Diseases and Injuries to the Head, Face and Neck

A Guide to Diagnosis and Management

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Volume I

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

Priya Rogers and Michael Perry

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

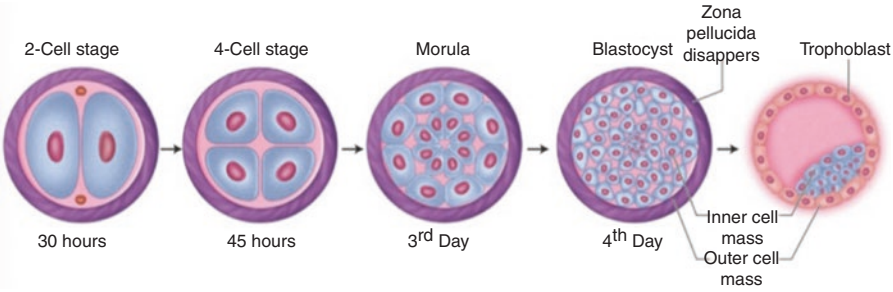


Fig. 1.1 Division of the zygote to produce a blastocyst stage embryo

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

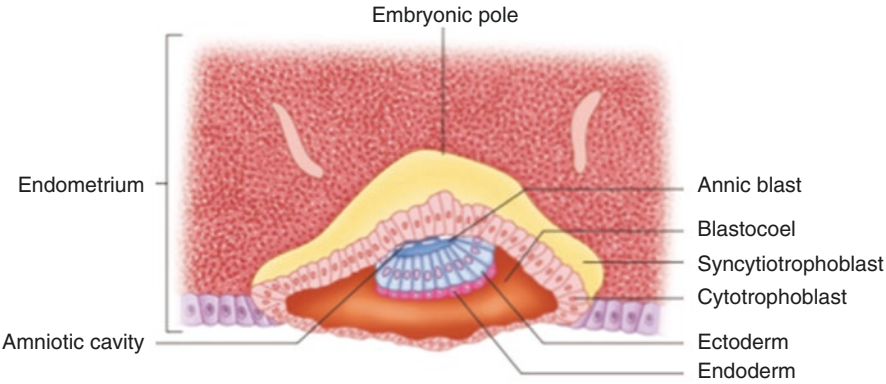


Fig. 1.2 Early stages of implantation

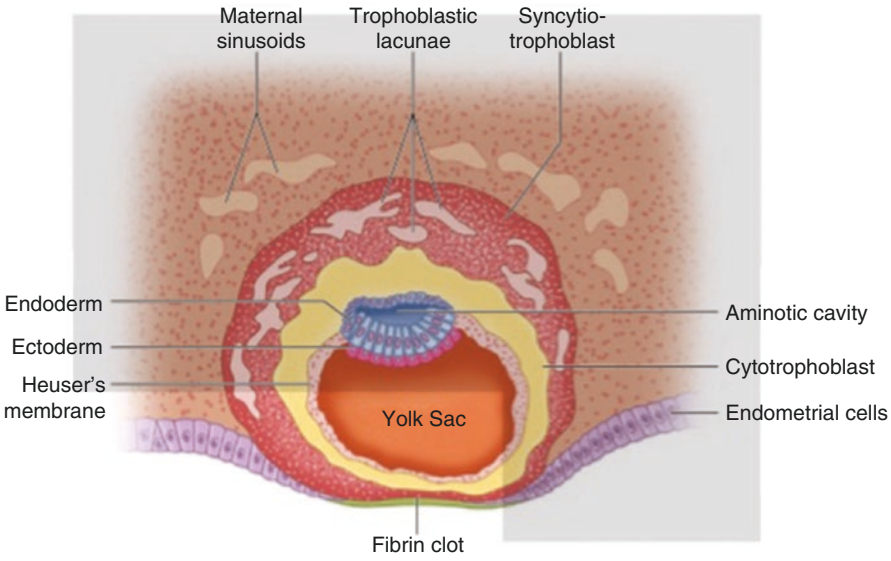


Fig. 1.3 Establishment of the embryonic layers and extra-embryonic membranes and cavities

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

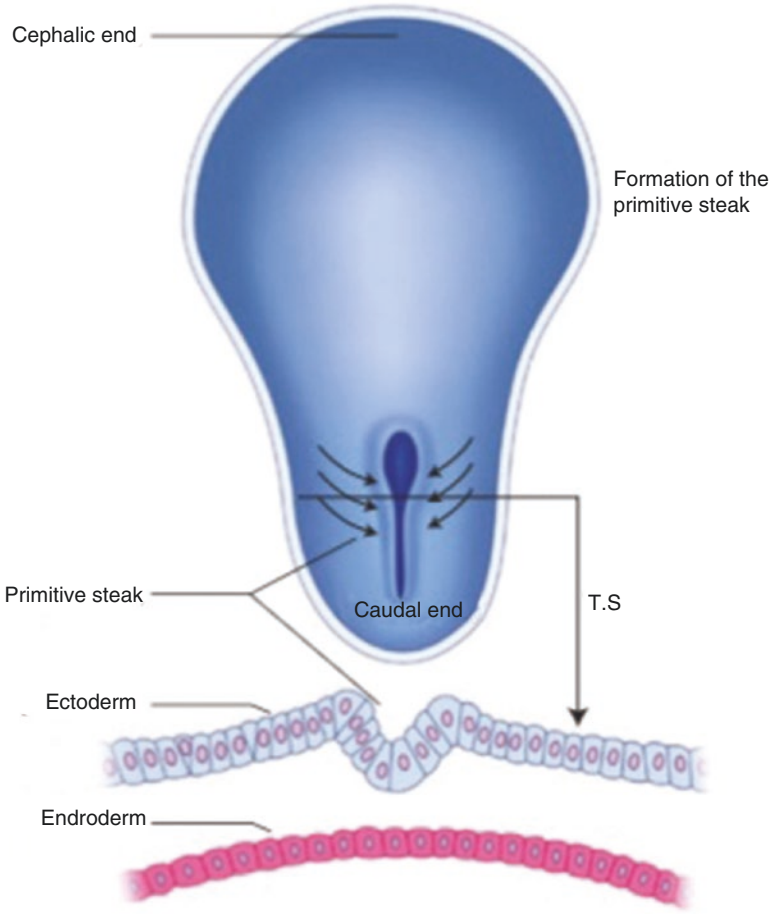


Fig. 1.4 Formation of the primitive streak signalling the start of gastrulation

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).

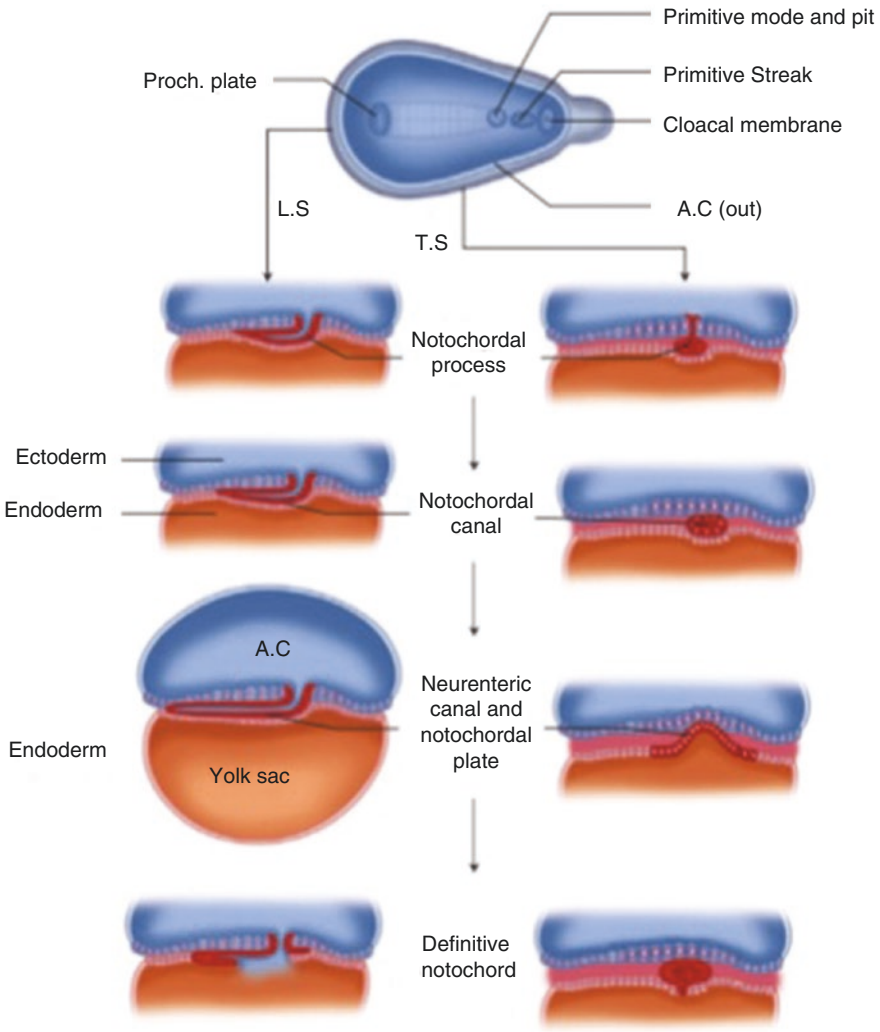


Fig. 1.5 Formation of the notochord

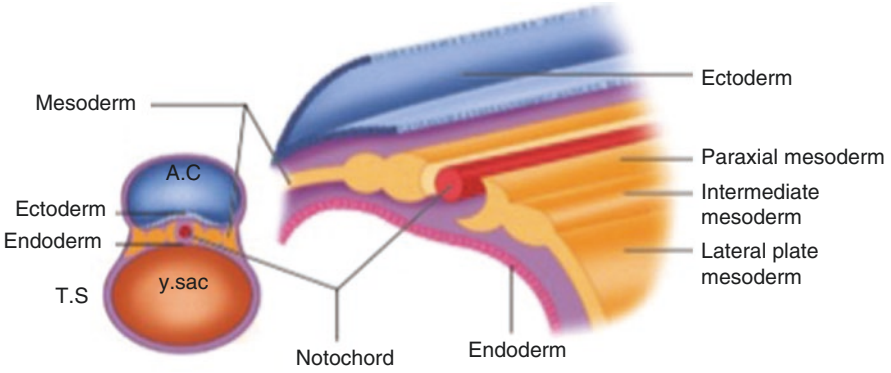


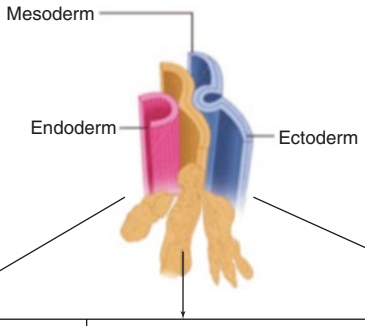
Fig. 1.6 Formation of the mesoderm layer

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.

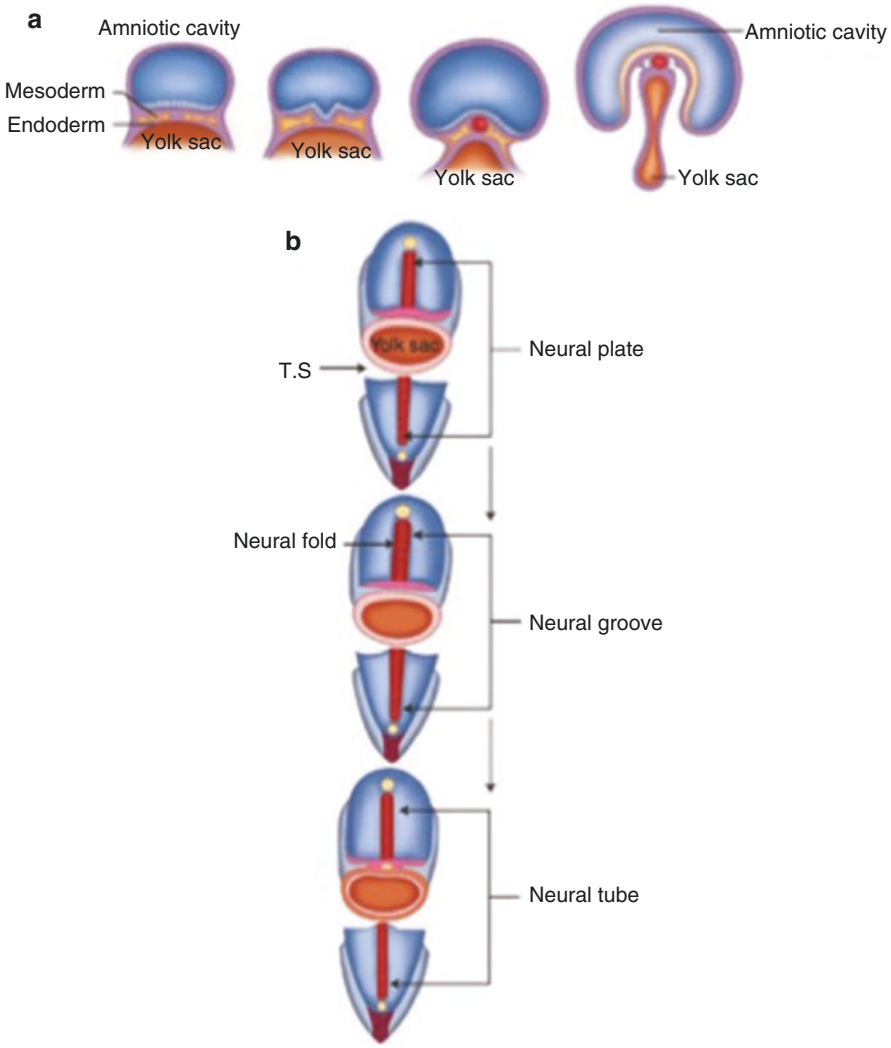


Fig. 1.8 (**a**) Establishment of the ectoderm layer from the embryonic disc. (**b**) Establishment of the neural plate from the ectoderm layer

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

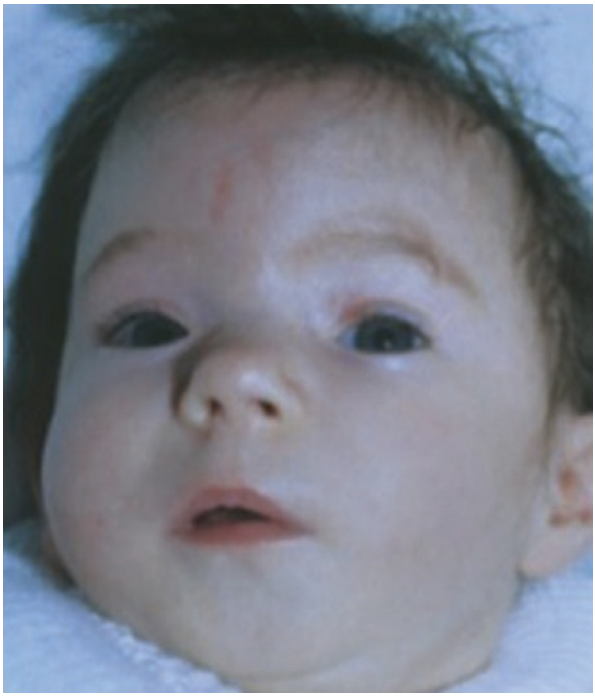


Fig. 1.9 Foetal alcohol syndrome

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.

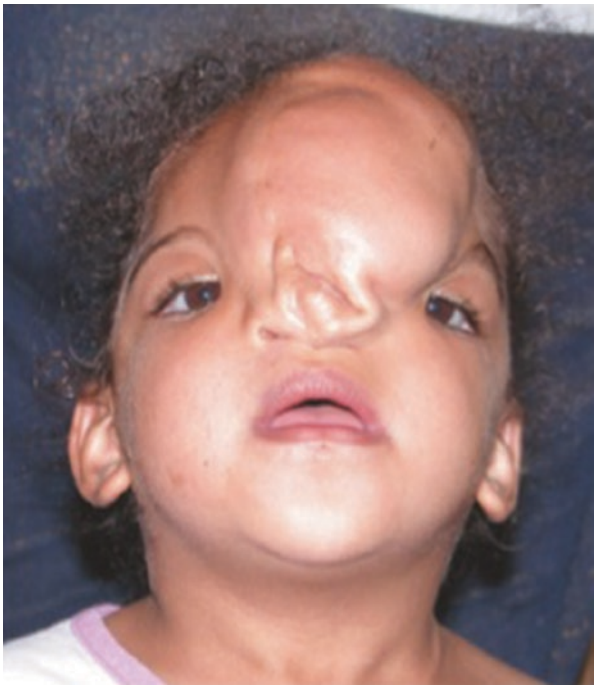


Fig. 1.10 Clinical picture of encephalocele anterior (face)

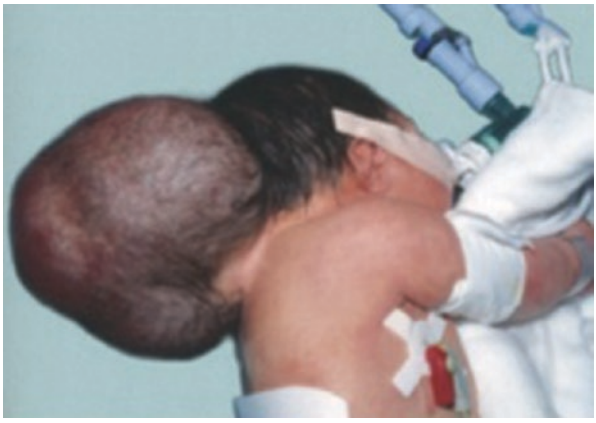


Fig. 1.11 Encephalocele

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).

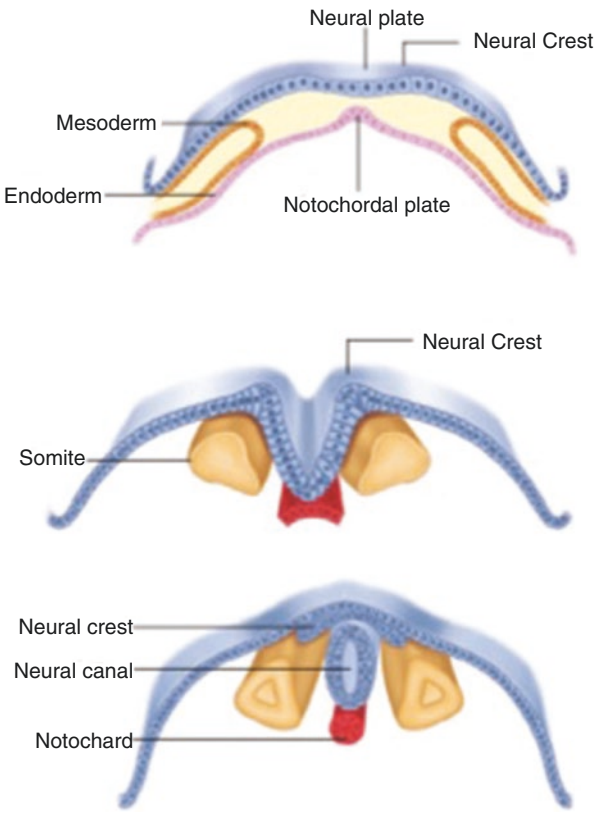


Fig. 1.12 Neural plate

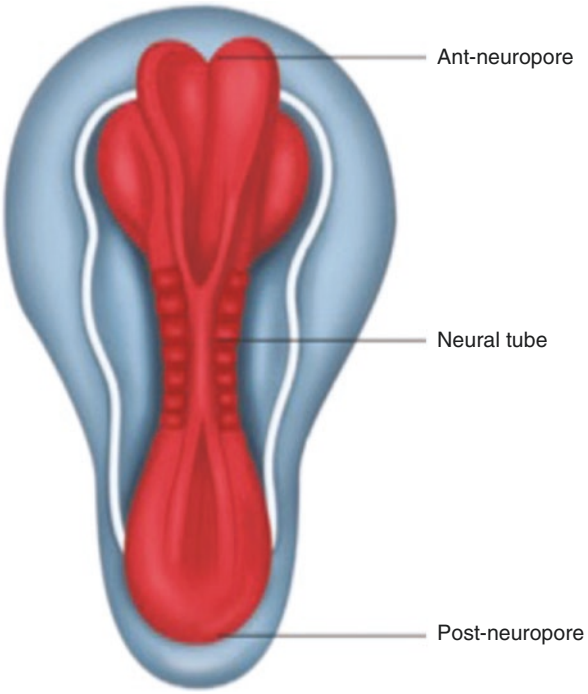


Fig. 1.13 The closed neural tube develops into the spinal cord and the brain

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

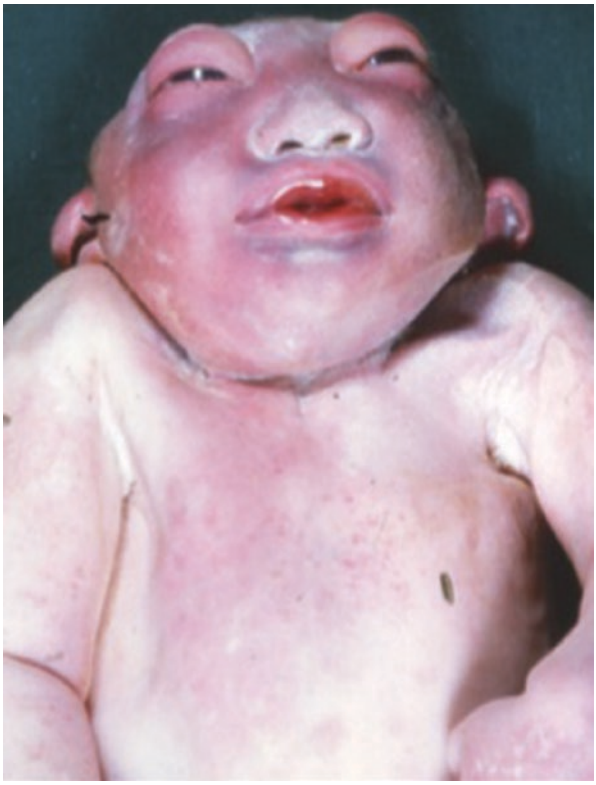


Fig. 1.14 Anencephaly

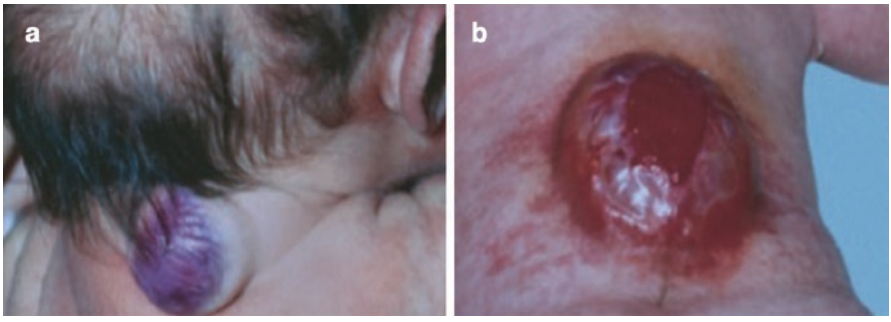


Fig. 1.15 (**a**) Meningocele. (**b**) Myelomeningocele

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

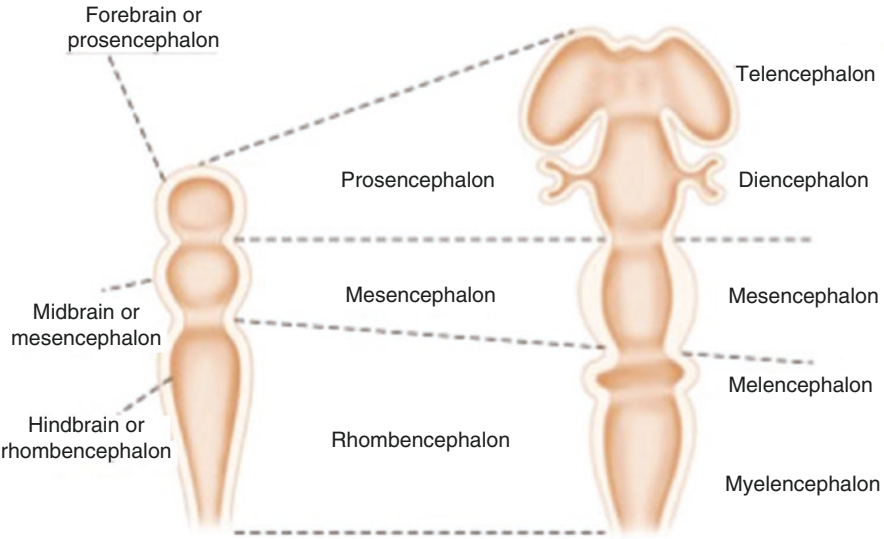


Fig. 1.16 Development of the brain—a lateral diverticulum appears on each side of the forebrain

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).

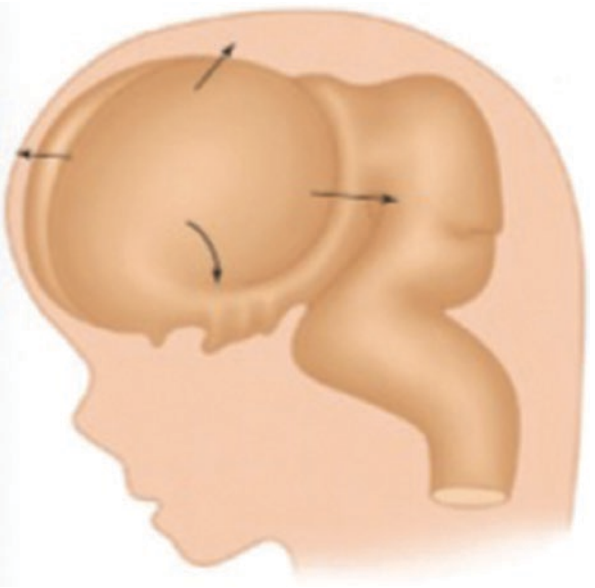


Fig. 1.17 Expansion of the cerebral cortex

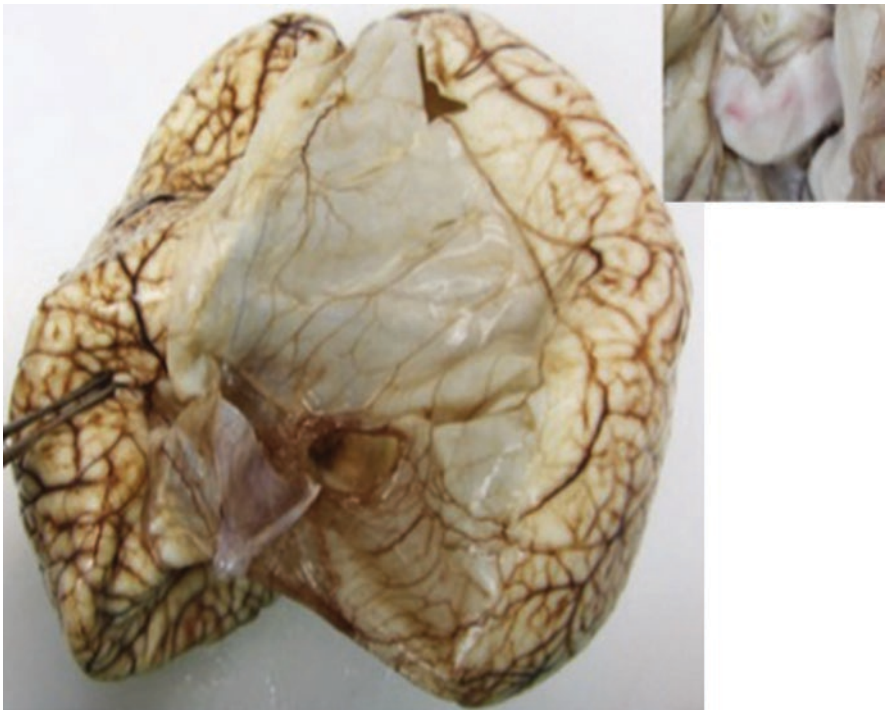


Fig. 1.18 Obstructive hydrocephalus due to congenital aqueduct (of Sylvius) stenosis (inset) caused by X-linked recessive *L1CAM gene* mutation

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

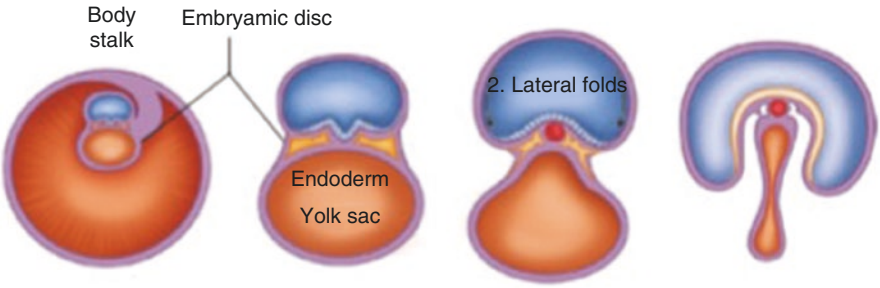


Fig. 1.19 (**a**) Embryonic folding during week 4 of development. (**b**) The end Result of early embryonic folding

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.