Motion preservation in cervical prosthesis surgery: Implications for adjacent segment degeneration

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Chapter 7

Association Between Modic Changes, Disc Degeneration, and Neck Pain in the Cervical Spine: A Systematic Review of Literature

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ABSTRACT

Objective

The objective of this study was to review current literature on the association between Modic changes (MCs), cervical disc degeneration, and neck pain.

Methods

A literature search was performed in PubMed, Embase and Web of Science using a sensitive search string combination. Studies were selected by predefined selection criteria and risk of bias was assessed using a validated Cochrane Checklist adjusted for this purpose.

Results

Fourteen articles that associated MCs with neck pain and/or cervical disc degeneration were included in the present study. Ten articles showed low risk of bias and four showed intermediate risk of bias. The prevalence of MCs in cervical spine varied from 5 to 40% and type II was predominant. Patients with MCs were reported to experience more neck pain and disability. Cervical disc degeneration was detected more frequently in patients with MCs.

Conclusions

MCs were found to be associated with neck pain and with disc degeneration. Therefore, the large variation in prevalence that is reported is highly dependent on the nature of the studied population.

INTRODUCTION

Peridiscal bone marrow changes in vertebral bodies can be visualized by magnetic resonance imaging (MRI) and are generally referred to as Modic changes (MCs) or vertebral endplate signal changes (VESC). In 1988, Modic et al.[1,2] described three types of signal changes in the bone marrow adjacent to the vertebral end plates. Type I lesions, hypointense on T1-weighted imaging (T1WI) and hyperintense on T2-weighted imaging (T2WI), represent marrow edema, and are associated with inflammatory changes in the vertebral endplates. Type II lesions, hyperintense signal on T1WI and hyperintense signal on T2WI, represent bone marrow ischemia with conversion of normal red hematopoietic bone marrow to yellow fatty marrow. Type III lesions, hypointense both on T1WI and T2WI, are considered to represent sclerotic changes of the endplates.

MCs, particularly type I, are believed to be associated with accelerated degenerative changes in the vertebral column[3]. It is therefore interesting to explore whether these MCs are associated with degenerative signs of the intervertebral disc or with clinical implications of degenerative changes. For evaluating intervertebral disc degeneration, several evaluation systems exist[4,5] of which the MRI Pfirrmann grading system is the most commonly used[6]. To evaluate the clinical implication of spine, degeneration pain (low back pain or neck pain), or loss of functionality are usually scored.

Although several studies have evaluated the role of MCs in relation to spinal pain, most of them concentrated on low back pain[7-9]. It would be interesting to evaluate the correlation in the cervical spine. Some studies have reported an association between cervical disc degeneration and neck pain[10,11] but literature on the association between MCs and neck pain in the cervical spine is scarce[5].

To the best of the authors' knowledge, there is no review discussing the association between cervical MCs, disc degeneration, and clinical symptoms. This literature review aims to shed a light on this relationship.

METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement[12].

Search strategy and study selection

In December 2016, the electronic databases PubMed, Embase, and Web of Science were searched using the search strategies (complete search strategies can be found in the Figure 1). To maintain inter-rater reliability, two of the authors (XY and DK) independently screened the articles by title, abstract or by full article, when necessary, to select the studies that met

the predefined selection criteria. Reference screening and citation tracking were performed on the identified articles and as a final check, the reviews found in the first search were studied to make sure no relevant articles were missed. Moreover, supplementary literature searches were performed from December 2016 to September 2017 and from September 2017 to September 2019 aiming to find recent articles.

Neck pain (performed 24.11.2016, 15.09.2017 and 17.09.2019)

PUBMED (417+24+167 results)
(MODIC[all fields] OR "Intervertebral Disc Degeneration"[majr] OR "Intervertebral Disc Degeneration"[ti] OR "Intervertebral Disc Degenerations"[ti] OR "Intervertebral Disk Degeneration"[ti] OR "Intervertebral Disk Degenerations"[ti] OR vesc[all fields]) AND (Neck[ti] OR cervical*[ti] OR cervix[ti] OR NDI[ti] OR VAS[ti] OR NRS[ti])
WEB OF SCIENCE (25+8+3 results)
(TS=(MODIC OR vesc) OR TI=("Intervertebral Disc Degeneration*" OR "Intervertebral Disk Degeneration*")) AND TI=(Neck OR cervical* OR cervix OR NDI OR VAS OR NRS)
EMBASE (437+5+35 results)
(MODIC.mp. OR exp *intervertebral disk degeneration/ OR "Intervertebral Disc Degeneration*".ti. OR "Intervertebral Disk Degeneration*".ti. OR vesc.mp.) AND (Neck.ti. OR cervical*.ti. OR cervix.ti. OR NDI.ti. OR VAS.ti. OR NRS.ti.)

Disc degeneration (performed 30.11.2016, 15.09.2017 and 17.09.2019)

PUBMED (130+37+57 results)
((MODIC[all fields] OR vesc[all fields]) AND cervic*[all fields] AND (disc[all fields] OR discs[all fields] OR disk[all fields] OR disks[all fields])) OR (cervic*[ti] AND (disc[ti] OR discs[ti] OR disk[ti] OR disks[ti]) AND ("Intervertebral Disc Degeneration/diagnosis"[Majr] OR "Intervertebral Disc Degeneration/pathology"[Majr] OR "Intervertebral Disc Degeneration/radiography"[Majr] OR "Intervertebral Disc Degeneration"[ti] OR "Intervertebral Disc Degenerations"[ti] OR "Intervertebral Disk Degeneration"[ti] OR "Intervertebral Disk Degenerations"[ti])) OR ((cervic*[ti] AND (disc[ti] OR discs[ti] OR disk[ti] OR disks[ti]) AND (degenerate*[ti] OR hernia*[ti]) NOT surgery[ti] NOT surgic*[ti] NOT medline[sb])

WEB OF SCIENCE (37+15+6 results)
(TS=(MODIC OR vesc) AND TS=cervic* AND TS=(disc* OR disk*)) OR (TI=cervic* AND TI=(disc* OR disk*) AND TI=Intervertebral AND TI=Degeneration*) NOT TI=surgery NOT TI=surgic*)

EMBASE (133+3+17 results)
((MODIC.mp. OR vesc.mp.) AND cervic*.mp. AND (disc*.mp. OR disk*.mp.)) OR (cervic*.mp. AND (disc*.ti. OR disk*.ti.) AND (exp *intervertebral disk degeneration/di OR "Intervertebral Disc Degeneration*".ti. OR "Intervertebral Disk Degeneration*".ti.)) NOT surgery.ti. NOT surgic*.ti.)

Figure 1 Search strategy

Inclusion criteria

Included were articles that reported the correlation between MCs occurring in the cervical spine with clinical outcomes (assessed by Neck Disability Index (NDI), Numeric Rating Scale (NRS) neck pain, or Visual Analogue Scoring (VAS) for neck pain) and/or cervical disc degeneration. The article had to be published in English in a peer-reviewed journal.

Exclusion criteria

Reviews, meta-analyses, animal studies and case reports were excluded.

Any discrepancy in selection between the two reviewers was resolved in an open discussion with a third reviewer (CVL).

Evaluation of risk of bias

The methodological quality of these studies was assessed by two independent reviewers (XY and DK), using an adjusted version of the checklist for cohort studies of the Dutch Cochrane Centre[13]. When there was no consensus about the assessment, a third reviewer (CVL) was consulted.

The items reviewed in the assessment were: well-defined patient group and study goal, selection bias, and outcome bias. Well-defined patient group and study goal: a maximum of three points could be assigned: one point for clear study objective and inclusion criteria, one point for a clear definition of MCs, and one point for detailed information on patient demographics. Selection bias being absent was assigned one additional point. Outcome bias could be assigned with a maximum of three points: one point if outcome was defined properly, an additional point for the presence of a scoring classification, and one point for the combination of a valid statistical analysis, an independent radiological evaluation (blinded to clinical results), and independence of investigators. Studies could be awarded a maximum of seven points indicating the lowest risk of bias. Studies were divided into a low (six-seven points), intermediate (four-five) or high (three or less points) risk of bias group using a method adapted from Furlan et al.[14].

Definition of Modic changes

In order to accurately judge MCs, we made an inventory of all different methods used in the gathered articles to grade MCs. Usually, MCs were scored by different types of bone marrow changes into type I (hypointense on T1WI and hyperintense on T2WI), type II (hyperintense on T1WI and isointense or hyperintense T2WI) and type III (hypointense on both T1WI and T2WI), based on the definition made by Modic et al.[2] in 1988. Miller[15] made a slight adjustment to this classification by adding a grade 0, meaning no MCs present. Another addition was made in the classification proposed by Weishaupt et al., focusing on the degree to which MCs are present. MCs according to Weishaupt et al.[16] are classified in four categories: *normal*, no abnormality in T1WI or T2WI; *mild*, the scope of signal intensity change equals or is less than 25% of the vertebral height; *moderate*, the signal changes occupy between 25% and 50% of vertebral height; *severe*, the signal changes are equal to or are more than 50% of vertebral height.

Definition of disc degeneration

In order to grade disc degeneration, several grading systems exist. We scored grading systems that were used in the assembled articles. The most frequently used score system is the Pfirrmann grading[6], which classified disc degeneration into five grades based on the T2WI. Other articles that were retrieved described additional scoring systems. According to the location category, the type of classification related to disc degeneration were identified into no disc degeneration, disc bulging, disc protrusion, disc extrusion and disc sequestration by Fardon

et al.[17]. Sive et al.[18] scored disc degeneration from 0 to 12 via different histologic features. Additionally, Griffith et al.[19] and Miyazaki et al.[20] scoring systems are upgraded scoring systems with higher resolution and derived from Pfirrmann grading system. According to Goffin scoring system, disc degeneration was defined based on the loss of disc height and the presence and size of anterior osteophyte formation on x-ray[21]. Matsumoto et al.[22] evaluated disc degeneration according to four features: decrease in signal intensity of intervertebral discs, posterior disc protrusion, disc space narrowing and foraminal stenosis.

Definition of neck disability

To evaluate clinical outcome, different patient-reported outcome measures were used. The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[23-25]. Additionally, NRS and VAS were used for patient-reported neck pain intensity.

Data extraction

Information was independently extracted by two reviewers (XY and DK). Data on study design, sample size, mean age, and sex were collected. With regard to outcomes, the prevalence and the type of MCs (I, II or III) in cervical spine, the prevalence and grading of disc degeneration, and the neck disability score were collected. All articles reported either on the relationship of MCs and neck pain or the relationship of MCs and cervical disc degeneration.

RESULTS

Characteristics of studies and risk of bias

A total of 1,556 articles were identified, of which 1,000 original articles were left after removing duplicates. Titles and abstracts were screened, resulting in 23 eligible articles. After reading full-text articles in total, 14 studies met all criteria to compare MCs with neck pain and/or cervical disc degeneration (Figure 2): seven of those articles discussed the relationship of MCs with both neck pain and disc degeneration[5,26-31]. Three articles evaluated the relationship of MCs with neck pain[32-34] and the other four studies correlated cervical disc degeneration to MCs[4,35-37].

Study characteristics are demonstrated in Table 1 and 2. A total of 5,252 patients were included, with a sample size varying from 44 to 1,520.

Risk of bias

Ten[4,5,27,28,30,31,33,35-37] studies were assessed to have a low risk of bias, meanwhile, and four studies[26,29,32,34] showed an intermediate risk of bias. In five of 14 studies[4,27,28,33,35], selection bias was absent (Table 3).

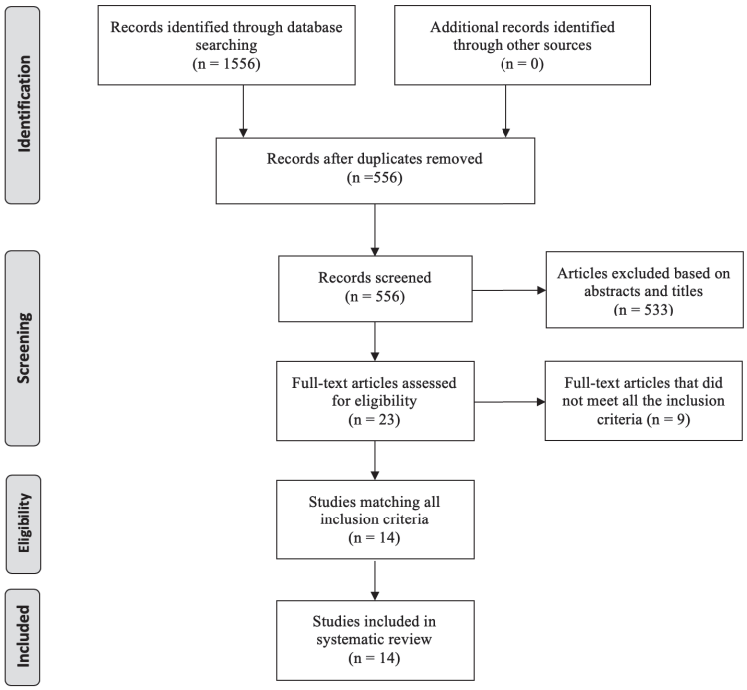

Figure 2 Flow diagram

Reliability of the classification system

Reliability of MCs classification was evaluated by calculating Cohen's Kappa statistics[38,39], and 11 studies provided the results for either or both interobserver and intraobserver reliability. Regarding intraobserver reliability on MCs classification, nine studies[5,26,27,29-31,33,35,36] reported κ values and values varied from 0.64 to 0.89, indicating substantial to excellent reliability. All 11 studies[4,5,26,27,29-33,35,36] reported κ values on interobserver reliability. Nine studies showed substantial to excellent reliability (0.62-0.89). One study reported a κ value of 0.11 (poor reliability)[31] and another one reported a κ value of 0.54 (moderate reliability)[36] (Table 4).

Prevalence of Modic changes

The prevalence of MCs in the cervical spine varied from 5% to 40%. Type II was predominant in the cervical spine and type III was the least prevalent. The prevalence of type I MCs varied from 1.8% to 14.8%, and type II from 1.4% to 33.2% (Table 1). Additionally, eight studies[5,26-30,35,37] that specifically reported the finding of MCs at the specific levels most frequently identified MCs to be present at C5-6.

Table 1 Characteristics of studies-patients with Modic changes

Study (year of publication)	Risk of bias		Type of study	Population	Mean age (years)	N of patient	N of patient with MCs	Type I	Type II	Type III
An (2017)	7*		Retrospective	Patients with cervical kyphosis	54.2 ± 12.2	286	102 (35.6%)	NA	NA	NA
Davies (2016)	7*		Prospective	Patients after cervical discectomy surgery for radicular pain	51 ± 11	90	NA	NA	NA	NA
Hayashi (2014)	7*		Prospective	Patients with neck pain	49.8 ± 10.0	437	84 (19.2%)	NA	NA	NA
Kang (2017)	6*		Retrospective	patients with one-level cervical degenerative diseases	50.7 ± 10.3	169	66 (39.1%)	3 (1.78%)	56 (33.14%)	7 (4.14%)
Kressig (2016)	**5***		Prospective	Patients with cervical disc herniation and neck pain	**44.73 ± 7.9**	**44**	**13 (29.5%)**	**NA**	**NA**	**NA**
Li, S-Y (2014)	6*		Retrospective	Patients with neck pain	44.9 ± 11.1	1520	132 (8.7%)	NA	NA	NA
Li (2017)	7*		Retrospective	Patients with or without nonspecific axial neck pain	50.9 ± 12.6	604	266 (44%)	65 (10.8%)	189 (31.3%)	12 (2.0%)
Mann (2011)	6*		Retrospective	Patients over the age of 50 with neck pain	61.7 ± 9.12	426	172 (40.4%)	63 (14.8%)	121 (28.4%)	0
Matsumoto (2012)	**5***		Prospective	asymptomatic healthy volunteers	**50.5**	**223**	**10 (4.5%)**	**7 (3.1%)**	**3 (1.4%)**	**0**
Average	-				50.0	375	-	-	-	-
Follow-up										
Kressig (2016)	5*	1y	Prospective	Patients with cervical disc herniation and neck pain	44.73 ± 7.9	40	11 (27.5%)	NA	NA	NA
Matsumoto (2012)	5*	11.6y	Prospective	asymptomatic healthy volunteers	38.9	223	31 (13.9%)	10 (4.5%) #	19 (8.5%) #	2 (0.9%)

NA: Not available
N: Number
MCs: Modic changes
#: 2 mixed type (MCs type I and II) was assigned to two groups

Table 2 Characteristics of studies-segments with Modic changes

Study (year of publication)	Risk of bias	Mean age (years)	N of segment	N of segment with MCs	Type I	Type II	Type III
An (2017)	7*	54.2±12.2	1430	113 (7.9%)	38 (2.7%)	75 (5.2%)	0
Davies (2016)	7*	51±11	106	42 (40%)	15 (14.2%)	22 (20.8%)	5 (4.7%)
Hayashi (2014)	7*	49.8±10.0	2185	109 (5.0%)	27 (1.2%)	72 (3.3%)	10 (0.5%)
Kang (2017)	6*	50.7±10.3	NA	NA	NA	NA	NA
Kressig (2016)	**5***	**44.73±7.9**	**NA**	**NA**	**NA**	**NA**	**NA**
Li, S-Y (2014)	6*	44.9±11.1	6138	108 (1.8%)	35 (0.6%)	70 (1.1%)	3 (0.05%)
Li (2017)	7*	50.9±12.6	1330	275 (20.7%)	70 (5.3%)	175 (13.2%)	12 (0.9%)
Mann (2011)	6*	61.7±9.12	1704	245 (14.4%)	74 (4.3%)	171 (10%)	0
Matsumoto (2012)	**5***	**50.5**	**1338**	**10 (0.7%)**	**7 (0.5%)**	**3 (0.2%)**	**0**
Average	-	50	1786	-	-	-	-
Follow-up							
Kressig (2016)	5* 1y	44.73±7.9	NA	NA	NA	NA	NA
Matsumoto (2012)	5* 11.6y	38.9	1297	41 (3.2%)	13 (1.0%)	25 (1.9%)	3 (0.2%)

NA: Not available
N: Number
MCs: Modic changes

Table 3 Risk of bias

Study (year of publication)	Risk of bias scale (7)	Well-defined patient group and study goal (3)	Properly outcome examined (3)	Absence of selection bias (1)	Risk of bias
An (2017)	*6**	***	**	*	Low
Davies (2016)	7*	***	***	*	Low
Hayashi (2014)	7*	***	***	*	Low
Kang (2017)	*6**	***	***	-	Low
Kressig (2016)	5*	**	***	-	Medium
Li, S-Y (2014)	6*	***	***	-	Low
Li (2017)	*7**	***	***	*	Low
Mann (2011)	6*	***	***	-	Low
Matsumoto (2012)	5*	**	***	-	Medium

Modic changes and neck pain

Three articles studied this. An et al.[33] studied patients with kyphosis. They included 283 patients of which circa half had neck pain (no scoring). They evaluated the presence of MCs (1/3 of patients) and demonstrated that MCs were associated with axial neck pain (odd ratio [OR] 5.356; 95% confidence interval [CI] 1.314-12.8; P<0.001). Kressig et al.[32] evaluated neck disability and neck pain in patients with a herniated disc. MCs were demonstrated in one-third of patients. The median NDI score in patients with MCs was 23 and higher than

the median NDI of 15 reported by those without MCs (P=0.04). Neck pain in patients with MCs was also higher (NRS 7) in comparison to patients without MCs (NRS 5.5), though this difference was not significant (P=0.08). Zhou et al.[34] included 117 patients who underwent anterior cervical discectomy and fusion, of which 24% of the patients were found to have MCs. They demonstrated that preoperative MCs adjacent to the operated vertebral body is a risk factor for developing postoperative axial symptoms (shoulder and neck pain, VAS neck pain) (OR 3.268, 95% CI 1.255-8.511, P=0.015).

Table 4 Inter- and intra-observer agreement

Study	Risk of bias	Intra-observer	Inter-observer
An (2017)	7*	0.81	0.72
Davies (2016)	7*	-	0.8
Hayashi (2014)	7*	0.74	0.78
Kang (2017)	6*	-	-
Kressig (2016)	5*	-	0.86
Li (2014)	6*	0.74-0.89	0.74-0.89
Li (2017)	7*	0.81	0.73
Mann (2011)	6*	0.82 (95% CI=0.72-0.92)	0.54 (95% CI=0.43-0.65)
Matsumoto (2012)	5*	0.64	0.62

Modic changes and disc degeneration

This was studied in four articles. Hayashi et al.[35] studied 437 patients that all suffered from neck pain, and MCs were detected in one-fifth of patients. It was shown that subjects with MCs were more likely to have severe disc degeneration (Miyazaki system, defined as over grade IV) at the same segmental level (OR 3.9, 95% CI 2.42-6.3) compared with those without MCs. Mann et al.[36] investigated 426 patients over the age of 50 and circa 40% of patients were found to have MCs. The risk ratio that compared the presence of MCs with disc extrusion at the same level was reported as 2.42 with 95% CI 1.93 to 3.04, suggesting patients with MCs are nearly 2.5 times more likely to have a disc herniation compared with patients without MCs. Kang et al.[37] studied 169 patients with neck pain, of which 30% had MCs, and those with MCs had a more aggravated grade of disc herniation (Matsumoto system; P<0.01). Davies et al.[4] studied 90 patients who underwent cervical discectomy surgery for radicular pain, and evaluated disc degeneration by means of radiological (Miyazaki system) and histological (Sive system) classification systems. In this study, circa 40% of patients were detected to have MCs, and no correlation was found for MCs compared with MRI grades of degeneration (Spearman Rho: 0.17, P=0.07) nor with histological grades (Spearman Rho=0.11, P=0.3, Table 5)

Table 5 Modic changes with cervical disc degeneration

Study (year of publication)	Risk of bias	Classification of degeneration	Prevalence of disc degeneration
Davies (2016)	7*	Miyazaki system (MRI) and Sive system (Histology)	Miyazaki system: Grade II: 2%; Grade III: 35%; Grade IV: 58%; Grade V: 5% Sive system: Mild (0-IV): 7%; Moderate (V-VIII): 59%; Severe (IX-XII): 34%
Hayashi (2014)	7*	Miyazaki system	Mild (I-III): 56.1% Severe (IV-V): 43.9%
Kang (2017)	*6**	Motsumoto system	Grade I: 26.5% Grade II: 37.9% Grade III: 25.6% Grade IV: 10%
Li, S-Y (2014)	6*	Pfirrmann system	Grade I: 8.3% Grade II: 27.5% Grade III: 59.4% Grade IV: 4.6% Grade V: 0.1%
Li (2017)	*7**	Schneiderman system	NA
Mann (2011)	6*	Type 1- disc bulge; Type 2-disc protrusion, herniation and extrusion	Type I: 13.3% Type II: 28.9%
Matsumoto (2012)	5*	1. Decreased signal intensity of the intervertebral discs; 2. Posterior disc protrusion; 3. Disc space narrowing; 4. Foraminal stenosis	The percentage with positive findings: 1: 29.4% 2: 20.1% 3. 6.5% 4. 2.7%

Modic changes with both neck pain and disc degeneration

This combination was studied in seven articles. Li et al.[5] studied 1,520 patients with neck pain, and 9% of patients were detected to have MCs. The prevalence of MCs was higher in patients with neck pain (no scoring system) (8.7% versus 3.3%, P=0.00). Furthermore, the prevalence of MCs increased with grade of cervical disc degeneration (Pfirrmann system; Spearman rank 0.220, P=0.000).

Matsumoto et al.[26] studied 497 asymptomatic patients and found that the association of development of MCs through 10 years follow-up was positively correlated with several indicators of progression of disc degeneration: posterior disc protrusion (OR 2.6, 95% CI 1.1-6.0), disc space narrowing (OR 4.2, 95% CI 1.9-9.5), and foraminal stenosis (OR 4.2, 95% CI 1.5-1.16). There was no association between MCs and neck pain (no scoring system) at the end of follow-up (P=0.16).

Li et al.[27] studied asymptomatic and symptomatic patients that consecutively visited the outpatient clinic with varying neck problems. A total of 266 patients with MCs were

compared with 338 patients without MCs. It was demonstrated that the patient group with MCs had more patients with axial neck pain (42.1% versus 26.6%, P=0.000) and higher disc degeneration score (Schneiderman system) compared to those without MCs (4.6 ± 2.8 versus 2.2 ± 2.5, P=0.032).

Kong et al.[31] studied 381 patients with cervical radiculopathy or myelopathy, and 47 of them had MCs. They demonstrated that MCs were not correlated with severe neck pain (defined as at least five points on the NRS), but MCs were found to be a predictive factor correlated with persistent neck pain (defined as at three points on the NRS for more than 12 months) (OR 2.308 95% CI 1.244-4.282, P<0.05). It was also demonstrated that severe disc degeneration (defined as over grade IV in Pfirrmann system) was associated with MCs (OR 2.423, 95% CI 1.169-5.023, P<0.05).

Qiao et al.[29] studied 539 patients who suffered from cervical spondylotic myelopathy, and 13% of them showed MCs. It was demonstrated that the presence of MCs was correlated with durations of axial symptoms (shoulder and neck pain, no scoring system) more than 18 months (X^2=23.438, P=0.000). This study also reported that a higher prevalence of MCs was found in patients with high grade of degenerative discs (defined as over grade III in Pfirrmann system, X^2=223.137, P=0.000).

Tsuji et al.[30] reported the finding of MCs with 20-year follow-up, of which the result of 10-year follow-up was reported by Matsumoto et al.[26]. A total of 193 patients were included in this study and 16% of patients were found to have MCs. Unlike with the result of 10-year follow-up, neck pain (no scoring system) was associated with the presence of MCs in this follow-up (OR 2.71, 95% CI 1.08-6.80, P=0.033). They also demonstrated that pre-existing posterior disc protrusions were associated with the development of MCs (OR 3.31, 95% CI 1.21-9.05, P=0.020).

Yang et al.[28] studied 223 patients with radiculopathy derived from two RCTs and reported the MCs findings both at baseline (18%) and at one-year follow-up (23%). They reported that there was no correlation between MCs and neck pain (scored by NDI neck pain intensity section and VAS neck pain), neither at baseline nor at one-year follow-up. However, they found that cervical disc degeneration (Goffin system) was correlated with the presence of MCs (OR 2.40, 95% CI 1.171-4.938) preoperatively, but this correlation disappeared at one year after surgery.

Conversion of Modic changes

Matsumoto at al.[26] studied MCs in asymptomatic patients during an average follow-up period of 11.6 years. Forty-one (3.2%) intervertebral levels were detected to be with MCs at follow-up compared with ten subjects (0.8%) in baseline. Of the 13 segments with MCs type I in follow-up, ten were newly developed, two remained as type I and one changed from type II to type I. Of 25 type II intervertebral segments, 22 were newly developed, one changed from type I to type II, and two remained as type II. All three type III segments at follow-up were

newly appeared. Four type I segments in the previous study had returned to normal at follow-up. Yang et al.[28] reported the conversion of MCs preoperatively and one year postoperatively. At one-year follow-up, they demonstrated that 13 MCs type II levels consisted of 11 newly developed and two maintained as type II. Of eight levels with MCs type I, seven were newly developed and one maintained as type I.

Modic changes and age

The mean age of patients in the included studies is 50.9 years with a range of 44.7 to 61.7 years. Seven studies[4,5,26,28-30,32] correlated age to the presence of MCs. Li et al.[5] reported that MCs significantly occurred more often in patients with older age in a 1,520 patient group with an age range of 19-86 years (spearman rank correlation: 0.217, P=0.000). Similarly, another study[26] demonstrated that age ≥40 years was a significant factor associated with the development of new MCs (OR 8.0, 95% CI 2.7-23.3, P=0.01) (223 patients, range of age 23-83). Qiao et al.[29] also showed that MCs tend to occur in patients over 40 years of age in a 539 patient group with an age of range 24 to 87 years (X^2=57.437, P=0.000).

Two much smaller studies could not demonstrate a correlation between age and MCs (Kressig et al.[32], 44 patients, P=0.099; Davies et al.[4], 90 patients, P=0.8). Similarly, another two studies with a group of circa 200 patients could not confirm this relationship neither: Yang et al.[28] (223 patients) and Tsuji et al.[30] (193 patients) did not found the correlation between age and the presence of MCs.

DISCUSSION

MCs in the cervical spine vertebrae are positively associated with the prevalence of neck pain and with the prevalence of disc degeneration. The huge variation of the presence of MCs that is reported in literature (5% to 40%) is highly dependent on the patient population studied. The lower part of the spectrum (5%) comes from a study in a group of asymptomatic volunteers, and the higher end of the spectrum (40%) is reported in a population with neck pain.

All the studies demonstrate that MCs type II are predominant in the cervical spine and that C5-6 is the most frequent level (and C6-7 the second most frequent level) at which MCs are diagnosed. As the endplates of C5-C7 sustain more weight than the higher levels and vertebrae are less limited in their excursion, greater momentum on the vertebral endplates are transmitted.

With a high quality of evidence, disc degeneration was positively correlated with MCs in the cervical spine, suggesting that the patients with MCs have more severe cervical disc degeneration. The only result of noncorrelation was described by Davies et al.[4] that only studied a small number of discs (106 discs) in comparison to the other studies (studying 256

to 6,138 discs). However, this is the only study using a histologic method to evaluate disc degeneration. Since histologic evaluation of intervertebral disc tissue is deemed the most accurate and sensitive method of identifying disc degeneration[40,41], more studies are needed to clarify the correlation between cervical disc degeneration assessed by histologic methods and MCs.

A significant association of MCs with age was demonstrated in two large studies (Li et al.[5] and Matsumoto et al.[26]). This association is confirmed by results of a study from de Bruin et al.[42] that showed an extremely low percentage (0.3%) of segments with MCs in a young patient group (average age of 30 years). Older patients are more likely to be suffering from disc degeneration, and from the positive association of MCs with disc degeneration, it is only logical that MCs are more often occurring in older. Likewise, patients with disc degeneration are more likely to suffer from neck pain and/or disability, and this correlation is therefore also not surprising. However, this correlation could not be affirmed in another four studies[4,28,30,32].

The correlation between MCs and pain has not been elucidated so convincingly in low back pain. El Barzouhi et al.[7] investigated 263 patients with sciatica of which half of the number of patients had also back pain. They demonstrated that disabling back pain was found in nearly the same proportion in patients with and without MCs. This group of patients however was suffering from recent onset sciatica and therefore results may be different than studies in groups of patients with longer lasting complaints, as in the cervical studies gathered in this review on cervical spine. A recent study on patients with long-term pain or disability did however also not demonstrate an association: Udby et al.[43] studied 170 subjects and concluded that MCs were not found to be associated with long-term pain or disability. A meta-analysis performed by Herlin et al.[44] indicated that the associations between MCs and low back pain-related outcomes were inconsistent because of the high risk of bias and the heterogeneity of studies. In agreement with our results though, Zhang et al.[45] and Jensen et al.[46] performed systematic reviews and reported that MCs were correlated to discogenic low back pain. In conclusion, both in neck and in low back pain correlations between pain and MCs have been demonstrated, but the results in the cervical spine are more convincing than those in the lumbar spine.

As we only included studies published in English, those articles reported in other languages were possible omissions, which is a limitation to the incomplete retrieval of identified study.

CONCLUSIONS

MCs are associated with more disc degeneration. Disc degeneration is highly likely to cause neck pain and disability. It is therefore not surprising that neck pain and disability is indeed positively associated with the presence of MCs.

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