach in a child with syndromic morbid obesity and acute heart failure

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Abstract. We report a case of a three years old child, a boy with acute heart failure associated at a rare complex genetic disorders characterized by severe obesity and hypotonia. The treatment consisted of acute phase diuretics and cardiotonic drugs, followed by chronic angiotensin-converting-enzyme (ACE) inhibitor (Enalapril) and an aldosterone inhibitor. The child recovered within a few days and remained clinically stable, with improvement of clinical, EKG and echocardiographic parameters at 2 and 6 - month follow-up.
Key words: child, severe obesity, acute heart failure, ACE-inhibitors.

Introduction. Prader-Willi syndrome (PWS) is a complex multisystem rare genetic disorder, with population prevalence at about 1 in 50,000, and it is the most frequent cause of syndromic obesity. A variety of phenotype features including severe neonatal hypotonia, hyperphagia and childhood-onset morbid obesity, short stature, hypothalamic hypogonadism, dysmorphic features, developmental delay, learning difficulties, behavioral and psychiatric problems characterize this syndrome. The affected persons have high rates and varied causes of morbidity and mortality throughout the natural history of the disease(Gunay-Aygun et al 2001; Goldstone et al 2008; Odent et al 2008). Death in patients with PWS takes place from teenage years into the 20s, 30s, and beyond. It is mostly often obesity related, due to cardiorespiratory failure, cor pulmonale exacerbated by obstructive and central apneea, septicemia due to skin infections and pneumonia (Marzullo et al 2007; Goldstone et al 2008).

In the followings we describe a case of a 3-year-old boy with PWS, a diagnose that has been established since the age of 9 months. The PWS diagnosis was confirmed by DNA methylation-specific technique, which was applied on the SNURF-SNRPN imprinted genes locus on chromosome 15q11-q13. The child has been treated since the age of 20 months with a gradually increased s.c. dose of human recombinant growth hormone (GH) up to the standard replacement GH dosage of 0.93 – 1 mg/m^2/d corresponding to 0.034 mg/ kg bw/d. The monitoring of clinical effects of GH therapy showed a progressive reduction of hypotonia, increase of muscular mass and physical strength and improvement of the motor skills with the independent walking at 26 months of age. In the second year of GH therapy (after 16 month of hormonal treatment) a routine clinical and laboratory assessment at the age of 3 years (September 2009) noted the characteristic feeding behavior with hyperphagia and permanent hunger. We obtained relevant child's nutritional history of unbalanced, high-fat, high-calorie diet and increased food supply. The unbalanced diet was determined by the lack of compliance by parents to dietetic recommendations during the last 6 months. Anthropometrics evaluation showed accelerated growth velocity with a sharp increasing of height during first 6 months of the GH therapy and of body weight and body mass index (BMI) during the last 6 months (Table 1). An increase of BMI with at least 5.5 units (28 kg/m^2 vs.

previously value of 22.5 kg/m^2) and a weight-for-height index of 183 (normal value < 110) were noted as measures of severe obesity. Other clinical findings at physical examination revealed respiratory and cardiac failure, manifested by dyspnea, tachypnea (48 breaths/m), facial and peripheral edema, perioral cyanosis, tachycardia (140 bpm), hepatomegaly, and decreased physical activity level. Systolic and diastolic blood pressure, as interpreted according to age, gender, and height, were in the upper normal limits.

Table 1

Dynamic changes of the anthropometrics and Astrup parameters under complex therapeutic intervention during three months of follow-up

Anthropometrics					*Astrup parameters**	
	A		*B*		*A*	*B*
Parameter	Child's values	Normal	Child's values	pH	7.39	7.31
Height (cm)	106	94	107.5	PO_2 (mmHg)	33.3	100.7
Z Score (SD)	+3.37	+2	+3.16	SaO_2 (%)	62.8	96.9
Weight (kg)	31	18.4	22	pCO_2 (mmHg)	61.4	40.9
WHI	183	110	125.7	HCO_3 (mmol/L)	37.7	20.6
BMI (kg/m^2)	28	18.2	19.03	CO_2(mmol/L)	39.7	21.8

Columns A and B - refer to evaluation from 36 and 39 months of age respectively
* In the room's air

Several parameters were considered as components of an obesity hypoventilation syndrome present in this child: associated hypersomnolence, daytime sleepiness and sleep-disordered breathing characterized by noisy breathing, snoring, repeated episodes of apnea, choking episodes, and frequent awakenings.

Respiratory failure, a common characteristic of acute heart failure (HF) in childhood, was documented by low oxygen saturation measured by pulse oximetry and Astrup parameters. Recorded date showed elevated serum bicarbonate levels, due to metabolic compensation for respiratory acidosis and increased peripheric blood partial pressure of CO_2 as the sign of hypercapnia.

EKG demonstrated abnormalities such as sinus tachycardia, signs of right heart strain with right atrial enlargement. The changes, suggestive of cor pulmonale, have been found, including rightward P-wave axis deviation, an S_1Q_3 pattern, and right bundle-branch block (Figure 1). A chest radiograph showed cardiomegaly and increased pulmonary vascular markings. The echocardiographic evaluation, which consisted of 2-dimensional echocardiographic and Doppler evaluation, identified dilated cardiomyopathy and signs of severe pulmonary hypertension (PH), normal left ventricular function and tricuspid valve regurgitation grade 3.

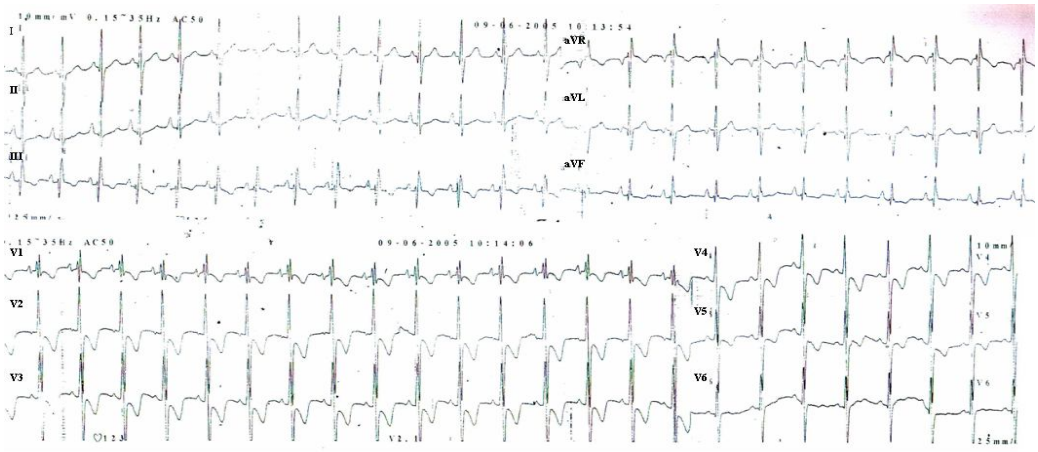

Figure 1. EKG changes associated with clinical signs of acute cor pulmonale.

Laboratory testing revealed normal serum creatinine and raised blood urea nitrogen and transaminases. The rapid deterioration, based on HF signs and symptoms, attributable to right ventricular dysfunction, required urgent therapy in order to relieve symptoms, reduce intracardiac pressures and improve cardiac performance. Oxygen and an intravenous diuretic with short onset and duration of action, loop diuretic Furosemide, in dose of 1 mg/kg bw/d were administered immediately. An i.v. inotropic agent, Digoxin in a dose of 0.02 mg/kg bw/d was associated. After six days of emergency therapy, the vital signs and lab results improved or normalized. A chronic therapy was initiated with a short-acting angiotensin-converting-enzyme (ACE) inhibitor, Enalapril, with an initial dose of 0.1 mg/kg. Previously s.c. dose of GH of 0.8 mg/day was maintained and the ACE inhibitor was titrated during the following weeks to the target dose of 1.25 mg per dose. Because of the fluid retention signs presented at the time of HF diagnosis, we associated an aldosterone antagonist, Spironolactone. Blood pressure, renal function, and serum potassium measurements have been repeated 1 week after initiation of treatment and again 1 week after each significant increase in dosage. The dietary recommendations of 60% of a daily recommended calorie intake for age were reinforced. The child remained clinically stable. Subsequently monitoring consisted in pediatric, endocrinologic and cardiologic evaluation at three month interval. Constant decrease in body weight, smaller height growth velocity, progressive clinical, EKG and ecographic improvement were noted at two last hospital readmission (Figure 2).

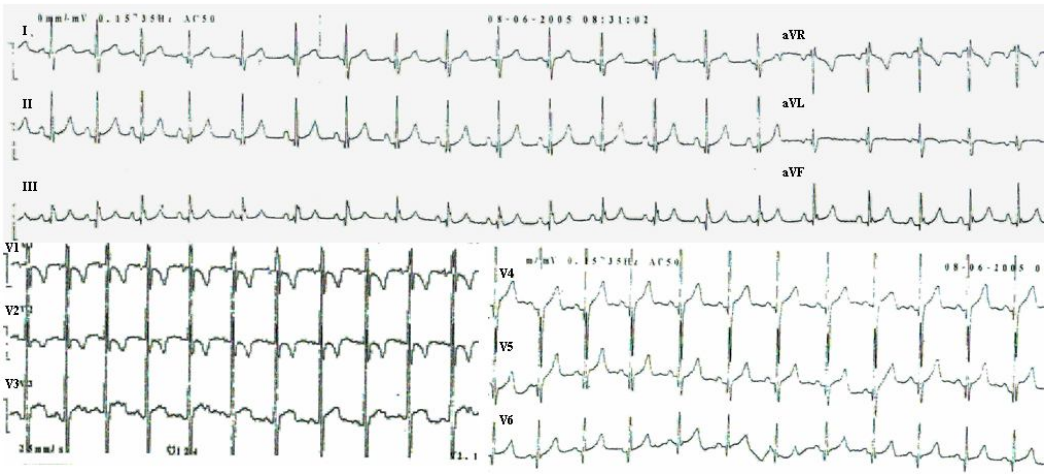

Figure 2. EKG findings after three months of ACE-inhibitor and diuretic therapy.

Discussion. HF has reached epidemic proportions in adults. Each year more than 1 million patients are hospitalized for a primary diagnosis of HF, now the most common discharge diagnosis among the elderly. Advances in the recognition and treatment of acute HF in adults have brought a growing awareness of the lack of insight for similar clinical situations in pediatric patients (Gheorghiade et al 2005; Macicek et al 2009).

HF in this patient diagnosed with PWS evolved with a preserved left ventricular ejection fraction (HFPEF), which is more common in obesity. There is a paucity of evidence-based therapy in acute HF in general and in HFPEF (Voelkel et al 2006; Zannad et al 2009). Loop diuretics work by blocking the sodium–potassium chloride transporter in the ascending loop of Henle and are the diuretics of choice in patients with concomitant renal dysfunction. There are no data on the safety and efficacy of angiotensin-converting enzyme (ACE) inhibitors when used early in acute HF (Gheorghiade et al 2005; Macicek et al 2009; Weintraub et al 2010).

Because of the characteristic features of acute HF at presentation and unpredictable outcome of a difficult medical condition as complicated obesity hypoventilation syndrome with PH and acute cor pulmonale, complex therapeutic approach was used in this case. In general, for a patient admitted for an acute episode of

HF, readmission rate and mortality are very high. The immediate post-discharge period is the most vulnerable period (Zannad et al 2009). There is evidence supporting the notion that continuous diuretic therapy is needed for chronic therapy (Weitzenblum 2003).

Renine–angiotensin–aldosterone system (RAAS) is one of the major mechanisms in transition from risk factor to overt HF as well as of the progression of the disease and its lethal complications. Therefore, RAAS inhibitors may be useful at different stages of the disease (Shibata et al 2008; Zannad et al 2009). ACE inhibitors are indicated throughout the spectrum of HF to preserve systolic function. They prevent the onset of HF better than calcium channel blockers, diuretics and first-generation beta-blockers. In real life, ACE inhibitors are under prescribed, and/or prescribed at smaller than optimal doses. It is still a challenge to apply this therapy to the majority of patients (Shibata et al 2008; Zannad et al 2009; Weintraub et al 2010). Diuretics should be used in combination with ACE inhibitors on the assumption that the latter will suppress the adverse neuroendocrine effects of the diuretic. Blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with severe heart failure (Zannad et al 2009; Pang et al 2010; Coons et al 2011).

Cor pulmonale plays an important role in the morbidity and mortality of patients with PWS. Among several other complications, such as systemic hypertension, cardiovascular disease, cor pulmonale may be caused by obstructive sleep apnea syndrome (OSAS). OSAS also may be caused by obesity, sticky saliva, kyphoscoliosis, or adenotonsillar hypertrophy in combination with the narrow upper airways (Goldstone et al 2008; Wijngaarden et 2009).

A complex pathogenetic mechanism of cardiovascular complications in our patient may be discussed. Respiratory muscle weakness and abnormalities in lung and chest wall compliance lead to reductions in vital capacity. Pulmonary hypertension (PH), a severe condition characterized by a progressive remodeling of small pulmonary arteries leading to elevated pulmonary vascular resistance and right ventricular failure, is frequently detected in patients with disorders of ventilatory control, including sleep apnea syndromes and obesity hypoventilation syndrome (Yuan et al 2005; Humbert et al 2006; Hernández-Díaz et al 2007; Humbert 2008; Ohno et al 2008).

PH in this case is likely the result of multiple factors including pulmonary vasoconstriction caused by alveolar hypoxia, acidemia and hypercarbia. The hypoxic pulmonary vasoconstrictor response is an important adaptive mechanism in human physiology, shunting blood away from hypoxic regions toward better-ventilated areas of the lung, thus improving ventilation-perfusion matching within the lung. Hypoxemia itself may lead to renal vasoconstriction, reducing urinary sodium excretion and also leading to edema. Acidosis increases pulmonary vascular resistance and acts synergistically with hypoxia (McGoon et al 2004; Yuan et al 2005; Han et al 2007).

The primary goal of GH replacement therapy is to promote linear growth in children. GH also has other important physiological functions influencing several key metabolic processes. The aims of GH treatment in children with PWS are to improve growth during childhood, adult height, and body composition (Lipshultz et al 2005; Goldstone et al 2008). Three years of GH therapy significantly increased our patient height and height *z* scores, but it controlled less the body weight growth, partially because of a less than rigorous parental involvement in diet management of their child.

In PWS, GH therapy may improve some cardiovascular features of the disease, particularly cardiac mass, body composition, and some markers of cardiovascular risk (Carrel et al 2002; Lipshultz et al 2005). However, GH therapy did not affect left ventricle diastolic and systolic function, and individual signs of deterioration in right ventricle function should be taken into account and warrant an appropriate surveillance. In addition, during GH treatment, close monitoring of clinical effects, particularly sleep apnea and avoiding high IGF-I levels should consider. The benefits of starting GH treatment as early as 2 years are well established, but there is increasing evidence of additional benefit in starting therapy between 6 and 12 months of age, particularly in terms of motor development, muscle, head circumference, and possibly cognition. A recent review including 64 children on GH treatment suggested a high-risk period of

death during the first 9 months of GH treatment (Carrel et al 2002; Lipshultz et al 2005; Goldstone et al 2008).

Obesity management involves environmental control with early institution of a low-calorie, well-balanced diet, with regular exercise, and rigorous supervision and restriction of access to food.

Appropriate consultation with cardiologists and pneumologists in severely obese individuals is essential. Use of continuous positive air pressure and nasal intermittent positive pressure ventilation may be beneficial, but oxygen should be used cautiously because of the risk of hypoventilation with reversal of chronic hypoxia (Shahar et al 2001; Atwood et al 2004).

Conclusions. Our report suggests the need for adequate monitoring of the cardiopulmonary function during GH therapy in patients with PWS. An integrated multidisciplinary approach is necessary in order to facilitate early diagnosis, optimize management, improve quality of life, prevent complications and prolong life expectancy of these patients.

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