MAJOR REVIEW

Dysmorphology and the Orbital Region: A Practical Clinical Approach

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Abstract. Dysmorphology is the field of medicine focusing on congenital developmental abnormalities due to exogenous teratogens, chromosomal anomalies, or to a defect in a single gene. Numerous syndromes have been reported and a growing number of genes or chromosomal anomalies are identified. The clinical observation of the face remains an essential part of the clinical evaluation of the patients. The orbital region, as other regions of the face, should be systematically evaluated. Orbital malformations can be isolated or part of a syndrome. In the diagnostic process, the orbital anomaly can be classified as a major feature (essential for the diagnosis), a moderate feature (important but not essential for the diagnosis), or a minor feature (contributing weakly to the diagnosis). The diagnoses of the main orbital anomalies in dysmorphology are reviewed and illustrated with relevant examples of syndromes that are presented as well as the usual landmarks used in clinical practice. Abnormal position of the eyes in syndromes such as hypertelorism, hypotelorism, primary or secondary telecanthus, asymmetry, and propotis are discussed. Eyelid anomalies, such as cryptophthalmos, ablepharon, blepharophimosis, euryblepharon, or anomalies at the level of the eyelashes and eyebrows are described. (Surv Ophthalmol 49:547–561, 2004. © 2004 Elsevier Inc. All rights reserved.)

Key words. dysmorphology • genetics • orbital anomalies

I. Dysmorphology: Definition and General Comments

A. WHAT IS DYSMORPHOLOGY?

Clinical dysmorphology is a medical discipline based on the assessment of patients presenting with congenital developmental abnormalities that can be isolated malformations or syndromes often associated with developmental delay. A number of developmental anomalies are the result of a single anomaly in morphogenesis leading to a cascade of subsequent defects defining a sequence.65

Four categories of developmental anomalies have been described: 1) a malformation as a single morphogenetic defect; 2) a deformation resulting from mechanical constrains on a normal embryo; 3) a disruption sequence resulting from the destruction of a normal structure; and 4) a dysplasia defined as the primary defect lying in the differentiation and organization of a given tissue.

There are various etiologies associated with congenital anomalies and they include in utero exposure to exogenous teratogens (i.e., a drug, an infectious agent, or alcohol) or to an obstetrical hazard (i.e., leakage of amniotic fluid); chromosomal anomalies (i.e., trisomy, monosomy, or structural rearrangement as deletion, duplication, or translocation) or a defect at the level of genes implied in development.38,39,89 More than 2,000 syndromes are assumed to be the result of an alteration (mutation) of a specific gene.129 The dramatic advances in molecular
beyond biology have opened the field to molecular investigations and a wide variety of genes have been identified as responsible for developmental syndromes. The genes related to abnormal development encode for a wide range of proteins: enzymes, transcription factors, growth factors, receptor proteins, transporter proteins, cell adhesion molecules, intercellular junction proteins, signal transduction proteins, and structural proteins. However, the clinical approach to these syndromes remains essential. Examination of the face is of great importance in this field as major or minor facial anomalies can be relevant for diagnosis. Morphological features are often so characteristic that it is well-known that patients with the same syndrome can resemble each other more than their own non-affected siblings. This review is focused on the description of orbital involvement in dysmorphology.

B. DISTINGUISHING NORMAL FROM ABNORMAL FEATURES IN DYSMORPHOLOGY

The clinical assessment of craniofacial features is based on the overall subjective clinical evaluation of the face but also on objective measurements that are important to validate the clinical impression.

Phenotypic anomalies can be subdivided roughly in two subgroups: qualitative and quantitative. Qualitative anomalies are relatively easy to define as present or absent compared to an “ideal” human phenotype. The frequency of the feature in the general population defined as a “variant” (present in more than 1% of human beings) has to be distinguished from an “anomaly.” A number of anomalies useful in dysmorphology are quantitative. This means that an objective definition of an abnormal phenotype requires the knowledge of the normal variation of the trait (usually defined as $-2$ to $+2$ standard deviations [SD] for any measurement) in a population of a given ethnic background or at a given age. In many circumstances, normal standards for parameters are unavailable or, when published data are available, they include only the Caucasian population. Finally, some anomalies are subjective as “a coarse face” for instance.

Morphological measurements can be easily performed with transparent ruler-derived measurements. However, these are less reliable than calliper-derived measurements, which are rarely used in practice. The measurements are compared to normal, such as the reference measures published by Feingold and Bossert in 1974 (Fig. 1).

Clinical photographs (at least the patient standing, the face and both profiles) should be a standard of any evaluation in dysmorphology. Those pictures are useful for reviewing purposes, for off-consultation discussion, and for the appreciation of the phenotypic evolution in the long term.

C. DIAGNOSIS IN DYSMORPHOLOGY

The diagnosis in dysmorphology is based on a systematic evaluation of the head and the body. The face is methodically evaluated by region: forehead, midface (periorcular region, nose, and ears), and lower part of the face (mouth and chin). The developmental anomaly of the orbit may be isolated or associated to other more or less obvious developmental anomalies. The orbital anomaly can be classified as a major feature (essential for the diagnosis), a moderate feature (important but not essential for the diagnosis), or a minor feature (contributing weakly to the diagnosis).

In order to help the clinician to diagnosis the syndrome, databases are available (see Method of Literature Search section) that are based on the systematic morphological analysis of the patient, guiding the clinician by submitting a list of possibly corresponding syndromes.

Genetic counseling and multidisciplinary care is often necessary to determine further investigations and patient care. Molecular diagnosis is performed in defined circumstances (diagnosis confirmation, genetic counselling or research project), provided that mutation screen services are available for the disorder under consideration. A growing number of genes known to be involved in human diseases are unfortunately not subject to routine screen.

This review focuses on the clinical examination of the orbital region in dysmorphology. The exploration of hard structures of the orbit and the surrounding soft structures are described. Abnormal development is illustrated with relevant clinical examples (gene identification concerning the syndromes cited as examples are summarized in Tables 1 and 2).

II. Dysmorphology and the Orbits

The orbits represent a bridge between the face and the cranium. Development of the orbital region, the junction between the cranial membranous bones and the basal enchondral bones, is complex. Perfect timing and harmony is required as seven different bones contribute to form the orbit (frontal, zygomatic, sphenoid, ethmoidal, maxillary, lacrimal, and palatinal bones).

Many cranial abnormalities appear to be due to a cessation of development of specific structures at a specific time. For example, the craniosynostosis syndromes are the result of premature fusion of cranial sutures inducing inhibition of growth perpendicular to the suture, hence determining the abnormal craniofacial shape. Defects in the apposition of the junction of embryological fissions are the basis for clefting syndromes or branchial arches anomalies.
Fig. 1. A: Schematic representation of measurements involved in the evaluation of the orbital region. OCD = outer canthal distance; ICD = inner canthal distance; IPD = interpupillary distance; PFL = palpebral fissure length. B: ICD measurements according to the age. C: OCD measurements according to the age. D: IPD measurements according to the age. E: Normal PFL measurements according to the age. These figures are reproduced with the permission of the March of the Dimes (Feingold and Bossert). The diagnosis of dystopia canthorum can be suggested by the W index. A = ICD; b = IPD; c = OCD; X = (2a – O.2119c-3.909)/c; Y = (2a – 0.22479b – 3.909)/b; W = X+Y + a/b. WS type 1 is diagnosed if the average of all affected members of the family is 1.95 or more.
<table>
<thead>
<tr>
<th>Name of Syndrome</th>
<th>Gene(s) identified (update May 2002)</th>
<th>General Clinical Comments</th>
<th>Orbital Manifestation</th>
</tr>
</thead>
</table>
| Holoprosencephaly                | SHH (sonic-hedgehog)\textsuperscript{91,101}  
MG3 (sine oculis homeobox 3)\textsuperscript{123}  
TGIF (TG interacting factor)\textsuperscript{54}  
ZIC2 (Zinc finger protein of cerebellum)\textsuperscript{13} | Malformation of the brain induces secondary craniofacial anomaly | Cyclopia or more or less severe hypotelorism |
| Apert syndrome                   | FGF2 (Fibroblast Growth Factor Receptor 2)\textsuperscript{92,127,128} | Severe craniosynostosis Major syndactyly | Hypertelorism  
Protrusion of the eyes |
| Crouzon syndrome and related syndromes (Pfeiffer syndrome [PS], Jackson-Weiss syndrome [JWS], Saethre-Chotzen syndrome) | FGF2-FGFR3 (Fibroblast Growth Factor Receptor 2 and 3)\textsuperscript{9,61,77,83,98,103,127}  
TWIST\textsuperscript{37,59} (Rarely FGFR2 and FGFR3) | Craniostenosis  
Severe to moderate  
Limb anomalies  
Absent in Crouzon  
Minor in JWS, PS | Hypertelorism  
Protrusion of the eyes  
Asymmetry of orbits |
| Waardenburg syndrome             | PAX3 (Paried-Box 3) (WS type 1)\textsuperscript{7,114}  
MITF (Microphthalmia Associated Transcription Factor) (WS type 2)\textsuperscript{60} | Variable craniosynostosis Minor limb and ear anomalies  
Iridal heterochromia  
Variable deafness  
White forelock | Ptosis as important feature  
Dystopia canthorum (distinguishes WS1 and WS2) |
| Treacher-Collins syndrome        | TCOFI (Treacher Collins Franchescetti gene 1)\textsuperscript{35,130} | First branchial arch syndrome | Down-slanting palpebral fissures  
Occasional colobomas of eyelids |
| Coffin Lowry syndrome            | RPS6KA3 (Ribosomal Protein S6 Kinase)\textsuperscript{318} | X-linked mental retardation syndrome | Hypertelorism  
Down-slanting Palpebral fissures |
| Stickler                         | COL2A1 (collagen 2A1)\textsuperscript{1}  
COL11A1 (collagen 11A1)  
COL11A2 (collagen 11A2)\textsuperscript{119} | Mid-facial hypoplasia, cleft palate, hearing loss, and specific spondyloepiphyseal dysplasia | Eye protrusion of mixed origin (midfacial hypoplasia and myopia) |

such as Goldenhar syndrome or Treacher-Collins syndrome.\textsuperscript{51,52}

**A. MORPHOLOGICAL LANDMARKS OF THE ORBITS**

The normal distance between the orbits varies during embryogenesis and after birth in accordance with the general craniofacial development. The embryonic separation of the globes, defined by the angle between the optic nerves at the chiasma of the fetus, progresses from a widely divergent \(180^\circ\) angle between the ocular axes in the first weeks of development to an angle of \(70^\circ\) at birth and \(68^\circ\) in adulthood.\textsuperscript{10,134}

The interorbital distance, defined as the shortest distance between the inner walls of the orbits, increases with age. The most accurate interorbital measurements are the Bony Inter Orbital Distances from radiographs (Waters [half axial projection] or from posteroanterior cephalograms) or computed tomographs used usually for presurgical purposes.\textsuperscript{21,25,29,81}

In everyday clinical practice evaluation of the interocular distances is based on the measurement of the following landmarks: interpupillary distance, inter inner canthal distance, outer inter canthal distances, and horizontal palpebral length (Fig. 1A) that can be easily compared to normal values.\textsuperscript{14,47,69,95,102,108} An approximate estimation of normality is to consider that the inter inner canthal distance is equivalent to the palpebral length (Fig. 1A).

Different quantitative methods have been reported for children and for adults with tables presenting the evolution of the interocular distances according to the age.\textsuperscript{76} The routine clinical method for assessing interocular distance is based on a biometric study done by Feingold and Bossert in 1974, which includes the measurement of the inner inter canthal distance,
TABLE 2

**Syndromes with Identified Genes with Eyelid Anomalies**

<table>
<thead>
<tr>
<th>Name of Syndrome</th>
<th>Gene(s) identified (update May 2002)</th>
<th>General Clinical Comments</th>
<th>Eyelid Anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPES type I and type II</td>
<td>FOXL2 (Forkhead Box C 2)</td>
<td>Genotype-phenotype correlations for BPES type I and BPES type II for female infertility</td>
<td>Blepharophimosis Ptosis Epicanthus Inversus Distichiasis Ptosis</td>
</tr>
<tr>
<td>Lymphedema-distichiasis syndrome</td>
<td>FOXC2 (Forkhead Box C 2)</td>
<td>Lymphedema of lower limbs</td>
<td></td>
</tr>
<tr>
<td>Lymphedema-ptosis syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hay wells-EEC3</td>
<td>P63 protein</td>
<td>Ectodrodactyly-Ectodermal dysplasia Clefting syndrome</td>
<td>Sparse eyebrows and eyelashes</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz</td>
<td>DHCR (sterol delta-7-reductase)</td>
<td>Mental retardation, hypogonadism, syndactyly of 2 and 3 fingers, genital anomalies</td>
<td>Ptosis</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>SNRP (Small nuclear ribonucleoprotein in polypeptide)</td>
<td>Obesity, hypogonadism, and mental retardation</td>
<td>Almond-shaped palpebral fissures</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>PTPN11 (Protein tyrosine Phosphatase non receptor type)</td>
<td>Weeding of the neck, cardiac malformation (pulmonic stenosis), pectus excavatum</td>
<td>Hypertelorism Down-slanting palpebral fissures Ptosis</td>
</tr>
<tr>
<td>Rubinstein Taybi syndrome</td>
<td>CBP (CRE-binding protein)</td>
<td>Broad thumbs and toes, characteristic facies, mental retardation</td>
<td>Heavy high arched eyebrows Down-slanting palpebral fissures Ptosis</td>
</tr>
<tr>
<td>Fraser syndrome</td>
<td>FRAS1 (extracellular matrix protein)</td>
<td>Renal agenesis or hypoplasia, laryngeal stenosis, syndactyly</td>
<td></td>
</tr>
</tbody>
</table>

the outer inter canthal distance, and the interpupillary distance in Caucasian individuals from birth to 14 years (Figs. 1B, C, and D). Alternative indices have been described, such as Farkas canthal index defined by inner to outer intercanthal ratio $\times 10^{45,125}$. Canthal index is higher than 42 in hypertelorism and lower than 38 in hypotelorism. This ratio is useful for off-clinic analysis of photographs. Ethnic variations of orbital features are important to be considered as the physiological distances may vary considerably compared to the published data. For example, a study comparing newborns from England and Africa showed that the Caucasian newborn and the African newborn had the same inner canthal distance, whereas the outer canthal distance and palpebral fissure length were significantly smaller in the Caucasian newborn than in the African newborn.

**B. TERMINOLOGY OF ABNORMAL DISTANCES BETWEEN THE EYES**

A considerable number of syndromes include abnormal distances between the eyes (Fig. 2).

1. **Hypotelorism**
   Ocular hypotelorism is defined as a reduced distance between the medial walls of the orbits with reduced inner and outer inter canthal distances.

2. **Hypertelorism**
   Orbital hypertelorism (or hyperteleorbitism) refers to the lateralization of the entire orbital structure. Ocular hypertelorism is defined as an increased distance of the inner and outer inter canthal distances (but not of the inner canthi only, a common mistake in dysmorphology literature). Clinically, the best parameter is the interpupillary distance. The definition is based on bony landmarks and the CT scan is useful. In most cases, the angle between the orbits is increased. Clinically, accurate measurements are required to exclude illusory, erroneous hypertelorism due to misleading adjacent structures such as a flat nasal bridge, epicanthic folds, exotropia, widely spaced eyebrows, narrow palpebral fissures, and isolated dystopia canthorum.
3. Exorbitism

Exorbitism is defined by some authors as prominent eyes due to underdeveloped or shallow bony orbits. For others, exorbitism is an increased angle of divergence of the orbital walls.

4. Telecanthus

Telecanthus is an increased distance between the inner canthi.

a. Primary Telecanthus

Primary telecanthus is defined as an increased distance between the inner canthi with normally spaced outer canthi and normal interpupillary measurement.

b. Secondary Telecanthus

Secondary telecanthus is defined by increased inner canthi distance associated with ocular hypertelorism.

5. Dystopia Canthorum

Dystopia canthorum is the lateral displacement of the inner canthi (telecanthus) together with lateral displacement of the lacrimal puncta. In this case, an imaginary vertical line passing through the lacrimal punctum cuts the cornea. The clinical evaluation of dystopia canthorum may be difficult. The W index, detailed in the legend of Fig. 1, has proven to be useful.

C. CONDITIONS SHOWING ABNORMAL DISTANCES BETWEEN THE EYES AND ORBITS

1. Conditions with Hypotelorism

Hypotelorism occurs in more than 60 syndromes. Hypotelorism can be the result of a skull malformation or a failure in brain development. For example, trigonocephaly, an uncommon type of craniosynostosis caused by premature closure of the metopic sutures, results in a triangular skull with a prominent frontal protuberance and hypotelorism.

Holoproencephaly is a rare major malformation of the brain frequently associated with craniofacial anomalies (Figs. 3.1 and 3.2). Severity of midfacial anomalies correlates usually, but not universally, with the severity of the underlying brain malformation. The related craniofacial anomalies constitute a spectrum extending from a single median orbit with more or less fused eye globes (cyclopia) with an overhanging proboscis to milder facial abnormality consisting of a single maxillary incisor with hypotelorism. Holoproencephaly results from an abnormal cleavage and morphogenesis of the embryonic forebrain with alobar or semilobar development of the cerebral hemispheres associated with missing or incomplete development of the midline structures of the face. This condition is related to the third week period of fetal development when the prechordal mesoderm migrates forward contributing to the development of the midface and induces the forebrain morphogenesis.

Holoproencephaly may be due to environmental/maternal factors (such as maternal diabetes), chromosomal abnormalities (trisomy 13, 18q deletion, etc.) or single gene defects (Table 1).

2. Conditions with Ocular Hypertelorism

Hypertelorism occurs in more than 550 disorders. Three possible pathogenic mechanisms have been suggested. The first is the early ossification of the
lesser wings of the sphenoid, fixing the orbits in fetal position. The second is the failure of development of the nasal capsule, allowing the primitive brain vesicle to protrude into the space normally occupied by the capsule resulting in morphokinetic arrest in the position of the eyes as in frontal encephalocele.20

The third mechanism is a disturbance in the development of the skull base as in craniosynostosis syndromes (such as in Crouzon or Apert syndromes) or in midfacial malformations (such as frontonasal dysplasia or craniofacial dysplasia) (Fig. 3.3).21,22,55,78,104

The widow’s peak (low median implantation on the scalp hair on the forehead) is a consequence of ocular hypertelorism as the two fields of hair-suppression are further apart than usual with the fields failing to overlap sufficiently high on the forehead.

Hypertelorism can be an important diagnostic feature in syndromes as in the Coffin-Lowry syndrome, an X-linked mental retardation condition (Fig. 3.4).

3. Telecanthus and Dystopia Canthorum

Telecanthus is a common feature in syndromes whereas dystopia canthorum is a specific feature of Waardenburg syndrome type 1 (MIM 193500). This condition is an autosomal dominant syndrome with variable expressivity, characterized by dystopia canthorum with a broad nasal root, poliosis (often a white forelock), heterochromia irides, and various degree of sensorineural hearing loss (Fig. 3.5).96,121

Waardenburg type 2 differs from Waardenburg type 1 by the absence of dystopia canthorum (type 3 is a variant of type 1 with limb anomalies, whereas type 4 is associated with Hirschprung disease).84

4. Abnormal Orbital Position of the Globes

a. Prominent Eyes

Prominent eyes is a clinical term corresponding either to a protrusion of the normal eyeballs, or to an increased volume of the eyeball, or to the combination of both conditions. Proptosis (also denominated exophthalmos) is defined as a forward displacement of the globe beyond the normal orbital margin (measured clinically with the Hertel exophthalmometer or on CT scan). Pseudoproptosis results from the enlargement of the ipsilateral eye due to bupthalmos, or it can be present in both eyes in high-degree myopia, giving the appearance of prominent eyes with normal orbits. Proptosis can be the result of a reduced orbital depth usually described as shallow orbits.

In craniosynostosis syndromes, such as Apert or Crouzon syndromes, underdevelopment of the orbital ridges and midfacial bones reduces the orbital
volume (Fig. 3.6). The premature closure of cranial sutures usually associates hypertelorism, exorbitism, and protrusion of the globe. Midfacial retrusion or hypoplasia is often associated with prominent eyes. Midfacial hypoplasia is frequently found in fetal syndromes due to maternal consumption of drugs (warfarin, retinoic acid, etc.) and also in genetically determined syndromes as illustrated by Stickler syndrome. This autosomal dominant condition is characterized by variable features, such as midfacial hypoplasia, cleft palate, hearing loss, and specific spondyloepiphyseal dysplasia. Prominent eyes are related to the classical midfacial hypoplasia ("flat face"). This feature is enhanced by the increased axial length due to high-degree myopia (Fig. 3.7).

Another syndrome that is associated with prominent eyes is Schinzel-Giedion syndrome, which is characterized by multiple malformations with central nervous system degeneration. The hallmark of the face of children in Schinzel-Giedion syndrome in the first months of life is bitemporal narrowing, midfacial hypoplasia, and a deep groove under the eyes, giving an appearance of a “figure eight”.

b. Sunken Eyes

Rarely in dysmorphology, the eyes may have a sunken appearance. This feature is the result of hyperdevelopment of the orbital ridges and walls, microphthalmos or melting of orbital fat-tissue. This last feature is observed in Cockayne syndrome, an autosomal recessive altered DNA repair condition, with dramatically sunken eyes (Fig. 3.8).

c. Abnormal Size and Asymmetric Orbits

Abnormal orbital shape may result from a primary developmental defect of the bony walls (i.e., craniosynostosis). Orbital growth is also mechanically driven by the growth of the intra orbital structures. Increased size of the orbit can be observed in any situation with a mass present in the orbit (encephalocele, cystic eye, tumor). Small orbit is a classic consequence of microphthalmos as the eyeball growth interacts mechanically with the growth of the orbital walls. In many circumstances, abnormal orbital size conducts to orbital asymmetry. Hemifacial microsomia (facial-auriculo-vertebral syndrome, Goldenhar syndrome) associates small ears with tags, epibulbar dermoids, vertebral anomalies and an asymmetric face. This sporadic condition is related to an abnormal field defect of the first and/or second branchial arch.

Asymmetric orbits can also result from congenital craniofacial tumors such as in sphenoid wing dysplasia in neurofibromatosis type 1 or from orbital hamartomas in Proteus syndrome (Fig. 3.9). 11

III. Adnexal Developmental Anomalies

Adnexal developmental anomalies include abnormal formation of the eyelids and their dermal components such as eyelashes or eyebrows. In humans, the eyelids differentiate at the sixth week of gestation with superior and an inferior mesodermal-ectodermal folds. They fuse after the eighth week until the fifth month. Specialized structures (orbicularis oculi muscle, tarsal plates and meibomian glands, lacrimal puncta and canaliculi, and skin appendages and the conjunctiva) and extraocular muscles develop during this period of time. At 7 months of development the eyelids are completely separated. 106

Clinical evaluation of the palpebral fissures is simple. Horizontal and vertical widths, palpebral fissures orientation and shape are the major clinical criterias. 49,66,116 The position of the eyelids are also evaluated: ptosis is a common feature in dysmorphology whereas retracted eyelids are less common.

A. MAJOR EYELID MALFORMATIONS

1. Cryptophthalmos

Cryptophthalmos is a rare malformation in which there is a complete failure of development of the eyelid folds with continuity of the skin from the forehead to the cheek. In Fraser syndrome, a rare autosomal recessive syndrome, cryptophthalmos is associated with hypoplasia of the genitalia, laryngeal stenosis and renal hypoplasia, or agenesis (Fig. 4.1). 12,74,109

2. Ablepharon

Ablepharon is defined as the absence of lids. It has been reported in the autosomal recessive ablepharon-macrostomia syndrome (Fig. 4.2). 55,58

B. PALPEBRAL FISSURES AND FOLDS

Superior and inferior eyelids are separated at the level of the palpebral fissure and delimited by several folds: horizontal (superior and inferior) folds and occasionally a vertical epicanthal fold.

1. Epicanthal Folds

Epicanthus palpebralis is defined as a vertical cutaneous fold arising from the nasal root and directed towards the internal part of the upper lids. It is a normal finding in fetuses of all races and commonly found in young children. Epicanthus palpebralis is present as a normal morphologic feature in adults of a large portion of the world’s population. Sometimes the fold may cover the inner canthus. As opposed to epicanthus palpebralis, epicanthus inversus is defined as a dermal fold arising from the lower lid and diminishing towards the upper lid (see section on blepharophimosis) (Fig. 4.3).
2. Orientation of the Palpebral Fissures

Normal palpebral fissures have a slight outer upward inclination as the outer canthus is positioned 1 mm or 2 mm higher than the inner canthus. The normal orientation of the eyelids can be variable, depending on the ethnic origin of the patient. Abnormal orientation of the palpebral fissures slants are often described as “up-slanting palpebral fissures” when the outer canthus is positioned higher than usual or inversely as “down-slanting palpebral fissures.”

In trisomy 21, upward slanting of the palpebral fissures though not specific, is the most common ocular and facial feature (Fig. 4.4).\(^4\,29\,41\,42\) Hypoplastic malar bones often result in down slanting palpebral fissures. It is a characteristic finding in first or second branchial arch malformations such as the Treacher-Collins syndrome characterized by a narrow face with hypoplasia of supraorbital rims, zygomas, and hypoplastic ears (Fig. 4.5).

C. ABNORMAL PALPEBRAL FISSURE OPENING

1. Ankyloblepharon

Ankyloblepharon is defined by partial or complete adhesion of the ciliary edges of superior and inferior eyelids. \textit{Ankyloblepharon filiforme ad natum} is usually a sporadic isolated malformation in which the upper and lower lids are joined by tags (easily cured by a rapid simple surgical procedure) (Fig. 4.6).\(^126\) Ankyloblepharon can be found in the Hay-Wells syndrome with ectodermal dysplasia and cleft lip and/or palate.\(^56\)

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\textbf{Fig. 4.} Clinical pictures of patients with eyelid anomalies. 4.1: Fraser syndrome in a still-born child (courtesy of Dr. Marie Gonzales, Paris, France). 4.2: Ablepharon macrostomia syndrome (courtesy of Dr. A. A. Cruz, Sao Paulo, Brazil). 4.3: Bilateral epicanthus inversus (BPES syndrome) (notice the thick eyebrows). 4.4: Up-slanting palpebral fissures in a boy with trisomy 21. 4.5: Down-slanting palpebral fissures in newborn with Treacher Collins syndrome. 4.6: Ankyloblepharon (Courtesy Dr. A. A. Cruz, Sao Paulo, Brazil). 4.7: BPES syndrome in a newborn child. 4.8: Blepharophimosis in a child with a 3p deletion (with thick eyebrows). 4.9: Long palpebral fissures in a child with Kabuki syndrome. 4.10: Patient with Anomiotic Deformation Adhesion Multilation Syndrome with cleft lip and palate (not shown) associated to eyelid coloboma (Courtesy Dr. M. Gonzales, Paris, France). 4.11: Female patient with Cohen syndrome showing the “wave shape” of the eyelid fissures. 4.12: Ptosis and craniosynostosis in a patient with Saethre-Chotzen syndrome.
an allelic variant of the ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome.16,73 Ankyloblepharon has been also reported in trisomy 18.6,18,40,126

2. Blepharophimosis

Palpebral fissure length increases during normal development as observed by Feingold and Bossert (Fig. 1E).44 A moderate reduction of the palpebral length may be the consequence of excessive curvature of the palpebral rim (“almond-shaped fissures”) and can be found in trisomy 21 and Prader-Willi syndrome. In this syndrome the palpebral fissure width is relatively narrower when the child grows older.14 Blepharophimosis is a malformation defined by a considerable reduction in the horizontal and vertical dimensions of the palpebral fissure. Blepharophimosis can be isolated or part of various syndromes and should not be confused with ptosis (normal horizontal distance).27

Fetal alcohol syndrome (due to alcohol consumption during pregnancy) associates growth retardation, microcephaly and cognitive impairment. It is one of the most common cause of blepharophimosis.112 Blepharophimosis, ptosis, epicanthus inversus syndrome (BPES) is an autosomal dominant condition defined by the presence of marked blepharophimosis, ptosis associated with hypoplasia of the tarsal plates and epicanthus inversus (Fig. 4.7).

Two clinical types of BPES have been defined: BPES I and BPES II.135 BPES I is characterized by infertility due to ovarian failure in the affected females, which is not the case for BPES type II.31

Ohdo syndrome is a usually sporadic syndrome defined by blepharophimosis, ptosis, dental hypoplasia, partial deafness, and mental retardation.66

Ptosis and/or blepharophimosis are also observed in chromosomal syndromes. Blepharophimosis with ptosis is, for instance, a hallmark of chromosome 3p deletion (Fig. 4.8).80

3. Increased Length and Eversion of Palpebral Fissures

The palpebral fissure length may be increased with an enlargement of the palpebral aperture. The lateral part is usually more everted defining euryblepharon. The whole length eversion of the lower lid defines congenital ectropion. Euryblepharon is characteristic of the Kabuki syndrome, defined by post natal growth retardation, mental retardation (Fig. 4.9) and a facial gestalt reminiscent of the make up of the actors of a traditional Japanese theatrical form.57,85 Inherited autosomal recessive congenital skin disorders may lead to congenital ectropion as for instance in congenital cutis laxa with looseness of the lid or the harlequin ichthyosic babies with cicatricial ectropion.

Other examples include macrostomia, ectropion, atrophic skin hypertrichosis syndrome, or the exceptional blepharo-cheilo-dontic syndrome.30,135

D. CLEFTING OR NOTCHING OF THE EYELIDS

Notches or clefts of the eyelid have been described as eyelid colobomas, although there is no embryological relation with the eyeball colobomatous anomalies due to malclosure of the embryological fissure. The exact causes of the so-called eyelid colobomas remain uncertain. For some authors they are equivalent to the facial clefts whereas it has been recognized that intrauterine factors can play a major role.115 The shape is usually triangular with the base at the lid margin and the size may vary from a discrete notch or the margin to a major defect of the eyelid with the threat of exposure keratopathy requiring surgical procedures.105 Amniotic bands may cause mechanical disruptive clefting of the eyelids in the Amniotic Deformity Adhesions Mutilations (ADAM) syndrome (Fig. 4.10).79

Coloboma of the upper lid can occur in the oculo auriculo vertebral dysplasia syndrome (Goldenhar syndrome). Coloboma of the lower lid is a common feature of the autosomal dominant Treacher-Collins syndrome.57,124 The palpebral fissure may have a “wave shape” in the Cohen syndrome defined by a specific facial gestalt, developmental delay and retinal degeneration (Fig. 4.11).17

E. LOWERING OF THE POSITION OF THE UPPER LID

In dysmorphology, lowering of the upper lid can be the secondary consequence of a reduced orbital volume related to microphthalmos or to diminished orbital volume. Primary congenital ptosis is the most common cause of lowering of the upper eyelid and is the result of a developmental dystrophy of the levator muscle and/or the tendon. Congenital ptosis is usually an isolated finding. It can be found in many syndromes, but it is rarely the hallmark of a syndrome. Although this review does not focus on inherited progressive neurologic disorders, we remind that the diagnosis of ptosis requires careful neuromuscular assessment to exclude a neuropathy, a myopathy with facial involvement, or a mitochondrial disorder.

Ptosis is a common feature of Smith-Lemli-Optiz syndrome or Noonan syndrome.5,70 Saethre-Chotzen syndrome is an autosomal dominant craniosynostosis syndrome, for which ptosis is a characteristic feature associated with minor limb anomalies (Fig. 4.12).36,97

F. EYELASHES, EYEBROWS, AND SKIN OF THE LIDS

Eyelashes and eyebrows show a wide range of normal intra- and interethnic variation. In some circumstances they may have a syndromic relevance.
Sparse or thickened eyebrows are the most common features associated with dysmorphic syndromes but are rarely decisive features in the diagnostic proceedings.

Prominent eyelashes with highly arched heavy eyebrows associated to down slanting palpebral fissures and/or ptosis are found for instance in Rubinstein-Taybi syndrome (Fig. 5.1).10,93 Heavy eyebrows, defined as thick and dense eyebrows, can be observed in patients with a coarse face in metabolic disorders such as in mucopolysaccharidosis (Fig. 5.2). Synophrys is defined as eyebrows extending to the midline and is commonly observed in persons with naturally developed pilosity. Synophrys, as well as long curly lashes, is a characteristic finding in Cornelia De Lange syndrome, a rare usually sporadic syndrome, defined by growth deficiency, limb reduction defect, a thin down turned lip, a long philtrum, and a low anterior hair line (Fig. 5.3).62,71

Long eyelashes, trichomegaly, can be acquired (i.e., adverse effect of a medical drug) or part of an inherited syndrome, such as Oliver-McFarlane syndrome, in which long eyelashes are associated with retinal dystrophy (Fig. 5.4).87 Eyelash and eyebrow anomalies are often found in syndromes with other dermatological features, such as ectrodactyly ectodermal dysplasia clefting syndrome. This autosomal dominant syndrome has a highly variable expression and is characterized by sparse or absent hair, sparse eyebrows and eyelashes, brittle nails, teeth anomalies and split hands, or ectrodactyly. In this condition, the lacrimal duct system is defective in more then 90%.75,82,100

Ectodermal Dysplasia Anhydrotic (EDA), an X-linked condition, is characterized in affected males by hypotrichosis, abnormal teeth, and absent sweat glands (Fig. 5.5). Late lymphedema with distichiasis (a double row of eyelashes) syndrome is an autosomal dominant condition (Fig. 5.6).63

IV. Conclusions

The examination of a patient with developmental anomalies includes the examination of the orbital region as well as other parts of the face and the body. Both severe or discrete anomalies may be involved in the establishment of the diagnosis. The precise analysis of these features, with the help of databases if necessary, may help the clinician in the diagnostic evaluation and guide molecular investigations if available, which may be useful in the overall care of the patient and his family.

V. Method of Literature Search

An online search of the international literature was conducted on PUBMED (http://www3.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=&DB=PubMed) covering years from 1966 to 2003 using the following key words: dysmorphology and eye, orbit and dysmorphology, dysmorphology and eye and syndromes, dysmorphology and review, hypertelorism, hypotelorism, craniosenosis and eye, eyelid and development, eyelashes and syndromes, eyebrows and syndromes. Online Mendelian Inheritance in Man (OMIM) database was used for the mentioned inherited syndromes: McKusicks-Nathans Institute for Genetic Medicine, John Hopkins University (Baltimore, MD), and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2000; http://www.ncbi.nlm.nih.gov/omim. The
London Dysmorphology Database (LDDDB) was also used as well as the POSSUM database.

References

DYSMORPHOLOGY AND THE ORBITAL REGION

559


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I. Dysmorphology: Definition and general comments
A. What is dysmorphology
B. Distinguishing normal from abnormal features in dysmorphology
C. Diagnosis in dysmorphology

II. Dysmorphology and the orbits
A. Morphological landmarks of the orbits
B. Terminology of abnormal distances between the eyes
1. Hypotelorism
2. Hypertelorism
3. Exorbitism

Outline
4. Telecanthus
   a. Primary telecanthus
   b. Secondary telecanthus
5. Dystoria canthorum
C. Conditions showing abnormal distances between the eyes and orbits
   1. Conditions with hypotelorism
   2. Conditions with hypertelorism
   3. Telecanthus and dystopia canthorum
   4. Abnormal orbital position of the globes
      a. Prominent eyes
      b. Sunken eyes
      c. Abnormal size and asymmetric orbits
III. Adnexal developmental anomalies
   A. Major eyelid malformations
      1. Cryptophthalmos
      2. Ablepharon
   B. Palpebral fissures and folds
      1. Epicanthal folds
      2. Orientation of the palpebral fissures
   C. Abnormal palpebral fissure opening
      1. Ankyloblepharon
      2. Blepharophimosis
      3. Increased length and eversion of palpebral fissures
   D. Clefting or notching of the eyelids
   E. Lowering of the position of the upper lid
   F. Eyelashes, eyebrows, and skin of the lids
IV. Conclusions
V. Method of literature search