CASE SERIES

Wolf-hirschhorn Syndrome in Malaysia

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ABSTRACT

Introduction: Wolf–Hirschhorn syndrome (WHS) is rare but a well-known clinical condition due to partial deletion of the short arm of chromosome 4 (4p). It is distinguished by a distinctive facial appearance known as the "Greek warrior helmet", impaired growth and development, intellectual incapacity and seizures. The features of WHS vary between individuals based on the size and location of the missing piece of chromosome 4. **Methods:** Six cases of unsuspected WHS were diagnosed from 2011 to 2020 using conventional cytogenetic and fluorescent *in situ* hybridization (FISH) with a WHS probe. **Result:** Four of them had a visible cytogenetic deletion on chromosome 4p whereas the remaining two were evaluated with fluorescent in situ hybridization (FISH) using a WHS probe. **Conclusion:** Conventional cytogenetic testing may yield normal findings and it does not rule out the syndrome. Targeted FISH with a WHS probe is a better option.
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INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) derives its name from Hirschhorn and Cooper in the 1960s and Wolf et al later (1). It is a congenital disorder affecting the neurocognitive and physical capacity in children and is distinguished by growth deficiency, developmental disability and dysmorphic craniofacial characteristics known as the "Greek warrior helmet". However, they may manifest a wide clinical spectrum due to terminal 4p deletions which sometimes lead to the atypical presentations and overlapping with the other syndromes. Clinical variability depends on the deletion size ranging from small deletion (less than 3.5 Mb) which is usually associated with a mild phenotype (4, 8). Large deletion (5 to 18 Mb) is the most frequent and associated with more severe manifestations and very large deletion (exceeding 22–25 Mb) is characterized by the most severe phenotype (4).

It affects about 1/50,000 newborns, with a female predominance (1). However, it is likely to be underestimated, as cases may be missed due to a lack of identification or insufficient cytogenetic analysis (3). The typical clinical characteristics especially facial dysmorphism usually lead to a genetic diagnosis in early life. However conventional cytogenetic studies may reveal normal findings and might miss the diagnosis. Conventional chromosomal analysis usually detects large chromosome deletions. Hence it is important to highlight syndromic children with high suspicion of WHS, to be further investigated utilizing molecular cytogenetic methods such as fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (aCGH). However, some patients might be presented with nonspecific features, making a clinical diagnosis challenging to identify a relevant gene panel test.

To date, there have not been any WHS cases reported in Malaysia. Although the syndrome is known to occur in Malaysia, neither a comprehensive study nor a case report has been published. This is the first case series regarding this syndrome in Malaysia. We presented six cases of unsuspected WHS diagnosed from 2011 to 2020 with the purpose to increase clinical awareness and to improve good practice guidelines for the care and support of families and professionals as they need lifelong care.

CASE SERIES

We have found six cases of deletion of the distal part of the short arm of chromosome 4 in the Malay community. Five of them were diagnosed within 30 days of life except for patient 6 who was diagnosed at 6 months of age. The first case was diagnosed in 2011 and the most recent was diagnosed in 2020.

Patient 1: An 11-day-old girl presented with facial dysmorphism and skeletal abnormalities. On examination, she has micrognathia, short sternum, a small pelvis, clenched fingers and rocker bottom feet. She was the second child in the family from non-consanguineous parents. Her elder sister (1-year-old) is not known to have any genetic disorder. She was initially suspected of Edwards syndrome. However, the conventional cytogenetic revealed 46, XX, del (4) (p14) (Figure 1).

Patient 2: A 12-day-old girl presented with facial dysmorphism. On examination, she had hypertelorism, a down nose, a flat nasal bridge, bilateral punctuated ear with a periauricular pit. She had a cardiovascular manifestation which was a small patent foramen ovale with a bilateral renal cyst diagnosed with ultrasound and sacral dimpling. She was the second child in the family. Her 2- year- old brother was healthy with no known dysmorphism or genetic disease running in the family. She was subjected to chromosomal studies and found to have 46, XX, del (4) (p15.2) consistent with WHS on conventional cytogenetics (Figure 1).

Patient 3: A day 3 of life baby girl, presented with facial dysmorphic features and was treated for sepsis in the neonatal intensive care unit. She was the first child in the family. She was suspected clinically to have Turner syndrome because she had low-set ears, a webbed neck, a wide space nipple and wide carrying angle. However, her cytogenetic studies revealed 46, XX, del (4) (p15.2) consistent with WHS (Figure 1).

Patient 4: A day 2 of life baby boy had facial dysmorphism with clinical findings of frontal bossing, low set ears, narrow bifrontal diameter and small chin. He also has skeletal abnormalities such as overlapping fingers, hypospadias and congenital talipes equinovarus. He also had mild mitral regurgitation due to a large patent ductus arteriosus and dilated right heart. He was the third child in the family with his two elder brothers not known to have any genetic disorder. He was suspected to have Edwards syndrome because of his facial dysmorphism. His conventional cytogenetic studies revealed doubtful deletion of 4p. WHS-specific FISH was performed and the final cytogenetic study revealed 46, XY, del (4) (15.2) which was consistent with WHS (Figure 1).

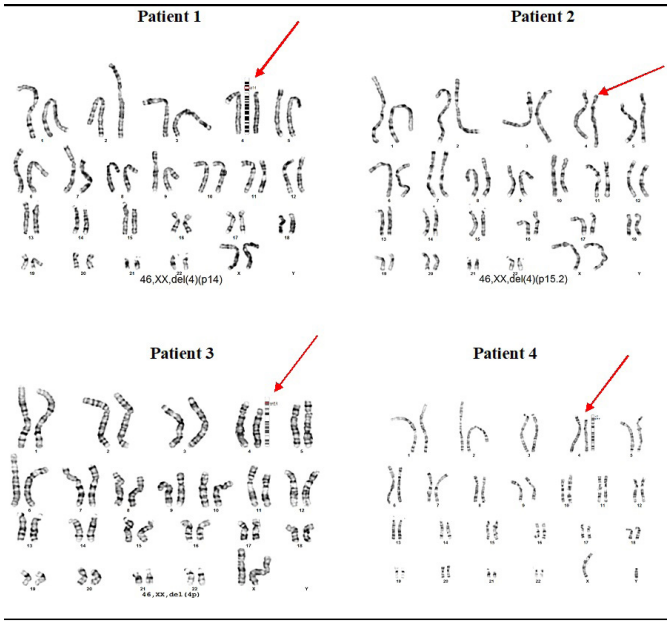

Figure 1 : G banding karyotype of patients 1-3 shows clear 4p deletion (red arrow). Patient 4 shows suspicion of deletion of 4p, WHS probe FISH was evaluated in this case.

Patient 5: A day 10-of-life baby girl presented with dysmorphic features and skeletal abnormalities. She was initially diagnosed with Pierre Robin syndrome. She had hypertelorism, flat nasal bridge, low set ear, down slanting eye, micrognathia and cleft palate with clinodactyly. She was the fourth in the family and had 2 healthy elder brothers and a sister. The conventional cytogenetic revealed no abnormalities. However, due to clinical dysmorphism, FISH proceeded and noted that there was only 1 red and 2 green for the WHS region probe indicating the deletion of the 4p region. Hence the cytogenetic was concluded as 46, XX, del (4) (p15.3) (Figure 2).

Patient 6: A 6-month-old, baby boy presented with facial dysmorphism. He has brachycephaly, a prominent forehead, a wide-spaced nipple, short neck, right ear bigger with hypotonia muscle tone. He was the youngest child of three siblings. Both of his sisters were normal without any chromosomal abnormalities. Like patient 5, the conventional cytogenetic showed no obvious abnormalities. However, due to clinical dysmorphism, FISH proceeded and noted that there was only 1 red and 2 green for the WHS region probe indicating the deletion of the 4p region. Hence the cytogenetic was retrospectively analysed and concluded as 46, XY.ish del (4) (p16.3p16.3) (Figure 2).

DISCUSSION

Clinical information remained very limited in all these cases and it is believed the syndromes are still misdiagnosed as another genetic condition until recently because some children may have very mild

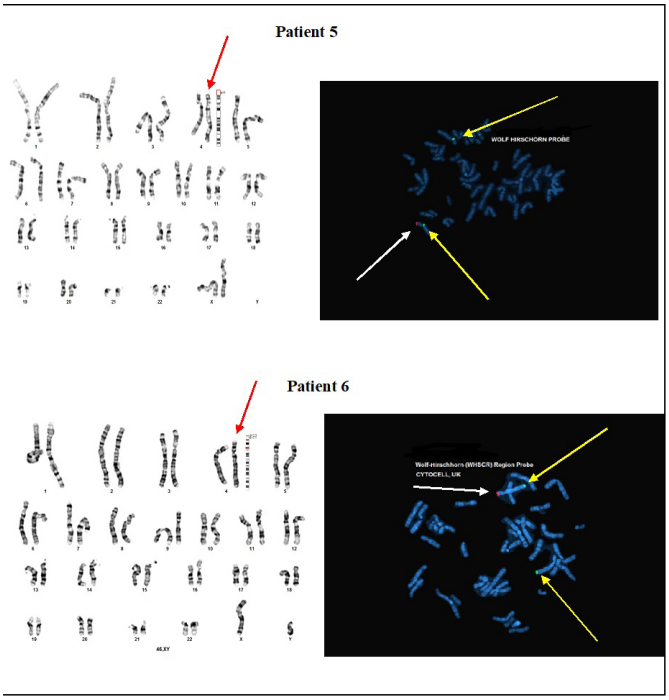

Figure 2 : The cytogenetic finding of patients 5 and 6 shows no obvious finding of 4p deletion (red arrows). WHS probe FISH shows deletion of 4p as demonstrated by 2 green (yellow arrow) and 1 red (white arrow) fluorescence signal.

symptoms. These cases may draw the attention of paediatricians to this clinical disorder that probably affects many more individuals with WHS than previously thought. This highlight that correct identification of a patient with highly suspicion index on the clinical presentation can lead to the most suitable laboratory testing which is cost-effective and targeted.

In our cases, none of them was suspected of WHS. Cytogenetic testing was done because of syndromic-looking neonates. Two cases were suspected of Edwards syndrome, one case was suspected of Turner syndrome and one case was suspected of Pierre Robin syndrome. The remaining two cases did not have any specific provisional diagnosis although the neonate presented with dysmorphic facies. It showed the syndrome is not well recognised although WHS has distinct and characteristic facial features. Typical facial dysmorphism includes a broad, flat nasal bridge and a high forehead associated with wide-spaced eyes and arched eyebrows giving rise to the "Greek warrior helmet" appearance (1, 6).

Other characteristic facial features include a short philtrum, a downturned mouth, micrognathia and poorly formed ears with small pits. They may have asymmetrical facial features and microcephaly (1, 9).

The failure of recognising the syndrome is possibly due to the rarity of cases as only 6 cases were diagnosed throughout 10 years as highlighted in these cases as compared to other common syndromes like Down syndrome. Further, the clinical features might overlap with other syndromes like Cri-du-chat syndrome, Down syndrome, Angelman syndrome, Williams syndrome and Smith-Lemli-Opitz syndrome (3). The most common overlapping features include mild facial dysmorphisms, developmental delays, short stature, failure to thrive, and microcephaly (3). Therefore making the clinical diagnosis is a challenge.

Most reviews and case reports do not ascertain the exact age of initial diagnosis but suggest ruling out WHS with Greek warrior helmet facial appearance soon after birth (2). All of our presented patients do not have the typical Greek warrior helmet appearance but facial dysmorphisms such as micrognathia, frontal bossing, hypertelorism, flat nasal bridge, low set ears and down slanting eye which was also described as facial features of WHS (3, 6). Congenital dysmorphism may exist in at least 10% of the referrals to neonatal intensive care, which involves underlying genetic conditions other than WHS. Other identifiable clinical features of WHS include mental retardation, congenital hypotonia, hypoplasia, congenital heart defects, midline defects and seizures. These features also might be seen in other syndromes making clinical recognition even more difficult. But still, it is important to recognize the clinical syndrome of WHS as it may aid in accurate diagnosis. Clinical recognition may bring the most effective initial step to screen indicated WHS patients for further FISH evaluation. Usually, a child with WHS is diagnosed based on the following symptoms: facial characteristics, growth problems, developmental delays and seizures that are resistant to treatment (9).

WHS being a microdeletion syndrome may be detected in both conventional and molecular cytogenetic techniques. However, standard cytogenetic can identify 50-60% of the cases whereas FISH can identify up to 95% of deletions (4). In our cases, 3 cases were identified by karyotyping alone (patients 1, 2 and 3) whereas the remaining 3 need FISH to diagnose. It is highlighted the limitation of standard karyotyping and the utility of FISH may yield more cost in diagnosing patients with WHS. Having a normal finding of regular G-banding on conventional cytogenetics in children with clinical dysmorphism does not rule out WHS as demonstrated in these cases. Type of chromosome abnormalities can be detected by using a conventional cytogenetic technique involving large deletions while terminal or interstitial microdeletions are detectable only by molecular methods. This could be the reason for patients 4, 5 and 6 do not show clear deletion of 4p on conventional cytogenetics however it was detected with WHS-specific FISH. Many researchers suggested that aCGH has allowed better identification of WHS with unremarkable previous karyotypes using G banding and WHS-specific FISH as some of the patients might have cryptic translocation (4, 5). aCGH can analyze the

entire genome at a significantly higher resolution over conventional cytogenetics to characterize especially the unbalanced rearrangements (7, 10).

CONCLUSION

Typical facial dysmorphism recognition with specific clinical features in WHS is important for clinical diagnosis. Normal cytogenetics analysis does not rule out the syndrome. Targeted FISH with a WHS probe or aCGH yield a better identification of the syndrome. Correct identification of the syndrome can lead to the correct diagnosis with efficient tools for diagnosis and comprehensive treatment efficacy can be in place.

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