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ORIGINAL ARTICLE

Expression of p63 and p73 in Acoustic Neuroma and Its Possible Clinical Relevance☆

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KEYWORDS
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Abstract
Objectives: Assess p63 and p73 expression in acoustic neuroma and its correlation with clinical and radiological findings.
Materials and methods: medical records of 34 patients who were operated on for acoustic neuroma during a 3-year period (2001–2003) were evaluated retrospectively. Immunohistochemical analysis of the schwannoma was performed with p63 and p73 antibodies and clinical patient characteristics were correlated with the immunoreactivity results.
Results: 41% of the acoustic neuroma specimens showed p63 and p73 staining. Correlation between both proteins was 100%. Age of the patients tended to be older when staining was positive, but no statistical significance was achieved. Likewise, tumour size was bigger for positive tumours but, again, this difference was not statistically significant. There was no correlation between gender and immunostaining.
Discussion and conclusions: Expression of p63 and p73 was demonstrated in almost half of the patients studied. Although both proteins were more prevalent in older patients and bigger tumours, this difference was not statistically significant, probably due to the reduced sample size. No differences were found in laterality, gender or audiogram. However, the expression of these two proteins in almost half of the tumours shows that they can play a role in the development and progression of acoustic neuromas, although further studies are needed.

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PALABRAS CLAVE
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Expresión de p63 y p73 en neurinomas del acústico y estudio de su posible relevancia clínica

Resumen
Objetivos: Determinar la expresión de p73 y p63 en muestras de neurinomas del acústico y estudiar su posible relevancia clínica.
Material y método: Se realiza un estudio retrospectivo de 34 neurinomas del acústico intervenidos durante un período de tres años (2001-2003). Se revisan sus historias clínicas y se realiza un estudio inmunohistoquímico para valorar la expresión de p63 y p73 en las muestras histológicas y la correlación con los hallazgos clínicos más relevantes.
Resultados: En el 41% de las muestras se observó una sobre-expresión de p63 y p73 siendo la correlación entre ambas proteínas del 100%. La edad de los pacientes con tinción positiva era mayor que la de los pacientes con tinción negativa sin llegar esta diferencia a ser estadísticamente significativa. El tamaño tumoral era mayor en los casos positivos, pero la diferencia tampoco ha llegado a niveles significativos. No existe correlación entre la expresión de los marcadores y el sexo, lado anatómico ni audiometría.
Discusión y conclusión: Se observa inmunotinción positiva para p63 y p73 en casi la mitad de los neurinomas estudiados. A pesar de encontrar que estas proteínas están más expresadas en casos de mayor edad y mayor tamaño, la diferencia no ha llegado a valores significativos, posiblemente por el número limitado de muestras en el análisis. Sin embargo, la expresión de estas proteínas en casi la mitad de los pacientes tratados, puede significar que juegan un papel en el desarrollo y progresión de estos tumores, aunque sería necesario realizar estudios futuros para determinar este papel.

Introduction

Acoustic neuromas (AN) are rare, slow-growing tumours that originate from Schwann cells of the 8th cranial nerve, generally from the vestibular nerve. Their molecular biology is still poorly understood, that hinders both the understanding of their origin and evolution and the development of a possible medical treatment.

A group of patients who develop AN also suffer an inherited, autosomal dominant disease known as type II neurofibromatosis (NF 2), which is clinically characterised by bilateral AN and other intracranial and spinal tumours. The *NF2* gene, located on chromosome 22q,[1] is a tumour suppressor gene that functions as a critical regulator of the growth of Schwann cells. Thus, *NF2* gene inactivation is an essential step in the tumourigenesis that occurs in these patients. The loss of chromosome 22q has been demonstrated in 45% of sporadic cases[2] and biallelic inactivation in almost 100% of AN in NF2 patients.[3] Sporadic forms account for 95% of all diagnosed AN.

In addition to the *NF2* gene, there are other genes involved in AN genesis. The genes of the neuregulin family appear to act as Schwann cell mitogens.[4] These proteins act via the c-erb family of receptors, with c-erb 2 and 3 being the main receptors in Schwann cells.[5–7] Fibroblast growth factors and their receptors (FGFR) also have a mitogenic effect on Schwann cells.[8] A relationship has been described between the expression of FGFR and tumoral growth.[9] The expression of various cytokines and other factors that may regulate the proliferation of Schwann cells has been described in several studies as listed below: studies on Ki-67,[10] proliferating cell nuclear antigen,[11] nerve growth factor receptor,[12] transforming growth factor receptor, fibroblast growth factor, endothelial growth factor, epidermal growth factor[6,7,12–16] and cyclin D1 and D3,[17,18] among others.

At present, the role played by p53, a tumour suppressor gene found mutated in over 50% of all cancers, in the genesis of AN is unknown. While several studies have shown that the contribution of p53 in AN genesis is unlikely,[19,20] another recent study indicates that loss of heterozygosity of the p53 gene occurs in a significant number of cases studied.[21]

The p63 and p73 genes belong to the p53 family and have numerous structural similarities. Their presence has been demonstrated in different types of human tumours, with a negative prognostic value in some of them, such as breast, bladder and hepatocellular carcinomas or B-chronic lymphocytic leukaemia.[22]

In this study we attempted to observe the expression of p63 and p73 by immunohistochemistry (IHC) in samples of AN intervened at our centre. We also attempted to assess the possible relationship of the expression of this protein with certain data obtained from the medical records of patients.

Material and Methods

Patients and Review of Medical Records

We reviewed the medical records of all patients diagnosed and intervened due to AN at the Otolaryngology Service of Donostia Hospital in San Sebastián between January 2000 and December 2002. We collected the demographic data of these patients: age, gender and symptoms, as well as information obtained from physical examinations and surgical