Mast cells and multiple sclerosis in females and males

Per Gøran Krüger, Sverre Mørk

Institute of Biomedicine and Institute of Pathology, University of Bergen, Bergen, Norway
Email: per.kruger@biomed.uib.no

Received 13 December 2011; revised 15 January 2012; accepted 1 March 2012

ABSTRACT

Mast cells were observed in autopsies from 11 females and 8 males. We confirm earlier observations that mast cells are more frequent in close vicinity to MS-plaques. In these plaque-border zone areas, defined as the area within 1 mm distance of the actual plaques, the average number of mast cells was 2.34/mm² in males and 4.77/mm² in females, which in average is 10 times more than earlier observed in MS. The difference in number of mast cells between females and males is significant (p < 0.005) and is of interest since females are more inclined to developing MS than males. Mast cells were rare in areas without visible plaques. The mast cells were preferably located close to capillaries and venules. A mechanism for the probable role of mast cells, based on diet-factors and mast cell mediators in the pathogenesis of MS is discussed.

Keywords: Mast Cells; Multiple Sclerosis; Quantification; Females; Males; Treatment

1. INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS. The presence of mast cells in border zones of plaques in multiple sclerosis have been confirmed by many scientists [1-7] and the significance of these observations have been evaluated [8-10]. The observation of elevated mast cell tryptase in cerebrospinal fluid of MS patients [11] supports the hypothesis that mast cells may be a functional element at the onset and in the maintenance of the MS disease process. The total numbers of mast cells observed has been low, approximately 1:100 that of normal skin [12], and therefore of most scientists suggested to be of no significance for the pathogenesis of MS. In the present investigation we studied the presence of mast cells in plaque/and normal appearing white matter from females and males dying after long periods with MS, employing immune-staining of the mast cell tryptase in autopsy samples, emphasizing differences in the numbers of mast cells in varying distances from MS-plaques.
in close apposition to the endothelium or in the adventitial layers (Figure 1).

3.3. Significance of Data (Students t-Test) (Tables 1 and 2)

Mast Cells/mm² in Areas with No Visible Plaques.
Females: 0.085 +/- 0.047 (n = 4), males: 0.04 +/- 0.03 (n = 3). No significant difference between females and males.

Mast Cells/mm² in Total Areas Including Plaques.
Females: 0.16 +/- 0.15 (n = 11), males: 0.091 +/- 0.04 (n = 8). No significant difference between females and males.

Mast Cells/mm² in Border Zones (Defined as the Area Covering 1 mm outside and around Actual Plaque Area Observed).
Females: 4.77 +/- 3.86 (n = 11), males 2.34 +/- 1.93 (n = 8). The difference between females and males is significant (p < 0.005).

4. DISCUSSION

Multiple sclerosis has been described as an inflammatory and genetically determined disease.

As discussed elsewhere [8], MS is probably not genetically determined traditionally defined, although epigenetics [14,15] and socio-dietary factors may explain effects of inherited lifestyles e.g. for MS. We do not know exact which dietary factors may be involved. Some decades ago, the frequency of MS was low in coastal areas of Norway, and, as discussed elsewhere [2,12] the recent change in nutritional habits may explain why MS is now just as common in coastal as in inland communities. The diet was earlier based on the easy available protein and fat sources as various cod-fishes, herring and mackerel. Salmon and trout were in fact far too expensive for everyday consumption in these communities. Today the farmed salmon is cheap and easily available, but unfortunately the nutritional value has been questioned due to altered composition of their fatty acids [16-18], resulting from modern aqua-cultivation of salmon.

Figure 1. Mast cells (arrows) at capillaries: (a)-(c) all 400×, and venule (d) 100× in plaque lesions border zones of MS.
Table 1. Numbers of mast cells in non-plaque- and plaque-border zone areas: females.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Total area observed (mm²)</th>
<th>Total numbers of mast cells</th>
<th>Calculated numbers of mast cells/mm²</th>
<th>Areas with no visible plaques</th>
<th>Areas with plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total area observed (mm²)</td>
<td>Total plaque area observed (mm²)</td>
</tr>
<tr>
<td>30</td>
<td>1050</td>
<td>29</td>
<td>22.2</td>
<td>74</td>
<td>3.3</td>
</tr>
<tr>
<td>37</td>
<td>400</td>
<td>3.6</td>
<td>9.9</td>
<td>22</td>
<td>2.2</td>
</tr>
<tr>
<td>41</td>
<td>880</td>
<td>36.9</td>
<td>24.7</td>
<td>353</td>
<td>14.3</td>
</tr>
<tr>
<td>48</td>
<td>650</td>
<td>38</td>
<td>25</td>
<td>38</td>
<td>1.5</td>
</tr>
<tr>
<td>48</td>
<td>710</td>
<td>58.7</td>
<td>30.7</td>
<td>162</td>
<td>5.3</td>
</tr>
<tr>
<td>48</td>
<td>730</td>
<td>24.1</td>
<td>20.5</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>50</td>
<td>540</td>
<td>125.9</td>
<td>42.8</td>
<td>256</td>
<td>6</td>
</tr>
<tr>
<td>42</td>
<td>290</td>
<td>10</td>
<td>0.04</td>
<td>580</td>
<td>12.8</td>
</tr>
<tr>
<td>45</td>
<td>300</td>
<td>19</td>
<td>0.06</td>
<td>1280</td>
<td>38.8</td>
</tr>
<tr>
<td>49</td>
<td>880</td>
<td>119</td>
<td>0.14</td>
<td>270</td>
<td>0.8</td>
</tr>
<tr>
<td>59</td>
<td>500</td>
<td>52</td>
<td>0.1</td>
<td>430</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Numbers of mast cells in non-plaque- and plaque- border zone areas: males.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Total area observed (mm²)</th>
<th>Numbers of mast cells</th>
<th>Calculated numbers of mast cells/mm²</th>
<th>Areas with no visible plaques</th>
<th>Areas with plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total area observed (mm²)</td>
<td>Total plaque area observed (mm²)</td>
</tr>
<tr>
<td>36</td>
<td>830</td>
<td>20.2</td>
<td>19.1</td>
<td>82</td>
<td>4.3</td>
</tr>
<tr>
<td>45</td>
<td>320</td>
<td>12.5</td>
<td>15.7</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>47</td>
<td>370</td>
<td>27.7</td>
<td>21.8</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>54</td>
<td>400</td>
<td>33.9</td>
<td>23.8</td>
<td>43</td>
<td>1.8</td>
</tr>
<tr>
<td>59</td>
<td>330</td>
<td>32.4</td>
<td>22.7</td>
<td>29</td>
<td>1.3</td>
</tr>
<tr>
<td>43</td>
<td>1040</td>
<td>26</td>
<td>0.03</td>
<td>260</td>
<td>20.8</td>
</tr>
<tr>
<td>56</td>
<td>190</td>
<td>13</td>
<td>0.07</td>
<td>520</td>
<td>6.3</td>
</tr>
<tr>
<td>79</td>
<td>1010</td>
<td>6</td>
<td>0.1</td>
<td>280</td>
<td>7.8</td>
</tr>
</tbody>
</table>

As proposed by others [19,12] the epigenetic effect of vitamin-D consumption by the mothers or grandmothers may be highly beneficial for the fetus, and may explain why MS was low in coastal areas since herring, mackerel and cod liver is high in vitamin-D [20].

The hypothesis that mast cells may be a cell element responsible for the onset, maintenance or enhancing factor in MS has generally been neglected. Their presence is hardly acknowledged, and the numbers are mostly assumed to be far too low to be of any significance. This neglect is partly due to improper staining procedures [3]. From the present investigation, it seems that the tracking of mast cells by the specific mast cell tryptase is more precise than other methods, and that the numbers of mast cells in close apposition to MS-plaques may be of significance.

The observation that total numbers of mast cells in the plaque border zones are higher in women than in men is of interest since females are more susceptible to developing MS than males [21]. Women even have a general higher incidence of inflammatory disorders than men [22]. These facts, as well as the finding that elevated concentrations of mast cell specific protease is present in the cerebrospinal fluid of MS patients [11], and the increase in mast cell transcripts within and outside MS-lesions [23], supports the importance of mast cells for the onset and/or maintenance of MS. The report that histamine-1 receptor antagonist hydroxyzine, which partially inhibits brain mast cells, may reduce MS symptoms in females and males [24] further emphasises the importance of mast cells in MS.

The presence of mast cells in the plaque border zones may be secondary to a primary infection in the CNS, and the effect of mast cell mediators may be enhancement of an ongoing demyelinating process. Injection of estrogen in mice results in an increased number of mast cells [25], and the effect was most pronounced in females. The synergistic action of estradiol and myelin basic protein on mast cell secretion [26] supports the importance of sex hormones in the demyelinating process. In addition, women is shown to have more perivascular mast cells than men as e.g. in the skin [27,28].

The primary secretagogue(s) for mast cells in CNS may be a metabolite (or several metabolites). Probably
dietary factors produced in the CNS itself, alone or in combination with hormone(s) which triggers the mast cells to the release of potent mediators such as histamine-inducing oedemas—and neutral proteases—dissolving myelin [29]. Neurotensine, substance P, ATP and catecholamines may stimulate mast cells in experimental animal in vitro systems [30-33].

The possible immediate treatment of MS, based on the assumption that mast cells have some key-role, would be the application of mast cell blockers, to inhibit secretion of histamine and proteases and/or antihistamines as recently designed by others [24] to inhibit the histamine-induced oedema formation and protease induced demyelination. Local down-regulation of the blood-brain barrier leads to enhanced mediator access onto the perivascular mast cells. The fact that acute stress situations both stimulate mast cells and lead to exacerbation of MS [9, 34] further indicates importance of mast cells in the enigmatic disease multiple sclerosis.

In addition the increased consumption of vitamin-D, as e.g. fat fishes like herring and mackerel, would prevent MS in coming generation(s).

5. CONCLUSION

In summary, our observations that the number of mast cells is high in the border zones of MS-plaques, and that they are more plentiful in females than in males, may indicate that mast cells are implicated in the pathogenesis of multiple sclerosis.

6. ACKNOWLEDGEMENTS

We are indebted to Bodil Hansen and Ingrid Gavlen for excellent technical assistance.

REFERENCES

transcripts are increased within and outside multiple sclerosis lesions. *Journal of Neuroimmunology*, **195**, 176-185.


