UNBALANCED TRANSLOCATED GENOME IN WOLF-HIRSHHORN SYNDROME (WHS) FROM INDONESIA: A RARE CASE REPORT AND LITERATURE REVIEW

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Abstract

Wolf-Hirschhorn syndrome (WHS) is a rare genetic disorder that involves partial deletion of the short arm of chromosome 4. Although rare, this syndrome may cause significant morbidity and mortality for the patients. We report a rare case of WHS in a 3-year-old girl. The patient came to the hospital with complaints of unprovoked generalized tonic seizure one and a half hours before hospital admission. The seizure duration was only 5 minutes without any behavioral changes before or after the seizure. The patient had a characteristic facial appearance which resemble a "Greek helmet", delayed growth and development, and clubfoot. Magnetic resonance imaging (MRI) examination revealed suspicion of bilateral cerebral hypoplasia. The electroencephalography (EEG) result was within normal limits. Echocardiography showed 2-mm patent foramen ovale (PFO) and 2-mm ventricular septal defect (VSD) with left-to-right shunt. The chromosomal analysis demonstrated a translocation between chromosome 4 with chromosome 8. A better understanding of the WHS process and its characteristics will allow healthcare providers to give appropriate and comprehensive multidisciplinary care.

Keywords: Wolf-Hirschhorn syndrome; genetic disorders; chromosome 4; neurology; pediatric

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1. INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is a rare congenital disorder caused by a microdeletion in the short arm (p) of chromosome 4.[1] This syndrome was first described by Cooper and Hirschhorn in 1961 in a child who had defects of midline fusion, low birth weight, poor development, and seizures soon after birth.[2] Not long after, in 1965, Wolf et al.[3] also reported a similar case. It was from these two figures that the name of this genetic disorder was taken.[2,3] In both cases, there were typical craniofacial characteristics, namely the presence of a prominent forehead, hypertelorism, and the wide bridge of the nose continuing to the forehead so that it is known as the "Greek warrior helmet appearance".[4]

This syndrome is quite rare because the incidence is estimated to be only around 1 in 50,000 to 1 in 100,000 live births.[5,6] In addition, the mortality rate caused by this syndrome is quite high, reaching 34% in the first 2 years of life.[7] Another study conducted in 2001 found that the mortality rate from WHS was as high as 21% in the first 2 years of life.[6] Given the enormous burden of this syndrome, evidence-based data regarding WHS is very important to give more information about the characteristics of WHS so earlier detection and comprehensive treatment may be possible. Unfortunately, studies on WHS are still very scarce.

Hereby, we report a case of WHS that occurred in a 3-year-old girl. We have followed CARE guidelines in compiling this case report.[8]

2. CASE PRESENTATION

A 3-year-old girl was brought by her parents to the hospital with the chief complaint of a seizure one and a half hours before hospital admission. The seizure occurred in the form of stiffness of both arms and legs (generalized type seizures) with a duration of 5 minutes. After experiencing a seizure, she fell asleep immediately without any changes in her behavior afterward. She experienced her first seizure when she was one year and eight months old and routinely consumed 30 mg/kg/day of valproic acid since October 2019. Other complaints in the form of fever, cough, runny nose, shortness of breath, and weakness of the limbs before the seizure were denied by her parents. Her parents confessed that for the last 2 months, she no longer came for a follow-up visits at the child neurology clinic and no longer took valproic acid. She had a history of treatment at the Paediatric Intensive Care Unit (PICU) in January 2022 due to status epilepticus. She also had global developmental delay which was characterized by the inability to sit up, the inability to say the words "father" and "mother", and often unable to respond when she was called. She had received complete basic immunizations in Indonesia (BCG, Polio, DTP, measles, and hepatitis B). There was no significant antenatal history because her mother routinely attended antenatal care (ANC) at the hospital. Her birth history indicated that she was born at 35 weeks of gestation via cesarean section (CS) for indications of placenta previa with a birth weight of 2400 grams and a birth length of 45 cm. Her family history was also unremarkable.

On the physical examination, she had a body weight of 7.5 kg with a body length of 76 cm which indicated severe malnutrition. Examination of the head revealed microcephaly (head circumference 42.5 cm) along with characteristic facial appearance, including frontal balding, high arched and sparse eyebrows, ocular hypertelorism, monocular strabismus, broad nasal tip, deep philtrum, exaggerated cupid's bow, and high palate. Examination of both lower legs showed flexion of the ankles, inversion of the legs, adduction of the forefoot, and medial rotation of the tibia. Other physical examination results were unremarkable.

In this patient, a series of supporting examinations were carried out to assist in establishing the diagnosis. Plain radiographs of the lower legs showed bilateral congenital talipes equino varus (CTEV) or clubfoot where the right side was heavier than the left side. The results of the head magnetic resonance imaging (MRI) examination depicted a suspicion of bilateral cerebral hypoplasia in which the cerebral sulcus and fissure appeared prominently. She also underwent an electroencephalography (EEG) examination to find out the seizure's focus but the results were within normal limits. Echocardiography examination found a 2-mm patent foramen ovale (PFO) with a left to right shunt and 2-mm ventricular septal defect (VSD) sub-arterial doubly committed (SADC) type with a left to right shunt. Finally, she also underwent a chromosomal analysis examination and the results showed a complete chromosome number with sex chromosome XX but there was a translocation of chromosome 8 to chromosome 4 (46, XX, t(8;4)(q22;p16,3)).

Based on these results, she was finally diagnosed with Wolf-Hirschhorn Syndrome. Valproic acid treatment was continued to prevent seizures in this patient. She also consulted with the nutrition department to improve her nutritional intake and nutritional status. In addition, she was also undergone physiotherapy to help stimulate her development and improve the posture of both legs.

3. DISCUSSION

Wolf Hirschhorn Syndrome (WHS) or also known as 4p- syndrome is a genetic disorder due to partial deletion of the short arm of chromosome 4.[1] The name WHS is derived from its discoverer, Hirschhorn et al.[2] and Wolf et al.[3], the first two persons who described this case. This syndrome is more commonly seen in women than men with a ratio of 2:1.[9] A recent study in 2022 showed that among 18 cases of pregnancy with WHS, 13 of them (72.2%) were female while the remaining 27.8% were male.[10] In our case, the patient is female.

WHS can affect all parts of the body and can be found even from the prenatal period (before birth).[11] During the prenatal period, fetuses with WHS will usually experience significant intra-uterine growth restriction (IUGR) so their birth weight tends to be low (below 2.5 kilograms).[11] Their growth will often be impaired and their development is delayed.[11] In this patient, she weighed around 2.4 kilograms at birth. Her growth chart indicated that she had severe malnutrition status. Based on the Denver Developmental Screening Test (DDST), she also had a global developmental delay.

During the postnatal period, one of the main features of WHS is seizures.[12,13] Seizures are usually found in more than 90% of WHS cases with onset within the first 3 years of life and have become a major concern for parents.[12,13] The most common seizure form seen in WHS cases is generalized tonic-clonic seizures (about 70%), followed by tonic spams (20%), focal seizures with impaired consciousness (12%), and clonic seizures in 7% of patients.[12,13] On EEG examination, patients with WHS will usually have distinctive features that can be seen even in patients without seizures.[12,13] EEG features typically seen in 90% of these cases are: (1) frequent, ill-defined, diffuse or generalized or with variable predominance over both hemispheres, high-amplitude, sharp element spike/wave complexes at 2 to 3.5Hz, occurring in long bursts (lasting up to 25 s), activated by slow-wave sleep; (2) frequent high-amplitude spikes–polyspikes/wave complexes at 4 to 6Hz, over the posterior temporal-parietal-occipital regions, often triggered by eye closure; (3) slow background activity; (4) poverty of the usual rhythmic activities both over the rolandic regions and over the posterior third of the head, on eye closure; (5) the sleep spindles, well recognized in most patients, were hardly recognized in a minority.[12,13] However, in 10% of cases, EEG results can be normal during the interictal period.[12,13] In our case, the patient came with a chief complaint of seizures 1 hour and 30 minutes before admission to the hospital. The patient's seizures were in the form of generalized tonic seizures but with normal EEG results. The patient also had her first seizure at the age of 1 year and 8 months.

Not only seizures, another major feature that can be found in patients with WHS is the presence of distinctive craniofacial features.[14] The head is usually small (microcephaly) which may be accompanied by a high/prominent forehead.[14] The space between the eyes is widened (ocular hypertelorism) with a broad nasal bridge and high-arched eyebrows.[14] The philtrum which connects the nose and mouth is relatively short.[14] The maxillary area is usually underdeveloped characterized by micrognathia and may be accompanied by a cleft lip and/or cleft palate.[14] The mouth is wide with down-turned corners and a short upper lip.[14] All of these craniofacial features resemble the "Greek warrior helmet" appearance.[14] In this patient, all of these features could be found, except for the maxillary features in which this patient did not have any micrognathia or cleft lip/palate.

In addition to the main features above, there are other features that can be found in patients with WHS in the form of defects in various organ systems of the body.[14] Defects in otolaryngology can include dysplastic ears, periauricular tags, cochlear deafness, recurrent otitis, and recurrent respiratory infections.[14] Ophthalmic defects may include iris coloboma, microphthalmia, and strabismus.[14] In the gastroenterology system, patients with WHS may experience difficulty in swallowing or gastroesophageal reflux.[14] In the cardiovascular system, congenital heart defects such as atrial septal defects (ASD) and ventricular septal defects (VSD) can be found.[14] In the genitourinary system, defects may appear in the form of hypospadias, renal agenesis, oligomeganephronia, bladder exstrophy, cystic dysplasia/hypoplasia, or obstructive uropathy.[14] In the musculoskeletal system, patients may have skeletal growth retardation.[14] The patient in our case has a defect in the cardiovascular system in the form of a small ventricular septal defect (VSD) measuring 2 mm which was proven through echocardiography. Besides that, the patient also has defects in the musculoskeletal system in the form of bilateral congenital talipes equino varus (CTEV) as evidenced by physical examination and plain radiograph results.

In making a diagnosis of WHS, additional tests are usually needed in the form of a genetic test with chromosome analysis to confirm the presence of abnormalities in the short arm of chromosome 4.[15]

The most common form of chromosome abnormality that can be seen in WHS cases is partial/terminal deletion of the short arm (p) of chromosome 4. (del(4p16.3)).[15] However, in some cases, translocations between the short arm of chromosome 4 and other chromosomes, such as chromosome 8p, 11p, or 15p, can also be found.[15,16] In our case, the results of the chromosomal analysis found a translocation between the short arm chromosome 4 and chromosome 8.

Some portions of manifestation in WHS caused by size of deletion in short arm chromosome 4, but however not all cases present similar between size of deletion and severity of syndrome. Enormous variation in non-deleted 4p region and distinct genetic backgrounds for every person could alter each phenotype of the patient. Previous studies stated that approximately 13 – 15% cases of WHS are also duplicated for other chromosome region due to an unbalanced of translocation, however the rate of sporadic translocations in WHS was approximately 2%.[17] Such proven type translocation in WHS was not commonly reported. In this case, the deleted 4p region that has also unbalanced translocation in 8p region making the patient had trisomy clinical manifestation for that gene material. Those some clinical manifestations with partial monosomy 4p and trisomy 8p are mental retardation, muscular hypotonia, prominent forehead, broad nasal bridge, congenital heart defect, and persistent seizure resulting in status epilepticus. [18]

There are some identified genes found to modify facial pattern, cartilage and forebrain formation. Further studies explained that whsc1, whsc2 and tacc3 are critical for early cartilage formation which can present craniofacial dysmorphism of WHS. On the other side, translocation at whsc1, whsc2, letm1 and tacc3 also had impact on forebrain size, resulting in decrease of psychomotor and language delay in the patient.[19] Further microdeletions or translocation at those genes significantly produce more severe intellectual disability and microcephaly. Whereas whsc2 depletion will cause reduction in midbrain size. On the other hand, deletion in letm1 gene become the major contributor for seizure development in children because this gene alters normal neuronal excitation and survival, as we can see in these WHS patient.

The exact prevalence of unbalanced translocations in WHS is hard to predict because conventional chromosome analysis such as karyotyping and fluorescence in situ hybridization (FISH) cannot detect all type of translocation during examination. FISH analysis has limitation such as only small regions of genome be examined at a time, and karyotype analysis can only analysed resolution in 5 – 10 Mb range.[20] Other studies recommend to use array comparative genomic hybridization that can examine entire genome with higher resolution rather than conventional cytogenetics and FISH technique. It can exhibit more translocated genome in patient presented with various phenotypes. The larger the size of translocation more diverse phenotype of WHS patients.

Because the manifestations of WHS are so diverse, the treatment and interventions given to the patients must be tailored to the needs of each individual.[21] Comprehensive management involving various scientific disciplines will provide more optimal results.[21] Rehabilitation support in the form of feeding therapy, assistive communication, speech therapy, physical therapy, occupational therapy, and school support can help stimulate the growth and development of patients who are delayed. Genetic counseling is also recommended for families who have children with WHS.[21] In our case, the treatment of the patient has involved pediatric neurologists, pediatric cardiologists, pediatric growth and development specialists, orthopedic doctors, medical rehabilitation specialists, and also nutritionists. Nutritional support and counseling were also provided to the patient to help improve her nutritional status and growth. Physiotherapy was also performed to stimulate the patient's development and improve the patient's leg posture.

4. CONCLUSION

Wolf-Hirschhorn syndrome is a rare genetic condition that is associated with a high risk of morbidity and mortality. It involves the genetic deletion of a portion of chromosome 4's short arm (p). The main characteristics of this disorder include a characteristic facial appearance known as the "Greek helmet", growth and development delays, intellectual impairment, and seizures. Knowing and understanding the process of WHS enables healthcare workers to ensure that an infant or child affected by WHS receives current, thorough, and appropriate multidisciplinary care. As healthcare providers become more knowledgeable, they will be able to give parents and families the appropriate educational assistance.

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