NEGATIVE BINOMIAL MODEL DESCRIBING THE DISTRIBUTION OF ENHANCING MRI LESIONS IN MS

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Introduction

Magnetic resonance imaging (MRI) is well established as the optimal imaging technique for the diagnosis of MS (1,2). It is also used as an objective endpoint in clinical trials of MS, being more sensitive and much more reproducible than clinical measurements. The use of gadolinium (Gd) with T1 weighted imaging increases the reliability and sensitivity in detecting active MS lesions (4). The number of new Gd-enhancing lesions is a widely used end point for monitoring disease activity and for evaluating the effect of treatments in phase II clinical trials. As a consequence, in these studies data are in the form of counts. The results of MRI monitored trials are usually analysed by means of non parametric tests and sample size calculations are carried out by means of computer simulations (2). So far, no statistical model has been proposed to describe the distribution of MS lesion counts across patients: its availability would permit a parametric approach in the evaluation of the effectiveness of new treatments and would provide a more powerful tool for the simulations that are used to estimate the necessary sample size. The NB model, including a random term reflecting unexplained variation among subjects, is specifically considered here to model the distribution of MRI lesion counts.

Material and methods

Patients MRI-data from fifty-six patients with clinically definite MS, selected from four European centers were used for these analyses. The cohort consisted of 38 patients with relapsing-remitting (RR) MS and 18 patients with secondary progressive (SP) MS. Patients were either involved in natural history studies (34 patients) or formed the placebo arms of treatment trials (22 patients). To be included, patients had to have had serial monthly gadolinium enhanced T1 weighted images for at least nine months.

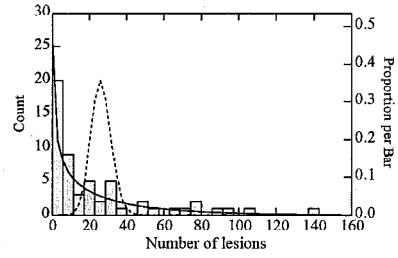
Mri- methods serial t2 weighted conventional spin echo or fast spin echo mr images were acquired at study entry and exit. T1 weighted imaging 5-15 minutes after injection of a conventional dose (0.1 mmol/kg) of gadolinium was also performed monthly throughout the study period. Scanner were not changed or upgraded during the study and image acquisition parameters were not modified between entry and exit. The number of new gadolinium enhancing lesions were identified on all monthly scans by experienced observers.

Statistical methods In the NB distribution, the number of counted lesions in a fixed period of time for patient i is assumed to be generated by a Poisson process. Each Poisson process has not a parameter with a 'true' value common to all the patients, but for each patient uncertainty remains about the location of the parameter, i.e., it has a probability distribution. The NB distribution has $E(y) = \mu$ and variance $Var(y) = (\mu + \mu^2/\vartheta)$ that is larger than for a Poisson distribution. The NB model has two parameters: the parameter μ and the parameter ϑ reflecting the uncertainty about μ.

Results

Figure 1 shows the distribution of the lesions counted over nine months in all the patients: the distribution is markedly asimmetric, with its modal value for counts = 0 (11% of the patients). The mean number of lesions observed over nine months was *24.6*, while the median value was *11* (range = *0-142*). The variance was *956.6*. Figure 1 plots also the curve obtained by fitting a Poisson distribution to our data (dotted line). The expected number of new lesions counted in nine months of follow up is set to the average of *24.6*. As a consequence the variance estimated under the Poisson assumptions is $Var(y) = E(y) = 24.6$, a value clearly smaller then the actual variance estimated directly from the data. Thus, these data are overdispersed with respect to an ordinary Poisson model: the histogram of lesion counts is dispersed away from μ, with more patients falling high on the upper tail or at $y=0$ than expected under the Poisson model. The deviance of the data from the fitted model was *1830.1* with *55* degrees of freedom. In Figure 1, the curve obtained by fitting a NB model to our data is also shown (solid line). This is compared with the predictions of the Poisson regression model and with the observed distribution of counts in the 56 patients. The NB model fits the data more closely than the Poisson model, accounting for the large number of patients without lesions and with many lesions (residual deviance = *66.6* with *54* degrees of freedom). The expected number of new lesions counted in nine months of observation (μ) is again *24.6*; the estimated value of ϑ is *0.6*. Hence, the estimated variance is $Var(y) = \mu + \mu^2/\vartheta = 1015.0$, a value very close to that calculated from the data.

Figure 1.



Conclusions

In our sample of 56 patients with RR and SP MS, it was shown that the distribution of the occurrence of MRI active lesions across patients over a nine months period is well described by a NB model. This finding , if confirmed, has several implications. First, the possibility to parametrize the occurrence of MRI active lesions would allow to describe the effect of a treatment on disease activity. Secondly, parametrizations of MRI counts can be useful in the design of MRI-based, MS trials in order to calculate the necessary sample size.

References

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