The Journal of Laryngology & Otology (2008), ***122***, *125–127.*

doi:10.1017/S0022215107000229
Printed in the United Kingdom
First published online 1 August 2007

Main Article

Expression and clinical significance of Ki-67, oestrogen and progesterone receptors in acoustic neuroma

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Abstract

Objective: The objective was to assess the presence of Ki-67, and oestrogen and progesterone hormone receptors as well as their clinical correlates in acoustic neuroma.

Methods: Medical records of 59 patients who were operated on for acoustic neuroma between 1995 and 2003 were evaluated retrospectively. Formaldehyde-fixed paraffin-embedded archival acoustic neuroma specimens of the patients were used for immunohistochemical assessments of oestrogen and progesterone hormone receptors, and Ki-67 proliferative marker.

Results: Tumour sizes were small (<19 mm), medium (20–39 mm) and large (>40 mm) in 21, 35 and 3 patients, respectively. On immunohistochemistry, all samples were (+) for progesterone receptor and (–) for oestrogen receptor staining. Ki-67 staining was encountered in 34 of 59 (57.6 per cent) patients, and Ki-67 values ranged from 0 per cent to 10.9 per cent (mean 1.36 per cent). There was no correlation between Ki-67, gender, tumour size and symptoms of the patients ($p > 0.05$).

Conclusion: Oestrogen is not an important hormone in acoustic neuroma due to the absence of oestrogen receptor expression in the tissue samples. Since the progesterone receptor is expressed in all acoustic neuroma samples, further studies are necessary to find out about the inhibitory effect of antiprogesterone treatment on acoustic neuroma growth, which may be important particularly in elderly people or high-risk patients. Although Ki-67 is expressed in the majority of acoustic neuromas, it is not an important marker in clinical practice due to a lack of any correlation with the clinical parameters.

Key words: Biological Tumour Markers; Estrogen; Progesterone; Ki-67 Antigen; Acoustic Neuroma

Introduction

Acoustic neuroma, which is a benign and encapsulated tumour of Schwann cell origin, constitutes 80 per cent of all tumours of the posterior fossa.[1,2] Oestrogen receptors may be detected in some intracranial tumours like meningioma and neurofibroma as well as acoustic neuroma.[3–5] This finding has promoted the search for an association of sex hormone receptors with acoustic neuroma. However, the clinical significance of oestrogen and progesterone receptors in acoustic neuroma has been debated.

Characterisation of the Ki-67 antibody revealed an interesting staining pattern. The antibody is reactive with a nuclear structure present exclusively in proliferating cells. A detailed cell cycle analysis revealed that the antigen is present in the nuclei of cells in the G1, S, and G2 phases of the cell division cycle as well as in mitosis. Quiescent or resting cells in the G0 phase do not express the Ki-67 antigen. Because the Ki-67 antigen is present in all proliferating cells (normal and tumour cells), presence of this structure is an excellent operational marker to determine the growth fraction of a given cell population. For this reason, antibodies against the Ki-67 protein have been increasingly used as diagnostic tools in different types of neoplasms.[6,7]

In this study, we aimed to assess presence of Ki-67, and oestrogen and progesterone hormone receptors as well as their clinical correlates in acoustic neuroma.

Materials and methods

Patients

Medical records of 59 patients with acoustic neuroma who were operated on in the Department of Otolaryngology between 1995 and 2003 were evaluated retrospectively. There were 32 female and 27 male patients. The ages ranged from 14 to 75 (mean 46.8) years. All patients had a posterior fossa approach for tumour removal. None of the patients was treated with steroids in the peri-operative period. Ages, genders, symptoms and duration of

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Accepted for publication: 7 June 2007.

symptoms of the patients were recorded. Tumour size was noted.

Histopathology and immunohistochemistry

Formaldehyde-fixed paraffin-embedded archival acoustic neuroma specimens from the patients were obtained from the department of pathology for immunohistochemical assessments. Five micron thick sections were obtained and the streptavidin-biotin indirect immunoperoxidase method was used. Oestrogen receptor Ab-148 (Clone 1D5+GF11), progesterone receptor Ab-8 (Clone hPRa2+hPPa3), and Ki-67 Ab-2 (Clone MB67) monoclonal antibodies were used. Breast and tonsil tissues were used as controls in the immunohistochemistry of oestrogen and progesterone hormone receptors, and Ki-67, respectively.

Hormone receptor staining was evaluated as present (+) or absent (−). For Ki-67 staining, dense staining areas were selected under light microscope. The numbers of Ki-67 positive cells per 1000 cells counted were calculated under high magnification (×400), and expressed as percentages.

Statistics

Pearson correlation and regression analysis tests were used for correlation analyses. Independent samples *t*-test and chi-square tests were used for comparisons between parametric and non-parametric data.

Results

Tumour sizes were small (<19 mm), medium (20–39 mm) and large (>40 mm) in 21, 35 and 3 patients, respectively. On immunohistochemistry, there was both nuclear and cytoplasmic staining for progesterone receptors. All samples were (+) for progesterone receptor and (−) for oestrogen receptor staining. Therefore, further statistical analyses could not be performed to evaluate association of the hormone receptors with the clinical data. Ki-67 staining was encountered in 34 of 59 (57.6 per cent) patients, of whom 11 were female and 14 were male patients. Ki-67 values ranged from 0 per cent to 10.9 per cent (mean 1.36 per cent). The mean Ki-67 values were 0.9 ± 1.8 per cent and 1.77 ± 2.6 per cent in male and female patients, respectively ($p > 0.05$). There was no correlation between Ki-67, gender, tumour size and symptoms of the patients ($p > 0.05$).

Discussion

Hormone levels that change in menopause and pregnancy might affect growth of intracranial tumours. It has been shown that cessation of oestrogen production that occurs in menopause may play a role in the development of brain tumours.[8] This assumption that was based on clinical observations has promoted the search for the significance of hormone receptors in acoustic neuroma. Although sex hormones like oestrogen and progesterone are considered to be associated with proliferation of acoustic neuroma, this issue has remained controversial.[9–13] Although oestrogen levels decrease and progesterone levels increase during pregnancy, no significant association could be shown between the presence or quantity of oestrogen or progesterone receptors and pregnancy, DNA ploidy, proliferation indices, or clinical data of the patients with acoustic neuroma.[14] A strict correlation between nuclear oestrogen and nuclear progesterone incidence was shown, and it was suggested that cytosolic progesterone levels inversely correlated with tumour size.[15] However, absence of oestrogen staining in our study indicates that oestrogen is not involved in acoustic neuroma occurrence or progression. By contrast, all samples showed positive staining for progesterone receptors. This may suggest an association between this hormone and acoustic neuroma.[16] In addition to that, antiprogesterone treatment of meningiomas was suggested to be promising in an animal model.[17] Therefore, the effect of this kind of treatment on acoustic neuroma may be investigated in the future.

- **This study aims to assess the presence of Ki-67, and oestrogen and progesterone hormone receptors as well as their clinical correlates in acoustic neuroma**
- **As the Ki-67 antigen is present in all proliferating cells, its presence is an excellent operational marker to determine the growth fraction of a given cell population**
- **Although Ki- 67 is expressed in the majority of acoustic neuromas it is not an important marker in clinical practice due to lack of any correlation with the clinical parameters**
- **Oestrogen is not an important hormone in acoustic neuroma**
- **Further studies are necessary to investigate the inhibitory effect of antiprogesterone treatment on acoustic neuroma growth**

Ki-67 is a proliferative marker that can be expressed in numerous neoplastic conditions. High Ki-67 expression shows rapid growth rate in a tumour.[18,19] Ki-67 staining may be more prominent in malignant intracranial tumours like anaplastic astrocytoma, glioblastoma, medulloblastoma and choroid plexus carcinoma, and may be less in benign tumours like ganglioma, ependymoma and meningioma.[20,21] High Ki-67 expression was also found in neurofibromatosis type 2.[18,19] Expression of this marker in acoustic neuroma has been investigated in numerous studies, and the rate of expression was found to range from 0 per cent to 11.6 per cent.[18,19,22,23] The expression rate of 1.36 per cent that was found in our study is comparable with the rates reported in the literature. It was also suggested that there may be a correlation between duration of the symptoms and Ki-67 expression.[24] Despite this contention, statistical analyses did not reveal any

https://doi.org/10.1017/S0022215107000229 Published online by Cambridge University Press

correlation between the marker expression and clinical parameters in our study.

In conclusion, oestrogen is not important in acoustic neuroma due to absence of oestrogen receptor expression in the tissue samples. Since progesterone receptors are expressed in all acoustic neuroma samples, further studies are necessary to find out the inhibitory effect of antiprogesterone treatment on acoustic neuroma growth. This may be particularly important in elderly people or high-risk patients, or after incomplete removal of acoustic neuromas. Although Ki-67 is expressed in the majority of acoustic neuromas, it is not an important marker in clinical practice due to lack of any correlation with the clinical parameters.

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Dr I Bayramoglu takes responsibility for the integrity of the content of the paper.
Competing interests: None declared