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BRANCHIO-OTO-RENAL (BOR) SYNDROME

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Summary

Introduction. This work is devoted to the problem of embryology of the ears and kidneys. First ear and kidney abnormalities were reported in 1946 by Edith Potter's association of crumpled and flattened ears with bilateral kidney agenesis. Ear malformations are associated with an increased frequency of clinically significant structural renal anomalies compared with the general population. These include specific multiple congenital anomaly syndromes, Townes-Brocks syndrome, branchio-oto-renal syndrome. The link can be explained by structural and functional similarities between tissues in the inner ear and in the kidney. Also, toxins that accumulate in kidney failure can damage nerves, including those in the inner ear.

Goal. To study the causes, clinical manifestations of Branchio-oto-renal (BOR) syndrome. Materials and Methods. Review of modern and foreign literary sources; methods - description, analysis, abstracting.

Results and discussion. Mutations in three genes, EYA1, SIX1, and SIX5, have been reported in people with BOR/BO syndrome. About 40 percent of people with this condition have a mutation in the EYA1 gene. SIX1 gene mutations are a much less common cause of the disorder. SIX5 gene mutations have been found in a small number of people with BOR syndrome, although researchers question whether mutations in this gene cause the condition. Some affected individuals originally reported to have SIX5 gene mutations were later found to have EYA1 gene mutations as well, and researchers suspect that the EYA1 gene mutations may be the actual cause of the condition in these people.

The proteins produced from the EYA1, SIX1, and SIX5 genes play important roles in development before birth. The EYA1 protein interacts with several other proteins, including SIX1 and SIX5, to regulate the activity of genes involved in many aspects of embryonic development. Research suggests that these protein interactions are essential for the normal formation of many organs and tissues, including the second branchial arch, ears, and kidneys. Mutations in the EYA1, SIX1, or SIX5 gene may disrupt the proteins' ability to interact with one another and regulate gene activity.

Conclusions. The link between ear anomalies and kidney function can be explained by structural and functional similarities between tissues in the inner ear and in the kidney. Additionally, toxins that accumulate in kidney failure can damage nerves, including those in the inner ear.

Key words: kidneys, ears, branchio-oto-renal syndrome, EYA1 gene.

Introduction. First ear and kidney abnormalities were reported in 1946 by Edith Potter's association of crumpled and flattened ears with bilateral kidney agenesis. Ear malformations are associated with an increased frequency of clinically significant structural renal anomalies compared with the general population. These include specific multiple congenital anomaly syndromes, Townes-Brocks syndrome, branchio-oto-renal syndrome. The link can be explained by structural and functional similarities between tissues in the inner ear and in the kidney. Also, toxins that accumulate in kidney failure can damage nerves, including those in the inner ear.

In the embryo, the kidneys develop from three overlapping sequential systems; the pronephros, the mesonephros, and the metanephros. They are all derived from the urogenital ridge. The otic ves-

icle lies beneath the surface ectoderm enveloped in the mesenchyme, forming the otic capsule. The statoacoustic ganglion also forms during the formation of the otic vesicle and splits into cochlear and vestibular portions. The otic vesicle differentiates to form all the components of the membranous labyrinth and ultimately gives rise to the inner ear structures associated with hearing and balance. The link between ear anomalies and kidney function can be explained by structural and functional similarities between tissues in the inner ear and in the kidney.

Goal. To study the causes, clinical manifestations of BOR syndrome.

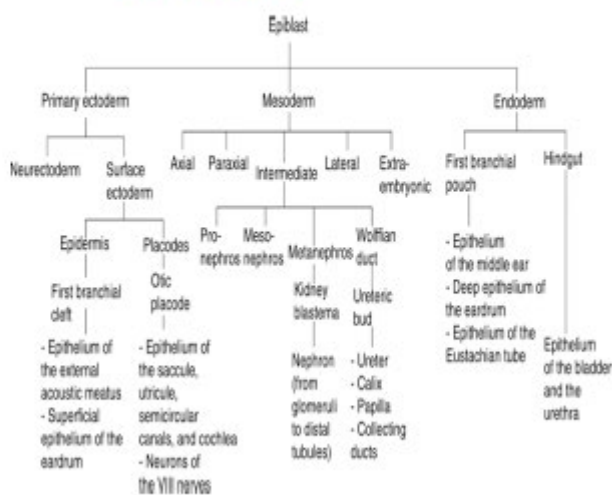
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Results and discussion. EMBRYOLOGY OF THE EAR



EMBRYOLOGY OF EAR AND KIDNEY

- The link can be explained by structural and functional similarities between tissues in the inner ear and in the kidney.
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(<https://www.google.com/search?q>)

The external ear. The external auditory meatus arises from the first pharyngeal cleft. It begins as an invagination of ectoderm between the first and second pharyngeal arches that extend inwards towards developing middle ear structures. After 5 weeks, the ectodermal diverticulum extends towards the pharynx and contains proliferating ectodermal cells that form a meatal plug that fills the entire lumen. At ten weeks, the bottom of the meatal plug expands circumferentially to create a disk-like structure. By the thirteenth week, this disk-like plug comes into contact with the primordial malleus medially, contributing to the future formation of the tympanic membrane. By the fifteenth week, the disk-like plug splits, leaving behind a thin ectodermal cell layer of the immature tympanic membrane. A continuation of the thin skin of the pinna lines the entire external auditory meatus and also the outer surface of the tympanic membrane. The external auditory meatus is completely patent and expands to its complete form by the eighteenth week.

The middle ear. The tympanic cavity and Eustachian tube originate from an extension of the endoderm of the first pharyngeal pouch called the tubotympanic recess. At 5 weeks, the tubotympanic recess extends laterally until it reaches the floor of the first pharyngeal cleft. The endoderm of the tubotympanic recess and the ectoderm of the first pharyngeal cleft are next to each other, with a fibrous layer derived from mesenchyme called the lamina propria sandwiched in between. It leads to formation of a trilaminar tympanic membrane made up of three separate germ layers i.e. ectoderm, mesoderm, and endoderm. The dorsal portion of the tubotympanic recess expands to form the tympanic cavity and is filled with loose mesenchymal tissue, while the ventral portion develops into the Eustachian tube. Anatomically, the tympanic cavity divides into upper (attic) and lower (atrium) chambers that surround the ossicles and other structures of the middle ear.

The tympanic cavity connects to the oral cavity via the Eustachian tube, that ventilate and drain the tympanic cavity. At birth, the Eustachian tube is more horizontal, shorter, and narrow than in adults and is a major reason infants have recurrent ear infections, grows most growth during weeks 16 to 28 of the fetal period.

The inner ear. The inner ear originates from the invagination of the otic placodes during the 4th week of development. The otic placodes are sensory placodes, which are a series of transiently thickened surface ectodermal patches that form pairs rostro-caudally in the head region during week 4 of development. Sensory placodes are involved in the development of special sensory systems like vision, olfaction, and hearing. The otic placodes are one of the first sensory placodes to form and contribute to the formation of the inner ear structures associated with hearing and balance. The otic placodes are located behind the second pharyngeal arch and give rise to the otic pits by invaginating into the mesenchyme adjacent to the rhombencephalon during the fourth week of development. Towards the end of the fourth week, the otic pits break off from the surface ectoderm to form a hollow piriform shaped structure lined with columnar epithelium called the otic vesicle.

At this point, the otic vesicle lies beneath the surface ectoderm enveloped in the mesenchyme, forming the otic capsule. The statoacoustic ganglion also forms during the formation of the otic vesicle and splits into cochlear and vestibular portions. The otic vesicle differentiates to form all the components of the membranous labyrinth and ultimately gives rise to the inner ear structures associated with hearing and balance. As the otic vesicle develops into the membranous labyrinth, its epithelium undergoes variations in thickness and begins to distort. The otic vesicle divides into a dorsal utricular portion and ventral saccular portion, with the dorsal utricular portion giving rise to the vestibular system and the ventral saccular portion giving rise to inner ear structures involved in hearing. The ventral saccular portion develops into the cochlear duct and saccule. The dorsal utricular portion forms into the utricle, semicircular canals, and endolymphatic tube.

EMBRYOLOGY OF KIDNEY

In the embryo, the kidneys develop from three overlapping sequential systems; the pronephros, the mesonephros, and the metanephros. They are all derived from the urogenital ridge.

Pronephros. The pronephros appears in the 4th week of development. Its development begins in the cervical region of the embryo. Segmented divisions of intermediate mesoderm form tubules, known as nephrotomes. In total, 6-10 pairs of nephrotomes are formed. These tubules join into the pronephric duct, which is a duct that extends from

the cervical region to the cloaca (distal end) of the embryo. This early system is non-functional and regresses completely by the end of week 4.

Mesonephros. The mesonephros develops caudally (inferiorly) to the pronephros. First, the presence of the pronephric duct induces nearby intermediate mesoderm in the thoracolumbar region to form mesonephric tubules. These tubules receive a tuft of capillaries from the dorsal aorta allowing for the filtration of blood and they drain into the mesonephric duct (a continuation of the pronephric duct). They act as a primitive excretory system in the embryo, with most tubules regressing by the end of the 2nd month. Additionally, the mesonephric duct sprouts the ureteric bud caudally, which induces the development of the definitive kidney.

Metanephros. The metanephros forms the definitive kidney. It appears in the 5th week of development and becomes functional around the 12th week. The ureteric bud from the mesonephric duct makes contact with a caudal region of intermediate mesoderm – the metanephric blastema. Collectively, these blastema form the metanephric system, which has two components: collecting system – derived from the ureteric bud. It dilates to create the ureter, renal pelvis, major and minor calyces and collecting tubules – terminating at the distal convoluted tubule. If the uretic bud splits too early, two ureters, or two renal pelvices connecting to one ureter may result.

Excretory system. It's derived from the metanephric blastema. Each collecting tubule from the collecting system is covered by a metanephric tissue cap which gives rise to the excretory tubules. These excretory tubules (along with the developing glomeruli) form the kidney's functional units – the nephron. The proximal end of the excretory tubule forms the Bowman's capsule around a glomerulus, while the distal end elongates to form the proximal convoluted tubule, loop of Henle and distal convoluted tubule. The definitive kidney initially develops in the pelvic region before ascending into the abdomen. In the pelvis, the kidney receives its blood supply from a pelvic branch of the abdominal aorta and as it ascends, new arteries from the abdominal aorta supply the kidney. The pelvic vessels usually regress, but can persist as accessory renal arteries.

EAR AND KIDNEY SYNDROME

Branchio-oto-renal (BOR) syndrome is a condition that disrupts the development of tissues in the neck and causes malformations of the ears and kidneys. The signs and symptoms of this condition vary widely, even among members of the same family. Branchiootic syndrome includes many of the same features as BOR syndrome, but affected individuals do not have kidney abnormalities. The two conditions are otherwise so similar that researchers often consider them together (BOR/BO syndrome or branchiootorenal spectrum disorders).

“Branchio-” refers to the second branchial arch, which is a structure in the developing embryo that gives rise to tissues in the front and side of the neck. In people with BOR/BO syndrome, abnormal development of the second branchial arch can result in the formation of masses in the neck called branchial cleft cysts. Some affected people have abnormal holes or pits called fistulae in the side of the neck just above the collarbone. Fistulae can form tunnels into the neck, exiting in the mouth near the tonsil.

“Oto-” and “-otic” refer to the ear; most people with BOR/BO syndrome have hearing loss and other ear abnormalities. The hearing loss can be sensorineural, meaning it is caused by abnormalities in the inner ear; conductive, meaning it results from changes in the small bones in the middle ear; or mixed, meaning it is caused by a combination of inner ear and middle ear abnormalities. Some affected people have tiny holes in the skin or extra bits of tissue just in front of the ear. These are called preauricular pits and preauricular tags, respectively.

“Renal” refers to the kidneys; BOR syndrome (but not BO syndrome) causes abnormalities of kidney structure and function. These abnormalities range from mild to severe and can affect one or both kidneys. In some cases, end-stage renal disease (ESRD) develops later in life. This serious condition occurs when the kidneys become unable to filter fluids and waste products from the body effectively.

Causes. Mutations in three genes, EYA1, SIX1, and SIX5, have been reported in people with BOR/BO syndrome. About 40 percent of people with this condition have a mutation in the EYA1 gene. SIX1 gene mutations are a much less common cause of the disorder. SIX5 gene mutations have been found in a small number of people with BOR syndrome, although researchers question whether mutations in this gene cause the condition. Some affected individuals originally reported to have SIX5 gene mutations were later found to have EYA1 gene mutations as well, and researchers suspect that the EYA1 gene mutations may be the actual cause of the condition in these people.

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The resulting genetic changes affect the development of organs and tissues before birth, which leads to the characteristic features of BOR/BO syndrome.

Some people with BOR/BO syndrome do not have an identified mutation in any of the genes listed above. In these cases, the cause of the condition is unknown.

PATHOLOGY

ALPORT SYNDROME

Alport syndrome is a genetic condition characterized by kidney disease, hearing loss, and eye abnormalities. People with Alport syndrome experience progressive loss of kidney function. Almost all affected individuals have blood in their urine (hematuria), which indicates abnormal functioning of the kidneys. Many people with Alport syndrome also develop high levels of protein in their urine (proteinuria). The kidneys become less able to function as this condition progresses, resulting in end-stage renal disease (ESRD). People with Alport syndrome frequently develop sensorineural hearing loss, which is caused by abnormalities of the inner ear, during late childhood or early adolescence. Affected individuals may also have misshapen lenses in the eyes (anterior lenticonus) and abnormal coloration of the light-sensitive tissue at the back of the eye (retina). These eye abnormalities seldom lead to vision loss. Significant hearing loss, eye abnormalities, and progressive kidney disease are more common in males with Alport syndrome than in affected females.

Etiology. Mutations in the COL4A3, COL4A4, and COL4A5 genes cause Alport syndrome. These genes each provide instructions for making one component of a protein called type IV collagen. This protein plays an important role in the kidneys, specifically in structures called glomeruli. Glomeruli are clusters of specialized blood vessels that remove water and waste products from blood and create urine. Mutations in these genes result in abnormalities of the type IV collagen in glomeruli, which prevents the kidneys from properly filtering the blood and allows blood and protein to pass into the urine. Gradual scarring of the kidneys occurs, eventually leading to kidney failure in many people with Alport syndrome. Type IV collagen is also an important component of inner ear structures, particularly the organ of Corti, that transform sound waves into nerve impulses for the brain. Alterations in type IV collagen often result in abnormal inner ear function, which can lead to hearing loss. In the eye, this protein is important for maintaining the shape of the lens and the normal color of the retina. Mutations that disrupt type IV collagen can result in misshapen lenses and an abnormally colored retina.

FECHTNER SYNDROME

Fechtner syndrome is a rare autosomal dominant disorder consisting of macrothrombocytopenia and leukocyte inclusions, associated with Alport’s syndrome (hereditary nephropathy, sensorineural

hearing loss, and ocular anomalies). Fechtner syndrome is a rare autosomal dominant progressive nephropathy associated with macrothrombocytopenia. Sensorineural hearing loss can also occur.

Fechtner syndrome shows the additional features of cataracts and blue leukocyte inclusion bodies (Doehle-like bodies). It is linked to mutations in MYH9, the nonmuscle myosin heavy chain.

HEARING LOSS - ASSOCIATED RESEARCH

Ear and kidney genes function

Genes	Ear	Kidney
Glial cell-line-derived neutrophic factor	Protects hair cells from damage	Essential for ureteric bud growth and branching morphogenesis of the ureteric bud epithelium
Fibroblast growth factors	Induces both the otic placode and the epithelial organization of the otic vesicle	Maintains the nephrogenic mesenchyme; induces its condensation and autocrine secretion of Wnt-4 converts it to epithelium
Bone morphogenic proteins	Proteins emanating from the otic epithelium influence chondrogenesis of the otic capsule.	Modulate ureteric bud branching and keep bud development in step with that of other tissue types
Wnt signaling and Frizzled receptors	Could be involved in several aspects of late cochlear differentiation or auditory function	Critically required for tubulogenesis in the pronephric kidney
Barttin	Crucial for renal salt reabsorption and potassium recycling in the inner ear	Increases surface expression and changes properties of ClC-K channels needed adequate salt reabsorption
ATP6B1	Role in endolymph pH homeostasis and in normal auditory function	Role in normal vectorial acid transport into the urine by the kidney encoding the B-subunit of the apical proton pump mediating distal nephron acid secretion
AQP-2	Role in the development of endolymph homeostasis	Regulated urinary diluting ability; important for rapid near-isosmolar transepithelial fluid absorption/secretion and for rapid vectorial water movement driven by osmotic gradient.

Experimentation. The experimental animals chosen were the rat and guinea pig. Anti-rat sera and anti-guinea pig sera were also produced using the goat or rabbit respectively as the antibody producing animal. In order to produce the antisera, specimens of stria vascularis were dissected from the cochlea. The collected specimens were then placed in saline and Complete Freund's Adjuvant, emulsified and then injected into subcutaneous sites of rabbits. After about 10 days the blood was withdrawn and the serum extracted from the blood. This crude serum was then used in subsequent experiments as the antiochlea antibody (AC Ab). In a similar manner glomerular basement membrane antibody was prepared (AGBM Ab). Two methods of immunofluorescent staining were used, namely, the indirect and direct method.

Preparation. In indirect method, Frozen sections of normal cochlea or renal tissue specimens were treated with the previously prepared AC Ab or AGBM Ab and then counterstained with Fluores-

cein labeled goat anti-rabbit gamma globulin serum (GARG-FI). In direct method, tissue specimens from guinea pigs that had been injected with either AC Ab or AGBM Ab were stained directly with GARG-FI. In a third part of the experiments, the left cochlea from each animal injected with either AGBM Ab or AC Ab was taken for light histology. Of marked significance in our studies is the observation that AC Ab is capable of staining renal tubular epithelium. This presents compelling evidence of antigenically similar epithelial components. There is a fascinating similarity between the cochlea and the kidney. This similarity extends through a variety of modalities. There is even experimental evidence of a possibility of antigenically similar epithelial components.

Conclusions. The link between ear anomalies and kidney function can be explained by structural and functional similarities between tissues in the inner ear and in the kidney. Additionally, toxins that accumulate in kidney failure can damage nerves, including those in the inner ear.

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РЕЗЮМЕ

БРАНХИО-ОТО-РЕНАЛЬНЫЙ СИНДРОМ

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Введение. Бранхио-ото-ренальный синдром (БОР) – аутосомно-доминантное заболевание, характеризующееся сочетанием нарушения слуха с преаурикулярными ямками, шейными свищами или кистами и аномалиями почек различного типа. Мутации в гене EYA1 обуславливают до 40% случаев БОР-синдрома.

Цель. Изучить причины, клинические проявления БОР-синдрома.

Материал и методы. Обзор современных и зарубежных литературных источников; методики – описание, анализ, реферирование.

Результаты и их обсуждение. «Oto-» и «-otic» относятся к уху; большинство людей с БОР-синдромом страдают потерей слуха и другими аномалиями уха. Потеря слуха может быть нейросенсорной, то есть вызвана аномалиями во внутреннем ухе; проводящей, то есть результат изменений мелких костей в среднем ухе; или смешанной, что означает, что это вызвано сочетанием аномалий внутреннего и среднего уха. «Почечный» относится к почкам. Синдром БОР характеризуется нарушением структуры и функции почек. Эти нарушения варьируются от легких до тяжелых и могут поражать одну или обе почки. Признаки и симптомы этого состояния сильно различаются даже среди членов одной семьи с расстройствами развития жаберно-почечного спектра.

Белки, продуцируемые генами EYA1, SIX1 и SIX5, играют важную роль в развитии до рождения. Белок EYA1 взаимодействует с несколькими другими белками, включая SIX1 и SIX5, чтобы регулировать активность генов, участвующих во многих аспектах эмбрионального развития. Исследования показывают, что эти белковые взаимодействия необходимы для нормального формирования многих органов и тканей, в том числе второй жаберной дуги, ушей и почек. «Жаберная дуга» относится ко второй жаберной дуге, ко-

торая представляет собой структуру в развивающемся эмбрионе, которая дает начало тканям в передней и боковой частях шеи.

Мутации в генах EYA1, SIX1 или SIX5 могут нарушить способность белков взаимодействовать друг с другом и регулировать активность генов.

Выводы. Связь между аномалиями уха и функцией почек можно объяснить структурным и функциональным сходством между тканями внутреннего уха и почек. Кроме того, токсины, которые накапливаются при почечной недостаточности, могут повреждать нервы, в том числе во внутреннем ухе, что проявляется снижением слуха при прогрессировании почечной недостаточности.

Ключевые слова: почки, уши, бранхио-ото-ренальный синдром, ген EYA1.

РЕЗЮМЕ

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Вступ. Бранхио-ото-ренальный синдром (БОР) – аутосомно-домінантне захворювання, що характеризується поєднанням порушення слуху з преаурикулярними ямками, шийними свищами або кістами і аномаліями нирок різного типу. Мутації в гені EYA1 обумовлюють до 40% випадків БОР-синдрому.

Мета. Вивчити причини, клінічні прояви БОР-синдрому.

Матеріал і методи. Огляд сучасних та іноземних літературних джерел; методики – опис, аналіз, реферування.

Результати та їх обговорення. «Oto-» і «-otic» відносяться до вуха; більшість людей з БОР-синдромом страждають втратою слуху та іншими аномаліями вуха. Втрата слуху може бути нейросенсорною, тобто викликана аномаліями у внутрішньому вусі; провідною, яка виникає як результат змін дрібних кісток у середньому вусі; або змішаною, що означає, що це викликано поєднанням аномалій внутрішнього і середнього вуха. «Нирковий» відноситься до нирок. Синдром БОР характеризується порушенням структури і функції нирок. Ці порушення варіюють від легких до важких і можуть вражати одну або обидві нирки. Ознаки та симптоми цього стану сильно розрізняються навіть серед членів однієї родини з розладами розвитку зяброво-ниркового спектра.

Білки, які продукуються генами EYA1, SIX1 і SIX5, грають важливу роль в розвитку до народження. Білок EYA1 взаємодіє з декількома іншими білками, включаючи SIX1 і SIX5, щоб регулювати активність генів, що беруть участь у багатьох аспектах ембріонального розвитку. Дослідження показують, що ці білкові взаємодії необхідні для нормального формування багатьох органів і тканин, в тому числі другої зябрової дуги, вух і нирок. «Зяброва дуга» відноситься до другої зябрової дуги, яка представляє собою структуру в розвиненому ембріоні та дає початок тканинам в передній і бічній частинах шиї.

Мутації в генах EYA1, SIX1 або SIX5 можуть порушити здатність білків взаємодіяти один з одним і регулювати активність генів.

Висновки. Зв'язок між аномаліями вуха та функцією нирок можна пояснити структурною та функціональною подібністю тканин у внутрішньому вусі та нирках. Крім того, токсини, які накопичуються при

нирковій недостатності, можуть пошкодити нерви, в тому числі у внутрішньому вусі, що проявляється зниженням слуху при прогресуванні ниркової недостатності.

Ключові слова: нирки, вуха, бронхіо-ото-ренальний синдром, ген EYA1.

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