Oligodendroglial tumors: correlation between tumor genotype and perfusion-weighted MR Imaging

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Resumen
Objetivo: realizar una evaluación retrospectiva respecto de la correlación entre la técnica de perfusión (PWI) por resonancia magnética (RM), el volumen sanguíneo cerebral relativo (VSCR) y el genotipo tumoral, en pacientes con neoplasias oligodendrogliales grado II.

Materiales y métodos: once pacientes (7 hombres y 4 mujeres), con un rango de edad entre los 28 y 64 años, con tumores oligodendrogliales (OD) grado II, fueron estudiados con RM convencional y PWI, con la finalidad de obtener un valor de VSCR. Se realizó el análisis genético en todos los pacientes para evaluar el estado de los cromosomas 1p/19q.

Resultados: cinco pacientes con tumores ODs grado II (45%) presentaron un VSCR < 1,75 y ausencia de alteraciones en 1p/19q. Tres pacientes tenían oligoastrocitomas (OA), 2 de ellos con alteraciones en 1p/19q y el restante con 1p/19q intacto. Dos de los pacientes con gliomas mixtos, uno con alteraciones en 1p/19q y el otro con 1p/19q intacto, presentaron un VSCR > 1,75, mientras que en el paciente restante con glioma mixto y deleción en 1p/19q, el VSCR fue de < 1,75. Dos pacientes con ODs grado II presentaron un VSCR > 1,75, uno con 1p/19q intacto y el restante con deleción en 1p/19q. El último paciente presentó un OD grado II con un VSCR < 1,75 y pérdida de 1p/19q.

Conclusiones: aproximadamente el 45% de los pacientes con los cromosomas 1p/19q intactos mostró un VSCR < 1,75, sugiriendo una neoangiogénesis tumoral limitada. Estos hallazgos podrían ser de utilidad para monitorizar respuesta a agentes antiangiogénicos. Los estudios realizados en series mayores podrían proporcionar información valiosa antes de la cirugía y contribuir a un mejor manejo de estos pacientes.

Palabras clave: Genotipo tumoral. PWI. RMI. Tumores Cerebrales.

INTRODUCTION

Magnetic Resonance (MR) perfusion-weighted imaging (PWI) is a well-known technique for the study of glial cerebral neoplasias. The relative cerebral blood volume (rCBV) shows a direct correlation between tumor grade and neoangiogenesis-related histopathological findings (1-4).

The evidence available supports the notion that rCBV could predict the clinical evolution of some glial tumors, basically low-grade tumors (5, 6), more accurately than conventional MR does.

Oligodendroglial (OD) tumors account for about 33% of all gliomas detected at adulthood (7-9). They pre-
sent a more indolent clinical evolution, with a longer survival compared with astrocytic tumors characterized by a similar histologic grade (WHO Staging).

It has been largely suggested that molecular genetics may be the best tool to identify the treatment choice in certain subgroups of glial tumors (6,9).

The combined loss of heterozygosity of the p arm of chromosomes 1 and the q arm of chromosome 19 is an early event in tumor genetics and a typical marker of the histogenesis of development in oligodendrogliomas, since it occurs in about 90% of the cases and in more than 50% of mixed gliomas (oligastrocytomas). 1p/19q loss is associated with a longer progression-free period (6-11), compared with oligodendrogliomas with intact 1p/19.

A significant correlation has been observed between PWI and the histology of gliomas (2,13,14).

However, to our knowledge only one manuscript has been reported, which describes the association between MR PWI and OD molecular subtypes (14), and which outlines the impact of rCBV on the post treatment outcome.

The aim of the present study was to retrospectively analyze a small sample of patients with a diagnosis of grade II OD to determine whether there is any correlation between PWI (rCBV) and tumor genotype.

MATERIALS AND METHODS

Patients

A retrospective study was carried out of patients with grade II OD, who underwent MR at our center between June 2006 and July 2007.

Eleven patients (7 men, 4 women, age range: 28-64 years) underwent conventional MR and PWI. This study was duly approved by our Institutional Review Board and the Ethics Committee.

Image processing

Imaging studies were obtained using a 1.5-Tesla scanner (General Electric Medical Systems). The following conventional pulse sequences were obtained: sagittal T1 Flair (TR 2000, TE 21.2/er, TI 750, Nex 1), diffusion images in the axial plane, FLAIR axial (TR 11002, TE 133.5, Nex 2), Axial T1 (TR 440, TE 16, Nex: 3), volumetric acquisitions (SPGR with IR) (TR 7.4, TE2.4, TI 450, Nex 0.81), Axial T2 (TR 4400, TE117.9/er, Nex 3), after the administration of intravenous contrast.

Before the latter sequence, echoplanar sequences (EPI) were carried out using PWI techniques through the lesion detected on the conventional T2- and FLAIR-weighted imaging. Ten 5-mm sections were acquired without gap throughout the neoplasia.

A standard dose of 0.1 mmol/kg contrast agent (dimeglumine gadopentetate) was injected manually as a bolus and was followed by saline solution.

T2-weighted images were acquired every 2 s during the first pass of the contrast agent through the cerebral tissue (higher temporal resolution). Image postprocessing was performed using commercial software (Functool 2000, Sun Microsystems, GE Medical Systems).

Depending on lesion morphology and size, a region of interest (ROI) was placed on the tumor (Fig. 1), and another region of identical dimensions was placed over brain mirrored in the contralateral brain hemisphere. Qualitative color maps, known as “Negative Integral” and equivalent to the rCBV, were acquired.

The 5-mm section with larger signal intensity in
the lesion (consistent with a higher rCBV) was chosen. Depending on tumor location, the ROI was placed on the white and/or gray matter.

No ROI was higher than 40 mm². Five measurements were acquired of each of the regions previously selected according to signal intensity and the highest numerical value.

Cystic, necrotic and hemorrhagic regions were avoided, as well as normal vascular structures.

Two experienced neuroradiologists blinded to neoplasia histology performed an independent analysis of the results.

For each observation, data were expressed using an rCBV value (mean ROI tumor / mean ROI normal brain). An rCBV cut-off of 1.75 was established in order to differentiate high-grade from low-grade angiogenesis. Thus, we revised previous publications reporting a quantitative difference between high-degree and low-degree tumors.

Genetic analysis

Loss of heterozygosity in 1p/19q was analyzed through microsatellite quantification using real time PCR (QuMA) (7,8).

The resulting microsatellites of the common regions of deletions in oligodendroglial tumors were amplified.

In 1p, D1S468 and D1S214 markers, including the 1p36 region, were studied. In order to determine the combined loss of heterozygosity in 19q, D19S596 and D19S408 markers, including the 19q13.3 region, were studied (16).

The Taqman system (Applied Biosystems) was used with a common probe and the following sequence: 5’FAM-TGTGTGTGTGTGTGTGTGTGTAMRA-3’. This probe recognized the CA repetition in microsatellites.

The Taqman kit (Applied Biosystems) and the following amplification conditions were used: 50º C incubation for 2 minutes, 95º C for 10 minutes, and then 40 cycles including incubation at 95º C for 20 seconds, 55º C for 20 seconds and 60º C for 45 seconds.

RESULTS

Table 1 shows comparative results between tumor histology, presence or absence of 1p/19q and rCBV data. Patients were classified into 4 different categories according to those values (Table 2). Five of these patients (45%) with a diagnosis of grade II OD presented intact 1p/19q and rCBV values < 1.75 (Fig. 2).

Two OD patients had a higher rCBV value (2.19 and 3.19): one with an altered 1p/19q and the other with intact 1p/19q (Fig. 3).

One OD patient with rCBV < 1.75 showed a deletion in 1p/19q.

Two of the 3 patients with a diagnosis of mixed glioma evidenced altered 1p/19q. Two of these three subjects presented an rCBV higher than 1.75 (2.78 and 3.19, respectively), and the other showed an rCBV equal to 0.62.

Imaging studies (conventional MR and PWI) performed to date reveal no clinical changes.

DISCUSSION

We found that 5 of our patients (45%) with a diagnosis of grade II OD had rCBV values < 1.75 and intact 1p/19q.

Jenkinson et al (14) reported similar results in their series, though with a slightly lower cut-off value (1.59) for rCBV.

Fig. 2. MR of a grade II oligodendroglioma with rCBV value < 1.75 and genetic analysis showing intact 1p/19q. (a) Hyperintense tumor lesion in FLAIR sequence located on the left frontal lobe at cortico-subcortical level. (b) Volumetric sequence with T1 SPGR-weighted axial reconstruction following gadolinium injection. Absence of tumor enhancement. (c) Perfusion sequence evidencing hypointense area with low rCBV (circle), consistent with the lesion described in A.
A cut-off of 1.75 for rCBV has been largely reported to differentiate between high-grade and low-grade gliomas \(^2\). However, other authors who have particularly focused on OD cases agree that rCBV values may be similar, regardless of their histology. In this sense, in our revision we found 3 cases of low-grade oligoastrocytomas (OA). Two of them had a cut-off value for rCBV > 1.75. In our opinion, the oligodendroglial component could have played a key role in these cases.

Jenkinson et al \(^6\) have previously reported that oligodendroglial neoplasias showed morphological differences depending on their particular genotype. Low-grade ODs with well-defined borders and homogeneous signal intensity on T2 and FLAIR sequences are generally associated with lack of alterations in 1p/19q. These findings are consistent with the characteristics observed in our cases.

ODs with rCBV < 1.75 and morphologic findings suggestive of low-grade neoplasias and no alterations in 1p/19q are expected to be associated with lower vessel development (lower tumor angiogenesis). This is crucial for the recent advent of the antiangiogenic treatment for the management of these tumors, since it will provide further presurgical data and contribute to treatment follow-up.

**CONCLUSION**

Our research has some limitations. First, our sample is too small to draw statistically significant conclu-
sions. Second, there was no systematic correlation between the conventional MR and PWI and tumor genotype. This correlation could provide additional data for a more accurate diagnosis before the procedure. This is crucial for the decision-making process and the “prediction” of the histologic grade. Thus far, this has been the main purpose in order to determine whether biopsy (either stereotaxic or not) or conventional surgery (either curative or palliative) is advisable.

However, our knowledge of ODs behavior in particular, and glial cerebral tumors in general, could be enlarged using larger series, other resources available to date with MR (such as spectroscopy) (17), and adequate clinical follow-up.

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References