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Wolf–Hirschhorn syndrome – a case report

Zespół Wolfa–Hirschhorna – opis przypadku

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Abstract

Wolf–Hirschhorn syndrome is a severe genetic condition that affects many systems of the human body. The genetic mechanism is based on the deletion of the distal portion of the short arm of chromosome 4 (4p). Individuals affected by the syndrome have a special phenotype: wide bridge of the nose, widely spaced eyes, micrognathia, microcephaly, growth retardation, cryptorchidism, heart defects, hearing loss and severe intellectual disability. The patient from our case report was hospitalised at the Lviv City Children's Hospital at the age of six hours in a severe condition, with distinctive features of a genetic syndrome, which was connected with intraventricular haemorrhage. At the age of three months, he showed delayed physical and neurocognitive development and a characteristic appearance, which led to a specialist consultation to diagnose the genetic disease. This time, on the basis of clinical, laboratory and instrumental findings, the boy was diagnosed with Wolf–Hirschhorn syndrome.

Keywords: Wolf–Hirschhorn syndrome, hypertelorism, microcephaly, micrognathia

Streszczenie

Zespół Wolfa–Hirschhorna jest ciężką chorobą genetyczną objawiającą się szeregiem wad wrodzonych dotykających różnych układów ludzkiego organizmu. Mechanizm genetyczny tego zespołu polega na delecji dystalnej części krótkiego ramienia chromosomu 4 (4p). Osoby dotknięte tym schorzeniem mają charakterystyczny fenotyp, na który składają się m.in. szeroka podstawa nosa, szeroko rozstawione oczy, mikrognacja, mikrocefalia, upośledzenie wzrostu, wnętrostwo, wady serca, ubytki słuchu oraz ciężkie upośledzenie intelektualne. Przedstawiony w pracy pacjent był hospitalizowany w Miejskim Szpitalu Dziecięcym we Lwowie w 6. godzinie życia w stanie ciężkim, z wyraźnymi cechami zespołu zaburzeń genetycznych oraz krwawieniem dokomorowym. W wieku 3 miesięcy, ze względu na wyraźnie opóźniony rozwój motoryczny oraz neuropoznawczy, a także charakterystyczne cechy fizjonomiczne, pacjenta skierowano do konsultacji genetycznej w celu ustalenia rozpoznania. W oparciu o wyniki badań fizykalnych, laboratoryjnych i genetycznych stwierdzono u niego zespół Wolfa–Hirschhorna.

Słowa kluczowe: zespół Wolfa–Hirschhorna, hiperteloryzm, mikrocefalia, mikrognacja

INTRODUCTION

Wolf–Hirschhorn syndrome is an exceptionally rare chromosomal disorder caused by partial deletion of the short arm of chromosome 4, accompanied by developmental delay, a characteristic facial appearance and a variety of heart and kidney defects. As the amount of the genetic material deleted varies, the symptoms of this syndrome also vary from case to case.

CASE REPORT

Below we present a personal observation of a child with Wolf–Hirschhorn syndrome.

A 10 months old boy was admitted into the paediatric department of the Lviv City Children's Hospital due to a rise in temperature to 38.9°C, convulsions and lethargy. Patient history revealed a pathological delivery by caesarean section at 37/52. Apgar score at birth was 6/8 points, weight – 2150 g, length – 47 cm. At the age of six hours, he was transferred to the neonatal intensive care unit of the Lviv City Children's Hospital. The infant's condition upon admission into the intensive care unit was severe. During the examination, he behaved sluggishly, with preserved consciousness and suppressed physiological reflexes. The findings included a high-arched palate, facial dysmorphia and covert spinal hernia. Auscultation of the lungs and heart showed no abnormalities. The abdomen on palpation was not painful. Examination of the genital organs revealed hypospadias (stem form) and right cryptorchidism. At the age of 7 days, he was transferred to the department of pathology of the newborn of the Lviv City Children's Hospital, where he was treated for 15 days. The diagnosis at the time included acute hypoxic-ischaemic encephalopathy, intraventricular haemorrhage, congenital malformation of the genitourinary system with renal hypoplasia, stem form of hypospadias, right cryptorchidism, a congenital heart defect consisting of an open oval window and bicuspid aortic valve, neonatal jaundice and deficiency anaemia.

At 3 months of age, the boy showed delayed physical and neurocognitive development and a characteristic appearance, which led to a genetic consultation to identify the genetic disease involved. This time, on the basis of the clinical, laboratory and instrumental findings, the boy was diagnosed with Wolf–Hirschhorn syndrome.

Upon admission to our department, the baby (10 months old) weighed 6000 g and was 69 cm long. The general condition of the child was moderate. The body temperature was 37.6°C, heart rate – 140 beats/min, breathing frequency – 40 breaths/min. There was a severe delay of neurocognitive development. The child's appearance was very characteristic, with widely spaced eyes and a flat nose. The skin was pale and clear, and the visible mucous membranes were hyperaemic and moist. Subcutaneous adipose tissue had developed slightly. Peripheral lymph nodes were not palpable. Respiratory system examination showed shortness of breath through the nose and serous discharge. Auscultation showed respiratory difficulty on both sides. Cardiovascular system: percussion border of the heart was not changed, auscultation heart tones were sonorous, rhythmic, auscultated systolic noise on top. Digestive System: mouth hyperaemic, granular. The abdomen presented normal, soft, available in all regions for palpation, with no signs of oedema. The liver was palpable 2.0 cm below the costal arch, smooth edge. Stool formed without pathological impurities, 2 times a day. Urination: free, adequate diuresis. Genitals: hypospadias.

No abnormal laboratory parameters in blood and urine tests were found. Radiography of the chest: indirect signs of heart disease, lungs without pathological changes. Electrocardiogram: sinus tachycardia, heart rate – 160 beats/min, metabolic changes in the myocardium. Echocardiography: bicuspid aortic valve with mild stenosis. Neurology consultation revealed severe delay of psychomotor development and hypotension caused by a genetic disease. Urology consultation showed renal hypoplasia and hypospadias – stem form.

On the basis of all the clinical data and accessory examinations, the final diagnosis for the patient was as follows: strep throat, Wolf–Hirschhorn syndrome, febrile seizures, delay of psychomotor development, congenital heart defect – bicuspid aortic valve, renal hypoplasia, hypospadias – stem form. After receiving symptomatic treatment for associated diseases, the boy was discharged home with relevant recommendations for Wolf–Hirschhorn syndrome-related health issues, including balanced nutrition, prevention of rachitis, and regular paediatric, cardiologic, urologic and neurologic care and check-ups.

DISCUSSION

The first mention of this syndrome dates back to 1961 when Hirschhorn and Cooper annotated their observations about a newly discovered genetic pathology that included severe mental retardation, heart defects, and hypertelorism. In 1965 Wolf and Hirschhorn, independently of one another, published articles that described well defined pathogenic mechanisms of the syndrome, its most common clinical manifestations, and thus brought the disease to the attention of geneticists and physicians around the world.

The prevalence of Wolf–Hirschhorn syndrome is estimated at one in 50,000 births. This ratio might be underestimated because as in many cases involving genetic diseases, pathology is not diagnosed in all affected individuals, especially in the cases of miscarriages in the early neonatal period. About 35% of children with Wolf–Hirschhorn syndrome die within the first two years of life. Typically death is caused by a heart defect, aspiration pneumonia, and other infectious complications. The highest life expectancy is established to be 20–30 years among all reported cases of patients with this syndrome. For unknown reasons, the syndrome is considered to be gender-sensitive, affecting more females than males, with 2:1 ratio respectively.

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The genetic mechanism of Wolf–Hirschhorn syndrome involves the removal of genetic material from the distal short arm of chromosome 4. Considering that the section strip 16.3 of chromosome 4 (4p16.3) is the most important region for the disorder, it means that removal of this area leads to the full expression of the syndrome. According to this pathogenetic process, other names for this syndrome are monosomy 4p, 4p- syndrome, chromosome 4p monosomy, partial monosomy 4p. A large deletion of several megabases (Mb) on the long arm of the chromosome is easily detected by standard chromosome analysis and correlates with the severity of defects. However, microdeletions in the band 4p16.3 are identified only by specific molecular tests and are usually not defined by significant manifestations of defects. There are three phenotype categories of Wolf–Hirschhorn syndrome. They are determined and correlate with the degree of 4p deletion. The first category consists in a small removal (≤3.5 Mb) that is usually associated with a mild phenotypic expression, insignificant and sometimes completely missing manifestations of major defects. The more common second category is caused by large deletions (5–18 Mb), which cause widely known expression of the syndrome's phenotype. The third category is caused by a great deletion that exceeds 22–25 Mb, creating a phenotype that can hardly be defined typical for Wolf–Hirschhorn syndrome[1]. Signs and symptoms of this disease are clearly associated with the loss of several genes on the short arm of chromosome 4. *WHSC1*, *LETM1*, and *MSX1* gene have been detected in patients with this disease. Their specific functions are still not fully known. *WHSC1* gene is associated with the common facial appearance and developmental delay. *LETM1* gene is associated with bursts of abnormal electrical activity in the brain. *MSX1* is responsible for dental abnormalities, cleft lip and palate[2].

Clinically, Wolf–Hirschhorn syndrome is characterized by considerable polymorphism. Almost all people with this disorder have their own distinctive features, including hypertelorism, broad nose, flat noseband and high forehead. This combination of facial features is referred to as "Greek warrior helmet" appearance. Additionally, low location of the mouth is observed, along with a small chin, a short distance between the nose and the upper lip, cleft palate and cleft lip, low-lying, small-sized ears with a narrow ear canal, which all together form the "fish face." Also, the patients have an asymmetrical face and microcephaly. Children with this syndrome may also have strabismus, ptosis, coloboma, changes in the iris, oblique eye slits, excess skin over the inner corner of the eye. Among skin manifestations, a crease across the palm, highly curved nails, not distinct fingerprints and dual crease on the thumb are common[3]. Development and growth are disturbed both before and after birth, weight-gain and growth are slow. The patients also have weak muscle tone (hypotonia) and underdeveloped muscles. Intellectual disability in Wolf–Hirschhorn patients ranges from mild to severe. Compared to people with other forms of mental retardation, their social skills are stronger, while verbal communication skills are generally much weaker. Also, heart defects (defects of atrial or interventricular membranes) and kidney defects (polycystic, aplasia/hypoplasia of one or both kidneys), cryptorchidism and hypospadias are all frequent manifestations of the syndrome.

The diagnosis of Wolf–Hirschhorn syndrome can be established prenatally by ultrasound in 50–60% of cases. Otherwise, it is diagnosed by the finding of a heterozygous deletion of the critical region on chromosome 4p16.3 by conventional G-banded cytogenetic analysis, chromosomal microarray or fluorescence *in situ* hybridization (FISH)[4]. There is no specific remedy for patients with Wolf–Hirschhorn syndrome other than symptomatic and supportive treatment. It is based on surgical correction of birth defects and team approach that may include special education, physical therapy, and other medical, social or professional services necessary to develop the full potential of the patients.

CONCLUSIONS

Genetic anomalies remain one of the biggest problems of modern paediatrics worldwide. There are no distinct etiological and pathogenic mechanisms we could influence to prevent a variety of chromosomal abnormalities. A wide range of laboratory – instrumental methods of diagnosis are now available, and the latest developments in treatment are used to improve the quality of life for patients with different genetic abnormalities, and help them to sufficiently adapt to society, even if long-term prognosis is unfavourable.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations that might negatively affect the content of this publication and/or claim authorship rights thereto.

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