Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Otorhinolaryngology/ maxillofacial disorders

14

KEY POINTS

- Upper respiratory infections are ubiquitous
- Voice changes may herald laryngeal cancer

The upper respiratory tract (URT) includes the nose, paranasal sinus, pharynx and larynx but the salivary glands and oral cavity are closely adjacent. Otorhinolaryngology specialists (ear, nose and throat; ENT) deal mainly with the nose, paranasal sinus, pharynx and larynx, and often employ binocular microscopy (Fig. 14.1) and nasendoscopy. Salivary disorders are discussed mainly in this chapter, as well as Chapters 18 and 22, oral disorders in Chapters 11 and 22. The URT may become damaged by pollutants such as smoke, soot, dust and chemicals, or infected with microorganisms from the inspired air. Pain from sinus or aural problems may radiate or be referred to the mouth; equally, oral problems may cause pain in the sinus or ear.

UPPER RESPIRATORY TRACT INFECTIONS (URTI)

A wide variety of respiratory pathogens may cause a single clinical syndrome and, *vice versa*, any one pathogen may cause a range of clinical diseases. Most URTI are viral.

The URT is also colonized by normal bacterial flora, which rarely cause disease, but may under certain circumstances cause upper or lower respiratory tract (LRT) or even systemic or transmissible infections. For example, the normal nasal bacterial flora may include *Staphylococcus aureus*, *S. epidermidis* and aerobic corynebacteria ('diphtheroids'). Some people carry meticillin-resistant *S. aureus* (MRSA) in their nose, which can cause disease (Ch. 21). Bacterial infection caused by a foreign body introduced into the nose of a child (e.g. a small toy) is a well-recognized cause of halitosis, as are tonsillitis and sinusitis. The nasopharyngeal bacterial flora may include non-encapsulated or non-virulent strains of *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*, which may cause meningitis. Pharyngitis can be caused by group A streptococci (and can rarely lead to rheumatic fever and occasionally rheumatic carditis; Ch. 5) or can be caused by Epstein–Barr virus (Ch. 21).

VIRAL UPPER RESPIRATORY TRACT INFECTIONS

Viruses frequently evade URT defences to produce infections; children have up to eight UTRIs per year, and adolescents up to four. Viral URTIs are highly infectious in the early stages and most are contracted by shaking the hands of infected persons or by touching things that they have touched (and then touching the nose, mouth or conjunctivae; Table 14.1); infection may also be spread via sneezes. The incubation periods rarely exceed 14 days. The incubation times of the common agents are:

- rhinoviruses, 1–5 days
- influenza and parainfluenza viruses, 1–4 days
- respiratory syncytial virus (RSV), 7 days
- Epstein–Barr virus (EBV), 4–6 weeks.

The three main clinical patterns of URTI are the common cold syndrome (coryza), pharyngitis and tonsillitis, and laryngotracheitis.

Other URTIs are discussed in Chapter 21.

The common cold syndrome

General aspects

The common cold is caused not by a single organism but usually by rhinoviruses; it can, however, be caused by more than 200 different viruses (Table 14.2), particularly by respiratory syncytial virus (RSV), coronaviruses, and para-influenza and influenza viruses).

Clinical features

Sneezing, mucus overproduction with nasal obstruction, nasopharyngeal soreness and mild systemic upset are common. Bacterial infection may supervene and cause sinusitis or middle ear infection (otitis media), but serious complications are rare in otherwise healthy patients.

General management

Only symptomatic treatment is available.

Dental aspects

Elective dental care is best deferred. General anaesthesia (GA) should be avoided since there is often some respiratory obstruction and

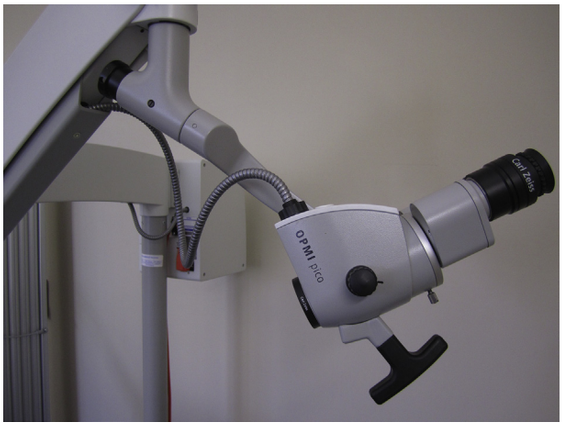

Fig. 14.1 Microscope.

Table 14.1 *The main respiratory viruses*

Viral respiratory pathogens	Presumed viral respiratory disease
Adenoviruses	Coronaviruses
Influenza viruses	Coxsackie viruses
Para-influenza virus	Cytomegalovirus
Respiratory syncytial virus	ECHO viruses
Rhinoviruses	Epstein–Barr virus
	Herpes simplex viruses
	Severe acute respiratory syndrome (SARS)

Table 14.2 *Upper respiratory tract infections and their main causes*

Condition	Micro-organisms
Common cold	Coronavirus
	Coxsackie viruses
	ECHO viruses
	Para-influenza virus
	Respiratory syncytial virus
	Rhinoviruses
Pharyngitis	Adenoviruses
	Coxsackie viruses
	ECHO viruses
	Epstein–Barr virus
	Beta-haemolytic streptococci
	Influenza viruses
	Candida
Tonsillitis	Adenoviruses
	Beta-haemolytic streptococci
	Enteroviruses
	Epstein–Barr virus
	Herpes simplex virus
	Influenza viruses
	Para-influenza viruses
Influenza	Influenza viruses
Sinusitis	*Streptococcus pneumoniae*
	Streptococcus milleri
	Haemophilus influenzae
	Moraxella catarrhalis
	Aspergillus
	Mucorales

infection can spread to the lungs. If a GA is unavoidable, it is best to intubate with a cuffed tube, so that nasal secretions do not enter the larynx. Antimicrobials may be indicated for prophylaxis. Xylitol chewing gum has been shown to reduce the risk of otitis media, presumably by inhibiting pneumococcal superinfection.

Pharyngitis and tonsillitis

General aspects

Most cases of pharyngitis and tonsillitis are caused by viruses (see Table 14.2), some by streptococci.

Clinical features

The throat is sore, with pain on swallowing (dysphagia) and sometimes fever and conjunctivitis. Enlargement of the tonsils with an infected exudate from the crypts, together with cervical lymphadenopathy, is characteristic of tonsillitis. Prominent submucosal aggregates of lymphoid tissue may be evident in those with pharyngitis. Complications are rare but may include peritonsillar abscess (quinsy), otitis media and, rarely, scarlet fever, acute glomerulonephritis or rheumatic fever.

General management

Infectious mononucleosis (glandular fever) or, rarely, diphtheria may need to be considered in the differential diagnosis.

Tonsillitis caused by bacterial infection is best treated with benzyl or phenoxymethyl penicillin, or, if the patient is allergic, by erythromycin or a cephalosporin. Ampicillin and amoxicillin should be avoided, as they tend to cause rashes, especially if the sore throat is misdiagnosed as a streptococcal sore throat but is due to glandular fever.

Pharyngitis is not often treated with antimicrobials, as there is no evidence that they accelerate resolution or reduce complications; an increasing body of opinion advises simple analgesics.

Box 14.1 *Factors predisposing to sinusitis*

- Diving – water may be forced into the nose and sinuses
- Barotrauma in air flight, conversely
- Foreign body in nose or sinus
- Peri-apical infection of upper posterior teeth
- Oro-antral fistula
- Prolonged endotracheal intubation and mechanical ventilation
- Rhinitis – vasomotor or allergic
- Viral upper respiratory tract infection

Dental aspects

Elective dental care is best deferred. GA should be avoided since there is often a degree of respiratory obstruction and infection may spread to the lungs.

Laryngotracheitis

General aspects

Various microbes may be involved, such as respiratory syncytial virus (RSV), particularly in children.

Clinical features

Hoarseness, loss of voice and persistent cough are common. In children, partial laryngeal obstruction may cause noisy inspiration (stridor or croup) and is potentially dangerous.

General management

Symptomatic treatment only is available but ribavirin or palivizumab may be appropriate in RSV infection in infants who may otherwise subsequently develop bronchiolitis.

Dental aspects

Dental treatment should be deferred until after recovery. GA must be avoided, as it may exacerbate progression of infection to the lungs. Antimicrobials may be indicated for prophylaxis.

BACTERIAL RESPIRATORY TRACT INFECTIONS

Sinusitis

General aspects

Infection of the paranasal air sinuses (maxillary most commonly, but also ethmoid, sphenoid and frontal) is usually bacterial. It may be preceded by viral or other factors (Box 14.1).

Table 14.3 *Paranasal sinusitis*

Sinus	Location of pain	Other features
Maxillary	Cheek and/or upper teeth, worsened by biting	Tenderness over antra
Frontal	Over frontal sinuses	Tenderness of sides of nose
Ethmoidal	Between eyes	Anosmia, eyelid swelling
Sphenoidal	Ear, neck, and top or centre of head	–

Clinical features

Headache on wakening is typical, with pain worse on tilting the head or lying down; there is also nasal obstruction with mucopurulent nasal discharge (Table 14.3).

General management

Diagnosis is from the history, plus tenderness over the sinus, dullness on transillumination, and radio-opacity or a fluid level on plain X-rays of the sinuses (sinus opacity may be due to mucosal thickening rather than infection, but a fluid level is highly suggestive of infection). Antral opacities in children can be difficult to evaluate since they are seen in up to 50% of healthy children under the age of 6 years. Computed tomography (CT) is now the standard care. Ultrasonography may be helpful. However, the gold standard for diagnosis remains sinus puncture and aspiration.

Sinusitis is classified as acute, chronic or recurrent.

In *acute sinusitis*, the bacteria most commonly incriminated are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Infection resolves spontaneously in about 50%, but analgesics are often indicated and antibiotics may be required if symptoms persist or there is a purulent discharge. Treatment is drainage using vasoconstrictor nasal drops, such as ephedrine or xylometazoline. Inhalations of warm, moist air, with benzoin, menthol or eucalyptus, may give symptomatic relief. In adults, a course of antimicrobials for longer than 7 days is indicated, using amoxicillin, ampicillin or co-amoxiclav (erythromycin or azithromycin, if penicillin-allergic), or a tetracycline, such as doxycycline, or clarithromycin. In children, high-dose amoxicillin, cefuroxime or co-amoxiclav is recommended especially if the child has received antibiotics during the 4–6 weeks prior to the infection.

Chronic sinusitis involves anaerobes, especially *Porphyromonas* (Bacteroides), and half are beta-lactamase producers. It may follow acute sinusitis, especially where there are local abnormalities, allergic rhinitis, or impaired defence mechanisms such as cystic fibrosis or human immunodeficiency virus (HIV) disease. Gram-positive cocci and bacilli, as well as Gram-negative bacilli, may also be found – especially in HIV/acquired immunodeficiency syndrome (AIDS) patients and those on prolonged endotracheal intubation. *Pseudomonas aeruginosa* (up to 5% of cases are caused by *Pseudomonas*, especially in cystic fibrosis), *Acinetobacter baumannii* and Enterobacteriaceae are also implicated. In immunocompromised persons, fungi may also be involved, including *Mucor*, *Aspergillus* or other species. Chronic sinusitis responds better to drainage by functional endoscopic surgical techniques (Fig. 14.2), plus antimicrobials, such as metronidazole with amoxicillin, erythromycin, clarithromycin or a cephalosporin.

Recurrent sinusitis should be treated with drainage, plus antimicrobials, and investigation to determine whether there is any underlying cause.

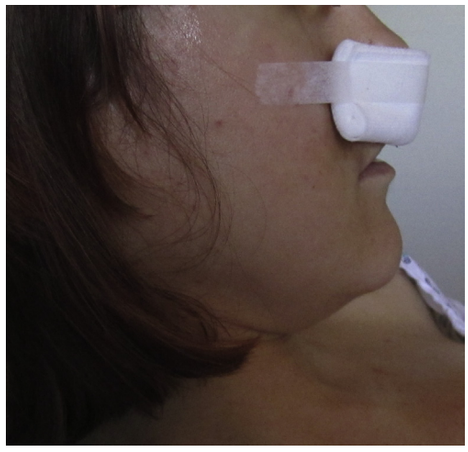

Fig. 14.2 Nasal pack, used after nasal and antral surgery.

Dental aspects

Dental treatment should be deferred until after recovery. GA should be avoided, since there is often some respiratory obstruction and infection can spread to the lungs. Inhalational sedation may be impeded if the nasal airway is obstructed

Mycoses may infect the sinuses in immunocompromised persons (Ch. 20).

Otitis media

General aspects

Otitis media is a common middle-ear infection in children; 3 out of 4 experience it by the age of 3 years. Otitis media usually follows a viral URTI, often followed by bacterial superinfection. The most common bacterial pathogen is *Streptococcus pneumoniae*, followed by non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*.

The most important predisposing factor is Eustachian tube (ET) dysfunction but immune defects and palatal dysfunction, such as cleft palate or submucous cleft, occasionally contribute. Interference with the ET mucosa by inflammatory oedema, adenoidal hypertrophy, negative intratympanic pressure or, rarely, a tumour facilitates direct extension of infections from the nasopharynx to the middle ear. Oesophageal contents regurgitated into the nasopharynx can enter the middle ear through the ET if it is patulous.

Clinical features

When the ears are infected, the ET becomes inflamed and swollen, the mucociliary pathways from the middle ear to the nasopharynx become paralysed or dysfunctional, and fluid is trapped inside the middle-ear cleft. The adenoids can also become infected and can block the openings of the ET, trapping air and fluid.

Acute otitis media is very painful, and is worse when the child is lying down. If the infection is not controlled, the eardrum ruptures and pus escapes through the perforation – otorrhoea – when there is an immediate decrease in pain. It may become evident that the child has diminished hearing in that ear. If ET dysfunction merely prevents the normal drainage of the middle-ear cleft, with or without previous acute infection, a condition referred to as otitis media with effusion or ‘glue ear’ becomes established. This also affects the hearing but is

painless. In either case, temporary speech and language problems may become evident as a result of the hearing loss, but usually resolve spontaneously with time. Complications that are rare but can be serious include mastoiditis, meningitis, brain abscess, lateral sinus thrombosis, otitic hydrocephalus, facial palsy, cholesteatoma and tympanosclerosis.

General management

Medical treatment includes antibiotics (usually penicillin) and decongestants and/or antihistamines together with analgesia. If fluids from otitis media stay in the ear for several months, drainage by surgery, usually myringotomy (incision of the ear drum) and grommets (small drainage tubes placed in the incision), may be recommended. Adenoidectomy may also be indicated.

MALIGNANT NEOPLASMS

Most head and neck cancers are squamous cell carcinomas; other tumour types include lymphoepithelioma, spindle cell carcinoma, verrucous cancer, undifferentiated carcinoma, Kaposi sarcoma and lymphoma. Use of computer guided surgery seems likely to improve outcomes, especially in patients whose anatomy has been altered.

MAXILLARY ANTRAL CARCINOMA

General aspects

Antral carcinoma is a rare neoplasm of unknown aetiology, seen mainly in older people.

Clinical features

From the outset, antral carcinoma presents with severe maxillary pain. As the tumour increases in size, the effects of expansion and infiltration of adjacent tissues also become apparent. There is intraoral alveolar swelling; ulceration of the palate or buccal sulcus; swelling of the cheek; unilateral nasal obstruction, often associated with a blood-stained discharge; obstruction of the nasolacrimal duct with consequent epiphora; hypoaesthesia or anaesthesia of the cheek in the infraorbital nerve distribution; proptosis and ophthalmoplegia consequent on invasion of the orbit; and trismus from infiltration of the muscles of mastication.

General management

Combinations of surgery and radiochemotherapy are usually required. Further details can be found in standard textbooks of otorhinolaryngology or maxillofacial surgery.

NEOPLASMS OF THE PHARYNX

Cancer can develop in the nasopharynx (see below and Ch. 22), oropharynx (consisting of the base of tongue, the tonsillar region, soft palate and back of the oral cavity) or the hypopharynx. Patients with pharyngeal cancer are at greater risk of cancer elsewhere in the upper aerodigestive tract.

Factors that increase the risk of pharyngeal cancers include smoking (both tobacco and marijuana) or chewing tobacco; alcohol use; leukoplakia; human papillomavirus (oropharyngeal carcinoma); Epstein–Barr virus (nasopharyngeal carcinoma); anaemia (Paterson–Brown-Kelly syndrome); radiation; and immune defects.

Pharyngeal cancer is treated by one, or a combination, of radiotherapy, chemotherapy or surgery.

NASOPHARYNGEAL CARCINOMA

General aspects

Nasopharyngeal carcinoma is a rare neoplasm that may be associated with Epstein–Barr virus and dietary nitrosamines; it is especially common amongst the southern Chinese, some Inuit races and people in parts of North Africa, such as Tunisia. A similar tumour, undifferentiated carcinoma with lymphoid stroma, is one of the most common salivary gland cancers in Inuits and southern Chinese.

Clinical features

Nasopharyngeal carcinoma often remains asymptomatic for some time, as it rarely obstructs the nasopharynx. The ways in which it presents include:

- isolated cervical lymph node enlargement
- unilateral conductive deafness (from obstruction of the Eustachian tube)
- abducens nerve palsy
- soft palate elevation and immobility
- ipsilateral pain, sometimes with anaesthesia, in the distribution of the major divisions of the trigeminal nerve, e.g. over the eye (ophthalmic division), tongue, lower teeth and lower lip (mandibular division)
- a combination of the above – known as *Trotter's triad*.

General management

Treatment is usually by radiotherapy.

LARYNGEAL CARCINOMA

Laryngeal cancer is found in the glottis, supraglottis or subglottis. It is most common in males, patients of both sexes over the age of 55 who smoke or drink alcohol, are infected with human papillomavirus or have immune defects. Risk factors may also include genetics (people of African descent are more likely than whites to be affected); a personal history of head and neck cancer; exposure to asbestos, sulphuric acid mist or nickel; or a diet low in vitamin A.

Clinical features

Symptoms and signs may include hoarseness, persistent sore throat, dysphagia, pain referred to the ear when swallowing, haemoptysis and cervical lymphadenopathy.

General management

Laryngoscopy, computed tomography (CT) and biopsy are required to confirm the diagnosis. Laryngeal cancer is treated by one, or a combination, of radiotherapy, chemotherapy or surgery. Laser surgery may be used for very early cancers of the larynx. A cordectomy removes the vocal cord. A supraglottic laryngectomy takes out only the supraglottis. A partial or hemi-laryngectomy removes only part of the larynx. A total laryngectomy removes the entire larynx and commits the patient to a permanent tracheostomy. Despite loss of part or all of the vocal apparatus, most patients are able to communicate by speech with or without further surgical procedures and electronic voice aids.

Box 14.2 *Risk factors for salivary neoplasms*

- Epstein–Barr virus infection
  - At least in Asian patients and Inuits
- Occupation
  - Rubber manufacturing
  - Plumbing industry
  - Woodworking
  - Hairdressing
  - Asbestos exposure
- Smoking
  - At least for Warthin tumour
- Other malignant disease
  - Breast cancer
  - Nasopharyngeal carcinoma
  - Thyroid cancer
- X-ray repair cross-complementing group 1 (XRCC1) single-nucleotide polymorphisms
- Radiation exposure, as in:
  - sun exposure
  - ionizing radiation exposure
  - survivors of atomic explosions in Japan (mucoepidermoid carcinomas and Warthin tumour)
  - survivors of childhood malignancies treated with radiation and chemotherapy
  - iodine-131 in the treatment of thyroid disease
  - radiotherapy to the head and neck
  - radiographs of the head and neck

ORAL AND OROPHARYNGEAL CARCINOMA

See Chapter 22.

SALIVARY NEOPLASMS

General aspects

A wide range of different neoplasms can affect the salivary glands but most are uncommon; they are epithelial neoplasms, which present as unilateral swelling of the parotid and are benign. Most salivary gland neoplasms are seen in older people. There is a female predisposition.

Neoplasms in the major salivary glands (parotid, submandibular) are most commonly pleomorphic adenomas but others are usually monomorphic adenomas (such as adenolymphomas), mucoepidermoid tumours or acinic cell tumours. Neoplasms in the minor salivary glands are most commonly pleomorphic adenomas but carcinomas, particularly adenoid cystic carcinomas, account for about 50%.

Salivary gland tumours are more common in certain geographical locations. Inuits, for example, have an increased prevalence. The aetiology is unknown but there are various associations (Box 14.2). A suggested association of parotid tumours with mobile phone use is controversial.

Apart from the above epithelial neoplasms, the next most common salivary neoplasms are lymphomas. Sjögren syndrome is recognized as predisposing to lymphomas, which have arisen in up to 6% of patients over 10 years in some studies.

Clinical features

Salivary gland swelling is the main clinical feature of a neoplasm (Fig. 14.3). A long history of gradual gland enlargement suggests a benign process, while pain, facial palsy, rapid growth and change in growth pattern are ominous and suggest carcinoma.

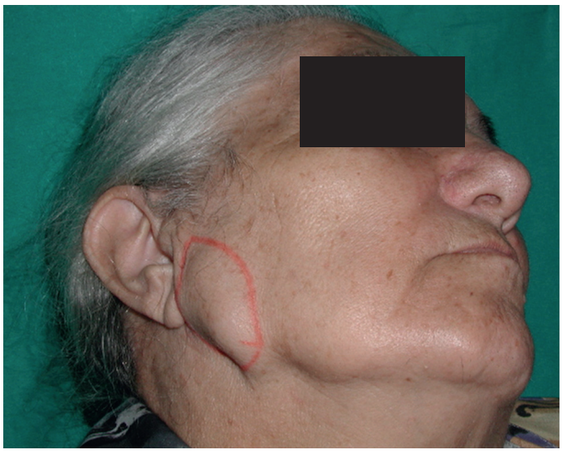

Fig. 14.3 Salivary gland neoplasms are mainly in the parotid gland.

General management

On clinical examination, a mass is usually palpable. In the case of the parotid, this will often be in the retromandibular region but is sometimes pre-tragal. Tumours confined to the deep lobe of the parotid present like other parapharyngeal tumours with medial displacement of the palate, tonsil and pharyngeal wall. A few malignant neoplasms may be small and almost impalpable, and present with pain only. Magnetic resonance imaging (MRI) is particularly helpful for diagnosing parotid and submandibular tumours. CT is often degraded in this region by amalgam artefacts. Ultrasonography has utility in determining whether a mass is in the tail of the parotid or posterior pole of the submandibular gland. Regardless of the image appearances, the precise diagnosis can only be firmly established by histological examination of either the operative specimen or, increasingly frequently, by fine-needle aspiration biopsy.

The treatment of choice for salivary gland neoplasms is surgical excision. Most salivary gland neoplasms are relatively radioresistant. Chemotherapy is used only on a very limited basis and as an adjunct in the treatment of some malignant salivary gland neoplasms, such as adenocarcinoma or adenoid cystic carcinoma.

LYMPHOMAS

See Chapter 8.

ORO-ANTRAL FISTULA

Oro-antral fistula is discussed in surgical textbooks. Palatal perforations can be caused by trauma, malignant neoplasms or the use of cocaine.

OBSTRUCTIVE SLEEP APNOEA SYNDROME

General aspects

Obstructive sleep apnoea syndrome (OSAS) is characterized by periods of prolonged apnoea during sleep. Patients with OSAS snore extremely loudly, often termed ‘heroic snoring’!

The cause is airway obstruction, usually in the region of the oropharynx; enlarged tonsils, nasal septum deformity, narrow dental arches and abnormalities in the larynx may contribute. Enlarged tonsils or tongue (macroglossia) are uncommon causes. Alcohol or other sedatives inducing muscle relaxation can aggravate the situation.

As the patient relaxes in the early phase of sleep, the tongue falls back into the oropharynx and causes obstruction. OSAS is the extreme end of a spectrum of sleep-disordered breathing (SDB), which may be related to weak activity of muscles in (or obstruction to) the tongue, palate and pharynx. SDB has as its minimal level simple snoring, then upper airways resistance syndrome (UARS) and, finally, OSAS, in which there are periods of apnoea during sleep; each period lasts for up to a minute and episodes range from the occasional one to hundreds per night, waking the patient. Sleep is lost and patients with significant OSAS have daytime sleepiness that often culminates in road traffic accidents, an increased risk of acute cardiopulmonary complications and stroke.

Oronasal obstruction in weak senile patients results from blockage of the nose and lack of teeth or dentures, causing the mouth to become overclosed. It may cause a dangerous degree of dyspnoea and cyanosis, even when the person is awake. Hypoxia, thus caused, may contribute to the death of these vulnerable patients.

Clinical features

Partial upper airways obstruction during sleep in anyone can cause snoring that is not OSAS. People with OSAS are characteristically obese middle-aged men. In OSAS, snoring is far more severe and, because there is apnoea, arterial oxygen saturation falls, and cardiac arrhythmias and stroke may develop, particularly in obese middle-aged men. In even more severe cases, pulmonary hypertension and right ventricular failure result. There is also a raised mortality rate from road traffic and other accidents, since affected patients are constantly drowsy.

General management

Severity of OSAS is scored by an apnoea/hypopnoea index calculated from the combined number of episodes per night (less than 20 is mild, 20–40 is moderate and more than 40 is classed as severe). Tiredness can be scored on the Epworth scale (Table 14.4); a score of 10 or more is considered 'sleepy', while 18 or more is 'very sleepy'. Diagnosis is assisted by polysomnography and measurement of arterial blood oxygen.

Treatment includes obesity reduction and nasal continuous positive airways pressure (CPAP). Other measures include various appliances (sometimes termed non-sleep apnoea dental orthotics [NADOs], e.g. *Silent Nite, Klearway, NAPA, Snore aid, Herbst, Silencer*), orthognathic surgery (maxillary–mandibular and hyoid advancement; MMA), or uvulopalatopharyngoplasty (UPPP), adenoidectomy, tonsillectomy or even tracheostomy.

UPPP using scalpel surgery or lasers has been the standard treatment for OSAS, but is often overprescribed and its efficacy is under review.

Dental aspects

Dental appliances that hold the mandible forward are claimed to be as effective as surgical measures and should certainly be tried initially. However, where the obstruction is predominantly hypopharyngeal, surgical advancement of the facial skeleton and hyoid (MMA) may effectively expand the airway. When there is both oropharyngeal and hypopharyngeal obstruction, UPPP may need to be combined with MMA.

Nasal obstruction may also have to be relieved, but staged maxillofacial surgery to assess the degree of improvement may relieve nocturnal hypoxia, snoring and daytime sleepiness.

Table 14.4 *Score sheet for Epworth daytime sleepiness scale*

Situation	Chance of dozing or sleeping[a]
Sitting and reading	Total = Epworth score
Watching TV	
Sitting inactive in a public place	
Being a passenger in a motor vehicle for an hour or more	
Lying down in the afternoon	
Sitting and talking to someone	
Sitting quietly after lunch (no alcohol)	
Stopped for a few minutes in traffic while driving	

[a]0 = would *never* doze or sleep; 1 = *slight* chance of dozing or sleeping; 2 = *moderate* chance of dozing or sleeping; 3 = *high* chance of dozing or sleeping.

FREY SYNDROME (GUSTATORY SWEATING)

General and clinical aspects

Parotidectomy or trauma to the parotid region is sometimes followed by sweating and flushing of the pre-auricular skin on that side, in response to stimulation of salivation. Similar conditions may follow surgery to other salivary glands.

Gustatory sweating is due to the joining of the damaged postganglionic parasympathetic nerve fibres with the sympathetic nerve endings, so that sweating and flushing occur rather than salivation.

General management

Antiperspirants, such as 20% aluminium chloride hexahydrate, may be effective in controlling the sweating.

DEVELOPMENTAL DISORDERS

By the third week after fertilization, the first of four paired swellings – the branchial arches – at the sides of the head end of the embryo have formed, as well as three germ layers (ectoderm, endoderm and mesoderm). Some craniofacial anomalies result from branchial arch defects and others from the germ layers.

Genes that orchestrate the development of craniofacial structures also direct the development of brain, limbs and some internal organs, such as the heart, lungs and liver. If affected very early in gestation, there may be widespread and devastating consequences. Craniofacial birth defects are rare but fortunately may be ameliorated by surgery, dental care, psychological counselling, and rehabilitation.

CRANIOFACIAL ANOMALIES CAUSED BY BRANCHIAL ARCH DEFECTS

The primary palate forms by merging of the two medial nasal prominences, which arise from the frontonasal process. The primary palate

Table 14.5 *Main genes involved in cleft palate development*

Defects	Genes implicated
Defects in growth of the palatal shelves	*Homeobox*-containing transcription factor *MSX1*
	Paired-related genes *Pax-1*, *3*, *6*, *7* and *9*
	Dlx transcription factors
	Activin A
	LIM homeobox genes
Elevation of palatal shelves	*Gli* transcription factors
	Jagged 1, 2
	BMP7/BMPreceptor1B
	Hox genes
Impairment of the midline epithelial seam, adhesion, dispersion	*Tgfβ3*
	Transforming growth factor (*TGF*)
Epithelio-mesenchymal transition	Fibroblast growth factor (*FGF*)
	Twist transcription factor
Cell deficiency (proliferation, differentiation, migration defects)	*SHH* (Sonic Hedgehog)
	Endothelin-1 (*Et-1*)

Box 14.3 *Drugs used in pregnancy that may induce cleft palate*

Drugs most commonly implicated

- Alcohol
- Anticonvulsants
- Cocaine
- Fluconazole
- Heroin
- Phenytoin
- Retinoids
- Tobacco
- Topiramate

Drugs occasionally implicated

- Antihypertensives
- Corticosteroids
- Cytotoxic agents
- Thalidomide

will fuse laterally with the maxillary processes of the first branchial arch during the sixth and seventh weeks, forming the upper lip. The palate contains the maxillary incisor teeth.

Secondary palate development involves bilateral palatal shelves arising from the maxillary processes in 6.5-week human embryos, which eventually make contact above the tongue. The palatal shelves adhere with each other over the space of about 10 days to form the midline epithelial seam. The epithelial seam disperses to allow merging of the mesenchyme to form fused palatal shelves, by the 10th week of gestation. The midpalatal seam often disappears incompletely, leaving epithelial rests or remnants (Epstein's pearls) in the midline. Impaired formation of the secondary palate results in cleft palate (CP), usually quickly recognized after birth, especially when associated with a cleft lip (CL). A submucous cleft can be more difficult to diagnose.

Pathogenesis of cleft palate

The development of the face and the upper lip takes place during the fifth to ninth week of pregnancy. Clefts of the lip with or without cleft palate, and cleft palate alone, result from the failure of the first branchial arches to complete fusion processes; they are the most common of all craniofacial anomalies. The male-to-female ratio of cleft lip/palate (CLP) is 2:1; the ratio for CP alone is just the reverse, 1:2.

Failed fusion of the palatal shelves can be caused by different gene defects (Table 14.5), culminating in:

- a problem in the formation of the midline epithelial seam
- small size of the palatal processes
- unsynchronized timing of the elevation or growth of the palatal shelves with the growth of surrounding structures such as the cranial base
- a small mandible preventing the downward relocation of the tongue, which mechanically may prevent palatal fusion.

CP as an isolated malformation behaves as an entity distinct from CL with or without CP. It has an incidence of 0.5 per 1000 births. The risk of recurrence in subsequent children is about 2% if one child has it, 6% if one parent has it, and 15% if one parent and one child have it.

Box 14.4 *Genes implicated in non-syndromic cleft palate*

- Transforming growth factor (*TGF*)
- Retinoic acid receptor alpha (*RARA*)
- Long arm of chromosome 2 (2q32)
- Chromosome 4
- Short arm of chromosome 6 (*Et-1* gene 6p24)

Non-syndromic cleft palate

Not all cases of clefting are inherited; a number of teratogens (environmental agents that can cause birth defects) have been implicated, as well as defects in essential nutrients. Environmental factors present during the first trimester of pregnancy, and which may generate CP, include maternal URTI in the first trimester, smoking (especially when the mother has glutathione-S-transferase theta 1 [GSTT1] – null variants), obesity, diabetes, stress or exposure to the agents shown in Box 14.3. Paternal smoking has also been implicated.

CLP is more prevalent in the lower socioeconomic classes. The teratogens incriminated include isotretinoin, used to treat acne, which causes birth defects such as brain malformations, learning disability and heart problems, as well as facial abnormalities. Thalidomide given to pregnant mothers was, and anticonvulsants (phenytoin, valproic acid, lamotrigine, carbamazepine) and corticosteroids may be, associated with an increased incidence. Phenytoin may act via an effect causing fetal arrhythmias and hypoxia. Systemic corticosteroids have been reported to increase the risk (this is controversial) and there are also concerns about possible effects from topical steroids used in the first trimester. There has been suspicion of aspirin and diazepam as possible causes but there is no real evidence. Folic acid given periconceptually may lower the risk but the evidence is weak.

Inheritance of non-syndromic CP is multigenic, with a number of genes implicated (Box 14.4).

Clefting can occur independently or as part of a larger syndrome that may include the heart and other organs. Affected infants have facial deformity and may have difficulty with feeding, breathing, speaking and swallowing; they are susceptible to respiratory infections.

General aspects

The primary palate or pre-maxilla includes that portion of the alveolar ridge containing the four incisors. The secondary palate forms the remaining hard palate and all the soft palate. Orofacial clefts result from an embryopathy in which there is failure of the frontonasal process and/or fusion of the palatal shelves. In the submucous CP, the palatal shelves may fail to join, but the overlying mucous membranes are intact and the muscle attachments of the soft palate are abnormal, causing velopharyngeal insufficiency. Bifid uvula may signify a submucous CP.

CP is the fourth most common birth defect, affecting approximately 1 in 700–1000 live births. There are also racial differences, with a high incidence in South-East Asians and a low incidence in Afro-Caribbean races. The common clefts are cleft lip with or without cleft palate (CL ± P) and CP only. The total incidence of facial clefting is between 2 and 3 per 1000 live births. A number of these do not develop as full-term fetuses. Facial clefts are associated with a syndrome in up to 15–60% of cases and are then termed syndromic clefts (see below). More than 400 syndromes may include a facial cleft as one manifestation, and CLP may be associated with many congenital syndromes.

The cause of non-syndromic cleft lip with or without cleft palate (NSCLP) is unclear but there is still a strong genetic component; there may be a family history of clefts and typically the same type of cleft is seen in affected members. In monozygotic twins, there is nearly 40% concordance. No single gene defect appears responsible, however. Several loci have been identified. Candidate genes in CLP include transforming growth factor alpha (*TGF*), poliovirus receptor-like 1 (*PVRL1*), retinoic acid receptor alpha (*RARA*), T-box transcription factor-22 (*TBX22*), specific isoforms of glutamic acid decarboxylase (*GAD*), interferon regulatory factor 6 (*IRF6*), *MSX1* (formerly *homeobox 7* – encodes a member of the muscle segment *homeobox* gene family) and fibroblast growth factor (*FGF*) (see Table 14.5).

Clinical features

Clefts have a major impact from birth from both aesthetic and functional viewpoints, since the neonate with a CP is unable to suckle. Later, speech development is also impaired. A person may have a CL, CP, or both.

A unilateral CL occurs on one side of the upper lip. A bilateral CL occurs on both sides of the upper lip. In its most severe form, the cleft may extend through the nose base.

CP may be incomplete, involving only the uvula and the muscular soft palate (velum). A complete CP extends the entire length of the palate. CP can be unilateral or bilateral. There may also be feeding difficulties and associated congenital defects such as dental, hearing and speech defects.

General management

Health-care providers that frequently participate in a multidisciplinary CP team include: audiologists; maxillofacial, ear, nose and throat, and plastic surgeons; geneticists; neurosurgeons; nurses; dentists (paediatric dentist/orthodontist/prosthodontist); paediatricians; social workers/psychologists; and speech and language pathologists.

A high percentage of patients with CP develop otitis media with effusion. Up to 20% have additional abnormalities that can affect management in various ways (Fig. 14.4). Systemic disorders are more frequent in patients with CP than in those with CL alone, and include especially skeletal, cardiac, renal and central nervous system defects.

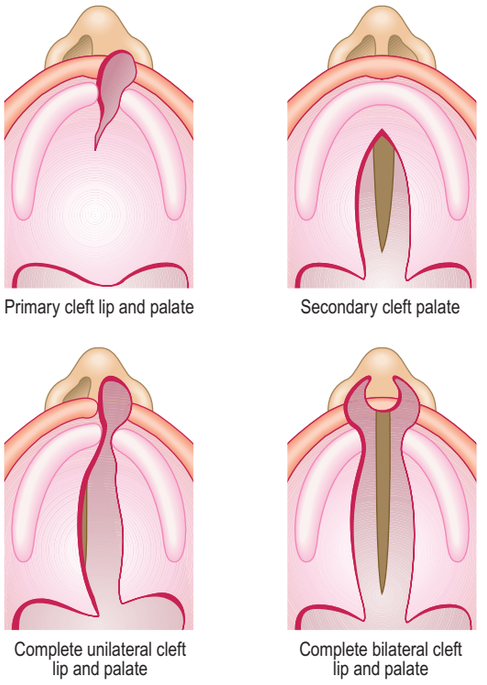

Fig. 14.4 Cleft palate.

Newborn to 12 months

Treatment of the airway takes priority and may be managed with positioning but, in severe cases, may need tracheostomy. There can be significant difficulties in management of the airway for anaesthesia in children under the age of 5 years, particularly in young infants and in those with feeding difficulties, bilateral clefts and/or retrognathia. Patients with mandibular dysostoses and those requiring midface advancement (Le Fort II osteotomy) have the greatest problems. Difficulties are common in Pierre Robin, Treacher Collins and Goldenhar syndromes, and the cervical spine may be problematic in Klippel–Feil syndrome. The laryngeal mask has been recommended as a guide to fibreoptic endoscopic intubation. Aesthetics is a major issue for parents (Fig. 14.5). One of the problems for the child is feeding; a Rosti bottle with Gummi teat often helps.

The timing of the initial CLP repair is controversial. In general, when the lip alone is cleft, initial cosmetic repair is carried out at about 3–6 months of age, though earlier operations are becoming popular. Many repair CLP within the first few days of life since, after repair, the appearance is dramatically improved, feeding difficulties are significantly minimized and speech develops better. If the palatal defect is too wide, it can be repaired 3 months later to allow for sufficient palatal growth. In any event, CP is now usually repaired before the child speaks, between 6 and 18 months, and typically at 6–12 months of age.

Years 1 to 18

Age 1–5 years is when it is important to have good hearing and normal appearance to avoid low self-esteem and help speech develop. These children need a hearing assessment; if hearing is impaired, ear ventilation tubes (grommets) may be indicated.

Age 5–13 years is when the orthodontist can help correct malocclusion, and alveolar bone grafting may be needed. Speech, if poor despite the best efforts on the part of the child and the speech pathologist, may be corrected with pharyngoplasty.

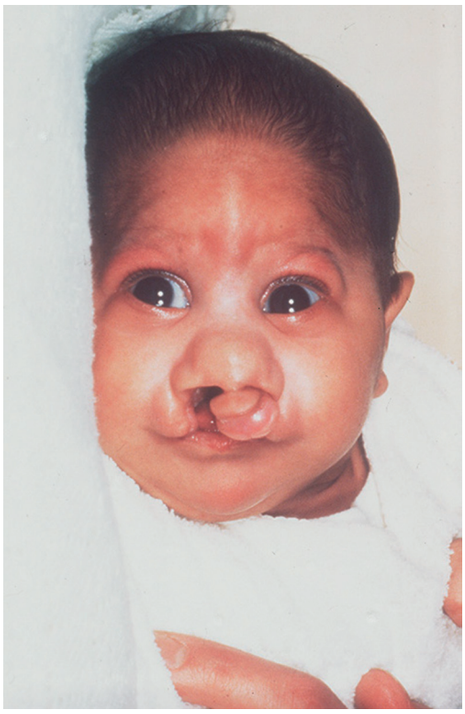

Fig. 14.5 Cleft lip.

Age 13–18 years is the time for final adjustments. Fine-tuning, such as scar revisions, rhinoplasty and orthognathic surgery, is carried out to enable the child's appearance and speech to be restored to as near normal as possible.

Dental aspects

Palatal ulcers seen in neonates with CLP appear to result from trauma from the tongue and resolve if a palatal plate is fitted. Dental abnormalities include malocclusion (almost 100%), hypodontia (50%), hypoplasia (30%) and supernumerary teeth (20%). Children may have a higher prevalence of caries in both primary and permanent dentitions, and significantly more gingivitis, especially in the maxillary anterior region. Adult CLP patients may have poorer oral hygiene and more gingivitis. Prevention and continuity of care are essential and a high rate of success can be achieved.

Submucous cleft palate can be recognized by a notched posterior nasal spine, a translucent zone in the midline of the soft palate and a bifid uvula, but not all these features are necessarily present and a bifid uvula may be seen in isolation. About 1 in 1200 births is affected and feeding difficulties, speech defects and middle-ear infections may develop in 90% of affected children. Adenoidectomy is contraindicated, as it may reveal latent velopharyngeal insufficiency. A minority have other issues such as Loeys–Dietz syndrome (similar to Marfan syndrome), where there is a risk of arterial aneurysm and rupture.

Syndromic cleft palate

Current molecular epidemiology investigations have examined both syndromic and non-syndromic (isolated) cleft lip/palate and cleft palate. Linkage studies have identified a number of candidate genes, including *MSX1*, *RAR*, an X-linked locus, and the genes for TGF beta-3 and TGF alpha.

Van der Woude and Waardenberg syndromes are associated with CL, with or without CP. Common syndromes with CP include Apert, Stickler and Treacher Collins syndromes. CLP may also be seen in velocardiofacial, Pierre Robin and KlippelαFeil syndromes and in various chromosome anomalies (Down syndrome, Edwards syndrome; Appendix 14.1).

A small subgroup of patients have CLP with median facial dysplasia and cerebrofacial malformations, while others have laryngotracheal oesophageal clefts (Opitz–Frias or G syndrome) or cranial asymmetry (Opitz or B syndrome).

One of the common syndromic forms of CLP, the van der Woude syndrome, is caused by an autosomal dominant form of inheritance at a locus on chromosome 1.

Other examples include:

- branchial arch syndromes
- craniosynostoses
- diseases associated with mutations in the Sonic Hedgehog pathway (*SHH*).

Branchial arch syndromes

Pierre Robin syndrome

Deficient development of the mandibular portion derived from the first branchial arch results in micrognathia, with the tongue set back and possibly obstructing the airway. CP may be another consequence. The infant is also at risk of cor pulmonale.

Treacher Collins syndrome (mandibulofacial dysostosis)

Treacher Collins syndrome has an autosomal dominant inheritance and is associated with mutation of the *Treacle* gene (5q32-q33.1), which encodes a phosphorylated nucleolar trafficking protein. First branchial arch structures are deficient, and all derivative craniofacial components are affected. Treacher Collins syndrome manifests with cleft palate; downward-sloping eyelids; partial absence of lower eyelashes; depressed cheekbones; a large, fish-like mouth; deformed ears with conductive deafness; a small, receding chin and lower jaw; a highly arched or cleft palate; and severe dental malocclusion. These defects result from defective cranial neural crest cell differentiation, migration and proliferation.

The underdeveloped facial structures can contribute to airway blockage and repeated upper respiratory infections, and maldevelopment of the ears leads to a conductive deafness.

DiGeorge syndrome, velocardiofacial syndrome (Shprintzen syndrome, CATCH 22)

General aspects. Velocardiofacial syndrome (VCFS; from the Latin *velum* – palate, *cardia* – heart, and *facies* – to do with the face) is a genetic disorder involving chromosome 22 (a deletion at 22q11). Its features include *c*ardiac defects, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate and *h*ypocalcaemia – hence it is termed 'CATCH 22'). It affects approximately 5–8% of children born with CP. There is a characteristic facial appearance, minor learning problems and speech and feeding difficulties, and heart defects. It is inherited in only about 10–15% and, usually, neither parent has the syndrome or carries the defective gene.

Also known as Shprintzen syndrome, craniofacial syndrome or conotruncal anomaly unusual face syndrome, at least 30 different defects have been associated with the 22q11 deletion of VCFS. DiGeorge syndrome is similar (Ch. 20).

Box 14.5 *Features of velocardiofacial syndrome (CATCH 22)*

- Cleft palate, usually of the soft palate
- Heart disease
- Facies (elongated face, almond-shaped eyes, wide nose, small ears)
- Learning difficulties
- Eye defects
- Otitis media
- Hypoparathyroidism
- Immune defects
- Weak muscles
- Short height
- Curvature of the spine (scoliosis)
- Tapered fingers

Clinical features. There is great variation in the features (Box 14.5), although none of these problems occurs in all cases.

Dental aspects. There may be difficulties associated with CLP, cardiac disease and immune defects.

Maldevelopment of the fourth branchial arch and the third and fourth pharyngeal pouches leads to deficiencies affecting the thymus, parathyroid glands and the great vessels. Facial features include a squared-off nasal tip, small mouth and widely spaced eyes. Similar facial features, along with heart defects, are seen in the velocardiofacial syndrome. Both syndromes are associated with deletions on the long arm of chromosome 22 (22q11).

The thymic defect severely compromises cellular immunity. Inadequate or missing parathyroid glands cause severe hypocalcaemia and seizures. The great vessel abnormalities lead to compromised circulation.

Features include:

- cardiac abnormality
- abnormal facies
- T-cell deficit due to thymic hypoplasia
- cleft palate
- hypocalcaemia due to hypoparathyroidism.

Craniosynostoses

The premature fusion of certain skull bones (craniosynostosis) prevents normal skull growth, affects the shape of the head and face, and puts pressure on the developing brain. It is seen in Crouzon, Apert, Saethre–Chotzen and Pfeiffer syndromes and in Boston-type craniosynostosis (Ch. 37).

Crouzon syndrome

Crouzon syndrome is a rare genetic disorder characterized by abnormal skull growth with wide-set, bulging eyes (hypertelorism; proptosis) and visual problems caused by shallow eye sockets; eyes that do not point in the same direction (strabismus); a beaked nose; and an underdeveloped maxilla. In addition, there may be cleft lip and palate, dental problems and hearing loss, which is sometimes accompanied by narrow ear canals. People with Crouzon syndrome are usually of normal intelligence.

Mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene cause Crouzon syndrome.

Apert craniofacial synostosis

Apert craniofacial synostosis is an autosomal dominant disorder, caused by mutations in the chromosome 10q26 gene encoding *FGFR2*. CP is associated more significantly with the *S252W* mutation.

Features include craniosynostosis, facial dysmorphology, hand and feet defects, and learning impairment.

Diseases associated with Sonic Hedgehog pathway (SHH) mutations

Holoprosencephaly

Holoprosencephaly affects neural crest cells populating the frontonasal mass and the forebrain, with associated midface defects. Some cases are caused by *SHH* mutations.

Features include wide phenotypic variation, a single central incisor, median cleft lip and palate, absent nasal bone, hypertelorism and cyclopia.

Basal cell naevus ('Gorlin') syndrome

This condition is due to a mutation in the *PTC* gene (Ch. 37).

CRANIOFACIAL DEFECTS SECONDARY TO OTHER DEVELOPMENTAL DISORDERS

Craniofacial defects may be secondary to a more generalized structural or biochemical defect.

Osteogenesis imperfecta

See Chapter 16.

Waardenburg syndrome

See Chapter 37.

Cleidocranial dysplasia

The inheritance of a regulatory gene defect in cleidocranial dysplasia leads to features that include delayed tooth eruption, supernumerary teeth, altered or missing collarbones, short stature, and possible failure of cranial suture closure. The exact mechanism of the associated gene, *CBFA1*, located on chromosome 6, has not been determined but appears to be essential for bone development.

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BMJ. <http://www.bmj.com/specialties/otolaryngology-ent>

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American Academy of Allergy, Asthma & Immunology. <http://www.aaaai.org/home.aspx>
Bandolier. <http://www.medicine.ox.ac.uk/bandolier/booth/booths/ent.html>
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APPENDIX 14.1 SYNDROMES THAT MAY INCLUDE CLEFT LIP/PALATE

- Apert syndrome
- Basal cell carcinoma naevoid syndrome
- Carpenter syndrome
- Cleidocranial dysplasia
- Craniosynostosis
- Crouzon syndrome
- Down syndrome
- Edwards syndrome
- Freeman–Sheldon syndrome
- Goldenhar syndrome
- Hallermann–Streiff syndrome
- Hemifacial microsomia
- Hydrocephalus
- Klippel–Feil syndrome
- Microtia
- Miller syndrome
- Moebius syndrome
- Nager syndrome
- Nasal encephalocoeles
- Neurofibromatosis
- Orbital hypertelorism
- Parry–Romberg syndrome
- Pfeiffer syndrome
- Pierre Robin sequence
- Saethre–Chotzen syndrome
- Shprintzen syndrome
- Stickler syndrome
- Treacher Collins syndrome
- van der Woude syndrome
- Velocardiofacial syndrome
- Waardenburg syndrome