

Prader-Willi syndrome due to an unbalanced chromosomal rearrangement

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Introduction

Prader-Willi syndrome is a genomic imprinting disorder occurring at a frequency of 1/10,000 to 1/20,000. It is characterized by hypotonia, feeding difficulties often associated with failure to thrive during infancy and global developmental delay. Around 1 to 4 years of age, children develop hyperphagia leading to obesity. These individuals have short stature, facial dysmorphism that includes almond shaped eyes and upslanting palpebral fissures, small hands and feet, cognitive impairment and hypogonadism. Other features include behavioural and sleep problems and neuroendocrine abnormalities.¹ It is caused due to the loss of paternally transmitted genes at the imprinted locus 15q11-q13. In 75% of the cases, the loss is due to deletion in the paternally derived chromosome 15q11-q13 region, 24% of the cases have maternal unipaternal disomy of chromosome 15, 1% of the cases are due to defects in the imprinting centre and <1% of the cases are due to chromosomal translocation. The diagnosis is suspected clinically and is confirmed by DNA methylation testing. Diagnosis can also be made by molecular cytogenetic methods such as Fluorescent in-situ hybridization (FISH), Multiplex ligation dependent probe amplification (MLPA) and chromosomal microarray in cases that have deletion in the 15q11-q13 region. It is important to elucidate the exact genetic mechanism to provide genetic counselling and recurrence risk in the family. In cases with de novo deletion or uniparental disomy, the recurrence risk is low (<1%), whereas it can be upto 50% in cases with an imprinting centre defect. However, when the deletion is the result of any chromosomal rearrangement, the risk of recurrence depends on the specific rearrangement

and the empiric risk is around 15% in cases with an inherited chromosomal translocation.²

Case Report



Figure 1 Facial features showing prominent metopic suture, microretrognathia and dolicocephaly.

A 3 month old female infant was referred to the Medical Genetics outpatient department for evaluation of failure to gain weight. She was the first child of non-consanguineous parents. She was born at 34 weeks gestation by emergency Caesarean section, done for decreased fetal move-

ments and polyhydramnios. Her birth weight was 1.6 kgs. After birth, she had weak cry and was unable to breast feed due to poor suck and had to be kept on bottle feeds. At 3 months of age, her weight was 3.9 kgs, length was 53.5 cm (between -3 and -4SD below the mean) and head circumference was 37.5 cm (3rd centile for her age). On examination, she had a dolicocephalic head, open anterior fontanelle, low set ears and microretrognathia (Figure 1). She had stridor and hypotonia with movement of all four limbs only in the plane of the couch and her deep tendon reflexes were weakly elicitable.

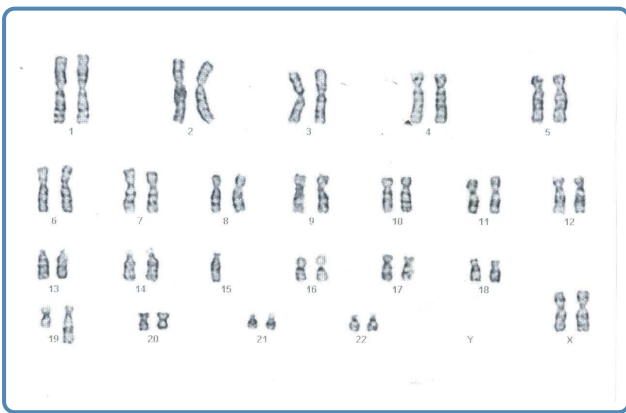


Figure 2 Karyotype of the proband showing unbalanced translocation involving chromosomes 15 and 19 [45,XX,der(19)(19pter→19q13.4::15q15→15qter),-15].

On investigation, her creatine phosphokinase was normal and there was no deletion in exons 7 and 8 of the *SMN1* gene. Her brain MRI showed corpus callosum hypoplasia with mild myelination lag. Due to the presence of dysmorphic features, growth delay and MRI findings, resolution G-banded karyotyping was done which revealed an unbalanced translocation involving chromosomes 15 and 19 [45,XX,der(19)(19pter→19q13.4::15q15→15qter),-15] (Figure 2). This chromosomal rearrangement had led to partial monosomy of 15q upto q15 and monosomy of 19q13.4 to qter. As the region from 15 centromere to 15q15 region contains the locus responsible for Prader-Willi syndrome, multiplex ligation-dependent probe amplification (MLPA) using probe sets P070 and P374 was done, which showed deletion of the chromosomal segment 15q11.2 (Figure 3). Karyotypes of both parents

were normal suggesting de novo origin of the translocation.

Discussion

As there are various causes of hypotonia during infancy including some treatable ones like Pompe disease, identification of the exact etiology is very crucial. Presence of hypotonia with poor suck has been listed as a clinical indicator of DNA testing for PWS.² Due to the absence of typical features of PWS in the neonatal period, it is difficult to make the clinical diagnosis especially in females. Methylation testing is the investigation of choice for confirmation of the diagnosis of Prader-Willi syndrome. However, other methods are required to identify the genetic subtype and to provide risk of recurrence to the family. This case illustrates the role of traditional cytogenetic analysis in the investigation of a hypotonic infant where the finding of a chromosomal rearrangement helped us to reach the correct diagnosis and to provide counseling and risk of recurrence in siblings. Earlier studies have also emphasized the role of conventional and molecular cytogenetic methods in the diagnosis of Prader-Willi syndrome.³ Till now, several chromosomal rearrangements involving chromosome 15/15 and chromosome 15 and other autosomes have been reported in PWS patients.⁴ Recurrent rearrangements involving specific regions on chromosome 15 have been identified. Mignon-Ravix et al. have demonstrated four cases of PWS caused due to translocation with the telomeric band of the partner chromosome in which the chromosome 15 breakpoint was clustered within a small 460 kb interval, located in the proximal 15q14 band.⁵ This region contains an LCR15 – duplicon sequence which favours meiotic recombination and all types of chromosomal rearrangements. Due to the presence of a cluster of recurrent translocation breakpoints and LCR15 – duplicon sequence in this region, it has been identified as a new breakpoint cluster (BP6). They also demonstrated that cases with a large deletion involving BP6 have a more severe or “expanded” phenotype.

In our case also, the breakpoint was present at 15q14 causing deletion of the proximal region and may lead to a severe phenotypic picture. As she was only three months of age at the time of presentation, further follow up is required to know the exact course of her development and her behavioural phenotype.

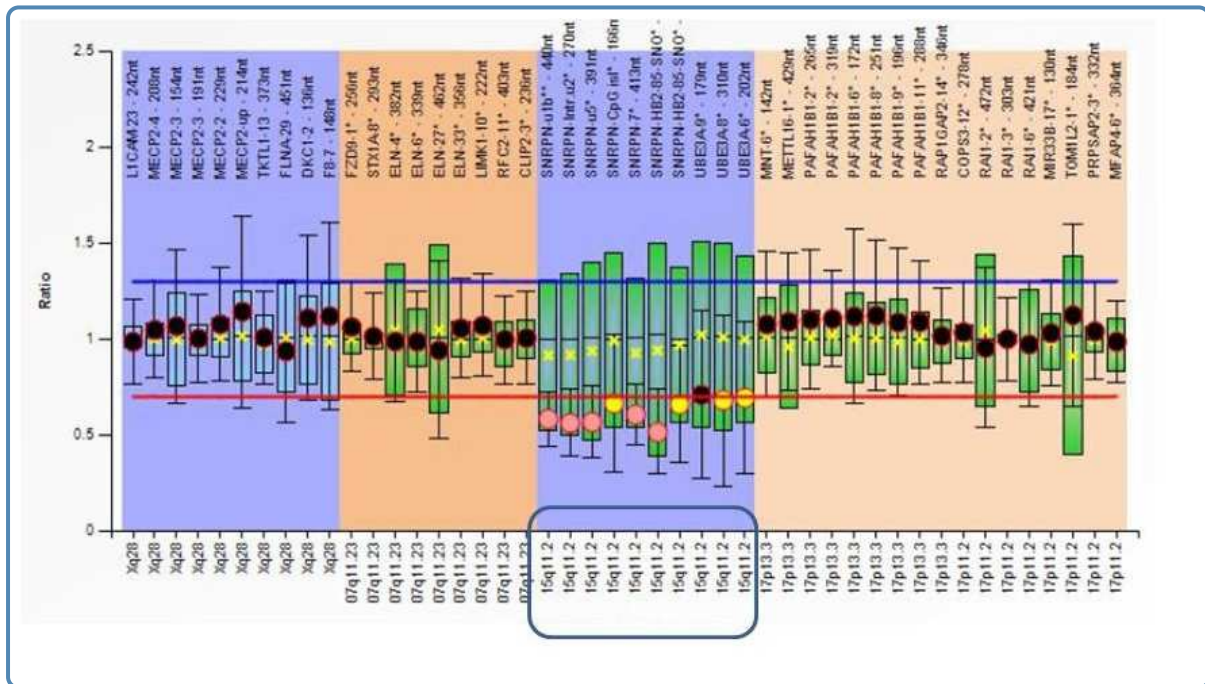


Figure 3 Multiplex Ligation dependent Probe Amplification showing deletion of the chromosomal segment 15q11.2.

Conclusion

Prader–Willi syndrome should always be considered as a possible differential diagnosis in a hypotonic infant and chromosomal abnormalities should be considered in the etiology of PWS. Also, in case of atypical large deletions involving 15q exact breakpoints should be delineated in order to determine the genotype-phenotype correlation and provide appropriate counseling to the family.

References

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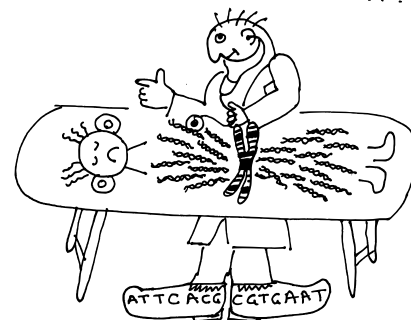
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