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Recurrent Klebsiella Meningitis Following Trans-sphenoidal Hypophysectomy for Nelson's Syndrome

Chloramphenicol resistance during relapse

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Three episodes of meningitis due to Klebsiella pneumoniae occurred in a young man following cerebral surgery. The patient had the features of Nelson's syndrome, and a chromophobe adenoma was removed by trans-sphenoidal resection. Intravenous chloramphenicol was effective in producing a temporary clinical response during the first episode of meningitis, but the organism became resistant to chloramphenicol during the second episode. Combined parenteral and intralumbar administration of gentamicin resulted in temporary improvement only. Subsequently, the subcutaneous cerebrospinal fluid (CSF) reservoir of Ommaya provided a safe, convenient way to administer prolonged intraventricular therapy which, combined with a definitive procedure to correct the cerbrospinal fluid rhinorrhea, ultimately cured the infection.

Gram-negative rod meningitis is being recognized increasingly in patients receiving immunosuppressive treatment. Klebsiella pneumoniae, often considered responsible for pneumonia, bacteremia, and urinary tract infection, is a rare cause of meningitis in adults. We recently treated a young man who had developed meningitis due to K. pneumoniae following trans-sphenoidal hypophysectomy for Nelson's syndrome. The infection was eventually cured by a definitive surgical procedure for cerebrospinal rhinorrhea as well as by intraventicular aminoglycoside treatment. Original cultures of K. pneumoniae were highly susceptible to chloramphenicol, but organisms obtained during relapse were resistant to the antibiotic.

Our case illustrates that: 1) meningitis associated with CSF rhinorrhea can recur; 2) chloramphenicol resistance may occur during treatment of Gram-negative rod meningitis; 3) intraventricular aminoglycoside treatment for associated ventriculitis may be required; 4) surgery to correct the dural defect may be needed when persistent infections occur after neurosurgical procedures.

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Case Report

A 21-year-old white man underwent trans-sphenoidal hypophysectomy on January 11, 1978. Cushing's syndrome with bilateral adrenal hyperplasia had been diagnosed at age 15. After pituitary irradiation of 5,000 rads failed to produce remission, bilateral total adrenalectomy was performed at that time. His subsequent course was marked by development of dermal hyperpigmentation in 1975, and sella turcica enlargement was demonstrated in 1977. Plasma ACTH levels reached 589 pg/ml before the hypophysectomy.

The patient tolerated the trans-sphenoidal procedure well, but the postoperative course was marked by profuse CSF rhinorrhea as well as by transient diabetes insipidus. Histology of the removed pituitary gland was consistent with chromophobe adenoma.

During the postoperative period, dexamethasone (8 mg per day) was administered intramuscularly, and oral hydrocortisone (20 mg b.i.d.) was resumed on the third postoperative day. On January 16, the persistant CSF leak was repaired with a bone and muscle graft from the right iliac crest. A CSF drain was inserted in the lumbar region and was removed seven days later. On January 24, the patient began to respond poorly with fever (38.4°C), projectile vomiting, nuchal rigidity, and incoherent speech. Cisternal puncture revealed a CSF pressure of 500 mm of water, and the spinal fluid was turbid with 12,800 WBC/cu mm, with a differential of 89% PMNs, 10% bands, and 1% lymphocytes. Spinal fluid glucose was undetectable, chlorides were 119 mg/dl, and protein 724 mg/dl. A Gram stain revealed numerous polymorphonuclear leukocytes and rare Gram-negative rods. Intravenous chloramphenicol (1 gm four times daily) was given after an inital dose

of 3 gm. Intravenous methicillin (12 gm/day in divided doses) was also administered during the first 48 hours. The spinal fluid culture grew K. pneumoniae susceptible to chloramphenicol, tetracycline, gentamicin, and tobramycin by disc sensitivity method. After the culture results were known, methicillin was discontinued and chloramphenicol was continued.

On this regimen, the patient became afebrile and showed progressive neurological improvement. A repeat spinal tap confirmed resolution of the meningitis on January 31 with an opening pressure of 210 mm of water. Spinal fluid analysis revealed 20 WBC/cu mm, protein 31 mg/dl, glucose 95 mg/dl, and chlorides 115 mEq/l. CSF culture was negative. Chloramphenicol was discontinued after two weeks of treatment, and the patient was discharged on February 9. At that time, he was afebrile and neurologically within normal limits. An intermittent CSF leak continued. His daily medications were hydrocortisone, 25 mg twice a day, and fludrocortisone acetate, 0.1 mg once a day.

On February 18, the patient was readmitted with headache, fever of 40°C, nuchal rigidity, irritability, and delirium. Physical examination revealed a markedly stiff neck, incoherent speech, and tachycardia with occasional premature ventricular contractions. Neurologic examination failed to reveal any focal motor or sensory deficits. The CSF was turbid with 6,540 WBC/cu mm, glucose undetectable, and protein 770 mg/dl. Peripheral WBC count was 17,200/cu mm with 30% PMNs, 15% bands, 32% lymphocytes, and 23% monocytes. A Gram stain of the spinal fluid revealed many Gram-negative rods. Therapy with chloramphenicol was reinstituted with a 2 gm loading dose and 1.5 gm given intravenously every six hours. The patient was comatose and also received dexamethasone (4 mg IM every six hours). Diabetes insipidus occurred again and lasted for 48 hours. The steroid support was then changed to oral hydrocortisone, 20 mg twice a day, and fludrocortisone acetate. Since the isolated organism (Klebsiella) was now resistant to chloramphenicol (M.I.C. >50% mcg/ml, 5 mg of gentamicin was administered by the intralumbar route every 18 hours and 80 mg was given intramuscularly every eight hours. When the antibiotic treatment was discontinued on March 6, the patient was alert and oriented with no neurologic deficits. On March 7, the spinal fluid was clear with 12 WBC/cu mm, glucose 53 mg/dl, and protein 37 mg/dl. Culture was negative. When he was discharged, he was receiving his usual steroid medication.

Four days later, he was readmitted with complaints of headache, vomiting, fever, nuchal rigidity, and back pain. Lumbar puncture revealed clear and colorless spinal fluid with 20 WBC and 20 RBC/cu mm. The patient deteriorated and became unresponsive. Repeat lumbar puncture 12 hours later revealed turbid CSF with a cell count of 11,600/cu mm with 91% polymorphonuclear leukocytes, glucose undetectable, and protein 736 mg/dl. The culture grew K. pneumoniae resistant to chloramphenicol (M.I.C. > 50 mcg/ml). Peripheral WBC count was 22,700/cu mm with 49% PMNs, 47% bands, 1 % lymphocytes, and 3% monocytes. Computerized axial tomography of the brain disclosed no mass lesions, although mild hydrocephalus was observed.

An Ommaya reservoir was inserted on March 13, and 5 mg of gentamicin was administered into the ventricles every 18 hours through the reservoir. On this regimen, the patient improved and by March 15 was afebrile, alert, and oriented. The ventricular fluid antibiotic concentration ranged from 18 to 105 mcg/ml. His improvement continued during three weeks of intraventricular gentamicin treatment, and parenteral gentamicin was discontinued after the second week. On March 17, the CSF leak was again repaired, and a permanent shunt of CSF fluid was placed from the lumbar subarachnoid space to the peritoneum. Repeat spinal fluid analysis was unremarkable.

On April 17, the patient was discharged and has had no recurrence of CSF rhinorrhea or meningitis. Plasma ACTH level was 84.2 pg/ml in May 1978, and no hormone replacement other than hydrocortisone and fludrocortisone has been required.

Discussion

Although trans-sphenoidal hypophysectomy for the treatment of pituitary tumors has achieved widespread popularity, persistent CSF leak and meningitis remain as dangerous complications. Wilson and Dempsey (1) reviewed the complications encountered in 200 cases and reported only a single death. The fatal outcome occurred in a patient with a large suprasellar tumor who experienced deteriorating vision, even after two courses of radiotherapy and an earlier craniotomy. Hospitalization was prolonged because of postoperative meningitis, and he died of massive pulmonary embolism. Wilson and Dempsey reported bacterial meningitis in 2% of their cases and aseptic meningitis in 1.2%.

Pituitary tumors associated with Cushing's syndrome and Nelson's syndrome have been considered to be more aggressive, invasive, and resistant to therapy than other pituitary adenomas. However, recent reports indicate that trans-sphenoidal hypophysectomy has been successful in almost all cases (2). The incidence of cerebral infection has not been disproportionate, despite the vulnerability of the hyperadrenal patient receiving corticosteroids. However, the level of steroid support given to these patients usually differs little from that provided for other patients undergoing hypophysectomy. The postoperative administration of large doses of dexamethasone, as in the present report, is predicated on neurosurgical and not on endocrine considerations (3,4).

Increasing recognition of Gram-negative rod meningitis is indicated by the recent report from a university hospital (5) at which Gram-negative meningitis comprised 4.2% of all cases of bacterial meningitis, 69% of neurological cases, and 42% of neonatal cases. The overall mortality was 40.3%. E. coli was the predominant organism in infants and Klebsiella sp. in children over one year of age and in adults. Infection was thought to be secondary to spread of infection from other body sites. According to the authors, Gram-

negative rod meningitis is a nosocomial infection which should be suspected in any patient who develops central nervous system infection while in the hospital. As was true with our patient, recurrent episodes of meningitis are always associated with intracranial injury, such as a dural tear or CSF rhinorrhea.

Recent studies on this subject focus on the treatment and pharmacodynamics of antibiotics, especially aminoglycosides in the cerebrospinal circulation (6,7). Chloramphenicol, polymixin B, kanamycin, carbenicillin, and gentamicin are suggested for initial treatment of Gram-negative rod meningitis (8). Parenteral chloramphenicol therapy has proved curative in many cases which were caused by susceptible organisms. However, meningitis caused by Gram-negative rods susceptible to chloramphenicol may not respond to this antibiotic unless high systemic doses are given. In cases with inadequate response with a susceptible organism, the therapy should be continued with very high parenteral doses. However, acquired resistance to chloramphenicol is a problem which can only be demonstrated by repeated spinal fluid analysis and culture. Acquired chloramphenicol resistance during treatment is reported to occur in as high as 30% of cases studied by McGee and Kaiser (9), but the mechanism of this resistance remains unknown.

Among the various antibiotic regimens currently recommended, chloramphenicol alone, chloramphenicol with an aminoglycoside, systemic aminoglycoside, intralumbar and systemic aminoglycoside, and intraventricular and systemic aminoglycoside may be considered. The last modality is recommended in seriously ill or moribund patients, patients infected with chloramphenicol resistant Gram-negative rods, but also in patients not responding to other methods of treatment (7). Rahal, et al suggested that gentamicin therapy for meningitis in adults should be initiated with 4 mg of intralumbar administration every 18 hours in addition to 5 mg/kg/day systemically. If cerebrospinal fluid cultures remain positive after 36 hours, intralumbar injections of 8 to 12 mg should be given every 24 hours (6). However, observations of McGee and Kaiser (7) and Lindsay, et al (10) indicate that these patients require the aminoglycoside administration by intraventricular route (4-8 mg every 18 hours) because administration by the lumbar route yields very poor concentration of the antibiotic in the ventricles. An intrathecal preparation of gentamicin for direct administration into the cerebrospinal fluid spaces is now available.

In addition to the problem of inadequate concentration of the aminoglycoside in the ventricles, recurrent meningitis following neurosurgical procedures requires a careful search for CSF rhinorrhea or other evidence of persistent dural defect. The defect must be corrected to effect permanent cure. Prophylactic antibiotics at the time of surgery have no proved value in preventing postoperative meningitis.

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