Prader-Labhart-Willi syndrome

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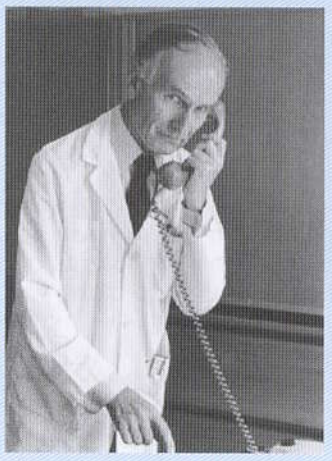
Introduction

Prader-Labhart-Willi syndrome (PWS), first described in 1956 *(Fig. 1)* [1], is a complex multisystemic congenital disorder associated with an abnormality of genetic material on chromosome 15 [2]. It is characterized by reduced fetal activity, infantile hypotonia, and failure to thrive in infancy, followed by the emergence of hyperphagia and the development of severe obesity in childhood [2]. Also characteristic of PWS are developmental and speech delays/cognitive dysfunction, cryptorchidism, hypogenitalism/hypogonadism, a particular facial appearance (narrow forehead, almond-shaped eyes, triangular mouth) that is present at or soon after birth, short stature, small hands and feet, strabismus, and behavioral and psychological problems including compulsive behavior and skin-picking *(Figs 2 and 3)* [2–4]. The multiple clinical abnormalities associated with PWS suggest an underlying dysfunction in several hypothalamic centers, including those concerned with energy balance, temperature regulation and secretion of pituitary hormones, including gonadotropins, GH and possibly ACTH [5–7].

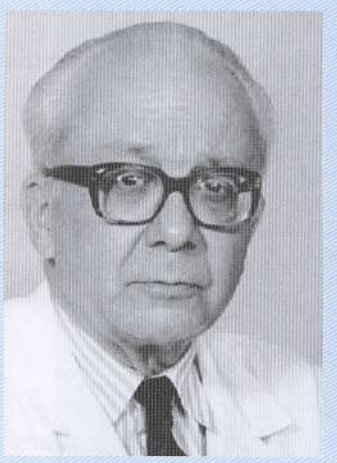
The prevalence of PWS has been estimated at 1 in 15,000–25,000 births [8, 9]. In one population-based study in the United Kingdom, the birth incidence of PWS was estimated at 1 in 22,000 and the death rate at 3% annually [9]. Until the early 1980s, death due to cardiorespiratory complications of morbid obesity often occurred in mid- to late adolescence, but, in recent years, life expectancy has been extended as improved methods of management have been developed. Respiratory complications, however, remain a major source of morbidity, and nearly 50% of people with PWS across all age groups have a history of recurrent respiratory infections [10].

Hypothalamic obesity and hypoactivity make it difficult to prove GHD

Since the 1990s it has been known that the GH response to insulin, arginine, clonidine and L-dopa in PWS were low-normal or blunted, as were sleep-induced GH secretion and 24-h integrated GH concentrations [3, 11]. Simple obesity is also known to be associated with a decreased circulating concentration of GH, and spontaneous 24-h GH secretion in PWS turned out to be low and similar to that of healthy obese controls [12].



Alexis Labhart



Andrea Prader

Heinrich Willi

Fig. 1: Andreas Prader, Alexis Labhart and Heinrich Willi.

Fig. 2: Six-month old infact with distinct hypotonia.

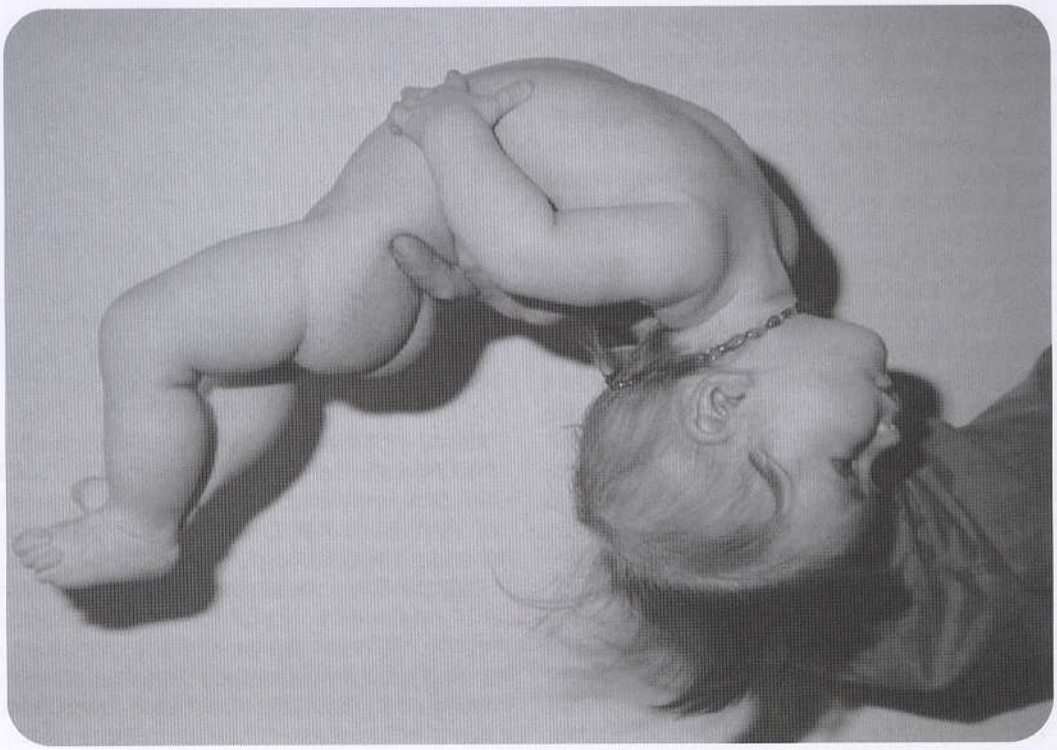
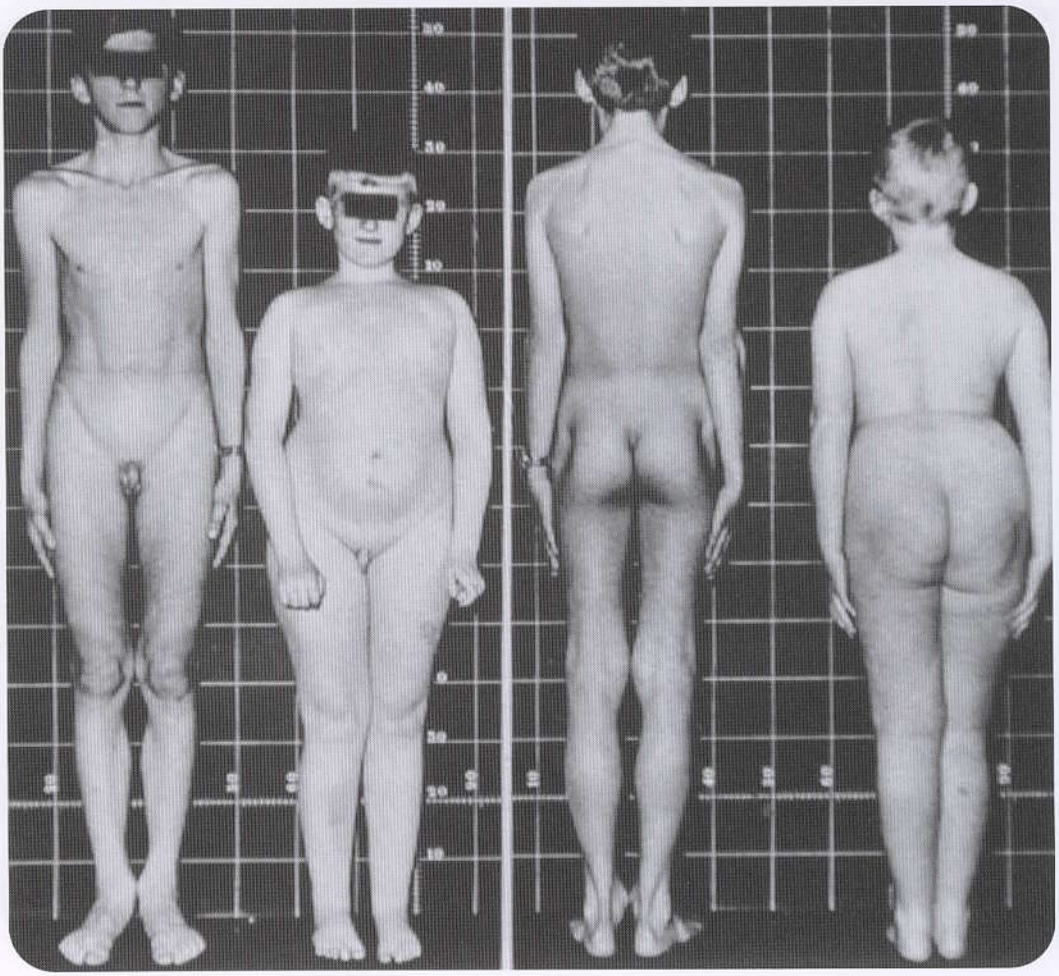


Fig. 3: Thirteen-year old twins, the boy on the right side with PWS.



However, GH secretion in simple obesity is not disturbed but downregulated, and is fully reversible by weight loss. Therefore there is some controversy as to whether insufficient GH secretion in PWS is the consequence of obesity or whether it represents genuine GHD due to hypothalamic dysfunction *(Table I)*.

In order to explore the presence or absence of GHD in PWS, we published in 2000 a comparison of the clinical and biochemical aspects of PWS with those of non-syndromal obesity and GHD without PWS [13]. The aim was to identify arguments for the presence of genuine GHD as part of PWS. Decreasing growth velocity in spite of onset of obesity, reduced lean body mass in the presence adiposity, small hands and feet, relatively low IGF-I and low insulin levels, as well as the dramatic effect of GH treatment on growth velocity were arguments that supported the presence of hypothalamic GHD in PWS. The article remains valid and is still cited and downloaded. Even though it may be difficult ultimately to prove GHD in PWS because of obesity-induced effects on GH secretion, many papers continue to confirm that GHD independently accounts for several features of PWS and that GH therapy dramatically changes the phenotype of PWS in childhood. Height and weight become normal and there is a sustained impact on the net loss of body fat *(Fig. 4)*. However, GH therapy is unable to completely normalize body composition even though fat mass decreases and lean mass increases to some extent with treatment [14].

- Children with PWS are short in contrast to children with non-syndromal obesity
- Catch-up growth under human GH in PWS is comparable to that in GHD
- Hands and feet are short in PWS, as they are in GHD
- Lean mass is decreased both in PWS and GHD, in contrast to non-syndromal obesity
- IGF-I is lower in PWS than in normal obesity
- Insulin secretion is decreased in PWS, as in GHD

Table I: Six arguments to support the presence of hypothalamic GHD in PWS [13].

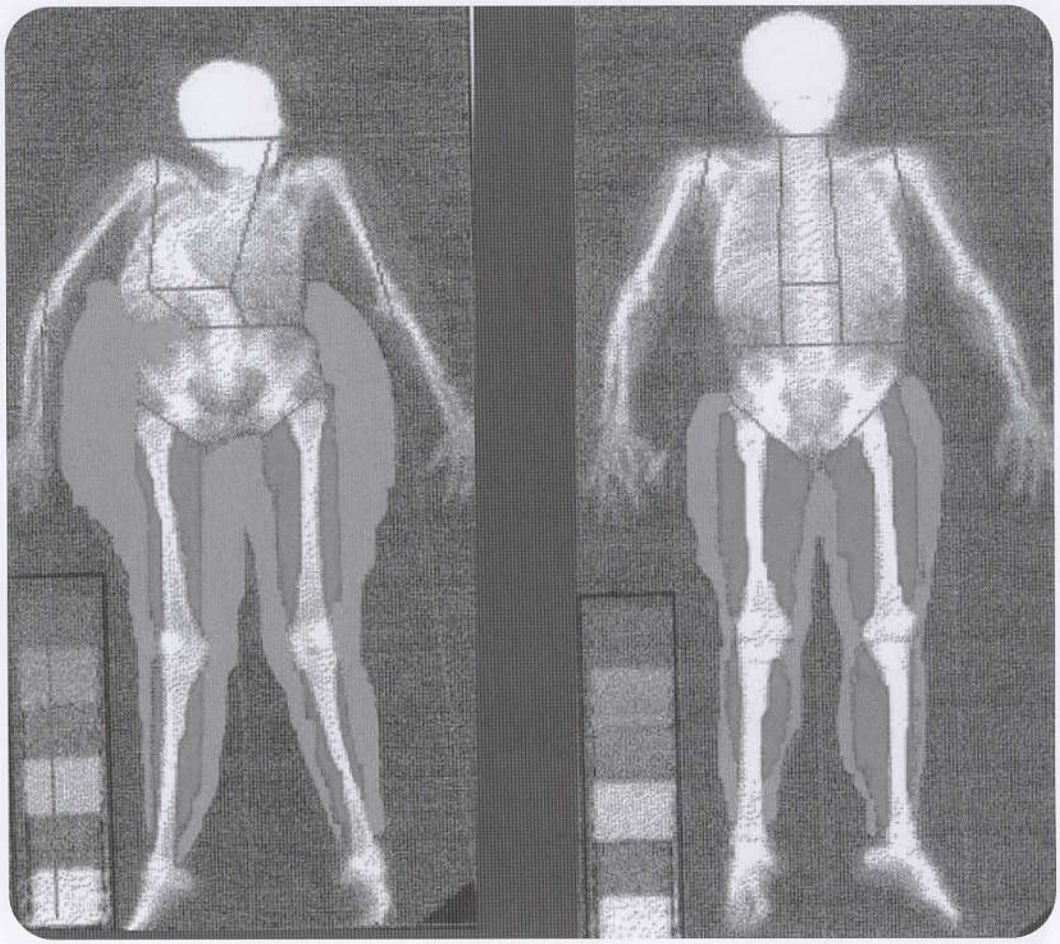


Figure 4: DXA scan. Left side patient with PWS, right side normal obesity. Fat in blue, muscles in red. Despite of a huge amount of fat in PWS, muscle mass is clearly reduced compared to normal obesity in which muscle mass is known to be increased compared to non-obese healthy individuals.

Why do fat mass and lean mass not normalize with GH treatment?

Greatly reduced spontaneous activity is one of the main symptoms of PWS and was mentioned in 1956 by Prader et al. [1]. Spontaneous activity was later found to be reduced to less than 50% of that of normal control children despite long-term GH treatment and in the absence of severe obesity [15]. From the fact that during training of the calf muscle, calf circumference increased, and calf skinfold decreased significantly in children with PWS as in healthy controls, we deduced that muscle mass in PWS adequately responds to enhanced physical activity. This points to diminished spontaneous physical activity as the primary cause for decreased muscle mass in PWS. In addition, spontaneous physical activity increased threefold at the end of a training program [15]. It seems therefore possible to increase muscle mass and spontaneous physical activity and improve physical capacity by means of a short daily physical training program.

Would gonadal hormones increase muscle mass further?

As consequence of hypogonadism, sexual maturation stops at mid-puberty and fat mass further increases during the early stages of puberty, even with GH treatment. The absence of a pubertal growth spurt and an insufficient increase in muscle mass during puberty [3, 5] further reduce the already decreased energy expenditure [16, 17]. Hence hypogonadism contributes to fat accumulation and morbid obesity due to the lack of pubertal muscle mass accretion in PWS males. Only when hCG was added did fat mass stabilize, most likely as a consequence of the normalized muscle mass *(Fig. 5)* [18].

We chose hCG injections to mimic physiological development and prevent significant fluctuations in testosterone levels, because anecdotal reports suggested that behavioral problems deteriorated during testosterone treatment in PWS patients and increased the risk of psychotic exacerbation. However, no study has examined whether hCG therapy carries a smaller risk in this regard than testosterone. The myth that gonadal replacement may lead to more aggressive behavior and aggravate temper tantrums was not confirmed by our observations. We think that in all PWS boys with hypogonadism, adequate replacement therapy should be started when gonadal maturation is absent or stops at the age of 13–14 years. However, it should be borne in mind that adolescence is a critical period in PWS [19], with psychotic episodes occurring in one-fifth of young adults [20, 21]. Even in healthy men, testosterone in high doses may induce psychotic disorders [22]. Sex hormone replacement in PWS patients must therefore be under the control of an experienced clinician.

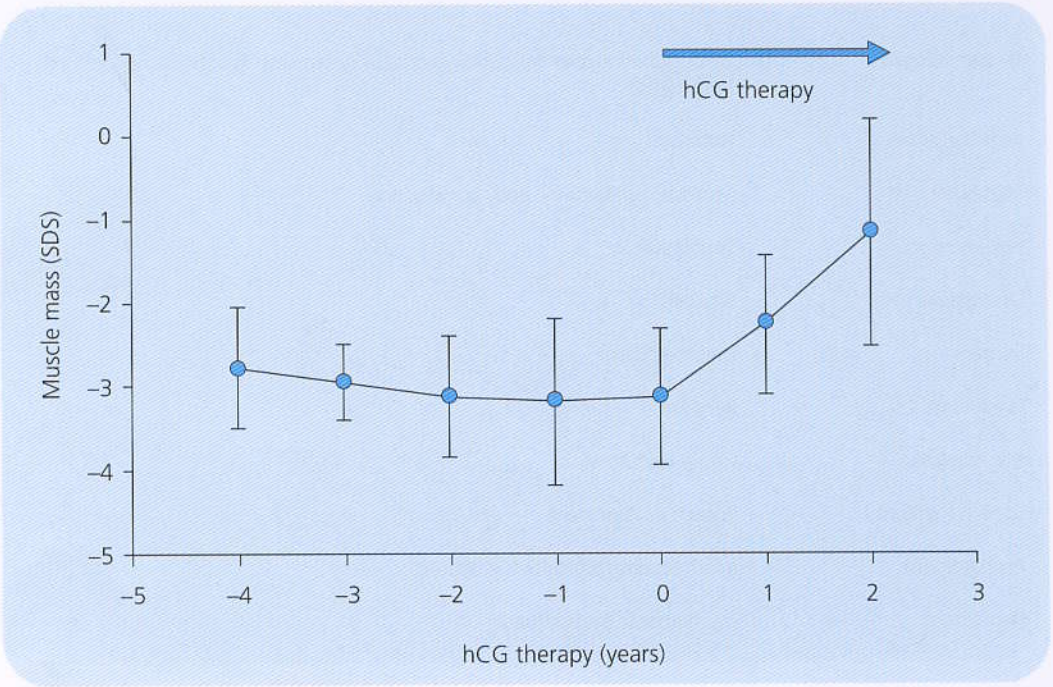


Figure 5:Increasing muscle mass SDS in male PWS patient after starting hCG treatment. Adapted from [18].

Normalization of muscle mass increases quality of life in PWS, but what else is needed beyond hormone replacement?

PWS is a complex syndrome. This is illustrated by the numerous specialists usually required to treat the same patient *(Table II)*. It is very difficult and harmful for patients and their families if any member of this specialist orchestra plays his or her melody without regard for the other instruments and their melodies. Parents may feel bewildered by the different specialists and numerous separate appointments, by hearing many different explanations and sometimes contradictory comments. Patients' quality of life may be severely impaired, due to limited family resources, by unnecessary investigations. It is desirable for one person to take charge and assume the role of case manager with the support of his or her colleagues and the child's family.

In most countries, pediatric endocrinologists have a privileged long-standing relationship with the families and children with PWS. It is therefore a duty of the endocrinologist to assume the leadership as case manager and protect the children and their families from too many investigations and routine visits. S/he should also act as counselor to the family and provide continuing education about PWS as well as explain each symptom in its correct pathophysiological context.

If the parents have unrealistic expectations, they should be told of this. At present, all adults with PWS live in care homes or with their parents, irrespective of their IQ and/or quality of care received during childhood. Unfortunately, there are no astonishing new findings that will change this inevitable outcome. Irrespective of treatment, even adults with PWS must be supervised 24 h a day in order to prevent obesity. Parental unrealistic expectations may transform into unrealistic expectations placed on the teenager with PWS and may promote a catastrophic outcome in the form of psychosis and depression. It is hard work facing these families in an honest way — not just once, but repeatedly, from the birth of the baby through to adulthood. Clearly, only experienced clinicians should be in charge of families with a PWS child, and not inexperienced doctors still undergoing training. These visits take much more time and demand much more experience, knowledge and engagement/empathy than, for instance, a visit by an average child with isolated GHD who is otherwise healthy.

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Endocrinologist	GHD, gonadotropin deficiency, hypoactivity, hyperphagia, body composition, bone density
Nutritionist	Nutrition
Physiotherapist	Scoliosis, hypoactivity, body composition
Pneumologist	Ventilation
Orthopedist	Scoliosis
Surgeon	Cryptorchidism
Psychiatrist	Behavior
Psychologist	Family resources
Speech therapist	Speech development
Perinatologist	Infant feeding difficulties, diagnosis
Neurologist	Psychomotor development

Table II: Complexity of PWS demands many specialists to care for each patient.

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