Matrix metalloproteinase-9 and -2 and tissue inhibitor of matrix metalloproteinase-2 in invasive pituitary adenomas

A systematic review and meta-analysis of case–control trials

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Abstract

The extracellular matrix is important for tumor invasion and metastasis. Normal function of the extracellular matrix depends on the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). The objective of this meta-analysis was to assess the relationship between expression of MMP-9, MMP-2, and TIMP-2 and invasion of pituitary adenomas.

We searched Pubmed, Embase, and the Chinese Biomedical Database up to October 2015. RevMan 5.1 software (Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. We calculated the standardized mean difference (SMD) for data expressed as mean±standard deviation because of the difference in the detection method.

Twenty-four studies (1320 patients) were included. MMP-9 expression was higher in the patients with invasive pituitary adenomas (IPAs) than patients with noninvasive pituitary adenomas (NIPAs) with detection methods of IHC (odds ratio (OR)=5.48, 95% confidence interval (CI)=2.61–11.50, P<0.00001), and reverse transcriptase-polymerase chain reaction (SMD=2.28, 95% CI=0.91–3.64, P=0.001). MMP-2 expression was also increased in patients with IPAs at the protein level (OR=3.58, 95% CI=1.63–7.87, P=0.001), and RNA level (SMD=3.91, 95% CI=1.52–6.29, P=0.001). Meta-analysis showed that there was no difference in TIMP-2 expression between invasive and NIPAs at the protein level (OR=0.38, 95% CI=0.06–2.26, P=0.29). MMP-9 expression in prolactinomas and nonfunctioning pituitary adenomas was also no difference (OR=1.03, 95% CI=0.48–2.20, P=0.95).

The results indicated that MMP-9 and -2 may be correlated with invasiveness of pituitary adenomas, although their relationship with functional status of pituitary adenomas is still not clear. TIMP-2 expression in IPAs needs to be investigated further.

Abbreviations: CBM = Chinese Biomedical Database, ECM = The extracellular matrix, IHC = Immunohistochemical staining, IPAs = invasive pituitary adenomas, MMPs = matrix metalloproteinases, MVD = microvessel density, NIPAs = noninvasive pituitary adenomas, OR = odds ratio, PAs = Pituitary adenomas, RT-PCR = reverse transcriptase-polymerase chain reaction, SD = standard deviation, SMD = standardized mean difference, TIMPs = tissue inhibitors of metalloproteinases.

Keywords: invasion, meta-analysis, MMP-2, MMP-9, pituitary adenomas, TIMP-2

1. Introduction

Pituitary adenomas (PAs) are highly prevalent central nervous system tumors derived from adenohypophyseal cells. Despite the benign nature of PAs, they may invade adjacent structures, including the diaphragm sellae, suprasellar cistern, third ventricle, sellar floor, sphenoid sinus, dura mater, cavernous sinus, clivus, and others. Such invasive tumors were defined as invasive pituitary adenomas (IPAs) by Jefferson in 1940. According to this diagnostic criteria, about 45% of PAs have evidence of dural invasion.[1] The therapeutic options include radical surgical resection, preoperative or postoperative radiotherapy, and medication, and except for prolactinomas, resection is the preferred option. It is, however, difficult for IPAs to be totally resected because of increased risk of cerebrospinal fluid leak and damage to cranial nerves and the internal carotid artery in the cavernous sinus.[2] Furthermore, IPAs have a higher rate of recurrence, lower rate of remission, and poorer prognosis than noninvasive pituitary adenomas (NIPAs). Gültekin et al[3] reported that the rate of recurrence (persistent and late recurrence) of invasive prolactinomas was 100% compared with 36% for noninvasive prolactinomas. To date, the pathogenesis of the invasion of PAs remains elusive.

Recent studies have reported the correlation between expression of matrix metalloproteinase (MMP)-9 and MMP-2 and IPAs. MMPs, also designated matrixins, are proteolytic enzymes containing a signal peptide, a propeptide, a catalytic domain, and a hemopexin domain[4,5] capable of degrading the extracellular matrix, which is essential for tumor invasion.[6] MMP-9 (gelatinase b) and MMP-2 (gelatinase a), classified as type IV collagenases, can degrade Collagen Types IV particularly,[7] which is the prominent component of the basement membrane.[8] Inasmuch as the basement membrane seems to play a critical role in tumor invasion,[7] expression MMP-9 and -2 is conceived as an...
important sign of the tumor invasion. Previous studies have reported the relationship between MMP-9 and -2 expression and invasiveness of craniopharyngioma,\textsuperscript{19} medullary thyroid carcinoma,\textsuperscript{11} gastric carcinoma,\textsuperscript{11} ovarian serous tumor,\textsuperscript{12} glioma cells,\textsuperscript{13} et al. Recently, Ceylan et al reported that pituitary capsule, medial wall of the cavernous sinus, and reticular fiber roof of the hypophysis mainly consist of type IV collagen.\textsuperscript{14} Furthermore, Kawamoto et al found that type IV collagen is the key component of the dura mater, although its main compartment is type I collagen.\textsuperscript{15} These findings all demonstrate the significance of expression of MMP-9 and -2 to the invasion of PAs. Many studies have shown higher expression of MMP-9 and -2 in IPAs than in NIPAs. However, some authors have found either contrary results or no relationship between MMP-9 and -2 expression and invasion of PAs. We hypothesized that MMP-9 and -2 may be correlated with invasiveness of PAs, and act as critical biological markers in IPAs. However, considering the inconsistent conclusions of previous studies, we performed a meta-analysis of the literature to verify our hypothesis. The results of this meta-analysis contribute to learning about the pathogenesis of the invasion of PAs further and provide a novel therapeutic strategy for physicians. Besides, our results may be helpful for surgeons to make a decision on whether they could have an operation on patients, to assess the rate of remission and recurrence and to decide whether it is necessary to give an adjuvant therapy after surgery.

2. Materials and methods

2.1. Protocol

This meta-analysis of case-control trials was performed according to the MOOSE (Preferred Reporting Items for Systematic reviews and meta-analyses of Observational Studies) recommendations. This study was not a human or animal experiment, thus ethical approval was not necessary.

2.2. Search strategy

We conducted a search of Pubmed, Embase, and the Chinese Biomedical Database (all up to October 2015) for potentially eligible trials, without any language restriction. The subject headings and keywords we used were as following: “pituitary neoplasms,” “pituitary adenomas,” “pituitary adenoma,” “pituitary macroadenoma,” “pituitary tumor,” “prolactinoma,” “acromegaly,” “Cushing disease,” “Cushing’s disease,” “Pituitary acth hypersecretion,” “matrix metalloproteinase 9,” “matrix metalloproteinase 2,” “gelatinase b,” “gelatinase a,” “type IV collagenase,” “MMP 9,” “MMP 2,” “MMP9,” “MMP2,” “MMP-9,” “MMP-2,” et al. A supplementary search of the reference lists from all retrieved trials and reviews was also performed. We contacted the corresponding author by mail if the articles were not available from databases.

2.3. Inclusion and exclusion criteria

Studies satisfying the following inclusion criteria were included: (1) case-control study design, (2) the detection method of MMP-9 and -2 expression were immunohistochemical staining (IHC) or (real-time) reverse transcriptase-polymerase chain reaction (RT-PCR), (3) results of IHC characterized by qualitative data and results of RT-PCR with average change and standard deviation (SD) were shown, and (4) diagnostic criteria for IPAs were met. Diagnostic criteria for IPAs were as following: (1) in modified Hardy’s classification, grade III-IV adenomas or stage C-E tumors were defined as invasive.\textsuperscript{16} (2) In Knosp’s classification, grade III-IV adenomas were defined as invasive.\textsuperscript{17} (3) Surgeons verified the penetration of sphenoid sinus or invasion of the parasellar nerve vasculature. (4) Invasion of the diaphragm sellae, sellar bone, or surrounding endocranium was confirmed pathologically. (5) There was damage of surrounding structures according to magnetic resonance imaging and computed tomography. The PAs were considered invasive as long as they met one of the five diagnostic criteria.

2.4. Endpoints and data extraction

The primary endpoint was detection of MMP-9 expression using IHC at the protein level and RT-PCR at the mRNA level. The second endpoint was detection of MMP-2 expression using IHC and RT-PCR. The third endpoint was the expression of the tissue inhibitors of metalloproteinase (TIMP)-2 at the protein level. The final endpoint was microvessel density (MVD). Data including date of publication, name of first author, study type, detection methods, patient characteristics (mean age, age range, number of patients, and sex ratio), tumor type, and the aforementioned four endpoints were extracted from the eligible studies using a standard data-extraction form. Database search, eligibility evaluation, and data extraction were all performed independently by 2 authors (hongyan liu and weijian gu), with disagreements resolved by a third author.

2.5. Assessment of methodological quality

The Newcastle–Ottawa Scale (NOS) criteria (case-control study) was used for assessment of methodological quality, which contained the three following categories: (a) subject selection: (1) case definition was independently valid, (2) cases were consecutive or representative, (3) controls were from the community, and (4) controls did not have the same disease as the cases had. (b) Comparability of cases and controls: (1) controls were selected and analyzed according to the most important factor, and (2) controls were studied for a second important factor. (c) Exposure: (1) records were secure, (2) blind method was employed, (3) cases and controls had the same detection method, and (4) the two groups had a same nonresponse rate.\textsuperscript{18} The aforementioned items indicated a NOS score of 10, and a score of 5 or more was considered the inclusion criterion.

2.6. Statistical analysis

The Cochrane Collaboration’s RevMan version 5.1 software was used for statistical analysis. Crude odds ratio (OR) with 95% confidence intervals (CIs) and standardized mean difference (SMD) with 95%CIs were used for qualitative and quantitative variables, respectively. SD was calculated according to the formula $SD = \sqrt{\sum (x_i - \bar{x})^2 / n}$, if the data were expressed as mean ± SE (standard error of mean). We assessed the heterogeneity between trials with the method of Cochran’s Q-statistic test and $I^2$ test, measuring the extent of inconsistency—derived from heterogeneity rather than chance—in the results of eligible studies.\textsuperscript{19} A random-effects model was adopted on condition that $I^2$ was more than 50% or $P$ (Q-test) less than 0.05, otherwise, a fixed-effects model was used. Subgroup analysis of data expressed as mean ± SD was carried out according to detection methods to establish the derivation of heterogeneity. Sensitivity analysis by omitting
any one study successively and funnel plots were conducted to assess the constancy of total estimate and publication bias, respectively. The drawing of forest plots and heterogeneity testing were completed in RevMan version 5.1 software.

3. Results

3.1. Study selection

We selected 213 candidate articles from our search, of which only 34 studies were regarded as eligibility. We discarded 10 studies for the following reasons: 4 inasmuch as they had duplicated subjects in other contained studies, 3 due to different detection methods [standard sandwich ELISA (enzyme linked immunosorbent assay) and Western blot], 2 in that some patients who met the diagnostic criteria for invasion, but were not included in the invasive group, and 1 owing to insufficient data. This resulted in a final total of 24 studies[2,3,15,20–40] (Fig. 1).

3.2. Study characteristics

We outlined the characteristics of 24 studies included in our analysis (Table 1). The detection methods of IHC and RT-PCR were both used in seven studies. The IHC results of three studies were excluded because they were shown as mean ± SD and had a shortage of adequate data. Sixteen studies employed IHC only, and 7 adopted RT-PCR only. All included trials in the present study were of case-control design. The first study about the relationship between type IV collagenase expression and invasion of PAs was conducted by Kawamoto et al.[15] thus the date of publications in the present study ranged from 1996 to 2015. There were a total of 1320 patients with PAs in the present meta-analysis. Two articles grouped the patients according to functional status of PAs rather than tumor invasion. The NOS score of methodological quality was summarized in Supplemental Table S1, http://links.lww.com/MD/B35.

3.3. Meta analysis

3.3.1. Relationship of MMP-9 and -2 expression and invasion of pituitary adenomas. At the protein level or RNA level, there was substantial heterogeneity among the studies, making the use of a random effects model. Fourteen studies (374 IPAs and 328 NIPAs) and seven studies (146 IPAs and 126 NIPAs) showed MMP-9 expression at the protein level and RNA level, respectively. The results indicated that when we compared patients with invasive and NIPAs, MMP-9 expression was higher in the former with detection methods of IHC (OR = 5.48, 95% CI = 2.61–11.50, P < 0.00001; Fig. 2A), and RT-PCR (SMD = 2.28, 95% CI = 0.91–3.64, P = 0.001; Fig. 2B). Seven studies (207 IPAs and 184 NIPAs) and four studies (91 IPAs and 97 NIPAs) showed MMP-2 expression at the protein level and RNA level, respectively. MMP-2 expression was increased in patients with IPAs at the protein level (OR = 3.58, 95% CI = 1.63–7.87,
| References                | Diagnostic criteria for IPAs | Inv. vs Non-in | PRL/GH/ACTH/TSH/LH or FSH/Non-fun/Mix | Detection method | Mean age (year) | Number (M V F) | Type of study | Index | Result analysis for IHC | NOS score |
|--------------------------|-----------------------------|----------------|--------------------------------------|----------------|----------------|----------------|---------------|-------|--------------------------|-----------|
| Gültekin et al [3]       | 1, 2, 3                     | 35 vs 22       | 57/0/0/0/0/0/0                        | IHC            | 40 (16–69)     | 28 V 29        | Case-control  | MMP-9/TIMP-2 | semiquantitative          | 8         |
| Chen et al [2]          | 2                           | 37 vs 46       | 1/8/13/0/4/2/1/16                     | Real-time RT-PCR | 40.3 (18–76)   | 35 V 47        | Case-control  | MMP-9/MMP-2  | semiquantitative          | 7         |
| Gao et al [22]          | 1, 2, 4, 5                  | 40 vs 35       | 2/8/18/3/2/0/2/4/4/2/16              | IHC            | 51.5           | 27 V 48        | Case-control  | MMP-9         | semiquantitative          | 8         |
| Chen et al (2010) [23]   | 1, 3, 4, 5                  | 40 vs 34       | 2/5/10/2/0/0/2/0/2/0/2/0/2/0/0/2/0   | IHC            | 38.3 (18–71)   | 39 V 35        | Case-control  | MMP-9/MMP-2  | semiquantitative          | 8         |
| Gong et al [2]          | 3, 4                        | 46 vs 27       | 3/11/9/0/0/5/0/0                     | Real-time RT-PCR | 51.5 (11–79)   | 37 V 36        | Case-control  | MMP-9         | semiquantitative          | 7         |
| Hussaini M. et al [24]   | 3                           | 3 vs 5         | 0/0/0/0/0/0/0                        | Real-time RT-PCR | 49.9 (18–76)   | 39 V 35        | Case-control  | MMP-9/MMP-2  | semiquantitative          | 6         |
| Yamada et al [25]       | 4                           | 20 vs 20       | 0/0/0/0/0/0/0                        | IHC            | 52.5           | 25 V 20        | Case-control  | MMP-9         | semiquantitative          | 7         |
| Liu et al [26]          | 1, 3, 5                     | 12 vs 42       | 11/12/4/1/1/2/0/2/1/2/0/2/0/2/0/0/0/0| Real-time RT-PCR | 49.9 (18–76)   | 20 V 34        | Case-control  | MMP-9/MMP-2  | semiquantitative          | 7         |
| Wang et al [27]         | 1, 2, 3                     | 20 vs 10       | 9/19/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| RT-PCR         | 43.8 (23–72)   | 18 V 12        | Case-control  | MMP-9/MMP-9/MMP-2/TIMP-2 | semiquantitative | 7         |
| Knapp et al [28]        | 3, 5                        | 50 vs 34       | 1/14/17/2/1/0/2/0/2/2/0/2/0/2/0/0/0  | IHC            | 53.1 (34–71)   | 0 V 20         | Case-control  | MMP-9         | semiquantitative          | 8         |
| He et al [29]           | 1                           | 49 vs 12       | 8/5/19/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 41 (19–64)     | 2 V 5          | Case-control  | MMP-9         | semiquantitative          | 9         |
| Yokoyama et al [30]     | 2                           | 10 vs 10       | 0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 5 (14–73)      | 26 V 34        | Case-control  | MMP-9/MMP-2  | semiquantitative          | 7         |
| Turner et al [31]       | 1                           | 11 vs 8        | 2/4/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 43.6 (17–73)   | 10 V 21        | Case-control  | MMP-9/MMP-9  | semiquantitative          | 7         |
| Tomita [32]             | 17/5/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 41 (19–64)                             | 2 V 5          | Case-control  | MMP-9         | semiquantitative          | 7         |
| Kawamoto et al [33]     | 3                           | 3 vs 4         | 2/1/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 43.6 (24–66)   | 52 V 44        | Case-control  | MMP-9         | semiquantitative          | 9         |
| Mao et al [34]          | 1, 2, 3, 4                  | 46 vs 50       | 11/9/2/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| RT-PCR         | 38 (15–79)     | 26 V 34        | Case-control  | MMP-2/TIMP-2 | semiquantitative          | 7         |
| Guo et al [35]          | 2, 3                        | 30 vs 30       | 11/9/2/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 36 (14–73)     | 28 V 32        | Case-control  | MMP-2/TIMP-2 | semiquantitative          | 7         |
| Guo et al [36]          | 2, 3                        | 30 vs 30       | 7/8/3/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 43.3 (18–73)   | 39 V 47        | Case-control  | MMP-9         | semiquantitative          | 7         |
| Li et al [37]           | 1, 2, 3, 4                  | 20 vs 20       | 14/11/2/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 35.8 (10–73)   | 22 V 29        | Case-control  | MMP-2/TIMP-2 | semiquantitative          | 7         |
| Li et al [38]           | 1, 2, 3, 5                  | 18 vs 23       | 2/10/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0/0| IHC            | 39 (15–75)     | 15 V 26        | Case-control  | MMP-2         | semiquantitative          | 7         |
| Liu et al [39]          | 3, 5                        | 40 vs 38       | 3/52 (14–65)                          | IHC            | 35.2 (14–65)   | 33 V 45        | Case-control  | MMP-9         | semiquantitative          | 7         |

ACTH = ACTH-type, FSH or LH = gonadotropin adenoma, GH = GH-type, IHC = immunohistochemical staining, Inv = invasive, IPAs = invasive pituitary adenomas, diagnostic criteria for IPAs, Mix = multiple hormone-type, Non-in = noninvasive, functional status of PAs, NOS = Newcastle–Ottawa scale, PAs = pituitary adenomas, PRL = PRL-type, RT-PCR = reverse transcriptase-polymerase chain reaction, TSH = TSH-type.1. Modified Hardy’s classification.2. Knosp’s classification.3. Observation at surgery.4. Confirmation of the invasion of diaphragm sellae, sellar bone, or surrounding endocranium pathologically.5. The damage of surrounding structures according to MRI and CT scans.
P = 0.001; Fig. 3A), and RNA level (SMD = 3.91, 95% CI = 1.52–6.29, P = 0.001; Fig. 3B). The results of sensitivity analysis indicated that no single study had a significant influence on the above four-pooled effect sizes (Supplemental Table S2–S5, http://links.lww.com/MD/B35). Subgroup analytical results found that detection methods had no influence on pooled SMD of MMP-9 (test for subgroup differences: I² = 0%, P = 0.64; Fig. 2B) and MMP-2 (I² = 0%, P = 0.97; Fig. 3B) at the RNA level.

### 3.3.3. Relationship of MMP-9 expression and functional status of pituitary adenomas.
MMP-9 expression in 97 prolactinomas and 91 nonfunctioning PAs was compared in five studies. There was no significant difference (OR = 1.03, 95% CI = 0.48–2.20, P = 0.95) between them using a fixed effects model (I² = 33%, P = 0.22; Fig. 5).

### 3.3.4. MMP-9 expression in primary and recurrent pituitary adenomas.
Three studies analyzed the difference in MMP-9 expression between primary and recurrent adenomas (Supplemental Table S7, http://links.lww.com/MD/B35), and the results showed a higher expression of MMP-9 in recurrent adenomas at the protein level (OR = 0.09, 95% CI = 0.01–0.53, P = 0.008) and at the RNA level (OR = 0.36, 95% CI = −5.15 to −2.17, P < 0.00001).

### 3.3.5. Relationship between MMP-9 expression and microvessel density of pituitary adenomas.
Two studies analyzed the relationship between MMP-9 expression and MVD of PAs, but P = 0.09 (MD = 4.42, 95% CI = −0.66 to 9.50; Supplemental Table S8, http://links.lww.com/MD/B35) demonstrated that there was no statistical significance between them.

### 4. Discussion
To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the importance of type IV
Collagenases expression in IPAs. The NOS scores of studies included ranged from 5 to 9, which meet the requirement of meta-analysis. Our outcomes indicated that high expression of MMP-9 and -2 may be a significant cause of PAs invasiveness. As mentioned in the introduction, destruction of the basement membrane by MMP-9 and -2 may play a central role in the process of invasion of PAs. In 2006, Malik and Kakar[41] found that pituitary tumor transforming gene facilitated tumor growth and metastasis through secretion of MMP-2 in vitro. One year later, Yoshida and Teramoto[42] reported that increased expression of the discoidin domain receptor-1 promoted invasion of PAs via higher expression of MMP-9 and -2 in vitro. Recently, some proteins related to PAs invasion have been reported to work through regulating the level of MMP-9 and -2 in succession, such as reversion-inducing cysteine-rich protein with kazal motifs,[43] FRα-targeted liposomal doxorubicin,[44] and β-catenin.[45] These all confirmed the central and critical role of MMP-9 and -2 in the invasion of PAs and were consistent with our results.

Pereda et al have suggested that high levels of MMPs (including MMP-9 and -2) stimulate pituitary cell proliferation and hormone secretion[46] for the reason of growth factor anchored to extracellular matrix generated by MMPs.[47] Meij et al found that macroadenomas (>40mm) were 46% more likely to be invasive than microadenomas (≤10mm).[1] According to their ideas, the expression MMP-9 and -2 is related to size and functional status of PAs. Unfortunately, we found only four trials that analyzed the relationship between MMP-9 expression and tumor size, and their conclusions were inconsistent. We were unable to perform a meta-analysis because of the difference in detection methods, form of data expression and cutoff values for tumor size, and the small number of trials. This implies that more studies need to be conducted. Prolactinomas (account for...
Figure 5. Forest plots for the relationship between MMP-9 expression and functional status of PA at the protein level. M-H = Mantel-Haenszel test, Fixed = a fixed effects model, CI = confidence intervals.

Figure 6. Funnel plots for the relationship between MMP-9 expression and tumor invasiveness of PAs. A. at the protein level. X and Y axes are OR and SE, respectively. B. at the RNA level. X and Y axes are SMD and SE, respectively.
50%–55%) and nonfunctioning adenomas (account for 20%–25%) were the two most common types of PAs. Therefore, we carried out a meta-analysis to compare MMP-9 expression in the two different types of tumor, but we failed to find any difference. Given the limited number of eligible studies, we could not make a conclusion that the level of MMP-9 had nothing to do with the functional status of PAs.

Five studies included in this meta-analysis gave information about TIMP-2 expression in IPAs and NIPAs, and there was a nonsignificant decrease in IPAs statistically. If the study of Gültekin et al that had a great effect on pooled OR was removed, the decrease would have statistical significance. One study that was excluded from this meta-analysis because of the different detection method also demonstrated a decreased level of TIMP-2 in IPAs (P < 0.05). The TIMPs are endogenous MMP activity inhibitors that bind competitively to the binding sites for specific substrates of MMPs. To date, 4 homologous TIMPs (TIMP-1, -2, -3, and -4) are found in vertebrates. All MMPs, apart from MMP-14, -16, -19, and -24, can be inhibited by these four TIMPs. TIMP-2 seems to be an inhibitor of PAs invasion. However, TIMP-2 is unique because the complex of MT1-MMP/TIMP-2 acts as a pro-MMP-2 receptor and contributes to the activation of pro-MMP-2 on the cell surface. Furthermore, Valacca et al reported that the MT1-MMP/TIMP-2 complex is able to protect tumor cells against apoptosis by activating the AKP pathway in vitro. Recently, Stetler-Stevenson et al found that TIMP-2 can bind to a cell-surface signaling receptor, and then promote cell proliferation in an MMP-independent manner. At the same time, the level of TIMP-2 was found to be increased in many malignant tumors, which often indicates poor prognosis. These findings may explain the contrary result of Gültekin et al. However, more well-designed studies are required for meta-analysis of TIMP-2 expression in IPAs, and to determine the mechanism of action of TIMP-2 in tumor invasion.

Tumor angiogenesis, the case of which could be reflected through MVD of tumor, plays a critical role in the initiation and progression of tumor invasion and metastases. There have been studies reporting that MVD had a greater increase in IPAs compared with NIPAs (Supplemental Table S9, http://links.lww.com/MD/B35). MMPs, especially MMP-9, could mediate tumor angiogenesis through mutual regulation and influence with vascular endothelial growth factor. According to the aforementioned, MVD of PAs may be correlated with MMP-9 expression. However, we found only two studies that investigated the relationship between them. And although our results suggested elevated MVD in MMP-9-positive PAs, there was no statistical significance, indicating that more studies need to be conducted. We also observed that the level of MMP-9 was higher in recurrent patients than that of primary patients, which means that patients with a high level of MMP-9 are likely to have poor prognosis.

There were several limitations to the present meta-analysis. First, given the relatively small number of studies included and overall sample size, the conclusion that MMP-9 and -2 acts as critical biological markers in IPAs should be treated with caution. Furthermore, the case–control study design was retrospective and had no rigorous quality control, and the grade of evidence was inferior to that of randomized controlled trials and cohort studies. Finally, despite sensitivity analysis and subgroup analysis conducted to search for the derivation of heterogeneity, we failed to minimize the high heterogeneity. Some potential reasons that resulted in great heterogeneity we thought are as following: Firstly, the data that we extracted were aggregated but individual, meaning that certain of baseline characteristics, such as age, sex, complications, and prognoses, were not taken into consideration. Secondly, although there are widely recognized diagnostic criteria of modified Hardy’s classification and Knosp’s classification for IPAs, making a definite diagnosis is still difficult because of unavoidable false negative and false positive results. Thirdly, there may be differences in detection methods of IHC among different laboratories.

In conclusion, the results of the present meta-analysis show that MMP-9 and -2 may be correlated with invasiveness of PAs, even though the study limitations mean our conclusions should be treated with caution. In consideration of the paucity of studies included, we cannot be certain of any differences in the level of
MMP-9 among patients with PAs of diverse functional status and size. It is still unknown whether TIMP-2 acts as an enhancing or inhibitory factor in invasion of PAs, necessitating more large sample and well-designed studies.

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References

[1] Meij BP, Lopes MB, Ellegala DB, et al. The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. J Neurosurg 2002;96:195–208.

[2] Gong J, Zhao Y, Abdel-Fattah R, et al. Matrix metalloproteinase-9, a potential biological marker in invasive pituitary adenomas. Pituitary 2008;11:37–48.

[3] Gültekin GD, Cabuk B, Vural C, et al. Matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-2: Prognostic biological markers in invasive prolactinomas. J Clin Neurosci 2015;22:1282–7.

[4] Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem 1999;274:21491–4.

[5] Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 2003;92:827–39.

[6] Amar AP, DeArmond SJ, Spencer DR, et al. Development of an in vitro extracellular matrix assay for studies of brain tumor cell invasion. J Neurooncol 1994;20:1–5.

[7] Liotta LA. Tumor invasion and metastases: role of the basement membrane. Warner-Lambert Parke-Davis Award lecture. Am J Pathol 1984;117:339–48.

[8] Yurchenco PD, Ruben GC. Basement membrane structure in situ: evidence for lateral associations in the type IV collagen network. J Cell Biol 1987;105:2559–68.

[9] Gong J. A preliminary research on the correlation between the matrix metalloproteinases and the invasiveness of craniopharyngioma. Child's Nerv Syst 2009;25:1335.

[10] Tomita T. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in thyroid c-cells and medullary thyroid carcinomas. Histopathology 1997;31:150–6.

[11] Wen FH, Sun LM, Li HL, et al. Expression of pituitary tumor-transforming gene I, matrix metalloproteinase-2 and matrix metalloproteinase-9 in gastric carcinoma. World J Gastroenterol 2015;21:3147–51.

[12] Tang J, Hui J. PTTG expression and its relationship with MMP-2 and VEGF in ovarian serous tumor. Chinese J Clin Oncol 2010;37:437–43.

[13] Yan H, Wang W, Dou C, et al. Securin promotes migration and invasion of matrix metalloproteinases in glioma cells. Oncol Lett 2015;9:2893–901.

[14] Ceylan S, Anik I, Koc K, et al. Microsurgical anatomy of membranous layers of the pituitary gland and the expression of extracellular matrix collagenous proteins. Acta Neurochir 2011;153:2433–43.

[15] Kawamoto H, Uozumi T, Kawamoto K, et al. Type IV collagenase activity and cavernous sinus invasion in human pituitary adenomas. Acta Neurochir 1996;138:390–5.

[16] Hardy J. Transsphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg 1969;16:185–217.

[17] Knope E, Steiner E, Kitz K, et al. Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery 1993;33:610–7.

[18] Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[19] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[20] Hui P, Xu X, Xu X, et al. Expression of MMP14 in invasive pituitary adenomas: relationship to invasion and angiogenesis. Int J Clin Exp Pathol 2015;8:3556–67.

[21] Chen Z, Li Z, Chang Y, et al. Relationship between NFκB, MMP-9, and MICA expression in pituitary adenomas reveals a new mechanism of pituitary adenomas immune escape. Neurosci Lett 2015;597:77–83.

[22] Quo L, He D, Fan X, et al. The expression of interleukin (IL)-17 and IL-17 receptor and MMP-9 in human pituitary adenomas. Pituitary 2011;14:626–75.

[23] Quo X, Yang W, Jiang M, et al. CD147 expression in pituitary adenomas and its significance for clinical outcome. Human Pathol 2010;41:1165–71.

[24] Hussaini IM, Troetter C, Zhao Y, et al. Matrix metalloproteinase-9 is differentially expressed in noninvasive and invasive pituitary adenomas and increases invasion in human pituitary adenoma cell line. Am J Pathol 2007;170:356–65.

[25] Yamada S, Ohyama K, Taguchi M, et al. A study of the correlation between morphological findings and biological activities in clinically nonfunctioning pituitary adenomas. Neurosurgery 2007;61:580–4.

[26] Liu W, Matsumoto Y, Okada M, et al. Matrix metalloproteinase-2 and 9 expression correlated with cavernous sinus invasion of pituitary adenomas. J Med Invest 2005;52:151–8.

[27] Wang J, Liu YS. Expression of MMP-9 and TIMP and invasiveness in pituitary adenomas. J Cent South Univ (Med Sci) 2004;29:647–50.

[28] Knappe UJ, Hagel C, Lisboa BW, et al. Expression of serine proteases and metalloproteinases in human pituitary adenomas and anterior pituitary lobe tissue. Acta Neuropathol 2003;106:471–8.

[29] He DS, Chen MZ, Wang HJ, et al. Role of matrix metalloproteinases-9, 2 and their inhibitor-TIMP-1, 2 in invasive pituitary adenomas biological behavior. Chinese J Can 2002;21:1124–8.

[30] Yokoyama S, Hirano H, Morokö K, et al. Are nonfunctioning pituitary adenomas extending into the cavernous sinus aggressive and/or invasive? Neurosurgery 2001;49:857–63.

[31] Turner HE, Nagy Z, Esri MM, et al. Role of matrix metalloproteinase 9 in pituitary tumor behavior. J Clin Endocrinol Metab 2000;85:2931–5.

[32] Tomita T. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in pituitary adenomas: possible markers of neuroendocrine cells. Endocr Pathol 1997;8:305–13.

[33] Mao T, Zhou K. Clinical features correlated with MMP-9 expression in invasive pituitary adenoma patients. Chin J Prim Med Pharm 2015;22:1300–2.

[34] Zhao Y, Liu J, Wang W, et al. Relationship between invasive and changes of mRNA expression of MMP-2, TIMP-2 and CD147 in human. Chin J Endocr Surg 2010;4:219–24.

[35] Guo Y, Suo X, Guo H, et al. Expression of matrix metalloproteinase (MMP)-2, tissue inhibitor of matrix metalloproteinase-2 (TIMP-2) and CD147 in pituitary adenomas and its correlation with invasion. Chin J Exp Surg 2008;25:100–1. fx1.

[36] Li X, Zhou H, Hui G, et al. Expressions of Ki-67 and MMP-9 and their relationship with the invasiveness in the pituitary adenomas. Chin J Endocr Surg 2008;24:762–4.

[37] Zhao J, Wang J, Liu Y, et al. Relationship between the expression of PTTG, bFGF and MMP-9 and the invasiveness of pituitary adenomas. Chin J Neurourosurg 2007;6:282–3.

[38] Li Y, Wei X, Song L, et al. Expressions of MMP-2 and TIMP-2 in pituitary adenomas and significance of their expressions. Chin J Neurourosurg 2007;6:931–4.

[39] Wang S, Liu Q, Xuan J, et al. Relationship of MMP-2 and microvesSEL density with the invasion of human pituitary adenomas. Chin J Neurourosurg 2006;5:30–2.

[40] Liu A, Huang W, Xiao S, et al. Relationship between invasiveness of pituitary adenomas and microvesSEL density and as expression of MMP-9. J Postgrad Med 2005;18:20.

[41] Malik MT, Kakar SS. Regulation of angiogenesis and invasion by human Pituitary tumor transforming gene (PTTG) through increased expression and secretion of matrilxin metalloproteinases-2 (MMP-2). Molecular cancer 2006;5:61.

[42] Yoshida D, Teramoto A. The use of 3-D culture in peptide hydrogel for analysis of discordin domain receptor 1-collagen interaction. Cell Adh Migr 2007;1:92–8.

[43] Yoshida D, Nomura R, Teramoto A. Regulation of cell invasion and signalling pathways in the pituitary adenoma cell line, HP-75; by reverser-inducing cysteine-rich protein with kazal motifs (RECk). J Neurooncol 2008;89:141–50.

[44] Liu X, Ma S, Dai C, et al. Antiinflammatory, antiangiogenic, and proapoptotic activity of folate receptor α-targeted liposomal doxorubicin in nonfunctional pituitary adenoma cells. Endocrinology 2013;154:1414–23.

[45] Zhao C, Zhang M, Liu W, et al. β-Catenin knockdown inhibits pituitary adenoma cell proliferation and invasion via interfering with AKT and gelatinses expression. Int J Oncol 2015;46:1643–50.
[46] Pereda MP, Ledda MF, Goldberg V, et al. High levels of matrix metalloproteinases regulate proliferation and hormone secretion in pituitary cells. J Clin Endocrinol Metabol 2000;85:263–9.

[47] Whitelock JM, Murdoch AD, Iozzo RV, et al. The degradation of human endothelial cell-derived perlecan and release of bound basic fibroblast growth factor by stromelysin, collagenase, plasmin, and heparanases. J Biol Chem 1996;271:10079–86.

[48] Beaulieu E, Kachra Z, Mousseau N, et al. Matrix metalloproteinases and their inhibitors in human pituitary tumors. Neurosurgery 1999;45:1432–40.

[49] Brew K, Dinakarpandian D, Nagase H. Tissue inhibitors of metalloproteinases: evolution, structure and function. Biochim Biophys Acta 2000;1477:267–83.

[50] Koutroulis I, Zarros A, Theocharis S. The role of matrix metalloproteinases in the pathophysiology and progression of human nervous system malignancies: a chance for the development of targeted therapeutic approaches? Expert Opin Ther Targets 2008;12:1577–86.

[51] Murphy G. Tissue inhibitors of metalloproteinases. Genome Biol 2011;12:233.

[52] Sato H, Takino T. Coordinate action of membrane-type matrix metalloproteinase-1 (MT1-MMP) and MMP-2 enhances pericellular proteolysis and invasion. Cancer Sci 2010;101:843–7.

[53] Valacca C, Tassone E, Mignatti P. TIMP-2 interaction with MT1-MMP activates the AKT pathway and protects tumor cells from apoptosis. PloS One 2015;10:e0136797.

[54] Stetler-Stevenson WG. The tumor microenvironment: regulation by MMP-independent effects of tissue inhibitor of metalloproteinases-2. Cancer Metast Rev 2008;27:57–66.

[55] Deryugina EI, Quigley JP. Tumor angiogenesis: MMP-mediated induction of intravasation- and metastasis-sustaining neovascuature. Matrix Biol 2015;44–46:94–112.

[56] Pan LX, Chen ZP, Liu YS, et al. Magnetic resonance imaging and biological markers in pituitary adenomas with invasion of the cavernous sinus space. J Neurooncol 2005;74:71–6.