1 Embryology of the Head and Neck: An Aid to Understanding Our Complex Anatomy and Some Interesting Anomalies

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1.1 Introduction

The head and neck is without doubt one of the more complex anatomical regions of the body. A number of highly specialised organs and structures are crammed into a relatively small space, each with their own functional, neural, muscular and vascular elements. Many highly specialised and varied tissues exist, notably neural, much of which is contained within a number of complex bony structures (the calvarium and vertebrae). These differ significantly in their structure from conventional "long bones". Consequently, the study of head and neck anatomy, not surprisingly can be quite daunting, and trying to understand some of the disorders that affect this region even more so. Yet the anatomy of this region is (in the most part) predictable and reproducible from generation to generation, and this is because of our 'preprogrammed' embryological development. When this process is broken down into 'bite-size' pieces of knowledge, head and neck anatomy and many disorders of the head and neck become much easier to understand and remember. Therefore a brief overview of this fascinating area of development, which the vast majority of us have all gone through, will be presented. This is just an synopsis and will not include all aspects in comprehensive detail. Embryological development of some of the specific organs and structures is also noted in their relevant chapters hereafter.

The term "embryogenesis" is often used to describe the ongoing process of cellular multiplication and differentiation which occurs in the embryo during the early stages of development. In our species, this all starts from a single cell zygote and ends with a fully developed human being. The normal period of gestation (pregnancy) is around 9 months, or 38 weeks.

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1.1.1 Germinal Stage

This refers to the initial development of the embryo, from its initial stage of fertilisation, until it becomes implanted in the uterus. This takes around 10 days. Approximately 1 day after fertilisation, the fertilised oocyte (egg) or 'zygote' divides into two cells called blastomeres. Subsequent divisions of these structures then occur around every 12–24 h. During these early days the zygote does not increase in size. At first, the cells are undifferentiated and remain clumped together as a small sphere. This is enclosed within a "zona pellucida"—a thick transparent glycoprotein membrane which prevents premature implantation of the cell mass as it passes along the fallopian tubes. This layer thus prevents the development of ectopic pregnancy. After several more divisions, when there are around 16 cells, the cell mass is referred to as a 'morula' (named after its apparent resemblance to the mulberry fruit). At this stage it is still very small and contain very little cytoplasm.

1.1.2 Blastulation

During this stage, the ever increasing number of cells arrange themselves to form a cavity, the 'blastocoele'. At this point, the morula becomes known as the 'blastocyst'. This is comprised of two different cell types, still enclosed within the zona pellucida:

1. An outer cell mass (the trophoblast). This will eventually make contact with the endometrium of the uterus and facilitate implantation and the development of the placenta.
2. An inner cell mass (the embryoblast). These cells will develop into the embryo itself, the amnion, yolk sac and allantois. These latter structures develop in parallel to the embryo, but will not be discussed further in this synopsis (Fig. 1.1).

The trophoblast cells soon secrete fluid into the blastocoele. As its cavity enlarges the outer cells become flattened. At the same time, the inner cell mass (embryoblast) becomes "compacted" and attached to the trophoblast at one pole—the 'embryonic

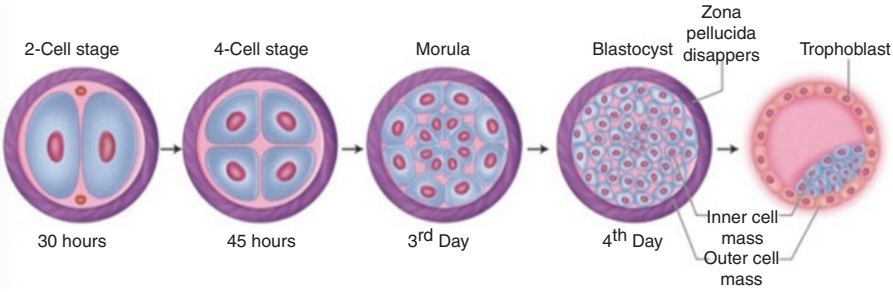


Fig. 1.1 Division of the zygote to produce a blastocyst stage embryo

pole'. As a result of the increase in size of the blastocyst, the zona pellucida becomes stretched and thinned and is eventually breached. It subsequently disintegrates, thereby enabling implantation of the blastocoele within the uterine endometrium. Occasionally the blastocyst will implant in other sites, such as the surface of the ovaries, within the fallopian tubes and even the peritoneal cavity. This implantation stimulates the development of new blood vessels at that site, which are prone to rupture as the embryo grows. This is known as an ectopic pregnancy and is treated as a gynaecological emergency if rupture occurs.

During the second week, both the trophoblast and embryoblast divide and develop into increasingly specialised cell types.

1. The trophoblast divides into the syncytiotrophoblast and the cytotrophoblast. The syncytiotrophoblast fuses with the uterine endometrium and becomes invaded by maternal blood vessels, forming an initial uteroplacental circulation. The cytotrophoblast (or layer of Langhans) contains stem cells that also play a role in implantation, by secreting proteolytic enzymes.
2. The embryoblast divides into an epiblast and hypoblast, thereby forming a two-layered structure—the 'bilaminar disk'. The hypoblast and epiblast layers will subsequently go on to form the "embryonic disc"—this will develop into the embryo proper. The amniotic cavity also forms within the epiblast (Figs. 1.2 and 1.3).

1.1.3 Gastrulation

Around the third week of embryonic development, the cells of the bilaminar disk (epiblast and hypoblast) undergo a highly specialised process called gastrulation. During this process, the two cell layers reorganise into three "germ cell" layers (the trilaminar disc). This involves complex cellular rearrangements including migration, invagination and differentiation of the epiblast. The future body axes (i.e. the

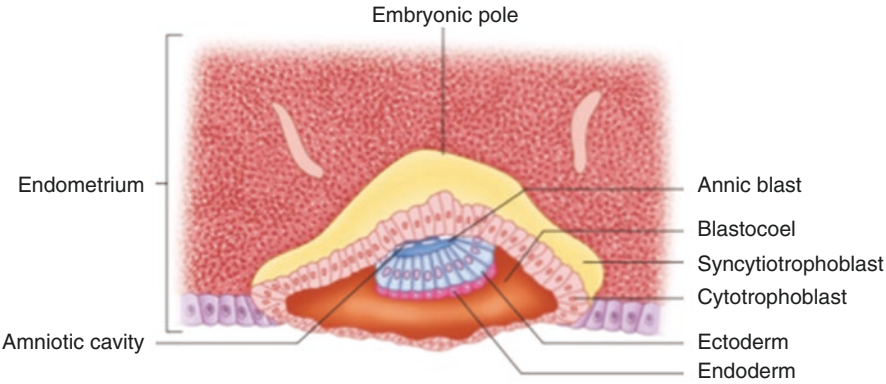


Fig. 1.2 Early stages of implantation

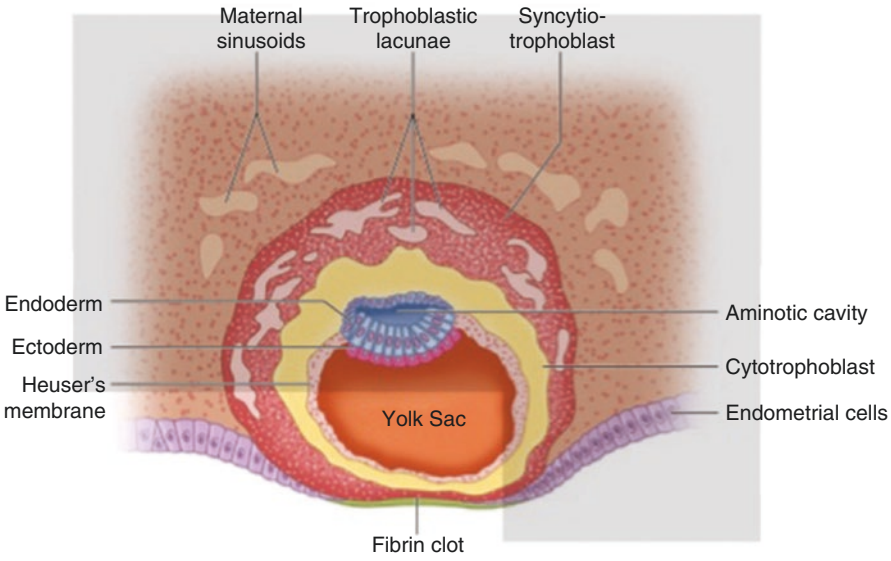


Fig. 1.3 Establishment of the embryonic layers and extra-embryonic membranes and cavities

head-to-tail, right/left and front-to-back orientation) also become established at this time. As a result of these processes, the initial spherical embryo becomes converted into the shape of a double-walled cup, or 'gastrula'. During this stage, any defects in the chemicals that control this process ("signalling proteins" and "transcription factors") can lead to a condition known as 'situs inversus visceral totalis'. In this anomaly the viscera in the fully developed embryo (heart, GI tract) are reversed from their normal positions. This is not a life-threatening or symptomatic condition, but those with it are encouraged to wear some form of medical identification, should injures or emergency surgery be required. Although the head and neck is a generally symmetric structure, interestingly, it has been suggested that this condition can also affect the development of the brain, resulting in cerebral asymmetry.

One of the many genes involved in this process of lateralisation is PITX2. Defects in this gene can give rise to Axenfeld-Rieger syndrome type I, a condition which affects the development of the eyes, teeth and anterior face. Most patients with this disorder have abnormalities involving the anterior segment of the eye and develop glaucoma. They will also commonly have microdontia, widely spaced eyes, and a flattened mid-face.

As the embryonic disc develops, at one of its ends a rounded area becomes thicker and more prominent than the remainder of the disc. This is termed the prochordal plate. With ongoing development of this plate, the head and tail ends of the embryo become determined. The end at which the prochordal plate appears is called the 'cranial' (head) end, the other end is termed the 'caudal' (tail) end. The prochordal plate thus determines the central axis of the embryo.

Gastrulation occurs around the time of development of the primitive streak. This streak is a linear band of ectodermal cells which proliferate and migrate towards the midline of the epiblast. These cells are pluripotent (i.e. they have the ability to transform into any type of cell). The primitive streak is an important structure, which undertakes several key functions during embryonic development:

1. It gives rise to the embryonic mesoderm, the notochord and the septum transversum (that subsequently develops into part of the diaphragm, pericardium and ventral mesentery of the foregut).
2. It determines the three dimensional orientation of the embryo (cranio-caudal, right-left, ventral-dorsal) (Fig. 1.4).

At the cranial end of the primitive streak a 'primitive node' (Henson's node) develops, and within the primitive node lies the primitive pit. From here, a cord of

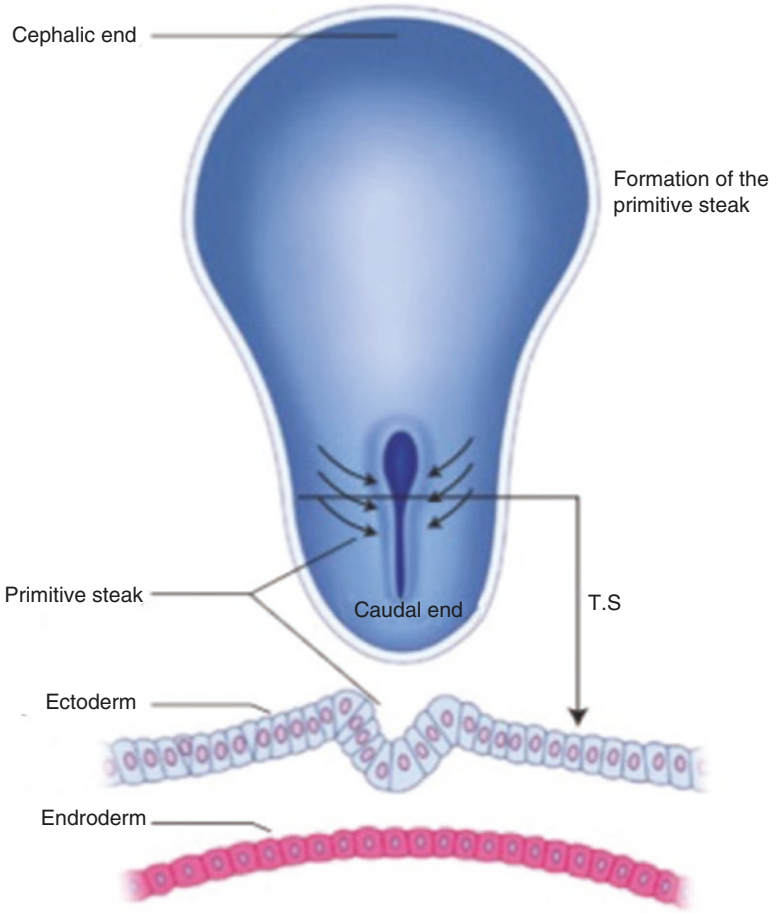


Fig. 1.4 Formation of the primitive streak signalling the start of gastrulation

cells grows cranially from the bottom of the pit to the prechordal plate. These will form the 'notochord'. The cells of the primitive streak then invaginate, forming a groove on its surface—the 'primitive groove'. From the bottom of this groove, the cells detach and migrate under the ectoderm to form the intraembryonic mesoderm—the 'third germ layer'. Thus three new germ cell layers become established

1. Ectoderm. This is formed by the epiblast cells that remain in position.
2. Mesoderm. This is formed by epiblast cells that have migrated through the primitive groove and lie between the epiblast and endoderm.
3. Endoderm. This is formed by the epiblast cells that have migrated through the primitive groove, displacing the hypoblast cells (Figs. 1.5 and 1.6).

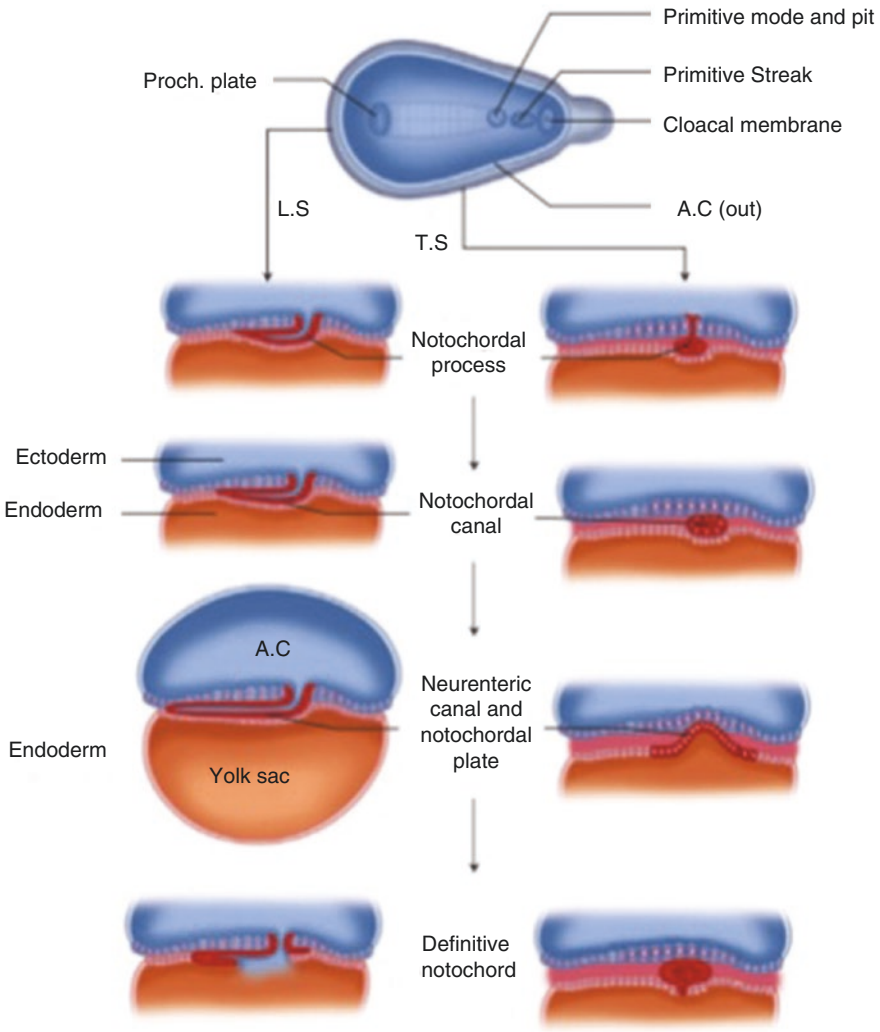


Fig. 1.5 Formation of the notochord

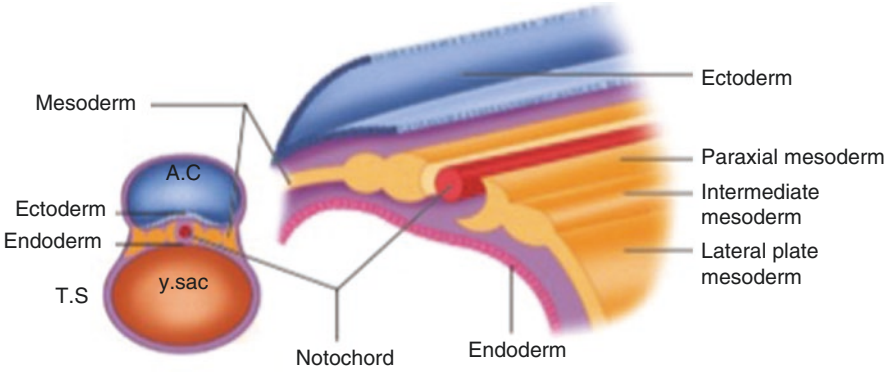


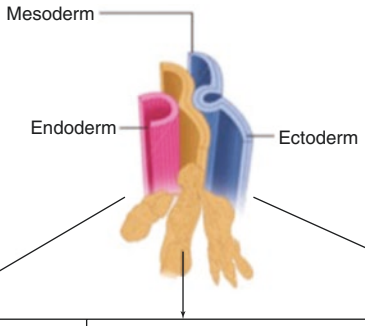
Fig. 1.6 Formation of the mesoderm layer

These changes all occur during the third week. During this time the embryonic disc elongates and becomes pear shaped, with a wider cephalic end and a narrower-shaped caudal end. Later, the primitive streak will regress and completely disappear by the end of the fourth week. Caudal remnants of the streak can give rise to a sacrococcygeal teratoma. Most sacrococcygeal teratomas are benign and will present in children less than 5 months in age. When these tumours present in older children, they are more likely to become malignant.

These three germ layers will ultimately become the source of all the different tissues that will make up the foetus. These varied tissues are derived through the processes of somitogenesis, histogenesis and organogenesis. All three germ layers are derived originally from the epiblast, but undergo differentiation. This process subsequently results in:

1. An upper layer of ectoderm, which gives rise to the outermost layer of skin and its appendages (the nails and hair), central and peripheral nervous systems, sensory epithelia of the eye, ear, and nose, the mammary glands, hypophysis and the enamel of the teeth.
2. A middle layer of mesoderm, which gives rise to the connective tissues, cartilage and bone, striated and smooth muscles, the heart walls, blood and lymphatic vessels, kidneys, gonads and genital ducts, serous membranes lining the body cavities, the spleen and the suprarenal (adrenal) cortices.
3. An inner layer of endoderm, which gives rise to the epithelial lining of the gastrointestinal and respiratory tracts, parenchyma of the tonsils, the liver, thymus, thyroid, parathyroids and the pancreas, the epithelial lining of the urinary bladder and urethra, tympanic cavity, tympanic antrum and auditory tube (Fig. 1.7).

During this time the three germ layers appear as three overlapping flat discs. The mesoderm spreads out in all directions throughout the embryonic disc, except in the following three regions.



Endoderm	Mesoderm	Ectoderm
I-Epithelial lining of (1) the alimentary canal except; -anterior part of mouth -lower part of anal canal (2) the respiratory tract (3) the urinary bladder (except the trigone) (4) most of urethra (5) Ear: (a)pharyngotympanic tube (b)middle ear cavity (c)inner layer of eardrum II- parenchyma of: (1) Tonsil (2) Thyroid & parathyroid glands (3) Thymus gland	(1) All types of connective tissue, cartilage. bone & jcints (2) All types of muscles: Skeletal, smooth and cardiac muscle (3) All cardiovascular system: the heart, blood vessels (4) Bone marrow & blood cells (5) Lymph vessels & all lymph tissue: Lymph nodes & spleen (6) Sercus membranes: pleura pericardium & pentoneum (7) Dura matter & microgtia of the nervous system (8) Dermis of the skin (9) Urogenital system except most of the urinary bladder & urethra (10) Cortec of the suprareral gland	(1) Nervous system -brain & spinal cord -Oia & arachnoid mater -sensory epithelium of the sense organs (2) Skin: epidermis. hair & mails (3) Giands: pitutary gland & the medula of suprarenal gland (4) Digestive system: lining of -ant part of the oral cavity -lower part of anal canal (5) Respiratory system: Epithelium of the nose (6) Ear: External auditory meatus & outer layer of eardrum

Fig. 1.7 Derivatives of the three germ layers

1. The prochordal plate where the ectoderm and endoderm are in firm contact with each other. This will form the buccopharyngeal membrane. Cranial to the prochordal plate the mesoderm from both sides is continuous with each other. This will later become the septum transversum.
2. The cloacal membrane, where the ectoderm and endoderm are also in contact with each other.
3. The notochord. This is found in the midline of the disc, between the prochordal plate and the primitive node (Fig. 1.8).

The septum transversum will later develop myoblast cells and derive its innervation from the adjacent ventral rami of spinal nerves C3, C4 and C5 (the precursor of the phrenic nerve). With subsequent development, the dorsal end of the embryo grows much faster than the ventral side. This results in an apparent descent of the septum transversum through the neck and chest. Thus the septum 'moves' to a more caudal position at the level of the thoracic vertebrae. As it does so, the fibres of the phrenic nerve follows. This process explains the motor and sensory innervation of the muscular diaphragm by the phrenic nerve and its long descending pathway through the neck and thorax.

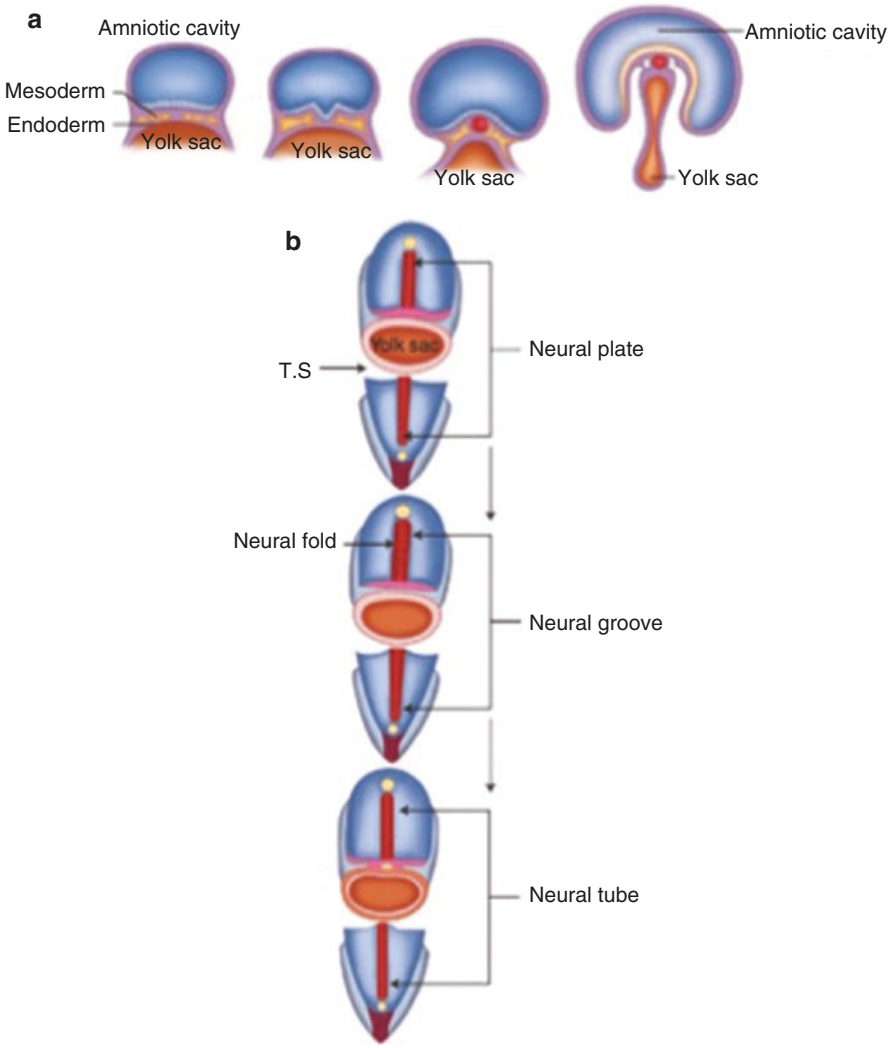


Fig. 1.8 (**a**) Establishment of the ectoderm layer from the embryonic disc. (**b**) Establishment of the neural plate from the ectoderm layer

Gastrulation abnormalities can lead to malformations either at the caudal or the cranial regions. Caudal dysplasia is usually secondary to insufficient mesoderm production in the caudal region of the embryo. This can lead to lumbar and sacral vertebral malformations, an imperforate anus, agenesis of the internal genitalia, and in some extreme cases fusion of the lower limb buds (sirenomyelia).

During this stage of development, alcohol-related toxicity can cause damage to the cells in the anterior midline germinal disc. This may lead to a deficiency in craniofacial structures in the midline. The resulting syndromes are referred to as

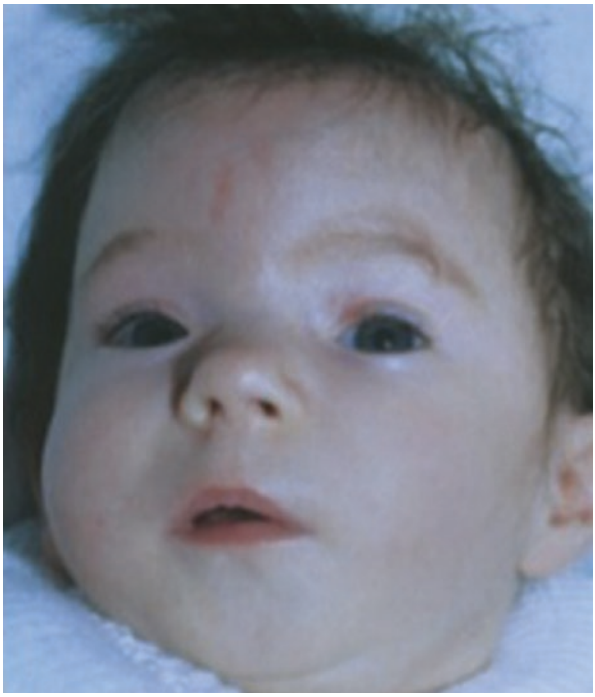


Fig. 1.9 Foetal alcohol syndrome

Foetal Alcohol Syndrome, of which holoprosencephaly (arhinencephaly) is the most severe form. In this condition there is a failure of midline cleavage of the embryonic forebrain (described later). As a result the telencephalon contains a single ventricle. This condition is also seen in trisomy 18 (Edward syndrome), Meckel syndrome and trisomy 13 (Patau syndrome), where the corpus callosum may be absent. It is characterised by the absence of olfactory bulbs and tracts (hence the name, arhinencephaly). Because the face develops at the same time as the brain, severe facial anomalies (cyclopia, cleft lip, cleft palate) are commonly associated (Fig. 1.9).

Holoprosencephaly manifests with microcephaly and congenital heart disease. It is the most severe manifestation of foetal alcohol syndrome, from alcohol abuse during pregnancy (especially in the first 4 weeks). Three types are described

1. Alobar prosencephaly (most severe form) occurs when there is complete absence of cleavage of the prosencephalon. Infants are stillborn or die shortly after birth and have cyclopia, a single rudimentary proboscis, cleft lip, cleft palate, hypotelorism, and micrognathia. There is a single horseshoe-shaped ventricle ('monoventricle') and a layer of undifferentiated cerebral cortex.

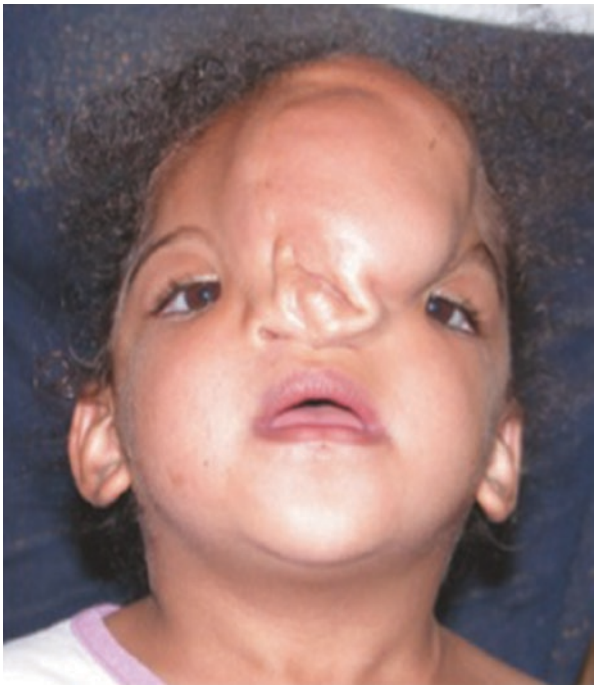


Fig. 1.10 Clinical picture of encephalocele anterior (face)

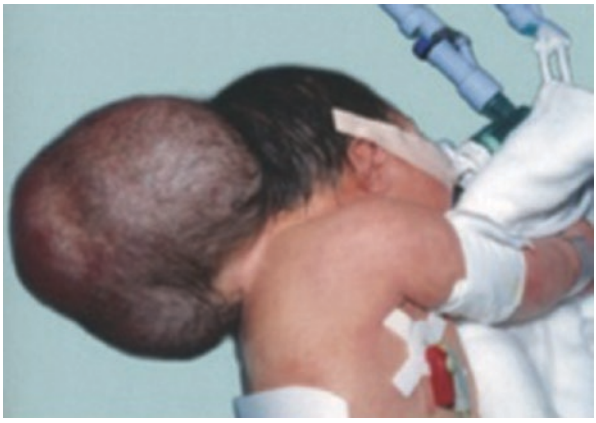


Fig. 1.11 Encephalocele

2. Semilobar prosencephaly (intermediate form). This occurs when there is failure to cleave the prosencephalon anteriorly, with only partial cleavage posteriorly.
3. Lobar prosencephaly (least severe form). This occurs when there is failure to cleave the prosencephalon anteriorly, but cleavage of the prosencephalon posteriorly (Figs. 1.10 and 1.11).

1.1.4 The Notochord

This is an important midline structure that develops between the primitive streak and the prochordal plate. It is derived from the primitive node. This structure forms the central axis of the embryonic disc and induces the formation of neural tube, which are described later. During development the cells of primitive node proliferate and produce a central depression called the 'blastopore'. From this site cells migrate forward in the midline between the ectoderm and the endoderm of the bilaminar germ disc, to form a solid cord of cells called the 'notochordal process'. The notochord increases in length caudally whilst the primitive streak regresses. Later the notochordal process becomes canalised to form the 'notochordal tube'. The cavity of this tube is continuous with the blastopore. The important notochord functions are to

1. form the central axis of the developing embryo
2. induce the formation of the 'neural tube', which is derived from the overlying ectoderm.
3. provide a central column, around which the vertebral bodies and intervertebral discs will later develop.

The notochord itself eventually disappears, but remnants remain and are found in the intervertebral discs, and in the apical ligament of the dens (second cervical vertebra). Current opinion suggests that notochord remnants secrete signalling factors that regulate function of the nucleus pulposus (in the vertebral disc), protect the nucleus pulposus from cytokine-related damage, and preserve the nucleus pulposus by inhibiting apoptosis.

Chordomas are tumours that arise from the remnants of notochord. There are therefore found in all places where the notocord once existed, including the clivus, sella turcica, foramen magnum, upper cervical spine and nasopharynx. In the head they are most commonly seen at the base of the skull. About 30% of chordomas are malignant or locally aggressive and have a tendency to spread into the nasopharynx. Chordomas account for approximately 20% of primary spinal tumours.

1.1.5 Neurulation

As development of the epithelial and neural tissues progresses along with formation of the neural tube, the gastrula becomes known as the 'neurula'. The neural tube is derived from the ectoderm overlying the notochord. The cells of the ectoderm in this region become differentiated into specialised neuroectodermal cells. These then proliferate to form a thick 'neural plate'—which will form the basis of the developing nervous system. The neural plate forms initially in the cranial region, and then develops caudally. The cranial-most end of the neural plate is much wider, and will eventually develop into the brain.

The process of neurulation converts the neural plate into the neural tube. The margins of the neural plate become elevated to form neural folds, as the "paraxial

mesoderm" (described later) proliferates and develops on either side of the notochord. This change in shape of the plate results in the formation of a "neural groove". With further growth the neural groove becomes deeper and the neural folds move towards the midline and begin to fuse together to form the cylindrical neural tube. The term neurulation specifically refers to this folding process, whereby the flat neural plate becomes the neural tube. This takes place during the fourth week.

Closure of the neural tube is an essential part of neural development and commences in the middle of the tube, extending in both cephalic and caudal directions. During this time the openings at both ends of the tube are called the 'neuropores'. Amniotic fluid enters these openings and circulates throughout the neural tube, providing nutrition. With the final closure of the neuropores some of the amniotic fluid gets trapped inside the tube. This marks the beginning of the CSF circulation. Cells at the tips of neural folds ('neural crest') do not take part in this process, but instead proliferate to form bilateral clusters, dorsolateral to the neural tube under the ectoderm. The neural tube later gives rise to three primary vesicles (described below), which divide further into secondary vesicles. The caudal part of the neural tube remains tubular and forms the spinal cord. Alpha-fetoprotein (AFP) is a protein found in amniotic fluid and maternal serum. Abnormal levels during pregnancy may indicate the presence of some neural tube defects (such as spina bifida or anencephaly). AFP levels are also reduced in foetuses with Down syndrome (Figs. 1.12 and 1.13).

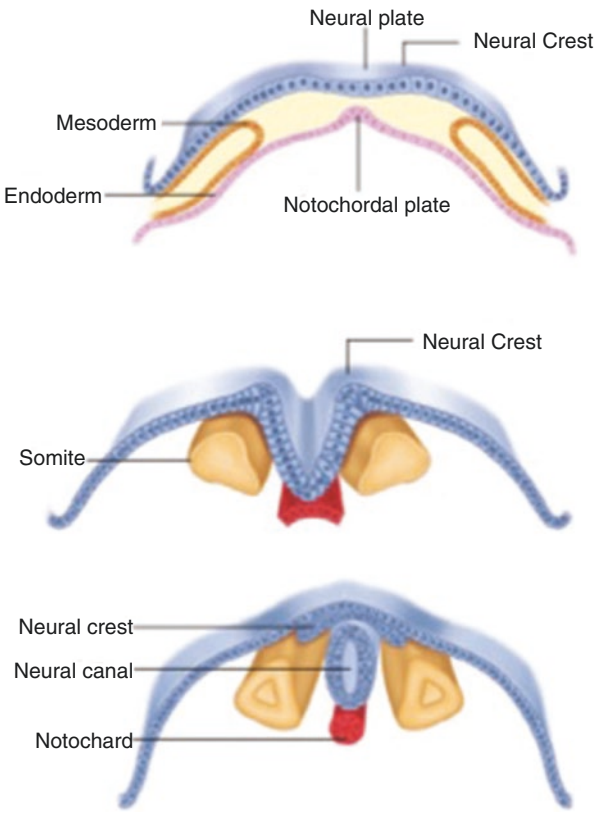


Fig. 1.12 Neural plate

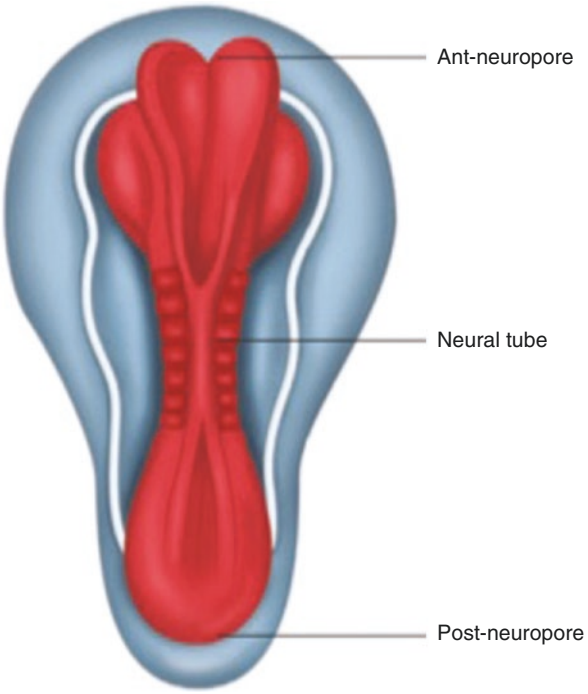


Fig. 1.13 The closed neural tube develops into the spinal cord and the brain

During this period, certain genetic anomalies or environmental factors can disrupt the normal process of development of the nervous system, and result in a wide range of defects which are collectively referred to as 'neural tube defects'. These comprise the second most common set of congenital defects worldwide. In the UK and other countries, all pregnant mothers are encouraged to take folic acid supplementation to reduce the risk of their foetus developing neural tube defects. Several types exist

1. 'Open' neural tube defects represent a failure of primary neurulation. Often these open defects are incompatible with life. Here, there is a failure of closure of the neural tube. One example includes anencephaly, in which there is absence of a significant portion of the brain, skull, and scalp. This occurs when a major part of the brain and cranial vault fails to develop. During development of the brain, anencephaly is usually preceded by exencephaly, in which the neuroepithelial tissues continue to differentiate, but become damaged, as they are exposed in utero. Anencephaly remains the most serious birth defect seen in stillborn infants. If not stillborn, infants with anencephaly survive only a few hours or at most, weeks. It can be diagnosed pre-natally by ultrasonography and a raised alpha-fetoprotein level.
2. Myelomeningocoele is a form of spina bifida in which the vertebral arches are unable to develop following failure of neurulation. In this anomaly, the spinal

cord may either be completely exposed to the amniotic fluid (termed myelocoele), or may be encased within a sheath of meninges to form a sac around the open lesion (meningomyelocoele).

3. Craniorachischisis is considered the most severe form of neural tube defect in which both anencephaly and myelocoele are present. In posterior rachischisis, the entire neural tube remains open. This is incompatible with life.
4. 'Closed' neural tube defects include 'occult' spina bifida, and represent a much less severe form of defect than 'open' defects. These comprise defects in axial skeleton development, and may also include abnormalities of the spinal cord. The aetiology of occult spina bifida is unclear, but it has been suggested that these lesions result from a failure of secondary neurulation. As a result, most of these closed defects affect the most caudal regions of the spine and spinal cord. Defects are often associated with tethering of the caudal end of the spinal cord, which can lead to neuropathic bladder problems and lower limb deficits. Examples include dimyelia, diplomyelia or diastematomyelia, in which there is duplication or splitting of the caudal spinal cord. Hydromyelia is a condition in which the central canal of the spinal cord is distended. Some closed defects may also be associated with anal atresia or anal stenosis.
5. 'Herniation' neural tube defects develop from deficiencies in the cranial mesoderm and lead to apertures in the skull. These are usually seen in the occipital region of the skull, but have also been described in the parietal and frontoethmoidal regions. These apertures permit the meninges to herniate out of the cranium, sometimes with brain tissue. These abnormalities are known as encephaloceles, of which three major types have been described (depending upon the tissues herniated): (1) meningocele, (2) meningoencephalocele and (3) meningohydroencephalocele. Cranium bifidum results from a defect in the occipital bone through which meninges, cerebellar tissue, and the fourth ventricle may herniate (Figs. 1.14 and 1.15).

1.2 Development of the Brain

The entire nervous system is derived from ectoderm, with the exception of its blood vessels and some neuroglial tissues. The brain itself develops from an enlarging cranial (rostral) swelling at the end of the neural tube. At about the end of fourth week, this swelling begins to develop three separate dilatations—the primary brain vesicles. Craniocaudally, these are (1) prosencephalon (forebrain), (2) mesencephalon (midbrain), and (3) rhombencephalon (hindbrain). All three are hollow and interconnected. These fluid filled cavities will eventually become the ventricular system of the adult brain. During the fifth week both the prosencephalon and rhombencephalon each divide further into two vesicles, thus producing five 'secondary brain vesicles'. These are

1. Telencephalon
2. Diencephalon. The prosencephalon gives rise to a rostral telencephalon and caudal diencephalon. The telencephalon grows substantially outwards bilaterally

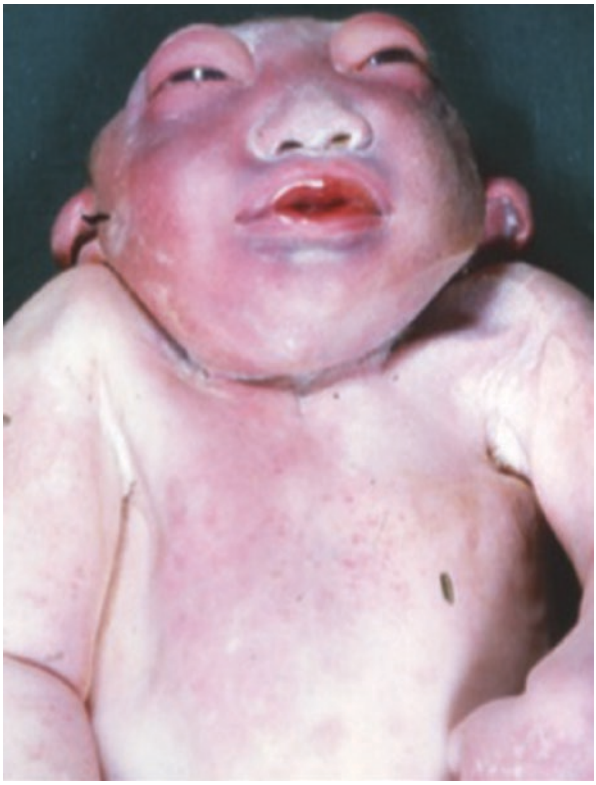


Fig. 1.14 Anencephaly

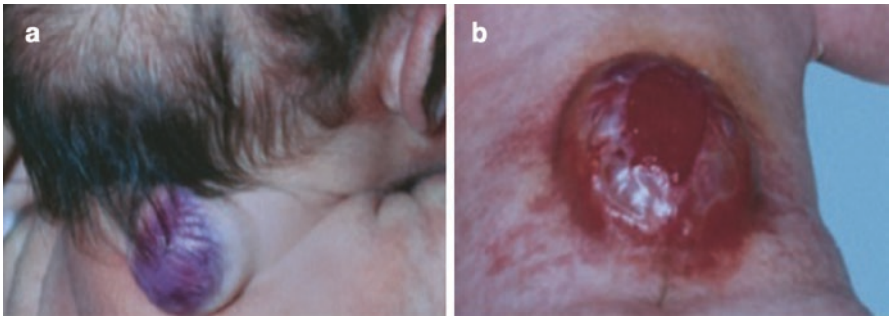


Fig. 1.15 (**a**) Meningocele. (**b**) Myelomeningocele

and surrounds the diencephalon. This becomes the cerebral hemispheres. The diencephalon is therefore hidden. It becomes the thalamus, hypothalamus, etc.

3. Mesencephalon—This gives rise to midbrain. Here, its central cavity narrows to form the cerebral aqueduct.
4. Metencephalon

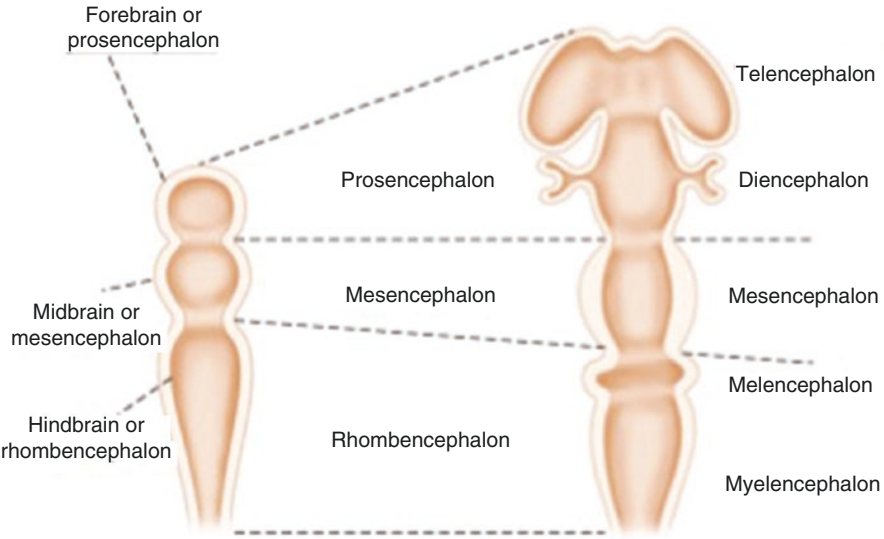


Fig. 1.16 Development of the brain—a lateral diverticulum appears on each side of the forebrain

5. Myelencephalon. The rhombencephalon divides into a cranial metencephalon (which becomes the pons and cerebellum) and a caudal myelencephalon, which becomes the medulla oblongata (Fig. 1.16).

1.2.1 Flexures and Ventricles

Whilst these changes are occurring, the developing brain also undergoes a number of folds, often called flexures. Three flexures arise (1) a ventrally concave cephalic (mesencephalic) flexure in the region of midbrain (2) a ventrally convex pontine flexure in the middle of the rhombencephalon and (3) another ventrally concave cervical flexure at the junction of the rhombencephalon with the spinal cord. This latter cervical flexure forms almost a 90° angle between the hindbrain and spinal cord, resulting in the fully developed brain being oriented almost at a right angle to the spinal cord. At the pontine flexure the shape of the tube also changes significantly, with its cavity becoming diamond-shaped—the fourth ventricle. This tapers superiorly in the midbrain (the aqueduct of Sylvius) and inferiorly in the lower medulla oblongata. The thin roof of this cavity also extends laterally and breaks down, to form several openings (the foramina of Magendie and Luschka). Through these, the cavity of the neural tube now communicates with the surrounding subarachnoid space. Failure of these tissues to break down can result in hydrocephalus and brain atrophy (Figs. 1.17 and 1.18).

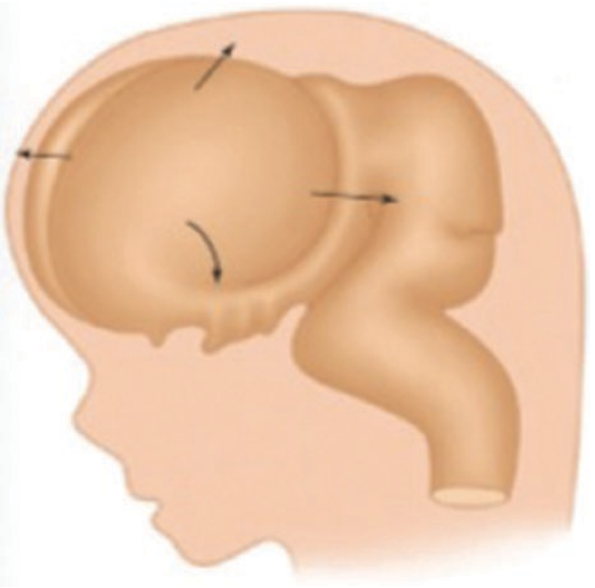


Fig. 1.17 Expansion of the cerebral cortex

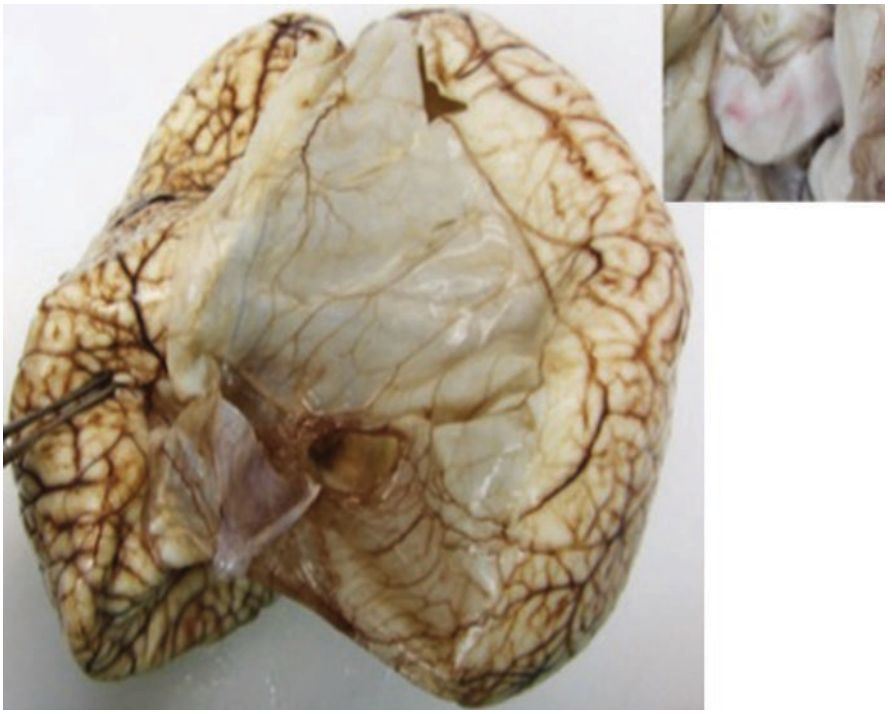


Fig. 1.18 Obstructive hydrocephalus due to congenital aqueduct (of Sylvius) stenosis (inset) caused by X-linked recessive *L1CAM gene* mutation

The cavities of these secondary vesicles eventually become the ventricular system of adult brain.

1. The right and left telencephalic cavities become the lateral ventricles.
2. The diencephalic cavity becomes the third ventricle.
3. The narrow mesencephalic cavity becomes the cerebral aqueduct (of Sylvius)
4. The hindbrain cavity becomes the fourth ventricle.

These changes thus form an interconnecting system of cavities (ventricles) and channels, through which cerebrospinal fluid (CSF) can circulate. The two lateral ventricles communicate with the third ventricle via the interventricular foramina (of Monro). The third ventricle communicates with the fourth ventricle through the cerebral aqueduct and the fourth ventricle continues into the central canal of the spinal cord. CSF plays an important role in brain development. Its flow exerts a pressure within the developing brain, stimulating growth and enlargement. If CSF is shunted away from the primitive ventricular system of the brain, or if too little CSF is produced, brain development will be stunted and result in a hypoplastic brain (reduced brain tissue).

More than 2000 different congenital malformations of the brain have been described in the literature, and their incidence is reported to be about 1% of all live births. Developmental anomalies during this stage include

1. Porencephaly (encephaloclastic porencephaly). This is the presence of one or more fluid-filled cystic cavities within the brain. These may communicate with the ventricles, but do not extend to the cortical surface. They occur as a result of localised brain damage early in development, before the brain is capable of producing a glial (scar tissue) response. The clinical effects of these depend on their location and the amount of damage sustained.
2. Schizencephaly. This is the presence of a fluid-filled cleft in the cerebral tissue that extends from the ventricles to the cortical surface. This forms as a result of abnormal neuronal migration during development of the brain.
3. Foetal brain disruption sequence. This has been suggested to arise from partial brain disruption during the second or third trimester. Interruption of the blood supply to selected areas of the brain (following viral infection or hyperthermia) results in severe microcephaly and calvarial collapse.

1.2.2 Cerebrospinal Fluid Production and Function

Cerebrospinal fluid (CSF) is formed by the choroid plexus in the lateral ventricles and passes into the subarachnoid space through the foramina of Magendie and Luschka. The choroid plexus develops in the roof of the rhombencephalon and diencephalon and within the choroid fissure of the telencephalon. It is derived from a layer of ependymal cells covered by a vascular pia mater—the tela choroidea. This proliferates to form tiny sac-like invaginations into the ventricles. The choroid

plexus produces around 500 mL of CSF per day. This is returned to the venous system via the arachnoid (granulations) villi of the venous dural sinuses (superior sagittal sinus). In adults, the primary function of CSF is to cushion and protect the brain within the skull, acting as a shock absorber for the central nervous system. It also provides nutrients and chemicals which have been filtered from the blood and removes some waste products from the brain.

Any condition affecting free passage of CSF can result in a condition known as hydrocephalus and raised intracranial pressure. Hydrocephalus that presents at birth or before birth is usually due to an anatomical anomaly which result in a mismatch between CSF production and absorption in the foetal brain (either increased production or reduced absorption). Hydrocephalus can be divided into either non-communicating or communicating types. In non-communicating hydrocephalus, obstruction occurs within the ventricular system or at the level of the fourth ventricular foramina. This prevents free flow of CSF between the ventricles. In communicating hydrocephalus, there is an obstruction or impairment of CSF flow distal to the fourth ventricular foramina, but CSF can still flow freely between the ventricles.

1. The commonest cause of foetal non-communicating hydrocephalus is the Arnold-Chiari (type II Chiari) malformation. This arises following development of a myelomeningocoele (described above). The Chiari malformations are a group of developmental anomalies that occur within the hindbrain, which result in impaired flow of CSF. The type II malformation occurs in 1:1000. In the presence of a meningomyelocoele, the medulla oblongata and the inferior vermis of the cerebellum sag downwards and herniates into the foramen magnum. This obstructs the flow of cerebrospinal fluid thereby causing the hydrocephalus.
2. Aqueductal stenosis is the second commonest cause of foetal non-communicating hydrocephalus. This can be identified on foetal MRI by the presence of enlarged lateral and third ventricles, but with normal sized fourth ventricles (indicating a stenosed Aqueduct of Sylvius). Aqueductal stenosis is usually caused by intraventricular haemorrhage, or congenital infections such as toxoplasmosis or cytomegalovirus. It can have severe adverse effects. Ventricular distension often results in damage to the corpus callosum and the overlying cortex. Specifically, this condition can result in agenesis of the cerebellar vermis, occipital meningocoele and agenesis of the corpus callosum. A rare X-linked form of aqueductal stenosis has also been reported, related to the L1CAM gene. This is termed ‘CRASH syndrome’—Corpus callosum hypoplasia, Retardation, Adducted thumbs, Spastic paraplegia and Hydrocephalus. Due to the X-linked nature of inheritance, this syndrome is only seen in males, but some female carriers may experience mild symptoms.
3. Other common causes of foetal non-communicating hydrocephalus include the Dandy Walker malformation, which has a frequency of 1:25,000. This may result from alcoholic abuse, ingestion of riboflavin inhibitors, posterior fossa trauma or some viral infections. It occurs following blockage of median aperture (Foramen of Magendie) and the lateral apertures (Foramina of Luschka). As a result, the

cavity of the fourth ventricle enlarges. This anomaly is limited to the posterior cranial fossa.
4. Rarer causes of foetal hydrocephalus include arachnoid cysts and posterior fossa tumours, as well as communicating hydrocephalus.

1.2.3 Further Growth and Myelination

With further growth, the developing cerebral hemispheres enlarge upwards, backwards and anteroinferiorly, to become the frontal, parietal, occipital and temporal lobes, also called the 'neocortex'. This curved expansion causes the structures related to it (lateral ventricle, corpus callosum and choroid fissure) to acquire their adult C-shaped forms. The cerebral hemispheres thus eventually surround the bulk of the midbrain. The three meninges (dura, arachnoid and pia mater) surrounding the brain and spinal cord are derived from the mesenchyme surrounding the neural tube (dura) and from neural crest cells (arachnoid and pia). The optic vesicle (which eventually becomes the optic nerve, retina and iris) develops at the base of the prosencephalon. This subsequently grows forwards to become the optic nerve.

Myelination begins in the fourth month of gestation. This is a very long and complex process. Myelination of the corticospinal tracts is not completed until the end of the second postnatal year, when the tracts become functional. Myelination in the cerebral cortex is reported to continue into the third decade of life. Myelination of the CNS is undertaken by oligodendrocytes. Myelination of the PNS is accomplished by Schwann cells. The presence of myelin enables rapid transmission of action potentials (by saltatory conduction) and protects the axons of the neurones. Disorders of myelin development comprise a group called the hypomyelinating leukodystrophies (as opposed to the degenerative leukodystrophies in which myelin is completed but is subsequently destroyed). The leukodystrophies cover a broad spectrum of pathologies, but most are inherited diseases. Usually these conditions present in neonates with axial hypotonia and nystagmus. These eventually progress to spastic quadriparesis. Most patients will develop cerebellar signs, but in a few cases they may exhibit extrapyramidal signs, cognitive dysfunction or peripheral neuropathy.

1.3 Embryonic Folding

Folding of the entire embryo is a complex process that occurs in both the median and horizontal planes, as a result of rapid differential growth of the entire structure. Consequently, the original flat embryonic disc becomes somewhat cylindrical in shape and becomes completely enclosed by the amniotic cavity. Also as a result, the ectodermal tissues now become the outer covering of the embryo. A depression soon develops between the head bulge and pericardial bulge (developing heart). This is called the 'stomodeum', and is separated from the cranial end of the primitive foregut by the buccopharyngeal membrane (the caudal end of primitive gut is

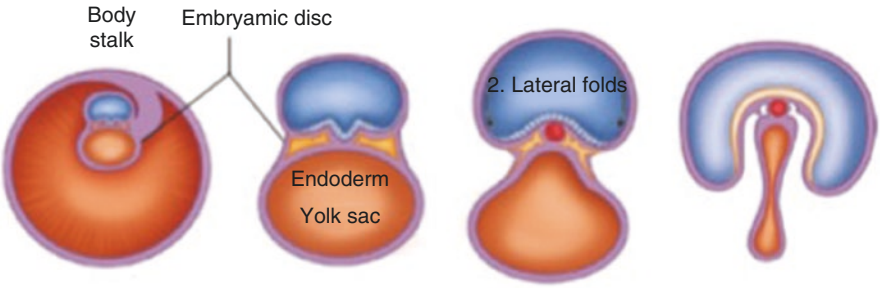


Fig. 1.19 (**a**) Embryonic folding during week 4 of development. (**b**) The end Result of early embryonic folding

separated from proctodeum by the cloacal membrane). The head, containing the brain, now forms the most cranial part of the embryo and lies above and behind the buccopharyngeal membrane (Fig. 1.19).

1.3.1 The Pituitary Gland (Hypophysis Cerebri)

The diencephalon develops a neuroectodermal downgrowth from the hypothalamus and floor of the third ventricle, the 'neurohypophysis'. This joins an ectodermal upgrowth from the primitive oral cavity (the stomodeum), called the 'adenohypophysis' (or 'Rathke's pouch'). Together they meet to form the pituitary gland. Thus the gland consists of two distinct parts (1) the adenohypophysis (anterior pituitary) and (2) the neurohypophysis (posterior pituitary). Later, Rathke's pouch becomes separated from the stomodeum. The anterior wall of Rathke's pouch at the pituitary then proliferates to form the pars anterior (anterior lobe) of the gland. Its posterior wall remains thin and forms the pars intermedia. Small clefts of Rathke's pouch often persist as the 'hypophyseal cleft', which separates the two parts.

Congenital pituitary anomalies can arise from either incomplete migration or growth of the adenohypophysis or neurohypophysis, or from abnormal proliferation of the tissues.

1. Craniopharyngioma (a tumour) develops from the remnants of Rathke's pouch. Rathke's pouch normally detaches from the primitive oral cavity during formation of the anterior pituitary (adenohypophysis). In the adult, the original site of attachment of this pouch is in the roof of nasopharynx. However remnants of Rathke's pouch can form a craniopharyngeal canal, which can sometimes give rise to a tumour (craniopharyngioma). This is seen in the roof of nasopharynx.
2. In some patients, in the event of agenesis of the hypophysis, accessory hypophyseal tissue may be found in the posterior wall of the pharynx.
3. Ectopic neurohypophysis can occur following incomplete downward extension of the diencephalon. This usually presents with growth hormone deficiency and dwarfism, and is often also associated with hyperprolactinaemia.

1.4 The Spinal Cord

The caudal part of the neural tube forms the spinal cord. Here, the cavity of the neural tube is almost like a vertical slit. This will eventually form the central canal of the spinal cord. The wall of the tube becomes subdivided and differentiates into three layers, (1) the inner ependymal, (2) mantle and (3) the outer marginal layers. Rapid growth of the mantle layer in the ventral part of the developing spinal cord, makes this region thicker and reduces the lumen of the tube ventrally. The nerve cells in this layer will become the neurones of the anterior grey column. The axons of these cells leave the spinal cord ventrolaterally and form the anterior (motor) nerve roots of the spinal nerves. Later, a line of demarcation appears in the lateral wall of the tube. This is known as the 'sulcus limitans'. Neural crest cells collect near the dorsolateral aspect of the neural tube. These will give rise to the dorsal root ganglion and the spinal ganglion.

1.5 The Neural Crest

Neural crest cells play a diverse but critical role in embryonic development. They first appear at the junction of the neural plate with the adjacent ectoderm. This is mediated by regulatory proteins, BMP-4 and BMP-7. As the neural tube closes (neurulation), clumps of neural crest cells break away from the neural folds and aggregate near the midline, dorsolateral to the neural tube. Unlike the neural tissues in the neural tube, neural crest cells migrate widely to distant sites in the developing embryo, including the skull, face, thyroid, dorsal root ganglion, skin and elsewhere. These cells ultimately differentiate into a wide range of cells and structures. The Neural crest plays a key role in the development of the following:

1. Neurones of the dorsal root ganglion
2. Neurones of the sensory ganglion of the cranial nerves V, VII, VIII, IX and X.
3. Neurones of the autonomic (sympathetic and parasympathetic) ganglia (including ciliary, submandibular, sphenopalatine and otic ganglia).
4. Schwann cells
5. Chromaffin cells of the adrenal medulla
6. Melanocytes in the skin
7. Parafollicular 'C' cells of the thyroid gland
8. Cells of the leptomeninges (pia and arachnoid mater).
9. Dental papilla, odontoblasts and dentine.
10. The skeletal and connective tissue elements of the branchial (pharyngeal) arches, which ultimately form the bones of the face. Migration of neural crest into the arches is not random, but follows a strict topographical relationship with their site of origin along the neural tube.
11. The vault of the skull.
12. The connective tissue of the thyroid, parathyroid, thymus and the salivary glands
13. The aorticopulmonary septum of the heart.

As one can imagine, there are many disorders that can occur as a result of neural crest disturbance. Neurocristopathy is the termed used to describe any disorder related to maldevelopment of neural crest cells. These can affect many different organ systems. Neurocristopathies commonly arise from either a defect of migration, differentiation or abnormal proliferation, and in some cases can result in tumours within neural crest-derived tissues. Some of the commoner neurocristopathic tumour syndromes include (1) the phaeochromocytomas, which arise within the tissues of the adrenal medulla (chromaffin cells), (2) the neuroblastomas, which also comprise tumours of the adrenal medulla or autonomic ganglia, (3) the carcinoid tumours involving enterochromaffin cells of the gastrointestinal tract and (4) medullary thyroid carcinomas involving the parafollicular cells of the thyroid gland.

The primary neurocutaneous syndromes are also examples of abnormal proliferation of neural crest cells and include neurofibromatosis, tuberous sclerosis and neurocutaneous melanosis (multiple melanotic tumours of the central nervous system and multiple melanotic naevi). The commonest differentiation defect involving neural crest cells is albinism, which leads to a complete or partial absence of pigment in the skin, hair, and eyes. Albinism is also associated with ocular defects such as photophobia, nystagmus, and amblyopia.

Neurocristopathic defects involving migration or abnormalities in differentiation can be divided into neural crest cells of the trunk or cranial regions. Hirschsprung's disease is the commonest defect of trunkal neural crest cells. This leads to congenital megacolon since the terminal part of the colon has no innervation. Cranial neural crest defects include (1) aorticopulmonary septal defects of the heart, (2) defects involving the anterior chambers of the eyes, (3) cleft lip or cleft palate (described later), (4) frontonasal dysplasia, (5) dental abnormalities and (6) DiGeorge syndrome. This latter syndrome results in hypoplasia of the thymus, thyroid and parathyroid glands and is associated with cardiovascular defects of the aortic arch. It is linked to a deletion on chromosome 22, which results in a defect of the neural crest associated with the third and fourth pharyngeal arches and the cardiac outflow tract. A risk factor for developing DiGeorge syndrome is high exposure to retinoids during embryogenesis.

CHARGE syndrome is a rare disorder involving defects in both cranial and trunkal neural crest cells. It is an understandable disorder, if the wide distribution of neural crest cell is remembered. Its cause is unknown, but it seems to involve an insult during the second month of gestation, presumably involving the development of the neural crest cells. Key features include (1) coloboma of the retina, lens or choroid, (2) heart defects (tetralogy of Fallot, ventricular septal defect [VSD], patent ductus arteriosus [PDA]); (3) atresia choanae, (4) retardation of growth, (5) genital abnormalities in male infants (e.g., cryptorchidism, microphallus) and (6) ear abnormalities and deafness.

Waardenburg's syndrome is another rare disorder involving defects of both the cranial and trunkal neural crest cells, and arises from mutations in the Pax-3 genes. Patients with Waardenburg's syndrome exhibit ocular hypertelorism, deafness, cleft palate, and pigmentation defects (commonly a white stripe in the hair and skin anomalies). Patients with type I Waardenburg's syndrome also have hypoplasia of the limb muscles.

1.6 Ectodermal Placodes

Prior to the completion of neural tube closure, the neural folds contains two different cell types—neural crest cells and neuroepithelial cells. Some of the neuroepithelial cells become incorporated into the surface ectoderm. These areas are then termed 'ectodermal placodes'. Ectodermal Placodes develop at specific sites and have important roles in the development of the special sensory systems. 'Integumentary' placodes are involved with hair follicle development. The sensory placodes contribute to the development of the special senses (vision, hearing and smell). Their initial position on the developing head is significantly different to their final position. They include

1. Adenohypophyseal placode
2. Otic placodes—the first placodes visible on the surface of the embryo
3. Olfactory (Nasal) placodes—these have medial and lateral components which become the olfactory epithelium
4. Optic (Lens) placodes—these will form the lens of the eye
5. Profundal/trigeminal placodes.

1.7 Development of the Face and Neck

Development of the face and neck begins in the fourth and fifth week. "Hox complex" genes have been described, which appear to be play an important role in early development. These control 'spatial patterning mechanisms' (i.e. the 'body plan') during development in all vertebrates. They are expressed during embryogenesis and control the sequential and orderly development of all the major elements that make up the body. Retinoic acid appears to be important in this regard. This is a derivative of vitamin A, and is particularly important in the normal development of the pharyngeal arches. Lack or excess of retinoic acid can result in striking facial anomalies. With excessive intake, this causes hypoplasia of pharyngeal arches 1 and 2. This is the reason why females taking isotretinoin for acne are required to take contraception and regular pregnancy tests throughout the duration of their treatment.

Initially, a forehead prominence appears as a result of the developing brain. This lies just above a depression called the 'stomodeum' (the primitive oral cavity). A pericardial prominence (formed by the developing heart) lies below the stomodeum. Within this relatively small area, growth and differentiation of the mesenchymal (connective) tissue results in the formation of a series of expanding arches—the 'pharyngeal' (or branchial) arches. This arrangement is referred to as the 'pharyngeal apparatus' and consists of four elements; (1) the pharyngeal arches, (2) pharyngeal pouches (3) pharyngeal clefts (grooves) and (4) pharyngeal membranes. This initially small region begins to grow caudally, pushing the developing heart downwards and elongating the developing neck. As previously noted, this explains the long course of the phrenic nerve.

The pharyngeal apparatus contributes to the formation of the face, neck, mouth, pharynx and larynx. As the arches develop, they are gradually separated from each other both externally, by a number of intervening clefts (the pharyngeal clefts or grooves), and internally, by corresponding invaginations in the lateral wall of the primitive pharynx (the pharyngeal pouches). These indentations do not normally communicate with each other and tissue remains between the two keeping them apart. As a result, the clefts separate the arches on the external (ectodermal) surface, whilst the pouches separate the arches on their internal (endodermal) surface. Each arch will thus come to have its own associated cleft, pouch, cartilage, nerve, muscle group and artery. There are six arches in total. Five of these play a key role in the development of the face and neck. At first the arches are located in the lateral wall of the primitive pharynx. However they gradually grow forwards and merge with their counterparts from the opposite side, in the floor of the primitive pharynx. This results in a stack of U-shaped cylindrical-type bars. Developmental defects arising from the arches can thus take many forms, including hypoplasia of its various tissues, or the development of cysts, sinuses or fistulas. Cystic hygromas are benign growths that are believed to arise from the pharyngeal arches. They are usually multiloculated cysts and occur in the anterior or the posterior triangles. They enlarge with infection and inflammation and can occasionally result in respiratory obstruction or swallowing problems. Usually surgical excision is recommended.

1.7.1 Pharyngeal Clefts

These ectodermal clefts appear during the fifth week of development. However most are temporary and only the first cleft remains in the adult, as the external auditory meatus. The second, third and fourth clefts become obliterated by the rapidly proliferating second pharyngeal arch (see the cervical sinus later).

1.7.2 Pharyngeal Arches

These are U-shaped cylindrical bars in the lateral and ventral walls of the primitive pharynx. They begin to form during the fourth week. Within each arch a cartilaginous rod develops, providing structural support. Each arch subsequently develops into a specific and predetermined structure within the head and neck. In some arches, part of the cartilage forms permanent bone and cartilage, whilst part of it disappears. In other arches the cartilage disappears, but its perichondrium persists to form a ligament or raphe. There are six pharyngeal arches initially, each consisting of a core of mesenchymal tissue covered on the outside by ectoderm and on the inside by endoderm. However, the fifth arch regresses soon after developing. Each arch is innervated by an its own cranial nerve and artery and has a muscular component, with a skeletal and cartilaginous supporting structure. Understanding these points helps understand the complex anatomy of this region. The arteries are connected ventrally to the ventral aorta, passing around the primitive pharynx (Figs. 1.20 and 1.21).

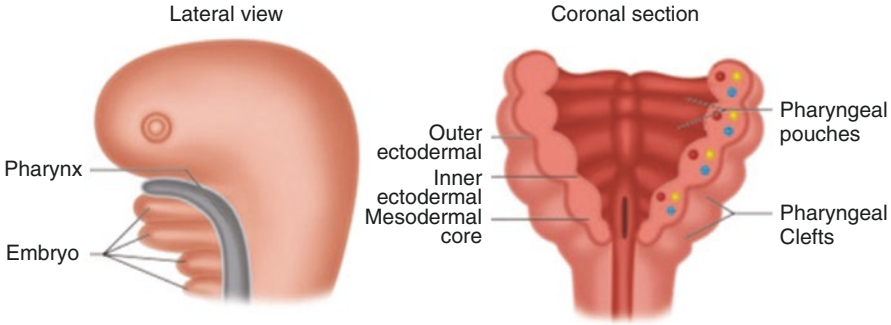


Fig. 1.20 Branchial arches

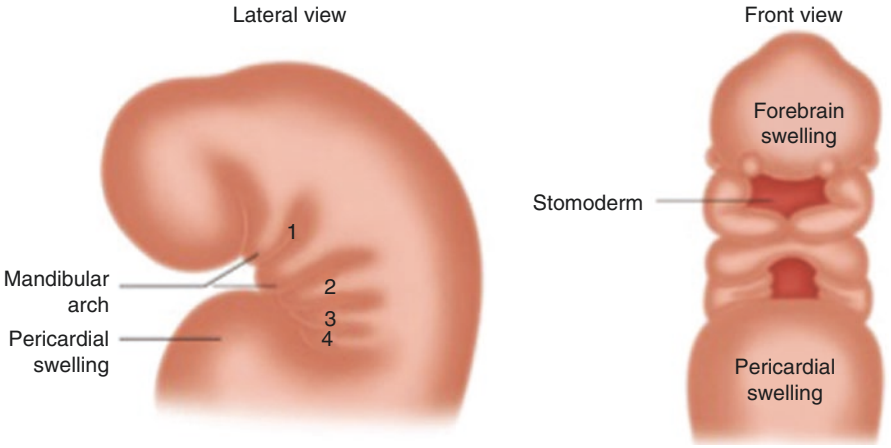


Fig. 1.21 Branchial arches 2

The nerve of each arch provides motor innervation to its muscles and sensory innervation to its overlying skin and mucosa. Wherever the muscle cells migrate to, they take their associated nerve with them. Strictly speaking morphologically, each pharyngeal arch is supplied by two nerves. One nerve runs along cranial border of the arch and is known as the post-trematic nerve. A second nerve runs along its caudal border and is called the pre-trematic nerve. In humans, the pre-trematic (caudal) nerves disappear from all the arches except the first arch, where it persists as the chorda tympani nerve. Some authorities consider that the tympanic branch of glossopharyngeal nerve and auricular branch of vagus nerve also represent the pre-trematic branches of their nerves.

1.7.2.1 The First Arch

This develops into two parts

1. An upper maxillary prominence. This will become the future maxilla, zygomatic bone and part of the temporal bone. It is associated with a maxillary cartilage.

2. A lower mandibular prominence. This will become the future mandible. It is associated with Meckel's cartilage. The dorsal end of the cartilage lies close to the developing middle ear. This persists and forms the malleus and incus. Ventrally (anteriorly), the cartilage is surrounded by mesenchyme that will form the mandible. Cartilage that becomes trapped within the developing bone degenerates and disappears. The remaining part of the cartilage between the mandible and ossicles also disappears, but its perichondrium persists as the anterior ligament of malleus and the sphenomandibular ligament.

The artery of the first pharyngeal arch eventually becomes the terminal portion of the maxillary artery, a branch of the external carotid. The nerve of the arch is the trigeminal nerve (CN V). The arch also gives rise to the muscles of mastication, the mylohyoid, the anterior belly of digastric, tensor veli palatani and tensor tympani. All these muscles are therefore innervated by motor branches of the trigeminal nerve. Sensory branches of the trigeminal nerve supply the skin of the face, the lining of the mouth and nose and general sensation to the anterior 2/3 of the tongue.

Anomalies of the first arch can be categorised into two main types

1. Type I anomalies are derived from the ectoderm and include duplication of the external auditory canal, usually located behind the pinna.
2. Type II anomalies involve ectoderm and mesoderm and usually manifest as a fistula along the external auditory canal, middle ear cleft or nasopharynx. These may pass adjacent to the facial nerve and terminate at the level of the anterior border of the sternocleidomastoid muscle.

First arch abnormalities can present with congenital unilateral facial palsy. They occur following a lack of migration of neural crest cells into the first pharyngeal arch. Presentation varies and facial anomalies are grouped under the diagnosis of 'first arch syndrome'. The more important are:

1. Treacher Collins syndrome (mandibulofacial dysostosis): This is inherited as an autosomal dominant trait and occurs in about 1/85,000 births. It presents with malar hypoplasia (due to underdevelopment of zygomatic bones), mandibular hypoplasia, Down slanting of the palpebral fissures and deformed auricles (Figs. 1.22, 1.23 and 1.24).
2. Pierre Robin syndrome: This is an autosomal recessive disorder which occurs in approximately 1/85,000 births. The primary defect is a small mandible. Infants present with a triad of micrognathia (small mandible), cleft palate and glossoptosis (posteriorly placed tongue).
3. Di George syndrome: This is caused as a result of a micro deletion on the long arm of chromosome 22. It results in abnormal development of the neural crest cells, notably with failure of the third and fourth pharyngeal pouches to differentiate into the thymus and parathyroid glands. The syndrome occurs in 1/25,000 births and is one of the most severe pharyngeal arch disorders. Infants lack a thymus and parathyroid glands and have cardiac outflow defects. They also have a "Fish mouth deformity" (shortened philtrum), low set notched ears and an increased susceptibility to infection (Fig. 1.25).

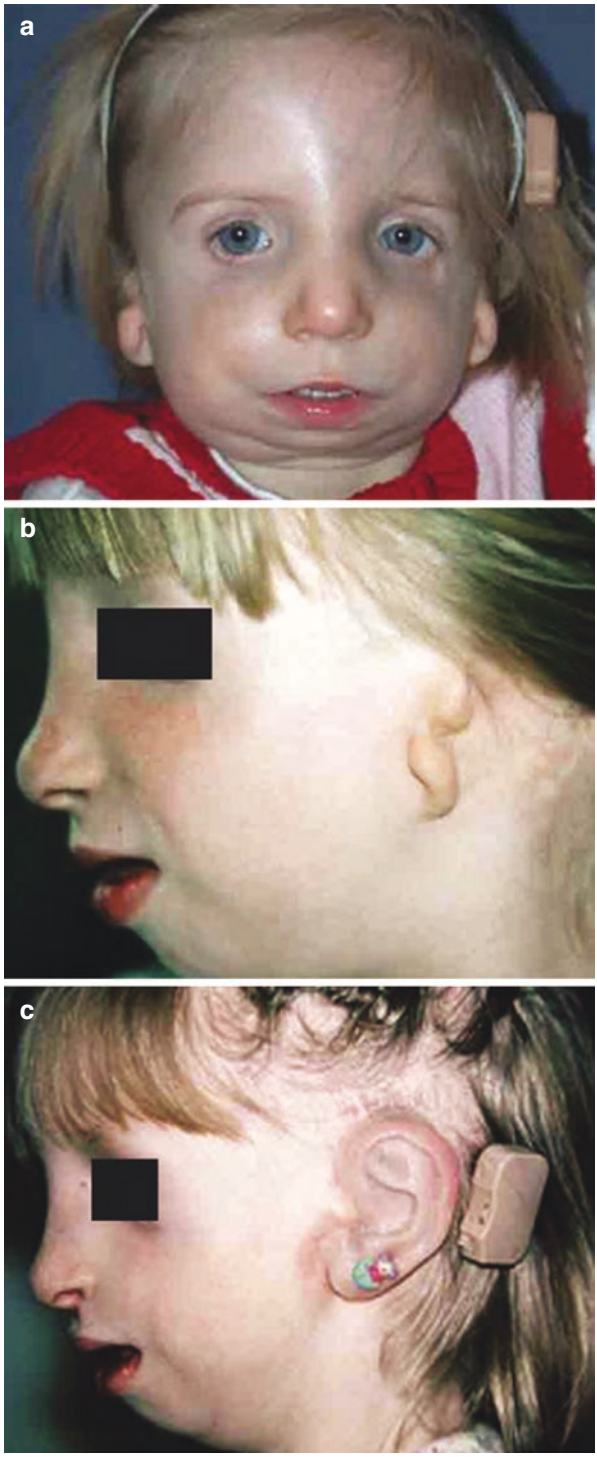


Fig. 1.22 (**a**) Child with bilateral atresia with a bone-anchored hearing aid mounted on a soft headband. (**b**) Child aged 6 years, before surgery to insert an auricular prosthesis and bone-anchored hearing aid. (**c**) The same child after placement of a bone-anchored hearing aid and bone-anchored auricular prosthesis

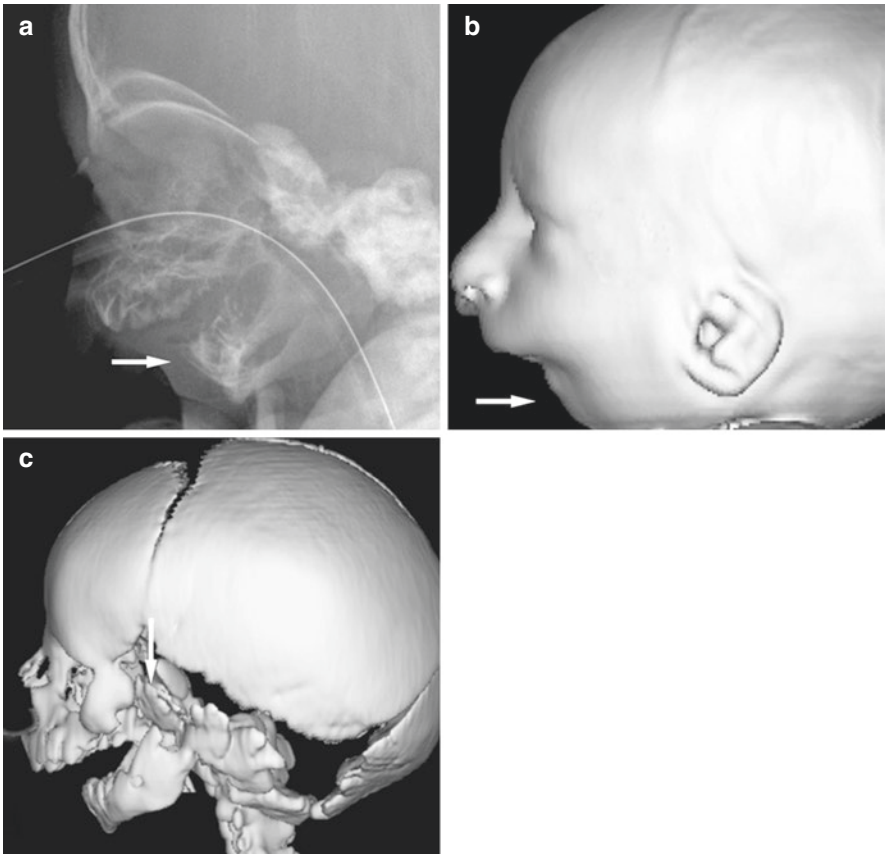


Fig. 1.23 Treacher Collins syndrome; newborn with respiratory distress. (**a**) Lateral view shows very small and retruded mandible (arrow), and air-way tube. (**b**) 3D CT image of the skin of a child, lateral view, shows severe micrognathia (arrow). (**c**) 3D CT image, lateral view of a child, shows absent zygoma (arrow)

1.7.2.2 The Second Arch

The cartilage component of this arch is called Reichart's cartilage. The dorsal end ossifies to become the stapes and more caudally the styloid process. It also becomes the stylohyoid ligament and the upper body and lesser horn of the hyoid bone. The nerve associated with the second pharyngeal arch is the facial nerve (CN VII). This innervates all the muscles derived from the arch, namely the 'facial muscles' as well as the stapedius, stylohyoid, platysma and the posterior belly of digastric. Sensation is also conveyed by the facial nerve, notably taste from the anterior 2/3 of the tongue (via the pre-trematic chorda tympani). This arch has two associated arteries

1. Stapedial artery. This connects the embryonic internal carotid, internal maxillary and middle meningeal arteries. It regresses before birth.
2. Hyoid artery—which gives rise to the corticotympanic artery in the adult.

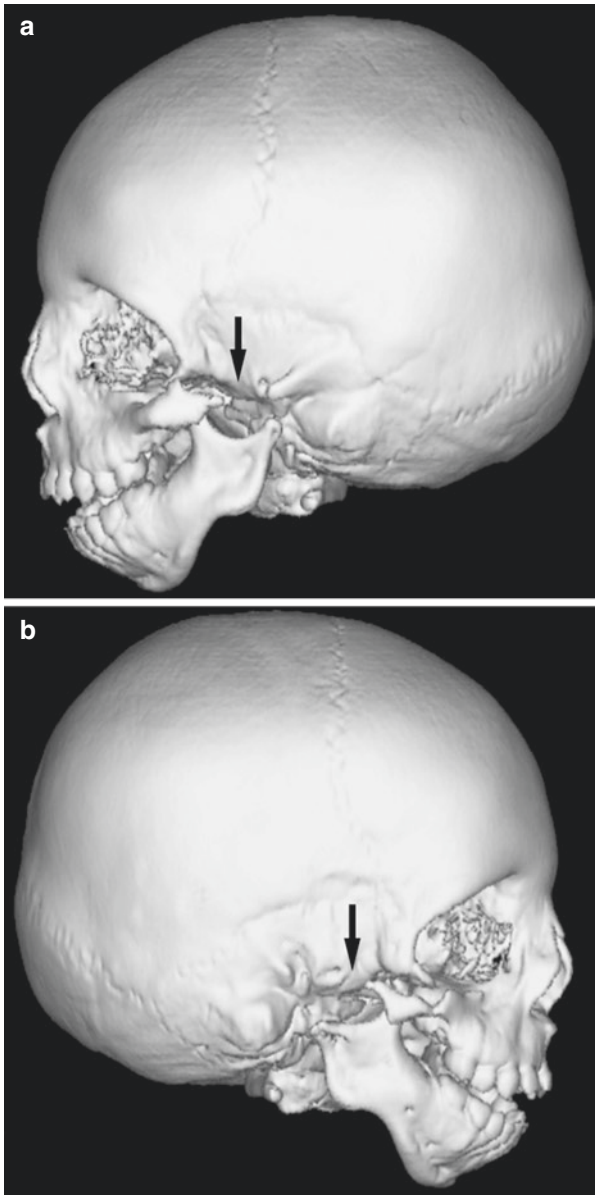


Fig. 1.24 Treacher Collins syndrome; 4-year-old male. (**a**) 3D CT image of left side of skull shows underdeveloped mandible with antegonial notching and part of zygoma with zygomatic arch absent (arrow); micrognathia with open bite, and small facial skeleton compared to skull. (**b**) 3D CT image of right side; similar absence of zygoma (arrow) and appearance of mandible as contralateral side, with the exception of a less developed condylar process

Abnormalities in the development of the second arch are more common that those of the first arch. These are usually unilateral and often present as cystic lesions, located anterior to the sternocleidomastoid muscle. These cysts are usually first noticed in the second decade of life, after puberty (when secretions of the epithelium increase). There are four main types of second arch defect, which can be classified according to location.

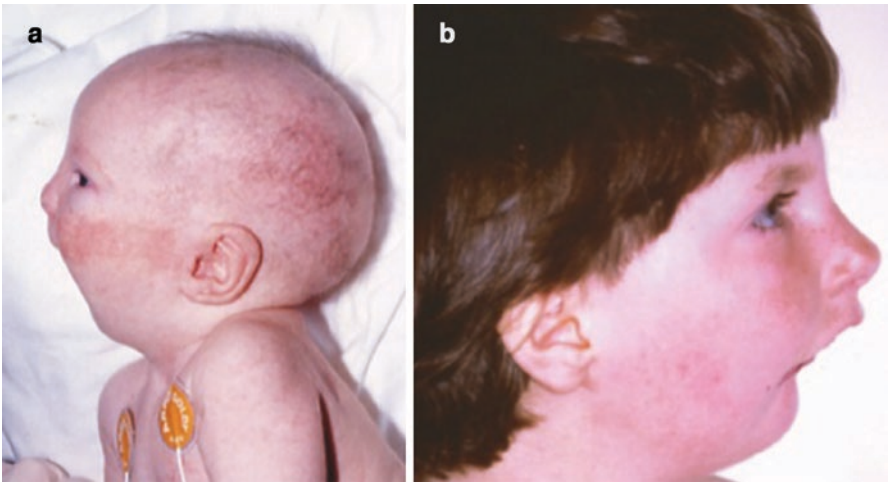


Fig. 1.25 (**a**) Micrognathia. (**b**) Pierre Robin syndrome

1. Type I defects are found anterior to the sternocleidomastoid muscle at the junction of the middle and lower thirds. They are usually deep to the platysma muscle.
2. Type II defects are found adjacent to the great vessels and can compress them if they grow large enough. These are common.
3. Type III defects course between the internal and external carotid arteries and extend laterally. They are usually superior to the glossopharyngeal and hypoglossal nerves.
4. Type IV defects are very rare and are located next to the pharyngeal wall.

Branchiootorenal syndrome is a second arch syndrome and is seen in approximately 2–3% of all deaf children. Features include deafness, auricular malformations, pharyngeal fistulae and renal problems. Some of the external pinna abnormalities involve tags, microtia and preauricular sinuses. There have also been reports of defects in the facial nerve and ear ossicles.

In rare instances, a midline cervical cleft is observed, and is believed to derive from incomplete fusion of the second and third pharygeal arches. It presents at birth and releases a serous discharge.

1.7.2.3 The Third Arch

The cartilaginous component of this arch is less complex than the first two arches, giving rise to the lower body and greater horn of the hyoid. Its associated cranial nerve is the glossopharyngeal nerve (CN IX). Its sensory function is to provide taste and general sensation to the posterior 1/3 of the tongue. The third arch also gives rise to stylopharyngeus muscle. The artery of the third pharyngeal arch becomes the common carotid artery and the proximal portion of the internal carotid artery. Defects of the third (and fourth) arches are difficult to delineate and are rare. Most third arch abnormalities manifest on the left side and present either as a neck abscess or as acute thyroiditis.

1.7.2.4 The Fourth Arch

The fourth arch gives rise to all the laryngeal cartilages (thyroid, cricoid, arytenoid, corniculate and cuneiform cartilages) except the epiglottis, which develops from the caudal part of hypobranchial eminence. The fourth arch's associated nerve is the superior laryngeal branch of the vagus nerve (CN X), which innervates the arch's muscular derivatives—the pharyngeal constrictors, levator palatini and cricothyroid. Sensation to a small area of the root of the tongue is provided by the superior laryngeal branch. The vascular derivatives of the fourth pharyngeal arch arteries in adults differ between the right and left.

1. Right—proximal portion of the subclavian artery
2. Left—part of the aortic arch

Defects of the fourth arch thus differ on the left and right sides according to these vascular derivatives. Fistulae or sinuses that develop on the right side pass beneath the subclavian artery and between the superior and recurrent laryngeal nerves, whereas on the left, similar abnormalities pass beneath the aorta and posterior to the common carotid artery. Usually sinuses or fistulae developing from the fourth arch will involve the thyroid gland or the cervical oesophagus. These can present with either abscess or stridor due to the pressure effects on the surrounding structures.

1.7.2.5 The Sixth Arch

The adult vascular derivatives of this arch also differ between the left and right:

1. Left—ductus arteriosus
2. Right—proximal portion of the pulmonary arteries

The associated nerve to this arch is the recurrent laryngeal nerve, a branch of the vagus nerve. As embryonic development progresses, the right and left recurrent laryngeal nerves take different paths within the thorax. On the left, the recurrent laryngeal nerve has a longer course than the right. This is because it hooks under the left arch artery (ductus arteriosus), whist on the right side, neither the sixth or fifth arch arteries persist and so the right nerve is restrained only by the fourth branchial arch artery (subclavian). As the heart descends and the neck elongates, the left nerve is therefore 'dragged' downwards into the developing thorax, hooked around the ductus arteriosus. Rarely, the right fourth branchial arch artery does not develop and the right recurrent laryngeal nerve is not restrained by the subclavian artery. It therefore divides from the vagus more superiorly. This anomalous nerve may therefore be damaged during thryoid surgery.

The recurrent laryngeal nerves innervate the intrinsic muscles of the larynx (except cricothyroid), which are derived from the sixth arch. Sensation is extensive and includes taste sensation from the epiglottis and pharynx, general sensation from the pharynx, larynx, oesophagus, tympanic membrane, external auditory meatus and part of the external ear. The recurrent laryngeal nerve also provides the efferent limb of the gag reflex and parasympathetic innervation to the viscera.

1.7.3 Pharyngeal Pouches

The pharyngeal pouches separate the pharyngeal arches on their inner (endodermal) surfaces. There are five pairs of pouches, with only four giving rise to adult structures.

1. First arch pouch—Eustachian tube and middle ear cavity
2. Second arch pouch—Lining of the palatine tonsils (tonsillar fossa)
3. Third arch pouch—the inferior parathyroid glands and the thymus
4. Fourth arch pouch—the superior parathyroid glands and possibly the parafolicular C cells (via the ultimobranchial body—see the fifth arch pouch).
5. Fifth arch pouch (ultimobranchial pouch). This is a transitory structure, like the fifth arch. However, in some lower animal species it develops into the "ultimobranchial body". In humans this structure joins the fourth pouch to form the 'caudal pharyngeal complex'. Parafollicular "C" cells of the thyroid may arise from this complex, although some authorities believe that they arise from the neural crest. The term ultimobranchial body should therefore not really be used in reference to humans as it only exists as a true entity in lower animal species. C cells secrete thyrocalcitonin, which stimulates deposition of the calcium in the bones.

Persistence of the pharyngeal pouches and grooves may give rise to structural abnormalities later in life, including cysts, sinuses, and fistulas, all of which are lined with epithelium. Cysts are enclosed cavities, whereas sinuses are open at one end and fistulas are open at both ends. The fistula and sinus openings are usually located anterior to the sternocleidomastoid muscle, but the precise location is determined from the structure it originates from.

Persistence of the thymus gland may develop from the third pharyngeal pouch, and is usually caused by incomplete descent of the thymus into the chest, or deposition of thymic tissue along its path of descent. Sometimes there is complete failure of the thymus gland to regress. These processes can lead to thymic cysts or a cervical thymus gland. When deposition of thymic cells occurs, there might be a collection of cysts that form along the descent tract. These sometimes contains thyroid or parathyroid cells. The cysts manifest during childhood and grow over time. Respiratory obstruction, mass effects or dysplasia may occur. Some patients can present with myasthenia gravis, a disorder with a known association with thymus neoplasms.

1.7.4 Pharyngeal Membranes

There are four pharyngeal membranes (1, 2, 3, and 4), located between the pharyngeal arches. These are initially formed by two layers (1) an inner endodermal lining from the associated pharyngeal pouch and (2) an outer ectodermal lining from the associated pharyngeal cleft. These two layers become separated by a thin layer of

mesoderm to form three layers. Only the first pharyngeal membranes persist (as the tympanic membrane). The remaining membranes disappear.

1.7.5 Cervical Sinus

The mesenchyme of the second pharyngeal arch rapidly expands and grows downward, such that the arch overlaps the second, third and fourth pharyngeal clefts. This later fuses with the epicardial ridge lower down. Thus, the second, third, and fourth pharyngeal clefts get buried under its surface. These join together to become a slit-like cavity lined by ectoderm—the cervical sinus. The sinus normally disappears as the neck continues to develops, however failure of the sinus to obliterate can result in the formation of a branchial cyst. This is described further in the chapter on the neck. Rupture of the cyst can result in the development of a branchial fistula. Fistulas may also arise following persistence of the pharyngeal grooves and incomplete closure of the cervical sinus. These may not clinically manifest until puberty, when they then expand as a result of increased epithelial secretions.

1.7.6 Development of the Face

The face develops from five 'facial prominences' that appear around the primitive mouth in the fourth week. These are derived from the first and second pharyngeal arches. They are composed mainly of mesenchyme derived from the neural crest.

1. The frontonasal prominence is a midline structure. This is formed by proliferation of mesenchyme ventral to the forebrain vesicle and forms the central part of the upper border of the stomodeum (primitive oral cavity). It is derived from nearby neural crest cells, which migrate from the ectoderm as the forebrain develops. These cells invade the adjacent space, becoming the frontonasal prominence. Structures derived from the frontonasal process are supplied by the ophthalmic nerve (V1).
2. The right and left maxillary and mandibular prominences are derived from the first arch. They surround the rest of the developing stomodeum. The maxillary prominence is above and lateral to the stomodeum, while the mandibular prominence is below it. These then fuse together. Structures derived from the maxillary processes are supplied by maxillary nerve (V2) whilst those derived from the mandibular processes are supplied by the mandibular nerve (V3) (Fig. 1.26 and 1.27).

During this time, nasal placodes develop on the frontonasal prominence within the overlying ectoderm. These thicken and sink in to form nasal pits, which deepen to form the nasal sacs. At the same time, the mesoderm proliferates around the placodes, to form the medial and lateral 'nasal prominences'. As the maxillary prominences continue to grow they fuse in a 'zip-like' fashion with the mandibular

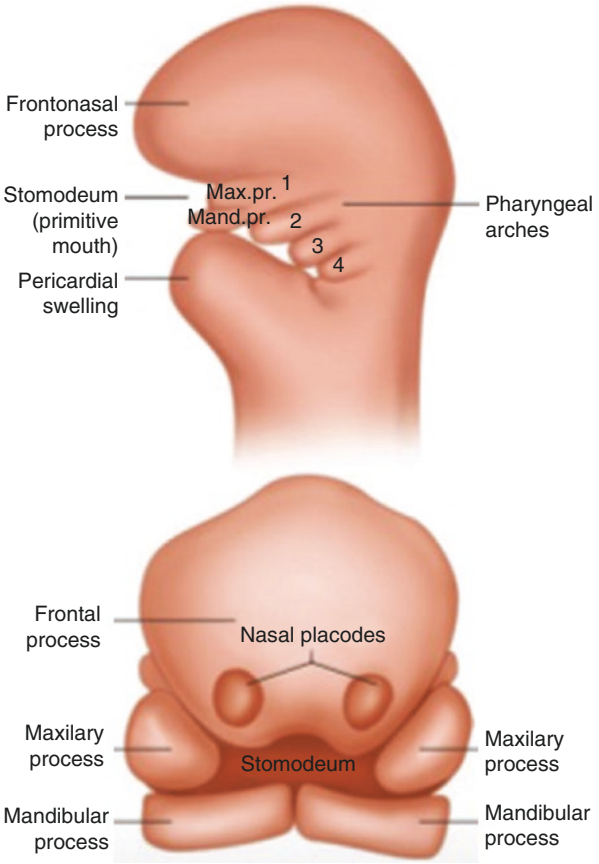


Fig. 1.26 Development of the face

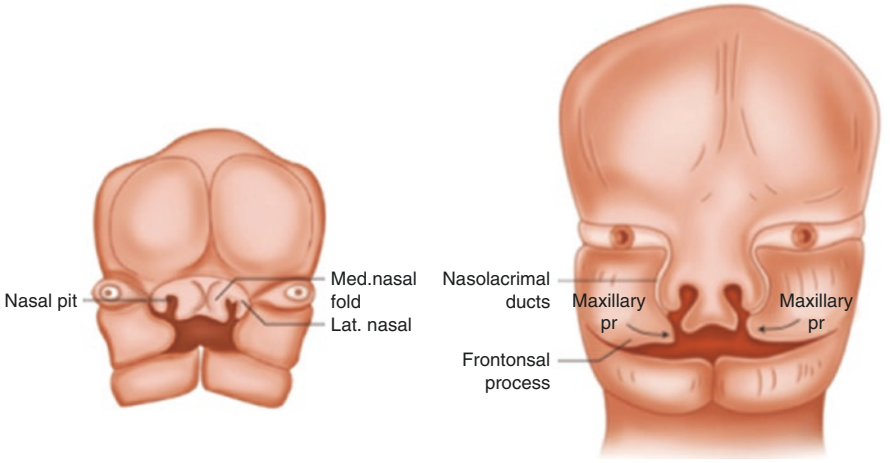


Fig. 1.27 Development of the face 2

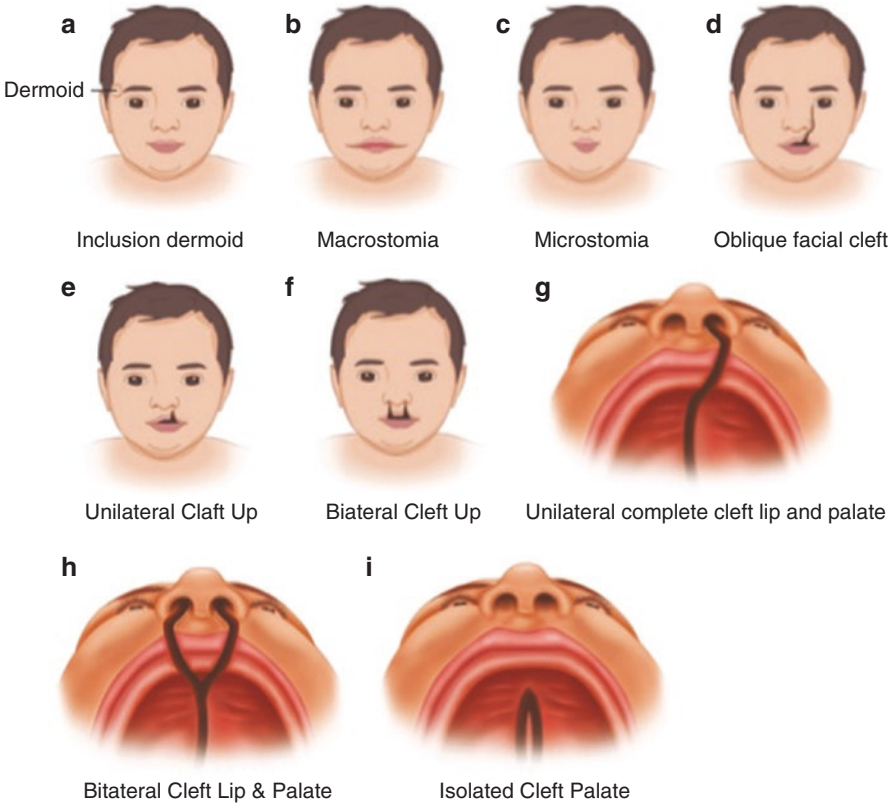


Fig. 1.28 (**a**–**f**) Congenital anomalies of the face and palate

prominences laterally, to form the cheeks. Further growth compresses the medial nasal prominences, resulting in fusion at around the tenth week of development. Thus the bridge of the nose and the 'intermaxillary segment' (both derived from the medial nasal prominence) are established. The intermaxillary segment will later develop into the central portion of the upper lip and the premaxilla. The lateral nasal prominence gives rise to the alae of the nose and also fuses with the maxillary prominence, except at the site of the nasolacrimal duct. The lacrimal and nasal bones here are derived from neural crest cells.

Facial clefting can occur when there is incomplete fusion between the five facial prominences. This can be partial or total. It can be unilateral or bilateral and is also a common feature in many congenital syndromes. The commonest clefting anomalies are cleft lip and cleft palate, but oblique facial clefting, microstomia, and macrostomia have also been described. Very rarely the two mandibular processes fail to fuse in the midline to cause cleft lower lip (Fig. 1.28, 1.29 and 1.30).

Cleft lip is most commonly seen in the upper lip and the incidence is approximately 1 in 1000 births. It is more common in males. The cleft forms when the

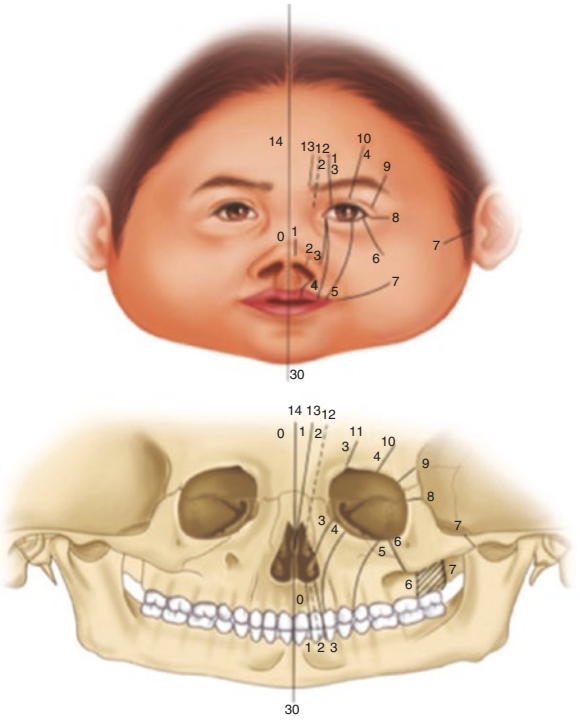


Fig. 1.29 Tessier clefting system. (**a**) Soft tissue clefts. (**b**) Bony clefts. Dotted lines represent uncertain localisation or uncertain clefting. Note that the northbound cranial line has different number than its counterpart southbound facial line. This system is descriptive and anatomic. It avoids aetiology and pathogenic speculation (Tessier P. J Maxillofac Surg 4:69, 1976) [1]

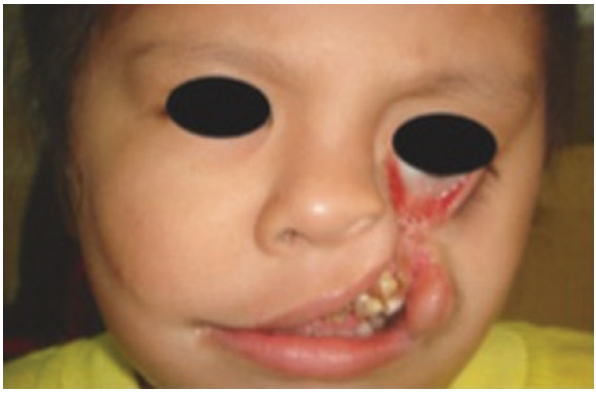


Fig. 1.30 Child with a right-sided Tessier 7 cleft with macrostomia and ridge in soft tissue of cheek, left-sided Tessier 4 cleft. Note the nostril elevation, absent eyelashes medially and hypoglobus. The cleft involves the maxilla and orbit

maxillary prominence fails to fuse with the intermaxillary processes. Specifically, there are three main types:

1. Unilateral cleft lip—This occurs due to failure of fusion of the maxillary process with the medial nasal process.
2. Bilateral cleft lip: This occurs due to failure of fusion of maxillary processes with the frontonasal process.
3. Central cleft lip/hair lip: This occurs due to failure of development of philtrum of the upper lip from the frontonasal process (Fig. 1.31).

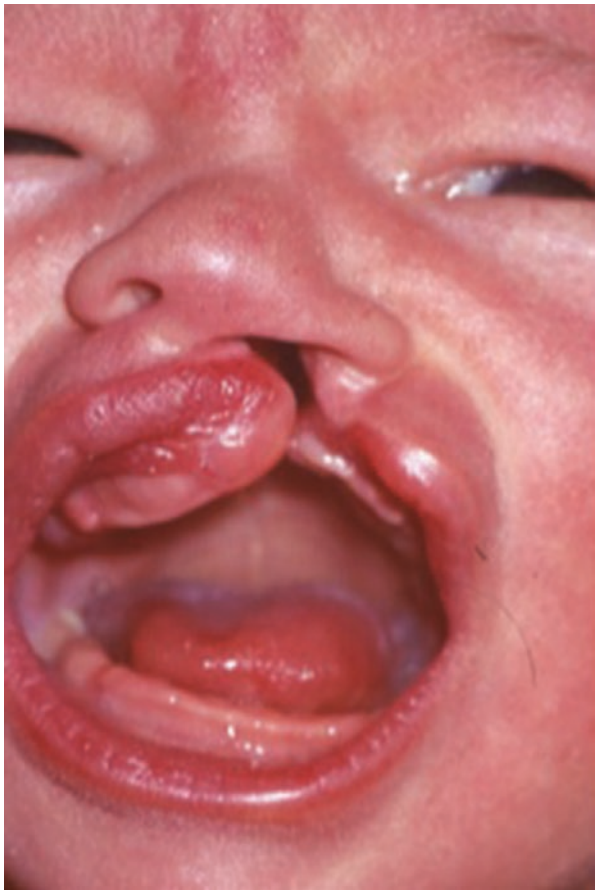


Fig. 1.31 Cleft lip intact palate

Severity of cleft lip varies considerably. In the most severe cases it completely separates the lateral lip from the philtrum and nasal cavity. Some cleft lips only involve the soft tissues, but sometimes the deformity can extend to the maxillary bone and can lead to dental deformities.

Cleft palate is formed when there is a failure of fusion of the palatal shelves along the midline. This is more common in females. This is described further in the chapter on the mouth. Bilateral complete cleft palate occurs if both maxillary processes fail to fuse with the premaxilla. The palate is divided in two by a midline cleft, with an anterior V-shaped cleft separating the premaxilla completely. Incomplete cleft palate is characterised by the presence of a bifid uvula or cleft of the soft palate. Failure of fusion of the palatal shelves may be due to a number of developmental anomalies including poor growth of the shelves themselves, inadequate elevation of the shelves or failure of the shelves to fuse.

Oblique facial clefts are rare congenital deformities which occur when the maxillary process fails to fuse with the lateral nasal process. A fissure persists between the inner corner of the eye and the upper lip, with exposure of the nasolacrimal duct.

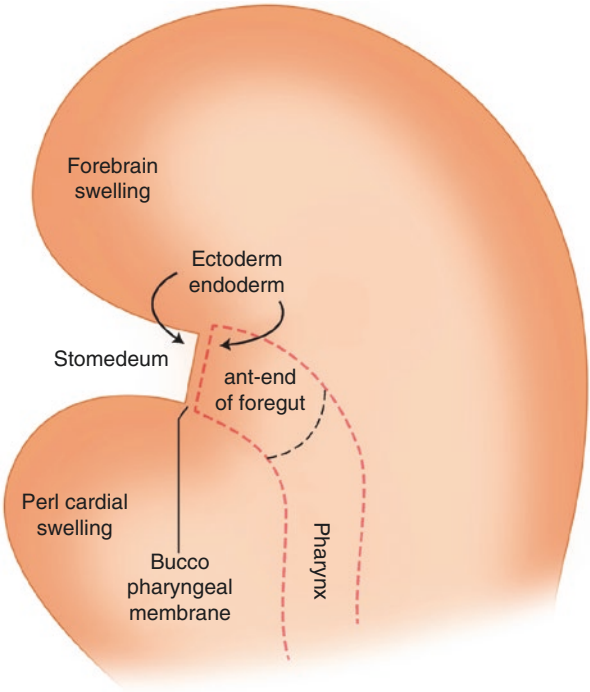


Fig. 1.32 Embryology of the oral cavity

This usually occurs bilaterally. Abnormalities of the side of the mouth can also occur following abnormal fusion between the maxillary and mandibular processes, resulting in lateral facial clefts. The oral commissures (corners of the mouth) are formed at the junction of the maxillary and mandibular processes. Initially they are sited laterally, close to the auricle. During normal development the commissures gradually shift medially as the maxillary and mandibular processes fuse in a zip-like fashion. Excessive fusion results in microstomia (small mouth), whilst failure to fuse fully results in macrostomia (large mouth) (Figs. 1.32 and 1.33).

1.7.7 The Paranasal Sinuses

These develop later during foetal life and do not reach adult size until the age of 12. The maxillary sinuses develop from invaginations of the nasal cavities at around birth and undergo rapid growth until the age of 6 years. A second growth spurt from the age of 7 then takes place. Chronic rhinosinusitis in childhood may affect this development, resulting in maxillary sinus hypoplasia. If severe this can also affect the shape of the orbit and ethmoids. The sphenoid sinuses also develop from birth. At the age of 6 the "presphenoid" is pneumatised. By the age of 12 this has extended below the sella turcica and may include the anterior clinoid and pterygoid processes. With extensive pneumatisation the optic nerves can enter the sinus cavity—this is important to remember during endoscopic sinus surgery. The ethmoid sinuses are

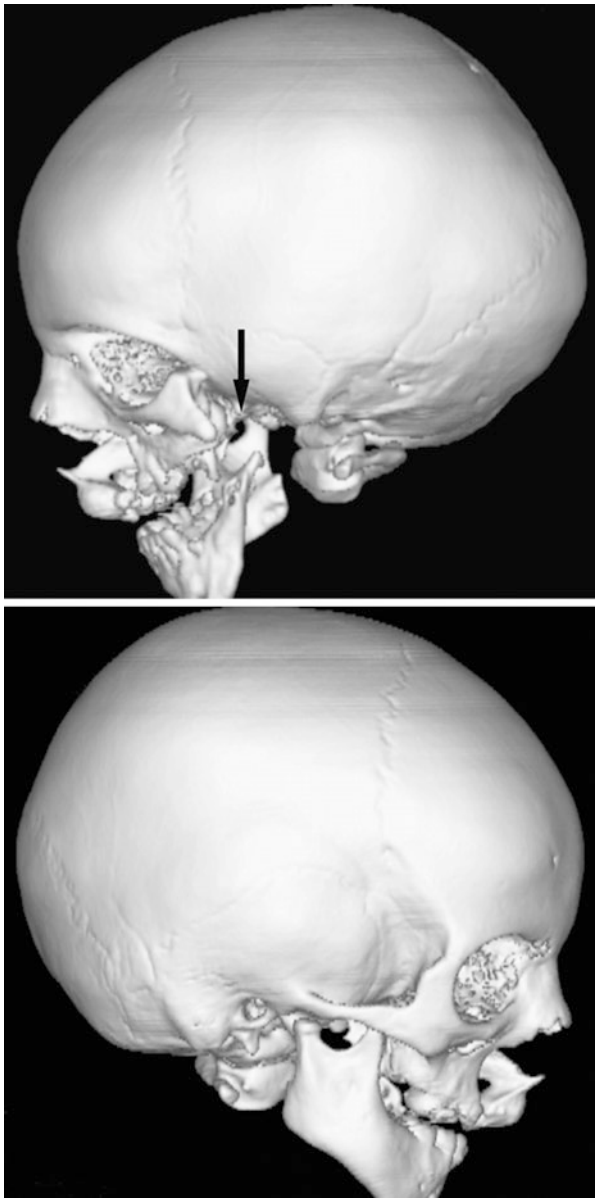


Fig. 1.33 Hemifacial microsomia; 4-year-old male with multiple anomalies including cleft palate and lip. (**a**) 3D CT image, lateral view, shows left-sided severely hypoplastic mandible and absent zygomatic arch (arrow). (**b**) 3D CT image, lateral view, shows normal right side for comparison

developed by the time of birth. Initially fluid filled, these become air-filled during the first year. Pneumatisation can vary widely. The frontal sinuses are the last sinuses to develop. These arise when the ethmoid recesses extend beyond the superior orbital rims, usually at the age of 6. In essence the frontal sinus is a variant of pneumatisation of the ethmoid sinuses. Aplasia and hypoplasia of the frontal sinuses is common.

1.8 Muscles of Head and Neck

The head and neck musculature is also partially derived from 'somitomeres' 1–7 in the head and neck region. These also contribute to the formation of the pharyngeal arches. The mesoderm of each pharyngeal arch is thus derived from two sources

1. Paraxial mesoderm (see below) which gives rise to most of the muscles of head and neck region.
2. Neural crest cells which give rise to the skeletal elements and connective tissues of the head and neck region (discussed above) (Figs. 1.34, 1.35 and 1.36).

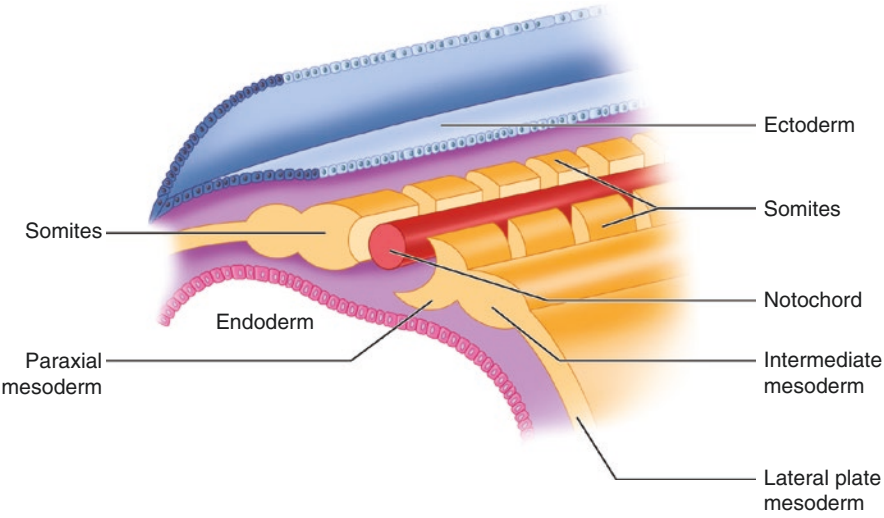


Fig. 1.34 Segmentation of the paraxial mesoderm into somites

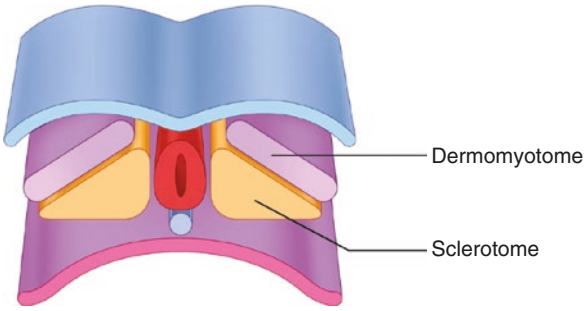


Fig. 1.35 Differentiation of the somites

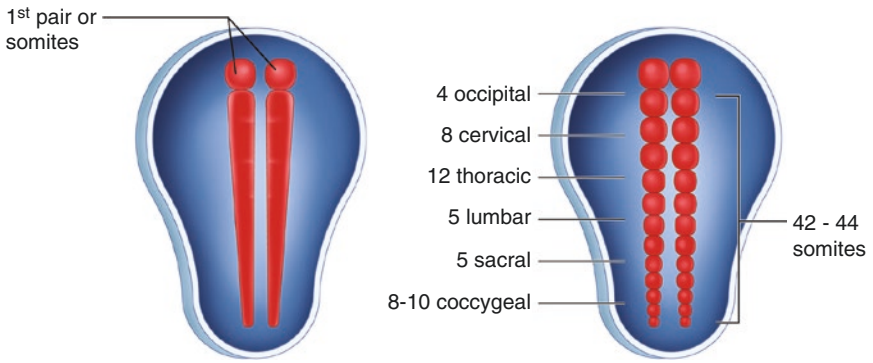


Fig. 1.36 Arrangement of the somites

1.8.1 Myotomes

A myotome is defined as a group of muscles that are innervated by a single spinal nerve root. This is clinically useful when determining whether damage has occurred to the spinal cord and if so, at which level. Skeletal muscle development begins with the appearance of somites. During the trilaminar stage, the middle layer (mesoderm) on either side of neural tube divides into three parts. These are the paraxial mesoderm, intermediate mesoderm and lateral plate mesoderm. The part that is directly adjacent to the neural tube is called paraxial mesoderm.

From about day 20 the paraxial mesoderm differentiates into segments called 'somites'. 44 pairs are initially formed, but 13 break down later, leaving 31 pairs of somites. Initially there are 4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and from 8 to 10 coccygeal. Caudal to the occipital region, the number of somites subsequently corresponds to the number of spinal nerves in the region. Thus, there are eventually 8 cervical, 12 thoracic, 5 lumbar, and 5 sacral somites, corresponding to same number of spinal nerves in these regions. Each somites is comprised of a ventral and a dorsal portion. The ventral portion consists of the 'sclerotome', the precursor to the ribs and vertebral column. The dorsal portion consists of the 'dermomyotome'. As the embryo continues to develop the myotomes proliferate and eventually develop into muscle. Most muscles in the upper and lower limbs are composed of multiple myotomes and therefore receive innervation from more than one spinal nerve root. For example, the biceps brachii muscle is innervated by the musculocutaneous nerve, which is derived from C5, C6 and C7 nerve roots. All three of these spinal nerve roots are associated with action of the muscle. With regards to the head and neck:

1. The extraocular muscles develop from three 'preotic myotomes', (Somitomeres 1–3), that are arranged around the developing eye. These myotomes are innervated by the IIIrd, IVth, and VIth cranial nerves, hence the extraocular muscles are supplied by IIIrd, IVth, and VIth cranial nerves.

2. The muscles of the tongue develop from precervical somites called ‘occipital myotomes’. These are innervated by the hypoglossal nerve. As the tongue develops in the floor of pharynx, the occipital myotomes migrate forwards and enter the tissues of the developing tongue to form the majority of its musculature, with the exception of palatoglossus. Thus, the long hypoglossal nerves supply the tongue muscles.
3. The muscles of the pharyngeal arches also develop from mesoderm that is derived from somitomeres. These include the muscles of mastication, facial expression, pharynx, and larynx. They are innervated by the associated nerves of the respective pharyngeal arches.
4. The stylopharyngeus muscle arises from seventh somitomere of the third arch and is supplied by the nerve of the third arch, the glossopharyngeal.
5. The laryngeal muscles are derived from occipital somites 1 and 2. These arise from the fourth and sixth pharyngeal arches and are thus supplied by the branches of vagus.

Congenital muscular torticollis is a term that describes a shortened tight sternocleidomastoid muscle, and is thought to be due to fibrosis within the muscle. The aetiology is unclear, but it is thought to be caused by crowding within the uterus, or injury during birth. Physiotherapy during the first weeks of life can help to gradually lengthen the muscles. Aglossia and microglossia are very rare anomalies, often associated with malformations in the extremities, cleft palate and dental agenesis. There develops a rudimentary, small tongue. As a consequence the alveolar arches do not develop transversely and the mandible does not fully develop, resulting a severe facial deformity. The cause is believed to be trauma during the first few weeks of gestation. A completely cleft or bifid tongue is another rare condition due to a lack of mesenchymal proliferation and merging of the lingual swellings. It is often found as one feature of the oral-facial-digital syndrome.

1.8.2 Dermatomes

A dermatome is defined as an area of skin that is innervated by a single spinal nerve. Along with myotomes, this is also of great diagnostic importance in determination as to whether there is damage to a cranial nerve or the spinal cord. Dermatomes develop in the third week. Following the development of the somites, the dorsal portion of each consists of the dermomyotome. Each dermatome migrates to form the dermis, taking its respective innervation along with it. Dermatome maps depict the dermatomes according to their segmental distribution. This is a commonly used map in the assessment of spinal injuries.

1.8.3 The Skull

Further details of this are described in the chapter on the head. The skull develops from mesenchyme around the developing brain. It is divided in two parts (1) the

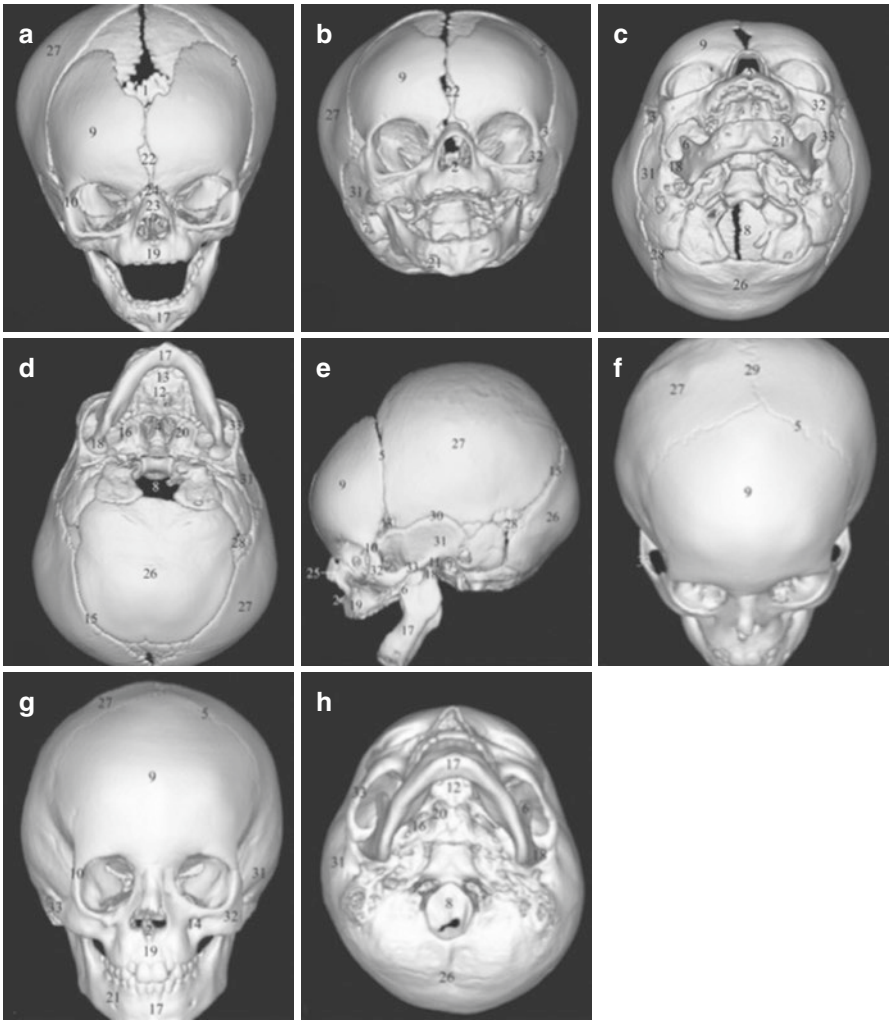


Fig. 1.37 Normal 3D CT bone anatomy of the face and skull; (**a**–**e**) 7-month-old, (**f**–**h**) 8-year old

neurocranium, that encloses and protects the brain and (2) the viscerocranium, that forms the skeleton of the face. The neurocranium consists of a cartilaginous skull base and a membranous cranial vault. The cartilaginous base of skull is formed by chondrification in the mesenchyme below the brain. It subsequently ossifies. The vault develops from the surrounding mesenchyme, derived from the neural crest cells and paraxial mesoderm. This undergoes membranous ossification to form a number of flat membranous bones, separated by the sutures and fontanelles (Fig. 1.37).

Following birth, rapid enlargement and changes in the curvature of the cranial vault occurs in response to further expansion of the brain. The periosteum of the bones contains cells which can differentiate into osteoblasts and osteoclasts. Changes in the shape and size of the calvarium is achieved by remodelling on the

extracranial and intracranial surfaces. By the age of 2, the brain and cranial vault have achieved about three quarters of their full growth. Most of the enlargement of the cranial vault is completed by around 8 years of age as a result of sutural growth and remodelling. After 8, growth is restricted to thickening of the bones and enlargement of the superciliary ridges. As growth slows and ceases the sutures develop 'interlocking fingers' of bone which subsequently makes the cranial vault very strong. Many abnormalities of skull shape related to disturbances in sutural growth have been described. These are known as synostoses. Examples include:

1. Scaphocephaly: Boat-shaped skull due to frontal and occipital expansions. It occurs due to premature fusion of the sagittal suture.
2. Brachiocephaly: Short skull due to premature bilateral fusion of the coronal suture.
3. Plagiocephaly: This occurs following premature fusion of the coronal and lambdoid sutures on one side only. This results in unequal curvatures of skull.
4. Acrocephaly: Pointed skull due to premature fusion of the coronal suture.
5. Microcephaly: Small skull due to failure of proper development of the brain.
6. Oxycephaly (turricephaly or acrocephaly): A tower-like skull caused by premature closure of the lambdoid and coronal sutures.
7. Kleeblattschädel: This is a clover leaf skull caused by premature closure of all the sutures, forcing the brain herniate and grow through the anterior and sphenoid fontanelles.
8. Crouzon syndrome. This is an autosomal dominant disorder caused by a mutation in the gene that encodes for fibroblast growth factor receptor 2. Clinical features include premature craniosynostosis, midface hypoplasia with shallow orbits, ocular proptosis, mandibular prognathism, progressive hydrocephalus but without mental retardation (Figs. 1.38 and 1.39).
9. Apert syndrome. This is also an autosomal dominant disorder. Clinical features include craniosynostosis leading to turribrachycephaly, syndactyl of hands and feet, various ankyloses, progressive synostoses of the hands, feet, and cervical spine and mental retardation.
10. Pfeiffer syndrome. An autosomal dominant genetic disorder resulting in craniosynostosis leading to turribrachycephaly, syndactyl of hands and feet and broad thumbs and great toes.
11. Schuller-Christan Syndrome: There are large defects in the skull bones (Figs. 1.40 and 1.41).

1.9 Arterial Development

As the pharyngeal arches develop, each receives a specific artery derived from the developing aortic sac. Thus, the aortic sac gives rise to six pairs of aortic arch (pharyngeal) arteries. These have been previously noted. The fifth pair soon disappears along with its corresponding arch. The remaining five aortic arch arteries are numbered I, II, III, IV, and VI. Each artery is embedded in the mesenchyme of its

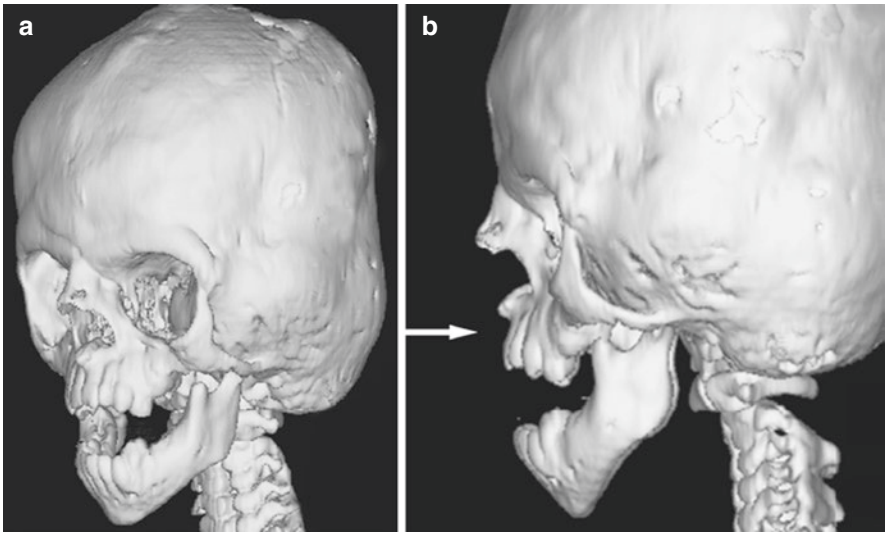


Fig. 1.38 Crouzon syndrome; 2-year-old. (**a**) 3D CT image, oblique view, shows superior elongation of skull and typically "opened mouth". The maxilla and zygomas are hypoplastic. (**b**) 3D CT image, lateral view, shows maxillary hypoplasia (arrow)

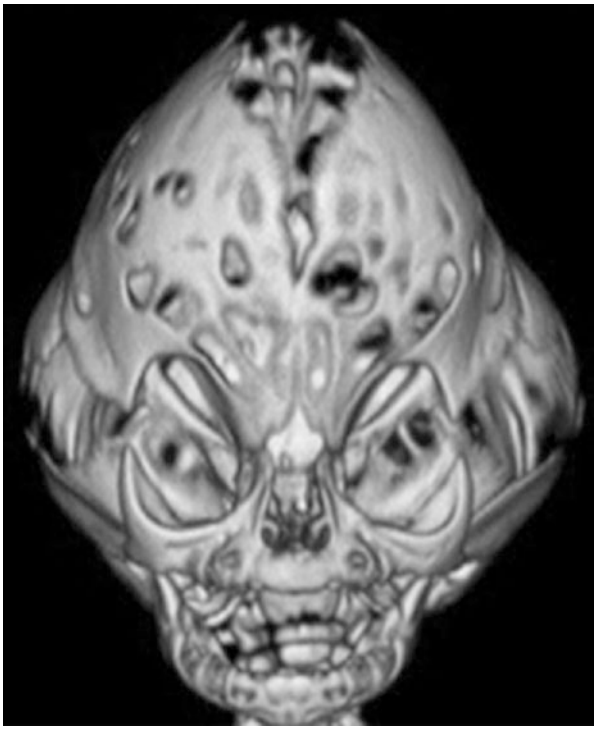


Fig. 1.39 Picture of 3D CT skull showing cloverleaf skull (kleeblattschädel deformity)

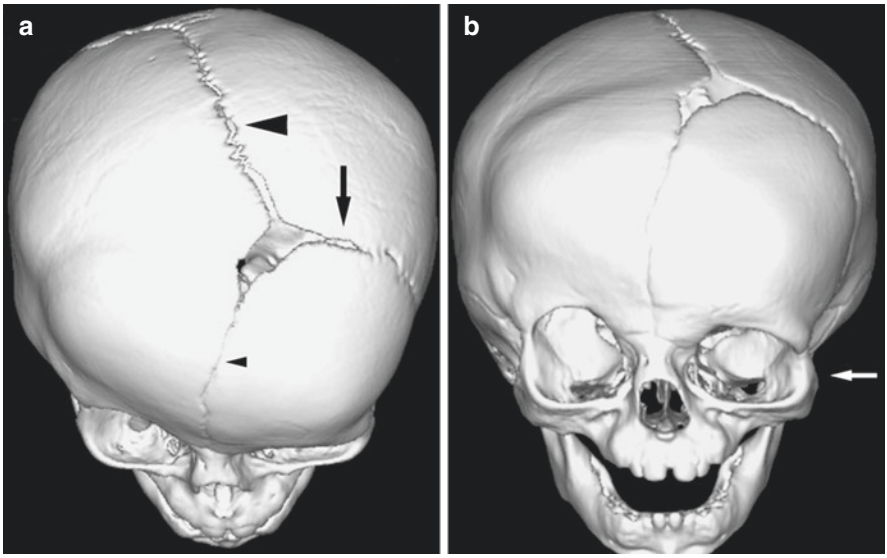


Fig. 1.40 Premature unilateral synostosis, 7-month-old male. (**a**) 3D CT image shows closure of right side of coronal suture but left side open (arrow), as is sagittal suture (large arrowhead). Anterior fontanelle open and metopic suture closed but can be seen (small arrowhead). Asymmetric deformity of anterior part of head. (**b**) 3D CT image shows evident asymmetry of right and left orbita (arrow) due to the abnormal growth

pharyngeal arch. The major arteries of the head, neck (and thorax) are derived from (1) the aortic (pharyngeal) arch arteries and (2) the aortic sac and its right and left "horns". Each of these arteries eventually regress to some extent as follows

1. The greater part of the first arch artery disappears, a small part remaining as the maxillary artery.
2. The greater part of second arch artery disappears. Its remaining part forms the hyoid and stapedial arteries in foetal life.
3. The third, fourth and sixth arch arteries open into the aortic sac. Each third arch artery gives off a bud that grows cranially to form the external carotid artery. The sixth arch artery on each side also gives off an artery to the developing lung bud. On the left side, a portion of this remains to form the ductus arteriosus.
4. On the right side, the third and fourth arch arteries arise from the right horn of aortic sac to form the brachiocephalic artery. As a result, the right common carotid artery and right subclavian artery appear as branches of the brachiocephalic artery.

Angiogenic factors stimulate growth of these major vessels. These are usually inhibited once the vessels have developed to an appropriate size. If these angiogenic factors fail to be inhibited, this can lead to continued growth of the blood vessels and congenital haemangiomas. Haemangiomas are the commonest tumours of infancy. Haemangiomas tend to grow in proportion with the child's growth. The vast

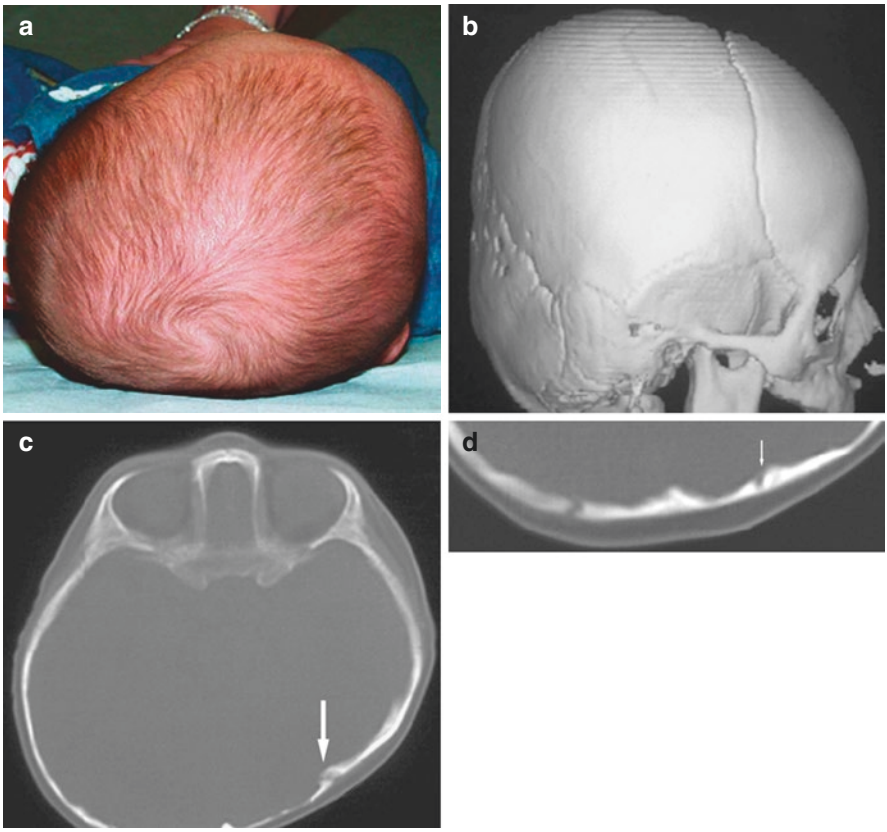


Fig. 1.41 Occipital plagiocephaly unrelated to craniosynostosis; patent lambdoid suture. (**a**) Baby sleeping supine on one side. (**b**) 3D CT image shows flat head. (**c**) Axial CT image shows patent suture (arrow) but left occipital plagiocephaly. (**d**) Axial CT image shows complete closure of lambdoid suture (arrow) representing true lambdoid craniosynostosis from different patient for comparison

majority remain benign, but occasionally they may differentiate into a haemangiosarcoma. Their location will also determine their clinical significance. Five classes of haemangioma are often described:

- Type I—Birth marks such as stork bite and naves flammus
- Type II—Formed from capillaries in the dermis, includes salmon patches, port wine stains, and congenital spider angiomas
- Type III—Capillary haemangiomas manifesting during childhood including strawberry marks, strawberry haemangiomas, and capillary cavernous haemangiomas
- Type IV—arteriovenous fistulas
- Type V—arteriovenous malformations and capillary haemangiomas

Syndromes involving haemangiomas include Von-Hippel-Lindau disease, Maffucci syndrome, Sturge-Weber syndrome, and Kasabach-Merritt syndrome.

Hydranencephaly results from bilateral widespread hemispheric infarction secondary to occlusion of the internal carotid arteries in utero. The hemispheres are replaced by hugely dilated cystic cavities. The brain stem and cerebellum are usually spared because the vertebrobasilar circulation is not affected. Other causes of this devastating condition include toxoplasmosis, rubella, cytomegalovirus, and herpes virus.

1.10 Understanding Congenital Anomalies

In addition to genetic defects, exposure to chemicals, drugs, viruses and other factors during development can result in a wide variety of anomalies. In severe cases early development fails completely and leads to miscarriage. Other severe anomalies may result in a still birth. In other cases exposure during the embryonic period can result in congenital malformations. Vertically transmitted infections can be passed from the mother to the unborn child at any stage of development. Teratomas and other types of tumour are thought to be related to primitive streak remnants, which would ordinarily disappear. In the head and neck a wide variety of disorders are therefore possible as a result of failure of the various processes of proliferation, differentiation, regression and migration (Fig. 1.42).

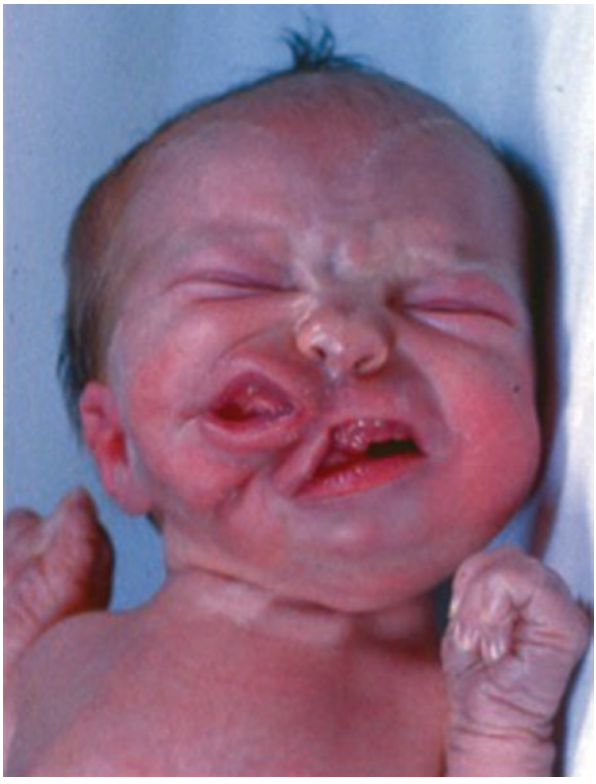


Fig. 1.42 Mouth duplication

Some of these congenital anomalies are described throughout this book. Cysts include thyroglossal duct cysts, which usually present during childhood in the first decade. These arise from persistence of the thyroglossal duct, which is an epithelial tract formed for descent of the thyroid during development. These cysts are usually soft, non-tender, and are mobile. Classically they move on swallowing. The commonest type is the infrahyoid type, but there are five other types based on its location in the midline of the neck (suprahyoid, juxtahyoid, suprasternal, intralaryngeal, intralingual). Sometimes these cysts may become infected and lead to abscess, which can cause respiratory obstruction if severe (Fig. 1.43).

Ectopic thyroid tissue is another relatively common abnormality, and can arise from the median "anlage" (precursor) or less commonly, the lateral anlage. The thyroid tissue may sometimes produce thyroid hormone, but could also be inactive. The commonest position for ectopic thyroid tissue is the tongue—this is important to remember if excising tongue lesions.

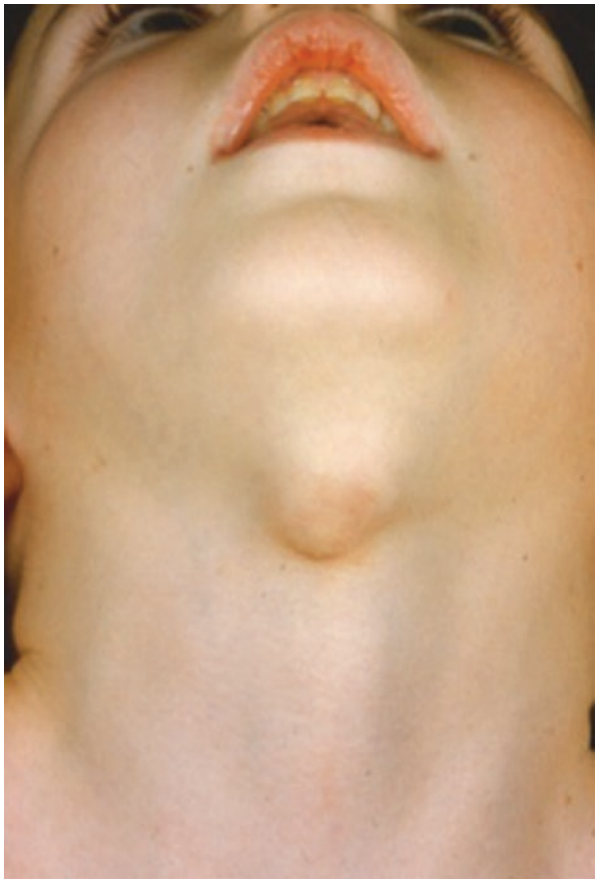


Fig. 1.43
Thyroglossal cyst

Cervical teratomas are rare lesions that present at birth. They usually extend in the midline from the thyroid gland and can obstruct the airway. Usually these teratomas arise from the thyroid gland, but sometimes they can develop from other parts of the neck. There is a risk of malignant degeneration so these tumours are usually excised as early as possible. The commonest teratomas of the cervical region are dermoid cysts which are derived from ectoderm, but can contain cells from all three germ lineages.

1.10.1 Teratogenic Agents

These are chemicals or substances that can cause birth defects when present during embryonic development. They include a wide array of drugs, chemicals, and infectious, physical and metabolic agents which can adversely affect the intrauterine environment of the developing foetus. Whist the first 2 weeks of life (prior to organogenesis), appear to be a relatively safe time for the embryo regarding teratogenic exposure, the next 45 days are especially dangerous. This is the period that most organs develop. Thus, most major malformations, such as amelia (absent limbs), cleft lip/palate, microtia and congenital heart anomalies, arise during the first 60 days of embryonic development. One notable exception is alcohol, which can result in malformations during the entire pregnancy. Craniosynostosis and hearing loss for example appear to develop after 60 days of conception.

The pathogenic mechanisms for teratogens are diverse, but ultimately produce alterations in form and function as well as cellular or embryonic/foetal death. The same teratogen can result in different defects depending on the times of exposure. For example, exposure to thalidomide around the 33rd day causes microtia and facial palsy, but later exposure results in aplasia of the arm bones. Exposure to rubella after the 55th day causes hearing loss and retinopathy but earlier exposure can cause cataracts and congenital heart anomalies. Most, but not all, teratogens have a threshold dose below which no malformations occur. However above the threshold dose, many teratogens exhibit a dose–response effect (Fig. 1.44).

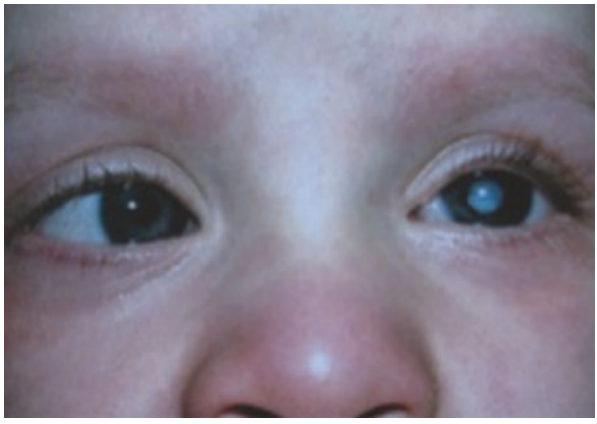


Fig. 1.44 Rubella cataract

1.10.2 Classification of Congenital Malformation of Brain

Congenital anomalies of the brain are extremely complex. A number of classification systems have been proposed, but a simplified classification of brain malformations is as follows:

1. Disorders of Organogenesis
   - Neural tube closure
   - Diverticulation and cleavage
   - Sulcation/cellular migration
   - Cerebellar hypoplasia/dysplasia
2. Disorders of Histogenesis
   - Neurocutaneous syndromes (Phakomatoses)
3. Disorders of Cytogenesis
   - Congenital vascular malformations
   - Congenital neoplasms of brain
4. Disorders of Myelination
   - Leukodystrophies

1.10.3 Craniofacial Deformations

Congenital deformations of the head and neck are common, but most resolve spontaneously within the first few days following birth. These usually arise from intrauterine constraints with severe foetal crowding. Deformations can occur in the nose, ear and mandible. Torticollis, nonsynostotic plagiocephaly, craniosynostosis may also result.

The Potter sequence (oligohydramnios sequence) is used to describe a series of compression deformities of the face and limbs, pulmonary hypoplasia, wrinkled skin, and growth restriction resulting from any pathologic condition that leads to oligohydramnios. The Amnion rupture sequence can result in three types of anomalies—disruptions, deformations and malformations. Disruptions are caused by adhesions, by tearing and constriction by amnionic bands. These can interfere with normal embryogenesis, resulting in malformations. In the head and neck they include bizarre facial clefting, encephaloceles and pseudoanencephaly. Deformations result from oligohydramnios and intrauterine crowding, as previously noted. Other malformations from the amnionic rupture sequence cannot be explained by these mechanisms but may include craniofacial disruptions, clefts and neural tube defects.

1.10.4 Congenital Lumps

These are common in the head and neck and make take various forms

1. Epidermoid cysts are of ectodermal origin and are therefore lined by stratified squamous epithelium. Dermoid cysts also include the dermis and therefore may

contain skin appendages, such as hair follicles, sebaceous glands and sweat glands. Both cysts arise from the inclusion of the elements of the developing skin during the fusion of adjacent tissue processes. When the central nervous system is involved, this occurs between the third and fifth week of development during closure of the neural tube. Such cysts then tend to be located in the midline and can be associated bone and skin defects with communications with the central nervous system. Dermoid cysts in the head and neck are estimated to account for about 10% of all dermoids. Common sites include the orbit, floor of the mouth and nose, with the rest found in the lip, palate, neck, frontal and occipital regions. Intracranial dermoids are uncommon are often occur in the midline of the posterior fossa, to involve the vermis and fourth ventricle. Epidermoid cysts may involve the skull vault, cerebellopontine angle and middle cranial fossa.

2. Hamartomas are localised growths of tissues indigenous to the site of origin. These are very uncommon but have been reported in the eye; sinuses; nasal cavity; pharynx; mouth; larynx; trachea and thyroid, parathyroid, and parotid glands. Hamartomas often contain a variety of tissues such as epithelium, vascular tissue and glands. Cartilaginous containing tissues can also occur in the larynx and trachea and secretory hamartomas in the upper respiratory tract. Whilst most are benign and do not need treatment, some may be sited in more critical places, such as the hypothalamus, which can predispose to seizures.
3. Teratomas are true neoplasms composed of multiple tissues, not normally found at their site of origin. At least two germ cell layers are present. The tissues contained may show varying degrees of differentiation. Teratomas are well described in the central nervous system (e.g. pineal region and sacrococcygeal), but are rare outside the skull in the rest of the head and neck. However they can occur in the nasopharynx, orbit, larynx, and tongue. The ‘epignathic’ teratoma is a rare type that may be discovered before during antenatal screening and which poses a threat to the airway. Other rare sites include the pharynx, middle ear and mastoid. Teratomas in adults are more likely to be malignant than those that occur in childhood.
4. Heterotopia, ectopia and aberrant tissues (choristomas) are developmental abnormalities in which mature tissue arises in an abnormal location. In the head and neck the two most common examples are ectopic thyroid and parathyroid glands. More unusual examples include gastric mucosa in the tongue and heterotopic salivary tissue found in many sites including the nose and middle ear. Rests of ectopic salivary tissue can also be found in the tonsils, lymph nodes, larynx, hypopharynx, neck, external auditory canal, middle ear, and thyroglossal duct. In some cases cystic development can occur, rarely neoplastic change (e.g. pleomorphic adenoma in any of these structures or ectopic thymoma in the thyroid).
5. Proliferative haemangiomas and vascular malformations are complex deformities that may present at or shortly after birth, or later in life. These are primarily a vascular developmental problem which can bleed, thrombose, become inflamed or infected. Proliferative haemangiomas are benign neoplasms that grow faster than the child in the postnatal period but then most often slowly involute. By contrast, malformations grow at the same rate as the patient although they can

increase in size under the influence of hormones during puberty and pregnancy. Deep sited lesions may affect the airway or interfere with the eye, swallowing, speech and hearing. Proliferative hemangiomas and malformations commonly arise in the skin, but can involve the mucosa of the nose, mouth, tonsil, palate, tongue and the neck. Parotid haemangiomas are a common cause of parotid swellings in children. Laryngeal subglottic vascular malformations need careful evaluation. Some malformations may be part of a more widespread syndrome (e.g. sturge-weber).