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DIAGNOSIS AT A GLANCE

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Distinct facial dysmorphism, pre and postnatal growth retardation, microcephaly, seizures, mental retardation and hypotonia

Dismorfismi facciali tipici, ritardo di crescita pre- e post-natale, microcefalia, ritardo mentale e ipotonia

Here we present three patients (Figs. 1-3) characterized by:

- distinct facial dysmorphisms;
- pre and postnatal growth retardation;
- microcephaly;
- seizures;
- mental retardation;
- hypotonia.

Fig. 1.

Fig. 2.

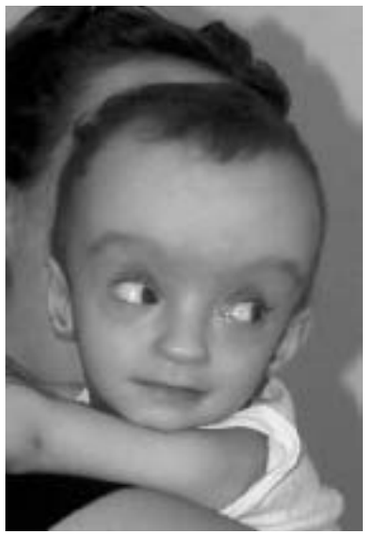


Fig. 3.

DIAGNOSIS

Wolf-Hirschhorn syndrome (OMIM # 194190)

DESCRIPTION AND INCIDENCE

Wolf-Hirschhorn syndrome (WHS) is named from the two authors that in 1965 described for the first time a clinical condition characterized by multiple dysmorphisms, pre and postnatal growth retardation, and mental retardation. The condition is due to a partial deletion involving the distal part of the short arm of chromosome 4 (4p -). Incidence of the syndrome is thought to be 1/50.000, with a female predilection of 2:1. However, some authors believe the incidence to be higher, due to the fact that a number of affected subjects is undiagnosed or misdiagnosed [1-5].

CLINICAL MANIFESTATIONS

The face is distinct and resembles a "Greek warrior helmet", with arched eyebrows, hypertelorism, epicanthic folds, prominent nasal bridge, short philtrum, down-turned corners of the mouth, micrognathia, low set ears with flattened helix and sometimes preauricolar pits or tags (Tab. I) [3-7]. Affected children show microcephaly and growth retardation of prenatal onset [8 9]. At birth, medium weight is 2.000 kg, length 44 cm, head circumference 30,7 cm. Subsequently, growth remains under the 3rd centile. This can be due to cleft lip and palate, with consequent difficulty in sucking; poor coordination in swallowing, and gastroesophageal reflux.

Psychomotor and mental retardation of variable degree is almost always present, and, according to recent publications, seems to be severe in 67% of subjects, moderate in 25% and mild in 8% [6 7]. Sleeping difficulties, including settling problems and nighttime waking, appear to be common, although easily overcome [6 7 10].

Among the major malformations, heart anomalies are recorded in 30-50% of the cases. Atrial septum defect is the most frequent, followed by pulmonary stenosis, ventricular septal defect, patent ductus arteriosus, aortic incompetence and Fallot tetralogy [6 7].

60-70% of patients show skeletal anomalies, including vertebral abnormalities, fused or supernumerary ribs, club foot. Structural anomalies of the central nervous system are reported in less than 50% of the subjects, including hypo-aplasia of the corpus callosum, decreased white matter volume or cerebellum hypoplasia [6 7].

Ocular anomalies, present in 40% of the children, include microphthalmia, coloboma, cataract, glaucoma, iris or optic disc defects [6 7]. Various genitourinary tract malformations can be observed in 25% of patients and include renal agenesis, cystic dysplasia or hypoplasia, oligomeganephroma, horseshoe kidney, renal malrotation, bladder extrophy, obstructive uropathy [6 7]. Vescicoureteric reflux has been described in 4/6 patients by Grisaru et al. [11]. These malformations can be observed in association with hypospadias and cryptorchidism in 50% of males. Abnormalities of the genitalia are less frequently observed in females, and are usually represented by aplasia or hyperplasia of clitoris, vaginal atresia, malformed or absent uterus, absent vagina, and ovarian cysts [8].

Delayed dental eruption with persistence of deciduous teeth, taurodontism, peg-shaped teeth and agenesis of some dental elements can be seen in as many as 50% of patients [6 7].

Seizures represent one of the major medical problems in children with 4p- syndrome. 50 to 100% [6 7 12] of them develops seizures between the 3rd and 23rd month of life. They can be unilateral, clonic or tonic with or without secondary generalization, or generalized tonic-clonic from the onset; are frequently associated with hyperpirexia. A partial or generalized clonic or tonic-clonic status epilepticus can be observed in a number of children. About 60% of patients develops atypical absences, usually accompanied by a myoclonic component. In 1/3 of cases seizures stop between the 2nd and 13th year of age [2 6 7].

In those patients in whom an EEG was performed, the following distinct abnormalities were observed: 2-3.5 Hz diffuse/generalized spike/wave complexes, activated by slow sleep, and occurring in long bursts (such anomalies were often associated with atypical absences); frequent 4-6 Hz spike/wave complexes, over the posterior third of the brain, facilitated by eye closure [2 6 7].

The frequent chronic otitis media can produce conductive hearing impairment, with negative consequences on the potential development of language. Sensorineural deafness has been reported less frequently. Exhaustive audiologic evaluation is recommended, and any hearing impairment must be specifically treated [13].

Antibody deficit, involving particularly IgA and IgG2, was observed in 69% of 4p- patients reported in an isolated study. This was thought to be responsible for the recurrent respiratory tract infections [14]. The survival of

Tab. I. Frequency of different features in WHS patients.

Anomalies	Percentage
Distinct face	75-100%
Pre-postnatal growth delay	75-100%
Psychomotor delay	100%
Severe	67%
Moderate	25%
Mild	8%
Hypotonia	100%
Seizures	50-100%
EEG anomalies	70%
Skeletal malformations	60-70%
Sleeping problems	81%
Heart malformations	30-50%
Teeth anomalies	50-75%
Hearing abnormalities	30-50%
CNS Malformations	33%
Ocular anomalies	30%
Renal malformations	25%

WHS patients is strongly influenced in the first months/years of life by the presence/absence of severe major malformations (cardiac defects, congenital hernia of diaphragm) [15].

GENETIC DEFECT

The phenotype of the patient (gestalt) usually suggests the diagnosis.

Loss of genetic material on the short arm of chromosome 4 (4p16.3) represents the basic defect. Such situation could originate by:

- wide deletions detectable with the chromosomal analysis (standard banding) (Fig. 4);
- unbalanced chromosomal translocation involving 4p16.3 region;
- microdeletion of distal 4p16.3 detectable only by in situ hybridization techniques (Fig. 5).

Actually fluorescence in situ hybridization (FISH) analyses is the tecnique of choice used for diagnostic confirmation.

When the diagnosis is confirmed FISH investigation have subsequently to be extended to both the parents of the patient to exclude the presence of cryptic chromosomal traslocations predisposing the occurrence of the microdeletion due to an unbalanced segregation; the knowledge of this predisposition is necessary to formulate a correct reproductive risk and to permit a specific prenatal diagnostic search for possible following pregnancies. Zollino and collaborators [16] have recently shown the existence of a correlation between the wideness of the deletion and the clinical manifestation of the disease. Patient with deletions > 3.5 Mb would manifest the classical phenotype while subjects with loss of genetic material among 2.8-3.5 Mb would result in a "mild" phenotype, characterized by typical facial appearance, hypotonia, growth and psychomotor retardation, in absence of major malformations.

In a following paper, Zollino and others [17] stressed that WHS has to be considered a contiguous gene syndrome with an increasing severity dependent from the extension of the deletion. The patients with the smallest deletions show the following clinical manifestations: typical facial traits, congenital hypotonia, growth and psychomotor retardation, epilepsy. These features define the fundamental clinical manifestations of WHS phenotype and should be considered as the minimum diagnostic criteria for this condition. As a result of overlapping deletion analysis, the WHS critical region (WHSCR) was restricted to the 165-kb interval on 4p16.3 by Wright et al. [15]. Genes locate inside this region should be therefore responsible of these essential clinical manifestations. Three candidate genes have been reported: WHSC1, WHSC2 and LEMT1 (recently described as a candidate gene for seizures). Deletions usually observed are generally larger than the WHSCR and include, therefore, all the candidate genes. Zollino and others have recently proposed a redefinition of the so-called critical region identifying a new different interval

Fig. 4. Wide deletions detectable with standard chromosomal banding.

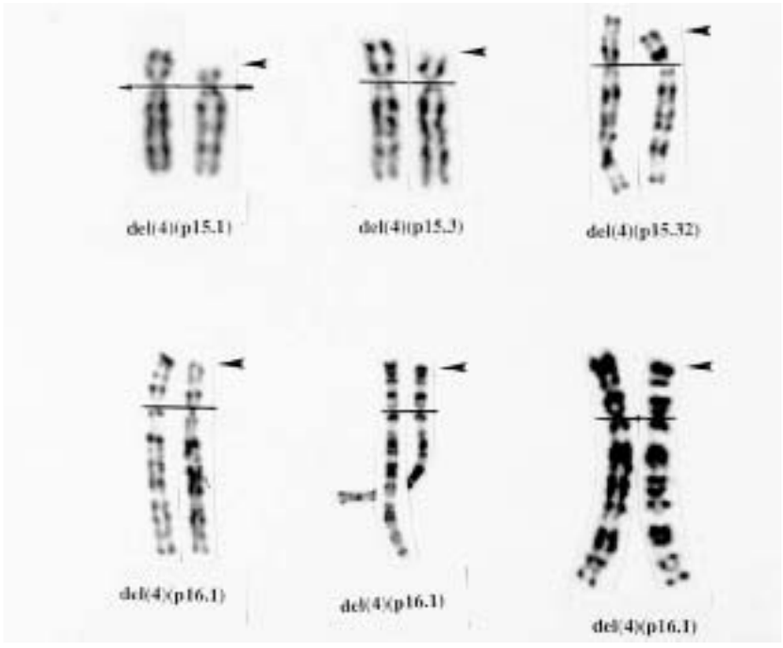
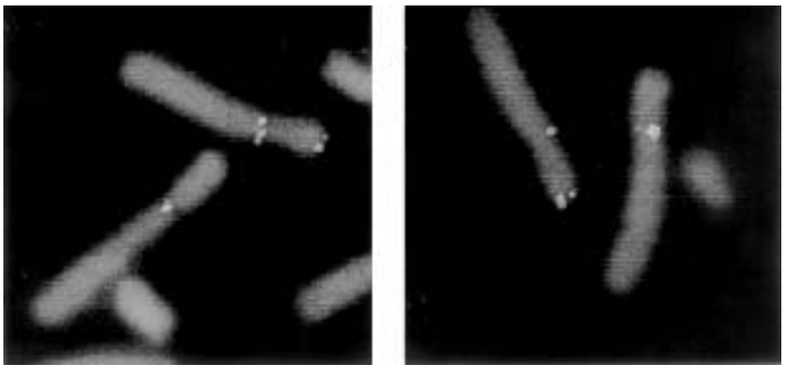


Fig. 5. Microdeletion of distal 4p16.3 detectable with in situ hybridization techniques.



(WHSCR-2), distally sets to the currently defined WHSCR. This new region includes some genes considered important in the determination of the WHS phenotype: the distal part of the WHSC1 gene, whose haploinsufficiency seems to account for some facial dysmorphism and LETM1 gene, which seems to be the best candidate gene for seizure.

HEALTH SUPERVISION GUIDELINES FOR PATIENTS WITH WHS

At diagnosis

– Clinical evaluation with measurement of growth parameters (weight, height, head circumference);

Neurological evaluation and video-EEG-polygraphic study (during wakefulness and sleep)

– Neuropsychiatric evaluation;
– Haematological examinations (whole blood count, renal and liver function parameters, nutritional indexes), urine analysis;
– Cardiologic evaluation (Heart auscultation, Electrocardiogram, Echocardiography);
– Abdominal ultrasound (with particular attention to the genital and urinary tracts);
– Brain CT/MRI;
– Ophthalmology consultation;
– Otolaryngological evaluation/audiological screening (BAERs);
– Orthopaedic evaluation (if malformations are present);
– Motoric evaluation.

0-3 years

To be repeated annually

– Clinical evaluation with measurement of the growth parameters (weight, height, head circumference);
– Haematological examinations (whole blood count, renal and liver function parameters, nutritional indexes), urine analysis;
– Neurological evaluation and video-EEG-polygraphic study (during wakefulness and sleep). In case of antiepileptic drug therapy, proceed with their plasmatic monitoring (to be repeated at follow-up only if necessary);
– Neuropsychiatric evaluation;
– Motoric evaluation;
– Ophthalmology consultation;
– Orthodontic evaluation;
– Otolaryngological evaluation, if necessary;
– In case of feeding problems: swallowing studies; evaluation of the presence of gastroesophageal reflux; dietetic assessment;
– Orthopaedic evaluation, if necessary;
– Immunological functional study in case of true recurrent infections.

Any other evaluation according to the clinical picture.

3-6 years

To be repeated annually

– Clinical evaluation with measurement of the growth parameters (weight, height, head circumference);
– Haematological examinations (whole blood count, renal and liver function parameters, nutritional indexes), urine analysis;
– Neurological evaluation and video- EEG-polygraphic study (during wakefulness and sleep). In case of antiepileptic drug therapy, proceed with their plasmatic monitoring (to be repeated at follow-up only if necessary);
– Neuropsychiatric evaluation;
– Motoric evaluation;
– Dietetic assessment;
– Orthodontic evaluation;
– Ophthalmology consultation;
– Otolaryngological evaluation, if necessary;
– Orthopaedic evaluation, if necessary;

Any other evaluation according to the clinical picture.

6-12 years

To be repeated annually

– Clinical evaluation with measurement of the growth parameters (weight, height, head circumference);
– Haematological examinations (whole blood count, renal and liver function parameters, nutritional indexes), urine analysis;
– Neurological evaluation and video-EEG-polygraphic study (during wakefulness and sleep). In case of antiepileptic drug therapy, proceed with their plasmatic monitoring (to be repeated at follow-up only if necessary);
– Neuropsychiatric evaluation;
– Orthodontic evaluation;
– Dietetic assessment;
– Orthopaedic evaluation;
– Motoric evaluation.

Any other evaluation according to the clinical picture.

12-18 years

To be repeated annually

– Clinical evaluation with measurement of the growth parameters (weight, height, head circumference);
– Haematological examinations (whole blood count, renal and liver function parameters, nutritional indexes), urine analysis;
– Neurological evaluation and video- EEG-polygraphic study (during wakefulness and sleep). In case of antiepileptic drug therapy, proceed with their plasmatic monitoring (to be repeated at follow-up only if necessary);
– Neuropsychiatric evaluation;
– Orthodontic evaluation;
– Dietetic assessment;
– Orthopaedic evaluation;
– Motoric evaluation.

Any other evaluation according to the clinical picture.

Over 18 years

To be repeated every 2-3 years

– Clinical evaluation with measurement of the growth parameters (weight, height, head circumference);
– Haematological examinations

(whole blood count, renal and liver function parameters, nutritional indexes), urine analysis;
– Neurological evaluation and video- EEG-polygraphic study (during wakefulness and sleep). In case of antiepileptic drug therapy, proceed with their plasmatic monitoring (to be repeated at follow-up only if necessary);
– Neuropsychiatric evaluation;
– Orthodontic evaluation;
– Orthopaedic evaluation;
– Motoric evaluation;
- Dietetic assessment.

Any other evaluation according to the clinical picture.

Italian reference

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SUMMARY

Wolf-Hirschhorn syndrome is a genetic condition firstly described in 1965, and characterized by multiple facial dysmorphisms, major malformations, pre and post natal growth retardation, hypotonia, seizures, and mental retardation of variable severity. Among the major malformations observed the most commonly affected organs and apparatus are heart, central nervous system, eyes, genito-urinary apparatus; seizures are presented in nearly all the patients. The incidence is thought to be 1/50,000; the genetic defect is a partial deletion involving the distal part of the short arm of the chromosome 4 (4p-). The wideness of the chromosomal deletion seems to be correlated with the severity of the phenotype. Here we propose healthcare indications for patients affected by Wolf-Hirschhorn syndrome.

Key words

Wolf-Hirschhorn syndrome • 4p deletion • Monosomy 4p • Growth retardation • Mental retardation • Seizures • Hypotonia

RIASSUNTO

La sindrome di Wolf-Hirschhorn è una condizione genetica descritta per la prima volta nel 1965, caratterizzata da dismorfismi multipli, malformazioni maggiori, ritardo di crescita pre e postnatale, ipotonia, epilessia e ritardo mentale di grado variabile. Gli organi maggiormente interessati dalla presenza di anomalie maggiori sono cuore, sistema nervoso centrale, occhi, apparato genito-urinario; le convulsioni sono presenti nella quasi totalità dei pazienti. Si pensa che la sua incidenza sia di 1/50.000; il difetto di base è rappresentato da una delezione parziale che coinvolge la parte distale del braccio corto del cromosoma 4 (4p-). L'ampiezza del difetto genetico sembra essere correlato con la gravità del fenotipo. Vengono qui proposte le linee guida assistenziali per i pazienti affetti da sindrome di Wolf-Hirschhorn.

Parole chiave

Sindrome di Wolf-Hirschhorn • Delezione 4p • Monosomia 4p • Ritardo di crescita • Ritardo mentale • Epilessia • Ipotonia

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