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Research Article

Prognostic Significance of The Ki–67 Labeling Index and P53 Protein Expression For Patient With Craniopharyngioma

Nagihan YALÇIN[1], Metin AKBULUT[1], Sedat ÇAGLI[2], Ferda BİR[1], Eren DEMİRTAŞ[3]

[1]Pamukkale University, School of Medicine, Department of Pathology, Denizli, Türkiye [2]Ege University, School of Medicine, Department of Neurosurgery, Izmir, Türkiye [3]Micropathology Laboratory, Department of Pathology, Izmir, Türkiye

Summary

Craniopharyngiomas are histological benign tumors. Craniopharyngiomas are slowly growing locally invasive intracranial tumors that can generate considerable morbidity and recurrences that are often difficult to manage. Reliable morphologic criteria for predicting clinical outcome of these tumors are lacking. The aim of the study was to investigate the prognostic value of Ki–67 labeling indices and p53 protein expression for recurrence in craniopharyngiomas. A series of 47 patients with craniopharyngiomas (29 male and 18 female; age range:4-74 years, mean years:31.4±17.8) were reviewed. Nine cases were papillary squamous and 38 cases were adamantinomatous variant. Tumors recurred in 10 (%21.2) patients (range 2-120, mean 23.2 months). Ki–67 labeling indices varied from 0 % to 12 % (mean 1.68±2.7 %). The ratio of p53 staining was 1-25% in 24 cases, in most majority (17 cases) it was under 10%. Ki–67 labeling index and p53 immunopositivity showed no statistically significant correlation with tumor recurrences and histological subtypes. Low Ki–67 labeling indices and p53 immunopositivity are common findings in the majority of craniopharyngiomas. Ki–67 labeling indices and p53 expression of primary tumors did not have prognostic value to predict tumor recurrence.

Key words: Ki–67, p53, craniopharyngioma, recurrence, prognosis

Kraniyofarinjiyomali Hastalarda Ki–67 Etiketleme İndexi ve P53 Protein Expresyonunun Prognostik Önemi

Özet

Kraniyofarinjiyomalar histolojik olarak benign tümörlerdir. Yavaş büyüyen, lokal olarak invaziv, tedavisi sıklıkla zor olan rekürrens ve önemli morbiditeye neden olabilen intrakranial tümörlerdir. Bu tümörlerde klinik gidişi belirleyecek güvenilir morfolojik kriterler yoktur. Bu çalışmanın amacı kraniyofarinjiyomalarda rekkürrens için Ki-67 proliferasyon indeksini ve p53 protein ekspresyonunun prognostik değerini araştırmaktır. Kraniyofarinjiyomalı 47 hasta (29 erkek, 18 kadın, yaş dağılımı:4-74 ve ortalama yaş: 31.4±17.8) çalışmaya alındı. 9 olgu papiller olguda skuamöz, 38 olgu ise adamantinomatöz tipti. 10 hastada (% 21,2) tümör nüksetti (2-120 ay, ortalama 23,2 ay). Ki-67 indeksi % 0-12 arasında değişiyordu (ortalama % 1.68±2.7). 24 olguda p53 immunpozitiflik oranları %1-25, olgularin büyük çoğunluğunda (17 olguda) % 10'un altında boyanmıştı. Ki-67 indeksi ve p53 immunpozitifliği ile tümör rekürrensi ve histolojik subtip arasında istatistiksel olarak anlamlı bir korelasyon saptanmadı. Kraniyofarinjiyomaların çoğunda düşük Ki-67 etiketleme indeksi ve p53 immunpozitifliği sık görülen bir bulgudur ve tümor rekürrensini belirlemede prognostik değeri yoktur.

Anahtar Kelimeler: Ki–67, p53, kraniyofarinjiyoma, rekürrens, prognoz

INTRODUCTION

Craniopharyngiomas are histological benign tumors arising in the sellar and third ventricular regions[5]. According to the classification of the World Health Organization (WHO), craniopharyngiomas correspond histological to tumoral grade I[19].

They comprise approximately 1.2–4.6 % of all cranial tumors and 5-10 % of the childhood non-neuroepithelial tumors[4].

They are composed of distinctive sheets of epithelial cells showing adamantinomatous or squamous-papillary histological types that were distinguished clinical and radiological[20].

A bimodal age distribution is observed, with peaks in children aged 5–14 years and in adults older than 50 years[4]. Although craniopharyngiomas are histological benign neoplasms, they do have a tendency to infiltrate the surrounding structures[4,5].

The cellular proliferation marker Ki–67 identifies a nuclear antigen that is expressed in the G1, S, G2 and M phases of the cell cycle. Ki–67 is an antigen that corresponds to a nuclear non- histone protein[3,7].

Mutations of the p53 tumor suppressor gene represent the most common genetic alteration in human tumors. The major functional activities of the p53 protein are cell cycle arrest, DNA repair, differentiation and apoptosis[13].

The aim of the study was to investigate the prognostic value of Ki–67 LI and p53 protein expression for recurrence in craniopharyngiomas.

MATERIAL AND METHODS

In this study, we reevaluated biopsy specimens that have been previously diagnosed histopathological and obtained from 47 patients at Ege and Pamukkale University Hospitals over a 14-year period (1987- 2001). Archival paraffin–embedded, formalin fixed tumor tissues and H&E stained sections formed the tissue resource for this study. Clinical information was obtained paraffin sections were immunostained with Ki–67μfrom the patients' records. 4 antigen (polyclonal antibody, rabbit anti-human; prediluted; DAKO) and p53 protein (monoclonal antibody, monoclonal mouse anti-human; prediluted; DAKO) on automated immunostainer (Ventana). A standard avidin-biotin-peroxidase technique was used with diaminobenzidine as the chromogen to obtain a brown nuclear reaction product. Negative and positive controls were included in the staining protocol.

Epithelial component was used to calculate LI % for uniformity and ease of comparison. The area with the highest epithelial Ki–67 labeling was identified and the number of Ki–67 immunolabeled nuclei within a 1000 cell field was counted manually under direct microscopy.

The degree of p53 expression was graded as follows: Score 0: no expression; Score 1: 1–10 %; Score 2: 11–25 %; Score 3: over 25 % expressions.

Data were expressed as mean +/- SD. Chi-square, Mann-Whitney U and Kaplan Meier tests were performed for statistical analysis. Chi-square test was used to test the association between p53 and clinical and histological characteristics of the patients. Mann-Whitney U- test was used to test the association between Ki-67 LI and clinical and histological characteristics of the patients. The Kaplan-Meier method was used to analyze the primary end point of recurrence of craniopharyngioma during follow up. Recurrence free survival was measured from the date of surgery to the date of relapse and was censored at the date of the last follow up. Statistical significance of differences and relationships was determined by p values of <0.05.

RESULTS

Biopsy specimens from 47 patients 29 (61.7 %) male, 18 (38.3 %) female, ranged in age from 4 to 74 were studied. The mean age of patients was 31.4±17.8 years.

Nine (19.1%) cases were papillary squamous and 38 (80.9%) cases were adamantinomatous variant.

31.50 months (range 3–168). Tumors±The mean follow-up period was 52.04 recurred in 10 (%21.2) patients (range 3–120 months). Four patients died during the follow-up period.

Ki–67 positivity was mainly confined to the peripheral palisaded epithelium of craniopharyngiomas. Ki–67 LIs varied from 0 % to 12% (mean 1.68±2.7 %) (Fig.1,2). No statistically significant difference in Ki–67 LIs was found between primary tumors and recurrent tumors. Ki–67 LIs did not show any statistically significant relationship with recurrence-free survival or overall survival, histological type, sex and ages of the individuals. Also the Ki–67 LIs of the primary tumors did not demonstrate any correlation with tumor recurrence, recurrence-free survival and overall survival. Recurrent tumors tended to display similar Ki–67 LIs like their primary counterparts.

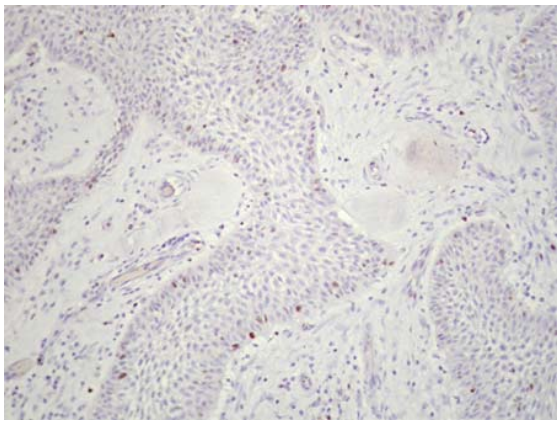

Fig 1: *Expression of Ki-67 in basal layers in craniopharyngiomas (Ki-67;200X)*

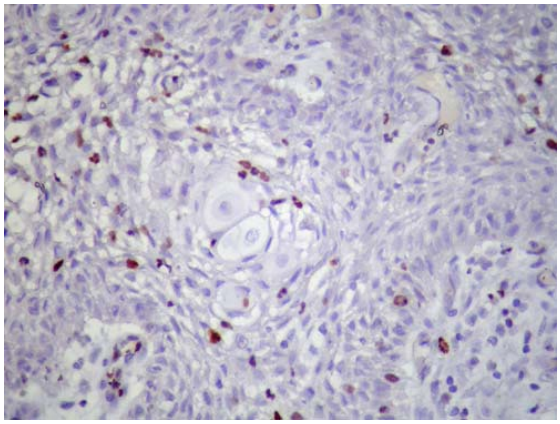

Fig 2: *Expression of Ki-67 in basal layers in craniopharyngiomas (Ki-67 ; 400X).*

Twenty-four (51.06 %) cases exhibited p53 immunopositivity. Seventeen (70.83%) cases showed p53 immunopositivity as score 1 (10 %) and 7 (29.17%) of them as score 2 (11–25 %) (Fig.3,4). There was a focal staining pattern, P53 staining was not diffuse throughout the epithelium. No significant relations were found between the p53 expression and tumor recurrence, histological type, age and sex. The p53 expression of the primary tumors did not demonstrate any correlation with tumor recurrence, recurrence-free survival and overall survival.

Clinical, histopathological and immunohistochemical findings were shown in Table 1.

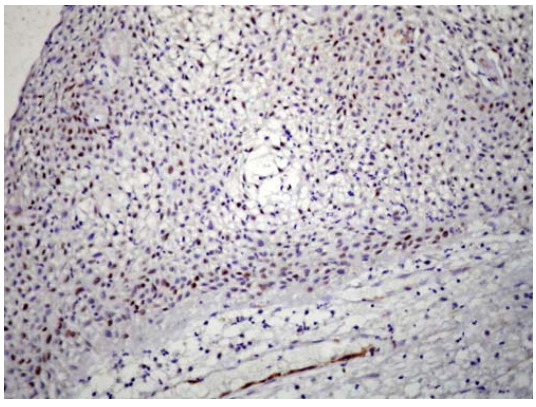

Fig 3: *Expression of p53 score 2 (p53: 200X).*

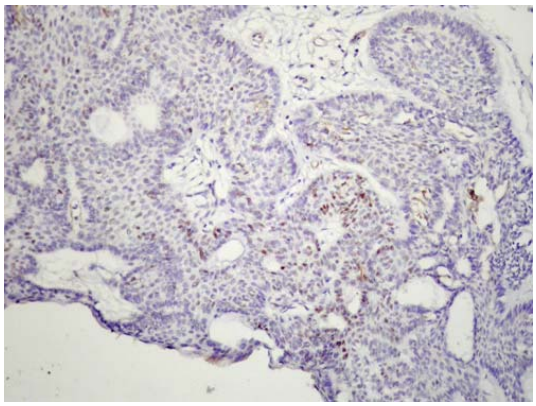

Fig 4: *Expression of p 53 sore 1 (p53: 200X).*

Table 1 Clinical, histopathological and immunohistochemical findings in craniopharyngiomas

Case no	Age	Sex	Histological type	Ki-67 (%)	P53 score	Recurrence	Recurrence First time (months)	Follow up (months)
1	29	M	P	0	1	No		60
2	17	F	A	0	0	No		60
3	54	M	A	0	0	No		60
4	15	M	P	0	2	No		60
5	11	F	A	0	0	Yes	2	12
6	36	F	A	0	1	No		168
7	55	M	A	0	0	No		60
8	4	F	A	0	0	No		60
9	30	M	A	0	0	No		60
10	11	M	A	0	1	No		60
11	12	M	A	1.4	1	Yes	8	36
12	17	M	A	0.3	0	No		60
13	48	F	A	1	0	No		120
14	4	F	A	4	1	Yes	24	36
15	22	F	A	0	0	No		36
16	19	M	A	1	1	Yes	6	12
17	46	F	P	7	1	No		120
18	45	M	A	0,2	0	No		72
19	62	F	P	3.4	1	No		60
20	14	F	A	0	1	Yes	24	48
21	36	M	A	0	0	No		36
22	16	F	A	0	1	No		60
23	37	M	P	0	1	No		72
24	66	M	P	6	1	No		12 exitus
25	24	M	A	0	2	No		36
26	34	M	A	0	1	No		84
27	12	M	A	0	1	No		60
28	12	F	A	0	1	No		36
29	24	F	A	2	0	No		60
30	43	M	A	5	0	No		38
31	18	F	A	0	0	No		36
32	58	F	A	3	0	No		48
33	14	M	A	0	0	No		12
34	47	F	A	0	0	No		60
35	40	M	P	12	0	No		36
36	38	M	P	2	0	No		48
37	26	M	A	1	0	No		48
38	10	M	A	0	2	No		48
39	11	F	A	0	0	No		24
40	74	M	P	0	0	Yes	7	36
41	44	M	A	4	0	Yes	11	17exitus
42	39	M	A	3	1	Yes	24	36 exitus
43	56	M	A	1.2	1	Yes	120	120
44	26	M	A	1	2	No		72
45	34	F	A	8	2	Yes	6	3exitus
46	53	M	A	8.8	2	No		24
47	33	M	A	2	2	No		24

DISCUSSION

Craniopharyngiomas are slow growing locally invasive intracranial tumors that can generate considerable morbidity and recurrences that are often difficult to manage. Reliable morphologic criteria for predicting clinical outcome of these tumors are lacking[17].

Kayaselcuk et al found that Ki–67 LIs varied from 0.20% to 3.60% (mean 1.90 ±2.40) in two cases. In our cases Ki–67 LIs varied from 0 % to 12% (mean 1.68±2.7 %) [9].

Nishi et al reported that craniopharyngiomas with Ki–67 LIs of 7 % or higher have a significantly higher tendency for recurrence[16]. But other studies demonstrated that Ki–67 LIs of the primary tumor did not have prognostic value for predicting tumor recurrence[1,6,10,14,15,17]. In our study, we found no significant correlation with primary tumors and recurrent tumors via Ki–67 LIs . Raghavan et 3,7) and in adults as±al reported Ki–67 LIs in children as 1,8–15 % (mean 6,3 9,8)±0,1–34,6 % (mean 8,9 [17]. In our study, we found no differences in Ki–67 LIs between children and adults. Kato K et al showed that the palisading cells of the typical adamantinamatous type craniopharyngiomas were more frequently Ki-67-positive (average 0.076) than the stellate cells (average 0.022). Basal and intermediate cells were stained in the papillary type craniopharyngiomas, the rates being 0.22 and 0.05, respectively. The surface cells were almost negative[8]. We observed similar staining pattern of Ki-67 in this study.

There are few reports concerning p53 positivity in craniopharyngiomas in the literature[11,12,15]. Lefranc et al. reported that p53 immunoreactivity may differ the process of keratin turnover in craniopharyngiomas[12]. Kristopaitis et al. reported that p53 was expressed in fewer than 10 % nuclei within the areas of typical craniopharyngioma but up to 75 % nuclei in areas of focal squamous cell carcinoma[11]. Similarly Boongird et al reported that p53 was expressed 98 % nuclei in malignant craniopharyngiomas[2]. The p53 protein was found in low levels in craniopharyngiomas[11,18].

Tena-Suck et al showed that p53immunoreactivity and the presence of whorl-like arrays were associated with recurrence[21]. Our study did not show any correlation with p53immunoreactivity and recurrence.

Momota et al. reported occasional and weak p53 immunopositivity in the two histological types of craniopharyngiomas. However p53 family members in two histological types of tumor, strong nuclear expression of p63 and moderate to intense nuclear expression of the p73 were observed in all cell layers[15]. We observed p53 immunoreactivity in 24 (51.06 %) cases. 17 (70.83 %) cases showed p53 immunopositivity as score 1 (10 %) and 7 (29.17%) of them as score 2 (11–25 %). This finding was consistent with literature knowledge as described above. But we failed to demonstrate any statistically significant correlation between p53 immunoreactivity and other biological and clinical features in craniopharyngiomas.

As a conclusion, p53 over-expression and Ki–67 labeling indices (LIs) of primary tumors did not have prognostic value for predicting tumor recurrence.

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Correspondence to:
Nagihan Yalcin
E-mail: nyalcin@pau.edu.tr

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