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CASE REPORT

Extremely Rare Co-Existence of Prader-Willi Syndrome with Triple X: A Case Report from Malaysia

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Abstract

Triple X syndrome is a chromosomal disorder with an extra X chromosome while PWS is a complex imprinting disorder caused by the lack of expression of paternally-inherited genes on chromosome 15q11-q13. Clinical features for most affected individuals with Triple X syndrome are mild. However, individuals with PWS may present with complications of the endocrine and neurology systems, as well as cognitive and behavioural changes. Here, we present a case of an eight-year-old Malaysian Malay girl with the co-existence of Triple X syndrome and PWS. At birth, this patient presented to us with craniofacial abnormalities, neonatal hypotonia, poor sucking, and minor hand and feet anomalies. Karyotype analysis was done at birth and showed she has Triple X syndrome. However, at four years old, she developed an increased obsession with food and appetite as well as having tantrums, especially when denied food. She has delayed speech and motor development (i.e., sitting up and walking). The facial features observed were a narrow face, almond-shaped eyes, a small appearing mouth with a thin upper lip, and down-turned corners of the mouth. She also has some cognitive impairment with learning and intellectual disabilities. The clinical features of the present case meet the clinical diagnostic criteria of PWS. MS-MLPA and FISH analysis confirmed PWS due to paternal deletion of 5q11-q13. In this case report, we highlighted the uniqueness of clinical characteristics of the individual with co-existence PWS and Triple X syndrome for a better understanding of the phenotype-genotype relationship.

Keywords: Triple X syndrome, Prader-Willi syndrome, FISH

Introduction

Triple X syndrome (47, XXX), is an aneuploidy of the X chromosome characterised by the presence of an extra X chromosome in females. It is an uncommon chromosomal disorder that affects around one in every 1000 female births (Otter *et al.*, 2010; Wigby *et al.*, 2016). The phenotypes are varied with some individuals very mildly affected while others with more significant physical and psychological features. The most common clinical features of affected individuals are tall stature (van Elst *et al.*, 2020; Liebezeit *et al.*, 2003), clinodactyly (abnormally bent or curved finger) and hypotonia in infants (poor muscle tone) (Wigby *et al.*, 2016). They also have delayed motor development and poor language skills (Lenroot *et al.*, 2009).

Meanwhile, Prader-Willi syndrome (PWS) is genetically regulated neuro-developmental abnormality caused by the absence of gene expression of imprinted paternal genes at 15q11-q13 region. There are three major genetic subtypes of PWS which are paternal 15q11-q13 deletion, maternal uniparental disomy (UPD) and imprinting defects with approximately 70%, 20 to 30% and 1-3% of affected individuals, respectively (Cassidy *et al.*, 2012) – refer Figure 1.

PWS is characterised by abnormal physical appearance (i.e., short stature, small hands and fingers), craniofacial anomalies (i.e., almond-shaped eye), intellectual disability, behavioural

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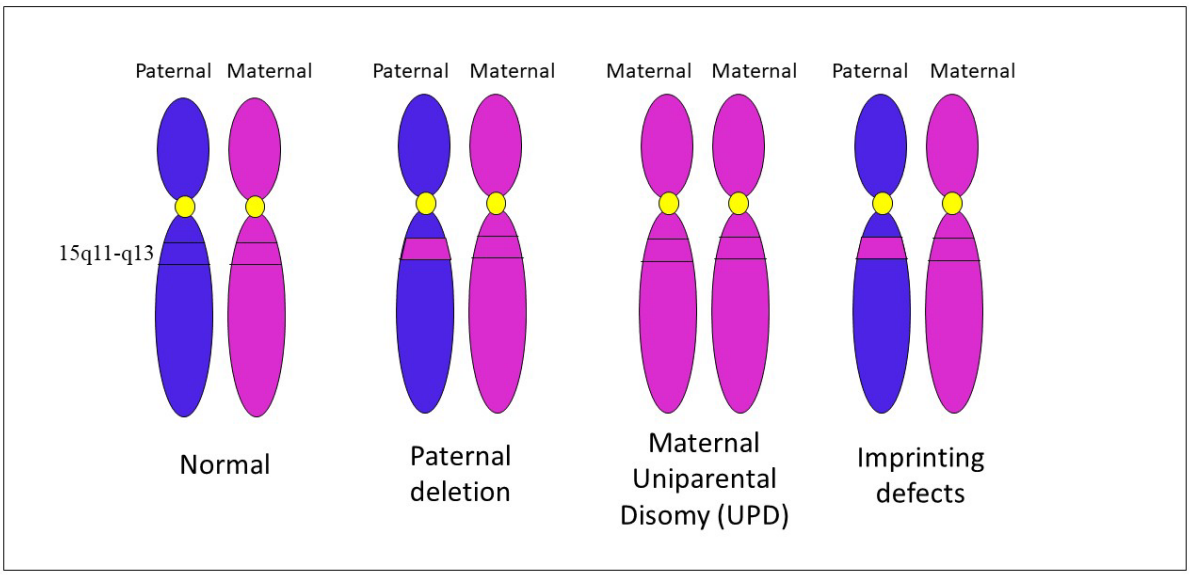

Figure 1. Normal and three major genetic subtypes of Prader-Willi syndrome.

problems, and endocrine complications (i.e., hypothyroidism, adrenal sufficiency, hypogonadism, hypogenitalism and growth hormone deficiency) (Miller *et al.*, 2008; Einfeld, 2005; Varela *et al.*, 2006). In newborns, there are difficulties in detecting PWS characteristics, however, we can observe PWS behaviour including tantrums and hyperphagia, leading to obesity in early childhood. In fact, PWS patients are suffered from many complications related to obesity, diabetes mellitus, metabolic syndrome, sleep apnea, respiratory insufficiency and cardiovascular disease (Raduan *et al.*, 2020; Crino *et al.*, 2018).

The co-existence of PWS and triple X syndrome in an individual is very rare. To the best of our knowledge, there are only four patients diagnosed with PWS and triple X syndrome. Three cases were affected by maternal UPD (Ferrante *et al.*, 1986; Devriendt *et al.*, 1997; Butler *et al.*, 1997) while another case was affected by paternal 15q11-q13 deletion (Pascanu *et al.*, 2010). Here, we report our patient, an eight-year-old girl with the co-existence of PWS and triple X syndrome, including her clinical presentations, laboratory diagnosis, genotype-phenotype associations, multidisciplinary management of the case, and treatment plan for the family.

Case report

Our patient is an eight-year-old Malaysian Malay girl. She was born to a non-consanguineous parent with birth weight of 2.35 kg. Her mother, who was 26 years old primigravida, was referred to one of the hospitals in the northeastern city of Kota Bharu for borderline oligohydramnios and fetal distress. Upon arrival at the labour room, she presented with meconium blood-stained liquor and ultrasound showed placental abruptio and instrumental delivery via forceps was carried out due to fetal bradycardia.

At birth, the baby was well but was noted to have dysmorphic features with a small forehead, prominent occiput, hypotelorism, low hairline, low set-ears, micrognathia, high arched palate, left upper molar tooth, short but not webbed neck, wide-spaced nipples, right single palmar crease, incurving of the little fingers, and right rocker-bottom foot. The baby developed respiratory distress and was subsequently admitted to the Special Care Nursery (SCN) for 14 days for congenital pneumonia. Cytogenetic analysis was carried out to determine the cause of the dysmorphism. Karyotyping was performed by G-banding techniques at 550 bands of resolution on metaphase chromosomes obtained by standard procedures from peripheral blood samples. The result showed that our patient has an extra X chromosome (Figure 2). The karyotyping result was later confirmed with fluorescence *in situ* hybridization (FISH) analysis at eight years old using whole chromosome probe (WCP) probe for X chromosomes as shown in Figure 3.

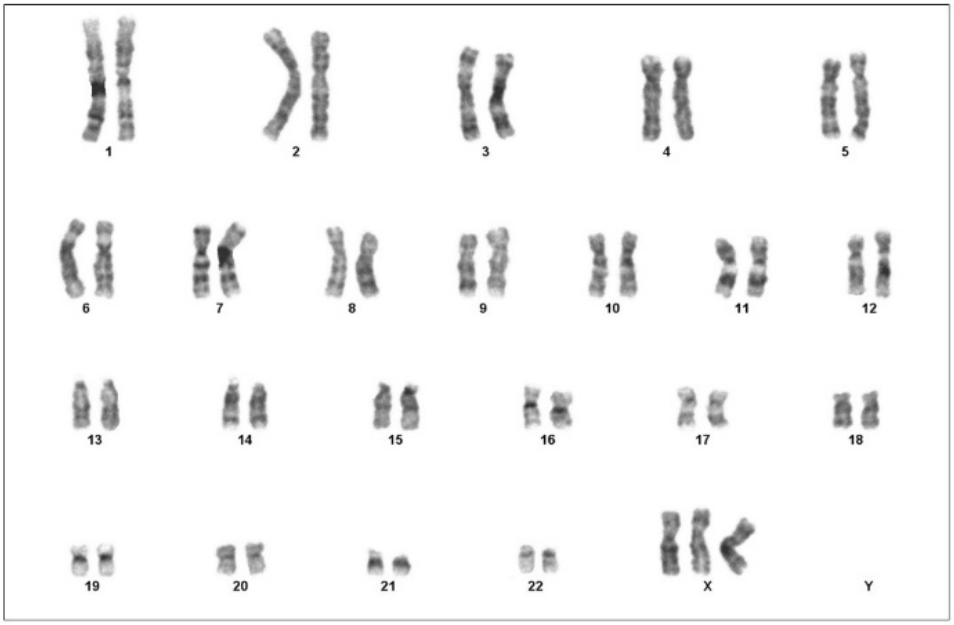

Figure 2. Karyotype showing the presence of an extra X chromosome (47, XXX).

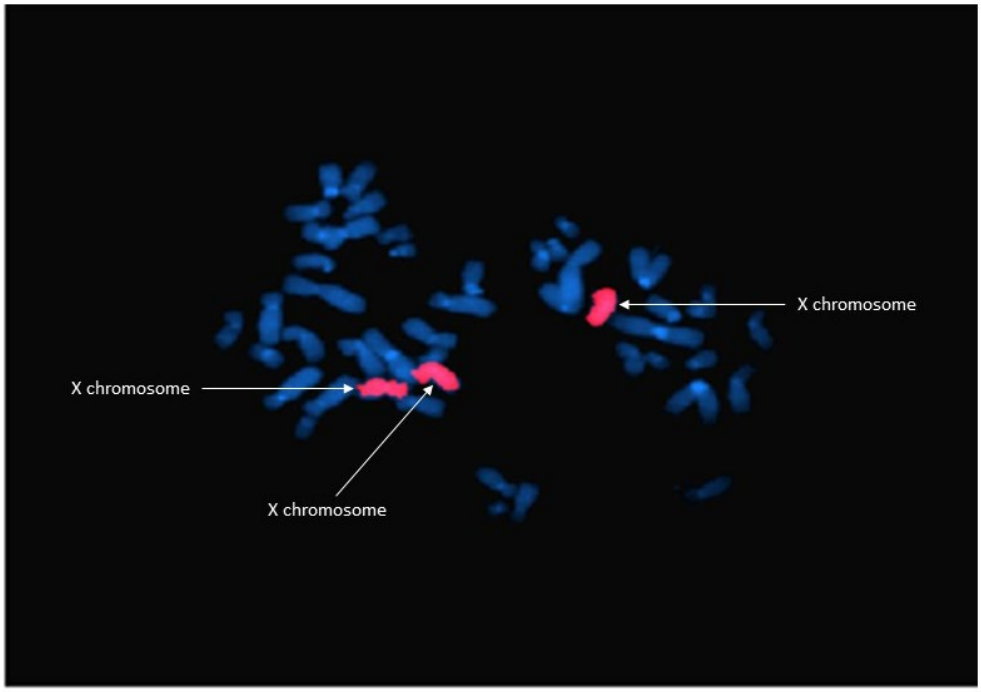

Figure 3. FISH using whole chromosome probes (WCP) probe for X chromosome showed the presence of three X chromosomes consistent with Triple X syndrome.

Our patient was also noted to have poor sucking reflex at birth and was referred to an occupational therapist for sucking stimulation as she was also unable to tolerate oral feeding. Due to the poor suckling reflex, the baby was started on Ryle's tube feeding until day 50 of life. The baby's parents were counselled regarding the baby's condition prior to discharge. Echocardiography (ECHO) revealed a Patent Foramen Ovale (PFO). She was also found to have laryngomalacia when she presented with inspiratory stridor on day 9 of life and was referred to the Otorhinolaryngology (ORL) team who decided on conservative management in view of the mild symptoms.

At the age of one year old, she was referred to the genetic clinic for genetic assessment of triple X syndrome and global developmental delay. On examination, she was short and underweight. She

also has facial dysmorphism; triangular chin, hypertelorism, bilateral low-set ears, bilateral rocker bottom feet, no cleft lip or palate hypotonia with severe head lag, poor axillary grip and weakness in all four limbs. She also had neonatal hypotonia and displayed a lower growth chart than the third centile. The developmental milestones of this patient were delayed. She started walking at three years old and uttered a single word at four years old, then her current speech was only short sentences. As for her social and academic development, she was placed at Special Stream School, not socialising with school friends and sitting at her seat doing work. She was on basic reading, writing alphabets and counting which was less than pre-school age.

Subsequently, she was lost to follow-up until the age of four years old, when she was found to have higher than normal weight growth for her age. On further enquiry, it was noticed that the patient's appetite increased at least for the last one year and she continued to have increased weight gain. Her body mass index (BMI) was 28 when she was seven years old (her weight was 36.8kg and height was 114 cm). The physical examination, when she was seven years old, showed she was an obese child, with a narrow face and bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, and down-turned corners of the mouth. These features suggested a probable diagnosis of PWS.

Gunay-Aygun *et al.* (2001) provided a set of diagnostic criteria for PWS (Table 1). The criteria were divided into two which were major and minor criteria.

Table 1. Major and minor criteria of PWS (Gunay-Aygun *et al.,* 2001)

No.	Major Criteria	Points counted
1	Neonatal and infantile central hypotonia with poor suck, gradually improving with age	1
2	Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive	1
3	Excessive or rapid weight gain on weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention	1
4	Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more are required).	1
5	Hypogonadism—with any of the following, depending on age: a) Genital hypoplasia, (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age (<5th percentile); female: absence or severe hypoplasia or labia minora and/or clitoris b) Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (Male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea/oligomenorrhea after age 16)	1
6	Global developmental delay in a child <6 years of age; mild to moderate mental retardation or learning problems in older children	1
7	Hyperphagia/food foraging/obsession with food	1
8	Deletion 15q11–13 on high resolution (>650 bands) or other cytogenetic molecular abnormality of the Prader-Willi chromosome region, including maternal disomy	1
	Minor Criteria	
1	Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age	½
2	Characteristic behavior problems–temper tantrums, violent outbursts, and obsessive-compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative	½

	possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)	
3	Sleep disturbance and sleep apnea	½
4	Short stature for genetic background by age 15 (in the absence of growth hormone intervention)	½
5	Hypopigmentation—fair skin and hair compared with family	½
6	Small hands (<25th percentile) and/or feet (<10th percentile) for height age.	½
7	Narrow hands with straight ulnar borders	½
8	Eye abnormalities (esotropia, myopia)	½
9	Thick viscous saliva with crusting at corners of the mouth	½
10	Speech articulation defects	½
11	Skin-picking	½

In order to score patients above three years of age, a total of 8 points was required and five or more points must be from the major criteria. The clinical diagnostic criteria for PWS of our patient were scored from the criteria as shown in Table 2. This score was made when she was seven years old. She had a total score of 7.5. The score obtained is less than the minimum score. However, we proceed to the molecular cytogenetic studies for confirmation.

Table 2. The list of diagnostic criteria for PWS seen in our patient.

Major Criteria Observed	**Point**
Neonatal hypotonia & poor sucking at birth	1
Unable to tolerate feeding since birth, requiring using RT feeding till day 50 of life	1
Excessive and rapid weight gain trend since 4 years-old until current age	1
Characteristic facial features observed: she has narrow face, almond-shaped eyes, small appearing mouth with thin upper lip, and down-turned corners of the mouth	1
Global developmental delay assessment with average IQ test.	1
Hyperphagia and increase obsession with food and appetite since 4 years old.	1
Minor Criteria Observed	
Eye: bilateral eye compound myopia and astigmatism.	½
Small hand	½
Short stature	½
Total score: (by clinical features)	7½

Note: A total score of 8 points was required to diagnose a patient as having PWS.

Molecular cytogenetic studies employing FISH technique using Prader Willi/Angelman Region Probe (SNRPN) and Imprinting Centre (IC) with subtelomere specific probe (15qter) showed microdeletion of chromosome 15 (Figure 4), confirming a clinical diagnosis of PWS. The physical appearance of our patient is shown in Figure 5 which met the clinical diagnostic criteria of PWS by Gunay-Aygun *et al.* (2001).

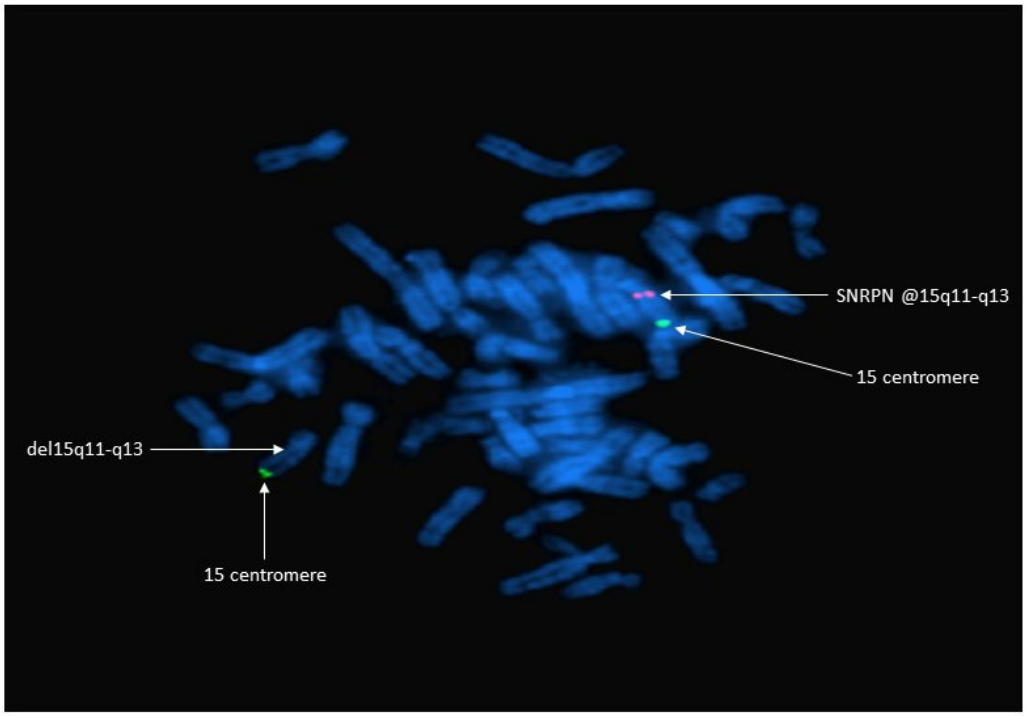

Figure 4. FISH analysis in metaphase with SNRPN/IC probes for chromosome 15 showed microdeletion of one of chromosome 15.

Figure 5. Physical appearance of our patient when she was eight years old. (A) Full picture showing she is an obese child. (B) Frontal view of the face shows a narrow face and bifrontal diameter, almond-shaped eyes, and a small-appearing mouth with thin upper lip. (C) Lateral view of the face shows a thin upper lip with down-turned corners of the mouth. (The picture was consented by this patient's parents to be used for medical purposes).

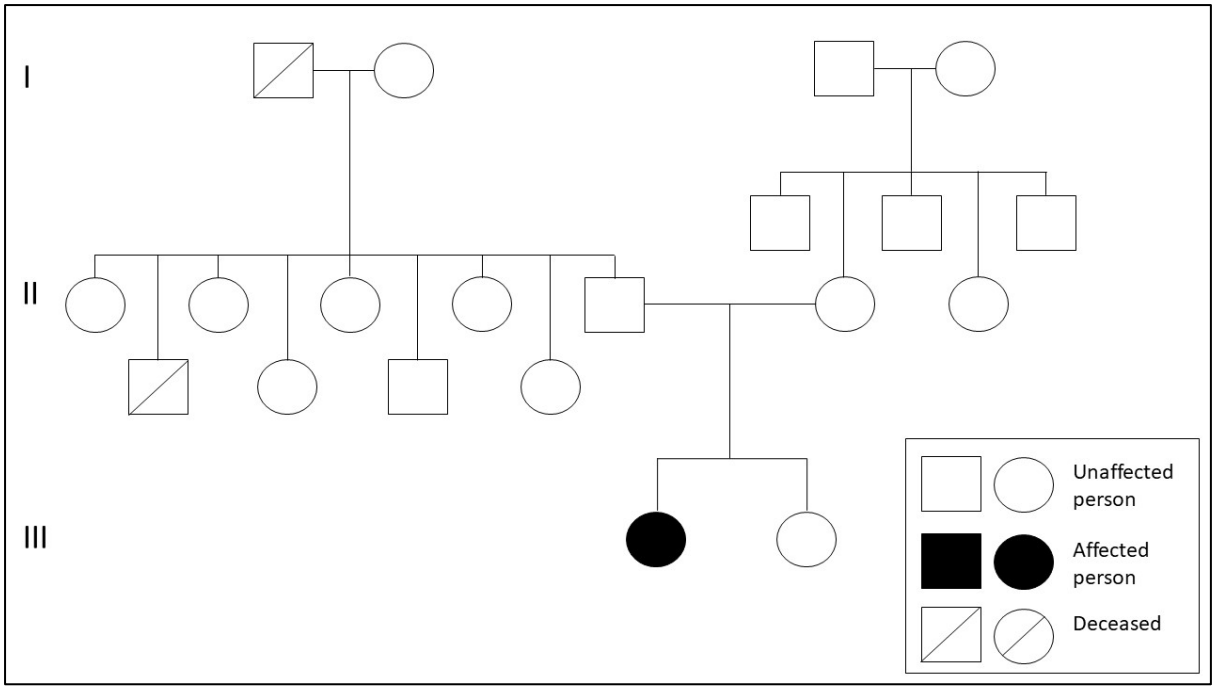

Figure 6. Three-generation pedigree family with PWS and triple X syndrome.

IQ test was done in February 2021 when she was seven years 10 months old using a few methods; SFBT (Seguin Form Board Test) and BGT (Bender Gestalt Test). Results revealed the developmental age of about 5-6 years old, while WNV (Wechsler Nonverbal Scale of Ability) revealed a score of 73, which is the borderline level of IQ.

Diagnosis of PWS was confirmed by genetic test methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) at the age of eight years old. The molecular cause for PWS in our patient was paternal deletion at 15q11-q13. The result was validated by molecular cytogenetic FISH using Prader-Willi/Angelman region probe (SNRPN/Imprinting centre IC). The final karyotype diagnosis for this patient was 47, XXX. Fish del(15)(q11q13/)(SNRPN/ICx1,15qterx2) confirmed the diagnosis of triple X syndrome and PWS.

Managing PWS patients requires a comprehensive approach that addresses physical, cognitive, and behavioural challenges. Our team of healthcare professionals, including physicians, dietitians, therapists, and social workers, has been working together to provide effective management plans for this patient. Our genetics expert has provided genetic counselling to individuals with PWS and their families. It involves discussing the genetic cause of the disorder, the risks of passing it on to future children, and the options for family planning. Our geneticists have worked with other healthcare professionals to manage this patient's medical and developmental issues. This includes developing a treatment plan for the individual's specific symptoms and coordinating care with other specialists.

As for nutritional management, the dietitian team has created a nutrition plan that is low in calories and high in nutrients. The patient and caregivers have been educated and encouraged in practicing a healthy balanced diet. They also monitored and adjusted the patient's diet as needed. Her family members also play a role in controlling patient's food intake. A gynaecologist expert has assisted in managing the reproductive health issues of this patient. Her delayed onset of puberty might affect her menstrual cycles and fertility. The gynaecologist team has dealt with these concerns, including providing advice on menstrual irregularities and how to cope with menses.

The psychologists team who manages this patient uses a few strategies to help this patient with stress, anxiety, and behavioural problems. They use cognitive-behavioural therapy, behaviour therapy, and social skills training to help this patient improve their social functioning. In 2021, the psychologist team redid the IQ assessment and her IQ was found to be improved. Endocrinologist has managed this patient with growth hormone replacement therapy. It is necessary to support the growth and development of this deficient growth hormone patient. Insulin tolerance test (ITT) also has been performed for this patient in 2022. She has a normal cortisol response. Endocrinology experts also have monitored this patient's thyroid function

since 2021 and the result for TSH and T4 level was normal until this case report was written.

Discussion

Triple X syndrome is characterised by an obsession of an additional X chromosome in females. Although females with this condition might be taller than average, triple X syndrome usually causes no obvious physical abnormalities or dysmorphism. Minor physical findings can be present in some individuals and may include epicanthal folds, hypertelorism, upslanting palpebral fissures, clinodactyly, overlapping digits, pes planus and pes excavatum as present in our patient. Her presentation such as neonatal hypotonia, craniofacial abnormalities, and short and malformation of fingers and feet are most probably contributed by her co-existent PWS. The clinical features of triple X syndrome can sometimes mask the clinical characteristics associated with PWS. Triple X syndrome is often identified in childhood due to abnormal development (i.e., dysmorphism), while PWS may not be diagnosed until later in life due to physical (i.e., developmental delays and obesity) and behavioural effects (i.e., tantrums). Having an early diagnosis of triple X syndrome has led to a delayed diagnosis of PWS. This delayed diagnosis of PWS may have clinical consequences in terms of early introduction of dietary and behavioural therapy as well as growth hormone therapy.

Our patient's clinical features obeyed the findings by Ferrazzo *et al.* (2014), which showed the weight and height of the affected case were below average. However, other studies showed that the affected females are apparently normal and may go unnoticed and undiagnosed, although the triple X syndrome has a high incidence (Afshan, 2012). They can grow normally and may even be tall-statured only (Jagadeesh *et al.*, 2008). However, our patient had delayed developmental milestones. Having a co-existing triple X syndrome has modified the developmental phenotype of PWS, which include underdeveloped muscles and growth hormone deficiency (Fong *et al.*, 2003; Cassidy *et al.*, 2012). Moreover, her general cognitive abilities including IQ level were below average compared to her peers. This is in agreement with typical features of PWS and the presence of triple X syndrome. A previous study showed females with triple X syndrome typically have normal intelligence but lower IQs (Afshan, 2012).

Our patient presented with paternal 15q11-q13 deletion PWS subtypes, which is the most commonly reported among PWS patients; 49.3% (Bohonowych *et al.*, 2019), 83.9% (Lu *et al.*, 2013) and 90% (Hudgins *et al.*, 1998). This deletion must have occurred de novo as the karyotypes of both parents were normal. By using MS-MLPA test, we were able to conclude that paternal q11-q13 deletion for chromosome 15 was present, explaining the PWS phenotype. A previous study showed that clinical features such as hypotonia, and feeding difficulties are also more likely to be present in the deletion subtype. Affected individuals may have more severe language impairment in particular receptive language and autistic traits compared to maternal UPD subtypes (Butler and Duis, 2020).

This case report highlighted the major clinical features of PWS seen in our patient including hypotonia, poor responsiveness, neonatal hypotonia and feeding difficulty. These findings are consistent with the findings from previous studies (Cassidy *et al.*, 2012; Zhan *et al.*, 2012). The facial features of PWS were also observed in our patient; narrow face, almond-shaped eyes, small appearing mouth with a thin upper lip, and down-turned corners of the mouth (Pascanu *et al.*, 2010; Hu *et al.*, 2021). She also had a global developmental delay assessment with an average IQ test, hyperphagia and increased obsession with food and appetite. Meanwhile, the minor criteria observed in this patient are bilateral eye compound myopia and astigmatism, small hand, and short stature (Fong *et al.*, 2003; Varela *et al.*, 2006; Cassidy *et al.*, 2012).

Six major clinical diagnostic criteria for PWS were seen in this patient. They are neonatal hypotonia with poor suck, feeding problems during infancy, excessive or rapid weight gain, mild to moderate mental retardation with learning problems, hyperphagia since four years old and having facial features with narrow face or bifrontal diameter, almond-shaped eyes, small appearing mouth with thin upper lip as well as down-turned corners of the mouth. The minor criteria observed are bilateral eye compound myopia and astigmatism, short hand and short stature. These major and minor clinical diagnostic criteria for PWS met the criteria set by Gunay-Aygun *et al.*, (2001). These clinical diagnostic criteria provide an important indicator before proceeding to cytogenetic analysis and giving counselling to affected individuals.

One of the major criteria of PWS is hyperphagia. Hyperphagia and food-related behaviors impair socialization and worsen the quality of patients' life of and also caregivers. This led to significant morbidity and mortality of PWS individuals (López-Bastida *et al.*, 2016). A multidisciplinary

approach is needed for the management of PWS patients. The family daily menu should be standardized to reduce the dissatisfaction of PWS individuals. In the community, counselling should be provided to parents and teachers. As for the pharmacological approach, risperidone has been used to control PWS individuals' psychological and behaviour. (Raduan *et al*., 2020).

Individuals with PWS generally survive into adulthood even though the mortality rates of PWS cases range between 1.25 to 3% per year (Butler *et al*., 2002; Whittington *et al*., 2015). According to Butler *et al*. (2017), the average age of death in the 486 individuals with PWS reported in 2017 was 29.5 years and 80% of them died were older than 18 years of age (Butler *et al*. 2017). Obesity-related complications significantly increase the risk of mortality in PWS (Schrander-Stumpel *et al*., 2004; Lionti *et al*., 2012). However, in a large survey of causes of death in PWS, the top causes were respiratory failure (31%), cardiac (16%), gastrointestinal (10%), infection (9%), obesity (7%), pulmonary embolism (7%), choking (6%), and accidents (6%) (Butler *et al*., 2017). The lives of individuals with PWS can be improved with an early diagnosis, especially individuals with obesity-related complications where healthcare providers can carefully manage their symptoms earlier.

Diagnosis of triple X syndrome is via conventional cytogenetic test, molecular cytogenetic or array CGH (Yilmaz *et al*., 2005; Prakash *et al*., 2014; Nassir *et al*., 2022). The main diagnosis of PWS is DNA methylation testing to detect abnormal parent-specific as done in the imprinting with the PWS critical region on chromosome 15. MS-MLPA detects more than 99% of affected individuals and able to differentiate between deletion and UPD in one setting. It is also able to detect imprinting centre deletion and differentiate between PWS and Angelman syndrome (Procter *et al*., 2006).

Knowing the specific genetic aetiology in individuals with PWS is essential for the appropriate counselling of the affected families. The majority of families have a recurrence risk of less than 1%. In general, the risk of recurrence is typically less than 1% for probands with a deletion or uniparental disomy (UPD), and the recurrence risk is as high as 50% for probands with imprinting defect or a mutation of UBE3A. Chromosome rearrangements may be inherited or de novo. If the mother has a 15q;15q Robertsonian translocation, the risk for spontaneous miscarriages can approach 100% (Kolgeci *et al*., 2013). Prenatal testing is practised for certain genetic mechanisms. The recurrent risk for triple X syndrome is also less than 1%. The risk of trisomies increases with advanced maternal age.

Conclusion

The uniqueness of clinical features of triple X Syndrome with PWS individuals may affect patients' diagnosis and prognosis as well as their quality of life and consequently could aid in a better understanding of the phenotype-genotype relationship.

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