Wolf-Hirschhorn Syndrome (WHS) – Literature Review on the Features of the Syndrome

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Abstract
Wolf-Hirschhorn syndrome (WHS) is a congenital disorder associated with 4 chromosome microdeletion. The patients suffer from various deformities. Among them, mental and growth retardation, even in the fetus, are observed. Most of the characteristics concern facial features. The “Greek warrior helmet appearance” is the most characteristic feature and refers to the facial view with prominent glabella, high arched eyebrow, broad nasal bridge and hypertelorism. Another characteristic feature is microcephalia with micrognathia. The features are more pronounced in infants. Clefts of lip and/or palate are observed in almost half of the cases. The characteristic thing is that the more genetic material is missing, the more pronounced are the dimorphic features of the syndrome. Mostly, the dental status does not differ much from that of the healthy individuals. It had been proven though that WHS-patients are more prone to anomalies in dental structures. Cone-shaped and taurodontic teeth were observed. Multiple tooth agenesis (mainly at premolars and molars) with over-retained deciduous dentition might be associated with MSX1-gene impairment (Adv Clin Exp Med 2014, 23, 3, 485–489).

Key words: 4p16.3 deletion syndrome, Wolf-Hirschhorn syndrome, MSX1 mutation, facial features.
The t(4;14)(p16.3;q32.3) chromosomal translocation (that also targets WHSC1 gene) results in the overproduction of WHSC1 protein in myelomas [6].

Birth incidence is stated at least 1:50,000 births and might be higher due to diagnostic difficulties. It occurs two times more frequently in females [11–13]. The more chromosomal material is missing, the larger expression of WHS is observed in patients [7]. The WHS is also known as chromosome deletion Dillan 4p syndrome [11].

Beside the Wolf-Hirschhorn syndrome, MSX1 gene is known from its most common mutation that is found to be (next to PAX9 gene) one of the most frequent causes of congenitally missing teeth (most frequently lateral upper incisors) and cleft deformities. The mutation in those cases usually refers to 4p16.1 locus [14–16].

## Congenital Defects

Hypospadias, congenital heart diseases, renal and ophthalmic defects (such as iris coloboma, microphthalmia, strabismus – crossed eyes) and skeletal anomalies (concerning limbs and skeletal development retardation) are often observed in patients with WHS. A typical deformity is a sacral dimple – a dimple on the lower part of spine. Hernia diaphragmatica and omphalocele are also observed. A typical complication is epilepsy [1, 4]. Mental retardation is also one of the characteristics [2].

Children with WHS present growth and developmental retardation, but also high mortality (ca. 30%) in first two years of life. The most common causes of death were: lower respiratory tract infection, multiple congenital anomalies, sudden unexplained death and congenital heart disease. Death occurs more frequently in patients with larger deletions. It had been proven that the larger deletion, the more severe congenital deformities one presents [1, 12, 17]. The other congenital defects include muscle hypotonia and urinary tract malformations (such as renal agenesis, oligomeganephronia, bladder exstrophy, cystic dysplasia/hypoplasia and obstructive uropathy) [18].

Respiratory infections (including aspiration pneumonia, otitis media, sinusitis or chronic cough) are very common finding in patients with WHS. This is caused by the muscular hypotonia, gastroesophageal reflux and recurrent aspiration [8]. Hyponatemia may also result in swallowing difficulties and other gastrointestinal disorders (including hepatic adenomas) [19].

Children also suffer from immunodeficiency (including IgA and IgG2 subclass deficiency with a normal T-cell immunity). This manifests itself with common variable immunodeficiency (CVID) and hypogammaglobulinemia. This suggests that patients with WHS represent mutations within the B-cell (CD19) system gene [6, 8].

The most common symptoms observed in WHS are summarized in Table 1.

## Facial and Dental Features

Characteristic facial features in patients with WHS are prominent glabella, high arched eyebrows and hypertelorism. Scalp defects and cranial

<table>
<thead>
<tr>
<th>Branch of medicine</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Otolaryngology</td>
<td>dysplatic ears, periauricular tags, deafness (cochlear), infections of respiratory tract, recurrent otitis, protruded eyes</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>ocular hypertelorism, extropia, blepharoptosis, colobomata of the iris, microphthalmia, strabismus</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>swallowing difficulties, gastroesophageal reflux, hepatic adenomas</td>
</tr>
<tr>
<td>Cardiology</td>
<td>congenital heart defects</td>
</tr>
<tr>
<td>Orofacial Surgery &amp; Dentistry</td>
<td>microcephaly, micrognathia, “Greek warrior helmet” appearance (broad bridge of nose), short philtrum, prominent glabella, high arched eyebrows, retardation in dental development, cranial asymmetry, cleft lip and/or palate, high forehead, wide mouth with short upper lip, cone-shaped teeth, hypodontia</td>
</tr>
<tr>
<td>Dermatology</td>
<td>epicanthal folds</td>
</tr>
<tr>
<td>Neurology</td>
<td>seizures, epilepsy, mental retardation, muscular hypotonia</td>
</tr>
<tr>
<td>Others</td>
<td>growth retardation, hypospadias, renal anomalies (renal agenesis, bladder exstrophy etc.), immunodeficiency (IgG, IgA), retardation of skeletal development, “sacral dimple”, scoliosis, high mortality, scalp defects</td>
</tr>
</tbody>
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### Table 1. Characteristic features in Wolf-Hirschhorn Syndrome
asymmetry are also observed, as well as a broad nasal bridge and a short philtrum. The maxilla is often underdeveloped (characteristic microgenia) and may be associated with cleft lip and/or palate [1]. Other characteristic craniofacial features are high forehead, protruding eyes and epicanthal folds. The mouth is distinct and wide with downturned corners and short upper lip. The whole craniofacial complex takes a characteristic look called “Greek warrior helmet” [20, 21]. “Greek warrior helmet appearance” refers mainly to the broad bridge of the nose, which continues to the forehead and microcephaly with high forehead. The nose is coracoid. Those characteristics are more pronounced during infancy [22, 23]. Cleft defects are observed in almost half of the cases [24]. Patients also suffer from ear deformations and cochlear hearing loss [25].

In most of the cases, the dental status does not differ from that of the rest of society. The inflammation within periodontium might be caused by improper oral hygiene due to the mental retardation of the individuals. Dellavia et al. [26] reported that a patient had cone-shaped teeth only in one case, while all other patients presented normal tooth shape and seizure. Due to the MSX1 anomalies in this syndrome, multiple tooth agenesis concerning mainly premolars and molars (including oligodontia) had been reported. Due to the lack of tooth buds, over-retained primary teeth are observed. Among various tooth anomalies, also taurodontism had been reported [27–29]. Another characteristic might be late dental development, which is specified as delayed tooth eruption and slower maturation expressed in dental age [30]. There had been observations of taurodontism, which is a dental trait, in which the dental pulp chambers are elongated and the bifurcation or trifurcation is displaced to the dental root apex. This also may influence dental eruption retardation with more difficulties due to larger tooth dimensions [31].

**Differential Diagnosis**

The initial diagnosis is given based on facial features after the birth. Some suggestions of WHS might occur with the observation of developmental retardation [22]. The final diagnosis is stated on the basis of a genetic examination. In WHS it is difficult, as gene(s) defect(s) in this case are unknown. There are some candidate genes. Among them the most commonly named are WHSC1, WHSC2 and fibroblast growth factor receptor 3 – FGFR 3 [32]. The only confined critical region is 165 kb. Several microdeletions (such as Rubinstein-Taybi syndrome with deletion of 16p13.3 or Smith-Magenis syndrome with deletion of 17p11.2) should be excluded [4].

Most of the problems of differential diagnosis concern the Pitt-Rogers-Danks syndrome. The syndrome is caused by microdeletions in locus 4p16.3 and might be a clinical variation of WHS. In some cases the names are used interchangeably [24] while other authors argue whether they are the same clinical entities [33]. The symptoms of those two are almost the same, but in Pitt-Rogers-Danks syndrome they have a milder expression [24].

Other similar anomaly might be the Opitz G/BBB syndrome, which is also a midline malformation syndrome. The characteristics are hypertelorism, hypospadias, clefts, developmental delay, cardiac defects as well as laryngotracheoesophageal abnormalities and an imperforate anus. In this case a differential diagnosis includes genetic examination – Opitz G/BBB syndrome is associated with MIDI mutation within the X-linked form, but unfortunately, the genes responsible for an autosomally dominant form had not been identified yet [34].

The skeletal anomalies, limited fetal growth, as well as hypospadias in males can be observed in the fetus during an ultrasound examination performed in the third trimester, and can be confirmed by a genetic examination during the pregnancy [35]. The more chromosomal material is missing, the easier it is to state the diagnosis, as a more severe syndrome is observed [7]. The prenatal diagnosis can be very difficult. Observation of prefrontal edema and other facial anomalies in fetus associated with growth retardation (even a borderline) should alert a gynecologist to investigate the 4p- deletion [22].

**Conclusions**

Wolf-Hirschhorn Syndrome is a rare congenital defect, in which the deletion of part of short arm of chromosome 4 (especially MSX1 gene) takes place. The diagnosis is difficult and due to a large diversity of expression of syndrome, some of the cases might be missing. To detect the anomaly FISH method of genotype screening is used. MSX1 takes most of its expression in mesenchyme and its mutations are involved in changes in ectodermal and mesodermal structures. The mutations within the MSX1 gene are not a rare aspect and result in hipodontia (congenital lack of tooth buds) and cleft deformities. It is also involved in WHS, Witkop syndrome and Pierre Robin syndromes, though mutations might be present in other congenital deformities and may accompany them. Therefore, the gene might be interesting for further studies [8, 36–38].
References


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