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Otolaryngological Diseases: A Genetic Overview

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Abstract: In a general population, otolaryngological diseases have a high incidence in with around 40% of consultations to health services is due to the ear, nose, and pharyngolaryngeal disorders. These pathologies are commonly misdiagnosed, which makes it difficult to establish a specific diagnosis, and leads to an inadequate therapeutic approach. Currently, there are different molecular techniques that facilitate the timely identification of some pathogens, and at the same time offer new treatment and management alternatives. Although, many of these still require more rigorous studies, however, they offer the possibility of developing new ways of approaching the patient.

Keywords: Otolaryngology; Otorhinolaryngological diseases; Genetics; Genetic polymorphism

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1. Introduction

The ear, nose, and throat (ENT) practices was implemented long ago, with the availability of records on ENT surgery dating back to 2500 BC, however, it's only became a specialize in the early 19th century, accompanied by the emergence and implementation of endoscopy. This is a specialty comprising the clinical and surgical management of pathologies of the ear, nasal cavities, paranasal sinuses, pharynx, and larynx with an approach based on the prevention, diagnosis, and treatment [1].

Otolaryngological diseases have a high incidence in the general population, both in acute and chronic pathologies, which is reflected by the primary medical care, where about 40% of the reasons for consultation in daily clinical practice are related to ear, nose, and pharyngolarynx problems [2,3].

It is of great importance to highlight that in the daily clinical approach to ENT pathologies, errors in establishing the specific diagnosis are common, mainly due to inadequate anamnesis, and incorrect or insufficient physical examination, consequently, patients receive an inappropriate therapeutic approach, thereby not referred to a specialized services care on time [4].

Currently, molecular biology, biochemistry, genomics, transcriptomics, and proteomics are specialized scientific areas that are presented as new alternatives to complement the ENT therapeutic approach based on the knowledge of the different genetic elements involved in ENT pathologies. The aim is to go beyond what is commonly known about the pathophysiology of the diseases, to take a more detailed approach to the aetiology, and altered processes within the disease, in order to intervene at the origin of the disease [5].

2. General

Acute otitis media (AOM) is a common ENT presenting disease in a pediatric population, with about 90% of children suffering from this disease it in their first 5 years of life [6,7]. The aetiopathogenesis of this condition is mainly attributed by the infectious processes, which can become recurrent therefore may lead

to various complications, such as tympanic membrane rupture, conduction deafness, language deficits or problems in educational development [6]. In addition, the Eustachian tube dysfunction often caused by the adenoid hypertrophy, allergic rhinitis and abnormalities in the nasal pyramid is the fundamental factor which causes the development of this disease [8].

AOM may be a secondary complication during an upper respiratory tract infection (URI). During these infections, cytokines play an important role as a defensive mechanism, due to their nature of functions, where, when activated it generates nasal discharge, induces inflammation, and subsequently the presence of severe respiratory infections [9].

The inflammatory process triggered in response to the aetiological agent is the characteristic of this pathology, where it is a critical step which contributes to the activation of the host defense mechanism; however, it sometimes becomes a harmful process for humans, significantly favoring the development and progression of otitis media (OM) with different clinical presentation, including OM with effusion, chronic purulent OM, and chronic OM with cholesteatoma [8].

Another common ENT pathology is allergic rhinitis (AR), which is defined as an inflammation of the nasal mucosa that is induced by allergens, where the causing symptoms are, such as sneezing, congestion, secretion, itching, and nasal obstruction. It is an atopic disease characterized by high levels of serum immunoglobulin E (IgE), overproduction of T-helper lymphocytes, cytokines, and accumulation of eosinophils in the nasal mucosa [10,11].

Symptoms related to the pharynx are another reason for frequent consultation in both the general and specialized services with acute pharyngitis occurs in 1.3% of hospitalized patients, its manifestations are very non-specific, further it can be confused with a common cold of viral origin. It is important to note that only 5-15% of cases in the adult population corresponds to bacterial aetiology (Streptococcus pyogenes), indicating that most of cases corresponding to the viral conditions do not require antibiotic treatment [12].

Next common ENT disorders in the environment are related to the daily life activities of the people. For example, for some professions the voice is the main means of work, which forces an overexertion of the voice which can gradually become a habit and consequently the mechanism of vocal production is altered in a prolonged manner, leading to conditions known as dysphonia [13]. The pathogenesis and maintenance of functional dysphonia can be better understood by focusing on the epidemiological factors both the triggers and facilitators which cause the vocal overexertion. At this point it is important to emphasize that, this disease is not only caused by the daily life activity, but also may cause by different acute or chronic conditions that participate in the pathophysiology of these vocal alterations. Among these aforementioned factors are pathologies such as [13]; Acute or reflux laryngitis; Laryngeal trauma; Allergic processes; Tonsillitis; Sinusitis; and Pharyngitis.

Finally, another pathology that is gaining importance in the environment due to its consequences is hypoacusis, where; around 50% of profoundly deaf children can be classified as having a genetic origin in which a large number of genes are involved, causing the heterogeneity in hereditary deafness [14].

3. Epidemiology

The distribution of ENT pathology has a predominance of those of otological origin, followed by chronic inflammatory diseases. In Chile, around 50% of consultations were reported to be due to otological pathology, where the most frequent reasons for consultation were chronic otitis media (CMO) with 20%, followed by tonsillar and rhinosinusal infectious pathology [2].

AOM is one of the most common pathologies of infectious origin, mainly in children under the age of 2 years, and is also the leading cause for antibiotic prescription at that early age. In Latin America and the Caribbean, there are reports of approximately 980,000 to 1,500,000 cases of AOM in 2009 [15]. The most frequent complication of AOM is acute mastoiditis (AM), although the use of antibiotics has reduced its

frequency, however, it currently has an annual incidence of 1.2 to 4.2 per 100,000 in children under the age of 14 years in developed countries [16].

An increase in childhood hearing loss has been observed with increasing age, starting from a perinatal incidence of 5 to 10 reports per 1,000 live births (including unilateral and mild hearing loss), and reaching figures of 7.6% between 6 and 11 years of age with 9% taking into account mild and unilateral hearing loss. It has been estimated that low-income countries have a higher prevalence of hearing loss, with 25% of those affected with the start of this pathological issue during childhood, which has been associated with poor school performance and continued poverty [17]. There are serious consequences of childhood deafness such as alterations in intellectual, social, and emotional development, despite these consequences, the mild and moderate hearing loss are the most difficult to diagnose, thereby this disease is not detected in about 50% of cases in children [17].

The most frequent otological pathologies in patients with genetic syndromes and congenital malformations are craniofacial pathologies, especially at the ears. Serous otitis media in patients with Down syndrome can be managed with ventilation tubes, but sometimes this procedure has to be repeated [18].

Among congenital malformations, cleft lip and palate, are the second most common with an incidence of 1/1,000 live births, of which cleft lip and palate, cleft palate and cleft lip account for 50%, 30%, and 20% respectively [18]. On the other hand, there are around 1-5% of prevalence of Fistula Auris, usually occur at the margin of the helix, where its main complication is infection, and may accompany with Treacher Collins, Goldenhar, and Brachiothorenal syndromes [18].

4. Genetics of ENT diseases

Single nucleotide polymorphisms (SNPs) are an important element in the genetics of many pathologies, as they include coding genetic sequences, non-coding regions of genes, and the intergenic regions, which may contribute to the changes in the expression of certain proteins, leading to the development of certain diseases [19].

AOM has an important genetic alteration, where heritability prevails, as well as being associated with other severe factors, such as pathogens, environment, young age, and others [7]. The susceptibility to inherit AOM is estimated to be between 40-60%, and the genetic factors associated with the increased susceptibility are related to genes that regulate cytokine production which may influence the severity, and inflammatory processes [7,20].

Components of the innate immune response that have been linked to the susceptibility to OM are Toll-like receptors (TLRs), CD14, mannose-associated lectins, and surfactants. TLRs belong to the pattern recognition receptors (PRRs), which are responsible for the release of proinflammatory cytokines and chemokines such as interleukins, Tumour Necrosis Factor-α (TNFα), and interferons. Meanwhile, CD14 plays an important role in the defense mechanism against microorganisms, especially during earlier ages. A functional polymorphism in the promoter of the CD14 gene has been reported by previous study, where the role of the T allele is being studied, which is thought to enhance transcriptional activity, thereby improve the immune response. Lectins are similar to TLRs, function as PRRs, and activate the complement system. Three SNPs known as B (Gly54Asp, rs1800450), C (Gly57Glu, rs36062788), and D (Arg52Cys, rs5030737) have been identified and are associated with the immune response process, therefore, play an important role in the disease development [21].

OM is a disease involving genetic alteration, therefore more research on the genetic modification related to OM should be conducted. More than 420 genes related to this pathology have been recently identified, including genes responsible for coding for TLR4, FBXO11, TNFα, and others. In addition, SNPs have been found related to certain loci such as, 19q13.43, 10q26.3, 2q31.1, 17q12, and 10q22.3 which are associated with the chronic and recurrent disease. Additionally, 2p23.1 encoding for CAPN14 and

GALNT14 genes, and 20q11.21 encoding for BPIFA gene associated with the OM development in general, however the associations of these SNPs with the disease have not been extensively studied or defined [22].

SNP in a gene encoding for cytokine, can modulate the overall production of the gene. For example, the production of interleukin-6 (IL-6) and TNF-α is normally associated with URI and OM, however, contrary to this, SNPs associated with IL-10, IL-1β, IL-5, and IL-8 have also been found and in this case protective functions of these cytokines in URI have been defined [9].

In non-syndromic congenital deafness, more than 100 involution loci have been identified, in addition to a high genetic variability, the most common pattern of inheritance is autosomal recessive, and is mostly caused by a mutation in the DFNB1 gene at 13q11-q12.8 locus, a location where the genes encoding the connexin 26 protein are located. There are other cases of autosomal dominant deafness and syndromic deafness that are related to mutations in the same gene, and often accompanied by dermatological manifestations [23].

Brain-derived neurotrophic factors (BDNFs) play an important role in the development of AR, including a secretory protein belonging to the neurotrophin family, which is involved in the stabilization of certain neural processes and contributes to the pathophysiology. Genetic variants of BDNF have been shown to be associated with the risk of severe asthma, including increased blood levels in patients with these phenotypes [24]. In both pathologies, an association between the protein tyrosine phosphatase non-receptor tyrosine phosphatase type 22-PTPN22 gene located on chromosome 1p13.2, and cytotoxic T lymphocyte-associated antigen-4-CTLA-4 has also been identified to likely play a role in the pathophysiology of these pathologies [19].

As mentioned above, variations in genes responsible for cytokine production have been shown to be associated with the development or complication of some ENT pathologies. For example, in the pathophysiology of RA, a SNP has been identified in the gene encoding IL-13, which is located on chromosome 5q31, where arginine is substituted to glutamine, thereby generating abnormalities in the functions of this interleukin, leading to poor IgE production due to the activation of certain molecules [11]. Likewise, SNPs in the rs40401 gene coding for IL-3 represent a risk factor for Rhinoconjunctivitis [25].

Rhinosinusitis is a pathology of multifactorial origin including predisposition and genetic deficiencies. Because of this, studies have been conducted to provide guidance on the inheritance of this pathology, mainly in the patients who are accompanied by nasal polyps with 14-42% heritability rate. In addition to these polyps, other alterations such as asthma have also been implicated [26]. Genes that related to the innate immune response associated with rhinosinusitis are including: Acyloxyacetyl hydroxylase; Interleukin-10; Interleukin-4; and Interleukin-4 receptor-associated kinase 4 (IRAK4) [26].

As mentioned above, the genetic alterations not only influence the development of pathologies, but also play an important role in the development of possible complications. For example, in sensorineural hearing loss, mutation in the mitochondrial DNA such as A1555G of the MTRNR1 gene is implicated in the worsening of the pathology after exposure to aminoglu-cosides such as streptomycin [27].

Recurrent tonsillitis is a very common ENT disorder in the pediatric population, treated primarily with antibiotics or surgical removal of the tonsils. This disease is caused by the sequential activity of pro-inflammatory cytokines such as interferon-γ (IFN-γ) and TNF-α, and the severity of this pathology is determined by the overproduction or deficit of the anti-inflammatory cytokines such as Inter- leukin-10 (IL-10) and Transforming Growth Factor-β (TGF-β) [27]. Accordingly, polymorphic mutations in the genes which are responsible for regulating the production of such cytokines have been found, such as SNP in which a 5' Thymine to Adenine shift occurs at the end of the CA repeat region in the first intron (+T874A) [28].

Numerous genetically encoded virulence factors have been found in streptococcal pharyngitis or pharyngotonsillitis, such as pili, M proteins, leukocidins, streptolysins, complement inhibitory proteins, and

superantigens, mechanisms which the micro-organism attacks the host immune system [29]. Furthermore, genetics factors, not only influences the changes in the natural history of the disease, but also plays an important role in the development of resistance to commonly employed treatments through efflux pumps, leukocyte evasion strategies, and a recently studied mechanism known as horizontal gene transfer (HGT), where these mechanisms not only confer additional virulence, but also allow the bacterium to have the ability to resist and alter the regulation of different genes by active flux through transmembrane pumps encoded by the MEF gene, and ribosomal modifications by Erm [29-31].

In addition to the aforementioned utilities, sequencing of the hypervariable N-terminal region of the gene coding for the M-protein (EMM) is also used in strep throat as the gold standard for the isolation of group A Streptococcus [32].

All this demonstrates that the extensive discoveries by molecular biology are tools that will soon be at the hand of the treating physician, not only as diagnostic tools but also as a molecular pharmacological approach to the patient.

5. Conclusion

ENT diseases are common pathologies in the daily clinical practice, with a wide spectrum disease, ranging from simple conditions that can be treated by the general practitioner for a very complex condition that required referral to a specialist; likewise, may occur in all ages through out of life.

Scientific and technology advances have made it possible to exploit new alternatives in the field of medicine focused on genetic approach on the management of pathologies. This gives an advantage for the doctors to learn the natural history of the disease, to predict the risk of developing a certain pathology, to know the possible outcome, and to have different molecular targets when choosing a targeted treatment.

Disclosure statement

The authors declare no conflict of interest.

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