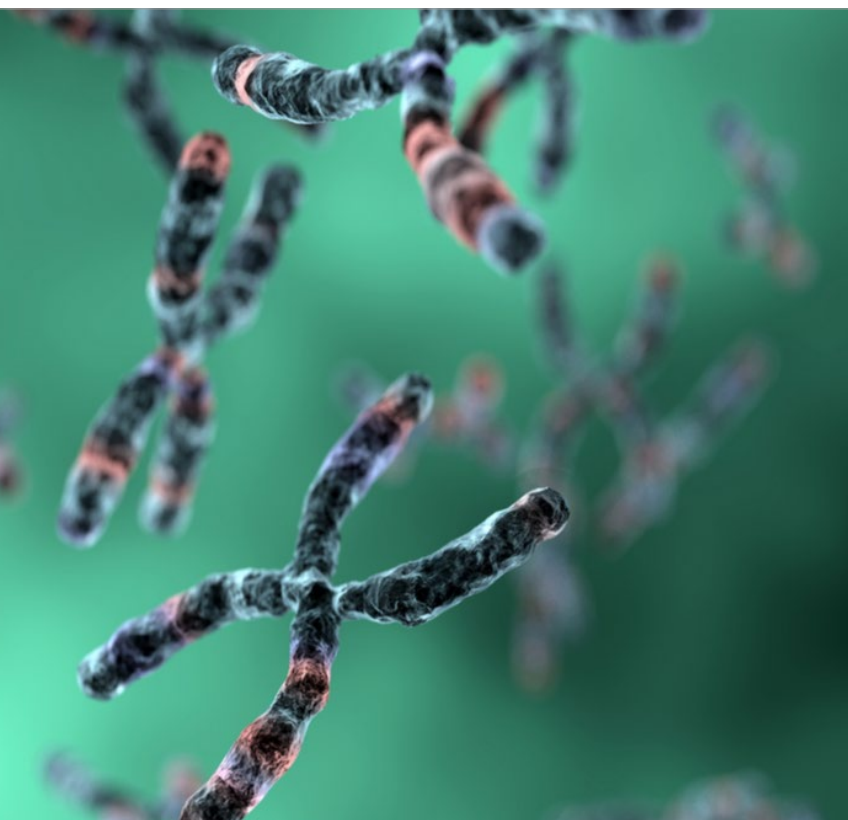


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Early diagnosis of  
Prader-Willi syndrome

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Prader-Willi syndrome (PWS) is a complex, multisystem, sporadic genetic disorder characterised by neonatal hypotonia, characteristic appearance, hypothalamic hypogonadism, developmental delay, behavioural dysfunction, and most notably food-related problems such as hyperphagia, food-seeking, and childhood-onset obesity (1, 2). PWS is caused due to the absence of expression of the paternally active genes in the proximal arm of chromosome 15.

It is estimated that PWS affects approximately 1 in 10'000 to 22'000 births with no distinguishing association with gender, race, or social status, and has a death rate of over 3 % per annum (3–6). The clinical diagnosis of PWS is made using a widely accepted consensus diagnostic scheme based on a point system of signs and symptoms (7). We present a case of a newborn illustrating characteristics of this rare syndrome and suggesting how a raised suspicion of PWS when examining a newborn can lead to early diagnosis and management.

## CASE REPORT

A baby girl was delivered to a 27-year-old G2/P2 at full term, in the Al Noor Specialist Hospital in Makkah. The Apgar scores were 8 and 9 at 1 minute and 5 minutes, respectively. Weight, height, and head circumference were 2.8 kg, 53 cm, and 35 cm, respectively.

The baby was noted to have poor muscle tone (hypotonia) and frog leg posture, and distinct facial features characterised by hypotelorism, almond-shaped eyes, turned-down mouth, thin upper lip, and a high-arched palate (Fig. 1 – 3). The baby had a weak cry and a poor suck. A few weeks before delivery, a prenatal ultrasound had revealed decreased fetal movements and polyhydramnios. This raised the impression of central hypotonia and Prader-Willi syndrome.

Soon after birth, physical examination revealed a mild inspiratory stridor and the baby was admitted to neonatal intensive care unit. The mild respiratory distress improved with oxygen supplementation through nasal cannula, and an oxygen saturation of 98% was achieved.

Work-up for Prader-Willi syndrome included brain MRI, which revealed mild subacute subdural hematoma overlying the parieto-occipital region. Brain ultrasound revealed no abnormality. Routine cytogenetic study showed a female karyotype with deletion in the proximal region of the long arm of chromosome 15 (15q11) (Fig. 4). FISH (fluorescent in situ hybridization)

**Fig. 1**

*Marked hypotonia with the legs are fully abducted at the hip and the lateral surface of the thighs resting on the bed's surface; the arms are extended next to the body with the elbows flexed.*

study showed a deletion affecting the SNRPN locus on chromosome 15 (SNRPN-) (Fig. 5). These findings confirmed the diagnosis of Prader-Willi syndrome.

Metabolic screening did not reveal significant abnormalities. Growth hormone level was 2.41 ng/mL. Cardiac examination revealed a systolic murmur, and a patent ductus arteriosus (PDA) was diagnosed on echocardiography.

Prior to discharge, the baby was on orogastric tube feedings which were continued post-discharge, for which the parents were counselled and an outpatient follow-up with neonatologist, pediatric endocrinologist, and pediatric cardiologist was recommended.



Fig. 2

*When pulling the infant from the supine to a sitting position, there is marked head lag.*



Fig. 3

*Marked hypotonia on ventral suspension with a rounded back, extended arms and legs, and dropping head.*



The Prader-Willi syndrome was first described by Prader, Labhart, and Willi in 1956. Two important genetic mechanisms, 'uniparental disomy' and 'genetic imprinting', which contribute towards a broader understanding of human genetics, are a result of genetic research in Prader-Willi syndrome (4). The birth incidence of PWS has been variably reported as one in 10'000 to 15'000 (3, 4), one in 20'000 (5), one in 22'000 (6), and one in 25'000 [8]. Population prevalence is estimated to be about one in 52'000 (6).

The causes of premature morbidity and mortality in PWS are majorly the consequences of food-related behaviours – consequences such as cardiovascular diseases, respiratory diseases, diabetes mellitus, and sleep disturbances (4). One study investigated the specific disorders prevalent in individuals with a confirmed diagnosis of PWS and found recurrent respiratory infections (50%), high rates of fractures (29%), non-insulin dependent diabetes mellitus (25%), leg ulceration (22%), sleep disorders (20%), and severe scoliosis (15% in childhood) in such individuals (6).

PWS typically presents with certain characteristic features, which are discussed below. It should be noted that the clinical characteristics in infancy – as in the presented case – might differ considerably from that in childhood and adulthood (3). Many of the characteristics have been speculated to be based on dysfunction of hypothalamic systems (9).

In almost all the cases of PWS, prenatal hypotonia is present, as was in our case. Hypotonia is associated with decreased fetal movements, abnormal position of the fetus, and difficulties during delivery. Neonatal hypotonia is associated with a weak cry, lethargy, and poor suck, which necessitate special feeding techniques. As a result of hypotonia, reflexes are affected and motor milestones are delayed. Though hypotonia gradually improves, adults with PWS remain mildly hypotonic (3, 5).

Prenatal-onset hypothalamic hypogonadism is another characteristic and manifests as genital hypoplasia, which usually persists throughout life and is associated with decreased sexual development. Hyperphagia develops between the ages of 1 and 6 years and obesity, which is usually central in distribution, begins (3, 5).

Short stature and dysmorphic appearance are other features, the former might not be apparent until after 25 years of age. Growth hormone deficiency is seen in most cases. Facial features are characteristic – these include a narrow bifrontal diameter, full cheeks, almond shaped palpebral fissures, narrow nasal bridge, and downturned mouth with a thin upper lip.

In most cases of PWS, delayed language development, poorly articulated speech, and mental retardation are apparent.

It has been noted that despite hypotonia, babies diagnosed with PWS do not have respiratory problems (10). Though this is contrary to the findings from our case, respiratory distress of the neonate improved with oxygen supplementation.

The genetics of PWS is complex. The disorder is a result of the absence of expression of the paternally active genes in the PWS critical region on 15q11-q13, which in turn is caused due to one of the following: deletion of this region from the paternal chromosome 15 (in about 70% cases); maternal uniparental disomy of chromosome 15 (in about 28% cases); mutation, deletion, or other defect in the imprinting centre (in < 2% cases) (1).

The clinical diagnosis of PWS is based on widely-accepted consensus diagnostic criteria, which classify symptoms into three groups – major, minor, and supportive. Each major criterion (total criteria – 8) carries one point, minor (total criteria – 11) carries half, and supportive (total criteria – 8) none. For children up to 3 years of age, 5 points are required for certainty of diagnosis (4 of which should come from the major criteria). For higher ages, a score of at least 8 points is required, 5 of which should belong to the major criteria (7).

Out of these criteria, our case presented with the following major criteria: (1) neonatal central hypoto-

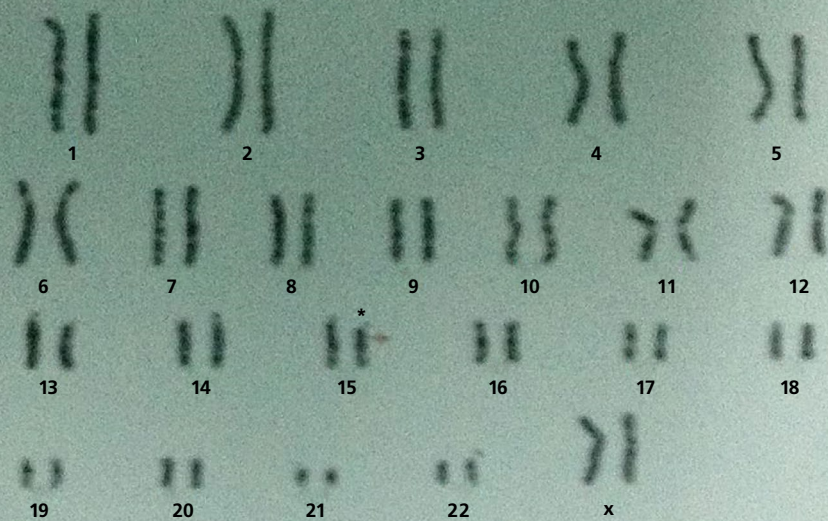


Fig. 4

*Femal karyotype(46, XX) with micro deletion of long arm of chromosome 15 (\*).*

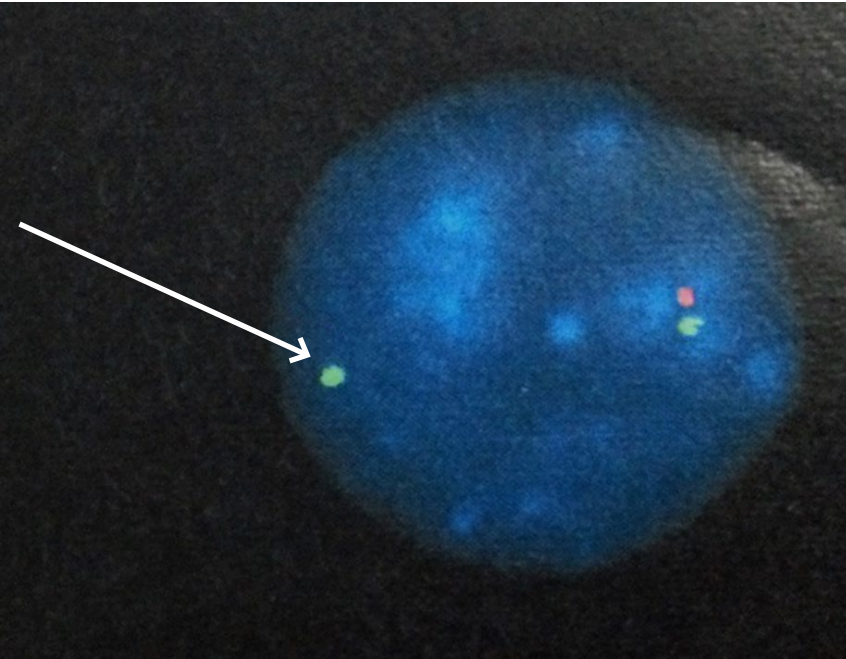


Fig. 5

*FISH: Two probes are used; the first probe (green) is a control probe used to identify both copies of the chromosome under test. The second probe (red) hybridises to the sequence that may be deleted. Deletion is usually found in only one of the chromosomes in a pair (arrow).*

nia with poor suck reflex, (2) feeding problems with need for special feeding techniques and failure to thrive, (3) characteristic facial features, (4) deletion of 15q11-q13 or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region, including maternal disomy. 'Decreased foetal movement or weak cry in infancy' was the minor criterion satisfied. It is interesting to note that in our case, diagnosis was established (and confirmed by genetic testing) very early in infancy and several other characteristic features of PWS may become apparent in later stages of life.

Nowadays, cytogenetic and molecular techniques can be reliably used to confirm diagnosis. DNA methylation analysis has a sensitivity and specificity of nearly 100% in detecting methylation pattern characteristics. FISH can detect nearly all individuals with deletions in the 15q11-q13 region. The current practice recommends methylation analysis for all newborns presenting with persistent hypotonia. On a positive methylation analysis, FISH should be performed to know if PWS is caused by paternal deletion or maternal uniparental disomy – research suggests that genetic subtypes display different risks for psychological and behavioural problems (5).

A four-year study has concluded that salutary GH-induced changes in children diagnosed with PWS can be sustained up to four years provided higher doses

are administered (12). GH has been shown to improve somatic symptoms – apart from improving psychomotor development and physical characteristics, GH therapy has also been known to elucidate behavioural and psychological benefits without significant side effects (5).

However, treatment is most effective when GH therapy is combined with appropriate behavioural intervention strategies. As obesity-related consequences are grave, managing food-related problems is helpful in the overall treatment of PWS. Administering a low-calorie, well-balanced diet and restricting access to food along with promoting adequate exercise is important. Applied behaviour analysis (ABA) procedures known to treat aberrant behaviour in individuals with autism have shown promise in increasing independence in individuals diagnosed with PWS, too. A speech-language pathologist can greatly enhance an individual's communication skills (5).

Our case illustrates an excellent example of how neonatal hypotonia should immediately raise a suspicion of PWS. This may aid in early confirmatory genetic diagnosis of PWS. Early diagnosis is likely to result in early management, giving parents an opportunity to provide adequate diets, which may have profound long-term benefits in the management of Prader-Willi syndrome.

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