Wolf-Hirschhorn syndrome

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Abstract
Wolf-Hirschhorn syndrome (WHS) is caused by a deletion of the band 4p16.3 and this deletion may be submicroscopic. The craniofacial phenotype (microcephaly, hypertelorism, prominent glabella, broad and/or beaked nose, short philtrum, micrognathia, downturned corners of the mouth, dysplastic ears, preauricular tags) in combination with mental retardation, seizures, congenital heart defects, genital and renal anomalies is indicative for the diagnosis. A familial translocation is responsible for 5 – 13% of the patients. The remainder of the patients have de novo deletions, usually on the paternal chromosome 4, or de novo translocations in 1.6 %. Submicroscopic deletions require molecular techniques, e.g. microsatellite analysis, or molecular-cytogenetic techniques, e.g. fluorescence in situ hybridisation (FISH), to detect the deletion. Fluorescence in situ hybridisation of the patient and his parents should be performed to confirm/exclude translocations. Recurrence risk is low in de novo deletions and translocations, but is remarkably increased in familial translocations. Prenatal diagnosis is possible.

Key words
Wolf-Hirschhorn syndrome, 4p- syndrome, partial deletion 4p, terminal deletion 4p

Disease name and synonyms
Wolf-Hirschhorn syndrome, 4p- syndrome, partial deletion 4p

Excluded diseases
Other chromosomal aberrations

Diagnostic criteria/ definition
Wolf-Hirschhorn syndrome (WHS) was first and independently published in 1965 by Wolf *et al.,* and Hirschhorn *et al.,* It refers to a wide spectrum of clinical signs in patients with terminal 4p deletions. The characteristic clinical signs consist of a typical craniofacial gestalt with hypertelorism, prominent glabella, broad and/or beaked nose, short philtrum, micrognathia, downturned corners of the mouth, cleft lip/palate, dysplastic ears, and preauricular tags and pits, microcephaly (90%), mental retardation (75%), low birth weight (77%), short stature (25-66%), muscular hypotonia (90%), seizures (50-85%), congenital heart defects (31-45%), colobomata of iris (30%), genital anomalies (30%), deafness (23%), and renal anomalies (23%). Mental retardation reaches from mild to profound. Acquisition of walking without support is between

30 and 60 months, many patients are never able to walk. Most of the patients do not develop active speech, only a few are able to make complex sentences. In those patients, first words were spoken between 18 and 48 months. The craniofacial phenotype resembles that of a Greek warrior helmet. The recognizable facial phenotype often leads the clinical geneticist to specific cytogenetic investigations (conventional chromosomal analysis and fluorescence in situ hybridisation/ FISH) to prove or exclude this diagnosis.

Differential diagnosis
Malpuech syndrome (Selicorni and Faravelli, 2000).

Pitt-Rogers-Danks (Wright *et al.,* 1998) and Lambotte (Herens *et al.,* 1997) syndrome were also considered to be separate entities. It is now known that they are also caused by deletions of 4p16.3. Pitt-Rogers-Danks syndrome is defined as the milder expression of WHS.

Frequency
Incidence is estimated to be about 1:50.000 births with a 2:1 female: male ratio.

Clinical description
During the first year of life
Patients are usually small for gestational age with an average birth weight of 2000 g at term. Muscular hypotonia is remarkable. The characteristic craniofacial phenotype consisting of microcephaly, craniofacial asymmetry, high forehead, broad nasal bridge with prominent glabella, hypertelorism, deep-set and dysmorphic ears, preauricular tags, short philtrum, and downturned corners of the mouth, is present at birth and usually gives a clue to the correct diagnosis (Battaglia *et al.,* 1999; Wieczorek *et al.,* 2000). Nearly 35% of patients die during the first year of life, due to congenital heart defects (Shannon *et al*,. 2001).

During toddler's age
The usually severe psychomotor retardation becomes obvious. Patients have a short stature and hypodontia. The fingers are tapering and sometimes ulnar deviated. The feet are characterized by camptodactyly and under- and overriding toes. This period of life is often complicated by respiratory tract infections. Seizures often occur in this period of life, medical treatment is often difficult. Only a very few patients with WHS learn to walk without support during this time. Those, who are able to walk, learn it between the age of 3 and 5 years. Active speech is also uncommon in patients with WHS, only a few patients are able to speak some words. The first two years of life mortality rate is 21% (Battaglia *et al.*, 1999; Wieczorek *et al.*, 2000; Shannon *et al.*, 2001).

Later childhood and adolescence
The facial phenotype is less characteristic in later life. Differentiation from other chromosomal aberrations is much more difficult (Ogle *et al.*, 1996; Wheeler *et al.*,1995; Rauch *et al.*, 2001) described a patient with a small interstitial deletion restricted to the WHSCR who presented only with a partial WHS phenotype consisting of low body weight for height, speech delay, and minor facial anomalies. Short stature, microcephaly, seizures and mental retardation were not present.

Management including treatment
There is no specific treatment. Physiotherapy and occupational therapy are recommended. Some patients require physical aids, *e.g*. wheel chair, splints, hearing aids etc. Patients with congenital heart defects, clubfeet, and cryptorchidism have to be surgically treated. Those with seizures need recurrent EEGs and antiepileptic drugs (Zankl *et al.,* 2001).

Etiology
WHS is caused by a deletion of the region 4p16.3 on the short arm of one chromosome 4. Most of patients with WHS have a *de novo* deletion, usually on the paternal chromosome (Tupler *et al.* 1992). De *novo* unbalanced translocations have also been described in 1.6% of WHS patients (Lurie et al., 1980). The translocation t(4;8)(p16;p23) (Wieczorek *et al.*, 2000) may be the most frequent after t(11q;22q), which is the most common reciprocal translocation in humans (Giglio *et al.*, 2002). A familial translocation is responsible for only 5 – 13 % of cases (Centerwall *et al.*, 1975; Lurie *et al.*, 1980). WHS is mostly maternally inherited with a 2:1 ratio female to males (Nahara *et al.*, 1984).

Diagnostic methods
High-resolution chromosomal analysis often detects the usually terminal deletion of the short arm of chromosome 4. Smaller deletions are not visible with a conventional chromosomal analysis. FISH analysis using probes of the critical region or microsatellite analysis, which requires blood samples of the parents, help to identify a submicroscopic deletion. It is often necessary to confirm a diagnosis suspected on the basis of cytogenetic findings with additional techniques. A cryptic rearrangement should be excluded by FISH in all patients with detected deletions.

Genetic counseling
Following detection of the deletion and confirmation of the WHS diagnosis, the occurrence of a translocation in both parents has to be excluded using conventional chromosomal analysis and FISH.

***De novo* deletion/translocation in the patient**

Recurrence risk for another child with WHS is low. Prenatal diagnosis can be offered in another pregnancy as somatic mosaicism cannot be completely excluded.

Familial translocation

Recurrence risk for another child with WHS is high. There is also a risk for an unbalanced translocation carrier with a partial trisomy 4p and a partial monosomy of the other chromosome involved in the translocation. No accurate data are available, but the risk for an unbalanced translocation carrier is high.

Antenatal diagnosis

Prenatal diagnosis after chorionic villus sampling or amniocentesis is possible. Besides a conventional karyotyping, additional FISH analysis or microsatellite analysis should be performed to confirm/exclude WHS in the child.

Unresolved questions

Although the two minimal critical regions for WHS, WHSCR-1 and –2 have been identified, the genes responsible for specific clinical signs are not known. The WHSCR-1 was restricted to a 165 kb interval on 4p16.3. Three genes localised in the WHSCR-1 critical region, *WHSC1* (Wolf-Hirschhorn syndrome candidate 1Stec *et al.,* 1998), *WHSC2* (Wright *et al.,* 1999) and *LETM1* (Leucine zipper-EF-hand containing transmembrane protein 1 Endele *et al.,* 1999), have been described as candidates for WHS. Zollino *et al.(*2003) recently reported a second Wolf-Hirschhorn syndrome critical region, WHSCR2, which is distally contiguous with the currently defined WHSCR-1. It is proposed that the full WHS phenotype results from the haploinsufficiency of several different genes. Some of them may directly correlate with specific clinical signs. It is currently debated whether the size of the deletions correlates with the severity of the clinical phenotype. There is substantial evidence that small deletions usually result in a milder phenotype with respect to the presence of congenital malformations and the degree of mental retardation (Wieczorek *et al.,* 2000; Zollino *et al.,* 2003). There is also a statistically significant relationship between deletion size and the overall risk of death in *de novo* deletion cases (Shannon *et al.*, 2001).

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