Gender differences in multiple sclerosis: evidence from brain lesions data

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Abstract. Analysis of Multiple Sclerosis (MS) brain lesions is here conducted in order to unravel differences between male and female patients. To this end, a unique dataset provided by the Netherlands Brain Bank is analyzed, which contains pathological information describing types of brain lesions found in MS patients. First, we apply univariate statistical tests to assess whether single types of brain lesions differ significantly between male and female patients. No significant difference results from this analysis. By using univariate tests, we do not correct for the relations among the background variables. Therefore, we also investigate logistic regression models of gender in order to identify associations between brain lesions and gender. This seems weird because predicting the gender of a patient from brain lesions is useless. This explains why biomedical (MS) data analysis uses gender only as predictive feature and not as outcome. However note that the goal here is not to predict, but to model associations between brain lesions and gender. According to the resulting models, the log of the odds of a patient being female is related to specific types of brain lesions. In general, results of our investigation indicate the effectiveness of logistic regression to unravel significant associations between brain lesions and gender in MS patients.

1 Introduction

Multiple sclerosis is a chronic inflammatory disease of the central nervous system. The disease usually causes relapsing-remitting attacks of inflammation, demyelination and axonal damage, leading to various degrees and spectra of neurological symptoms and disability. MS has been shown to be more prevalent in women than men but more severe in men. This has led to extensive studies of differences in the immune system or nervous system between women and men, which might be caused by the effects of gonadal hormones, genetic differences, as well as different environmental exposures and modern lifestyle in men and women (see e.g. [3]). Since MS has both an inflammatory and a neurodegenerative component in its pathogenesis, neuroimaging and neuropathological studies have focussed
on the neurodegenerative process in MS. Neuroimaging has identified atrophy, particularly in gray matter (see the review [7]).

In general, involvement of the gray matter is now recognized to be an important pathological feature of MS (see for instance [2]).

Gender differences according to a number of conventional and nonconventional MRI measures in patients with MS have been investigated in [1]. The authors used general linear model analysis, corrected for MS disease type. In the MS group male patients showed lower normalized peripheral gray matter (p-value < 0.001) and normalized gray matter (p-value = 0.011) volumes than female patients. Female patients presented lower normalized white matter volumes (p-value = 0.011). These gender effects were not observed in a normal control group.

In this paper we focus on the relation between gender and types of brain lesions in MS patients. To this end, we consider a unique dataset provided by the Netherlands Brain Bank, containing pathological and clinical information about MS patients. In particular, the dataset contains a detailed account about the various types of brain lesions observed in these patients. We investigate this dataset using statistical tests and machine learning techniques in order to identify significant associations between types of brain lesions and gender. First, we apply univariate statistical test to assess whether each type of brain lesion differs in male and female patients.

Next, we apply logistic regression to model associations between brain lesions and gender, where gender is used as the outcome variable. This is a non-standard way to analyze gender in the bio-medical, and in particular, MS data analysis. Indeed, at first sight it does not seem to make sense to build a logistic regression model of gender based on brain lesions, since it is not interesting to predict the gender of a patient (from brain lesions). However, the goal here is not to use the model for prediction, but to identify relevant associations (and correct these associations for the associations among the background variables).

Results of univariate tests show that none of the brain lesion types differs significantly between female and male patients. Logistic regression analysis unravels interesting associations between brain lesions and gender. Specifically, according to a logit model of gender, the log of the odds of a patient being female is positively related to chronic lesions (p-value < 0.05). This result indicates that the adjusted (i.e. marginal) contribution of chronic lesion is significant. Results also indicate that the log of the odds of a patient being female is positively related to grey matter (p-value =0.067).

Although interesting, these findings should be interpreted with care. It remains to be investigated whether these results are possibly related to the sample characteristics. For instance, an independent study with a larger heterogeneous group of patients should be conducted in order to substantiate these findings.

Our contribution is not original in a methodological sense, since we do not introduce any new method for data analysis. Nevertheless, its originality relies in the way a method can be used in a medical application. Moreover, the data used in this analysis is unique.
2 Brain lesions data

We consider a unique dataset from the Netherlands Brain Bank (NBB) containing information about brain lesions in multiple sclerosis patients. In table 1 we show few characteristics of the datasets related to the type of MS and duration of disease (that is, number of years from the clinical diagnosis to the death of the patient).

<table>
<thead>
<tr>
<th>nr</th>
<th>age</th>
<th>dod</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>Miss</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>20</td>
<td>57.5</td>
<td>25.2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>1.1(1.6)</td>
<td>1.9(5.1)</td>
<td>6.1(10.0)</td>
<td>2.8(3.7)</td>
<td>4.2(9.8)</td>
</tr>
<tr>
<td>F</td>
<td>32</td>
<td>63.1</td>
<td>24.3</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>15</td>
<td>1(2.2)</td>
<td>3.4(5.1)</td>
<td>4.8(6.1)</td>
<td>3(3.8)</td>
<td>7.4(13.8)</td>
</tr>
<tr>
<td>Tot</td>
<td>52</td>
<td>60.9</td>
<td>24.6</td>
<td>17</td>
<td>6</td>
<td>2</td>
<td>29</td>
<td>1.0(2.0)</td>
<td>2.8(5.1)</td>
<td>5.4(7.8)</td>
<td>2.9(3.7)</td>
<td>6.2(12.4)</td>
</tr>
</tbody>
</table>

Table 1. Dataset used in our analysis. M = male, F = female, Tot = total, age = average age, ‘dod’ = average duration of disease, T1 = RRMS, T2 = PPMS, T3 = PRMS (types of MS disease), ‘Miss’ = missing values for the type of disease, 1-6 average and standard deviation between brackets of number of lesions of type 1 to 6.

In 2009, the Neuroimmunology Research Group (IMM) of the Netherlands Institute for Neuroscience (NIN) started a project to stage and characterize the MS tissue collection of the NBB in a standardized way. In particular, lesion stages were scored according to the scheme for autopsy described below and illustrated in figure.

The following six main types of brain lesions were distinguished (see [5,6]):

- 1: reactive (groups of HLA positive microglial cells, no demyelination);
- 2: active lesion (hypercellular, demyelination, HLA-positive microglial cells throughout the lesion);
- 3: chronic active lesion (hypocellular core, active border with HLA-positive myeloid cells);
- 4: gliotic inactive hypocellular lesion (some limited HLA-positive microgliosis);
- 5: grey matter lesion;
- 6: shadow plaque.

The brain lesion types are ranked by the severity of the lesion type 1 meaning mild lesion and type 6 severe lesion. This division applies to all types except type 5 lesion. Lesion types 1-4 and 6 are all white matter lesions and are scored according to their severity. Lesions type 5 are grey matter lesions can also been subdivided in four types according to their severity, but in this study we consider them as a whole.
3 Methods

Univariate statistical tests

We use Wilcoxon rank-sum and unpaired t-test to assess whether brain lesion types differed between male and female patients.

The t-test is a statistical hypothesis test in which the test statistic follows a Student’s t distribution if the null hypothesis is supported. It is most commonly applied when the test statistic follows a Normal distribution.

The Wilcoxon rank-sum test is a nonparametric alternative to the two sample t-test which is based solely on the order in which the observations from the two samples fall. The test is still valid for data from any distribution, whether Normal or not, and is much less sensitive to outliers than the t-test.

Logistic regression models

Logistic regression (LR) is a multivariable method that was devised for modeling associations that involve binary outcomes, such as decision making (yes/no) or patient state (diseased/healthy) [4]. In LR one models the logarithm of the odds of a positive outcome (where positive is defined by the encoding of the outcome variable, that is, Y=1).

The model has the following form:

\[ \text{logit}(Y) = \log(\text{odds}) = \ln(p/(1 - p)) = \alpha + \beta_1 X_1 + \ldots + \beta_n X_n, \]
where

\[ p = \text{Probability}(Y = 1 \mid X_1 = x_1, \ldots, X_n = x_n) = \frac{1}{1 + e^{\alpha + \beta_1 x_1 + \ldots + \beta_n x_n}}. \]

The logit in logistic regression is a special case of a link function in a generalized linear model: it is the canonical link function for the Bernoulli distribution.

The coefficients \( \alpha, \beta_1, \ldots, \beta_n \) are typically estimated by the maximum likelihood method. The resulting model provides useful information about the association between variables and outcome: the coefficient of each variable describes the relative contribution of that variable to the outcome variable, automatically controlling for the influences of the other predictor variables. That is, the coefficients provide estimate of the marginal contribution of each variable to the probability of a positive outcome. These are marginal contributions: how much would the log-odds for the probability of a positive outcome change if the considered variable changed by one unit while the other variables in the model did not change. The statistical significance of individual regression coefficients is here tested (in Matlab) using the Wald chi-square statistic.

In the context of our work the outcome variable is gender (male/female) and we encode female as positive outcome (\( Y=1 \)). The variables used in the model are brain lesions.

### 4 Results

We used the Matlab functions `ttest2` and `ranksum` to compute t-test and Wilcoxon rank-sum test. The resulting p-values are shown in table 2.

<table>
<thead>
<tr>
<th>Wilcoxon rank-sum</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>summed</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>0.8024</td>
<td>0.1895</td>
<td>0.4416</td>
<td>0.7158</td>
<td>0.4427</td>
<td>0.6485</td>
<td>0.2626</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unpaired t-test</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>summed</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>0.8641</td>
<td>0.3375</td>
<td>0.5719</td>
<td>0.8555</td>
<td>0.3846</td>
<td>0.3594</td>
<td>0.5610</td>
</tr>
</tbody>
</table>

**Table 2.** Results of Wilcoxon rank-sum and unpaired t-test, over number of lesion in male vs female patients, the identifiers denote the type of lesion (1-6) and their sum (`summed`).

These results show that no brain lesion type is significantly different in male and female patients.

We show in the sequel that there are strong associations between lesions types and gender, which can be modeled using logistic regression. Specifically, we used the following Matlab function:

\[
[b, dev, stats] = glmfit(x, y, 'binomial');
\]

The resulting model is:
<table>
<thead>
<tr>
<th>Feature</th>
<th>Coefficient (b)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.6246</td>
<td>0.0609</td>
</tr>
<tr>
<td>Reactive</td>
<td>-0.3579</td>
<td>0.4963</td>
</tr>
<tr>
<td>Active</td>
<td>1.1086</td>
<td>0.0943</td>
</tr>
<tr>
<td>Chronic</td>
<td>-1.6755</td>
<td>0.0163</td>
</tr>
<tr>
<td>Gliotic</td>
<td>0.0776</td>
<td>0.8298</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>1.3563</td>
<td>0.0670</td>
</tr>
<tr>
<td>Shadow</td>
<td>0.4519</td>
<td>0.3259</td>
</tr>
</tbody>
</table>

**Table 3.** Estimated model parameters and their p-values.

logit(Female) = 0.63 - 0.36(Reactive) + 1.11(Active) - 1.67(Chronic) + 0.08(Gliotic) + 1.36(Grey) + 0.45(Shadow).

The p-value for a variable is computed using a likelihood ratio test (a model with and without this variable is fit and the difference in fit is measured). We do not analyze the goodness of fit and other properties of the model related to its predictive performance, since we focus on the identified association model and the contribution of variables (see Table 3).

The estimated coefficient of ‘chronic active lesions’ is -1.6755. This indicates that the log-odds of being female decrease by 1.6755 for every additional unit of chronic lesion, all other variables held fixed. The low p-value (0.0163) associated to this variable indicates that the adjusted (i.e. marginal) contribution of chronic lesion is significant.

The coefficient of ‘gray matter lesions’ is estimated to be 1.3563, suggesting that the log-odds of being female increases by 1.3563 for every additional unit of gray lesion, all other variables held fixed. The relevance of ‘gray matter lesions’ is less strong (p-value =0.0670).

We tested whether this model is a better fit over the null model (all variable coefficients are zero) using the following Matlab procedure.

```matlab
[b0, dev0, stats0] = glmfit(x(:,1:0), y, 'binomial');
yfit0 = glmval(b, x,'logit');
pval = 1 - chi2cdf(dev0-dev,1);
```

Application of a chi-square test resulted in a p-value equal to 0.000916.

### 4.1 Removing variables

We analyze the effect of discarding each of the three variables estimated as highly relevant for the model: ‘gray matter lesions’, ‘active lesions’ and ‘chronic lesions’.

When the variable ‘gray matter lesions’ is discarded, active and chronic active lesions become both relevant, with similar significance (p-value slightly bigger than 0.05): see figure [4].

Removing active lesions results in a model with estimated parameters and p-values showed in table [5]. In the resulting model ‘gray matter lesions’ becomes
the only significant variable (p-value < 0.05). We did not find any work on MS research that could provide an explanation about why this phenomenon occurs.

Finally, if the variable ‘chronic lesions’ is discarded, then none of the variables contributes significantly to modelled associations between brain lesions and gender. This result suggests that ‘chronic lesions’ plays a central role in the model.

5 Discussion and conclusion

We presented a novel application of logistic regression in the study of pathological MS data to unravel evidence for associations between brain lesions and gender.
Results of the analysis identified a specific type of brain lesion (chronic active) which provides a significant contribution in the association model. In particular ‘chronic active lesions’ was identified a significant variable of the model. When the ‘active lesions’ variable is discarded ‘gray matter lesions’ becomes the most important variable. The underlying mechanism of this result in relation to disease type and gender remains to be investigated.

In general our results should be interpreted with care, due to the small size of the dataset, and possibly to the presence of biases in the considered group of patients. For instance, the dataset contains mainly patients relapsing-remitting MS (RRMS) disease cases (which is the most occurring type of MS). This is a bias that could have influenced the results.

Future work includes an extension of this investigation to link our findings with results obtained by analyzing other pathological features such as disease type as well as clinical features, like duration of the disease and age.

Acknowledgements

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References