Preventing Labyrinthitis Ossificans

The Role of Steroids

Christopher J. Hartnick, MD; Hank Y. Kim, MD; Patricia M. Chute, EdD; Simon C. Parisier, MD

Objective: To identify a possible relationship between the administration of steroids at the time of diagnosis of bacterial meningitis and the development of labyrinthitis ossificans.

Design: Retrospective analysis of the charts of 38 children requiring cochlear implantation who presented with bacterial meningitis and then developed bilateral profound deafness. The patients’ charts were reviewed for age at diagnosis, the type of antibiotic administered, and the administration, dosage, and duration of steroid (dexamethasone) therapy. Labyrinthitis ossificans was established by preoperative computed tomographic and/or magnetic resonance imaging and by the intraoperative findings as described in the operative report.

Patients and Methods: Patients were 38 children who received cochlear implantation by a single senior otolaryngologist for bacterial meningitis–related deafness. Ten patients’ charts (26%) were available for full review; 9 of these 10 patients had documented pneumococcal meningitis and the other patient had Haemophilus influenzae–type meningitis.

Results: One of the 6 patients who received steroid therapy at the time of initial illness had documented evidence of labyrinthitis ossificans either radiographically or at the time of surgery. All 4 patients who failed to receive steroid therapy developed labyrinthitis ossificans. The results achieve statistical significance by $\chi^2$ analysis and a $t$ test ($P<.01$).

Conclusion: The results of this retrospective study are highly suggestive of a role for steroids in preventing the development of labyrinthitis ossificans in children with pneumococcal meningitis.


Hearing loss following an episode of bacterial meningitis is a well-documented phenomenon, with an incidence ranging from 5% to 35%.1-4 A subset of patients who develop such hearing loss have profound bilateral loss for which cochlear implantation becomes a surgical option. In one prospective series that reported a 10.3% (19 of 185 patients) incidence of hearing loss following an episode of bacterial meningitis, 7 (37%) of the 19 affected patients were deafened bilaterally.5 By performing these implantations, surgeons realized that one particular aspect of the disease process was that there is a high incidence of labyrinthitis ossificans following bacterial meningitis that complicates the surgical procedure and may affect the long-term outcome.6 Eisenberg et al7 reported that 80% of children who became profoundly deaf following a bout of meningitis had some level of labyrinthitis ossificans. It is conceivable that any factor that might affect the development of labyrinthitis ossificans might improve the surgical exercise of implantation as well as the long-term results.

In the hopes of discovering treatment strategies that would decrease the incidence of developing hearing loss following an episode of bacterial meningitis, much work has been done to identify the 5% to 35% of patients at risk. Less work has been done to characterize patients who develop labyrinthitis ossificans and to identify treatment strategies. One treatment strategy that has been examined with regard to hearing loss following meningitis is the use of steroids. In 1988, Lebel et al7 reported that there is a statistically significant effect in using steroids to prevent hearing loss for children who have Haemophilus influenzae–type meningitis. There were not enough patients with non–H influenzae–type meningitis in this series to comment on the efficacy of steroids in these situations. With the American Academy of Pediatrics’ official decla-
PATIENTS AND METHODS

A retrospective chart review was performed on all patients who received cochlear implantation by one senior otolaryngologist at either the Lenox Hill Hospital or the Manhattan Eye, Ear, and Throat Hospital, New York, NY, for postmeningitic hearing loss. The patients and their families were contacted and signed an informed consent form allowing the release of information from the hospital at which the patient was initially treated. Thirty-eight procedures were performed between 1983 and 1997. Twenty-eight patients (74%) could not be contacted for release of medical records; inpatient medical records from the acute illness were obtained from 10 patients (26%).

These records were reviewed, and the age at time of illness; the etiologic agent; the use, dosage, and duration of steroids; and the antibiotic used were elucidated. Preoperative temporal bone studies were reviewed and correlated with intraoperative findings to determine the presence of labyrinthitis ossificans.

The null hypothesis for this study was that steroids do not affect the development of labyrinthitis ossificans. A χ² analysis and a t test were used to analyze the data.

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ration in 1991 that H influenzae type b vaccine be universally administered, the incidence of H influenzae–type meningitis has dropped dramatically and the role of steroids in non–H influenzae–type meningitis has since assumed a greater importance. Controversy persists as to whether to administer steroids universally to children with non–H influenzae–type meningitis. Various avenues of research have been pursued to dispel this controversy. One of these avenues is to examine the role of steroids not on hearing itself, but rather on the long-term outcome of patients who became deaf as a result of meningitis and who seek cochlear implantation. Since one of the major factors that influences the long-term outcome of cochlear implantation is labyrinthitis ossificans, it is argued that if steroids inhibit the development of labyrinthitis ossificans, then steroids should be given universally for the treatment of non–H influenzae–type meningitis.

This study was designed as a retrospective review of the charts of children who received cochlear implantation by one surgeon for bacterial meningitis–related hearing loss. The aim was to ascertain whether the use of steroids affected the development of labyrinthitis ossificans.

RESULTS

The mean age at the time of acute illness was 13.7 months, ranging from 4 months to 30 months of age. Streptococcus pneumoniae was the etiologic agent in 9 of 10 patients. H influenzae was the agent in the other case. Antibiotics were initiated immediately after the diagnosis of meningitis, and ceftriaxone sodium was the antibiotic used most often. Five patients received ceftriaxone alone and 2 received it in combination with vancomycin hydrochloride. One patient received a combination of ampicillin sodium and gentamicin sulfate. The exact antibiotic regimen could not be ascertained from the charts of 2 patients.

Six patients received dexamethasone for 4 days, and 4 patients did not receive steroids throughout their entire clinical course. Five of the 6 patients began receiving steroids at the same time as the initiation of antibiotics. The other patient began receiving steroids 3 days later after culture confirmation of bacterial meningitis. The exact dosage of dexamethasone ranged from 0.5 to 1.0 mg/kg daily, with a mean of 0.6 mg/kg daily. The patients who were treated with steroids were, as a group, older than the patients who were not, although the difference was not statistically significant. Five of 6 patients treated with steroids during the acute illness were not found to have cochlear ossification either radiographically or at the time of surgery. By contrast, the 4 patients who did not receive steroid therapy developed labyrinthitis ossificans intraoperatively (Table). A χ² analysis and a t test were used to demonstrate a statistical significance (P < .01). The average time from acute illness to implantation in those who developed labyrinthitis ossificans was 42.5 months compared with an average of 11 months for those who did not develop labyrinthitis ossificans.

COMMENT

The goal of this study was to determine the role that steroids might have in preventing the development of labyrinthitis ossificans. To this end, the results are statistically significant in positing such a role. The importance of this study stems from the controversy surrounding the use of steroids in the scenario of bacterial meningitis. The 1994 Report of the Committee on Infectious Diseases recommends steroid use for H influenzae–type meningitis but cautions that the use of steroids for pneumococcal meningitis, although recommended, has not been proven to be effective. This has left an unresolved question where there is no treatment algorithm for patients with non–H influenzae–type meningitis. This lack of resolution is further accentuated in light of the decline of H influenzae–type meningitis since 1991 and the relative rise of pneumococcal and neisserial meningitis. To add to this dilemma, there are data showing that pneumococcal and meningococcal meningitis produce a higher incidence of hearing loss than does H influenzae meningitis. Dodge et al reported in 1984 on a prospective series of 185 children who had bacterial meningitis; 31% of those with streptococcal pneumonia–type meningitis had hearing loss compared with 10.5% of the Neisseria–type population and 6% of the H influenzae–type population.

It is possible to view the decision as to whether to give steroids to children with non–H influenzae–type meningitis (in hopes of preventing labyrinthitis ossificans) in the context of a decision to which there seems to be a resolution, namely, the decision to give steroids to prevent hearing loss in children with H influenzae–type meningitis. In analyzing this recommendation, one can infer...
the thresholds that were drawn as far as concerned the relative risks of steroid administration compared with their benefits. In the article by Lebel and colleagues,7 15.5% of patients who did not receive dexamethasone had some form of hearing loss as opposed to only 3.3% of patients who received dexamethasone. To decrease the incidence of hearing loss by 12%, they advocated giving dexamethasone to every child with bacterial meningitis. They justified this claim by noting the low incidence of adverse effects (in their series, namely, gastrointestinal bleeding) attributable to the steroid administration. In their series, 2 (1%) of 200 patients had gastrointestinal bleeding and needed transfusion therapy. One of these 2 had a bout of gastroenteritis just prior to admission. Another 2 patients had hemepositive stools without frank bleeding. The Committee on Infectious Diseases reviewed the study by Lebel and colleagues7 among others and weighed the risks and benefits of steroid administration. They set the benchmark by noting that, for the sake of that small fraction of children who would face the sequelae of meningitis, it is worthwhile to administer steroids universally to children with H influenzae–type meningitis.

The data of Lebel and colleagues7 and the risk-benefit analysis used to analyze the use of steroids to prevent hearing loss in H influenzae–type meningitis lead one to address the issue of steroid administration in the contemporary era where pneumococcal and neisserial meningitis predominate. While the issue of steroids affecting the development of hearing loss in these strains of meningitis remains controversial, other issues have not been explored. What about the population of children who do in fact develop hearing loss and present for possible cochlear implantation? The question arises as to whether the use of steroids would help this population. At this point, the question of labyrinthitis ossificans arises. By examining data such as that published by Rauch et al11 from the Massachusetts Eye and Ear Infirmary, Boston, and by Eisenberg et al,8 one can infer that 70% to 80% of patients who became deaf as a result of meningitis will develop labyrinthitis ossificans. Following this logic, 5 of the 7 patients in the series by Dodge and coworkers2 are at risk for developing labyrinthitis ossificans. If steroids were to ameliorate the problem of cochlear ossification, then, using the relative risk thresholds established here for steroid administration to prevent long-term hearing loss, the logical conclusion would argue for the administration of steroids to all patients with bacterial meningitis. These data for and the conclusions drawn from this present study are framed by this argument and derive importance from it.

To draw widespread conclusions from this study, it is important to address its limitations. First, it was a retrospective study designed to identify potential causal relationships. Its weakness is that of any retrospective study—there are no careful designs to eliminate other potential confounders. To establish without doubt one-to-one causal relationship, a prospective study would be required; animal studies would help provide corroborating evidence.

The second problem that these data do not directly address but that would need clarification prior to the universal administration of steroids is the question of timing, duration of administration, and dosage. In the article by Lebel and coworkers,7 dexamethasone was administered at a daily dose of 0.6 mg/kg in 4 divided doses for 4 days beginning as soon as a diagnosis of meningitis was made. Rasmussen et al9 published data on 94 patients followed up for sequelae of pneumococcal meningitis and found that steroid treatment did not significantly alter the development of hearing loss. In the series by Rasmussen and coworkers,9 steroids were given in the form of prednisone, 40 mg orally, beginning for at least 1 week, starting after the etiologic diagnosis was made. Because the time to identify the exact etiologic organism may take 2 to 3 days, the delay between diagnosis of meningitis and administration of steroids was a matter of days in many cases. The take-home message may well be that for steroids to be effective, they may have to be administered as soon as a diagnosis is made. As concerns the present study, the only patient who developed labyrinthitis ossificans after the administration of steroids was given steroids 3 days after admission when the etiologic diagnosis of bacterial meningitis was made.

This article describes a small series of patients for whom the administration of steroids appears beneficial in preventing the development of labyrinthitis ossificans. It remains difficult to explain this clinical finding because of the paucity of data regarding the development of labyrinthitis ossificans. The exact mechanism of

### Table: Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Age at Time of Illness, mo</th>
<th>Antibiotic</th>
<th>Daily Dexamethasone Dosage, mg/kg</th>
<th>Time From Diagnosis Until Steroids Given, mo</th>
<th>Duration of Deafness Until Implantation, mo</th>
<th>Presence of Labyrinthitis Ossificans</th>
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<tr>
<td>1/M</td>
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<td>28</td>
<td>Yes</td>
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*Streptococcus pneumoniae was the bacterial organism that affected all patients, except patient 2, who was affected by Haemophilus influenzae.*

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the development of labyrinthitis ossificans is controversial. Its existence was noted as far back as the 1890s when Scheibe and Steinbrugge described the association between suppurative labyrinthitis and labyrinthine ossification. Wittmaack separated labyrinthine inflammations into those arising from tympanic, hematologic, and meningeal sources. Paparella and Sugira outlined the pathologic stages where an initial inflammatory phase was followed by a fibrosis and then ossification. They postulated that the cell responsible for fibrosis and ossification was the undifferentiated mesenchymal cell. Exactly how and where the focus of infection spreads from the meninges to the cochlea remains debated. It has been noted that the most frequent area of ossification is at the scala tympani in the basal turn of the cochlea. This finding lends support to the theory that infection spreads from the meninges to the inner ear by way of the cochlear aqueduct. This finding is also of surgical relevance because it is at this area of the cochlea where the implant will be inserted. Others have postulated that infection spreads to the labyrinth from the meninges by way of the internal auditory canal.

Understanding the pathophysiology of labyrinthitis ossificans would allow for a greater understanding of how steroids might exert their effects. The current theory as to the mechanism of steroids’ action on preventing hearing loss after meningitis stems from the knowledge that with brain edema and increased intracranial pressure found in the scenario of meningitis, there can be resulting reduction of cerebral perfusion with resultant hypoxia of regional tissues. The local hypoxia and ischemia are associated with elevations of arachidonic acid metabolites. Steroids seem to have some role in inhibiting the production of these arachidonic acid metabolites by pathways that involve interleukin 1 and cachectin.

Mechanistic studies involving the role of steroids in preventing the development of labyrinthitis ossificans require some animal model. A review of the literature shows both animal models for bacterial meningitis and subsequent labyrinthitis as well as an animal model for labyrinthitis ossificans after pneumococcal meningitis. Brodie et al used the Mongolian gerbil as an animal model and found that 14 of 15 gerbils injected intrathecally with live S pneumoniae organisms had cochlear fibrosis, ossification, or both. In a recent article, Nabili et al used this animal model to delineate the chronology of labyrinthitis ossification following bacterial meningitis. They used fluorochromes that are incorporated into osteoid as it is mineralized to follow the development of labyrinthitis ossificans. Ossification began as early as 3 weeks following initial infection and calcification, and remodeling was complete by 1 year. The authors write of the importance of knowing the chronology of the development of labyrinthitis ossificans to gain experience in the proper timing of early implantation.

The present study was designed to examine the question posed from a clinical context. Although the number of patients is small, the results argue for the administration of steroids in particular dosages given at the time of diagnosis to children with bacterial meningitis. The suggestion that steroids be given to all children with bacterial meningitis to help facilitate the surgical insertion and long-term outcome of cochlear implantation for those few children who, first, will become profoundly deaf and receive implantation and, second, will develop labyrinthitis ossificans without the administration of steroids is not lightly asserted. The results of our preliminary clinical study warrant further prospective studies to isolate a possible causal relationship and further clarification by means of animal studies where the influence of steroid administration can be carefully examined.