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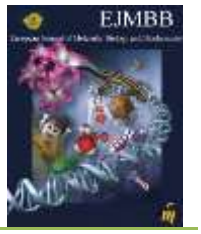

CLINICAL EXPLORATION OF OSSIFICATION OF POSTERIOR LONGITUDINAL LIGAMENT ASSOCIATED WITH SERUM BIOMARKER OF ESR AND HS CRP

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ABSTRACT
Ossification of the spinal ligaments is the term used to describe heterotopic ossified lesions that occurs in the spine. Ossification of the posterior longitudinal ligament (OPLL) is done by means of ectopic new bone formation which replaces the ligamentous tissues. The present study aims to find out the association of serum ESR and hs CRP as biomarkers in the clinical assessment of ossification of posterior longitudinal ligament. A prospective study conducted at Swamy Vivekanandha Medical College Hospital and Research Institute, Tiruchengode and all patients with OPLL and controls were selected from the Department of Orthopaedics. The diagnosis of OPLL was based on radiographs and computed tomography (CT) scans of the cervical, thoracic and lumbar spines. A total of 95 patients with OPLL (56 men and 39 women: average age 75.3 ± 17.4 years, range 40±85 years) were available for a follow-up of more than 2 years with radiological examinations. The average follow-up duration was 5.2 ± 2.1 years (range, 2±10 years). The outcome of the study is that serum hs-CRP and ESR of the patients with OPLL is higher as compared to the controls. The hs-CRP within the OPLL progression group is higher than in the non-progression group, indicating that infection might arise in OPLL. The observation is that these findings give us a better understanding the disease process and management of OPLL.

INTRODUCTION

Ossification of the Posterior Longitudinal Ligament is a spinal condition where the posterior longitudinal ligament becomes calcified, thickened and becomes less flexible. The ossification occurs by means of ectopic new bone formation by replacing the ligamentous tissue. [1] Thus the OPLL of cervical spine causes narrowing of the spinal canal and causes of neurological impairment, together with myelopathy and radiculopathy.

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The epidemiological studies have confirmed that cervical OPLL has more male predominance than the female and thoracic OPLL is more predominant in women. In addition, a recent genome study has shown that the patients may have genetic predisposition also. [2] Therefore, the onset and growth of ossified lesions can be closely related to sex hormones and genetic historical past also.

Many authors reported on OPLL, inclusive of its epidemiology, surgical remedy, and radiological findings.[3] Computed tomography (CT) has been extensively used to evaluate bone structure and the distribution of ossification inside the entire spine. It has been documented that the onset and development of neurological signs are connected with the extend of canal

narrowing due to OPLL and the segmental mobility at the level where OPLL is present. [4] Patients with OPLL and excessive spinal cord compression due to OPLL often have a couple of other sites in the course of the spine. For example, the thoracic OPLL is often associated cervical spine level ossification, and so it is important that the screening needs to be done at different segments of spinal column.

When the symptoms are progressive, the treatment of choice is surgery to relieve spinal cord compression and neurological involvement. It has been reported that several biomarkers, such as leptin and insulin, are related to OPLL. However, we do not know whether or not inflammation occurs in OPLL. A previous study demonstrated that the C reactive protein (CRP) level is increased in patients with heterotopic ossification after total hip replacement [6]. The present study is prospectively designed to determine whether or not or no longer the serum CRP and serum (ESR) are altered in patients with OPLL so that if there is raised level it can be understood that inflammation is one of the causes and for that reason anti-inflammatory therapy might be beneficial in these patients.

When symptoms are moderate and nonprogressive, conservative treatment is enough and sufficient. However, if the signs and symptoms of myelopathy are present and neurologic symptoms are inevitable, the treatment of preference is surgery to alleviate spinal card compression and neurological deficit. It has been reported that several biomarkers, together with leptin and insulin, are associated with OPLL.[5] The aim of the present study is to find out whether or not the serum CRP and serum (ESR) are altered in sufferers of OPLL so that the diagnosis and treatment can be initiated at an earlier stage of the problem and avoid surgery and other major complications.

MATERIAL AND METHODS

A prospective study conducted at Swamy Vivekanandha Medical College Hospital and Research Institute, Tiruchengode after approval from the regional ethical committee. All patients with OPLL and controls were selected from Department of Orthopaedics. The diagnosis of OPLL was based on the findings of radiographs and computed tomography (CT) scans of the cervical, thoracic, lumbar spine. Ankylosing spondylitis and metabolic diseases associated with OPLL, such as hypophosphatemic rickets/osteomalacia and hyperparathyroidism, were excluded.

A total of 95 patients with OPLL (56 men and 39 women: average age 75.3 ± 17.4 years, range 40±85 years) were available for a follow-up of more than 2 years with radiological examinations. The average follow-up duration was 5.2 ± 2.1 years (range, 2±10 years). Plain radiographs were used in 35 patients and CT images were used in 60 patients for the evaluation of the ossified lesions of OPLL and to determine OPLL progression. OPLL extension of more than 2 mm during the follow-up was judged to be OPLL progression. The controls were age-matched patients with a diagnosis of cervical spondylosis, lumbar degenerative disease and/or spinal disc disease.

Of the 100 controls, 22 had cervical spondylosis, 73 had lumbar degenerative disease, 3 had cervical disc herniation and 2 had lumbar disc herniation. The diseases were confirmed by image studies, including plain radiographs, CT and MRI. None of the controls had spinal canal ossifications, as confirmed by CT. They were also checked for any OPLL, inflammatory diseases (such as collagen diseases and rheumatoid arthritis), infections, trauma, myocardial infarction, cerebral infarction or malignant tumors and if present were strictly excluded. No patient or control was on non-steroidal anti-inflammatory drugs and steroids.

A blood sample was obtained from all participants in the morning of the hospital visit. The hs-CRP was analyzed using an ultrasensitive latex-enhanced immunoassay (L-Latex CRP II) employing the BN ProSpec nephelometer (Dade Behring, Newark, DE). [7] This immunonephelometric assay is a high-sensitivity assay capable of measuring hs-CRP at a concentration of 0.00095 mg/dl. And also included were other routine investigations, such as glucose (Glu), calcium (Ca), inorganic phosphate (Pi), erythrocyte sedimentation rate (ESR) at 1 hour and 2 hours, white blood cell count (WBC), hemoglobin (Hb) and platelet count (PLT).

The two groups were compared using the unpaired t-test, Mann-Whitney U test, and chi-squared test as appropriate. The data were presented as the mean _ standard deviation. All statistical analyses were performed using SPSS for Windows (ver. 22.0; IBM Corp. Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The comparison of the serum biomarkers between the OPLL group and the controls. The mean serum hs-CRP concentration was 0.133±0.151mg/dL in the OPLL group and 0.087±0.115mg/dL in the controls, yielding a statistical difference between the two groups ($p = 0.048$). ESR-1h and ESR-2h in the OPLL group were higher than those in the control group $p = 0.004$, $p = 0.003$, respectively.

In the present study the segmental type of OPLL was found to be most common type accounting for 44% followed by mixed type (23%), continuous type (20%) and localized type (12%).

The comparison of the serum biomarkers between the progression group and the non-progression group done. The mean serum hs-CRP concentration was 0.19 ± 0.17 mg/dL in the progression group and 0.097 ± 0.13mg/dL in the non-progression group, and a statistical

difference between the two groups is (p = 0.0015). There were no differences among the other biomarkers in the two groups

Table 1: Demographic data of the patients with OPLL (case) and the control

	OPLL	Controls	P value
Gender (M/F)	**56/39**	**73/27**	**0.44**
Age	**75.3 ± 17.4**	**79.3 ± 18.6**	**0.25**
Height	**167.2±39.9**	**158.9±9.6**	**0.15**
weight	**65.1±15.6**	**59.0±11.7**	**0.09**
BMI	**26.1±4.6**	**24.1±2.5**	**0.38**

Table 2: Comparison of the biomarkers between the patients with OPLL (case) and the controls

		OPLL	controls	P value
Glucose	Mg/dl	249±80.9	119±38.0	0.6
calcium	Mg/dl	9.12±0.39	9.22±4.07	0.15
hs-CRP	Mg/dl	0.133±0.151	0.087±0.115	0.048
ESR at 1 hour	mm	17.3±16.5	11.9±7.6	0.004
ESR at 2hours	mm	35.6±25.9	26.3±16.5	0.003
WBC	X100µ/mL	69.3±56.3	62.3±16.3	0.29
Hemoglobin	g/dl	16.6±4.9	14.9±3.6	0.38
PTL	X10000µL	22.6±7.5	21.5±5.6	0.9

Table 3: Distribution of study group as per the radiological type of OPLL

Types of OPLL	Number of samples	Percentage
Segmental	42	44.2%
Mixed type	22	23.1%
Continuous type	19	20%
Localized type	12	12.6%

Table 4: Comparison of the biomarkers between the progression group and the non-progression group

		progression group	Non-progression group.	P value
Glucose	Mg/dl	125±45.3.9	123±42.9	2
calcium	Mg/dl	9.12±0.8	9.06±0.35	0.72
Hs CRP	Mg/dl	0.19±0.17	0.097±0.13	0.0013
WBC	X100µ/mL	61.5±14.3	57.6±16.4	0.29
Hemoglobin	g/dl	13.2±1.98	14.5±1.66	0.25
PTL	X10000µL	20.3±6.8	21.6±6.8	0.6

DISCUSSION

The present study exposed two important factors concerning the pathogenesis of OPLL: one being inflammation and the other, calcium phosphate metabolism. The serum concentration of hs-CRP in the OPLL group was higher compared to the control group and ESR was also significantly higher. Additionally, this study showed that serum hs-CRP in the OPLL progression group was significantly higher than that in the non-progression group correlated with Gabay C, Kushner et al. [8] This may be due local inflammation is associated with the pathogenesis of OPLL. CRP is one of the most useful acute phase markers to detect inflammation after tissue injury. Pro-inflammatory cytokines, such as interleukin 6 (IL-6), interleukin 1β and tumor necrosis factor alpha (TNF-α) are responsible for the induction of CRP synthesis in the liver. The rise of both hs-CRP and ESR indicate the presence of inflammation in OPLL. OPLL shows ectopic bone formation in the spinal ligaments and ossification progression was observed. Sell S et al studies have demonstrated that the CRP level is increased in patients with heterotopic ossification following total hip replacement and in those with heterotopic ossification after traumatic spinal cord injury. [9] Even though, in present study, there was no inclusion of any surgical specimens that show local inflammation at the ectopic bony lesion of OPLL, the endochondral ossification process is consistently observed.

Current study confirmed that the level of CRP was raised in 89.4% cases of continuous type, 90% cases of localised type, 69.2% cases of mixed type and 92.8% cases of segmental type. The level of ESR was raised in

81.4% cases of continuous type, 65.7% cases of localised type, 51.5% cases of mixed type and 73.0% cases of segmental type. These observations correlated with the findings of Jagadish T et al. [10]

CONCLUSION

The outcome of the study shows that the level of hs-CRP and ESR in the patients with OPLL turned into higher as compared to the controls. The hs-CRP within the OPLL progression group is higher than in the non-progression group, indicating that inflammation might arise in OPLL. Timely diagnosis using these biomarkers helps the patient in early diagnosis and better management of OPLL. The findings observed in this paper strengthens the importance of these biomarkers as suggested by many authors.

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