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Meningiomas are one of the most frequent intracranial tumours, with 13 histological types and three grades according to the 2007 WHO Classification of Tumours of the Central Nervous System. p53, as one of the most potent tumour suppressor proteins, play a role in nearly 50% of human tumours. Poly ADP-ribose polymerase (PARP) is a DNA repair enzyme with high ATP demand. It plays a role in apoptosis by activating apoptosis inducing factor, and in necrosis by consuming NAD+ and ATP. Only PARP1 has been investigated in details in tumours out of the 17 members of the PARP superfamily; however, its role has not been studied in meningiomas yet. The aim of this study was to determine the role of p53 and PARP1 in meningiomas of different grade and to establish whether there is any correlation between the p53 and PARP1 expression. Both PARP1 and p53 has been expressed in all examined meningiomas. PARP1 labelled grade II tumours with higher intensity as compared to grade I and III neoplasms, respectively. Increased p53 expression was noted in grade III meningiomas. There was no statistical correlation between p53 and PARP1 expression. Our data indicate that both PARP1 and p53 activation is a feature in meningeomas of higher grade, PARP1 overexpression being an early whereas p53 a late event in tumour progression.

Keywords:

Meningioma, Poly ADP-ribose polymerase (PARP), p53

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PARP1 and p53 labelling index correlates with tumour grade in meningiomas.

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Abstract

Meningiomas are one of the most frequent intracranial tumours, with 13 histological types and three grades according to the 2007 WHO Classification of Tumours of the Central Nervous System. p53, as one of the most potent tumour suppressor proteins, play a role in nearly 50% of human tumours. Poly ADP-ribose polymerase (PARP) is a DNA repair enzyme with high ATP demand. It plays a role in apoptosis by activating apoptosis inducing factor, and in necrosis by consuming NAD+ and ATP. Only PARP1 has been investigated in details in tumours out of the 17 members of the PARP superfamily; however, its role has not been studied in meningiomas yet. The aim of this study was to determine the role of p53 and PARP1 in meningiomas of different grade and to establish whether there is any correlation between the p53 and PARP1 expression. Both PARP1 and p53 has been expressed in all examined meningiomas. PARP1 labelled grade II tumours with higher intensity as compared to grade I and III neoplasms, respectively. Increased p53 expression was noted in grade III meningiomas. There was no statistical correlation between p53 and PARP1 expression. Our data indicate that both PARP1 and p53 activation is a feature in meningeomas of higher grade, PARP1 overexpression being an early whereas p53 a late event in tumour progression.

Key words

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Introduction

Meningiomas are frequent primary brain tumours representing approximately 30% of all primary intracranial tumours. The incidence is increasing with age and has slight female predominance [32, 59]. The aetiology is not entirely understood, but the increased risk after whole brain radiation therapy is well-known [38]. There are several subtypes, like meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte rich, sometimes with crystalline inclusions [5], metaplastic, choroid, clear cell, rhabdoid, papillary and other rare or miscellaneous types [34]. According to the ultrastructural findings, some of the intranuclear vacuoles are produced during autophagy [18]. The heterogeneous glycosylation pattern has also been demonstrated in different subtypes of meningiomas, and it indicates the usefulness of lectins in the evaluation of pluripotential differentiation of meningioma cells [56]. The current prediction of clinical behaviour is based on the morphological findings, brain invasion, mitosis index and Mib1 immunostaining [1, 47, 48]. Meningiomas show positive immunoreactivity for epithelial membrane antigen, oestrogen and progesterone receptors [45]; however these immunohistochemical markers do not help with the determination of the grade. CD31 immunostaining is good for revealing the blood vessel number that is higher in atypical meningiomas than WHO Grade I tumours [31], but this marker is not used in routine diagnostic work-up. Despite of these findings there is need of more “malignant” markers for meningiomas that can be used in routine diagnostic work and a group of them could be the DNA repair genes like p53 or Poly ADP-ribose polymerase (PARP) in the future.

PARP protein superfamily has 17 members. All of them have four domains: catalytic, auto-modification, caspase-cleaved and DNA-binding domain. Some of them have PARP activity as PARP1 or PARP2 and some of them do not, as PARP3 or PARP6.

PARP1 is a 113 kDa protein, located in the nucleus. The gene of PARP1 located on the long arm of chromosome 1 (1q42.12). The cDNA isolated and sequenced firstly by Kurosaki *et al.* [26]. One of the main functions of PARP1 is role in the repair of single-stranded DNA brakes (SSB). After detecting the SSB damage by chemical, radiation or metabolic induction, the enzyme is activated and binds to the DNA, undergoes a structural transformation before it produces poly ADP-ribose (PAR) chain by a nicotinamide adenine dinucleotide (NAD+), consuming process. PAR is a signal for other repair genes during base excision repair (BER) [9, 29, 35]. Activated PARP1 can poly ADP-ribosylate (PARylate) nuclear enzymes thereby increasing the negative charge and preventing the interaction with other anionic molecules including the DNA. Among the DNA repair functions, activated PARP1 has a vital role in apoptosis by translocation of the apoptosis inducing factor (AIF) from the mitochondria to the nucleus [60, 61]. However, if there is a high level of DNA damage, necrotic cell death is triggered by activating a large number of PARP1, consuming NAD+ and the ensuing ATP depletion [3]. The role of PARP1 activation cascade has also been demonstrated in neuronal stem cell transplantation after brain injury in rats [27], as well as PARP1 also activated in the ischemia-reperfusion injury [55], and the early activation of PARP1 after cold lesion that is - at least in part - related to neuronal NO synthetase (nNOS) induction [16]. The role of PARP1 has been revealed in the regulation of glycogen synthase kinase-3 (GSK3) that is responsible for the hyperphosphorylation of tau [54], and the amyloid peptide affected signal transduction to PARP1 in Alzheimer disease [2].

It has been demonstrated that the PARP1 has a role in the BRCA1/BRCA2 mutated breast carcinomas because PARP1 inhibitors can trigger the effectiveness of the chemotherapeutic

agents by inhibiting the SSB-repair, when the double-stranded DNA repair is also diminished by the BRCA mutation [11]. The role of PARP1 has been described in other tumours as breast [51], ovarian [6], pancreatic carcinomas [24], gastric carcinomas [62], prostate carcinomas [53], melanomas [13, 40] and glioblastomas [12, 21] but has not been investigated in meningiomas yet.

p53 is one of the most significant tumour suppressor proteins, encoded by *TP53* gene on the short arm of the chromosome 17 (17p13.1) [17, 33]. The physiological functions of p53 are cell cycle regulation and conserve the stability of the genome by preventing mutations. The 393 amino acid long, 43.7 kDa weight protein has 7 domains, such as two activation domain (AD1 and AD2), a prolin-rich domain, a DNA-binding core domain (DBD), a signalling domain, a homo-oligomerisation domain (OD) and a C-terminal downregulation domain. p53 can be activated by DNA damage, oxidative stress, osmotic shock, ribonucleotide depletion or oncogene expression. The activation is marked by an increase in the half-life of p53 and a change of its conformation [22]. Mdm2 is responsible for the low level of p53 in an unstressed cell, by binding to p53 and preventing its action, and it also transports p53 to the cytosol, and attaches ubiquitin to it covalently.

The anticancer activity of p53 works through several mechanisms: it activates DNA repair proteins, induces growth arrest at the G1/S regulation point through p21 [10] or initiates apoptosis if the DNA damage is irreversible. Mutagens can damage *TP53* causing unregulated cell proliferation more than 50 percent of human tumours contain a deletion or mutation of TP53 gene [15]. p53 was voted the molecule of the year in 1993 by Science magazine [25], due to its key roles.

The role of p53 has already been examined in the meningiomas: some of the examinations ended with negative or equivocal findings [43, 48-50], but some of them showed a significant correlation between the p53 status and the grade or recurrence of the tumour [4, 7, 8, 19, 20, 28, 37, 41, 44, 46, 57]. It is also described that p53 immunopositive cells are more frequent in the perinecrotic areas of post-embolised cases than in preserved parts of the tumour [39].

Several theses have been written about the interaction between the PARP1 and the p53. Wieler *et al.* showed that the inhibition of endogenous PARP1 functions suppresses the transactivation function of p53 in response to ionizing radiation; hence PARP1 is a key regulator of the p53 response to DNA damage [58]. Malanga *et al*. showed that ADP-ribose polymers play role in regulating the DNA binding properties of p53 by preventing and reversing p53 binding to the palindromic p53 consensus sequence [36]. Lee *et al.* recently discovered a novel role for PARylation of p53 in the gene-specific regulation of the transcriptional mode of p53 on the promoter of MTA1 [30]. Godoy *et al.* revealed overexpression of PARP1 and p53 in high grade and advanced stage tumours in epithelial ovarian cancer, and it indicated that these 2 markers might serve as an marker of aggressive disease behaviour [14]. Sabisz *et al.* showed the crucial part of PARP1 activity in the maintenance of the G2 arrest induced by DNA damaging drugs; thus inhibitors of PARP1 may be used as non-genotoxic agents to activate p53 in cancer cells with non-functional p53 pathways [52]. PARylation of transcription factors such as p53, NFkB, and Sp1 prevents their binding to DNA and formation of transcription complexes [42].

The aim of this study is to find any correlation between the PARP1 and p53 immunostaining and the WHO grade of the tumours, and there is some correlation between the PARP1 and p53 immunopositivity.

Materials and methods

The histological slides of 31 meningioma patients have been studied. Patients have been divided into three groups according to the WHO Classification of Tumours of the Central Nervous System [34]. After the surgical removal sections were created and stained for haematoxylin-eosin (H&E) from formalin fixed and paraffin embedded (FFPE) blocks for routine diagnostic procedure in the Institute of Pathology. All of the cases have been revised by a consultant neuropathologist (TH).

Immunohistochemistry (IHC) has been performed according to standardized methods as described in details, in earlier publications [17, 33]. In brief, 4 µm thick sections from FFPE blocks have been stained for PARP1 rabbit polyclonal antibody (ab6079) (Abcam Plc., Cambridge, England) and p53 DO-7 mouse monoclonal antibody (M7001) (DAKO, Denmark) according to the manufacturers' protocol. Using a 1:500 and 1:700 dilution for PARP1 and p53, respectively with Novocastra Bond™ Polymer Refine Detection kit on Leica Bond Max™ fully automated IHC stainer, with negative controls (Fig. 1.).

100 cells in 10 fields of vision on 40x magnification have been examined; the staining intensity has been evaluated as none (O), weak (1+), moderate (2+) and strong (3+) from all of the slides for both PARP1 and p53 (Fig. 2.). We have created two parameters in all cases regarding to the staining intensity (Si) ratio of the 1+, 2+ and 3+ cells Si1-3, and ratio of the 2+ and 3+ cells Si2-3, similarly as HER2 immunohistochemistry evaluation in breast carcinomas (Table 1.).

The results have been analysed by SPSS 19.0 for Windows statistical software. After comparing with Kruskall-Wallis H test the Si1-3 and Si2-3, performing Mann-Withney U test on all of the grade pairs for both PARP1 and p53. As next, we have created two groups – low grade (WHO Grade I) and high grade (WHO Grade II and WHO Grade III) [23] and have compared them by Mann-Withney U test. We also have performed Spearman's rank order correlation analysis to determine whether there is any correlation between the PARP1 and p53 immunopositivity.

Ethical approval has been sought from the Institutional Research Ethics Committee.

Results

Both PARP1 and p53 has been expressed in all of the 41 cases.

There was a significant correlation between tumour grade and presence of PARP1 expression (staining intensity (Si)1-3) (p=0.001) and presence of explicit positivity (Si2-3) for p53 (p=0.012), respectively, with Kruskall-Wallis H test. In contrast, there was not any statistically significant association between grade and Si2-3 for PARP1, Si1-3 for p53, p=0.523 and p=0.141, respectively.

As next, we have compared different grades and performed Mann-Whitney U test. The Si1-3 for PARP1 between grade I and grade II as well as grade II and grade III (Fig. 3A.); and the Si2-3 for p53 between grade I and grade III (Fig. 3B.) significantly correlated with the WHO Grades (p=0.001 and p=0.005, p=0.002, respectively). The grade II tumours showed the highest mean index of the PARP1 staining (Fig. 3A.), while grade III tumours had the highest staining index for p53 (Fig. 3B.).

The Man-Whitney U test, have been performed on the low grade, and high grade groups showed a significant correlation between Si1-3 for PARP1 (Fig. 3C.) and Si2-3 for p53 (Fig. 3D.), p=0.028 and p=0.018, respectively.

Among the grade I tumours there were 11 meningothelial, 8 transitional, 1 secretory, 1 fibrous and 1 microcystic; among grade II tumours 8 atypical and 3 clear cell; all the grade III tumours were anaplastic (i.e. no papillary and rhabdoid). There was no significant difference between the staining intensity of PARP and p53 between subtypes of any grades; however the case numbers were rather low to make statistically valid comparisons.

There was no significant correlation between PARP1 and p53 with Spearman's rank order correlation analysis (Fig. 4.).

Discussion

Meningiomas are one of the most frequent intracranial tumours with diverse morphological variants. The current WHO classification [34] distinguishes 13 histological types. 9 of them belong to grade I; 2-2 belongs to grade II and grade III, respectively. There are morphological criteria that define atypical (WHO Grade II) and anaplastic (WHO Grade III) meningiomas; however, distinction is often difficult. Until now there is no highly trusted immunohistochemical marker that can separate the different WHO Grades reliably.

PAPR1 protein role has been demonstrated in the repair of the damaged DNA, however this protein also has an important role in the caspase independent apoptotic pathway and in necrotic cell death. p53 is one of the most important tumour suppressor protein, it has a role in almost half of the human tumours. Several studies have been performed about the p53 marker,

but those ended with equivocal results. PARP1 protein expression in meningiomas has not been examined yet.

In this study all of the 41 cases showed immunopositivity for both PAPR1 and p53. The proportion of positive cells (Si1-3) was higher in grade II tumours for PARP1, as compared to grade I and grade III meningiomas, respectively. Increased immunopositivity (Si2-3) was noted in the grade III tumours for p53. Comparing the immunopositive cells in the low grade meningiomas (grade I) and in the high grade meningiomas (grade II and grade III) we found and more immunopositive cells (Si1-3) for PARP1 and higher staining intensity (Si2-3) for p53 in the high grade tumours.

Performing a Spearman's rank order correlation and linear regression there was no statistical correlation between either the presence of positivity or the intense immunoreactions for p53 and PARP1, thus the expression of these two proteins does not appear to be related to each other. We suggest that PARP1 activation increases in grade II tumours to cope with the DNA damage, whereas in grade III tumours PARP1 activity is decreased as a consequence of apoptotic-necrotic cell death and preceding overactivation and consecutive consumption of the protein and substrates.

Our data confirm that p53 protein plays a role in meningiomas, and indicate that the p53 activation might be a late event in the progression of meningothelial neoplasms.

Although further studies are necessary to elucidate the role of PARP1 and p53 in meningiomas, our date indicate that PARP1 and p53 immunohistochemistry are useful and simple methods aiding the accurate diagnosis and grading of meningiomas.

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Legends:

Table 1. Data sheet on cell counts showing staining intensities and their respective proportion to all counted cells.

Staining index (Si)1-3 is ratio of the immunopositive (1+, 2+, 3+) cells; and the Si2-3 is ratio of the intense positive (2+, 3+) cells. (PARP1 - Poly ADP-ribose polymerase 1)

Figure 1.: p53 and PARP1 immunostaining in meningiomas of different WHO grades.

Haematoxylin-eosin (A, B, C) and immunohistochemical staining for p53 (D, E, F) and PARP1 (G, H, I) of grade I (A, D, G), grade II (B, E, H) and grade III (C, F, I) tumours. (PARP1 - Poly ADP-ribose polymerase 1) (scale bar 100µm).

Figure 2.: Representative images of the different staining intensities.

Immunostaining are performed for p53 (A, B, C, D) and PARP1 (E, F, G, H). There are negative (A, E), weak – 1+ (B, F), moderate – 2+ (C, G) and strong – 3+ (D, H) positive cells. (PARP1 - Poly ADP-ribose polymerase 1) (scale bar 10µm)

Figure 3.: p53 and PARP staining intensity varies according to the tumour grade.

Mean values of the staining index (Si)1-3 for PARP1 (A, C) and Si2-3 for p53 (B, D) regarding to the WHO grades (A, B), and low grade – WHO grade I and high grade – WHO grade II and WHO grade III (C, D). Error bars +/- standard error of mean (SEM). p values are calculated by Mann-Whitney U test. (PARP1 - Poly ADP-ribose polymerase 1; staining index (Si)1-3 is ratio of the immunopositive (1+, 2+, 3+) cells; and the Si2-3 is ratio of the intense positive (2+, 3+) cells)

Figure 4.: Correlation between p53 and PAPR1 staining intensity.

There are dot plot and linear correlation of the results of staining indices. The p values are evaluated by Spearman’s rank order correlation test. There are not significant correlations between the staining indices. (PARP1 - Poly ADP-ribose polymerase 1, staining index (Si)1-3 is ratio of the immunopositive (1+, 2+, 3+) cells; and the Si2-3 is ratio of the intense positive (2+, 3+) cells)

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Table 1

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Patient No.	Slide No.	WHO Grade	Subtype	PARP1						p53					
				0	1+	2+	3+	Si1-3	Si2-3	0	1+	2+	3+	Si1-3	Si2-3
1	1	I	meningothelial	5	85	9	1	0.95	0.1	49	34	14	3	0.51	0.17
2	2	I	meningothelial	16	39	37	8	0.84	0.45	49	43	8	0	0.51	0.08
3	3	I	meningothelial	22	74	4	0	0.78	0.04	70	27	3	0	0.3	0.03
4	4	I	transitional	10	65	25	0	0.9	0.25	46	50	4	0	0.54	0.04
5	5	I	meningothelial	26	50	13	11	0.74	0.24	57	39	4	0	0.43	0.04
6	6	I	meningothelial	8	83	9	0	0.92	0.09	76	24	0	0	0.24	0
7	7	I	transitional	32	66	2	0	0.68	0.02	75	24	1	0	0.25	0.01
8	8	I	meningothelial	15	83	2	0	0.85	0.02	52	34	14	0	0.48	0.14
9	9	I	secretory	22	75	3	0	0.78	0.03	75	17	7	1	0.25	0.08
10	10	I	meningothelial	23	37	38	2	0.77	0.4	71	23	6	0	0.29	0.06
11	11	I	fibrous	21	30	24	25	0.79	0.49	47	50	3	0	0.53	0.03
12	12	I	transitional	15	66	19	0	0.85	0.19	53	38	9	0	0.47	0.09
13	13	I	meningothelial	7	93	0	0	0.93	0	86	12	2	0	0.14	0.02
14	14	I	meningothelial	11	68	20	1	0.89	0.21	76	23	1	0	0.24	0.01
15	15	I	microcystic	5	36	59	0	0.95	0.59	83	17	0	0	0.17	0
16	16	I	transitional	10	85	4	1	0.9	0.05	52	43	5	0	0.48	0.05
17	17	I	transitional	6	89	5	0	0.94	0.05	73	21	6	0	0.27	0.06
18	18	I	transitional	16	33	48	3	0.84	0.51	79	18	3	0	0.21	0.03
19	19	II	atypical	10	77	11	2	0.9	0.13	60	30	10	0	0.4	0.1
20	20	II	atypical	8	64	26	2	0.92	0.28	76	24	0	0	0.24	0
21	21	II	atypical	1	67	32	0	0.99	0.32	85	13	2	0	0.15	0.02
22	22	II	clear cell	2	80	18	0	0.98	0.18	68	29	3	0	0.32	0.03
23	23	II	atypical	14	71	10	5	0.86	0.15	78	18	4	0	0.22	0.04
23	24	I	transitional	9	72	16	3	0.91	0.19	69	31	0	0	0.31	0
24	25	II	atypical	6	71	21	2	0.94	0.23	80	18	2	0	0.2	0.02
25	26	II	atypical	1	84	15	0	0.99	0.15	72	23	5	0	0.28	0.05
25	27	II	clear cell	1	44	53	2	0.99	0.55	44	39	15	2	0.56	0.17
25	28	II	clear cell	0	27	49	24	1	0.73	38	32	27	3	0.62	0.3
25	29	I	meningothelial	10	81	9	0	0.9	0.09	67	29	4	0	0.33	0.04
25	30	I	meningothelial	4	77	16	3	0.96	0.19	71	21	6	2	0.29	0.08
25	31	I	transitional	9	82	9	0	0.91	0.09	67	27	6	0	0.33	0.06
26	32	II	atypical	0	33	63	4	1	0.67	35	39	26	0	0.65	0.26
27	35	III	anaplastic	10	81	9	0	0.9	0.09	59	29	10	2	0.41	0.12
27	34	III	anaplastic	8	42	40	10	0.92	0.5	30	47	22	1	0.7	0.23
27	33	II	atypical	4	83	10	3	0.96	0.13	71	21	7	1	0.29	0.08
28	36	III	anaplastic	10	74	15	1	0.9	0.16	42	28	17	13	0.58	0.3
28	37	III	anaplastic	20	66	14	0	0.8	0.14	49	20	17	14	0.51	0.31
28	38	III	anaplastic	4	47	48	1	0.96	0.49	79	19	2	0	0.21	0.02
29	39	III	anaplastic	14	71	14	1	0.86	0.15	68	22	7	3	0.32	0.1
30	40	III	anaplastic	25	73	2	0	0.75	0.02	54	26	13	7	0.46	0.2
31	41	III	anaplastic	28	62	10	0	0.72	0.1	76	15	9	0	0.24	0.09

Figure 1

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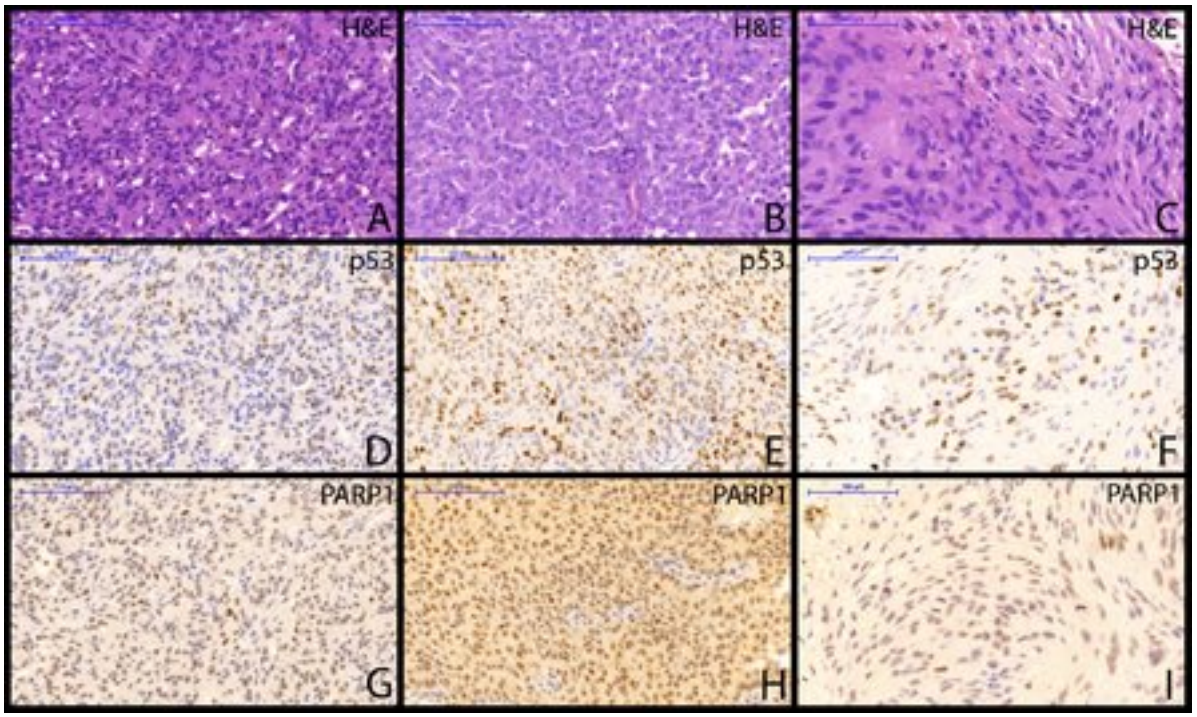

p53 and PARP1 immunostaining in meningiomas of different WHO grades.

Figure 2

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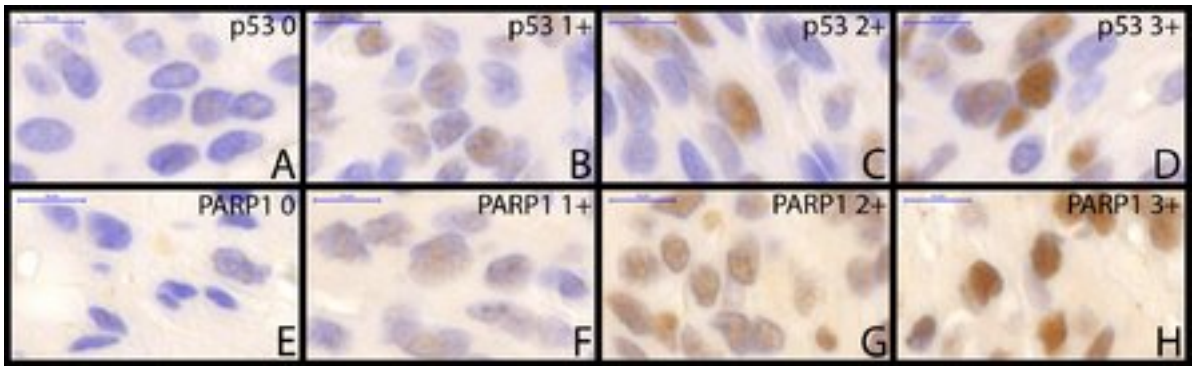

Representative images of the different staining intensities.

Figure 3

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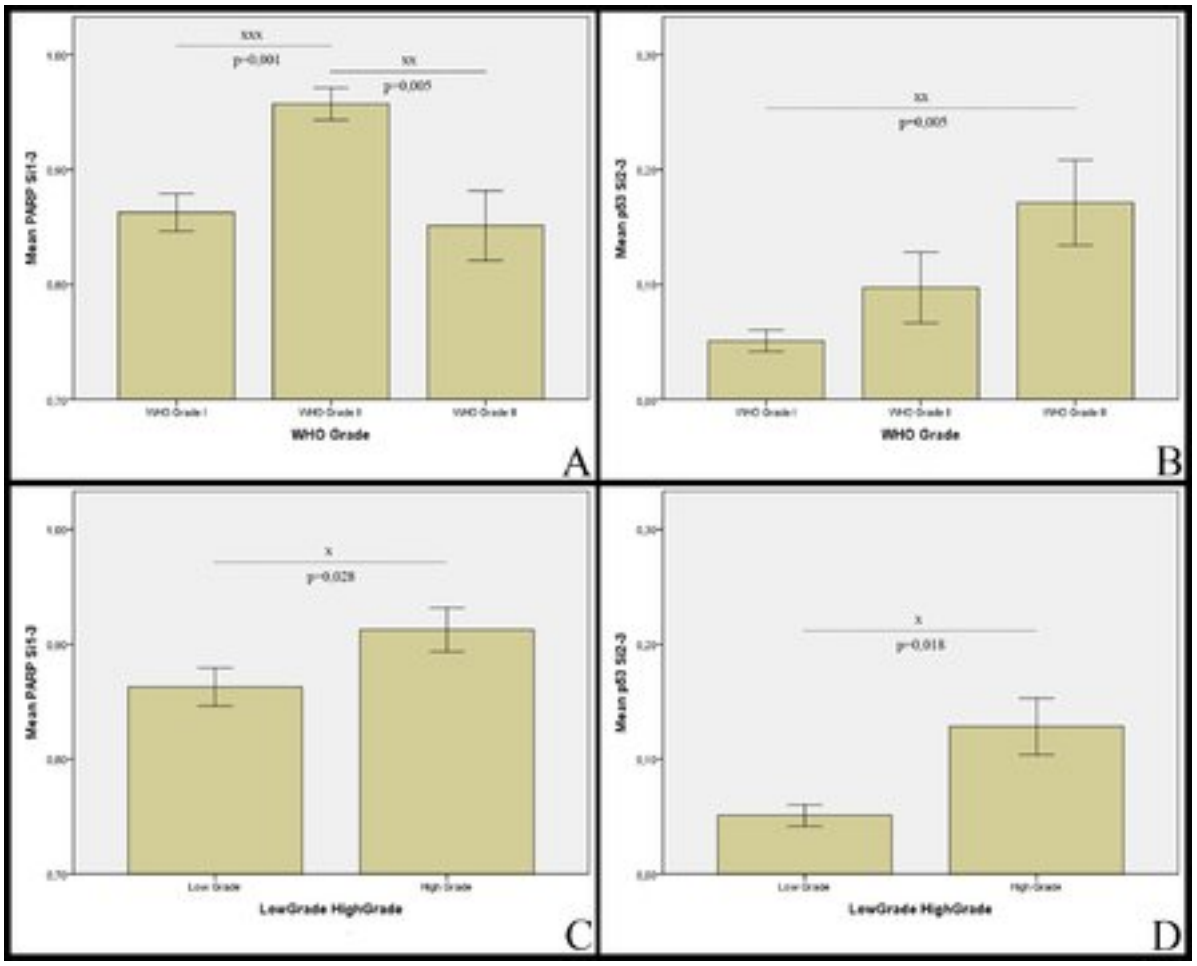

p53 and PARP staining intensity varies according to the tumour grade.

Figure 4

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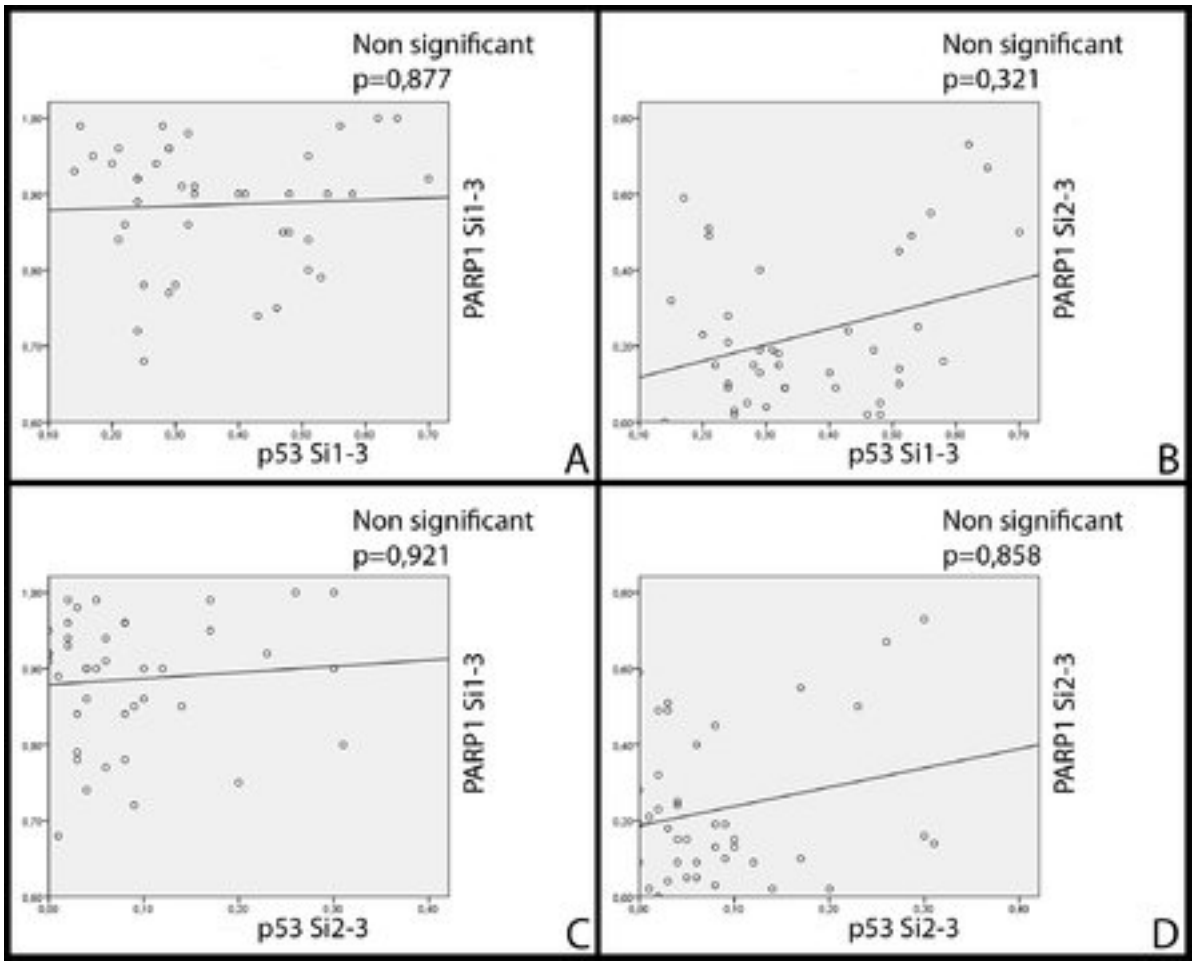

Correlation between p53 and PAPR1 staining intensity.

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