

WOLF-HIRSCHHORN SYNDROME - A CASE WITH 4p16 DELETION DEMONSTRATED BY STANDARD CHROMOSOME ANALYSIS

**Valerica Belengeanu¹, Kinga Rozsnyai¹, Adrian Lacatusu²,
Simona Farcas¹, Cristina Gug¹**

REZUMAT

Am descris un caz cu o deleție terminală 4p, evidențiată prin examen citogenetic utilizând metoda standard cu bandare G. Examenul clinic a relevat multiple semne fenotipice caracteristice pentru sindromul Wolf-Hirschhorn clasic. Prezentăm date recente legate de corelații fenotip-genotip și trecem în revistă ultimele descoperiri privind patologia moleculară a acestui sindrom.

Cuvinte cheie: deleție 4p, sindrom Wolf-Hirschhorn, fenotip clasic

ABSTRACT

We present a case with a 4p terminal deletion, evidenced in GTG-banded chromosome preparations. On clinical examination a large number of phenotypic signs described in the classical Wolf-Hirschhorn syndrome were found. We discuss recent data related to phenotype-genotype correlations and summarize the latest results regarding the molecular pathology of the syndrome.

Key Words: 4p deletion, Wolf-Hirschhorn syndrome, classic phenotype

INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is caused by variable sized deletions of the short arm of chromosome 4, and is characterized by a wide spectrum of clinical signs, encompassing an easily recognizable, typical facial appearance, that resembles a "Greek warrior's helmet" and includes a high forehead, prominent glabella, highly arched eyebrows, hypertelorism, epicanthal folds, wide nasal bridge/beaked nose, short philtrum, fish-like mouth with downturned corners and low set ears, simplified in form, in combination with microcephaly, congenital

hypotonia, low birth weight, failure to thrive and variable degree of mental retardation.

CASE REPORT

The patient was the fourth child of non-consanguineous healthy parents. He was born with a birthweight of 1500 g and length of 44 cm.

On examination at the age of 11 months, he was found to have severe growth retardation: a weight of 5700 g and a length of 65 cm, both below the 3rd percentile. Head circumference was 42 cm (below the 3rd percentile).

He presented with distinctive facial features: he had a high forehead with a prominent metopic suture, high frontal hairline, prominent glabella, hypertelorism, epicanthal folds, sclerae with a blue tint, broad nasal root, prominent philtrum, thin upper lip, downturned mouth and low-set ears. (Figure 1) He had high-arched palate and a short, broad neck. None of the teeth had erupted by the age of 11 months.

¹ Department of Medical Genetics, Victor Babes University of Medicine and Pharmacy, Timisoara, ² IInd Department of Pediatrics, Timisoara University Hospital

Correspondence to:

Valerica Belengeanu, Dept. of Medical Genetics, Victor Babes University of Medicine and Pharmacy, Piata Eftimie Murgu 2, Timisoara, Tel: +40256204476
Email: belvtim@yahoo.com

Received for publication: Apr. 23, 2004. Revised: Jul. 21, 2004.



Figure 1. Facial appearance of the patient with high forehead, hypertelorism, broad nasal bridge, carp-like mouth and low-set ears

Examination of the limbs revealed short arms, (Figure 2) small, square hands with long thumbs and tapering fingers, camptodactyly of the fourth fingers and clinodactyly of the fifth fingers. Dermal ridges were found to show an abnormal pattern: thenar crease was absent, and there was a short hypoplastic midpalmar crease. (Figure 3) The fifth finger had a single flexion crease on their volar surface.



Figure 2. Growth retardation with relatively short limbs



Figure 3. Abnormal palmar creases: absent thenar crease and short midpalmar crease

The infant had undescended testes.

Neurological examination revealed: generalized hypotonia, delayed psychomotor development, hypokinesia with sporadic voluntary movements. The child was not able to sit unsupported. Social smile, interest for the ambiance and reactivity to visual stimuli were present, but he did not react to auditory stimuli.

Chest X-Ray showed horizontalized ribs. X-ray examination of hands (Figure 4) revealed the relative shortness of tubular bones, especially of the distal

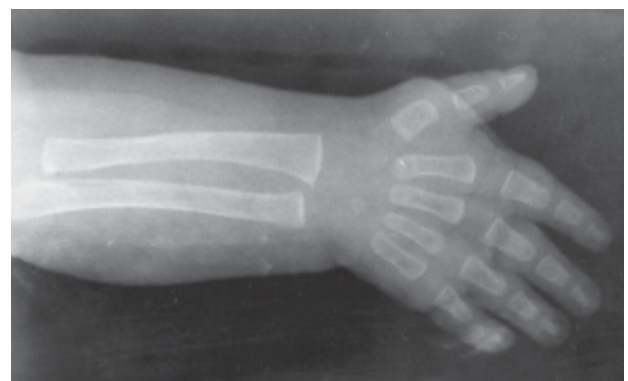


Figure 4. X-rays of the left hand showing hypoplasia of the middle phalanx of the fifth finger

phalanges. The middle phalanges of the fifth fingers were hypoplastic. Bone age was delayed; a single ossification center was visible in each carpal region.

Electrocardiogram and echocardiography did not show any abnormality.

Cytogenetic analysis from peripheral lymphocyte culture, using GTG banding, demonstrated a deletion of the 4p16 region. (Figure 5)

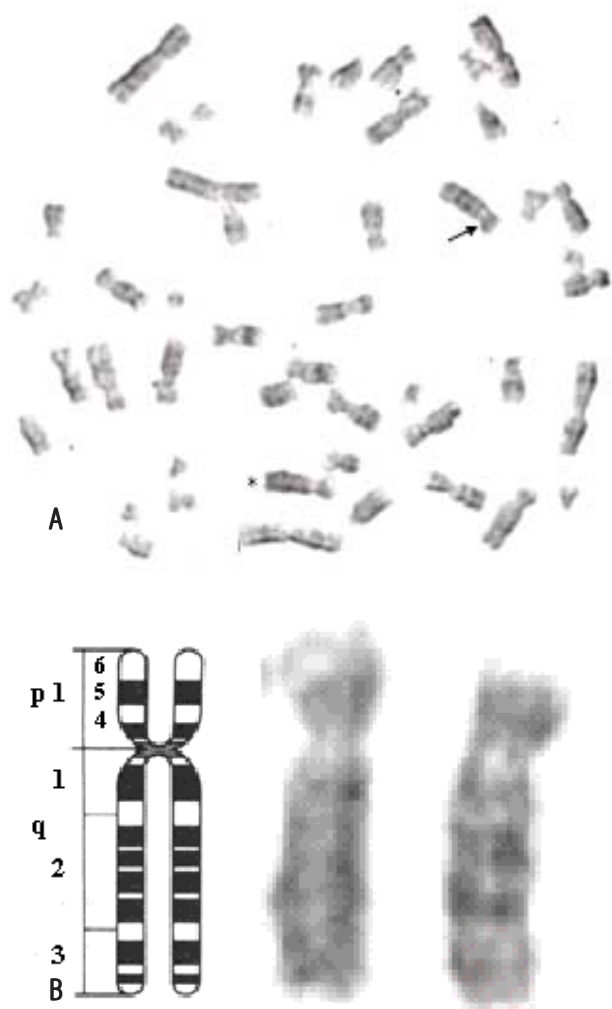


Figure 5. A. Metaphase spread showing the deleted chromosome 4 (arrow) and the normal homolog (*); B. partial karyotype and idiogram of chromosome 4.

DISCUSSION

WHS is caused by variable, partial deletions of the short arm of chromosome 4, from large deletions, detected with routine karyotyping methods to deletions visible only with high resolution chromosomal analysis, or even deletions of several kilobases long chromosomal segments detectable by the means of molecular-cytogenetic techniques, like fluorescence in situ hybridization (FISH).¹

From previous studies^{2,3} it appears that the severity of the phenotype mostly depends on the extent of

the deletion, although contradictory data exist.^{4,5} Large deletions usually are associated with a more severe phenotype, including multiple malformations (heart defects, genitourinary malformations), while microdeletions, detected by FISH, result in a milder phenotype,² that consists in the typical facial appearance, congenital hypotonia and mild mental and growth retardation. The critical region responsible for this “minimal” phenotype was mapped to the 4p16.3 region and it was restricted to several hundred kilobases,^{6,7} that contain 2 candidate genes: WHSC1, which was found to be largely expressed during in early development and WHSC2 with unknown function by now. The neighbouring region contains several candidate genes too, like FGF3 and LETM1, that are deleted in the majority of patients, so they may play a role in some aspects of the phenotype (the latter is thought to be pathogenetically involved in seizures).¹ The 4p16.3 region also contains a gene DFNA6 for autosomal dominant hearing loss, and a gene MSX1, required for oral and tooth development,⁸ which may account for dental anomalies (oligodontia, delayed dentition) frequently seen in WHS patients.

Our patient, having a terminal 4p deletion large enough to be detected using standard GTG-banding method, lines up a large number of clinical manifestations of the classical WHS phenotype: the characteristic craniofacial dysmorphism, hypotonia, microcephaly, growth retardation, severe psychomotor retardation, numerous skeletal abnormalities, abnormal dermal ridges, hearing loss and cryptorchidism. Curiously, he does not have any heart defect, the most important factor in the clinical outcome. Up to the moment of examination, he did not have seizures, although the age of onset of these varies between 3 and 23 months. The motor abilities, as well as communicative abilities were noted to improve in time.⁹

Although it would have been of interest, cytogenetic investigation of other family members was not possible, as the child had been abandoned by his parents and currently is in the care of a council home.

CONCLUSIONS

WHS is a contiguous gene syndrome, in which the phenotype depends on the deletion of several different genes and the allelic variants present in the homologous chromosome region.

We described a case with a large deletion of 4p, which exhibits a wide palette of clinical signs, but no cardiac or other internal organ malformations, these being of crucial importance in the prognosis.

REFERENCES

1. Wolf-Hirschhorn syndrome; www.ncbi.nlm.nih.gov/entrez/dispomim.cgi, accessed on April 12th, 2003
2. Zollino M, Di Stefano C, Zampino G, et al. Genotype-Phenotype correlations and clinical diagnostic criteria in Wolf-Hirschhorn syndrome. *Am J Med Genet* 2000;94:254-61
3. Wiczorek D, Krause M, Majewski F, et al. Effect of the size of the deletion and clinical manifestation in Wolf-Hirschhorn syndrome: analysis of 13 patients with a de novo deletion. *Eur J Hum Genet* 2000;8:519-26
4. Battaglia A, Carey JC, Cederholm P, et al. Natural history of Wolf-Hirschhorn syndrome: experience with 15 cases. *Paediatrics* 1999;103:830-64.
5. Meloni A, Shepard RR, Battaglia A, et al. Wolf-Hirschhorn syndrome: correlation between cytogenetics, FISH, and severity of disease. *Am J Hum Genet* 2000;67:149
6. Wright, TJ, Ricke DO, Denison K, et al. A transcript map of the newly defined 165 kb Wolf-Hirschhorn syndrome critical region. *Hum Molec Genet* 1997;6:317-24.
7. Zollino M, Lecce R, Fischetto R, et al. Mapping the Wolf-Hirschhorn syndrome phenotype outside the currently accepted WHS critical region and defining a new critical region, WHSCR-2. *Am J Hum Genet* 2003;75:590-7.
8. Nieminen P., Kotilainen J, Aalto Y, et al. MSX1 Gene is Deleted in Wolf-Hirschhorn Syndrome Patients with Oligodontia. *J Dent Res* 2003;82:1013-17.
9. Battaglia A, Carey JC. Update on the clinical features and natural history of Wolf Hirschhorn syndrome (WHS): experience with 48 cases. *Am J Hum Genet* 2000;67:127