INTRODUCTION

An understanding of the embryology of the head and neck is vital for understanding many of the congenital disorders seen in pediatric otolaryngology. Because the subject is vast and far more complex than could be covered in a one hour lecture, the goals of this presentation are to present those topics which are of high-yield for both clinical practice and board examinations, with emphasis on the clinical disorders of the head and neck that directly result from anomalies of embryogenesis.

BRANCHIAL ARCHES

Question 1. Which of the following embryonic structures gives rise to medullary thyroid cancer?
   A. Foramen cecum
   B. Third branchial pouch
   C. Fourth branchial pouch
   D. Fifth branchial pouch

Five paired branchial (pharyngeal) arches composed of mesoderm are evident around the primitive foregut by the fifth week of gestation. Of note, the fifth arch is sometimes called the sixth arch, depending on the developmental theory one follows. Each arch is associated with a cranial nerve, a muscle or group of muscles, an artery, and a group of skeletal or cartilaginous derivatives. The connecting tissue between the arches forms the branchial clefts and pouches; the clefts are composed of ectoderm and the pouches are composed of endoderm.
The branchial arches have the following derivatives:

First Arch (Mandibular Arch)

- Trigeminal nerve (CN V)
- Terminal branch of maxillary artery (degenerates)
- Muscles: muscles of mastication (temporalis, medial & lateral pterygoids, masseter), anterior belly of digastric, mylohyoid, tensor tympani, and tensor veli palatini
- Meckel’s cartilage
  - Upper part: malleus head & neck, incus body & short process
  - Lower: contributes to ramus of the mandible

Second Arch (Hyoid Arch)

- Facial nerve (CN VII)
- Stapedial artery (degenerates)
- Muscles: muscles of facial expression, posterior belly of the digastic, stylohyoid, stapedius
- Reichert’s cartilage: manubrium of the malleus, long and lenticular processes of the incus, stapes superstructure, styloid process and stylohyoid ligament, lesser cornu and upper body of the hyoid

Third Arch

- Glossopharyngeal nerve (CN IX)
- Common and internal carotid arteries
- Only one muscle: stylopharyngeus
- Cartilage derivatives: greater cornu and lower body of the hyoid

Fourth Arch

- Superior laryngeal nerve (CN X)
- Aortic arch (left) and proximal subclavian artery (right)
- Muscles: cricothyroid, cricopharyngeus, inferior constrictor
- Cartilage derivatives: Thyroid cartilage and cuneiform cartilage

Fifth (Sixth) Arch

- Recurrent laryngeal nerve (CN X)
- Pulmonary artery (bilateral) and ductus arteriosus (left only)
- Muscles: intrinsic muscle of the larynx
- Cartilage derivatives: cricoid, arytenoid, corniculate
The branchial pouches have the following derivatives:

- First pouch: incorporated in the temporal bone to form the lining of the middle ear space and the medial surface of the tympanic membrane (endoderm)
- Second pouch: palatine tonsil
- Third pouch: inferior parathyroid gland and thymus
- Fourth pouch: superior parathyroid gland
- Fifth (sixth) pouch: ultimobranchial body

Infiltrated by neural crest cells, then detaches and migrates to the dorsal thyroid, where it forms the parafollicular C cells (source of calcitonin and medullary thyroid cancer)

The first branchial cleft forms the external auditory canal and the outer layer of the tympanic membrane; the remaining clefts obliterate.

Branchial cleft anomalies.

When considering branchial cleft anomalies, it is helpful to first define a cyst, sinus, and fistula. A cyst is a mucosa or epithelium-lined structure with no external opening. A sinus is a tract, with or without a cyst that communicates with the pharynx or skin. A fistula is a tract connecting the pharynx and skin. For sinuses and fistulae, the tract runs deep to its respective arch and superficial to more distal arches. All tracts run anterior to the sternocleidomastoid muscle and superficial to cranial nerve XII. For simplicity, the anomalies are called cysts below, but the information also applies to sinuses and fistulae.

First Branchial Cleft Cyst

- Work type I: duplication of the membranous external canal; ectoderm only; no communication with the external canal; passes lateral to facial nerve
- Work type II: ectoderm and mesoderm; communicates with the external canal; passes medial to the facial nerve

Second Branchial Cleft Cyst

- Most common type
- Passes superficial to CN IX and CN XII
- Passes between external and internal carotid arteries
- Pierces middle constrictor
- Opens into tonsillar fossa

Third Branchial Cleft Cyst

- Passes deep to CN IX and superficial CN XII
- Passes posterior to the internal carotid artery
- Pierces thyrohyoid membrane
- Opens into piriform sinus
Fourth Branchial Cleft Cyst
- Very rare
- Tract descends along the carotid sheath, passes around the subclavian artery (right) or aortic arch (left), and ascends back into the neck to open into the piriform sinus
- Majority occur on the left
- Can present as suppurative thyroiditis or thyroid abscess → Direct laryngoscopy with focus on the piriform sinus for these patients

**EAR DEVELOPMENT**³,⁷

**Question 2.**
What is the most common cochlear aplasia?
A. Alexander aplasia
B. Michel aplasia
C. Mondini aplasia
D. Scheibe aplasia

**DEVELOPMENT OF THE AURICLE**

At 4 to 6 weeks gestation, 6 mesenchymal condensations (hillocks of His) appear around the future external canal. The hillocks fuse by 8 to 9 weeks; by 28 weeks the adult structures are evident. Hillocks 1-3 arise from the first branchial arch and give rise to the tragus, helical root, and helical crus. Hillocks 4-6 arise from the second branchial arch and give rise to the antihelix, antitragus, and lobule.

**Development of the external canal, tympanic membrane, and middle ear**

The tympanic ring (first arch derivative) at 9 weeks develops around the medial first branchial cleft and begins diving deeper into the temporal bone. Meanwhile, the first branchial pouch is expanding to form the tubotympanic recess. As the first cleft and pouch meet to form the tympanic membrane, a thin layer of first arch mesoderm remains to form the fibrous layer of the tympanic membrane. A meatal plug fills the external canal until 21 weeks; at that point resorption begins and is complete by 28 weeks. Failure of resorption of the plug results in congenital aural atresia. Residual rests of epithelial cells within the tympanic membrane or tympanic cavity can give rise to congenital cholesteatoma.

**Notable anomalies of the external and middle ear**

- Fissures of Santorini (cartilaginous EAC) and foramina of Huschke (bony EAC)
  Connect the EAC to the parotid gland
  Can lead to spread of infection/tumor from one location to the other
- Hyrtrl fissure
  Connects the middle ear space to the meninges; possible route for intracranial spread of otitis media
- Dehiscent facial nerve
  Tympanic segment
  30 to 50% of patients
Increases the likelihood for facial paralysis from otitis media or middle ear surgery

**Inner ear development**

The bony labyrinth is formed from mesoderm while the membranous labyrinth is formed from ectoderm. The formation of the membranous labyrinth begins with the appearance of the otic placode lateral to the hindbrain at 3 weeks gestation; by 4 weeks gestation the placode has deepened to form a cup whose edge come together, forming the otic vesicle. The otic vesicle rapidly undergoes extensive development, such that the membranous labyrinth is nearly mature by the 8th week of gestation. The superior portion of the otic vesicle gives rise to the 3 semicircular ducts and utricle; the superior duct is formed first, the posterior duct second, and horizontal duct last. The inferior portion of the otic vesicle gives rise to the saccule and cochlea. The cochlea has 1.5 turns by the 8th week, 2 turns by the 10th week, and the normal 2.5 turns by the 25th week.

**Inner ear malformations**

- **Michel aplasia**
  Complete agenesis of the petrous portion of the temporal bone; no cochlear structures present
- **Mondini aplasia**
  Deformed cochlea with only the basal turn clearly identifiable; usually 1.5 turns present
  Associated syndromes: Pendred, Waardenburg, Treacher Collins, Wildervanck, and CHARGE (which includes absent semicircular canals)
- **Scheibe aplasia (pars inferior dysplasia)**
  Most common inner ear aplasia
  Normal bony labyrinth and superior membranous labyrinth
  Deformed tectorial membrane and collapsed Reissner’s membrane
  Associated syndromes: Usher, Refsum, Waardenburg, Jervell and Lange-Nielsen, and congenital rubella
- **Alexander aplasia**
  Basal turn of the cochlear duct is poorly developed
  Bony and membranous labyrinth are otherwise normal
  Results in high-frequency hearing loss

**NASAL, LIP, AND FACIAL DEVELOPMENT**

Question 3.
A newborn is discovered to have a unilateral cleft lip. This was caused by failure of fusion of which of the following pairs of embryonic structures?

A. Medial nasal process and maxillary prominence
B. Lateral nasal process and maxillary prominence
C. Medial nasal process and lateral nasal process
D. Palatine shelf and medial nasal process

**Development of the midface**

The basic morphology of the midface is formed in weeks 4 through 10 by five prominences: the frontonasal prominence, paired maxillary swellings, and paired mandibular swellings. At week 5, a pair of ectodermal thickenings, the nasal placodes, appear on the frontonasal process and begin to
enlarge. At week 6, a nasal pit forms in the center of each placode and invaginates. The pit divides each placode into a medial and lateral nasal process. The nasolacrimal groove lies between the lateral nasal process and maxillary swelling; it invaginates in week 7 to form the nasolacrimal duct. During week 6, the medial nasal processes fuse to form the future nasal dorsum, septum, and columella. The inferior portion of the fused medial processes forms the intermaxillary process, which gives rise to the premaxilla and philtrum; this process fuses bilaterally with the maxillary prominences to form the upper lip. The lateral nasal processes give rise to the nasal alae.

**Midline nasal defects**

The foramen cecum is a defect in the anterior skull base at the apex of the prenasal space. During weeks 3 through 8, the dura projects through the foramen cecum into the prenasal space to reach the ectoderm of the developing nasal bones; normally, the dura regresses and the foramen closes. If the dura captures ectoderm and brings it back along its path of regression, a dermoid cyst, sinus, or fistula can occur. Premature closure of the foramen can result in isolated heterotropic glial tissue (nasal glioma). Failure of the foramen to close can result in an open connection to the central nervous system (meningocele or encephalocele).

**Cleft lip and palate**

Palatogenesis occurs during weeks 5 through 12. The medial nasal processes fuse to form the intermaxillary segment, which forms the premaxilla (primary palate). Failure of the intermaxillary segment to fuse with the ipsilateral maxillary prominence results in unilateral cleft lip with or without a primary palate cleft. Bilateral failure of fusion results in a bilateral cleft. The secondary palate is formed by the palatine shelves, which arise as outgrowths of the maxillary prominences; at week 6, the shelves are angled obliquely downward. By week 7, the palatine shelves migrate to lie horizontally above the tongue; from this point, the shelves fuse medially to form the secondary palate. Secondary palatal fusion occurs from anterior to posterior, beginning at the incisive foramen at week 8 and finishing at week 12 with uvular fusion.

**Characteristics of cleft lip nasal deformities**

**Unilateral cleft lip nasal deformity**
- Nasal tip is deflected toward the cleft side
- Short medial crus and longer lateral crus on the cleft side
- Lateral crus is caudally displaced
- Columella and nasal septum are deflected to the non-cleft side from the pull of the orbicularis oris
- Nostril on the cleft side is horizontally oriented (rather than normal vertical)
- Alar base on the cleft side is displaced laterally, inferiorly, and posteriorly

**Bilateral cleft lip nasal deformity**
- Columellar length is too short, which is one of the major challenges of bilateral cleft repair
- Premaxilla is displaced anteriorly and superiorly
- Alae are laterally displaced, resulting in horizontally oriented nostrils
Congenital nasal pyriform aperture stenosis

- Caused by bony overgrowth of the nasal process of the maxilla
- Can be associated with holoprosencephaly and a central mega-incisor (which is caused by dysgenesis of the premaxilla)

Nasolacrimal duct cysts

- Nasolacrimal duct obstruction occurs to some degree in 30% of all neonates, but very few develop symptomatic cysts in the inferior meatus
- Can cause respiratory distress, especially if bilateral
- Symptomatic cysts can be marsupialized endoscopically

Choanal atresia

- The nasal pits deepen to form nasal pouches that lie above the buccal cavity; these pouches remain separated from the primitive nasopharynx by the nasobuccal membrane
- Failure of the nasobuccal membrane to rupture in week 5 or 6 results in choanal atresia
- Alternative theory is that the atresia is caused by abnormal neural crest cell migration
- Two thirds are unilateral
- More common on the right
- 70% are mixed bony/membranous; 30% are pure bony

THYROID DEVELOPMENT\textsuperscript{11-14}

Question 4.
The most common site of congenital ectopic thyroid tissue is:

A. Anterior neck
B. Mediastinum
C. Tongue
D. Thyroglossal duct cyst

Between weeks 3 to 4, the median thyroid anlage arises at the foramen cecum at the junction of the anterior two-thirds and posterior one-third of the tongue; this gives rise to the majority of the future thyroid gland. Between weeks 5 to 7, the gland descends in the neck to its normal position in the neck, passing close to the hyoid, usually anterior, but sometimes intra-hyoid or posterior to the hyoid. The lateral thyroid anlages consist of the ultimobranchial bodies (paired), which become incorporated into the median anlage during week 5.

The process of thyroid development can lead to ectopic thyroid tissue anywhere from the foramen cecum to the mediastinum; the most common site for ectopic thyroid tissue is the tongue base (lingual thyroid, 90%) and the anterior neck (10%).

Lingual thyroid

- Caused by failure of descent of the thyroid from the foramen cecum
- Contains the only functioning thyroid tissue in the majority of cases
- Diagnosis can be confirmed with a radioiodine scan ➔ uptake in the base of tongue and none in the normal thyroid position
• Many patients are hypothyroid → gland enlargement → dysphagia; this can often be treated with thyroid hormone replacement

**Thyroglossal duct cyst**

• Caused by failure of obliteration of the tract of descent of the thyroid from the foramen cecum
• Most common congenital neck mass (3 times more common than a branchial cleft cyst)
• Midline mass (only 1% occur lateral of midline)
• Anchored to the hyoid and moves with tongue protrusion
• Infections are common, are often the first time the cyst is noticed, and can sometimes lead to a cutaneous fistula
• 1% develop thyroid carcinoma (usually papillary)
• Sistrunk procedure is the operation of choice, which includes removal of the central portion of the hyoid bone
• Important to remember ectopic thyroid in the differential diagnosis → pre-operative ultrasound or radioiodine scan is needed to confirm the thyroid is present in the normal position

**LARYNGEAL DEVELOPMENT**

Question 5. What is the correct order, from most frequent to least frequent, for causes of stridor in an infant?

A. Laryngomalacia, subglottic stenosis, vocal fold paralysis, laryngeal web
B. Vocal fold paralysis, laryngomalacia, subglottic stenosis, laryngeal web
C. Subglottic stenosis, laryngomalacia, laryngeal web, vocal fold paralysis
D. Laryngomalacia, vocal fold paralysis, subglottic stenosis, laryngeal web
E. Laryngomalacia, laryngeal web, subglottic stenosis, vocal fold paralysis

The lower respiratory system begins as a diverticulum in the primitive pharynx in week 4. Bronchopulmonary buds form as the diverticulum lengthens and give rise to the lungs. The tracheal cartilages form from mesenchyme that surrounds the diverticulum. The laryngeal cartilages and muscles are formed from the fourth and fifth branchial arches. The endoderm of the diverticulum forms the epithelium of the larynx, trachea, and lungs. The laryngotracheal opening is initially a sagittal slit between the 4th and 5th arches that becomes T-shaped as the hypobranchial eminence and arytenoid swellings develop. The hypobranchial eminence gives rise to the epiglottis. As these masses grow during weeks 5 to 7, the laryngeal lumen is obliterated. In week 9, recanalization occurs and forms an oval lumen. The arytenoids are initially separated by an interarytenoid notch, which is later obliterated.

**Laryngomalacia**

• Most common cause of stridor in an infant and most common congenital laryngeal anomaly
• Precise etiology has not been determined
  Immature neuromuscular control (favored)
  Immature cartilage structures
• Findings:
Prolapse of arytenoid tissue into the airway (57%)
Shortened aryepiglottic folds (15%)
Posterior collapse of the epiglottis (12%)
Combination of the above (15%)
• Majority of patients can be observed, with supraglottoplasty reserved for those with feeding
difficulties, failure to thrive, apneas, cyanosis, or pectus excavatum
• Median age of resolution of stridor is 9 months; stridor is resolved in 75% of patients by 18
months of age
• Reflux is frequently associated with laryngomalacia and can exacerbate symptoms; it should be
trated if present

Laryngeal clefts
• Caused by failure of the posterior cricoid lamina to fuse and incomplete development of the
tracheoesophageal septum
• Numerous classification systems; Benjamin-Inglis is shown on the slides
• Presenting symptoms:
  Feeding difficulties/aspiration
  Stridor
  Recurrent pneumonias
  Chronic cough
• Mild clefts can be subtle, with only interarytenoid fullness or no apparent abnormality on
flexible endoscopy; direct laryngoscopy with palpation is essential for the diagnosis
• Treatment ranges from reflux medication only for the very mildest clefts, to endoscopic repair
for Type 1 and some Type 2 clefts, to anterior laryngofissure and median sternotomy for Type
4 clefts

Congenital laryngeal stenosis and webs
• Caused by incomplete recanalization after obliteration of the laryngeal lumen during
development
• Degree of recanalization dictates the type of lesion: complete atresia vs stenosis vs webbing
• Cricoid is often abnormal
• 65% of patients with an anterior glottic web will have a chromosome 22q11.2 deletion
 (velocardiofacial syndrome); all patients with such a web should under go fluorescent in-situ
hybridization genetic analysis for the deletion
• Treatment usually requires an open approach
  Laryngotraacheal reconstruction
  Anterior laryngofissure with keel placement

Congenital subglottic stenosis
• Third most common cause of stridor in an infant (2nd is vocal fold paralysis)
• Membranous
  most common, pictured in the slides
  fibrous tissue in the subglottis
- Cartilaginous
  Elliptical or otherwise malformed cricoid
- Patient has no history of intubation (which causes 90% of acquired subglottic stenoses)
- Congenital form predisposes to the acquired form
- Treatment options
  Endoscopic dilation/laser treatment
  Anterior cricoid split
  Laryngotracheal reconstruction
  Cricotracheal reconstruction

CONCLUSIONS

This is just the tip of the iceberg—head and neck development from embryo to birth is intricately complex. Anomalies during development—including lack of fusion of two structures, persistence of a structure that should regress, trapping of one tissue within another, or failure of a vital structure to form—underlie the majority of the congenital lesions in the head and neck. Knowledge of the normal developmental pathways and the manner in which anomalies arise is essential for any surgical treatment of congenital lesions.

ANSWERS TO QUESTIONS

1. D
2. D
3. A
4. C
5. D

REFERENCES