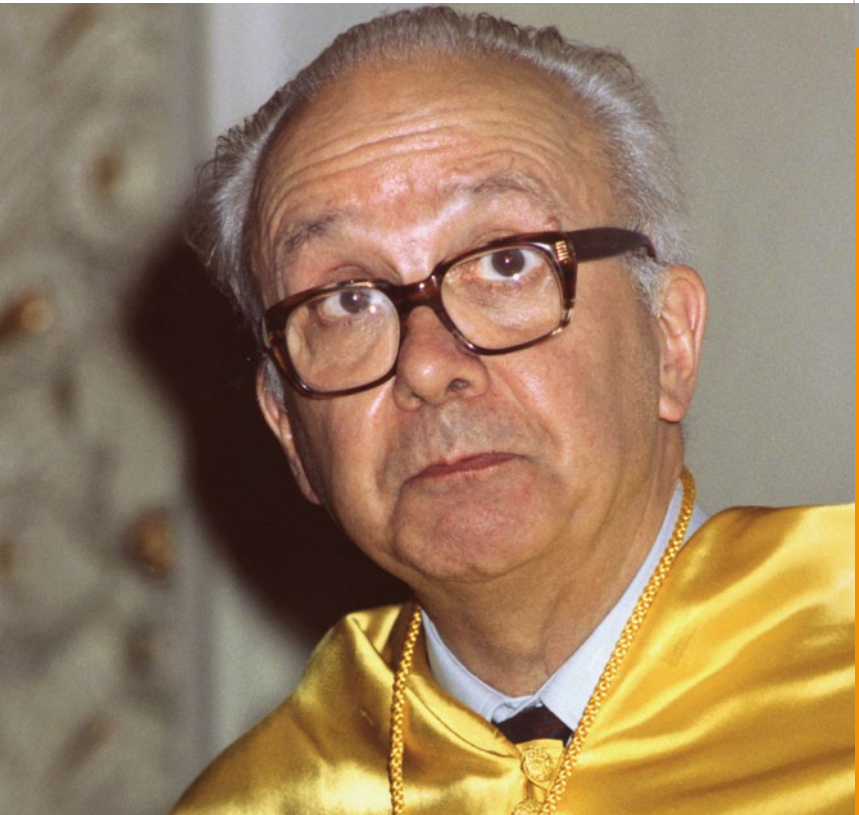
SWISS SOCIETY OF NEONATOLOGY

Prader-Willi-Labhart syndrome



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Title image: Andrea Prader (1919-2001)

This female infant was born at 38 0/7 weeks gestation to a 33-year-old G2/P2 by Cesarean section secondary to progressive IUGR. No resuscitation was required at birth. She weighed 1760 g (P < 10) with a length of 43.5 cm (P < 10) and a head circumference of 32 cm (P 10-50).

On examination, we found the newborn to be floppy with central muscular hypotonia and no suck reflex (Fig. 1). We also noted that she had a narrow bifrontal diameter of the head (Fig. 2). The remainder of the physical examination was unremarkable.

On further questioning the mother told us that she had felt decreased fetal movements during pregnancy. Family history was negative. The following days, persistant hypotonia and a weak cry were noted. The child showed no resistance to having blood taken. She was also unable to take oral feeds and had to be fed by NG tube.

Laboratory results as well as ultrasound and MRI of the brain were unremarkable. The ophthalmologist noted a fundus with little pigmentation. DNA analysis confirmed the suspected Prader-Willi-Labhart syndrome and the marker on chromosome 15 showed maternal disomy.

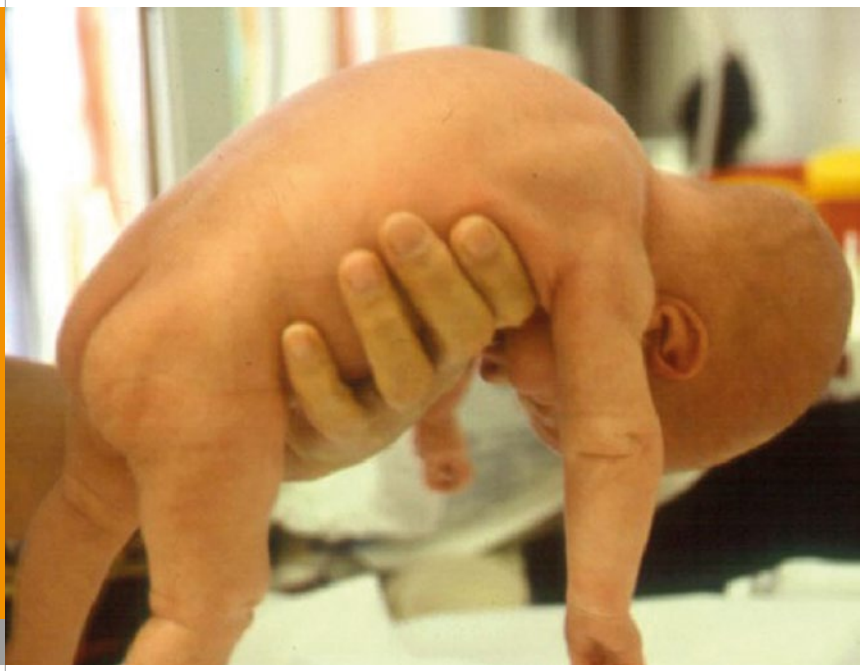

Fig. 1

Poor muscle tone.

Fig. 2

Narrow bifrontal diameter of the head, almond shaped eyes.

DISCUSSION

Prader-Willi-Labhart syndrome (PWS) was first described in 1956. The characteristics that the authors described were growth retardation, muscular hypotonia in infancy, mental retardation, cryptorchidism and voracious appetite with obesity.

In 95% of PWS cases, the deletion of 15q is found to be paternal in origin, 70% of these are deletions, in 20-25% this occurs due to maternal disomy and in 2-5% due to methylation-defects. Very few cases result from a new translocation or duplication.

70% of PWS cases are due to a deletion at 15q11-13 inherited from the father. Deletion of the maternal 15q11-13 results in Angelman syndrome. This phenomenon, whereby genetic material is expressed differentially depending on wheather it is paternal or maternal, is called genomic imprinting (Fig. 3).

In 20-25% of the patients, PWS is the result of maternal disomy of chromosome 15, this means both chromosome 15 are maternal in origin (Fig. 4). In some instances both apparently intact maternal chromosomes were present (heterodisomy) and in other instances two copies of the same maternal chromosome were present (homodisomy). In Angelman's syndrome the phenomenon of uniparental paternal disomy has been reported in 5% of cases.

Clinical features during fetal and neonatal life include:

decreased fetal movements, poor feeding/tube feeding, abnormal/no cry, axial hypotonia/limb dystonia, genital hypoplasia and cryptorchidism, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thinner upper lip, down-turned corners of the mouth.

The following signs are characteristic during infancy and aerly childhood: failure to thrive, developmental delay, delayed speech, fair hair/blue eyes (poor pigmentation in 75%).

Later on, during childhood and adolescence, the following features can be noted: voracious appetite, obesity, short statue (final height in females 147 cm, in males 155 cm), scoliosis (95%), small hands and feet, temper tantrums, mental retardation (average IQ 62), delayed/incomplete secondary sexual development, sleep apnoe, diabetes mellitus, behavioural problems

Physiotherapy, logopedics and growth hormones are effective therapies, whereas appetite suppressants or gastric banding have not been shown to be effective.

Patients with PWS suffer from gonadotropin deficiency. Most PWS patients have short stature and a decreased lean body mass and increased body fat. They also have a low-normal or blunted GH response to clonidine, arginine or insuline and sleep-induced GH secretion and a decreased 24-hour GH secretion. Therefore, it has

been assumed that there is an additional deficiency in GH. However, obesity itself can result in low levels of GH. Facts that support the theory of a GH deficiency (GHD) in PWS are: 1) IGF-1 (insuline-like-growth-factor) is increased in obese patients whereas in PWS and GHD-patients it is decreased, 2) PWS-patients treated with GH show an acceleration of their growth velocity and the final height prediction reaches the parental target height range. Observations that do not support GHD are: 1) PWS-patients do not have a delayed bone maturation and 2) that PWS-patients show a slow growth velocity for the first 3 years of life but a normal growth velocity thereafter.

There is a decreased life expectancy because of obesity and its complications; years ago, most patients did not live into their forties; nowadays, most patients live into their sixties. Patients with uniparental disomy have a milder phenotype and better cognitive abilities.

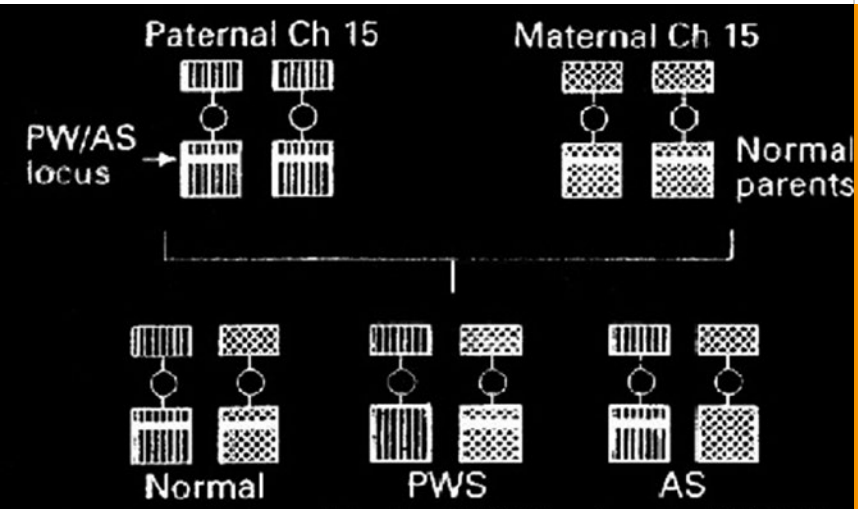

Figure 1 Deletion of Prader-Willi/Angelman's (PW/AS) locus resulting in Prader-Willi syndrome (PWS) or Angelman's syndrome (AS) according to the parental origin of affected chromosome.

Fig. 3

Genomic imprinting.

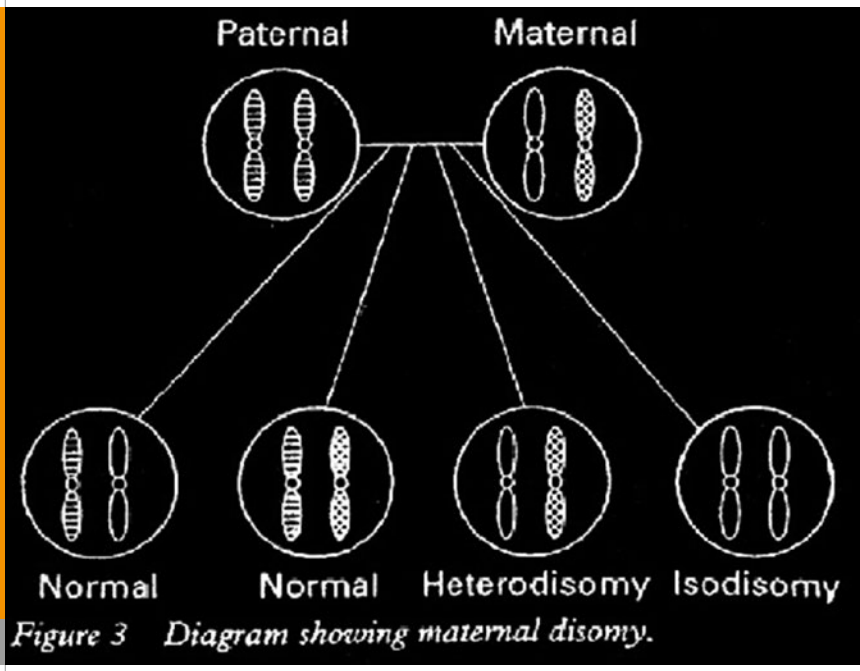

Fig. 4 *Figure 3 Diagram showing maternal disomy.*

Maternal disomy.

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2. Eiholzer U. Prader-Willi syndrome. Effects of human growth hormone treatment. In: Endocrine Development (Savage MO, editor), Vol. 3 (2001), Karger AG, Basel, Switzerland

3. Relevant internet links: www.medgen.unizh.ch and *www.prader-willi.ch*

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