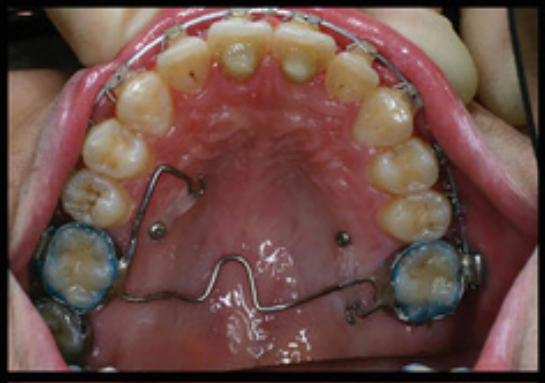
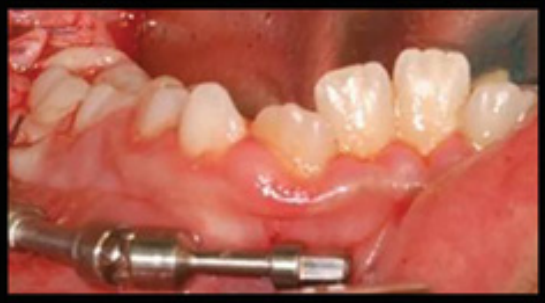
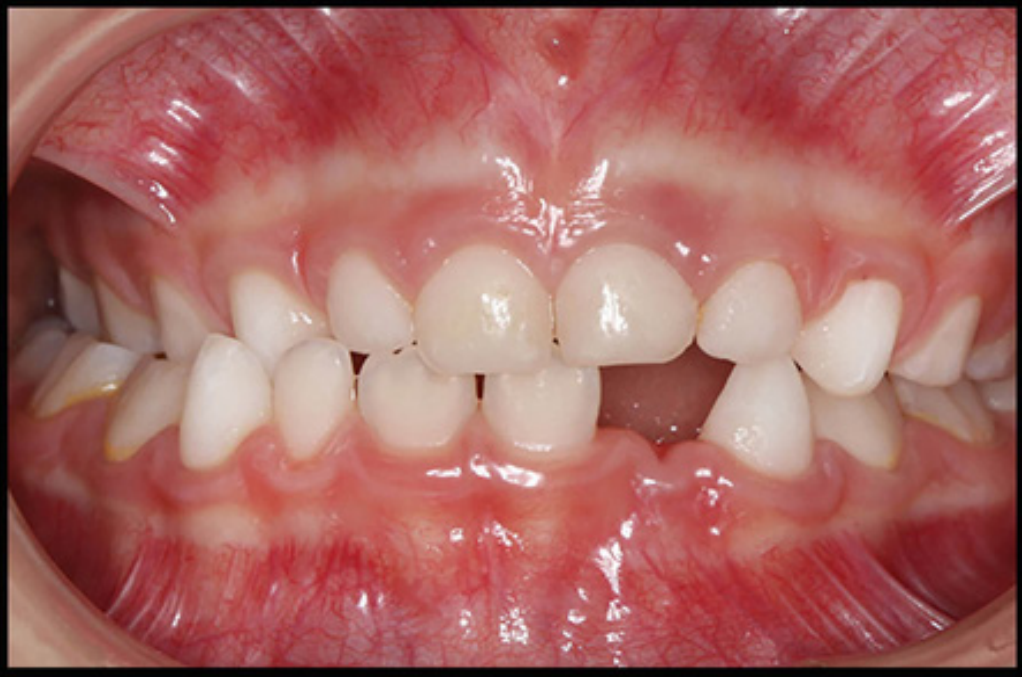
Dentofacial and Occlusal Asymmetries

Edited by **Birte Melsen** | **Athanasios E. Athanasiou**







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1

Introduction

Birte Melsen and Athanasios E. Athanasiou

CHAPTER MENU

Although each person shares with the rest of the population many characteristics, there are enough differences to make each human being a unique individual. Such limitless variation in the size, shape, and relationship of the dental, skeletal, and soft tissue facial structures are important in providing each individual with their identity (Bishara et al. 2001).

Dorland's Medical Dictionary defines symmetry as "the similar arrangement in form and relationships of parts around a common axis or on each side of a plane of the body" (*Dorland's Illustrated Medical Dictionary* 2000).

The absence of symmetry is asymmetry and is frequently experienced by man in their facial features, both structurally and functionally.

The term symmetry is generally used in two different contexts:

The first meaning is a precise and well-defined concept of balance or "patterned self-similarity" that can be demonstrated or proved according to the rules of a formal system, namely geometry, physics, or otherwise.

The second meaning is an imprecise sense of harmonious or esthetically pleasing proportionality and balance reflecting beauty or perfection. As such, symmetry was demonstrated within art by Leonardo Da Vinci in his Vitruvian Man in 1492 (Figure 1.1) (Baudouin and Tiberghien 2004).

Asymmetry has, on the other hand, been part of the features characterizing the unpleasant and the unharmonious (Edler 2001; Rhodes et al. 2001).

Whereas symmetry in art is used to express harmony, beauty, and peace, asymmetrical layouts are generally more dynamic, and by intentionally ignoring balance, the designer can generate tension, express movement, or convey a mood such as anger, excitement, joy, or casual amusement (Komoro et al. 2009).

Facial asymmetry, being a common phenomenon, was probably first observed by the artists of early Greek statuary who recorded what they had found in nature – normal facial asymmetry (Lundstrom 1961).

A perfect facial symmetry is extremely rare and practically all normal faces exhibit a degree of asymmetry (Figure 1.2). As in art, where the side has an importance in the interpretation of a movement displayed on a painting, the two sides of the face may express feelings (Schirillo 2000).

The left side of the face is considered more emotionally expressive and more often connotes more negative emotions than the right side. Also interestingly, artists tend to expose more of their models left cheek than their right. This is significant, in that artists also portray more females than males with their left cheek exposed. These psychological findings lead to explanations for the esthetic leftward bias in portraiture (Schirillo 2000; Powell and Schirillo 2009).

The studies of asymmetry of the craniofacial region can be divided into two categories. One is focusing on facial asymmetry in various populations and its impact on perception of the individual's attractiveness and health. The second category is dealing with the influence of asymmetry

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on treatment of patients receiving orthodontic treatment or craniofacial surgery.

Studies of various populations belong to the first category, and facial symmetry has been associated with health, physical attractiveness, and beauty of a person. It is also hypothesized as a factor in interpersonal attraction, and relevant research indicates that bilateral symmetry is an important indicator of freedom from disease and worthiness for mating (Edler 2001).

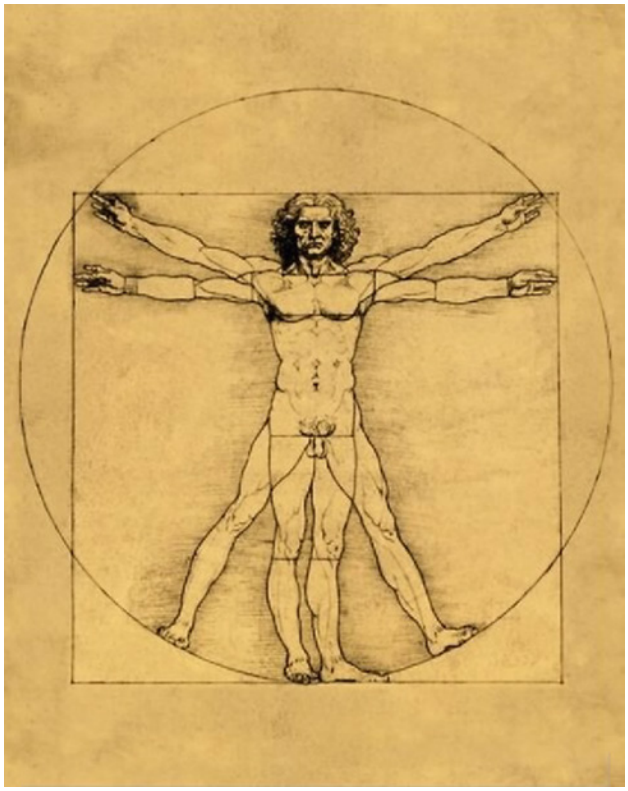

Figure 1.1 Vitruvian Man drawn by Leonardo Da Vinci in 1492 demonstrating the symmetry of the ideal body.

Most facial asymmetries among nonpatients are, however, fluctuating meaning that they have no significant influence on the attractiveness of the face. The perception of a face as attractive is more influenced by averageness meaning: what do the persons I like in "my tribe" look like. The beauty ideal is clearly changing with time and between various populations (Rhodes et al. 2001). The impact of averageness was studied by Komoro et al. (2009) who let laypeople evaluate the effect of symmetry and averageness on photographs and found that symmetry had a limited if any influence on attractiveness, thus confirming earlier findings by Baudouin and Tiberghien (2004). In a more recent study, it was found that symmetry on one hand reduced attractiveness by decreasing perceived normality, but on the other hand could also increase attractiveness by promoting the perceived symmetry (Zheng et al. 2021). Furthermore, it has been suggested that completely symmetrical faces might appear unemotional and thus less attractive (Swaddle and Cuthill 1995).

The second category of studies deal with asymmetry in relation to treatment. In reference to the need for treatment, it should be noted that the point at which normal asymmetry becomes abnormal cannot be easily defined and is often determined by the clinician's sense of balance and the patient's perception of the imbalance (Bishara et al. 2001). Minor asymmetry of the craniofacial skeleton and in the dentoalveolar region is often not easily detected. This can be the reason for which the optimal result of an orthodontic treatment cannot be reached since the asymmetry will often interfere with a satisfactory finishing.

The true prevalence of asymmetries in a population has never been described. Methodological limitations related to etiological factors, timing of appearance, degree of severity, progressing characteristics, and individuals' age, have enabled relevant studies only in subgroups of patients with facial asymmetry (i.e. hemofacial

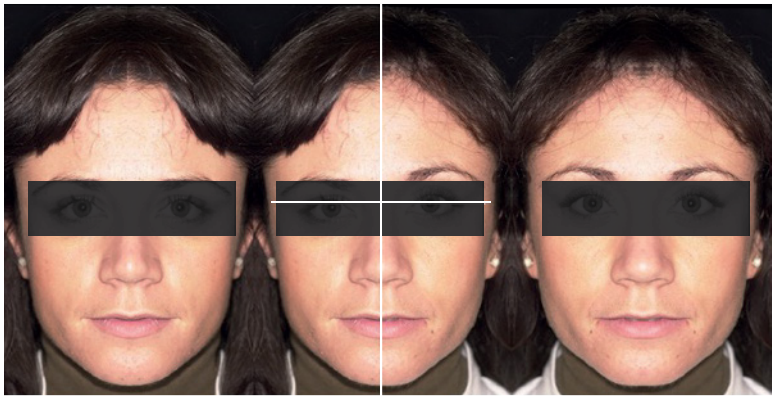

Figure 1.2 Three images where the right face is composed of two right sides, the middle one is the real face, and the left one is composed of two left sides.

microsomia) or dentofacial deformities in university orthodontic clinics.

When studying dentofacial deformity patients at the University of North Carolina, it was found that 34% demonstrated an apparent facial asymmetries. When present, asymmetry affected the upper face in only 5%, the midface (primarily the nose) in 36%, and the chin in 74% (Severt and Proffit 1997).

Recently, Evangelista et al. (2022) performed a review of the prevalence of mandibular asymmetry in different skeletal sagittal patterns and found that there was a significant difference between findings reported from different studies varying from 17.43 to 72.95%, and indicated that the more severe malocclusions exhibited more severe chin deviations than the nonorthodontic population.

Whereas most of the relevant studies have been focusing on facial asymmetry, Sheats et al. (1998) looked into the occlusal status of patients being treated in a graduate clinic and found that in 62% of the patients, the mandibular midline deviated from the facial midline.

An important part of this book will focus on the treatment of patients with various types of facial and dentoalveolar asymmetry focusing on interception, correction, or camouflage. The interception can only be performed for asymmetries related to functional deviations or/and eruption of teeth. Corrections and camouflage in some patients with skeletal asymmetries start at an early age and often continue for the remaining growth period. In adult patients, treatment comprises displacement of teeth and dentoalveolar modeling with goal-oriented biomechanics and orthognathic surgery when needed. For asymmetries with different localization, their etiology and the possible treatment modalities from a biological, biomechanical, and surgical viewpoints will be discussed. In relation to management, generating symmetry is among the goals of most treatment plans. However, when the outcome of orthodontics is assessed, even minor asymmetries are frequently impossible to generate a result that is compatible with ideal morphology and function.

The challenges in dealing with problems related to facial asymmetry are numerous and, to the knowledge of the editors, many of them have not been dealt with systematically. The purpose of this book is to satisfy the need for a comprehensive text on etiology, localization, and treatment of asymmetries within the craniofacial region. It is our hope that this books will cover all aspects of asymmetry starting with localization followed by etiology, congenital, or acquired through disease or trauma. In addition, it is crucial to verify if what is detected is reflecting a static or a developing deviation. Not only the localization and the morphological characteristics are important when categorizing the different types of asymmetries, but also the etiology should be established before a treatment plan can be worked out.

All contributing authors of this publication are prominent colleagues recognized as experts each within their specialization and the assigned subject within face asymmetries. It is our hope that this book will serve as inspiration for the colleague to approach a goal-oriented therapy based on all-inclusive diagnoses, localization of the asymmetry, and the definition of a comprehensive treatment goal.

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2

The Etiology of Dentofacial and Occlusal Asymmetries – An Overview

Birte Melsen

CHAPTER MENU

Introduction

Before generating a treatment plan, the etiology of the asymmetry should be determined.

Asymmetries can be congenital or acquired. The congenital asymmetries will be either deformation or malformation occurring prenatally, some of which may be part of various syndromes. Some of the etiologies related to congenital asymmetries have been reviewed in the past (Bishara et al. 1994; Cohen 1995a, 1995b, 1995c), but almost 30 years later a lot of their aspects remain unclear (Medina-Rivera 2016).

Congenital

The deformation generated prenatally will be dependent on the space available and, therefore, more frequent in the case of twins or triplets or after a hard delivery. Mild plagiocephaly is routinely diagnosed at birth as it may be the result of a restrictive environment (Flannery et al. 2012; Looman and Flannery 2012).

The congenital deformation will have strong tendency to self-correct postnatal and this is underlined when advising the importance of the sleeping posture. Among the congenital deformations that led to an asymmetry of the craniofacial skeleton, in the side of the skull, the sleeping posture is considered important. A mild and widespread form is characterized by a flat spot on the back or on one side of the head caused by remaining in a supine position for prolonged periods (Laughlin et al. 2011). Plagiocephaly is a diagonal asymmetry across the head shape. Often it is a flattening of one side at the back of the head that will lead to some facial asymmetry. Depending on whether a synostosis is involved, plagiocephaly can be divided into two groups: If there is premature union of skull bones, this is more properly called craniosynostosis (malformation) or nonsynostotic (deformational) (Kadom and Sze 2010). Surgical treatment of these groups includes the deference method; however, the treatment of deformational plagiocephaly is controversial.

The incidence of deformational plagiocephaly has increased dramatically since the advent of recommendations for parents to keep their babies sleeping on their

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backs. Data also suggest that the rates of plagiocephaly are higher for twins and multiple births, premature babies, babies who were positioned in the breech position or back-to-back, as well as for babies born after a prolonged labor (Ditthakasem and Kolar 2017).

The most frequently seen asymmetry visible at birth is cleft palate followed by some kind of plagiocephaly or hemifacial microsomia. Hemifacial microsomia is the asymmetry the cause of which is mostly unknown. Chen et al. (2018) suggested different etiologies for a disruption which occur during the first weeks of gestation. One would be external factors as various types of medication, or maternal intrinsic factors as maternal diabetes or genetic factors. In addition, three other causes have been proposed for hemifacial microsomia including a physical damage to the Meckel's cartilage, an abnormal development of the cranial neural crest cells, and a vascular abnormality and hemorrhage model. However, none of these proposed etiological factors can account for the asymmetry and the related deformation. The impact of the vascularization is, however, stressed also when analyzing the effect of maternal factors either genetic or related to disease as diabetes or medication. Contributing to some of the congenital asymmetries may be expression of genetically determined malformations that attack only tissues on one side. This abnormality may be of all tissues, cleft palate and hemifacial microsomia being the most prevalent. The abnormal growth may be of all parts of the craniofacial skeleton. It may be the size of all the tissues or only the skin. However, according to Tingaud-Sequeira et al. (2022) none of these etiologies account for the abnormal development of the first and second branchial arches described by Kjær (2017).

Postnatally

Thumb Sucking

The etiology of asymmetry developed postnatally will, if not related to a congenital disease, be the result of lifestyle or trauma to hard or soft tissues. The most frequent lifestyle cause of asymmetries is the nonnutritional sucking either by pacifier or thumb sucking. During the nonnutritional sucking, the mandible is kept back and the baby does not have to move the mandible forward, a movement as is normally done when sucking and swallowing take place simultaneously. The nonnutritional sucking has been found to be related to open bite and lateral crossbite. The latter may lead to asymmetry and crowding (Dimberg et al. 2010). Apart from the narrow upper arch, an asymmetrical arch form can also be the result of a prolonged thumb sucking (Figure 2.1).

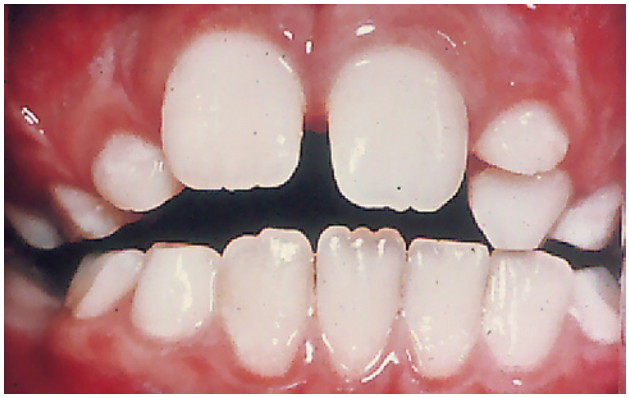


Figure 2.1 Asymmetric anterior open bite generated by prolonged thumb sucking.

Mandibular Fractures

A frequent etiology postnatally can be that trauma both in relation to birth or during early childhood will influence the growth. The most prevalent fractures resulting in asymmetry are the unilateral condylar fractures (Figure 2.2). According to the literature between 25% and 40% of all mandibular fractures are condylar fractures (Enghoff and Siemssen 1956; Müller 1963; Rowe and Milley 1968; Zachariades et al. 2006). In addition, epidemiological studies indicate that the majority of the fractures occur in growing individuals (Lautenbach 1967). The literature comprised description of patients with unilateral fractures where the fractures led to reduced growth on the fracture side whereas others demonstrated the opposite effect, an overgrowth of the fracture side. On this background, Lund (1974) decided to perform a cephalometric radiographic registration on both sagittal and frontal images taken with small intervals in order to be able to describe the changes occurring shortly after the trauma. The age of the 38 patients ranged from 4 to 17 years. He performed an examination of individuals who had been seen in the emergency hospital clinic following severe accidents. He realized that in a major part of the patients, the fractured condyle demonstrated not only healing, but also regeneration toward a normal morphology. He developed a classification of the condylar fractures based on their localization. They were categorized as high when they involved the condylar head or the condylar neck or as low if located in the condylar process. He also classified the fractures according to the position of the head in type 1 where the condylar head was situated in contact with the articular fossa and type 2 where the condylar head was displaced outside the articular fossa. It was demonstrated that type 2 was dominant in relation to high fractures whereas type 1 was seen more frequently in relation to low fractures. Type 2 fracture was also the only one seen in the

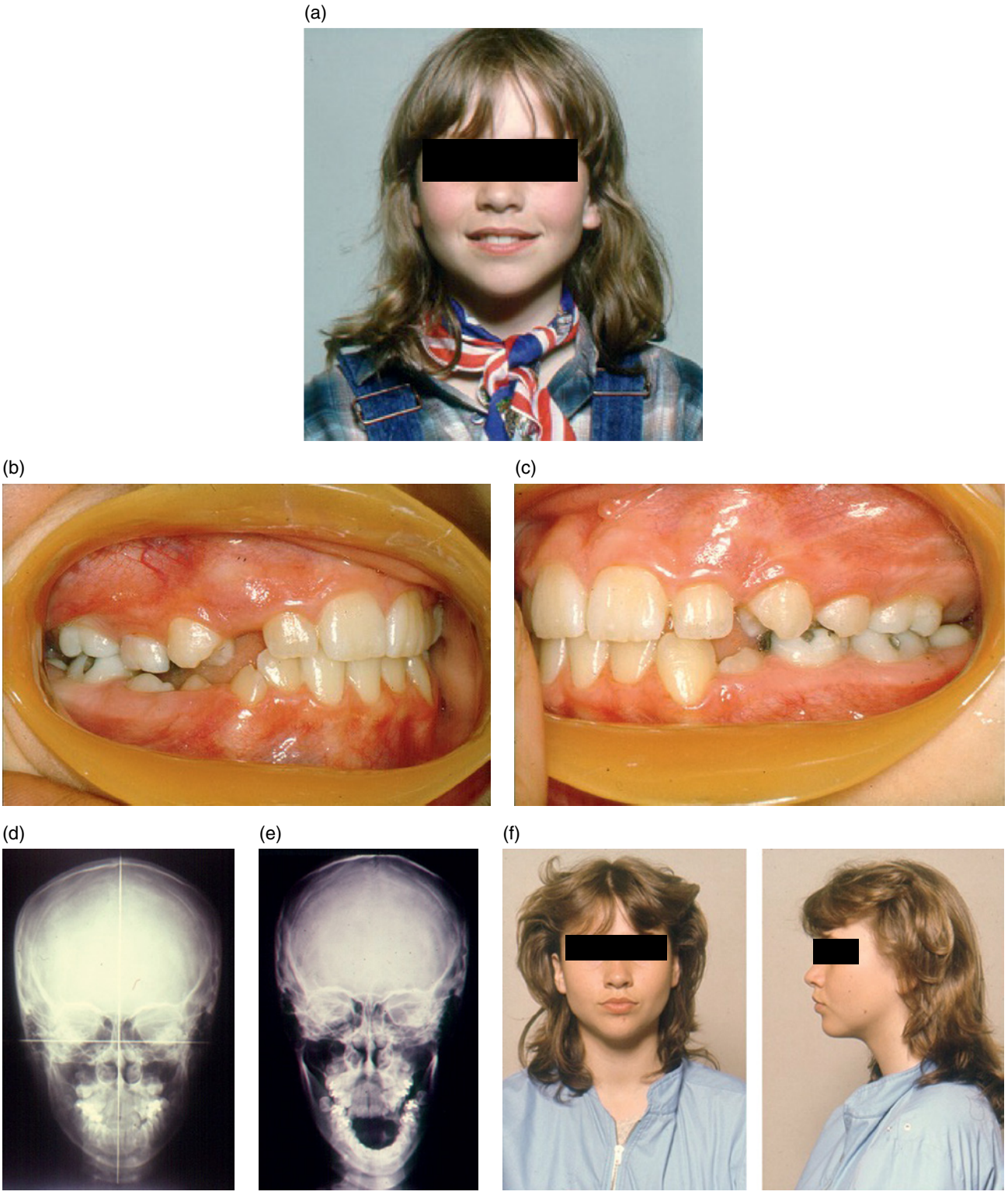


Figure 2.2 Twelve-year-old girl referred for treatment of maxillary space deficiency. (a) Extraoral images reveal a slight face asymmetry; (b and c) intraoral images exhibiting neutral molar occlusion bilaterally, normal overjet, and overbite. There was a midline discrepancy of the lower midline almost one tooth width to the left and space deficiency especially in relation to the upper left canine. The lower arch was characterized by moderate crowding; (d) frontal cephalometric radiograph disclosing an asymmetry, the lower midline displaced to the left; (e) frontal radiograph of the patient with an open mouth. There is an obvious deviation of the mandible to the left; (f) extraoral images of the patient after two years of treatment. The asymmetry is less visible.

older age group. The conclusion drawn from this thorough report was that the changes, namely compensation, occurring following the fracture led to growth that in many cases was larger than that of the healthy side so that an asymmetry characterized by midline displacement to the healthy side was observed. Unfortunately, the classification of the fractures and the systematic way of analyzing the changes occurring after the fracture were not followed up in the multitude of reports on condylar fractures published later. When Strobl et al. (1999) followed 55 patients aged between 2.6 and 9.9 years with the same combination of cephalogram and orthopantomogram as Lund (1974) they found that within the first year there was a very varying reaction to a treatment with a myofunctional appliance, but generally the younger patients (4–7 years old) had no or only minor condylar deformity at the end of the observation period whereas the 7–10 years old children exhibited everything from moderate deformity with reduced height to increase growth and hypertrophy. Unfortunately, this publication did not focus on the influence on the facial asymmetry and midline discrepancy.

Later epidemiological studies collecting data from patients with condylar fractures only assembled information obtained at one point of time. Based on a review of 466 cases seen in an emergency hospital clinic Zachariades et al. (2006) concluded that most fractures occurred between 21 and 30 years of age and, thus did not interfere with growth. Most fractures were exhibiting a displacement of the condylar head but had still contact between the mandible and the fractured condyle. In these cases, it seemed as if the best treatment was done with a functional treatment or intermaxillary fixation. The authors formulated a conclusion regarding type of fracture and need for surgical treatment, but none of their observations or their references who also described fractures in children focused on the midlines or the asymmetries nor at the fracture moment or at the end of growth.

When adult individuals present at a hospital after an accident which may involve several organs the focus is rarely at the occlusion, but later the patient may complain over changes in the way he/she bites, e.g. a gradual opening of the bite and an asymmetry. The panoramic radiograph does not render very much information while cone-beam computed tomography (CBCT) images providing sagittal and frontal images make it obvious that a condylar fracture has taken place (Figure 2.3). An interference with normal development that may lead to asymmetry can be a fracture that actually does not get detected until the consequences,

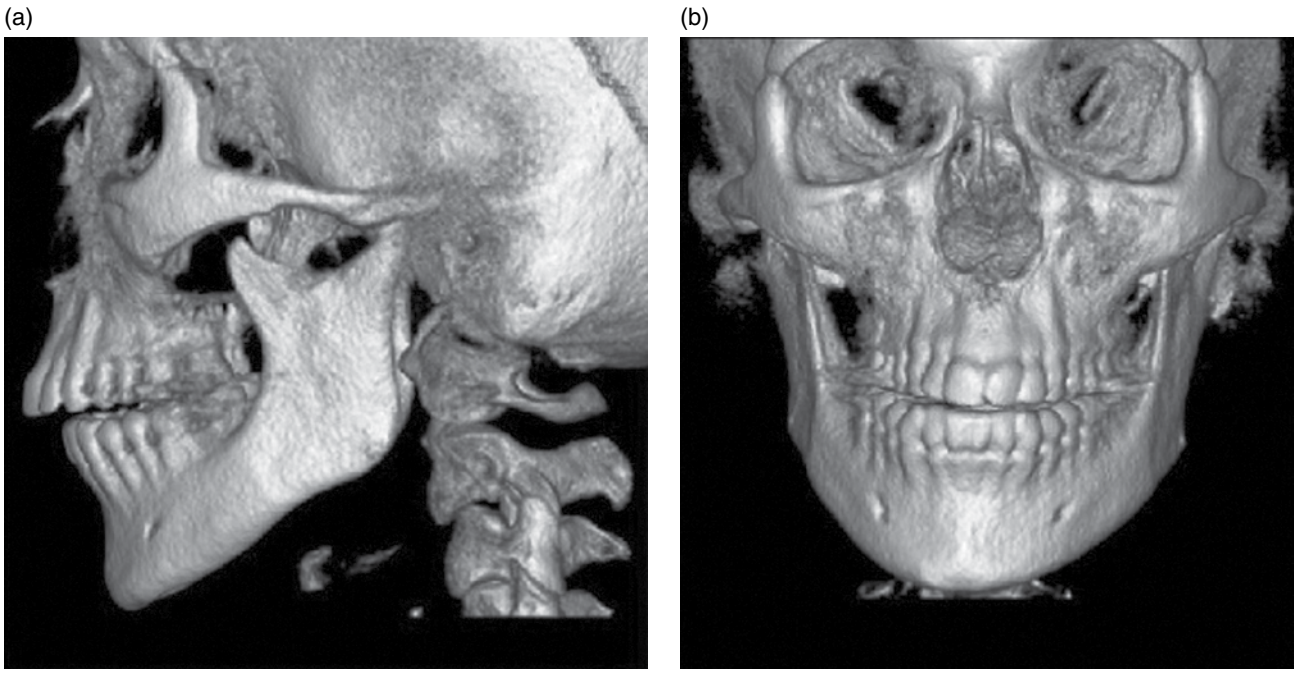


Figure 2.3 (a–c) Radiographs of a patient who days after a trauma detected an opening of the bite and an asymmetry, the reason being a condyle fracture on the right side. (a and b) CBCT images of the patient. A midline discrepancy toward the right side can be observed; (c) the panoramic radiograph does not clearly illustrate what happened to the condyle, but sift of the mandibular midline toward the trauma side can be observed; (d and e) lateral image observed from the traumatized side. It can be observed that the posterior border of the traumatized condyle is pulled back; (f and g) focus on the traumatize condyle on the CBCT image does however illustrate an abnormal morphology; (h) the result of the tomogram clearly illustrate the displacements of the fractured condyle. These images explain why the fracture cannot always be verified on the panoramic radiograph.

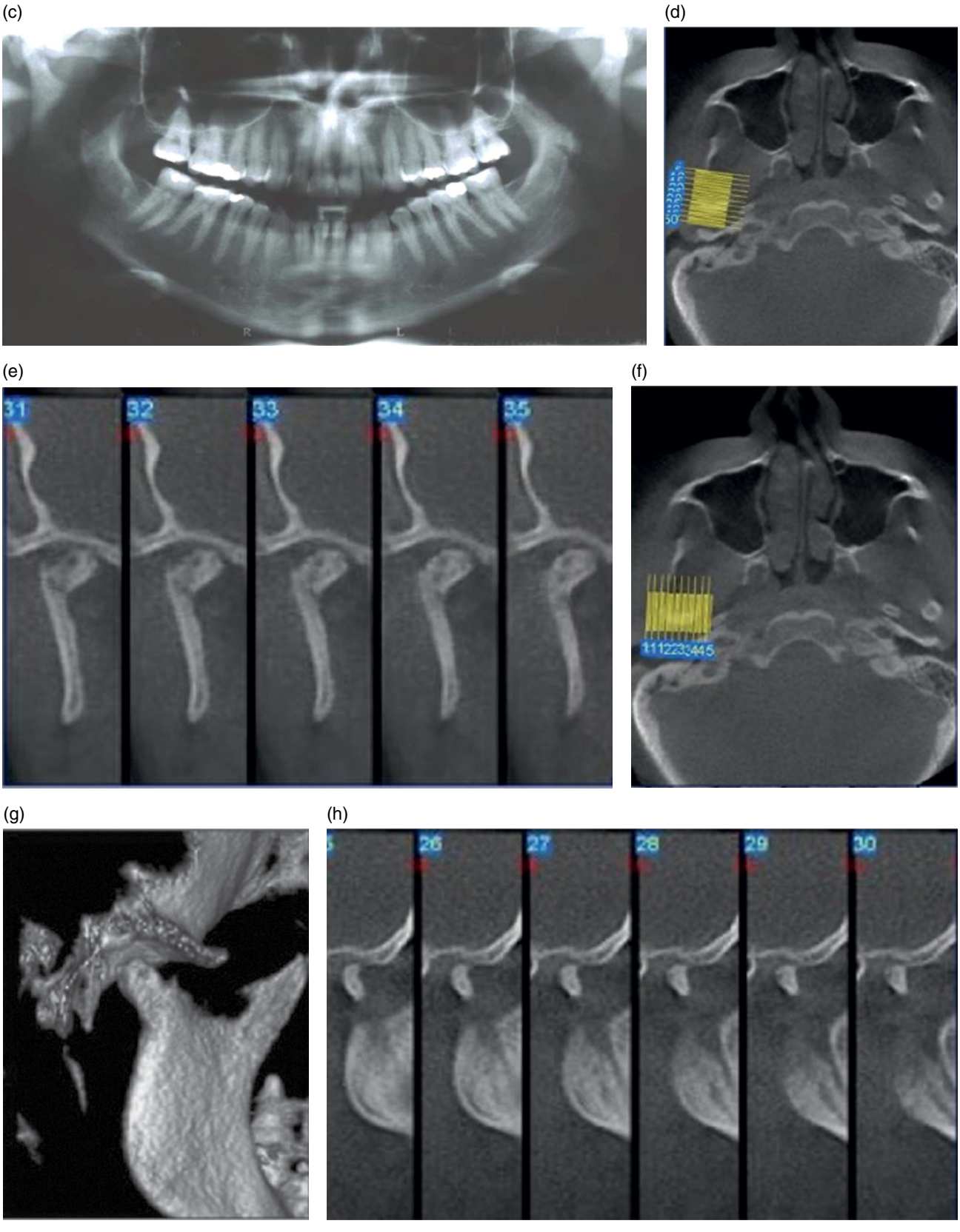


Figure 2.3 (Continued)

in terms of asymmetry in the occlusion and an open bite become obvious.

Soft Tissue Burning

Soft tissue trauma can result in asymmetry. The patient in Figure 2.4 was referred to the orthodontist for crowding in the canine region and minor midline discrepancy. The etiology was a soft tissue burning when the child was playing with an electric cord and contacted the facial soft tissues. This resulted in a scar that influenced the development of the alveolar process of the mandible and a midline discrepancy occurred. Since the result of this kind of trauma, the electric cords have been changed in Denmark so that this kind of damage cannot occur.

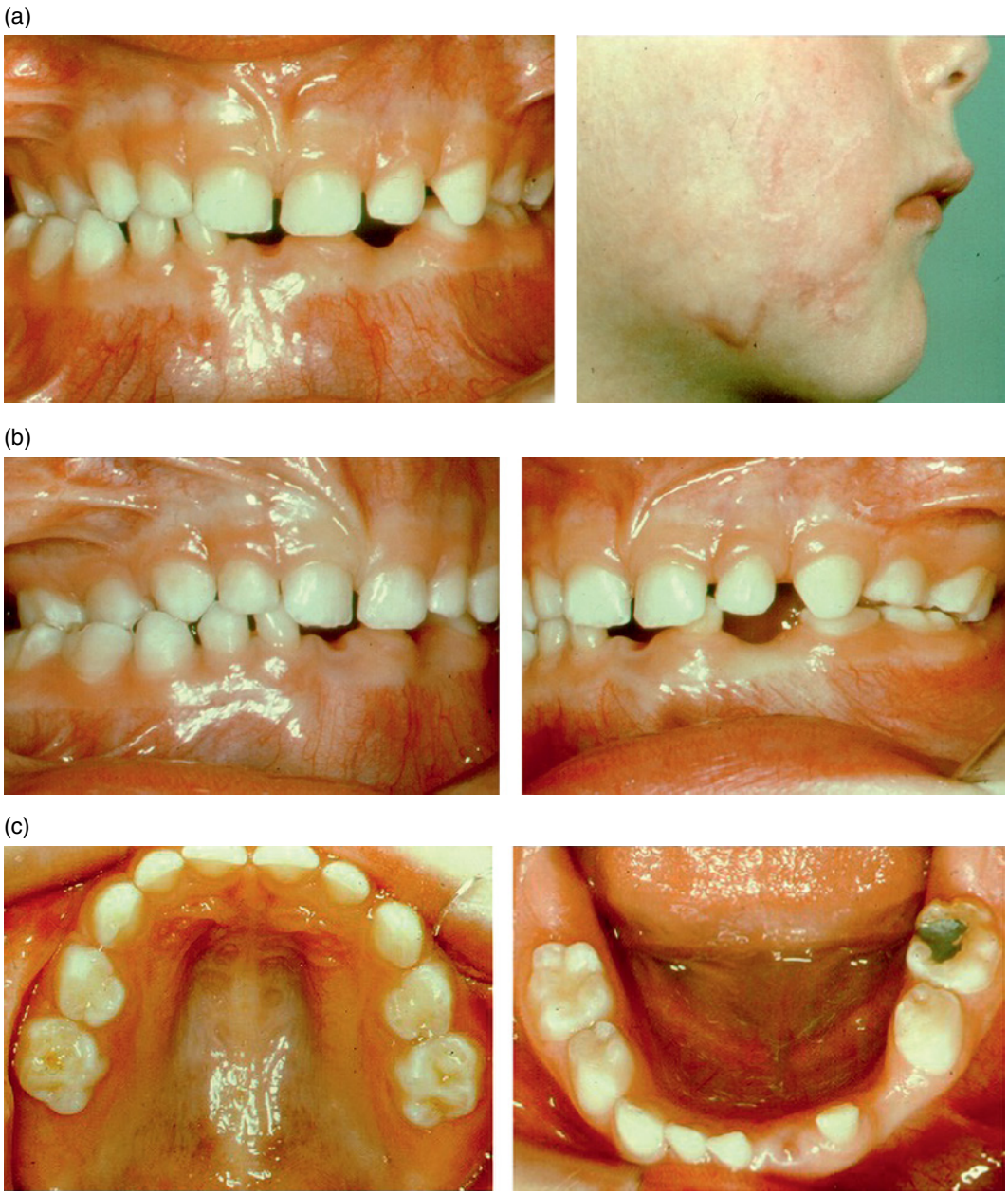


Figure 2.4 (a–b) Extraoral and intraoral images of a patient that had experienced a burning of the check with an electric cord. On the right cheek, a scar can be observed; Intraoral image of the "scar side" demonstrating a cross bite and a severe mandibular midline displacement towards the scar side; (c) Occlusal views demonstrating dentoalveolar asymmetry.

Iatrogenic Trauma

The orthodontist has to be aware of the fact that asymmetries may be generated by orthodontic treatments. Both intra- and inter-arch appliances can generate asymmetries (Grippaudo et al. 2020). If a leveling with super elastic wires is performed in an arch with crowding, the occlusal plane can be influenced (Figure 2.5). Such a standard appliance can easily be part of the etiology of an asymmetry when used for leveling without taking into consideration the effect of the applied force system on the dentoalveolar region (Figures 2.6 and 2.7).

Late Maxillary Expansion

An expansion of the upper dental arch when the midpalatal suture has become interdigitated, as described by Melsen (1975), will lead to a fracture the healing of which prevents further widening of the airways and the patients become mouth breathers. When correction of this situation is attempted, a dentoalveolar asymmetry with periodontal problems may develop.

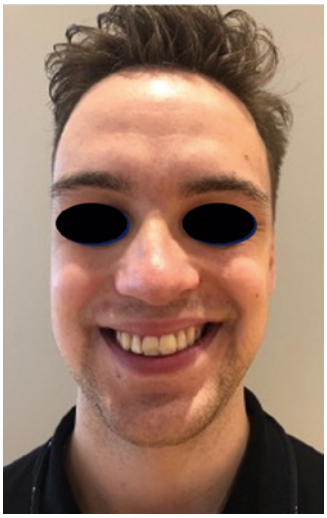
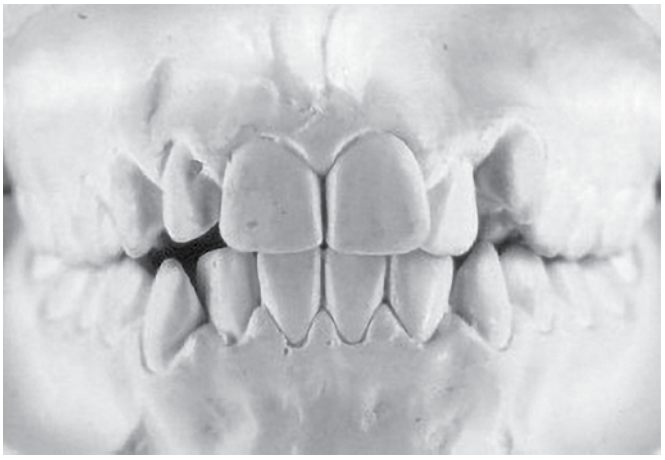


Figure 2.5 Result of a straight-wire treatment with unilateral Class II elastics.

(a)



(b)

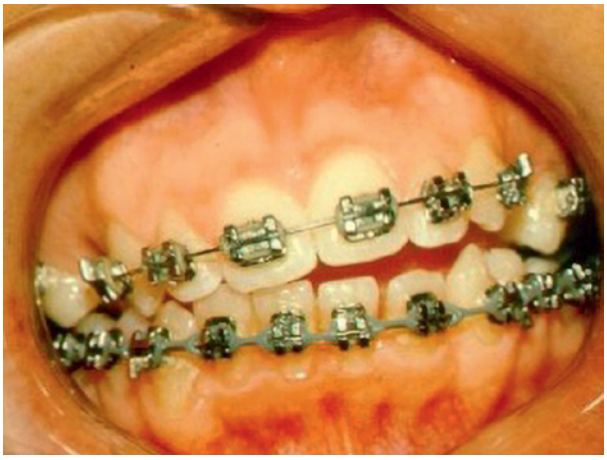
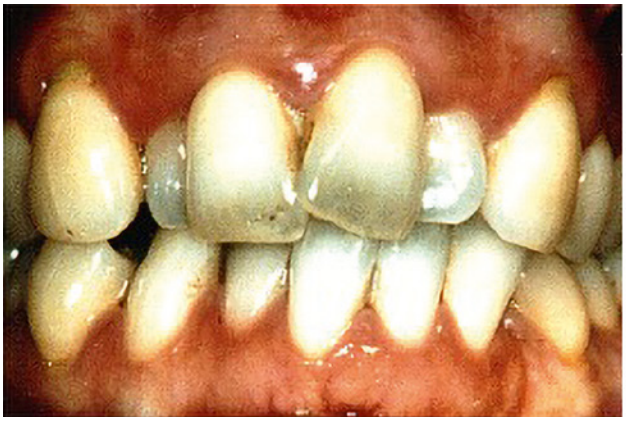


Figure 2.6 (a) Plaster model of a patient with a canine with high labial position; (b) patient where an indiscriminant leveling with Ni–Ti wires had taken place.



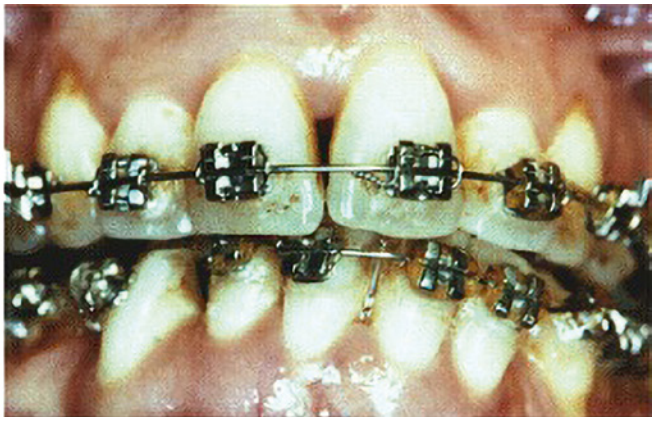


Figure 2.7 A patient who has been treated with a straight-wire appliance.

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3.1

Distortion/Malformation

Pertti Pirttiniemi

CHAPTER MENU

Etiology – Definition

A malformation is a condition where some body part is not properly formed and usually has existed so from the birth, at least so to some degree. A synonym to malformation can be distortion or deformity. These descriptions do not include the etiology of the condition. Therefore, the etiology can be genetic, multifactorial, or due to external conditions for example during the intrauterine period.

When it comes to asymmetric growth of the face, or possible effects on occlusion, various malformations can cause disturbances in normal growth. Therefore, the proper diagnosis and the etiology of the condition are very important, also from the clinical point of view.

The following division does not include cleft lip or palate, or specific syndromes.

Craniosynostosis

Craniosynostosis is a congenital condition where one or several sutures between cranial bones have been prematurely closed. Craniosynostoses are the second most common craniofacial anomaly after the clefts.

Craniosynostosis can be linked to a specific syndrome or it can be separate, with different and often unknown origin. The condition causes abnormal cranial growth and facial dysmorphism. In some cases, the dental occlusion is affected, depending on the location of the premature fusion of the suture (Kreiborg and Björk 1981; Arvystas et al. 1985).

At the moment, about 85% of the craniosynostoses are not linked to any known syndrome. However, this number is continuously decreasing due to advances in genetics (McKusick 2017).

The fusion of craniofacial sutures or the existence of a functional suture is dependent on a group of cytokines, growth factor receptors, and transcription factors. Especially in syndromic craniosynostoses specific mutations in gene coding have been revealed. There are, however, some findings of nonsyndromic craniosynostoses with genetic background, usually with incomplete penetrance (Heuzé et al. 2014).

Single suture craniosynostosis is the most common involvement, being found in 85–90% in all craniosynostoses. Of the single suture craniosynostoses, the most common involvement is the sagittal suture. The next in prevalence are metopic and coronal sutures (Kolar 2011). Premature fusion of cranial suture, as a single suture fusion

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comprises about half of all single fusions. No asymmetric occlusal involvement has been reported with this type of craniosynostosis. Typically, asymmetric dentofacial growth when linked to nonsyndromic craniosynostosis, has been reported in association with unilateral fusion of coronal suture. In unilateral craniosynostosis of the coronal suture the midface often shifts to the affected side and the mandible does not shift to the same degree, the condition causing a midline shift in the occlusion. However, the dental midlines may be coinciding, due to compensatory mechanisms in the orofacial region, especially in the mandible. The functional occlusion is important in maintaining the symmetry, especially in the oral region (Kreiborg and Björk 1981; Arvystas et al. 1985; Pelo et al. 2011).

Plagiocephaly

The term plagiocephaly is used when there is flattening or bossing of the skull anteriorly or posteriorly. This can be either unilateral or bilateral. Plagiocephaly can be associated with craniosynostosis, or it can be caused by outer forces (Valkama et al. 2019), when it is called positional plagiocephaly. Anterior or frontal plagiocephaly, when linked to craniosynostosis, is usually linked to fusion of the coronal suture and posterior plagiocephaly linked to premature fusion of the lambdoid suture.

Pelo et al. (2011) examined the occlusion and craniofacial structures of 21 patients with unilateral coronal craniosynostosis. They found many craniofacial and dental alterations. The overbite and the overjet were increased in the craniosynostosis group and the lower midline deviation, when compared to the upper midline, was significant. However, as the authors state, the real asymmetry was difficult to measure, as nearly all the structures in the patient group were to some degree asymmetric and a clear reference line in cephalometry is difficult to find. Their conclusion was that the found mandibular asymmetry in the craniosynostosis group with the unilateral coronal synostosis would primarily be dependent on the altered position of the glenoid fossa on the affected side. Thus, the mandibular asymmetry is the consequence of the skull base asymmetry in these cases. Lebuis et al. (2015) did a study on a group of patients with scaphocephaly, where the premature fusion of the sagittal suture causes craniofacial alterations. They found an increase in the prevalence of Class II malocclusion. There was not any increase in asymmetry of the face or lateral malocclusions in these patients and the lateral cephalometric values were mostly within the limits of normal range, which finding could be related to the fact that the primary premature fusion of the suture in these cases was symmetric in the midsagittal plane and not affecting the symmetry of the developing skull or occlusion.

Deformation Plagiocephaly

Deformation plagiocephaly can frequently occur in healthy infants, the highest frequency being found at about three months of age. Deformation plagiocephaly can arise from unevenly distributed external forces on the head of the child which causes the growth direction asymmetrically. Deformation plagiocephaly can be expressed as occipital flattening or unilateral frontal baossing and anterior shifting of the ear. One possible etiological factor has been suggested to be congenital muscular torticollis. However, a high risk for the development of the condition has been shown to be the one-sided positioning and the infant positional preference of the child during the first months of life (Aarnivala et al. 2016). In this respect, it is interesting that it has been shown that by giving parental guidance on the infant sleeping positions, a significant resolution of the condition has been shown to occur (Aarnivala et al. 2015).

Muscular Torticollis

Congenital muscular torticollis is relatively common congenital condition causing asymmetry of the growth, the incidence being reported from 0.3 to 1.3% in newborn population. In muscular torticollis, abnormal cervical muscle function causes abnormality in head posture but also affects orofacial structures which in turn are related to the development of occlusal asymmetry. The etiology of muscular torticollis is multifactorial, but often thought to be a trauma or developmental disorder during the intrauterine period that causes tightness or dysfunction in the sternocleidomastoid muscle. In most cases, head is tilted and the mandible is shifted to the opposite side. When it comes to the increased risk of malocclusions, a high prevalence of lateral crossbites has been reported in the cases of congenital muscular torticollis (Pirttiniemi et al. 1989; Kawamoto et al. 2009). Typically, if the condition is left without treatment in the early childhood, the asymmetric development in the orofacial area is advancing with more severe asymmetry, with many structures distorted. Then the occlusal plane in the frontal view becomes tilted and the mandible becomes asymmetric, which condition is difficult to correct without surgery. In early childhood, the treatment may include operative actions on the affected muscle or physiotherapy only, but most essential is to facilitate the normal balanced muscular function in the neck region.

Developmental Dysplasia of the Hip

Developmental dysplasia (DDH) of the hip is a common musculoskeletal disorder with a hip subluxation and dislocation in newborns with an incidence of 0.1–1%. The etiology of DDH is multifactorial, and like in the cases of muscular torticollis, often thought to be associated with difficulties in intrauterine position, like breech presentation and development of facial asymmetry. One possible risk factor for cranial molding is suggested to be the common treatment method of hip dislocation, where the children are held on their back for a long time to fix the hip to immobilize the hip when using a splint therapy of the joint. In addition, female sex and genetic factors are listed as risk factors (Hanis et al. 2010; de Hundt et al. 2012; Launonen et al. 2018).

By using a stereophotogrammetric method, it has been shown that there is distinct facial asymmetry linked to congenital hip dislocation, which is advancing in nature during growth (Hanis et al. 2010; Tolleson et al. 2010; Launonen et al. 2018). The found asymmetry in the cases of hip dislocation is associated with occlusal asymmetry. There were three times more lateral crossbites in the hip dislocation cases than in the controls and there were significantly more crossbites on the right side and a significant preference for girls (Harila et al. 2012).

Scoliosis

Idiopathic scoliosis is a rather common condition affecting about 3% of adolescent youth. The exact etiology is multifactorial and according to a recent systematic review, there is moderate evidence that there is no known distinct genetic cause of idiopathic scoliosis (Maqsood et al. 2020; Sarwark et al. 2021). However, there is some evidence that in some cases scoliosis may be genetically determined, as a recent GWAS study demonstrated various unknown genetic loci that could explain over 4% of the phenotypic variance of idiopathic scoliosis (Kou et al. 2019).

An increase in facial asymmetry associated with idiopathic scoliosis has been shown in many studies. Because there is a close anatomical relationship between the cervical column and the mandible, it can easily be suspected functional consequences in the orofacial region, if the symmetric development in the spine or trunk is affected.

Most typical findings, associated with scoliosis, concerning asymmetry are midline deviation in the upper and lower dental arch, mandibular deviation, as well as differences in bilateral molar occlusion (Huggare et al. 1991; Ben-Bassat et al. 2006; Saccucci et al. 2011; Nakashima et al. 2017). The found mandibular deviation has been shown to correlate with the degree and direction of the scoliosis curve. Most often reported finding associated with scoliosis, in addition to the occlusal midline shift or differences in molar occlusion, is lateral crossbite (Saccucci et al. 2011). There is also evidence that when the degree of scoliosis becomes more severe, the frequency of lateral crossbite becomes more frequent, while the side of the crossbite being opposite to the deviation in the curve of spine (Sambataro et al. 2019). In many studies, a spine curvature of 10° or over has been considered to be significant in respect to the development of dentofacial asymmetry. Korbmacher et al. (2007) studied a group of children with orthopedic diagnoses. They selected a group with lateral malocclusions and a group with normal lateral occlusion. They found that in the lateral malocclusion group, there were significantly more pathological orthopedic findings, like scoliosis, in the children with crossbite. Based on the occlusal findings with frequent crossbite and unilateral Class II malocclusion, the review of Saccucci et al. (2011) suggests regular orthodontic screening for this patient group, to avoid further development of asymmetry in the dentofacial area.

Hemifacial Hyperplasia

Hemifacial hyperplasia is a condition, which can be diagnosed at birth and thus is a congenial malformation with manifest overgrowth of the half of the soft and bony facial tissues, the other half remaining normally developing. It is interesting that also teeth on the affected side can be enlarged, which fact could point to a genetic origin in these cases. The affected side grows with higher rate than the nonaffected side worsening the asymmetry during growth. Hemifacial hyperplasia must be distinguished from hemimandibular elongation and unilateral condylar hyperplasia, which conditions develop much later and therefore cannot be considered in most cases congenital (Pirttiniemi et al. 2009; Dattani and Heggie 2021).

The etiology of hemifacial hypertrophy has mostly remained unresolved. Recently, Nolte et al. (2020) in a case study revealed mosaicism mutation in condylar tissue of a patient with hemifacial hyperplasia. There are many other attempts to explain the etiology of hemifacial hypertrophy. Most of these studies have a low level of evidence and most of them are based on case presentations (Dattani and Heggie 2021). One explanation for the etiology has been presented by Pollock et al. (1985) where they suggest that there is an increased number of neural crest cells on the affected side in the neural tube area during embryonic development.

The clinical severity of the hemifacial hypertrophy depends on the extent of the growth rate of the involved tissues, as well as the region of the affected tissues. The overgrowth in affected tissues, however, ceases when somatic growth is over (Dattani and Heggie 2021).

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3.2

Syndromes and Rare Diseases with Asymmetry in the Craniofacial and Dental Regions

Hans Gjørup and Dorte Haubek

CHAPTER MENU

Syndromes and Rare Diseases

Syndromes and rare diseases might be associated with facial asymmetry and/or asymmetry of the oral cavity, the dental arches, or the dentition. The present chapter demonstrates examples of syndromes and rare diseases, which in different ways may cause asymmetry. The presentation is mainly restricted to inherited conditions, and it is not the intention to cover all syndromes with asymmetry.

In the medical world, a syndrome is defined as a recognizable complex of symptoms and physical findings, which indicate a specific condition deviating from normal, and for which a direct cause is not necessarily understood (Spranger et al. 1982). However, nowadays the genetic background for many syndromes has been discovered, e.g. Apert syndrome, which is associated with a pathologic variant of a specific gene, *FGFR2* (Hamm and Robins 2014). Other syndromes are characterized by a diversity of genetic associations, e.g. Cornelia de Lange syndrome, which is associated with pathologic variants of one out of six different genes (Goldenberg and Vera 2021).

The definition of a rare disease varies according to national or regional criteria. According to EU regulations, a disease is rare, if the prevalence is equal to or less than 5 in 10,000 inhabitants (European Commission 1999). In the present context, we use the Danish/Scandinavian definition (Danish Health Authority 2014). According to this, a rare disease is defined as a congenital, complex, and serious disease or condition, which requires access to professionals with special knowledge and expertise. In addition, the rare disease needs well-coordinated and highly

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Table 3.2.1 Overview of conditions included in the chapter.

Unilateral overgrowth of craniofacial and/or oro-dental structures		**Unilateral underdevelopment of craniofacial and/or oro-dental structures**				
Overgrowth syndromes	***Hamartoneoplastic syndromes***	***Branchial arch and oral-acral disorders***	***Syndromic cranio-dysostosis***	***Syndromes affecting skin and mucosa***	***Syndromes with unusual facies***	***Rare dental anomalies***
Primary condylar hyperplasia	Klippel–Trenauneau syndrome (KTS)	Oculo-auriculo-vertebral spectrum	Saethre–Chotzen syndrome (SCS)	Focal dermal hypoplasia (Goltz syndrome)	Progressive hemifacial atrophy	Regional odontodys-plasia
Congenital infiltrating lipomatosis of the face (CIL-F)	Proteus syndrome	Hypoglossia-hypodactyly syndrome		Incontinentia pigmenti		Oligodontia
Segmental odonto-maxillary dysplasia (SOD)				Hypohidrotic ectodermal dysplasia		

specialized diagnostic setting, where relevant procedures, treatments, follow-ups, and controls are carried out. Furthermore, the prevalence of a rare disease has to be equal to or less than 1–2/10,000 inhabitants.

Basically, the craniofacial and dental asymmetries, which may develop in syndromes and rare diseases, are associated with either unilateral overgrowth or unilateral underdevelopment of the structures (Table 3.2.1). Thus, the following description of syndromes is divided into these two main categories, and each of them is subdivided according to a modification of Gorlin's classification of syndromes with impact on head and neck (Gorlin et al. 2001). The diseases and syndromes are defined according to definitions by Orphanet® ("Orphanet: an online database of rare diseases and orphan drugs" 1997).

Unilateral Overgrowth of Craniofacial or Dental Structures

Syndromes with unilateral overgrowth can be divided into overgrowth and hamartoneoplastic syndromes. Selected conditions within these two main groups will be addressed in the following text and illustrations (Table 3.2.1).

Primary Condylar Hyperplasia

Primary condylar hyperplasia is a rare temporomandibular joint anomaly characterized by progressive, nonneoplastic overgrowth of a mandibular condyle. Normally, it is unilateral and leads to progressive facial asymmetry with the chin of the mandible deviating to the nonaffected side. It is hard to delineate bilateral condylar overgrowth from the development of mandibular prognathism, and bilateral cases are seldom reported (Obwegeser 2001). In the present context, only unilateral occurrence is of relevance. Previously, the condition was suggested to be divided into two types: hemimandibular hyperplasia affecting the whole ramal and corporal part of the mandible in the affected side and hemimandibular elongation with an extended vertical dimension of the condyle only (Obwegeser and Makek 1986). The etiology of the condition remains unclear, but it has been associated with excessive formation of articular cartilage or an extended zone of the proliferation zone of the condyle (de Bont et al. 1985; Pirttiniemi et al. 2009).

Craniofacial and Dental Characteristics

The maxilla adapts to the asymmetric development of the mandible and becomes asymmetric as well. A severe canting of the occlusal plane evolves in addition to malocclusion with midline-shift to the unaffected side and a tendency for lateral open bite in the affected side (Arora et al. 2019). In addition to facial disfigurement, the patients may experience severe attrition of the teeth in the nonaffected side because of the unbalanced occlusion. The recommended treatment in the active phase of the condition is high condylectomy, articular repositioning, and orthognathic surgery as alternatives to orthognathic surgery alone (Wolford et al. 2002, 2009). Recontouring of the mandibular inferior border by osteotomy is a treatment

option in cases with moderate facial asymmetry and minor or no malocclusion.

Congenital Infiltrating Lipomatosis of the Face (CIL-F)

Congenital infiltrating lipomatosis of the face (CIL-F) is a very rare disorder in which mature unencapsulated lipocytes invade muscle and soft tissues of the facial region (Slavin et al. 1983). It is a unilateral facial condition, characterized by hypertrophy of both soft and hard structures on the affected side and the absence of malignancy. The hypertrophy of the affected side evolves gradually, and the resulting facial asymmetry becomes clearly visible during childhood (Frimpong et al. 2018; Li et al. 2018). The etiology of CIL-F is unknown. However, it has been suggested that the condition might share its pathogenesis with other overgrowth syndromes, i.e. pathologic variants of gene *PIK3CA* (Couto et al. 2017; Maclellan et al. 2014; Sun et al. 2019).

Craniofacial and Dental Characteristics

In addition to the marked facial asymmetry, macrodontism, early eruption of teeth, maxillary and mandibular hypertrophy, macroglossia, and the proliferation of parotid gland on the affected side have been described. Furthermore, some case reports mention agenesis of permanent teeth (MacMillan et al. 1990; Padwa and Mulliken 2001; Sun et al. 2013). The unilateral overgrowth may be extreme and the dental midline of affected jaws can move dramatically to the contralateral side in addition to an obvious vertical effect with canting of the occlusal plane and rima oris (Figure 3.2.1).

Surgical treatment of the soft tissue is controversial because of the infiltrating nature of the condition, and recurrence of facial hypertrophy is common. Surgical treatment might include excision and liposuction (Kamal et al. 2010; Padwa and Mulliken 2001). Extraction of macrodontic teeth, orthodontic treatment, and orthognathic surgery might be indicated to solve the dental problems. Reports on outcome of dental treatment are, however, absent in the scientific literature.

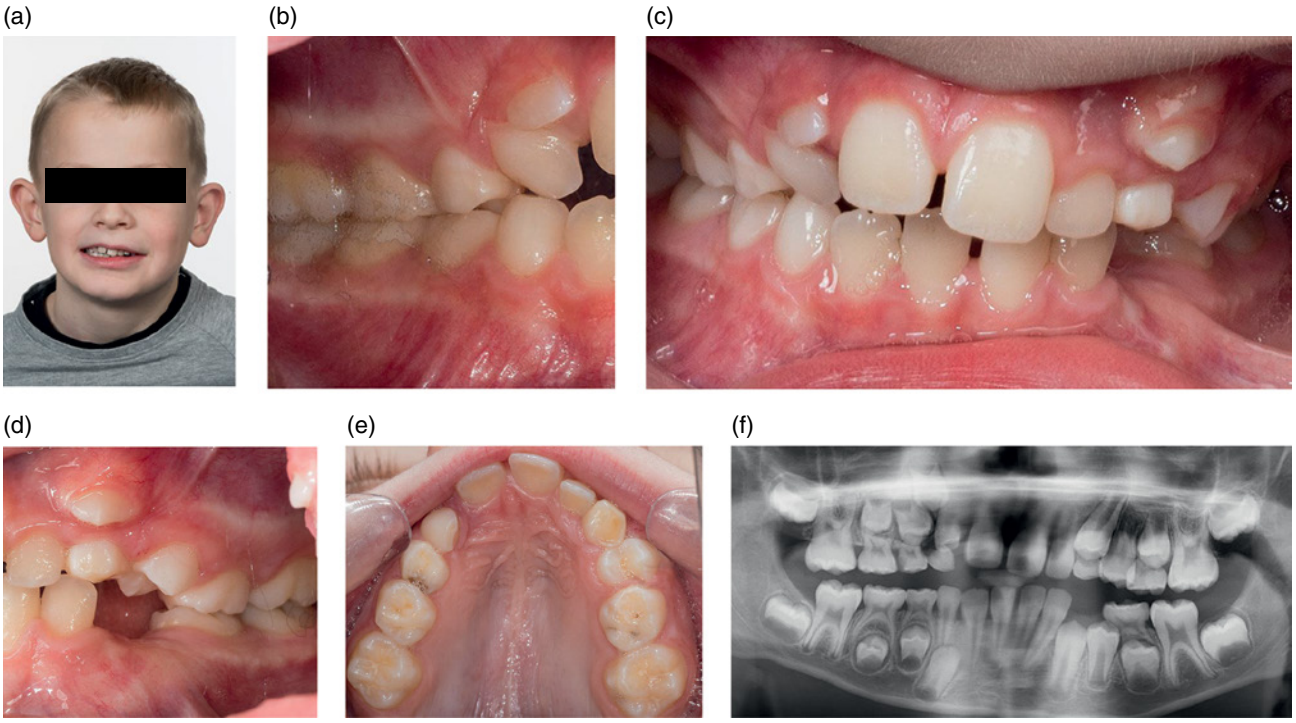

Figure 3.2.1 Boy 9, 3 years of age with congenital infiltrating lipomatosis of the face (CIL-F). (a) Facial asymmetry because of infiltration of lipocytes into soft tissues of the face in left side; (b–d) occlusion with canting of occlusal plane; (e) upper dental arch demonstrating hypertrophic left side processus alveolaris; (f) panoramic radiograph showing asymmetric in dental maturation and eruption, the left side being advanced compared to right side.

Segmental Odontomaxillary Dysplasia

Segmental odontomaxillary dysplasia (SOD) is a rare disorder characterized by unilateral enlargement of the right or left maxillary alveolar bone and gingiva in the region from the back of the canines to the maxillary tuberosity, including dental abnormalities (Danforth et al. 1990). The term SOD was introduced in 1990 as a specification of the term "hemi-maxillofacial dysplasia" (HMFD), which previously was the denomination (Miles et al. 1987).

Craniofacial and Dental Characteristics

In the enlarged region, dental abnormalities, such as missing premolars, abnormal spacing, and delayed dental eruption, occur. Deciduous as well as the permanent molars of the affected region have an abnormal morphology: An enlarged crown, enamel hypoplasia, and widely spread roots of the deciduous molars, which typically present with primary or secondary retention; irregular outer contours and enamel hypoplasia of the permanent molars, which also may be retained or erupted very late. The bone of the affected area appears dense and sclerotic on radiographs. Histologically, the bone is irregular and immature. SOD has been reported in a limited number of case reports, some of them with reviews of cases (Alakeel 2020; Becktor et al. 2002b; González-Arriagada et al. 2012; Prusack et al. 2000; Whitt et al. 2011) (Figure 3.2.2).

In addition to the symptoms in bone, teeth, and mucosa, facial asymmetry and symptoms of the skin may also be present. Often, the facial asymmetry is moderate, and the facial appearance cannot be characterized as syndromic. The skin symptoms have been reported as unilateral erythema, hypertrichosis, hairy nevus, or Becker nevus. Thus, the condition has by some authors been denominated HATS (*H*emifacial enlargement, *A*symmetry of the face, *T*ooth abnormalities) (Alakeel 2020; Welsch and Stein 2004).

The etiology of SOD is unknown. A vascular theory has been suggested. Recently, a genetic background to SOD has been suggested: Mosaicism with a pathologic variant of *PIK3CA* gene expressed in the affected region (Gibson et al. 2021).

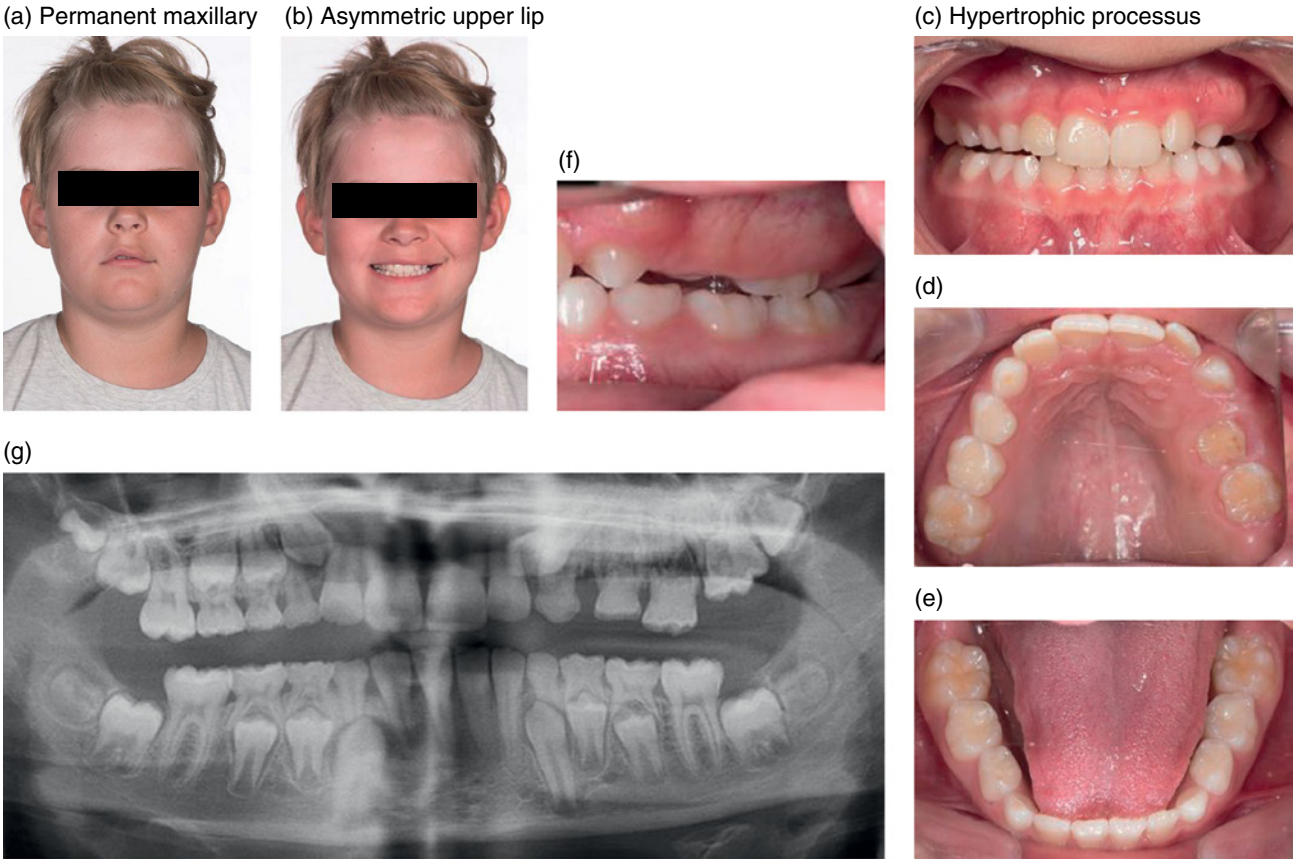

Figure 3.2.2 A boy, 10.5 years of age with segmental odontodysplasia (SOD). (a and b) Two en face pictures; (c) frontal view of dentition in occlusion; (d) dentition in upper jaw; (e) dentition in lower jaw; (f) occlusion left side; (g) panoramic radiograph showing enlarged left decidious maxillary molars, aplasia of 34,35, dysplastic permanent molars 26,27, and impacted permanent maxillary canines. Note asymmetric upper lip and hypertrophic processus alveolaris in left side of the maxilla.

The prognosis of the malformed teeth in the affected side is less favorable and implant-supported prosthesis to replace missing teeth is a prevalent need in young adults with SOD. However, the number of reports on the outcome of implant treatment is very limited (Whitt et al. 2011). With lack of eruption and/or early loss of teeth in the affected side, there is a risk of over-eruption of mandibular teeth and a succeeding canting of the mandibular occlusal plan. Reports on the outcome of orthodontic interventions are nonexistent.

Proteus Syndrome and Klippel–Trenauneau Syndrome

Proteus syndrome (PS) is a rare and complex hamartomatous overgrowth disorder, characterized by progressive overgrowth of the skeleton, skin, adipose, and central nervous systems. Normally, the onset of PS occurs from 6 to 18 months of age, and the disease is characterized by asymmetric overgrowth mainly of the hands or feet, but may in addition include unilateral overgrowth of other structures, e.g. facial structures. The skeletal overgrowth occurs rapidly and progressively resulting in the development of distorting and irregular calcified overgrowth in the tubular bones of the limbs, the skull, and vertebral bodies. PS has been reported to be associated with pathologic mutations in one of two components of the phosphatidylinositol 3-kinase (PI3K)-AKT signaling pathway: *PTEN* and *AKT1*. The gene deviations may occur as either a *de novo* mutation or a somatic mosaic mutation (Keppler-Noreuil et al. 2016).

Klippel–Trenauneau syndrome (KTS) (Synonyms: Klippel–Trenaunay–Weber syndrome or Angio-osteohypertrophic syndrome) is a congenital vascular bone syndrome (CVBS) characterized by the presence of an arteriovenous malformation in a limb, which results in overgrowth of the affected limb (You et al. 1983). The disease is associated with deviation in *PIK3CA* (John 2019). Craniofacial and oro-dental involvement in terms of overgrowth and venous varicosities and skeletal and dental hypertrophy may occur (Auluck et al. 2005; Fakir et al. 2009).

Craniofacial and Dental Characteristics

PS, and in some cases also KTS, may be associated with a severely asymmetric development of both craniofacial and oro-dental structures. The result is an obvious disfigurement of the face due to a unilateral overgrowth of skeletal structures and soft tissue. In addition, the maturation of the dentition in the affected side is accelerated, and the physical dimensions of the teeth increase in comparison to teeth of the unaffected side. Furthermore, the patients develop dental crowding and malocclusion with obvious midline-shift toward unaffected side and a canting of the occlusal plane (Munhoz et al. 2021). Idiopathic root resorptions and dysfunction of the temporomandibular joint have also been described in cases with PS (Becktor et al. 2002a) (Figure 3.2.3).

Unilateral Underdevelopment of Craniofacial or Dental Structures

The second overall topic, being unilateral underdevelopment of craniofacial and/or dental structures, can be divided into many subgroups as illustrated in Table 3.2.1, where an overview of the conditions addressed in the present chapter is given.

Oculo-Auriculo-Vertebral Spectrum

Branchial arch disorders include oculo-auriculo-vertebral spectrum (OAV), previously denoted "hemifacial microsomia" (HFM) or Goldenhar syndrome. The phenotypic spectrum of OAV ranges from isolated mild facial asymmetry to severe bilateral craniofacial microsomia and additional multiple extracranial abnormalities. The craniofacial involvement is in most cases unilateral and includes auricular abnormalities, preauricular appendages and/or fistulas, hypoplasia of the mandible, the maxilla, the malar bone, and/or the zygomatic arch, and epibulbar dermoids. The extent of involvement varies from mild and hardly recognizable to severe with socially handicapping dysmorphic appearance (Rath 2017). Next to cleft lip and palate, OAV is the most common facial anomaly affecting one in 5000 births. Unilateral occurrence in terms of HFM is much more prevalent than bilateral occurrence, and it is a well-known background for facial asymmetry. The etiology of OAV/HFM is debatable, but it is suggested to be associated with incidents occurring during the development and migration of neural crest cells, responsible for the mandibular arch formation (the first branchial arch). In the more severe cases, the second branchial arch is also affected (Gorlin et al. 2001). Embryonic vascular abnormality or hemorrhage might be another explanation to HFM (Hartsfield 2007).

Craniofacial and Dental Characteristics

The variation in severity is the background for a classification according to the degree of mandibular hypoplasia. In mildly affected cases, the contour of the mandibular ramus and condyle is fairly normal, but reduced in size, and the facial asymmetry is moderate. In the most severely affected cases, the condyle and most of the ramus are absent, and the facial asymmetry is severe (Kaban et al. 1988).

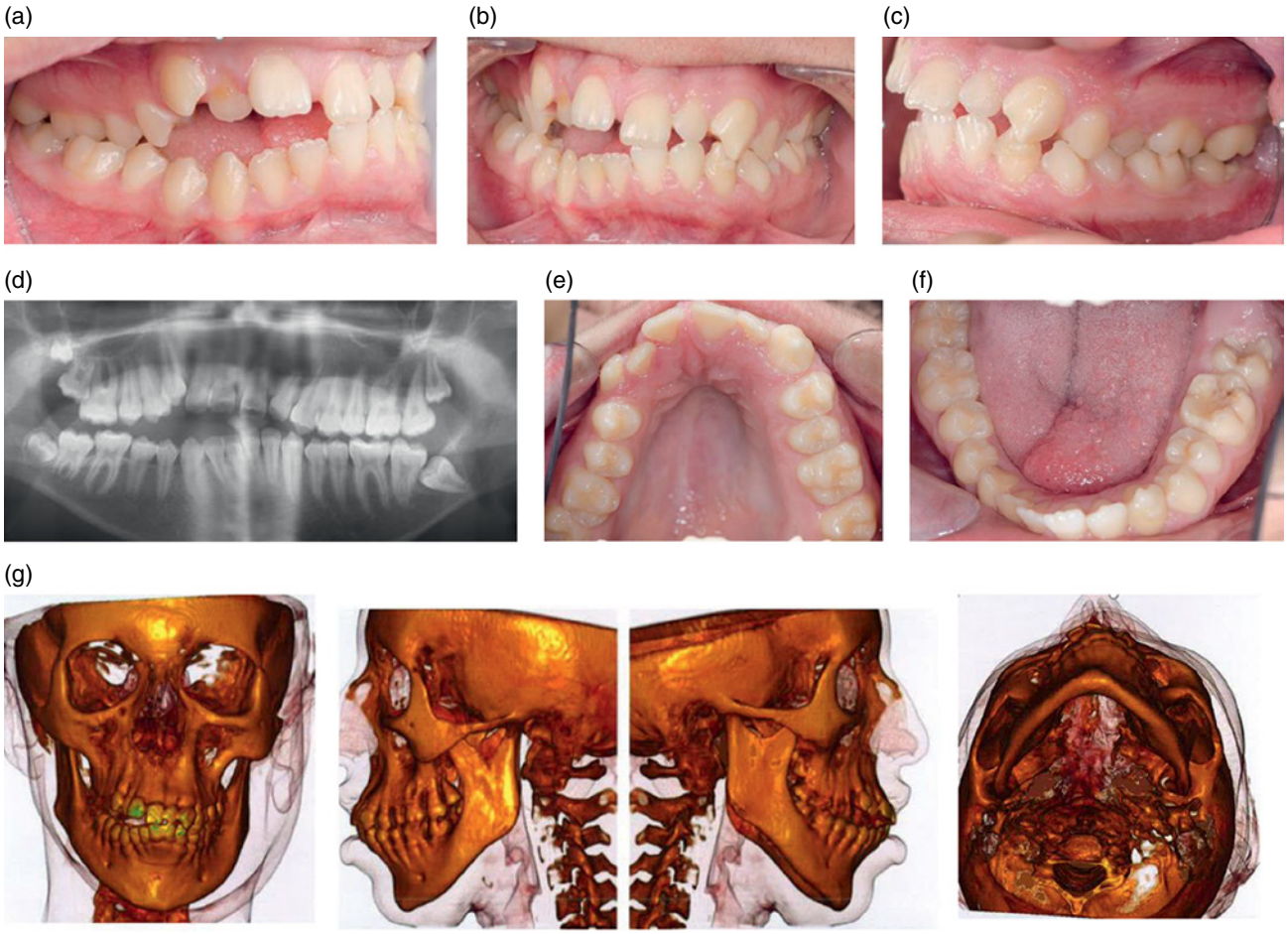

Figure 3.2.3 Clinical photos of a 16-year-old girl with Klippel–Weber–Trenaunay syndrome, including orthopantomography and CBCT of the cranium. (a) Right side of dentition; (b) frontal view of upper and lower jaws with teeth in occlusion; (c) left side of dentition; (d) panoramic radiograph; (e) dentition in upper jaw; (f) dentition in lower jaw; (g) CBCT of cranium. Pictures (a–g) show left-side over-growth of jaws and tongue, increased dimension and advanced maturation of teeth in left side compared to right side. Malocclusion develops in right side, contralateral to the over-growth side.

Agenesis of mandibular teeth is prevalent in individuals with HFM compared to unaffected individuals, and the occurrence of dental anomaly in the affected side seems to be associated with the severity of HFM (Maruko et al. 2001; Silvestri et al. 1996). Further, dental eruption and maturation might be delayed (Farias and Vargervik 1988).

The deviation in mandibular growth induces malocclusion in terms of distal molar relationship and unilateral crossbite in the affected side, and furthermore, a canting of the occlusal plane develops. The vertical development of both the mandibular ramus and the maxilla of the affected side is diminished. Thus, the occlusal plane cants cranially in the affected side.

The majority of children with HFM undergo craniofacial surgery. The mandible becomes reconstructed by distractions-osteogenesis, costochondral rib craft or other bone-graft, or by conventional mandibular sagittal split osteotomy. Additional correction of the maxilla is often requested, and it is performed as a Le Fort I osteotomy or surgically assisted rapid maxillary expansion. In the severe cases with absence of outer ear, a multistage reconstruction with the usage of costo-chondral graft is an option nowadays (Pluijmers et al. 2019).

Saethre–Chotzen Syndrome (SCS)

The most common type of syndromic cranio-synostosis, Crouzon syndrome is normally not associated with asymmetries in the oral and craniofacial structures. In contrast, Saethre–Chotzen syndrome (SCS) presents with unilateral or bilateral synostosis of coronal, eventually in conjunction with sagittal, metopic, or lambdoid, sutures resulting in abnormal skull shape and facial asymmetry, ptosis, and small ears, especially in unilateral cases. Digital

abnormalities are also often present. Intelligence is normal in most cases. Some may experience conductive and/or sensorineural hearing loss. Less common manifestations include short stature, hypertelorism, cleft palate, bifid uvula, maxillary hypoplasia, lacrimal duct stenosis, parietal foramina, vertebral anomalies, radio-ulnar synostosis, obstructive sleep apnea, and congenital heart malformations (Gallagher et al. 1993). SCS is due to point mutations or deletions involving the *TWIST1* gene (7p21), which encodes a basic helix-loop-helix (bHLH) transcription factor responsible for cell lineage determination and differentiation (Howard et al. 1997).

Craniofacial and Dental Characteristics

In unilateral cases, asymmetries of the neurocranium may be reflected in the craniofacial region and predispose for dental malocclusion in terms of mandibular overjet and lateral crossbite. The relevant treatments during the period of growth may be different types of neurocranial procedures (fronto-orbital advancement, monobloc biparticipation, forehead cranioplasty) followed by orthognathic procedures (e.g. Le Fort I maxillary expansion and advancement) (Abulezz et al. 2020).

Focal Dermal Hypoplasia (Goltz Syndrome)

Focal dermal hypoplasia (FDH), also called Goltz syndrome, is a rare dysmorphic syndrome characterized by abnormalities in ectodermal- and mesodermal-derived tissues. The classical symptoms are skin abnormalities, limb defects, ocular malformations, and facial dysmorphism (Lombardi 2019). The skin abnormalities include patchy skin hypoplasia, subcutaneous fat herniation, hypoplastic nails, sparse hair and peri-orificial skin, and mucous membranes papilloma. Typical ocular abnormalities include congenital microphthalmia (occasionally anophthalmia), cataracts and iris, and chorioretinal colobomas. Finally, FDH may include craniofacial deviations and dental anomalies (Bostwick et al. 1993).

FDH is caused by mutations in *PORCN,* located at the X-chromosome (Xp11.23), which encodes the porcupine *O*-acyltransferase, involved in the secretion and signaling of WNT proteins. A number of different mutations and deletions have been described (Wang et al. 2014). The inheritance is X-linked dominant, which normally is associated with lethality in boys. However, due to the presence of post-zygotic mosaicism in *PORCN,* FDH has also been reported in boys (Happle 2016).

Craniofacial and Dental Characteristics

Craniofacial dysmorphism includes facial asymmetry, notched nasal alae, small, underfolded pinnae, low-set and protruding ears, mid-facial hypoplasia, and a pointed chin. Dental anomalies in terms of enamel hypoplasia with longitudinal grooving and irregularity of enamel surface are common. Microdontia, peg-shaped teeth, and other irregularities in dental morphology may occur. The irregularities include talon cusps or marked incisal notching of incisors and canines, and molars may have anomalous forms with supernumerary cusps. Hypodontia with dental agenesis is common, and some of the teeth may be delayed in eruption (Murakami et al. 2011). In general, the clinical signs on FDH are more severe on one side than on the other. Interestingly, the asymmetric pattern of symptoms is reflected in the dentition, being most severely affected in one side (Murakami et al. 2011) (Figure 3.2.4).

Incontinentia Pigmenti

Incontinentia pigmenti (IP) is an X-linked syndromic multi-systemic ectodermal disease, which neonatally in females present with a bullous rash along Blaschko's lines (BL), followed by verrucous plaques and hyperpigmented swirling patterns. Furthermore, IP is characterized by abnormalities in other ectodermal tissues, which may include alopecia, nail dystrophy, and tooth anomalies. Ophthalmologic anomalies in terms of microphtalmia or retinal detachment may also be present in addition to central nervous system (CNS) abnormalities (Scheuerle 2019). The neonatally bullous rash evolves from stage I to a verrucous stage II and further to stage III with hyperpigmentation along BL. In adulthood, the skin symptoms remain as hypo-pigmented, hairless regions following BL. IP is caused by mutations of the NF-kappaB essential modulator gene *IKBKG* (formerly *NEMO*), and the inheritance is X-linked dominant (Smahi et al. 2000). Primarily females are affected because of the dominant X-linked inheritance. However, due to the presence of post-zygotic mosaicism, males with IP have also been reported (Gregersen et al. 2013).

Craniofacial and Dental Characteristics

Dental anomalies are described as major diagnostic criteria in line with the dermatologic characteristics and pathologic variant of *IKBKG* (Bodemer et al. 2020). The main dental anomalies are agenesis of multiple teeth in both dentitions (90% of cases have absence of multiple permanent teeth), deviations in crown morphology (in approximately 70% of cases), delayed dentition, and various types of dental malocclusion, arched palate, and eventually an orofacial cleft. In the permanent dentition, the pattern of agenesis follows the pattern in other patients with hypodontia, i.e. absence of the lateral incisors, second maxillary premolars, and mandibular premolars being the dominant

Figure 3.2.4 14-year-old female with focal dermal hypoplasia (FDH). (a) En face picture; (b) right side of face; (c) left side of face; (d) frontal view of upper and lower jaw with teeth in occlusion; (e) dentition in upper jaw; (f) dentition in lower jaw; (g) dental occlusion from right perspective; (h) dental occlusion from left perspective. Notice asymmetry of external facial structures (nose and outer ears) and oro-dental structures. The morphology of teeth is most irregular in right side.

trait (Santa-Maria et al. 2017). The clinical crown of the incisors is frequently peg-shaped or with other morphological abnormalities. Molars may appear with fewer cusps than normal. Clinical variability is marked in IP, and especially in IP-males, asymmetry in the dental arches may occur, as consequence of the mosaic nature of the condition in boys. An example of a boy with IP demonstrates the absence of four permanent maxillary teeth (22,25,26,27) in the left side and only two absent teeth in the right side (12,17) (Figure 3.2.5). In relation to the retained mandibular deciduous canines, the permanent successors erupt distally to the deciduous canine in the right side and mesially in the left side. In left side only, the deciduous molars (65,75) are retained both in the upper and the lower jaw. It is noteworthy that the right-left asymmetry in the dental symptoms, being most severe in left side, mirrors the asymmetry of the ophthalmologic symptoms, the boy being blind at the left eye and having normal vision in right eye.

Hypohidrotic Ectodermal Dysplasia

Hypohidrotic ectodermal dysplasia (HED) is a genetic disorder of ectoderm development, characterized by hypotrichosis (underdevelopment of scalp and body hair),

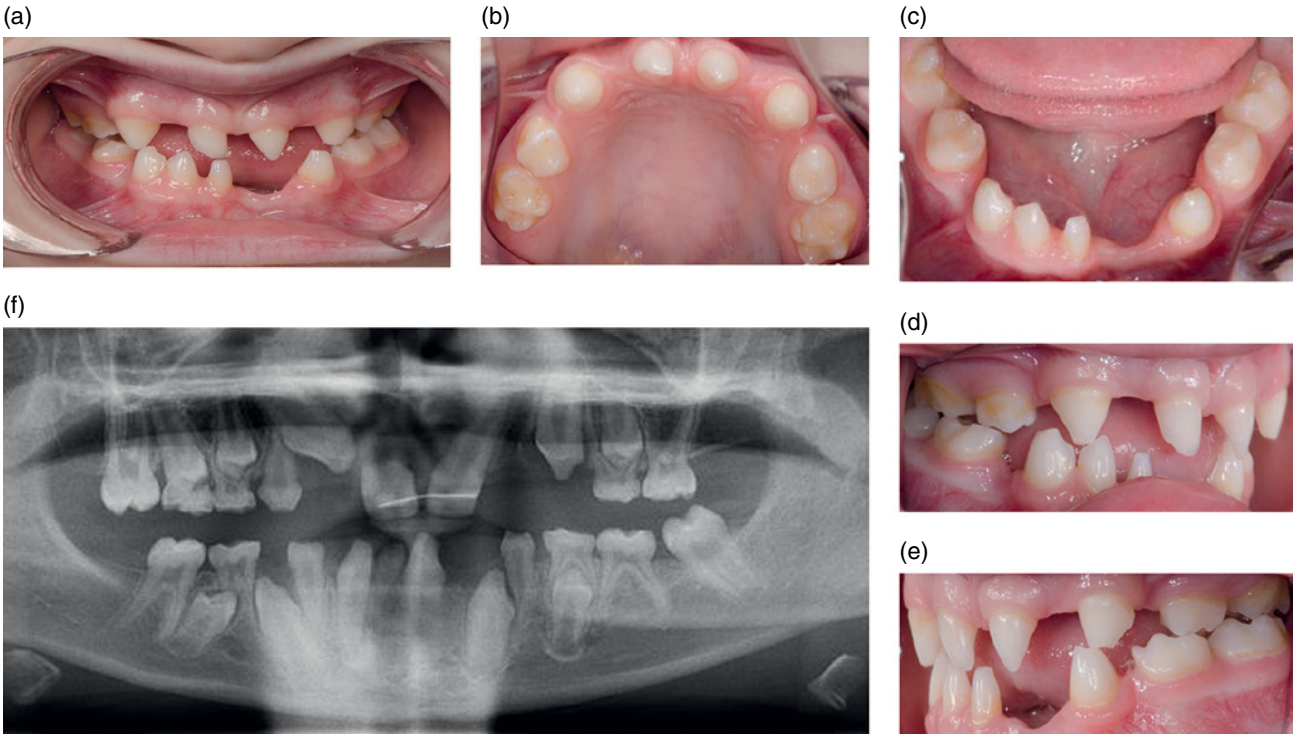

Figure 3.2.5 Boy (5 years of age) with incontinentia pigmentia (IP) and with agenesia of 12 permanent teeth. (a) Frontal view of upper and lower jaw with teeth in occlusion; (b) dentition in upper dental arch; (c) dentition in lower dental arch; (d) dental occlusion (right side); (e) dental occlusion (left side); (f) panoramic radiographs at the age of 11 years of age showing agenesis of multiple (5) permanent maxillary teeth in left side and of few missing teeth in right side (2), ectopic position of canine in left side of upper jaw and fully preserved roots of primary molars in left side of jaws. Notice abnormal shape of incisors.

hypohidrosis (underdevelopment of sweat glands), and hypodontia (underdevelopment of teeth). It comprises three clinically subtypes with impaired sweating as the key symptom: X-linked HED (synonym: Christ-Siemens-Touraine syndrome), autosomal recessive (AR), and autosomal dominant (AD) HED. Furthermore, a fourth subtype of HED with immunodeficiency as an additional symptom exists (HED with immunodeficiency). X-linked HED is the classical and most prevalent type of HED. The prevalence of HED has been estimated to be 1/15,000 (Schneider 2012). In a Danish register study, the prevalence of molecular confirmed X-linked HED was 1.6:100,000 (Nguyen-Nielsen et al. 2013). Children with HED have a decreased or absent ability to sweat (hypohidrosis), which leads to heat intolerance, which may cause recurrent, potentially life-threatening hyper-thermic episodes. Dry eyes, nasopharyngeal furness, and hyposalivation are common characteristics. In X-linked HED, males are more severely affected than females, in whom the symptoms may be mild and in some females even remain unrecognized. HED is caused by mutations in genes of the ectodysplasin/NF-kappaB pathway, which is necessary for the development of ectodermal structures. Mutations in *EDA*, which is located at the X-chromosome (Xq12-q13.1), explain X-linked HED. Mutations in *EDAR* (2q13), encoding the EDA-receptor, or *EDAR-ADD* (1q42.3), encoding the EDAR-associated death domain (EDAR-ADD) protein, cause AR as well as AD HED. Mutations in *IKBKG* (Xq28) mutations cause HED with immunodeficiency. Some few HED cases are associated with mutations in other genes (Wright et al. 2017).

Craniofacial and Dental Characteristics

Agenesis of teeth and deviations in tooth morphology are cardinal symptoms of HED. Congenital absence of nearly all deciduous and permanent teeth or even absence of all teeth (anodontia) is a dominant symptom in males with X-linked HED. Typically, the crown of the present anterior teeth is conical and widely spaced (Bergendal 2014). The few deciduous molars, if present, may be retained for many years and support the prosthodontic replacement of missing teeth. In general, females with X-linked HED have a much higher number of natural teeth in both dentitions, eventually nearly all teeth are present, and they are described as carriers of the disease. However, some females may have severe dental symptoms equivalent to symptoms

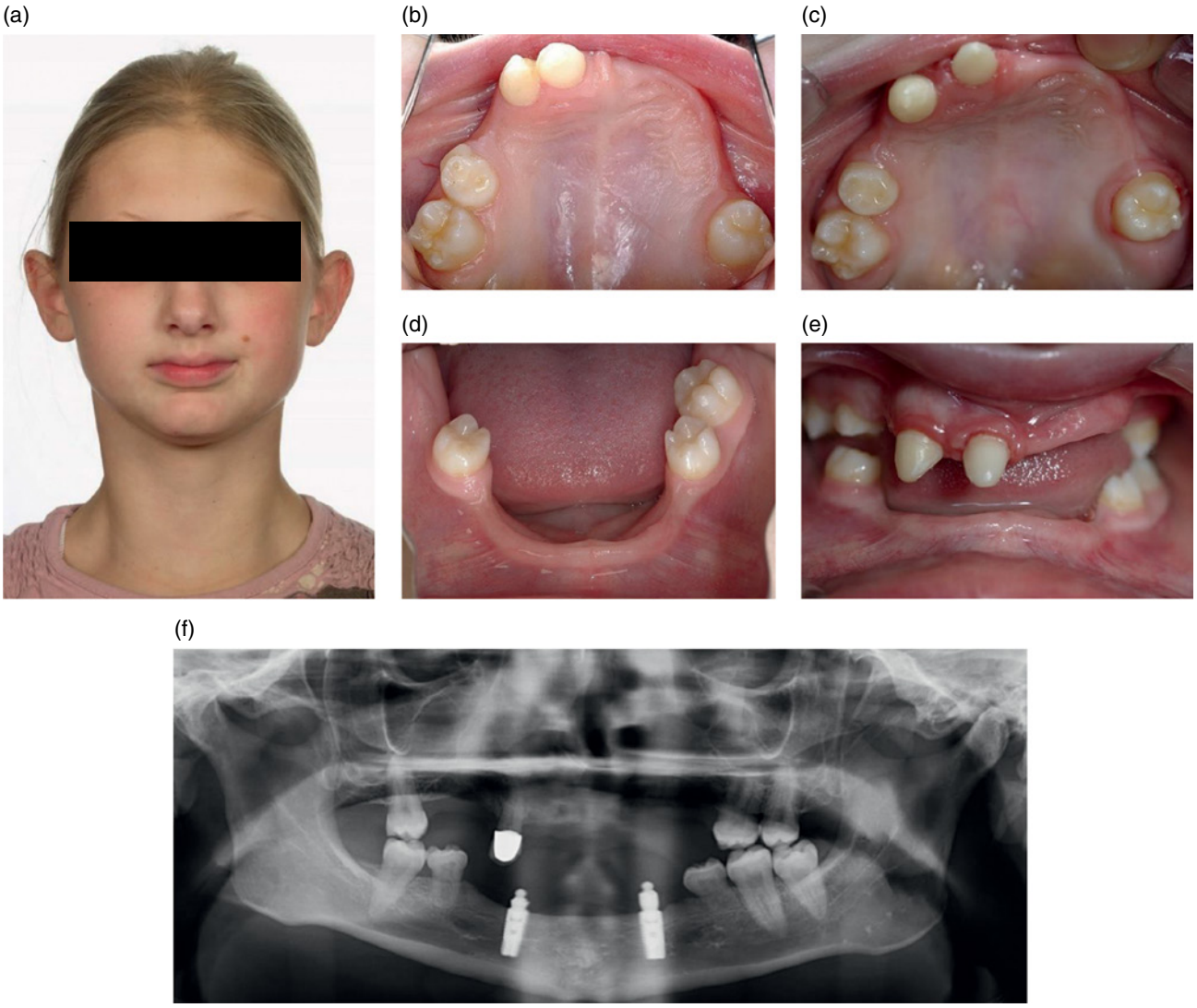

Figure 3.2.6 Female with hypohidrotic ectodermal dysplasia (HED), 10 years old. (a) En face picture; (b) intraoral view before and (c) after orthodontic separation of two pegshaped maxillary incisors (11,51); (d) lower dental arch; (e) anterior occlusal view; and (f) panoramic X-rays after implant insertion at 13 years of age. The deciduous incisor (51) is exfoliated and the 55 has been extracted because of infraposition.

of males, presumably because of a high degree of inactivation of the normal allele (Lexner et al. 2008). Figure HED shows a girl with X-linked HED and demonstrates how the dental arches in addition to absence of teeth is affected by asymmetry. In the upper dental arch, one permanent and one deciduous peg-shaped incisor was developed in the right side and none in the left side. Posteriorly, the right side contained one permanent and one deciduous molar, and the left side contained two permanent molars. In the lower arch, the asymmetry was minor: The right side contained one permanent and one deciduous molar in contrast to two permanent and one deciduous molar in left side. The treatment of the children with HED exhibiting severe phenotypes of oligodontia or anodontia may call for implant-supported prosthesis at a very early stage, long before growth has ceased. However, not younger than seven years of age and primarily in the anterior mandibular region (Wright et al. 2017) (Figure 3.2.6).

Progressive Hemifacial Atrophy

Parry in 1825 and Romberg in 1845 first described progressive hemifacial atrophy (PHA), synonymously Parry–Romberg syndrome. It is a rare acquired disorder,

characterized by unilateral progressive atrophy of the skin and soft tissues of half of the face (Tolkachjov et al. 2015). Muscles, cartilage, and the underlying bony structures may also be involved in addition to neurological symptoms, like seizures (Chen et al. 2020). The unilateral atrophy includes the territory of one or more branches of the fifth cranial nerve and develops slowly during the first two decades of life. The condition is self-limiting. In many ways, PHA and "morphea en coup de sabre" are alike, and PHA may be considered as a facial subtype of localized scleroderma (Paprocka et al. 2006). The etiology of PHA is unknown, but autoimmunity has been suggested, and treatment with methotrexate and other immune-suppressing drugs is common. Other potential etiologies to PHA are localized vascular dysfunction, trauma, or infection (Tolkachjov et al. 2015).

Craniofacial and Dental Characteristics

It is of relevance for the dental function to be aware of the common presence of unilateral tongue atrophy and hypoplastic masticatory muscles of the affected side. In addition, the salivary glands may be absent or hypoplastic, which is a caries risk factor. To a varying degree, both the maxilla and the mandible are underdeveloped in the HPA affected side, e.g. with a reduced ramal height of the mandible. Depending on the degree of underdevelopment, the face becomes more or less asymmetric. In the affected side, short roots, missing teeth, and crowding of teeth may be present. In addition, deviations in dental occlusion (crossbite) may occur (Al-Aizari et al. 2015; O'Flynn and Kinirons 2006).

Conjunctional to the pharmacological treatment of PHA, surgical treatment has to be considered.

Regional Odontodysplasia (ROD)

Regional odontodysplasia (ROD) is a localized developmental anomaly of the dental tissues. In the affected region of the jaw, the teeth are usually hypoplastic, small, and atypically shaped with irregular and discolored surfaces. ROD is more common in the maxilla than in the mandible, and the condition is generally unilateral. Other common features include eruption failure or delay, and abscesses or fistulae in the absence of caries. Radiographically, ROD is characterized by ghost-like teeth with large irregular pulp chambers and absence of the normal contrast between the irregular layers of dentin and enamel. Histologically, the affected teeth are characterized by mixed areas of cellular, amorphous, and interglobular dentin in addition to a hypoplastic and hypocalcified enamel. The surrounding bone is unaffected. The etiology of the condition is unknown, but circulatory disorders, viral infections, and local trauma have been suggested as causative (Cahuana and Gonzalez 2007).

Craniofacial and Dental Characteristics

In general, the overall bony craniofacial structures are unaffected or only mildly affected by ROD. In contrast, the abnormal and missing teeth may influence both the psychosocial and the masticatory function of the dentition. Due to the unilateral nature of ROD, varying degrees of dental arch asymmetry and malocclusion may also evolve: Examples given are tipping of teeth adjacent to the affected region, midline shift towards the affected side, and overeruption of antagonists (Nijakowski et al. 2022) (Figure 3.2.7). Furthermore, the patient with ROD needs prosthodontic treatment starting with provisional solutions during childhood. When the patient has grown up, the treatment continues with fixed partial dentures, which nowadays typically are implant supported (Abdel-Kader et al. 2019; Hess et al. 2020).

Oligodontia

Clinical features of nonsyndromic oligodontia include six or more missing teeth, lack of development of maxillary and mandibular alveolar bone height, and reduced lower facial height. Deviation in tooth morphology is also observed along with problems in tooth development, eruption, and exfoliation (Bloch-Zupan and Clauss 2013). Oligodontia may be associated with pathogenic variants in one of the genes *PAX9, MSX, WNT10A, EDA, LTBP3,* or others ["Online Mendelian Inheritance in Man (OMIM)" 2022]. The prevalence of oligodontia in Denmark has been estimated to be 0.16% (Rølling and Poulsen 2001), which is in accordance with the reporting (prevalence = 0.14%) in the meta-analysis by Polder et al. (2004).

In cases with oligodontia, the pattern of dental agenesis seems to be associated with the genetic background (Arzoo et al. 2014; Bergendal et al. 2011). According to meta-analysis on hypodontia, unilateral agenesis of the respective tooth types occurs nearly as often as bilateral agenesis (Polder et al. 2004). Unilateral agenesis introduces asymmetry in the dental arch in relation to the dental midline. In rare oligodontia cases, the asymmetry can take extreme forms, e.g. by the congenital absence of all teeth in the left side of the mandible in addition to both mandibular central incisors (Figure 3.2.8). A similar case, including their management of the patient, has been reported by others (Ephraim et al. 2015).

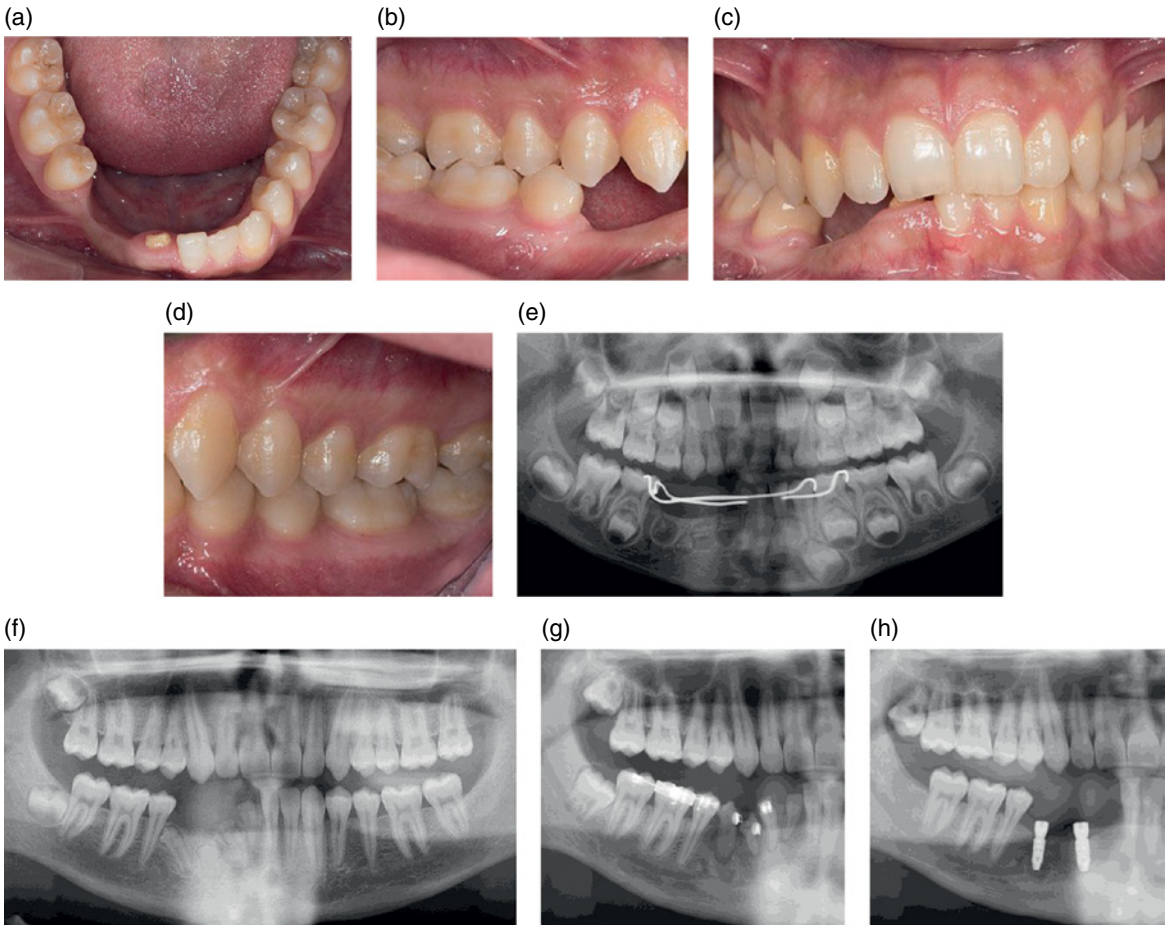

Figure 3.2.7 Male 18 years old with regional odontodysplasia. (a–d) Clinical view demonstrating three absent mandibular teeth (44,43,42) in right side and one dysplastic incisor (41); (e–g) panoramic radiographs showing the unilateral presence of dysplastic, ghost-like mandibular teeth at age seven years (e), at 18 years before initiation of multidiciplinary treatment (f), at age 21 years after orthodontic treatment (g), and after insertion of implants (h).

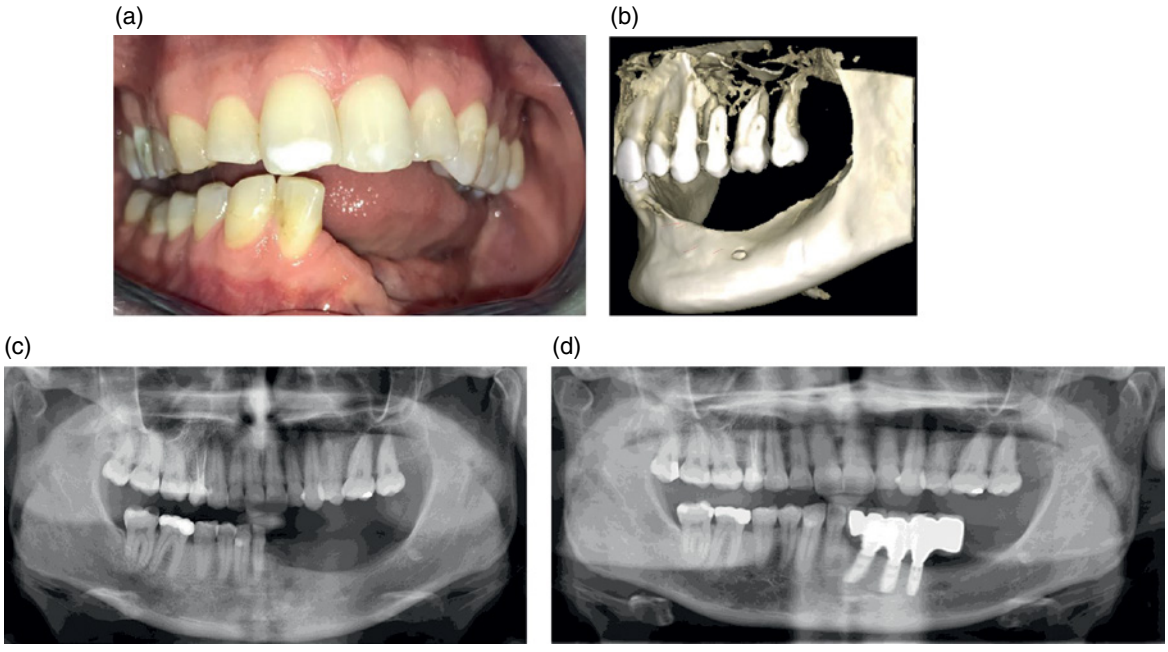

Figure 3.2.8 Male with agenesis of all mandibular teeth in left side. (a) Intraoral photo showing edentulous left side of mandible and absent 41; (b) CBCT-scanning left side of jaws; (c and d) panoramic radiographs before and after treatment with implant-supported fixed partial denture in lower left side.

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