Eur Arch Otorhinolaryngol (2006) 263:971–976
DOI 10.1007/s00405-006-0095-x

REVIEW ARTICLE

Enlarged vestibular aqueduct: looking for genotypic–phenotypic correlations

José Ángel González-García · Andrés Ibáñez · Rafael Ramírez-Camacho · Antonio Rodríguez · José Ramón García-Berrocal · Almudena Trinidad

Received: 6 February 2006 / Accepted: 18 May 2006 / Published online: 8 July 2006

Abstract The aim of this work is to provide a guide for clinical and genetic diagnosis and classification of the enlarged vestibular aqueduct syndrome based on a review of the literature and computerized databases with the words large and enlarged vestibular aqueduct. No more than 40 articles described association between the EVA phenotype and a known genetic alteration. Pendred's syndrome, distal renal tubular acidosis, waardenburg's syndrome, X-linked congenital mixed deafness, branchio-oto-renal syndrome, and otofacio-cervical syndrome can express their genotypic alteration as enlarged vestibular aqueduct syndrome. We also found articles reporting familiar cases of enlarged vestibular aqueduct with no identified mutations in studied genes.

Keywords Vestibular aqueduct · Endolymphatic sac · Hearing loss · Inner ear · Abnormalities

Introduction

The association of congenital sensorineural hearing loss with enlarged vestibular aqueduct (EVA) was initially determined from histopathologic studies of inner ear malformations [4]. Radiologic detection of this anomaly was first described in 1978. In the context of an investigation to elucidate the anatomical variations of the endolymphatic sac and its possible association with endolymphatic hydrops, Valvassori and Clemis [25] reported their conventional polytomographic findings in 50 patients, and named this condition the ''Large Vestibular Aqueduct Syndrome'', also known as enlarged vestibular aqueduct syndrome (EVAS). Most authors have defined a large vestibular aqueduct as one greater than 1.5 mm in diameter as measured midway between the *common crus* and the *external operculum* [12].

Phenotypic expressions associated with EVAS are heterogeneous; as it can be seen as normal hearing, total deafness, progressive sensorineural hearing loss, fluctuating sensorineural hearing loss or sudden sensorineural hearing loss, sometimes subsequent to head trauma. The syndrome can also include vestibulopathy. Down-slopping hearing loss is the typical feature in EVAS. Patients can also present with mid frequency peak, flat curve, up-slopping, and low frequency with mixed component audiograms. One third of patients show a fluctuating loss but approximately 50% have a stable audiogram [3] (Fig. 1).

Enlarged vestibular aqueduct syndrome can include the enlargement of the endolymphatic sac (Fig. 2). Surrounded by a rich network of lymphatic vessels and fenestrated capillaries, the endolymphatic sac contains immunocompetent cells, lymphocytes, and macrophages. The currently available data of the human endolymphatic sac and its associated cell populations support the assumption that the epithelium is metabolically active and capable of processing and presenting antigens to different lymphocyte subpopulations. It can also produce inmunoglobulines,

J. Á. González-García · A. Ibáñez · R. Ramírez-Camacho · A. Rodríguez · J. R. García-Berrocal · A. Trinidad
Grupo de Investigación Otológica (Otologic Research Group), Department of Otorhinolaryngology, Servicio de Otorrinolaringología, Hospital Universitario Puerta de Hierro, Calle San Martín de Porres 4, 28035 Madrid, Spain
e-mail: joseangelgg@seorl.net

especially secretory IgA. These findings characterize the endolymphatic sac as a mucosa-associated lymphoid tissue. Other studies provide evidence for a possible role of the human endolymphatic sac in the physiopathology of inner ear hereditary deafness and immune-mediated inner ear disease [10].

Enlarged vestibular aqueduct syndrome is the most common inner ear anomaly associated with congenital hearing impairment and it has been associated with diverse systemic syndromes. In 1997 Tong determined the familial incidence of EVAS detected by CT and MR imaging in patients' relatives, and proposed the genetic inheritance of EVAS. Based on the pedigrees of the familial cases, the pattern was most consistent with autosomal recessive inheritance. Recent advances in molecular genetic techniques have enabled us to understand more about the molecular basis of several genetic syndromes associated with EVAS.

The objective of this review is to carry out an exhaustive literature search, using the Medline database, to identify relevant publications showing the different diseases with known responsible genes whose alterations can present with an EVAS phenotype.

Materials and methods

A literature search was conducted using the Medline and Pubmed databases to identify studies describing relationships between EVA and syndromic or non-syndromic diseases genetically identified. Previous

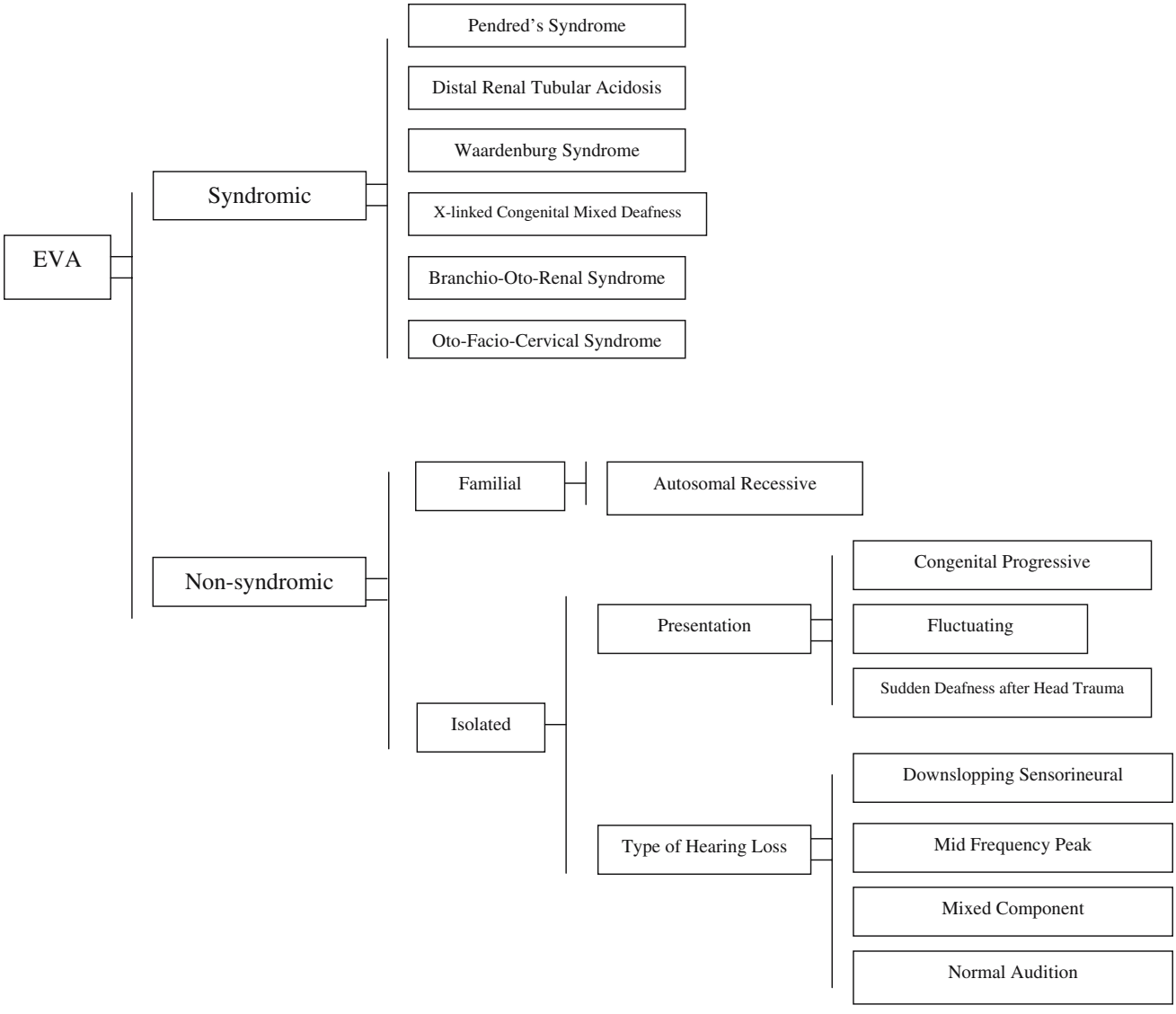

Fig. 1 Clinical diagnosis of enlarged vestibular aqueduct syndrome

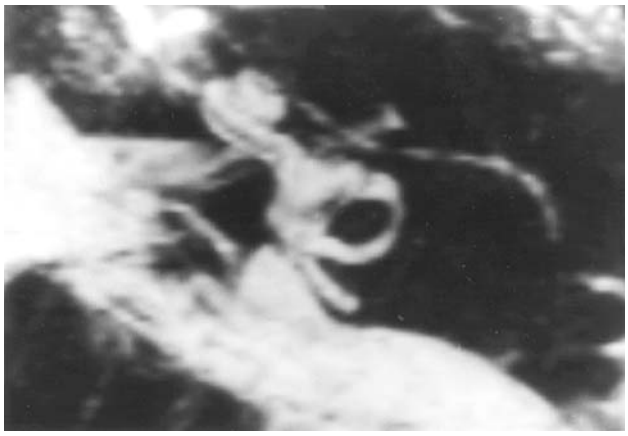

Fig. 2 3-D MRI of an enlarged endolymphatic sac accompanying an enlarged vestibular aqueduct

review of these citations was then conducted to determine which articles should be analyzed. Reference lists of relevant articles were reviewed to identify further studies. Searches were undertaken in September 2005. The initial search was made using Medline. To limit and also to complete the search the keywords were linked on ''on-line'' medical libraries OVID, Science Direct, Proquest, Springerlink, British Medical Journals, and the ''Agencia Laín Entralgo'' Virtual Library.

Results

The keywords ''large vestibular aqueduct'' or ''enlarged vestibular aqueduct'' revealed 129 articles. We have found relationships between EVA and six different otologic and nonotologic syndromes genetically identified in 15 articles (excluding the Pendreds syndrome articles). Concerning Pendred's syndrome, we reviewed our own previously published references and the most recent works. We found more than fifty references about description of enlarged vestibular aqueduct, clinical features, embryological development, inheritance and treatment. No more than 40 articles described association between the EVA phenotype and a known genetic alteration, most of them related to Pendred's syndrome. We also found five articles reporting familiar cases of EVA with no identified mutations in studied genes (Table 1).

Discussion

The presence of EVA and enlarged endolymphatic sac belongs to a heterogeneous group of inner ear alterations accompanying diverse vestibular and auditory manifestations. Up to date, known physiopathologic mechanisms do not justify the different types of hearing loss related to the enlargement of vestibular aqueduct. Although CT and MRI provide excellent anatomical diagnostic images we are unable to detect changes inside the membranous labyrinth. Future investigations directed to study the organ of corti in patients with EVAS could provide information about its clinical manifestations. The short number of histopathologic studies in this kind of patients is restricting our knowledge. However, the identification of the genotype of diseases that present with an EVAS could make possible a clinical or phenotypic characterization.

EVA and Pendred's syndrome

Pendred's syndrome is an autosomal recessive condition, in which congenital deafness is associated with goitre, which accounts for 4–10% of hereditary hearing loss. Mutations in the SLC26A4 gene, located on chromosome 7, are responsible for the syndrome. This gene encodes an 86-kDa protein named 'pendrin' (780 amino acids), a member of the SLC26A family of anion transporters. In addition to the classical Pendreds syndrome, mutations in the SLC26A4 gene may also produce non-syndromic recessive deafness (DFNB4) [9, 24].

The classical criteria for the diagnosis of Pendred's syndrome include profound prelingual deafness, goiter, and an abnormal result in the perchlorate test because of the deficient processing of iodide. Other associated features include inner ear malformations, such as an enlarged vestibular aqueduct (Fig. 3) and Mondini's malformation. However, the clinical features of Pendred's Syndrome are quite variable [4].

Everett demonstrated a SCL26A4 expression throughout the endolymphatic sac and duct, utricle, and saccule in a mouse model. In different families with nonsyndromic hearing loss with EVA and normal perchlorate test, mapping to 7q31was found, and later, seven mutations have been found in SLC26A4 [24].

A postulation was made that mutations in SLC26A4 cause both syndromic and nonsyndromic hearing loss. Mutations in SLC26A4 associated with Pendreds syndrome had complete loss of Pendrin-induced chloride and iodide transport, while alleles unique to people with DFNB4 were able to transport both iodide and chloride, but at a lower rate than wild-type pendrin [19].

Table 1 Syndromic and familiar enlarged vestibular aqueduct

References	Syndrome	EVA	Associated defects	Inheritance	Year/identified gene (chromosome)	Type of affection
UsaMI [24] Stinckens [19] Arellano [1]	Pendred's syndrome	+	Mondini type cochlea goitre	AR	1997/PDS (7) [9]	Familiar
Karet [13] Berretini [5]	Distal renal tubular acidosis	+ (Only AR form)	Metabolic renal acidosis.	AD/AR	1999/A1 subunit H^+-ATPase (2) [13]	Familiar
Madden [14]	Waardenburg's syndrome	+	Heterochromia irides. White forelock dystopia cantorum.	AD	1992/PAX3 (2) [23] 1994 MITF (3) [22]	Familiar
Talbot [21] Arellano [2]	X-linked congenital mixed deafness	+	Fixation stapedial footplate. Gusher.	X-linked	1992/DFN3 (X) [6]	Familiar
Ceruti [7] Stinckens [20]	BOR syndrome	+	Renal dysplasia second branquial arch fistula auricle malformation.	AD	2001/EYA1 (8) [7]	Familiar
Megarba-ne [15]	Oto-facio-cervical syndrome (BOR-like syndromes)	+	Branchial defects ear pits renal abnormalities development delay	AR?	2001/EYA1 surrounding region (8) [8–18]	Sporadic
Griffith [11] Ramírez-Camacho [17]	Familiar EVA	+ (Isolated)	None	AR	None	Familiar

EVA and distal renal tubular acidosis (dRTA)

Distal renal tubular acidosis is a disorder characterized by a defect in urinary acidification accompanied by various degrees of metabolic acidosis in the absence of aminoaciduria or glycosuria. The reduced ability to acidify urine despite systemic metabolic acidosis or acid loading is due primarily to a defect in hydrogen ion secretion. Both autosomal dominant and autosomal recessive inheritance of primary dRTA has been observed. The dominant form is generally milder. The recessive form of the disease, on the other hand, is a more severe disorder that usually presents in early childhood with acute metabolic illness. A down-sloping sensorineural hearing loss may be present in one third of cases, with widely variable severity (from mild to profound) and progressive deterioration [13].

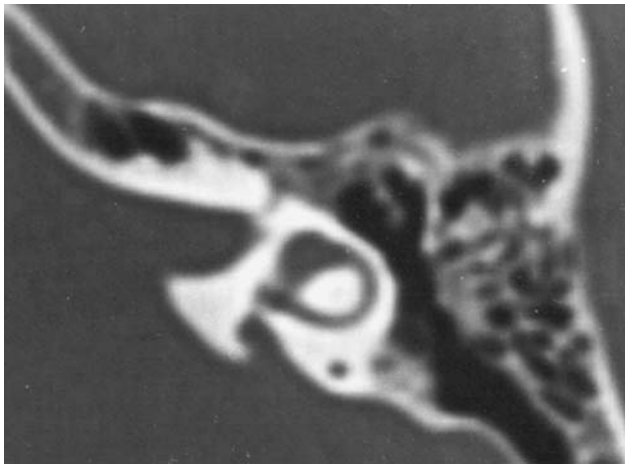

Fig. 3 Axial TC showing enlarged vestibular aqueduct in a patient affected by the Pendred's syndrome

Two loci, ATP6B1, and ATP6N1B, have been identified as being responsible for recessive dRTA associated with sensorineural hearing loss. These genes, localized on chromosome 2, encode the B1 subunit of hydrogen adenosine triphosphatase (H^+-ATPase). Local expression of H^+-ATPase in the inner ear is required for normal cochlear development and function. It has been supposed recently that the EVA associated to dRTA results from an aberrant growth of the vestibular aqueduct during fetal life and the first 3 or 4 years of postnatal life due to a hydroelectrolytic imbalance, such as in Pendred's syndrome [5].

EVA and Waardenburg's syndrome (WS)

Waardenburg's syndrome is a genetic disorder of autosomal dominant inheritance in which congenital hearing loss is associated with pigmentary disturbances of the eye, skin, and skin appendages. *Heterochromia irides*, white forelock or early greying and congenital sensorineural hearing loss are some of the major phenotypic characteristics of the disorder. Waardenburg's syndrome accounts for 2–5% of all congenital hearing loss and an incidence of 1:40,000 live births. Various genetic mutations have been identified, such as

those for WS types 1 and 3 in the PAX3 gene, for WS type 2 in MITF and for WS type 4 in EDN3, EDNRB, and SOX10 [22–23].

EVAS has only been demonstrated in patients affected of WS types 1 and 2. The migration of melanocytes from the neural crest during the eighteenth gestational week gives rise to the intermediate cells of the stria vascularis. The failure of melanocyte migration in WS causes the absence of the intermediate cells, is associated with atrophy of the *stria vascularis* and cochleosaccular degeneration, and is presumed to be related to the hearing loss.

Madden et al. [14] reported a study of four boys and three girls with WS types 1 or 2 and hearing loss. Overall, three of the six children (50%) had enlarged vestibular aqueducts on their temporal bone CT scans. These findings broaden the pathophysiologic scope in this disorder, ranging from anomalies at a cochleosaccular level to abnormalities of the temporal bone development, as seen on CT scans.

EVA and X-linked congenital mixed deafness

The association of congenital X-linked mixed hearing loss, fixed stapes footplate and stapedectomy gusher (XDFG) was reported in 1968. The syndrome is transmitted as an X-linked trait. A fistulous connection between the internal auditory canal and the perilymphatic space of the scala vestibuli was proposed as the cause for perilymphatic gusher following a disturbance of the stapes footplate [16]. Talbot and Wilson [21] presented three cases of enlarged vestibular aqueduct and the XDFG complex in 1994, after the location of the responsible gene had been mapped to the Xq21 location of the X chromosome [6], later named DFN3. DFN3 type hearing loss constitutes approximately 50% of sex-linked nonsyndromic deafness. The gene POU3F4 encodes a transcription factor that is expressed during embryonic development in the otic capsule and point mutations in this gene are responsible for about half of familiar DFN3 cases. Arellano et al. [2] also described a familiar case of DFN3 type deafness keeping POU3F4 intact, suggesting that the Xq21 region contains another deafness gene or a regulatory element that controls the expression of POU3F4. In this family, phenotypic characterization depended on the patient's sex.

EVA and branchio-oto-renal syndrome (BOR)

Branchio-oto-renal syndrome has an autosomal dominant pattern of inheritance. Main features are slight malformation of the auricles, preauricular sinuses, hearing loss, branchiogenic cervical fistulas of the second branchial arch and renal dysplasia. Penetrance of the disease is almost totally complete, but expression of the symptoms varies, particularly the severity of the hearing loss and renal abnormalities. Hearing loss can be of the conductive, mixed or sensorineural type. Hypoplasia of the cochlea has been demonstrated histologically and radiologically. A widened vestibular aqueduct has been described after histological and radiological examination. The BOR syndrome gene is EYA1, which lies on 8q13.3. The BOR syndrome is genetically and clinically different from similar branchiogenic syndromes, which are not linked to the EYA1-locus [20]. Large vestibular aqueduct has been reported in patients with the BOR syndrome. This finding, when bilateral, implies progression of hearing loss on serial audiograms, which may have been explained by a large vestibular aqueduct [7].

EVA and BOR-like syndromes

Some clinical syndromes are incomplete or similar forms of branchio-oto-renal syndrome. Recently Estefanía et al. [8] and Rickard et al. [18] have identified new deletions of the EYA 1 gene and surrounding region in patients with complex phenotypes involving features of BOR syndrome and multiple malformations that led to the diagnosis of oto-facio-cervical dysplasia. Megarbane et al. [15] described an oto-facial syndrome with delay of development and middle ear malformations associated with enlargement of the vestibular aqueduct.

Familiar EVA

Some authors [11] have observed families with congenital sensorineural hearing loss and isolated enlarged vestibular aqueduct. They proposed an autosomal recessive pattern of inheritance, but no molecular investigation was carried out. In 2003 a family with isolated unilateral familial EVA was presented. Mutations in genes GJB2 (conexin 26 gene), mitochondrial 12sRNA and PDS gene were studied without positive results. In this family, there was a special characteristic consisting of a unilateral EVA in all members, suggesting that the genetic alteration is transformed to phenotypic expression in one ear because of the hypothetical existence of genes that regulate bilateral development of paired organs. All previous reports of familial EVAS described it as bilateral [17].

Conclusions

The knowledge of Enlarged Vestibular Aqueduct genotypic localization could make possible a phenotypic characterization. The mechanism of hearing loss is unclear but further histopathologic, metabolic immunity and genetic investigations of the temporal bone and the endolymphatic sac could apply information about this topic.

References

1. Arellano B, Pera A, Ramírez-Camacho R Villamar M, Trinidad A, Garcia JR, Moreno F, Hernandez-Chico C (2005) Pendred's syndrome and non-syndromic DFNB4 deafness associated with the homozygous T410M mutation in the SLC26A4 gene in siblings. Clin Gen 67:438–440
2. Arellano B, Ramirez-Camacho R, Garcia-Berrocal JR et al (2000) Sensorineural hearing loss and Mondini dysplasia caused by a deletion at locus DFN3. Arch Otolaryngol Head Neck Surg 126(9):1065–1069
3. Arjmand EM, Webber A (2004) Audiometric findings in children with a large vestibular aqueduct. Arch Otolaryngol Head Neck Surg 130:1169–1174
4. Beal DD, Davey PR, Lindsay JR (1967) Inner ear pathology of congenital deafness. Arch Otolaryngol 85:135–142
5. Berrettini S, Forli F, Franceschini SS, Ravecca F, Massimetti M, Neri E (2002) Distal renal tubular acidosis associated with isolated large vestibular aqueduct and sensorineural hearing loss. Ann Otol Rhinol Laryngol 111(5):385–391
6. Brunner HG, van Bennekom A, Lambermon EM, Oei TL, Cremers WR, Wieringa B, Ropers HH (1988) The gene for X-linked progressive mixed deafness with perilymphatic gusher during stapes surgery (DFN3) is linked to PGK. Hum Genet 80(4):337–340
7. Ceruti S, Stinckens C, Cremers CW, Casselman JV (2002) Temporal bone anomalies in the BOR syndrome: detailed computed tomographic and magnetic resonance imaging findings. Otol Neurotol 23(2):200–207
8. Estefania E, Ramirez-Camacho R, Gomar M, Trinidad A, Arellano B, Garcia-Berrocal JR, Verdaguer JM, Vilches C (2005) Point mutation of an EYA-1 gene splice site in a patient with oto-facio-cervical syndrome. Ann Hum Genet 0(0):doi: 10.1111/
9. Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED (1997) Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 17(4):411–422
10. Garcia Berrocal JR, Ramirez-Camacho R (2000) Immune response and immunopathology of the inner ear: an update. J Laryngol Otol 114(2):101–107
11. Griffith AJ, Arts A, Downs C, Innis JW, Shepard NT, Sheldon S, Gebarski SS (1996) Familial large vestibular aqueduct syndrome. Laryngoscope 106(8):960–965
12. Jackler RK, De La Cruz A (1989) The large vestibular aqueduct syndrome. Laryngoscope 99:1238–1442
13. Karet FE, Finberg KE, Nelson RD, Nayir A, Mocan H, Sanjad SA, Rodriguez-Soriano J, Santos F, Cremers CW, Di Pietro A, Hoffbrand BI, Winiarski J, Bakkaloglu A, Ozen S, Dusunsel R, Goodyer P, Hulton SA, Wu DK, Skvorak AB, Morton CC, Cunningham MJ, Jha V, Lifton RP (1999) Mutations in the gene encoding B1 subunit of H+-ATPase cause renal tubular acidosis with sensorineural deafness. Nat Genet 21(1):84–90
14. Madden C, Halsted MJ, Hopkin RJ, Choo DI, Benton C, Greinwald JH Jr (2003) Temporal bone abnormalities associated with hearing loss in Waardenburg syndrome. Laryngoscope 113(11):2035–4441
15. Megarbane A, Chouery E, Rassi S, Delague V (2005) A new autosomal recessive oto-facial syndrome with midline malformations. Am J Med Genet A 132(4):398–401
16. Ramirez Camacho R, Arellano B, Garcia Berrocal JR (2000) Gusher perilinfático. Mitos y Realidad. Acta Otorrinolaringol Esp 51(3):193–198
17. Ramírez-Camacho R, García-Berrocal J, Arellano B, Trinidad A (2003) Familial isolated unilateral large vestibular aqueduct syndrome. ORL J Otorhinolaryngol Relat Spec 65(1):45–48
18. Rickard S, Parker M, van't Hoff W, Barnicoat A, Russell-Eggitt I, Winter RM, Bitner-Glindzicz M (2001) Oto-facio-cervical (OFC) syndrome is a contiguous gene deletion syndrome involving EYA1: molecular analysis confirms allelism with BOR syndrome and further narrows the Duane syndrome critical region to 1 cM. Hum Genet 108:398–403
19. Stickens C, Huygen PM, Van Camp G, Cremers CW (2002) Pendred syndrome redefined. In: Cremers WR, Smith RJ (eds) Genetic hearing impairment. Adv Otorhinolaryngol. Basel, Karger, 61:131–44
20. Stinckens C, Standaert L, Casselman JW, Huygen PL, Kumar S, Van de Wallen J, Cremers CW (2001) The presence of a widened vestibular aqueduct and progressive sensorineural hearing loss in the branchio-oto-renal syndrome. A family study. Int J Pediatr Otorhinolaryngol 59(3):163–172
21. Talbot JM, Wilson DF (1994) Computed tomographic diagnosis of X-linked congenital mixed deafness, fixation of the stapedial footplate, and perilymphatic gusher. Am J Otol 15(2):177–182
22. Tassabehji M, Newton VE, Read AP (1994) Waardenburg syndrome type II caused by mutations in the human microphthalmia (MITF) gene. Nat Genet 8:251–255
23. Tassabehji M, Read AP, Newton VE Harris R, Balling R, Gruss P, Strachan T (1992) Waardenburg's syndrome patients have mutations in the human homologue of the Pax-3 paired box gene. Nature 355:635–636
24. Usami S, Abe S, Weston MD, Shinkawa H, Van Camp G, Kimberling WJ (1999) Nonsyndromic hearing loss associated with enlarged vestibular aqueduct is caused by PDS mutations. Hum Genet 104:188–192
25. Valvassori GE, Clemis JD (1978) The large vestibular aqueduct syndrome. Laryngoscope 88:723–728