INTRODUCTION

S100 proteins are acidic low molecular weight proteins of 9 – 12 KDa. Originally, these proteins were isolated from a sub-cellular fraction of bovine brain.1 S100B protein was originally believed to be specific to glial cells and Schwann cells,2 but it is also expressed in a variety of tissues including astrocytes and melanocytes.3

S100B has been extensively studied and its role in tumorgenesis especially in relation to p53, has been documented.4,5 The clinical significance of S100B protein as a common melanoma marker has been investigated by several groups. Serum S100B has been used to monitor the progression of malignant melanoma,6 and in patients with metastatic disease, including lymph node metastasis.7 Increased expression of this protein has also been demonstrated in low grade astrocytic tumours, T-cell leukaemia, adult T-cell leukaemia and hepatosplenic \( \gamma \delta \) T-cell lymphoma.8-11

S100B released from CNS from astrocytes is detectable in serum after injury and is commonly used as a marker to estimate the extent of brain injury. This protein is released into the serum when blood-brain barrier (BBB) is disrupted.12 Loss of BBB function is a hallmark of brain pathogenesis.13 Elevated concentrations of this protein in CSF and serum have been reported after a variety of cerebral lesions and injuries including brain tumours,14 stroke and head injury,15,16 therefore, considered as markers of central nervous damage.

The aim of this study was to measure pre- and postoperative serum S100B values in patients with brain tumours undergoing craniotomy.

METHODOLOGY

The study was carried out at Neurosurgical Ward, Jinnah Postgraduate Medical Centre. Karachi, from May 2007 to April 2008. The study design was approved by the Institutional Ethical Review Board (IERB) of Jinnah University for Women (JUW), Karachi. This work was funded by the Department of Biochemistry, Jinnah University for Women, Karachi, Pakistan.

Equal number of patients undergoing craniotomy for brain tumours and age and gender matched healthy controls were inducted in the study.

Only those patients were included in this study who did not receive chemotherapy of any kind in any form pre-operatively. Patients with CNS metastases and other...
Serum S100B in patients with brain tumours undergoing craniotomy

RESULTS

Demographic data including age, gender, and previous medical history were obtained from patient's medical record in Neurosurgical Ward at JPMC. This observational study comprised 18 patients diagnosed with brain tumours, among them were 9 males (50%) and 9 females (50%) with mean age 30.3 ± 13.5 years. Eighteen normal healthy controls, who had no previous medical condition, were also recruited in this study and comprised of 9 males and 9 females with mean age of 33.1 ± 10.3 years. These patients underwent an initial computed tomography (CT) and magnetic resonance imaging (MRI) and were diagnosed with different types of brain tumours. Pathologies included 5 gliomas, 5 meningiomas, 2 pituitary tumours, one ependymoma, one arteriovenous malformation (AVM), one lymphoma, one medulloblastoma, one acoustic neuroma and one orbital neuroblastoma. The duration of surgery varied from 2 to 6 hours with duration of mean 4 ± 2 hours. Pre- and postoperative serum concentrations of S100B were measured on day 1, 2 and 7 in 18 patients who underwent brain tumour resection. The S100B concentrations in serum of normal healthy controls were also monitored.

All patients and healthy controls were fully informed about the study and consent to participation was obtained from each.

Anaesthetic protocols and criteria were the same in all patients. All the surgeries were performed under general standard neurosurgical procedures. Pre-operatively, a single-shot antibiotic (cefazolin) was applied in all cases. Patients did not receive chemotherapy of any kind in any form either pre- or postoperatively.

Blood samples were taken on the day before surgery (pre-operatively) and on postoperative day 1, 2 and 7 after surgery. Serum was separated within 30 minutes of collection (pre- or postoperatively) and was stored at -70°C until analysis. Blood samples were also collected from normal healthy controls (n = 18) and processed in similar fashion. The measurement of serum concentrations of S100B was carried out on the Liaison Analyser using the Sangtec Kit (Cat. No.314.701, Diasorin Wokingham, Berkshire, UK). The difference of each postoperative sample (days 1, 2 and 7) from the pre-operative sample value (baseline) was calculated and the mean of the difference compared.

Experimental data were statistically analysed with Statistical Package for Social Sciences (SPSS) version 20. Since the overall trend of median and mean concentration of S100B was almost similar in normal healthy controls and patients, therefore, mean was considered to present the data. All data were compared by Mann-Whitney (unpaired) or Wilcoxon (paired) non-parametric tests.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD (µg/L)</th>
<th>Range (µg/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td>0.03 ± 0.01</td>
<td>0.02 - 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Pre-operative patients</td>
<td>0.19 ± 0.12</td>
<td>0.09 - 0.60</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>0.90 ± 1.07</td>
<td>0.17 - 4.52</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Postoperative day 2</td>
<td>0.84 ± 0.57</td>
<td>0.11 - 2.12</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Postoperative day 7</td>
<td>0.44 ± 0.43</td>
<td>0.09 - 1.47</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table I: Comparison of S100B values in the studied group.

Significantly raised serum S100B concentrations were observed in all postoperative samples when compared with pre-operative samples. Almost half of the patients had peak concentrations of S100B in serum on postoperative day 1 and the other half on postoperative day 2. However, the trend of overall mean concentration of S100B suggested that the release of this marker from damaged nervous tissue peaked on postoperative day 1 and decreased afterwards.

DISCUSSION

This study was done to measure the pre- and postoperative concentrations of S100B in serum of patients with brain tumour who had undergone brain tumour resection. Neurosurgical procedures such as craniotomy may result in bleeding, blood clots, retention of fluid causing swelling (oedema), or un-intended injury to normal tissues. The CSF is the main source of S100B as the concentration of this protein is 3-fold higher than in serum.12 The secretion of number of cytokines due to tissue injury causes loss of integrity of BBB,13 resulting in leakage of S100B from CSF into serum. Thus, the elevation of S100B in serum may also be considered as a useful marker of BBB dysfunction. There are many conditions that cause the loss of blood-brain barrier integrity preceding brain injury. For instance, serum concentrations of S100B increased within 6 hours after intra-arterial mannitol or/and methotrexate infusions in patients with primary CNS lymphoma suggesting that such increased in serum concentration of S100B is unlikely due to tissue injury.12 These observations suggest that breaching the BBB integrity with or without tissue injury could increase S100B in serum. S100B is also considered as a neurochemical marker of brain damage in head injury and stroke.15,17

Meningioma, which constitute 15% of primary brain tumours in adults, are extra-axial, slow-growing, and histologically mostly benign.16 In this study, 5 of the 18
patients were diagnosed with meningioma. Out of 5 patients, 3 patients showed elevated pre-operative serum S100B concentrations i.e. > 0.15 µg/L. All of these 5 patients with larger tumour size (> 4 cm) who underwent meningioma resection had high serum S100B concentrations (> 0.4 µg/L) on postoperative day 1 and 2. Interestingly one meningioma patient had exceptionally high serum S100B concentration in pre-operative sample (0.60 µg/L), and on postoperative days 1 (2.56 µg/L), 2 (2.04 µg/L) and 7 (0.85 µg/L), respectively. These results are consistent with the results of previous studies which showed that patients with larger tumours size (> 4 cm) had elevated postoperative serum S100B concentrations (> 0.4 µg/L), suggesting these patients had a 9-fold greater risk of neurological deterioration. Other studies also reported some cases of meningioma were positive for S100B using immunostaining techniques for S100B protein expression.

The literature on S100B expression in the context to pituitary tumours in human is sparse. Earlier studies reported S100 expression in pituitary tumours i.e. adenoma of pituitary gland. Elevated pre-operative S100B concentrations (> 0.15 µg/L) were found in 2 patients with pituitary tumour. The results were not surprising as S100B is also present in the non-nervous tissues i.e. stellate cells of pituitary gland. However, to the best of our knowledge, this is the first report that demonstrated the serum concentration of S100B in patients with pituitary tumours.

Malignant gliomas (MGs), including glioblastoma and anaplastic astrocytoma, are the most common primary brain tumours of adults and other include oligodendroglioma and angiocentric glioma. Contrasting results have been reported regarding the S100B protein expression and glioma. A study reveals that S100B immunoreactivity decreased according to degree of malignancy in oligodendroglioma, while in angiocentric glioma, high expression of S100B was observed. Two out of 5 glioma patients had elevated serum S100B concentrations i.e. (≥ 0.2 µg/L), consistent with the results of previous study who demonstrated the high plasma concentration of this protein in MGs patients.

Medulloblastoma is an invasive embryonic tumour arising in the cerebellum with a preferential manifestation in children and an inherent tendency to disseminate via the cerebrospinal fluid. It is the most common childhood intracranial tumour, accounting for 20 – 25% of paediatric brain tumours; in adults it is less frequent, representing about 1% of all brain tumours. This study has also demonstrated increased serum concentration of S100B in one of the patients diagnosed with medulloblastoma. This patient, who died after a week of surgery, also had increased pre-operative serum concentration of S100B i.e. 0.32 µg/L. He later showed the serum S100B concentrations as 0.26 µg/L, 2.12 µg/L and 1.33 µg/L, on postoperative day 1, 2 and 7, respectively.

The patients who were diagnosed with ependymoma and lymphoma had pre-operative serum S100B concentrations within the normal range i.e. < 0.15 µg/L, while in a patient with acoustic neuroma, the pre-operative serum concentration was slightly above the normal range. However, a study reported the S100B immunoreactivity in patients with ependymomas. Significantly raised serum S100B concentrations were observed in all postoperative samples when compared with pre-operative samples (baseline). The mean S100B concentrations in serum significantly increased on postoperative day 1 while decreased on day 2. On day 7 the concentrations were further declined and reaching towards the basal values. There was a decline of 56.3% and 61.7% of S100B concentrations on day 7 when compared to day 2 and 3 respectively. It was inferred that the serum concentrations of S100B on postoperative day 1 and 2 should be considered as normal physiological release pattern due to the invasive surgical procedure. The reduction in serum concentration of S100B on postoperative day 7 reflects the recovery period and any rise from this point would also be alarming.

Neurological deficit i.e. cognitive dysfunction, after post-craniotomy of brain tumours is commonly observed and require subsequent neuroimaging (MRI/CT) for confirmation of such clinical deterioration. In this study, there were no major postoperative neurological deficit observed in any of the patients, and elevated serum concentration of S100B on postoperative day 1 and 2 appear as a normal release pattern resulting from craniotomy. An immediate therapeutic intervention will only be required if the serum concentration of S100B elevates from levels on postoperative day 7.

The limitation of present study was the sample size. Therefore, the identification and analysis of additional cases will be necessary for better understanding of the association of both pre- and postoperative serum S100B concentrations with intracranial tumours.

CONCLUSION

A heterogeneity of S100B expression existed in brain tumours. The raised pre-operative elevation in these patients could be the consequence of the released from tumour or/and necrotic tissues, while postoperative elevated concentrations appear as an aggregate value of S100B release from the damage tissues resulting from surgical procedures. Measurement of S100B in serum may be preferable for predicting postoperative complications, neurological deficits and further future management.
REFERENCES


