Case Number 16
Prader-Willi Syndrome

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Case summary:

Demographic details:
Ms. LS, female
Referred from: Children's Out-patients

Ms. LS is a three-year old girl, suffering from Prader-Willi Syndrome, a rare genetic disorder with characteristic, easily recognisable dysmorphic features. She was seen at Children's Out-patients as part of a follow-up regimen, performed every three months. This consultation was held on the 3rd October, 2012 and another one was planned for the 5th of January, 2013.

The clinical picture of developmental signs and symptoms are very characteristic and early diagnosis is beneficial for the anticipation of complications, reduction in unnecessary investigations and improved prognosis.

Presenting complaint:

The main complaint was the insatiable hunger of the child and her unusual food-seeking behaviours, such as binge eating. The mother was aware from beforehand that this might happen. During their discussion, the mother was asking the doctor on how to approach the child and what sort of diet she should provide her with.

History of presenting complaint:

Ms. LS had experienced increased appetite for the past one and a half months. She increased her food portion size and the frequency of meals. Her mother noticed that the child was putting on weight more rapidly than usual and decided to be more stringent with meal times and snacks. A week prior to the consultation, the mother found her daughter eating food from the garbage bag.
On observation and examination, the child weighed 15.1kg and her height was 85.7 cm.

Past antenatal and perinatal history:

Ms. LS was born to a 35-year-old primagravida, blood group O positive mother, at 29 weeks gestation on the 28th of September, 2009. She was delivered via an emergency lower segment caesarean section under general anaesthesia, after a persistent history of intra-uterine growth retardation. The estimated date of delivery was on the 12th of December of the same year. Her birth weight was 870 grams.
The paediatric patient had a cephalic occipito-anterior presentation, the liquor was clear and no abnormalities in the placenta were detected but it was sent for histology.
The baby girl had an Apgar score of 6 in the first minute and on ventilation she improved it to 10, after 5 minutes.

The Apgar Score:

Apgar Score Criteria	After 1 Minute	After 5 Minutes
Heart Rate	2	2
Respiratory effort	1	2
Muscle tone	1	2
Reflex irritability	1	2
Colour of skin	1	2
TOTAL SCORE	6	10

Table 1: The Apgar score during the first minute and first five minutes post-delivery. The child was ventilated between the end of the first minute and the end of the fourth minute

The baby was transferred to the Neonatal and Paediatric Intensive Care Unit for elective intubation with an endotracheal tube and ventilation with surfactant. Neonatal examination showed a patent anus. Thyroid and thallassaemic screens were taken and results were normal.

During her first day, Ms. LS was kept on the ventilator and fluids were pushed in. Urgent blood tests were organised. A complete blood count (CBC), urea and electrolytes (U&E), random blood glucose and arterial blood gases, blood cultures and surveillance swabs and a cross match were taken. These were drawn through an umbilical artery catheter at the level of T7. The young girl was anaemic and was transfused. Her blood group is A positive and she received group O positive blood. Her random blood glucose was 22.6 mmol/L and she was put on an insulin infusion of 0.1mg/hour. Her pH level was 7.3.

A chest X-ray was performed. The lungs had a ground glass appearance and the endotracheal tube and umbilical catheter at the level of T7 were seen.

Soon after, the baby girl, was prescribed and administered cefuroxime (25mg, 12 hourly, intravenously), as prophylactic antibiotics in the light of her vulnerable preterm state and being on the ventilator. B2P (45mg, 12 hourly, intravenously) and Vitamin K (0.3mg, stat, intramuscularly). These two drugs were given as supplements to prevent vitamin deficiency bleeding.

On day 2, the baby had her arterial blood gases rechecked and a decision to extubate her was taken. She was put on nasal continuous positive airway pressure. Naloxone (0.09 mg, one dose, intramuscularly) an opiod inverse agonist, was added to her drug chart.

Up till day 3, the baby girl had never opened her bowels. On examination, the child had depressed fontanelles, her capillary refill time was three seconds and the pubes were palpable. Chest movements were symmetrical with minimal recessions. The abdomen was soft. The plan was to continue on nasal continuous positive airway pressure, keep the intravenous fluids and switch to total parenteral nutrition, have her bloods repeated and maintain the first line antibiotics for 10 days. The child was also given caffeine and exposed to phototherapy for early signs of neonatal jaundice.

On day 4, the child was clinically pink and well perfused. She had no signs of oedema. A decision to restrict her fluid intake was taken in review of a patent ductus arteriosus. The established fluid intake was 120mls/g/day and total parenteral nutrition at 2mls per hour. 20 ml of packed cells were given over 4 hours. Intravenous infusions were stopped. Standard dopamine (1ml/hour) was started and insulin infusion was continued at 0.3ml per hour. In view of her deterioration in blood gases (Ph- 7.18, pO2- 63.6, pCO2- 2.53, HCO3- 17.6.), the patient was intubated via an uncuffed endotracheal tube. Phototherapy was continued.

An atrial septal defect and a patent ductus arteriosus were found.

Past medical and surgical history:

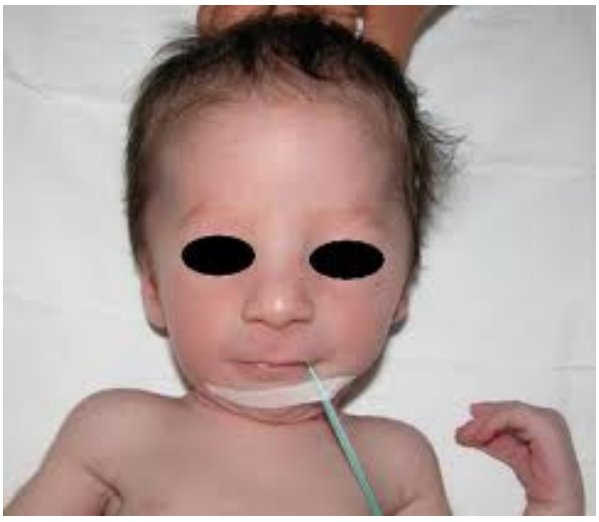
Past medical history:

During the period from 18.11.2009 to 17.12.2009 there was persistent hypotonia complicated by an episode of aspiration pneumonia. The hypotonia was such that there was no:

a) reaction to touching stimuli
b) rooting reflex
c) gaping reflex
d) sucking reflex
e) gagging reflex

The child was provided with a pacifier to stimulate the sucking reflex.

On January 7th, 2010, genetic testing excluded mytonic dystrophy Type 1 and established a karyotype of 46 XX. At the age of 4 months and 22 days, on examination, the child had a box-like face reminiscent of Prader-Willi Syndrome (PWS). The infant had good peripheral/abdominal tone with very good limb reflexes but still decreased central tone. By the age of 7 months, the girl was weaned off on solids and her weight went up to 4 kg. Parents claimed that the child is sleeping for more than usual.



Picture 1: A photograph of a three month old Prader-Willi affected child, already showing some of the characteristic facial features.[4]

Picture 2: A diagrammatic representation of assessing hypotonia in the neonate.[5]

On observation and examination, the child was noticed to spontaneously move all of her four limbs but was still hypotonic. She had not started talking. Ms. LS was noticed to have almond-shaped eyes with thin, down-turned lids, small hands and dolichocephaly in infants with narrow face and bifrontal diameter.

Another genetic consultation was made. Blood was withdrawn and sent for molecular genetic analysis for PWS.

A month later, genetic testing results confirmed Prader-Willi Syndrome. The syndrome was explained to the parents who were offered testing. The diagnosis had raised family dispute between the unmarried couple and eventually separation followed.

A 29-year-old healthy male had a female Prader-Willi affected child from a 35-year-old healthy lady. They were cohabiting together at one point but currently they are not. The daughter is living with her mother, although this is not shown in the pedigree.

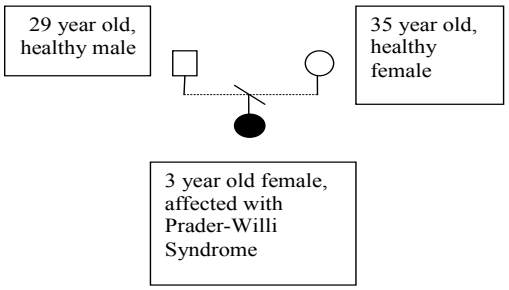
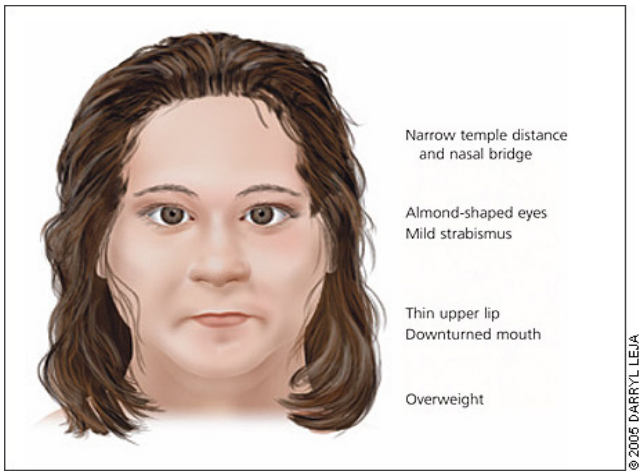


Figure 1: The Pedigree of the family



Picture 3: A diagrammatic representation of a Prader-Willi dysmorphic face[6]

During that visit, the parents reported that the girl had started to babble and make sounds with her mouth. She was passing hard stools with difficulty, on average incidence of once weekly. On observation and examination, there was no shortness of breath. The child was still hypotonic. Heart sounds were recorded as S1 + S2 + 0, with a split S2. The chest was clear.

At the age of 1 year, the head control had improved but was not completely achieved. Truncal support had also improved but she still required support to keep upright. Hence, the child was still unable to sit unaided. The child weighed 6.692kg and her height, measured by a stadiometer, was 69.5cm. An endocrinological referral was made to investigate the child for hormone deficiencies, particularly growth hormone. The doctor opened a discussion with the mother regarding hormonal therapy.

At the age of one year 7 months a detailed assessment of the child was made. Gross motor skills had improved. She was cruising, holding onto furniture, yet she could not walk independently. She was sitting by herself but could not stand. With respect to fine motor skills, the child was transferring objects between hands and developed a good pincer grip. Her speech revolved around mama and papa. She continued to babble and started to understand simple commands. Her social interaction had improved. She was smiling, recognising faces and her play had developed. Her diet consisted of cow`s milk and a balanced mixed diet with some solids. Occasionally, she continued passing hard stools though the frequency had significantly gone down to once every three weeks. On observation and examination, the girl was alert and oriented. She was well perfused with no signs of rashes or oedema. She was sitting by herself and had good head control. The child weighed 8.4kgs and her height measured 73cm. Her head circumference was 43cm. These values were all under the third centile following a steady rate of growth. Her heart sounds were S1+ S2 + 0. Chest was clear. The abdomen was soft and non-tender. No organomegaly was present and femoral pulses were easily palpable, of normal character and rhythm. There was nothing abnormal in the ear, nose and throat. A neurological examination showed that she was grossly intact, slightly hypotonic and moved all four limbs against resistance.

Two months later, at the age of 1 year 9 months the child weighed 9.16kgs and her height was 7.22cm. A hormone profile was taken, particularly for assessment of the level of the growth hormone.

On the 18th of October, 2011, the child was diagnosed with growth hormone insufficiency and was started on treatment. Growth hormone at a dose of 0.3mg per day equivalent to 14.7 units/m^2/week was prescribed.
A month later, on the 24th of November 2011, the mother reported that the child is suffering from nocturnal headaches since the onset of the growth hormone treatment. Hence the dose was decreased to 0.2 mg per day.

During the month of April 2012, at the age of 2 years 7 months, Ms. LS started walking unaided. She had no problems during sleep, such as sleep apnoea and her hormone levels were within their respective normal ranges. In June 2012 her dose of growth hormone was increased, to increase GH, to 0.4mg/day equivalent to 15.6units/m^2/week.

Drug history:

Drug	Dosage	Frequency	Type	Reason
Growth hormone	0.4 mg	daily	Peptide hormone	To support growth in a child with growth hormone insufficiency

Family history:

Mother and father are both healthy. No significant distant family history.

Social history:

Ms. LS was born to an unmarried couple. Since the diagnosis of Prader-Willi syndrome and its association with a paternal defective chromosome, the father left the house to go and live with his friends. Her mother is Maltese. Her father is of African origin. At the time, the daughter was living with her caring mother and they enjoy a very good relationship. Her father was visiting her frequently at her mother`s house, in the presence of the mother.

Systemic enquiry:

- General Health: the child had characteristic dysmorphic features of Prader-Willi Syndrome. She had almond-shaped eyes with thin, down-turned lids, small hands and dolichocephaly with a narrow face and reduced bifrontal diameter, a small mouth with thin upper lip and down-turned corners of mouth. She had a short stature and a weighty appearance.
- Cardiovascular System: heart sounds were S1+S2+0. A physiologically closed patent ductus arteriosus and a stable and silent atrial septal defect.
- Respiratory System: chest was clear. No sleep apnoea.
- Gastrointestinal System: hyperphagia with an insatiable appetite. Once every two weeks, she was finding difficulty in passing hard stools.
- Genitourinary System: nil to note.
- Musculoskeletal System: short stature, small hands and feet for height and age, with tapering of fingers. Her face was long and narrow.
- Central Nervous System: nil to note.
- Endocrine System: growth hormone deficiency was being treated. The child was not on insulin or any other anti-glycaemic agents. The child did not show any sign of pubic hair development.

Current therapy:

Growth hormone at a dose of 0.4 mg daily to treat growth hormone deficiency and support her in her growth. No other drug treatments. The mother ensured that her daughter eats healthy and involved her in physical activity.

Discussion of results of general and specific examinations:

On observation and examination, the three-year-old girl had a syndromic face and general appearance. Her height and weight were constantly under the third centile following a steady increase.
She did not show any signs or precocious puberty such as deposition of pubic hair or breast development. On auscultation her heart sounds were normal (S1+S2+0). Her chest was clear. Her abdomen was soft and non-tender.

Blood investigations showed a euthyroid state (TSH: 2.38 mlU/L), with a normal free T4 level, towards the lower end of the reference range (fT4: 10.6 pmol/L). This result necessitated a repeat of the thyroid function test. A hypothyroid state may predispose toward weight gain. The early morning cortisol level is within reference range (Cortisol: 320 nmol/L) and the insulin-like growth factor is low (IgF-1: 278 mg/mol (SD1- 303). This is needed for growth, height and protein catabolism.

Differential diagnosis:

- Anxiety Disorder: Obsessive-Compulsive Disorder
- Cryptorchidism
- Failure to Thrive
- Fragile X Syndrome
- Growth Hormone Deficiency
- Hypogonadism
- Obesity
- Obesity-Hypoventilation Syndrome and Pulmonary Consequences of Obesity
- Obstructive Sleep Apnoea Syndrome
- Osteoporosis
- Short Stature
- Sleep Apnea[1]

Diagnostic procedure:

Medical examination:

The child had a syndromic face of Prader-Willi Syndrome. She had almond-shaped eyes with thin, down-turned lids, and dolichocephaly with narrow face and bifrontal diameter. She had short stature, small hands and feet for height age, with tapering of the fingers.

Genetic examination:

Genetic studies confirmed Prader-Willi Syndrome. She was diagnosed at the age of 8 months. The clinical features and the genetic study result were consistent with a diagnosis of Prader-Willi Syndrome.

Therapy:

Drug treatment:

Drug	Dosage	Frequency	Type	Reason
Growth hormone	0.4 mg	daily	Peptide hormone	To support growth in a child with growth hormone insufficiency

There is no cure for the insatiable hunger apart from monitoring the child`s diet.

Diagnosis:

The child is suffering from Prader-Willi Syndrome (PWS). PWS is a genetic disorder which gives rise to a collection of signs and symptoms.

The genetics of PWS:

The PWS chromosomal region is found at 15q11-13. The paternal copy of this chromosomal region has to function for normal development; in its absence, a child will develop PWS.

The genetic cause is loss of yet unidentified genes normally contributed by the father[1]. Occurs from three main genetic errors: Approximately 70% of cases have a non-inherited deletion in the paternally contributed chromosome 15; approximately 25% have maternal uniparental disomy (UPD)—two maternal 15s and no paternal chromosome 15; and 2–5 % have an error in the "imprinting" process that renders the paternal contribution non-functional. The prevalence for all sexes and all races varies between, 1:12,000 and 1:15,000[3].

Genetic studies provide the best modality of diagnosing this condition. DNA methylation analysis confirms diagnosis of PWS. FISH and DNA studies can locate the the genetic defect and estimate the risk of recurrence.

The major clinical features:

- Neonatal and infantile central hypotonia, improving with age
- Feeding problems and poor weight gain in infancy
- Excessive or rapid weight gain between 1 and 6 years of age; central obesity in the absence of intervention
- Distinctive facial features—dolichocephaly in infants, narrow face/bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip and down-turned corners of mouth
- Hypogonadism—genital hypoplasia, including undescended testes and small penis in males; delayed or incomplete gonadal maturation and delayed pubertal signs after age 16, including scant or no menstruations in women
- Global developmental delay before age 6; mild to moderate mental retardation or learning problems in older children
- Hyperphagia/food foraging/obsession with food[3]

The minor clinical features:

- Decreased fetal movement, infantile lethargy, weak cry
- Characteristic behaviour problems—temper tantrums, violent outbursts, obsessive/compulsive behaviour; tendency to be argumentative, oppositional, rigid, manipulative, possessive and stubborn; perseverating, stealing, lying
- Sleep disturbance or sleep apnoea
- Short stature for genetic background by age 15
- Hypo-pigmentation—fair skin and hair compared with family
- Small hands and/or feet for height age
- Narrow hands with straight ulnar border
- Eye abnormalities (esotropia, myopia)
- Thick, viscous saliva with crusting at corners of the mouth
- Speech articulation defects
- Skin picking[3]

Developmental analysis:

Motor skills - Motor milestones in these children are typically delayed. They are born with hypotonia which improves by time. However, other motor skills, such as strength, coordination, balance and motor planning are deficient to different degrees. Occupational therapy and physiotherapy provide these patients with better adaptation to daily living.

Oral motor and speech - Hypotonia may create feeding problems, poor oral-motor skills and delayed speech. A speech and language pathologists can help these children in their communication. Sign language and picture communication are aids that one can make use of, depending on the severity of the case.

Cognition - IQs range from 40 to 105, with an average of 70. Those with normal IQs typically have learning disabilities. Problematic areas may include attention, short-term auditory memory and abstract thinking. Common strengths include long-term memory, reading ability, and receptive language. Early infant stimulation should be encouraged and the need for special education services and supports assessed in preschool and beyond.

Growth - Failure to thrive and short stature are common features in PWS, in spite of their food intake. They tend to have a high BMI and tend to fall under the third centile on the adjusted growth charts. A metabolic component is responsible for this. Growth hormone may be needed since growth hormone deficiency causes short stature, lack of pubertal growth spurt and a high body fat ratio, even in those with normal weight. This may not always be indicated and the drug has its own side effects.

Sexual Development - Sex hormone levels (testosterone and oestrogen) are typically low. Cryptorchidism in male infants may require surgery. Both sexes have good response to treatment for hormone deficiencies, although side-effects have been reported. Early pubic hair is common, but puberty is usually late in onset and incomplete.

Quality of life:

The general health and well-being of an affected individual are not usually compromised if they follow an adequate eating pattern. This constant need for food restriction and the tantrums that these patients might show are often distressing to the families and may be a cause of non-compliance to medical advice. Behavioural and family counselling is often needed.
Their life expectancy can be normal. These patients can lead a normal life and also work under supervision.

Final treatment and follow-ups:

Drug treatment:

Drug	Dosage	Frequency	Type	Reason
Growth hormone	0.4 mg	daily	Peptide hormone	To support growth in a child with growth hormone insufficiency

There is no cure for the insatiable hunger apart from monitoring the child`s diet.

Follow-up:

Blood tests were to be repeated. These include a thyroid function test, including T3 levels, an early morning serum cortisol and the insulin-like growth factor-1 (IgF-1). A sleep study was rebooked.

Fact Box 16:

Title: Prader-Willi Syndrome, (PWS)

Short Description: PWS is a genetically inherited condition.

The PWS chromosomal region is found at 15q11-13. The paternal copy of this chromosomal region has to function for normal development; in its absence, a child will develop PWS.

There are no significant risk factors towards the disease.

Symptoms:

- Narrow temple distance and nasal bridge
- Down-slanting eyes
- Narrow upper lip and down-turned mouth
- Short stature

Signs:

These children tend to:

- Be hypotonic
- Have neonatal feeding difficulty
- Fail to thrive
- Have hypogonadism
- Have developmental delay
- Have learning difficulties

Difficulty in feeding turns into insatiable hunger at the age of around three years. Such a condition cannot be prevented but early diagnosis would allow for better prognosis and anticipation of complications to decrease morbidity and improve the achievement of activities of daily living.

References:

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6. http://www.aafp.org/afp/2005/0901/afp20050901p827-f2.jpg- accessed on the 15th of March, 2013.