PSEUDOMONAS MENINGITIS IN AN INFANT SUCCESSFULLY TREATED WITH NEOMYCIN

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PSEUDOMONAS aeruginosa (B. pyocyaneus, P. pyocyanea) was first isolated by Gessard in 1872. There had been little interest in the significance of this organism as a primary invader in human beings until recently, when it has become apparent that infections caused by this organism are occurring with ever-increasing frequency. It is often found on the normal human skin, particularly in the axillary and ano-rectal regions. It has also been grown from the air in surgical wards, and has frequently been isolated from contaminated solutions of distilled water, boric acid, physiologic saline, anesthetic agents, penicillin, etc. Consequently, although the invasive power of this organism is reputedly low, there have been a number of cases of Ps. aeruginosa meningitis occurring as a direct result of the introduction of contaminated solutions into the cranial or spinal subarachnoid space, or through cranio-cerebral trauma.

The first proved case of Ps. aeruginosa meningitis was reported by Kossel in 1893. Evans in 1936 reviewed the literature to that time, finding a total of 40 cases and adding three of her own. Stanley in 1947 studied 86 cases, almost 80% of which followed lumbar puncture or brain injury.

The mortality rate of this disease is high, ranging from 39% to 55% and, where the meningitis is secondary to a focus elsewhere, the mortality rate runs to 86%. All six cases in infants studied by Stanley died. The reasons for this extremely high rate are twofold. First, the disease tends to occur in infants and in adults with chronic debilitating diseases and secondly, the organism is usually highly resistant (either original or acquired) to the available chemotherapeutic agents. Treatment has been uncertain and generally unsatisfactory, including vaccines, antiserums, repeated spinal drainages, heavy metals, sulfonamides, various antibiotics and numerous other substances.

Harris, Buxbaum and Appelbaum reviewed the results of combined sulfonamide and penicillin therapy in this disease; of the 21 patients they studied, 15 died, a mortality rate of 71.5%. Keefer and Hewitt included 11 cases of Ps. aeruginosa meningitis in their monograph on the value of streptomycin therapy; these had a mortality rate of 36%. Weinstein and Perrin reported three cases resulting from infection during the course of induction of spinal anesthesia that were treated with streptomycin and sulfonamides. All three patients survived, but all developed residual deafness. Neter et al. used intravenous aureomycin in one case, with recovery, although aureomycin, chloramphenicol and terramycin have generally been ineffective in other cases against infections caused by this organism. Hayes and Yow treated one case with polymyxin B, with recovery, but the patient developed some hearing loss. Schoenbach, Bryer and Long reported good results...

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with polymyxin B against Ps. aeruginosa infections. Wallerstein and Schoenbach used polymyxin B successfully in a case of pyocyanus sepsis. Tombin reported a case secondary to a urinary tract infection which was treated with polymyxin B. This drug shows such an alarming incidence of serious neurotoxic and nephrotoxic reactions that its therapeutic effectiveness when given parenterally is likely to be limited.

Frank, Wilcox and Finland studied the in vitro sensitivities of Ps. aeruginosa to penicillin, streptomycin, bacitracin, aureomycin, chloramphenicol and polymyxin, and found it resistant in attainable clinical ranges to all save the latter two. Bliss and Todd in a similar study found essentially the same results. Neomycin was not tested in these series. Waisbren and Spink studied the effect of neomycin, as well as the other antibiotics, and found it to be effective in vitro against the majority of their strains. Waksman, Katz and Le Chevalier found that strains of Ps. aeruginosa varied in sensitivity to neomycin from 8 to 33 u./cc. A total of 38 pathogenic strains of Ps. aeruginosa studied in this laboratory, however, showed minimal inhibitory concentrations ranging from 0.2 to 50.0 u./cc., with a mean of 2.3 u./cc.

Neomycin has as yet not been extensively used clinically because of its reputed neuro- and nephrotoxic effects when given parenterally. Waisbren and Spink studied the use of the drug in a wide variety of infections, including tuberculosis. They reported beneficial effects in Proteus and Pseudomonas infections, although in the dosages used and in the group of patients they studied, several manifested untoward reactions. Demonstrable levels were present in the blood, pleural fluid and spinal fluid. Duncan et al. found that neomycin was dramatically successful in eradicating organisms sensitive to it. They encountered toxicity in only one of the 10 cases they studied. Lazar and Fishman, using neomycin in otitis media in infants topically and intramuscularly, found that clinical improvement was striking when the infection was caused by sensitive strains of Ps. aeruginosa. Lazar, Goldin and Auerbach in a study of a large series of Ps. aeruginosa infections in this institution found similar gratifying results. In over 200 cases, no evidence of an untoward reaction was encountered in the dosages employed, and the clinical response was often more striking than the in vitro sensitivity of the invading organism would indicate.

Although both polymyxin and neomycin display activity against Pseudomonas that is superior to the other available antibiotics, both display a certain degree of toxicity when used parenterally in a high concentration. It is possible, however, that by combining these drugs the amount of each used may be reduced below the toxic levels with no decrease in effectiveness. Studies along these lines are in process in this laboratory.

Variants of Ps. aeruginosa exposed to neomycin possessed only a low degree of resistance. These variants displayed the "penicillin" rather than the "streptomycin" type of resistance; that is, resistance developed only slowly and in a step-wise fashion. Similar findings were found in this laboratory. In a large series of strains, resistance in vitro could be induced only with difficulty and only to a low degree. These observations lead to the conclusion that the rapid appearance of resistant variants might not present the problem during neomycin treatment that they do under streptomycin therapy.

The promising results obtained in other Ps. aeruginosa infections, the resistance of this organism to other chemotherapeutic substances and the sensitivity in vitro of this strain to neomycin prompted the use of this drug in the case described. The excellent clinical response obtained prompted the reporting of this case in the hope that this antibiotic might be of benefit in other similar infections.
PSEUDOMONAS MENINGITIS TREATED WITH NEOMYCIN

CASE HISTORY

A white male infant was born to a mother, gravida I, para I, after an uneventful 9 mo. gestation. Cesarean section was performed because of difficult labor due to a face presentation.

Initial examination revealed a thin-walled meningoymlocele, partially ulcerated in the center, lying over the region of the 3rd and 4th lumbar vertebrae. There were few spontaneous leg movements. The lower extremities appeared flaccid and the deep reflexes were absent. The anus was relaxed and pouting, being associated with saddle anesthesia. The fontanel was slightly tense and the sutures were separated. The skull measured 37 cm, compared to the sitting height of 32 cm. The impression at the time was that this was a case of meningoymlocele, myelodysplasia and early hydrocephalus. The child was given 150,000 units of crystallin daily.

RGs of the spine demonstrated defects in the lumbosacral spine between L4 and L5 with a soft tissue prominence. The skull films showed thinning of the bones with marked digital impressions.

Separation of the sutures was present, suggesting increased cranial pressure.

From birth to the 10th day of life, the infant was afebrile and alert. The fontanel remained slightly tense. Ten days after birth, the child was operated by Dr. Milton Tinsley, who reported: "A large thin sac and a necrotic surface was resected with a transverse incision. The dura and a large part of the cauda found in the sac were dissected free. The dura was closed and the fascia imbricated."

The biopsy tissue was a membranous structure 3.5 by 2.5 cm. in greatest dimensions. One surface was partly covered by skin except for a central area 1.5 cm. in diameter which was covered by a smooth, yellow, jelly-like exudate. The other surface was denuded and hemorrhagic.

Microscopic examination showed the surface to be covered partly by stratified squamous and hornified epithelium resembling skin with the other layers having the usual appendages of the skin. The grossly exposed area was covered with a fibrinous and leukocytic exudate. The leukocytes were enmeshed in a network of fibrin. Underneath there was granulation tissue and many blood vessels, fibroblasts and loose connective tissue. In some places, multinucleated giant cells were seen engulfing foreign matter. The lower surface in the area of the granulation tissue showed central nervous tissue with ganglion cells densely adherent to the granulation tissue. Diagnosis: meningoymlocele, subacute meningitis.

Postoperative course: The child took his feedings well and maintained an afebrile course during his hospital stay. The infant's fontanel continued to give the impression of slight tenseness, which was thought to be caused by the hydrocephalus. On the seventh postoperative day the surgical wound was noted to be grossly infected, culture of which showed E. coli, Staph. aureus hemolyticus, coagulase positive and Ps. aeruginosa. Aureomycin was given in the dosage of 50 mg. every 6 hr.

A right ventricular puncture yielded cloudy fluid from which Ps. aeruginosa was isolated in pure culture. Spinal fluid studies showed a 520 cell count, 70% of which were polymorphonuclears, glucose 55 mg./100 cc., and protein 45 mg./100 cc. The infant, weighing 4.3 kg., was given neomycin, 1700 units intramuscularly every 4 hr., and the aureomycin was discontinued. In vitro sensitivity tests showed the organism to be inhibited by 3.12 μg./cc. of neomycin. Twelve days after operation, a repeat ventricular tap again revealed Pseudomonas on culture of the spinal fluid. The anterior fontanel had continued to bulge during this period. Four days later, the surgical wound appeared clean and the fontanel no longer showed tenseness. Examination of the spinal fluid at this time revealed no organisms and a protein determination of 117 mg./100 cc. The remainder of the hospital course was uneventful. The head continued to enlarge, reaching an occipital frontal circumference of 51 cm. by 3rd mo. of life, at which time the patient was discharged from the hospital in good condition aside from the hydrocephalus. When last seen, 8 mo. after discharge, he showed no residual effects of the meningitis.

SUMMARY

A case of meningitis caused by Ps. aeruginosa in an infant treated successfully with neomycin is reported. The present-day therapy of this infection is discussed and the value of intramuscular neomycin in this condition is illustrated.

REFERENCES


**SPANISH ABSTRACT**

**Meningitis a Pseudomonas en un Niño Tratada con Neomicina con Resultado Satisfactorio**

Los autores hacen una revisión breve de la literatura de las meningitis a Pseudomonas aeruginosa y discuten la mortalidad y el tratamiento presente de esta infección. Se indica, qué a pesar de los resultados favorables de estudios recientes sobre la susceptibilidad "in vitro" de este organismo a la neomicina, su uso clínico ha sido limitado debido a los efectos tóxicos reportados siguientes a el uso parenteral de esta droga. Se presenta un caso de meningitis a Ps. aeruginosa ocurrida en un niño siguiente a una reparación quirúrgica de un meningocele. La infección no respondió a un tratamiento con penicilina y aureomicina, pero el organismo resultó ser sensitivo "in vitro" a una concentración de neomicina de 3.12 microgramos/cc. El tratamiento de 1700 unidades de neomicina intramuscular cada cuatro horas durante nueve días resultó en la curación rápida de la infección. El paciente fue examinado ocho meses más tarde demostrando no evidencia de recurrencia de esta afección.

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