Risk factors for neurological complications and sequelae in childhood acute bacterial meningitis

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Dear Editor,

Bacterial meningitis is associated with a high rate of morbidity and mortality. The risk of death or development of complications is related to age, underlying conditions, causal agent, disease severity and duration during the acute phase, and, occasionally, delay in starting effective antimicrobial therapy.[1]

In a recent issue of Jornal de Pediatria, the retrospective study by Antoniuk et al.[2] confirms some statistically significant associations for the development of acute complications, namely: seizures at admission, low neutrophil counts, and *Streptococcus pneumoniae* as the etiologic agent. In the multivariate analysis, the occurrence of seizures at admission (odds ratio, OR = 5.6) and cerebrospinal fluid protein concentration > 200 mg/dL were selected as risk variables for the development of neurological sequelae. Below we present some comments about this important clinical study, which addresses a little explored topic in scientific publications in developing countries like Brazil.

Our first note is related to the statistics used by Antoniuk et al.[2] Although the authors have described the sample calculation method, we did not find reference to the number of patients needed to achieve a significance level of 0.05, a type II error rate of 10%, and a magnitude of effect of 15% for the different outcomes. A sample of 44 children seems to be a little too small – for the above-mentioned parameters. Calculated sample sizes often include some hundreds of patients. It would be interesting to make the calculated sample size available to readers. Even though this would not invalidate the significant associations found by Antoniuk et al.,[2] a calculated sample size above 44 would mean a higher probability of type II errors,[3] possibly rendering misleading the statement that certain outcomes are not statistically associated with acute neurological complications or neurological sequelae.

Secondly, while analyzing Table 1 in the article by Antoniuk et al.,[2] we observed significance levels below 0.05 for some signs and symptoms that are not confirmed by the OR informed in the table (in classical statistics, when the confidence interval of the OR includes 1, there cannot be a significant difference). Thus, we have recalculated the values in Table 1 using Fischer's exact test and the chi-squared test, as applicable. We found the following p values: bulging fontanelle, p = 0.068 rather the published p = 0.01, with OR = 3.3 (0.4-24.4); irritability, p = 0.044 rather than the published p = 0.08, with OR = 4.4 (1.1-17.5). Even though these values change the level of significance reported in the article, it is our opinion that performing statistical analysis with the ideal calculated sample size is of vital importance. In this sense, if the calculated sample size is far above 44, bulging fontanelle and other non-significant factors in the authors' analysis could become significant, avoiding type II errors. The result could be a better understanding of the prognostic factors involved in bacterial meningitis.

Third, although the authors have reported a male predominance (63.6%),[2] we did not find any statistical analysis confirming such association. In a recent systematic review, Jongue et al.[4] evaluated 31 studies on prognostic factors that had significantly predicted sequelae and mortality after childhood bacterial meningitis. The results of that review showed that young age and male sex were statistically significant prognostic factors in more than one study of moderate/high quality; other factors included a clinical history lasting for more than 48 hours before admission, coma/altered level of consciousness, prolonged seizures, prolonged fever, shock, peripheral circulatory failure, respiratory failure, absence of petechiae, *S. pneumoniae* as the causal pathogen, different alterations in the cerebrospinal fluid and in leukocyte counts. In another study, Oostenbrink et al.[5] observed that, when considering male sex, atypical seizures in the clinical history, hypothermia at admission, and presence of the pathogen *S. pneumoniae* as independent predictors of neurological sequelae or death in bacterial meningitis, it was possible to obtain an area under the receiver operating characteristic (ROC) curve with a prediction accuracy of 0.87 (95% confidence interval = 0.78-0.96)[4]. This finding suggests that it is always important to conduct a detailed analysis of male sex in any study on bacterial meningitis.

These notes do not, in any way, diminish the importance of the study by Antoniuk et al.,[2] once the early recognition of prognostic factors of acute neurological complications and the sequelae presented by the authors are extremely valuable in the individual treatment of each of these patients, both with regard to initial treatment measures and during hospitalization, and also in the multidisciplinary approach adopted in the follow-up. We believe that a larger sample size could be obtained by either including more patients treated by the authors or by establishing multicenter collaboration with other services, thus contributing toward a better understanding of the prognostic factors of this important condition in our setting.

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No conflicts of interest declared concerning the publication of this letter.

Authors' reply

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Dear Editor,

First of all, we are very grateful for the great contribution that this discussion has provided in terms of new thoughts about biomedical statistics, applicable not only to this but also to several other publications, including some studies found in this issue.

Clinical studies usually investigate several characteristics, and establishing an ideal sample size for such investigations certainly remains a challenge, given the difficulties involved in mathematically dealing with such complexity.[1,2] In this scenario, sample calculation involves different combinations of accuracy, confidence and variability for each characteristic assessed, in addition to the peculiarities of sample calculation *per se*, e.g. type, frequency, and distribution, which define different methods of statistical treatment.[3]

In our study, sample size was calculated taking into consideration the most important quantitative and qualitative variables, which determined, on average, a minimum sample size of 25 individuals in each group. For the variable seizure, for example, we used an estimated frequency of 50% in the group with neurological complications and of 5% in the other group, with a confidence level of 90% and a significance level of 5%. This calculation indicated a minimum sample of 19 individuals in each group. Some of our calculations, depending on the variable considered, led to an estimated sample size of more than 200 individuals in each group, as rightly indicated by our colleagues. Had this calculation been rigorously followed, our study would probably turn into another file-drawer study, resulting in no contribution. We do not discuss, in any way, the relevance of scientific rigor; notwithstanding, using our convenience sampling method, we sought to establish the minimum sample size that would allow to investigate the relationship between the main variables and the outcomes. Indeed, the inclusion, in one single study, of several variables with different estimated frequencies, which were not all considered in their totality when calculating sample size, may have caused the occurrence of type II errors, possibly masking significant associations. However, for the differences indicated as significant, the sample was considered large enough according to parameters previously defined.

In theory, sample calculation is almost mandatory and has received due attention by journal reviewers and readers. However, it is equally necessary to think about other issues beyond statistics, e.g. sampling techniques, logistics, and viability. As previously indicated, the concern lies particularly in non-significant results, which may be the result of a low statistical power.[1,4] Undoubtedly, the continuation of our study by including new cases or via collaboration is the best way to achieve a better understanding of the relationship among the variables assessed and prognosis, especially in complex conditions such as the one investigated in our paper.

Table 1 indeed needs to be corrected. The frequencies reported for bulging fontanelle are misleading, once not all patients included in the study were infants. Absolute frequencies are correct, but percentages should be corrected according to the number of infants in each group: nine in the group with neurological complications and 17 among patients without complications (66.6 and 17.6%, respectively; p remains equal to 0.01). On the other hand, the p value indicated for irritability was recalculated using the two-tailed Fischer's exact test (applicable to 2 x 2 tables with n < 100) and it seems correct to us, i.e. exactly p = 0.087.

As to sex, although males have predominated in the group as a whole, in the sample studied, of the 17 cases without neurological complications, 11 were male (64.7%), compared to 17 among the 27 cases with complications (63.0%) (p = 1.00). Male-female ratios were identical when patients were assessed for the presence of sequelae: 28.6% for male patients in both groups (p = 1.00).

The present discussion brought to our minds a recent publication by Bacchetti et al.[5] that addresses this frequent difficulty while conducting research involving humans: achieving balance between calculations and statistical indicators on the one hand, and the viability of studies on the other. The authors literally quote the proposal made by Cohen in 1965, of setting statistical power at 80%: "this is a conventional value... when no other basis is available," and also "like all conventions, this

value is arbitrary." Cohen's paper also points to the fact that when an idea brings about a fundamental development, it may be clear even from data of a relatively small study; in this case, a larger sample would not add scientific value – rather, it would only produce additional costs for all parties involved. When an idea does not work, the same takes place: it is neither necessary nor appropriate to allocate larger samples and resources to get to the same conclusion. Only in intermediate cases could a larger sample add scientific knowledge, but still to a limited extent, at the risk of spending a great amount of efforts and costs to obtain a few additional results.[5]

The issues raised by Shieh et al. are extremely relevant; in our view, the balance between statistical power and study viability potentially lies in calculations based on characteristics that have strong associations with the outcome. These calculations will lead to the establishment of low-cost, effective, sufficient, small samples, in addition to those called borderline, which will certainly require larger investments, but will also bring benefits in terms of good-sense evaluations and calculations.

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