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Review Article

Deafness secondary to genetic syndromes: A review

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Abstract

Background

Deafness may be classified in: conductive, sensor neural, mixed, and central type. The degree of severity is divided in: low, moderate, severe and profound. Among other causes, genetic syndromes are responsible for hearing loss in an important number of cases.

Methods

We review cases from our genetic consultation which causes conductive, sensorineural, mixed and central hearing loss.

Results

We find four cases of conductive hearing loss- Treacher-Collins, Pierre-Robin, Gondenhar and Crouzon; one case of recessive sensor neural deafness- Jervell-Lange-Nielsen; seven cases of dominant sensor neural deafness- Waardenburg type 1, neurofibromatosis type 1, Noonan, Turner, Patau, CHARGE association and Zellweger; one case of recessive x-linked sensor neural deafness; Hunter, one case of mitochondrial hearing loss, two cases of mixed deafness; Stickler and Larsen.

Conclusion

The sooner we identify genetic syndromes responsible for sensor neural deafness and conductive hearing loss, the easier will be for us to do the genetic counseling in the future pregnancy.

Introduction

Deafness occurs in 1 to 2 per 1000 newborns and in 2 per 1000 young children. The prevalence of moderate deafness, severe and profound is around 1/900 a 2500 newborns.

Hearing loss may be classified in: conductive (involving any cause that in some way limits the amount of external sound that gains access to the inner ear), sensor neural (involving the inner ear, cochlea, or the auditory nerve) mixed (which is a combination of conductive and sensor neural hearing loss) and central, involving higher brain centers and auditory neuropathy or auditory neuropathy spectrum disorder.

The degree of severity is divided in: low (20 a 40 dB), moderate (41 a 60 dB), severe (61 a 90 dB) and profound (>90 dB).

The external ear develops between 8-28 weeks of gestational age.

Absent, malformation or stenosis of the external ear, are responsible for conductive hearing loss, in most cases with moderate degree of severity [1,2,3,4].

The genetic syndromes which causes this conductive hearing loss are: Treacher-Collins, Pierre-Robin, Gondenhar and Crouzon syndromes [5,6,7,8].

Sensor neural deafness occurs in 1/2000 newborns. Genetic cause is responsible for 50% of total cases:

- 80% recessive
- 15% dominant
- 2% X – linked (more recessive)
- 1% mitochondrial

The recessive sensor neural deafness is caused by: Pendred, Jervell-Lange-Nielsen and Alport syndromes [9,10,11].

"The most frequent genetic dominant hearing loss is: Waardenburg type 1and 2, Neurofibromatosis type 1, Patau, Noonan, Turner, CHARGE and Zellweger [12,13,14,15,16,17,18].

Hunter and Alport are the genetic syndromes responsible for x-linked deafness [19, 20].

Mitochondrial disease is a rare cause, with only 1% of all cases presenting as sensor neural hearing loss [21].

The mixed causes of hearing loss are attributed to CHARGE, Sticker and Larsen syndromes [22,23].

Methods

We review cases from our genetic consultation of Pediatric Department of Centro Hospitalar Vila Nova de Gaia/Espinho, which causes conductive, sensorineural, mixed and central hearing loss.

Results

We find four cases of conductive hearing loss- Treacher-Collins,

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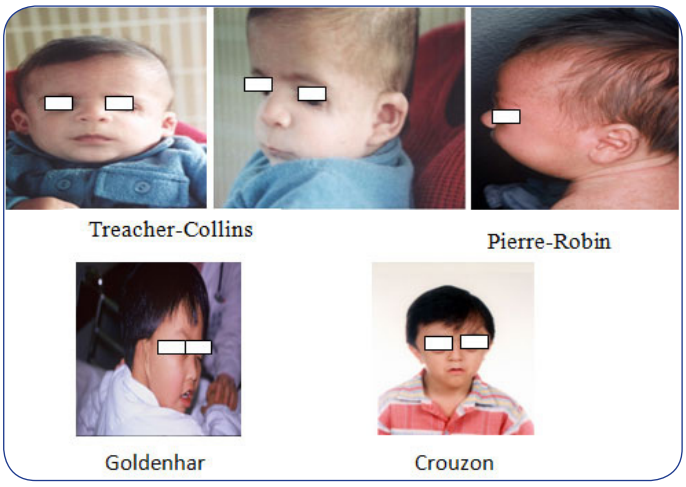
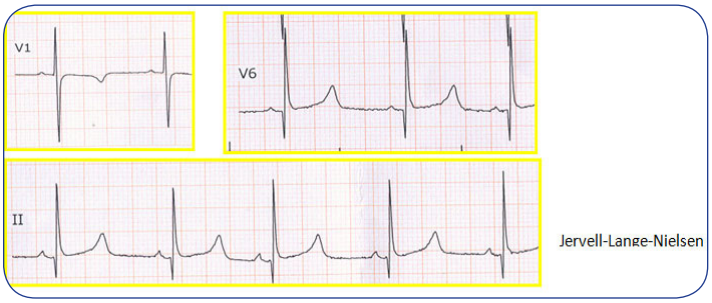
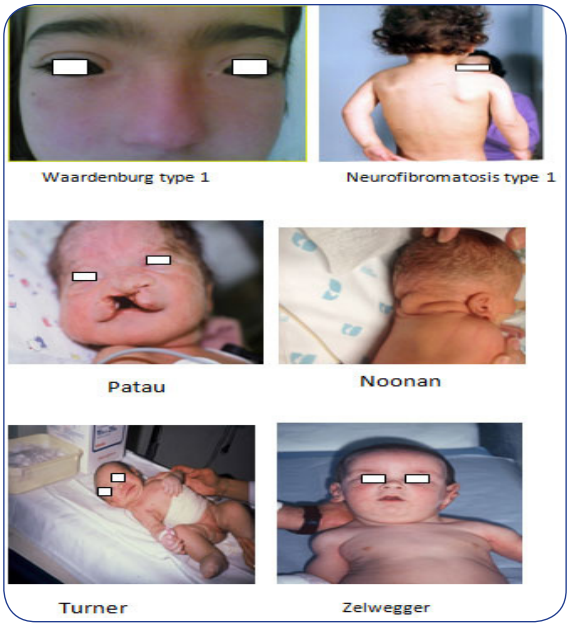
Pierre-Robin, Gondenhar and Crouzon (Figures 1);



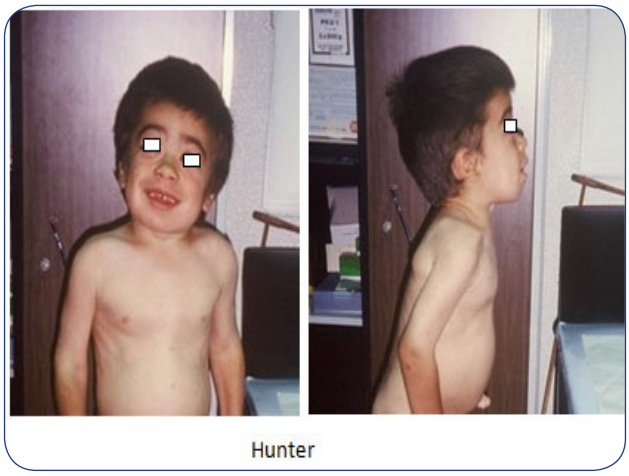
one case of recessive sensor neural deafness-Jervell-Lange-Nielsen;



"six cases of dominant sensor neural deafness- Waardenburg type 1", neurofibromatosis type 1, Noonan, Turner, Patau and Zellweger;

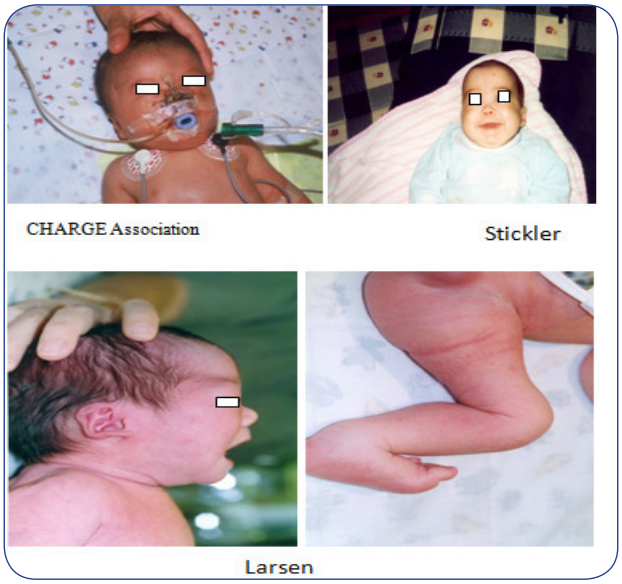


one case of recessive x-linked sensorineural deafness- Hunter;



one case of mitochondrial hearing loss

and three cases of mixed deafness- CHARGE association, Stickler and Larsen.



Gene studies were performed in all cases requiring molecular confirmation: Jervell-Lange-Nielsen, Waardenburg type 1, neurofibromatosis type 1, Noonan, Hunter and mitochondrial disease.

All syndromes are resumed in Tables 1-6.

Table 1: Conductive hearing loss

DISEASE	INHERITANCE	HEARING LOSS	MAJOR FEATURES	MOLECULAR STUDY
Treacher-collins	Autosomal dominant	Conductive	Malar hypoplasia, Malformation of auricle, Downward slanting palpebral fissures, Lower eyelid coloboma, Cleft palate, Mandibular hypoplasia	TCOF1
Pierre-Robin	Autosomal recessive, X-linked form and associated with trisomy 18 and other syndromes	Conductive	Robin sequence, Micrognathia, Retroglossia, U-shaped posterior cleft palate	SOX9
Gondenhar	Autosomal dominant	Conductive	Facial asymmetry ,Unilateral external ear deformity, Preauricular tags, External auditory canal atresia, Microtia, Upper eyelid coloboma, Cleft palate, Ventricular septal defect , Multicystic dysplastic kidney, Vertebral anomalies, Arnold-Chiari malformation, Agenesis of corpus callosum	TCOF1, EYA1, SALL1
Crouzon	Autosomal dominant	Conductive	Craniosynostosis, Brachycephaly, Frontal bossing, Maxillary hypoplasia, Mandibular prognathism, Proptosis, Shallow orbits, Cervical spine abnormalities	FGFR2

Table 2: Sensorineural deafness - dominant

DISEASE	INHERITANCE	HEARING LOSS	MAJOR FEATURES	MOLECULAR STUDY
Waardenburg type1	Autosomal dominant	sensorineural deafness	Dystopia canthorum, Heterochromia iridis, Hypopigmented skin lesions, Premature graying of hair	PAX3
Waardenburg type 2	Autosomal dominant	sensorineural deafness	Hypopigmented irides, Anosmia, Premature graying, Axial hypotonia ,Increased muscle tone	SOX10
Neurofibromatosis type 1	Autosomal dominant	sensorineural deafness	Lisch nodules, Neurofibromas, Plexiform neurofibroma, Cafe-au-lait spots, Axillary freckling, Optic glioma	NF1
Patau	Unknown	sensorineural deafness	Holoprosencephaly, colobomata of iris,, clef lip, clef palate, polidactaly, ventricular septal defect	
Noonan	Autosomal dominant	sensorineural deafness	Short stature, Micrognathia, Webbed neck , Pulmonic stenosis, Cubitus valgus, Low posterior hairline, Articulation difficulties	PTPN11
Turner	Unknown	sensorineural deafness	Short stature, congenital lymphedema of the hands and feet, webbed neck,, high-arched palate, and short fourth metacarpal.	
Zellweger	Autosomal recessive	sensorineural deafness	Large fontanelles, High forehead, Pigmentary retinopathy, Pulmonary hypoplasia, Ventricular septal defects, Pyloric hypertrophy,Hepatomegaly, Hypotonia, areflexia	PEX1, PEX2, PEX3, PEX5, PEX6, PEX12, PEX14, PEX26

Table 3: Sensorineural deafness - recessive

DISEASE	INHERITANCE	HEARING LOSS	MAJOR FEATURES	MOLECULAR STUDY
Jervell-Lange-Nielsen	Autosomal recessive	sensorineural deafness	Long QT interval. ventricular tachyarrhythmias. Syncope, sudden death	KCNQ1

Table 4 : Sensorineural deafness - X-linked

DISEASE	INHERITANCE	HEARING LOSS	MAJOR FEATURES	MOLECULAR STUDY
Hunter	X-linked recessive	sensorineural deafness	Short-trunked dwarfism, Mildly coarse facial features , Corneal opacities, Valvular heart disease , Flaring of rib cage , Cervical subluxation, Kyphosis, Ovoid vertebral bodies, Constricted iliac wings, Cervical myelopathy	IDS

Table 5: Sensorineural deafness - mitochondrial

DISEASE	INHERITANCE	HEARING LOSS	MAJOR FEATURES	MOLECULAR STUDY
Mitochondrial	recessive, dominant, x-linked, maternal or sporadic	sensorineural deafness	Ophthalmoplegia, Optic atrophy, Nystagmus ,Strabismus, Ptosis, Respiratory failure, Hypotonia, Ataxia, Dystonia, Dysarthria, Spasticity, Hyperreflexia, Seizures, Brainstem abnormalities, Mental retardation , Microcephaly, Lesions in basal ganglia, brainstem, cerebellum, thalamus, spinal cord characterized by demyelination, necrosis, gliosis, spongiosis, and capillary proliferation, Hypothyroidism, Hypoparathyroidism, Hyperinsulinism , Growth hormone defect	MTND2, MTND3, MTND5, MTND6, MTATP6, MTCO3, MTTV, MTTK, NDUFA2, NDUFA10, NDUFA12, NDUFV3, NDUFS1, NDUFS4, NDUFS7, NDUFS8, SDHA, FOXRED1, BCS1L, SURF1, COX15, C8ORF38, TACO1, C20ORF7, COX10, MTFMT, PET100, M2 B

Table 6: Mixed hearing loss

DISEASE	INHERITANCE	HEARING LOSS	MAJOR FEATURES	MOLECULAR STUDY
CHARGE association	Autosomal dominant	mixed	Postnatal growth retardation, Microcephaly, Micrognathia, Small ears, Colobomas (iris, choroid, retina, disc, and optic nerve) , Posterior choanal atresia, Tetralogy of Fallot, Atrial septal defect, Ventricular septal defect, Tracheoesophageal fistula, Duodenal atresia,Micropenis, Hypoplastic labia , Monodactyly, Ulnar hypoplasia, Tibial aplasia	CHD7, SEMA3E
Stickler	Autosomal dominant	mixed	vestigial gel in the retrolental space, bounded by a highly folded membrane,	COL2A1
Larsen	Autosomal dominant	mixed	Dislocation of the hip , Joint laxity , Dislocations of the elbows, Dislocations of the wrists , Dislocations of the knees	FLNB

Conclusions

In our review, we did not find any case of central deafness. Two of the most frequent causes of recessive conductive hearing loss (Pendred and Alport) and dominant sensor neural deafness (Warrensburg type 2) were also not detected.

The sooner we identify genetic syndromes responsible for sensor neural deafness and conductive hearing loss, the easier will be for us to do the genetic counseling in the future pregnancy.

Summary

Deafness occurs in 1 to 2 per 1000 newborns and in 2 per 1000 young children. Hearing loss is classified in: conductive, sensor neural, mixed and central type. The degree of severity is divided in: low (20 a 40 dB), moderate (41 a 60 dB), severe (61 a 90 dB) and profound (>90 dB).

Deafness has many causes, but genetic syndromes play an important role in his etiology.

In this review, we will talk about deafness secondary to the most important genetic syndromes.

References

1. Kral A, O'Donoghue GM (2010) Profound deafness in childhood. N Engl J Med 363: 1438.
2. Downs MP, Yoshinaga-Itano C (1999) The efficacy of early identification and intervention for children with hearing impairment. Pediatr Clin North Am 46: 79.
3. Parker M, Bitner-Glindzicz M (2015) Genetic investigations in childhood deafness. Arch Dis Child 100: 271.
4. Grundfast KM, Atwood JL, Chuong D (1999) Genetics and molecular biology of deafness. Otolaryngol Clin North Am 32: 1067.
5. Bowman M, Oldridge M, Archer C, O'Rourke A, McParland J, et al. (2012) Gross deletions in TCOF1 are a cause of Treacher-Collins-Franceschetti syndrome. Europ. J. Hum. Genet 20: 769-777.
6. Tan TY, Kilpatrick N, Farlie PG (2013) Developmental and perspectives on Pierre Robin sequence. Am J. Med Genet 163C: 295-305.
7. Beleza-Meireles A, Clayton-Smith J, Saraiva JM, Tassabehji M (2014) Oculo-auriculo-vertebral spectrum: a review of the literature and genetic update. J Med Genet 51: 635-645.
8. Goriely A, Lord H, Lim J, Johnson D, Lester T, et al. (2010) Germline and somatic mosaicism for FGFR2 mutation in the mother of a child with Crouzon syndrome: implications for genetic testing in 'paternal age-effect' syndromes. Am J Med Genet 152A: 2067-2073.
9. Fugazzola L, Mannavola D, Cerutti N, Maghnie M, Pagella F, et al. (2000) Molecular analysis of the Pendred's syndrome gene and magnetic resonance imaging studies of the inner ear are essential for the diagnosis of true Pendred's syndrome. J Clin Endocr Metab 85: 2469-2475.
10. Duggal P, Vesely MR, Wattanasirichaigoon D (1998) Mutation of the gene for IsK associated with both Jervell and Lange-Nielsen and Romano-Ward forms of Long-QT syndrome. Circulation 97: 142.
11. Mochizuki T, Lemmink HH, Mariyama M (1994) Identification of mutations in the alpha 3(IV) and alpha 4(IV) collagen genes in autosomal recessive Alport syndrome. Nat Genet 8: 77.
12. Pardono E, van Bever Y, van den Ende J, Havrenne PC, Lughetti P, et al. (2003) Waardenburg syndrome: clinical differentiation between types I and II. Am J Med. Genet 117A: 223-235.
13. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, et al. (2007) Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 44: 81-88.
14. Jones KL (1997) Smith's Recognizable Patterns of Human Malformation. 5th ed. Philadelphia, Pa: W.B. Saunders Company: 18-23.
15. Limal JM, Parfait B, Cabrol S, Bonnet D, Leheup B, et al. (2006) Noonan syndrome: relationships between genotype, growth, and growth factors. J Clin Endocr Metab 91: 300-306.
16. Saenger P, Wikland KA, Conway GS (2001) Recommendations for the diagnosis and management of Turner syndrome. J Clin Endocrinol Metab 86: 3061-3069.
17. Davenport SLH, Hefner MA, Mitchell JA (1986) The spectrum of clinical features in CHARGE syndrome. Clin Genet 29: 298-310.
18. Ebberink MS, Mooijer PAW, Gootjes J, Koster J, Wanders RJA, et al. (2010) Genetic classification and mutational spectrum of more than 600 patients with a Zellweger syndrome spectrum disorder. Hum Mut 32: 59-69.
19. Vellodi A (1999) Long-term follow-up following bone marrow transplantation for Hunter disease. J Inherit Metab Dis 638-648.
20. Mencarelli MA, Heidet L, Storey H, van Geel M, Knebelmann B, et al. (2015) Evidence of digenic inheritance in Alport syndrome. J Med Genet 52: 163-174.
21. Hoefs SJG, Dieteren CEJ, Distelmaier F, Janssen RJRJ, Epplen A, et al. (2008) NDUFA2 complex I mutation leads to Leigh disease. Am J Hum Genet 82: 1306-1315.
22. Rose PS, Levy HP, Liberfarb RM, Davis J, Szymko-Bennett Y, et al. (2005) Stickler syndrome: clinical characteristics and diagnostic criteria. Am J Med Genet 138A: 199-207.
23. Bicknell LS, Farrington-Rock C, Shafeghati Y, Rump P, Alanay Y, et al. (2007) A molecular and clinical study of Larsen syndrome caused by mutations in FLNB. J Med Genet 44: 89-98.