Escherichia Coli Meningitis in Adults: Neurosurgical and Neuropathological Considerations*

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Meningitis resulting from infection with Escherichia coli is uncommon in adults when compared to the relative frequency of occurrence in infants. In adults E. coli meningitis has been reported associated with urinary tract infection, abortion, and liver disease as well as in instances without a readily demonstrable portal of entry or primary focus of infection. Meningeal infection is probably blood-borne in most cases excluding those infections resulting from penetrating head wounds of combat, compound fracture of the skull, or contamination of the cerebrospinal fluid during lumbar puncture.

The clinical findings in three adults with E. coli meningitis are presented with emphasis upon certain neurosurgical implications arising during the course of the illness. Two of these patients died, one entirely unsuspected of harboring this intracranial infection; the third developed persistent hydrocephalus, which was ultimately relieved by a cerebrospinal fluid shunt. Postmortem observations are also presented to further our awareness of this organism as it affects the nervous system of the older individual.

Case Reports

Case 1. A 57-year-old white housewife was admitted on August 9, 1965, in a confused, tremulous state. Nine days earlier she had sustained contusions of the right orbital region. There was a history of excessive alcohol intake for many years, with several episodes of delirium tremens.

Examination. The patient was restless and incoherent and had visual hallucinations. Her temperature was 103.8°F. There were extensive ecchymoses of the right periorbital and temporal regions and a stiff neck. The lower border of the liver was 3-fingers' breadth below the right costal margin. There was good muscle strength of the extremities, and the deep tendon reflexes were symmetrically active except for the ankle jerks, which were absent. A Babinski sign was observed on the right side. The patient perceived painful stimuli, but finer sensory testing could not be evaluated.

The clinical impression was meningitis, although subdural hematoma, delirium tremens, and hepatic encephalopathy were also considered. The white blood cell count was 5200 per cu mm. X-rays of the skull and chest and an echoencephalogram were negative. Lumbar puncture yielded cloudy-yellow fluid under a pressure of 80 mm of water; the white blood cell count was 3000 per cu mm, virtually all polymorphonuclear leucocytes, and the red blood cell count 8000 per cu mm. The CSF protein was 730 mg%, and glucose was 49 mg%. A spinal fluid smear revealed gram-negative rods, and both blood and CSF cultures grew E. coli. The patient was started on treatment with intravenous cephalothin, chloramphenicol, and colistimethate sodium. Corticosteroids were given, and a hypothermic blanket reduced her body temperature to normal. Lumbar puncture on the third day revealed cloudy xanthochromic CSF under pressure of 140 mm of water, a protein of 920 mg%, a glucose of 103 mg%, and a white blood cell count of 3790 per cu mm with 80% polymorphonuclear leucocytes. An electroencephalogram showed diffuse slow-wave activity.

The patient remained in a coma, deteriorating gradually without localizing neurological signs. She died on the seventh hospital day.

General postmortem findings. There were ecchymoses over the right temporal and periorbital regions. No fracture of the skull or nose was found. The liver showed fatty change and portal fibrosis, the pancreas was diffusely fibrotic. E. coli were cultured from the CSF and blood.

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Neuropathologic observations. There was no blood within the subdural space. The brain weighed 1200 gm. The leptomeninges over the convexity and basilar surfaces of the brain were clouded by yellow-green exudate. The gyri were flattened and the sulci narrowed. There was minimal arteriosclerosis.

After fixation in 10% formalin for 1 week the brain was coronally sectioned. The ventricular system was moderately and uniformly dilated. The ventricular surfaces were covered with a thick, shaggy, yellow-green exudate. No other lesions were observed grossly within the cerebrum, cerebellum, brain stem, or spinal cord. Blocks of tissue from the cerebrum, including basal ganglia, pons, medulla, cerebellum, and spinal cord were embedded in paraffin, sectioned, and stained with hematoxylin and cosin, and with special stains for bacteria and fungi. A heavy exudate, composed predominantly of polymorphonuclear leucocytes with some mononuclear cells, erythrocytes, and fibrin, was seen within the subarachnoid space extending deeply along the perivascular spaces of the cerebrum. The exudate was most prominent in the cerebellar and medullary subarachnoid space, where there was an acute arteritis and phlebitis (Fig. 1). Similar vascular lesions were observed in the subependymal regions. The ependymal lining was coated with a purulent exudate which was also present in the choroid plexus and among the cranial nerve roots. There were foci of astrocytic and microglial proliferation in the superficial layers of the cerebral cortex and focal loss of neurons in the cerebellum. The special stains for fungi and bacteria were unrevealing.

Case 2. A 69-year-old white man was admitted on June 27, 1966, in an unconscious state. He had fallen and had sustained a head injury at home following an episode of heavy drinking 3 days before. He had remained at home in a dull state of consciousness but partially responsive for 1½ days, and was then admitted to another hospital where x-rays revealed a skull fracture. He developed increasing depth of coma; focal seizures of the right side of the face and right arm appeared 12 hours before his transfer to this hospital. For the preceding 10 years he had had diabetes mellitus which was being treated with Orinase.

Examination. The patient was unresponsive to painful stimulation. His temperature was 102.8°F. There were no localizing neurologi-

Fig. 1. Case 1. Heavy infiltrate of mononuclear cells, occasional lymphocytes, and rare polymorphonuclear leucocytes is seen throughout the wall of a meningeal vein. H. & E., ×250.
cal signs. X-rays showed extensive bilateral parietal fractures, with extension into the petrous portion of the right temporal bone. An echoencephalogram was negative. Despite intravenous fluids, correction of diabetic acidosis, and antibiotics (streptomycin and penicillin), coma and fever persisted.

On the third day, subdural hematomas of 30 ml on the left and 70 ml on the right were drained through temporal and parietal burr holes. The patient remained unresponsive and had several left-sided seizures. Low-grade fever continued with bouts of tachypnea. There was a leucocytosis of 14,450 white blood cells per cu mm, with a shift to the left. Cultures of urine yielded no growth, but those of the endotracheal secretions, on the 10th hospital day, were positive for E. coli. The patient remained somnolent and failed to respond other than to vigorous physical stimulation.

On the 13th day, marked weakness of the right arm and leg was apparent. Lumbar puncture yielded slightly cloudy, xanthochromic fluid under a pressure of 250 mm of water, with a red cell count of 335 per cu mm, mostly crinated, and no white blood cells. The CSF protein was 106 mg% and bacterial culture was negative. A second lumbar puncture, performed on the 18th day, revealed cloudy, xanthochromic CSF under pressure of 88 mm of water, with a protein of 120 mg%, 3380 red blood cells per cu mm, mostly crinated, and 50 white blood cells per cu mm with 29 lymphocytes, 17 polymorphonuclear leucocytes, 2 monocytes, and 2 band forms. The CSF culture was again negative.

The patient died on the 24th hospital day, following a sudden episode of Cheyne-Stokes respiration and hypotension.

General postmortem findings. There were linear temporoparietal fractures bilaterally, with the right fracture extending into the petrous pyramid. The right mastoid bone was yellow-green and grossly necrotic. The lungs were diffusely congested. There were no other significant findings referable to the viscera. Bacterial cultures of the lungs, right mastoid bone, and CSF yielded E. coli, but blood culture did not.

Neuropathologic observations. Residual, bilateral organizing subdural hematomas were seen. The brain weighed 1310 gm, and there were signs of increased pressure with flattening of the gyri and narrowing of the sulci. There was minimal arteriosclerosis. Small focal subarachnoid hemorrhages were present over the basal aspects of the frontal and temporal lobes and at the sites of contusions; there was a diffuse white exudate in the subarachnoid space, particularly at the base of the brain. Multiple coronal sections of the brain revealed a thick white exudate covering the ventricular system throughout. In the medial portion of each frontal lobe there was an abscess measuring 3 × 4 × 3 cm with moderately well-demarcated borders. A well-defined zone of recent, slightly hemorrhagic necrosis was present in the right parieto-occipital region involving the cortex and white matter. No focal lesions were noted within the cerebellum, brain stem, or spinal cord.

Blocks of tissue were processed as in the first case. Microscopic examination revealed slight to marked focal fibrosis of the leptomeninges and focal obliteration of the subarachnoid spaces. Several small arteries contained recanalized thrombi. A dense exudate of polymorphonuclear leucocytes and some plasma cells, lymphocytes, and mononuclear cells was present within the subarachnoid space, particularly over the medulla. Purulent exudate was also present in the choroid plexus, among the cranial nerve roots, and over the ependyma, which was focally disrupted. An arteritis and phlebitis were seen subependymally and in the leptomeninges, with some arteries occluded by recent thrombi (Fig. 2). In the subependymal tissue, there were fresh hemorrhages and polymorphonuclear leucocytes around necrotic vessels. In the frontal cerebral cortex and white matter there were large regions of recent necrosis, both hemorrhagic and ischemic, with central zones of tissue disintegration and abscess formation. A few small foci of subacute necrosis with gitter cells were also noted. Slight to moderate focal loss of neurons, with corresponding increase of swollen astrocytic nuclei, was observed in the basal ganglia, cerebral cortex, Purkinje cell layer, and dentate and inferior olivary nuclei. The inner aspect of the dura was covered with a thin fibrovascular membrane, containing hemosiderin-laden macrophages and superficially fresh blood. Special stains for fungi and bacteria were negative.

Case 3. A 56-year-old white man was transferred in a disoriented and unresponsive state
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Fig. 2. Case 2. An organizing thrombus is seen in a meningeal artery with a heavy leucocytic infiltrate in the surrounding subarachnoid space. H. & E., X250.

from another hospital on September 9, 1965, because of suspected brain abscess. He had developed right upper abdominal and epigastric pain 1 month earlier, but an oral cholecystogram had failed to visualize the gall bladder and an upper G.I. series had been negative. Within 24 hours of this examination he became acutely ill with fever, stiff neck, and progressive loss of consciousness. He was hospitalized on August 11, and a diagnosis of E. coli meningitis established by CSF culture. He was treated intravenously with penicillin, chloramphenicol, and sulfadiazine. Three days later he developed a right hemiplegia and became deeply comatose with fever of 103°F. After 1 week, the fever subsided, consciousness was regained, and the right hemiplegia receded. However, the patient remained lethargic and incoherent, and CSF studies showed persistently high protein levels and pleocytosis. A brain abscess was then suspected.

Examination. On admission, the patient was pale, lethargic, and incoherent. There was slight weakness of the right arm and leg. The deep reflexes were symmetrically active and the plantar responses were flexor. There were no signs of cranial nerve disturbance. The fundi showed no papilledema or retinopathy. His temperature was 100.8°F. The white blood count was 12,350 per cu mm with a shift to the left. Lumbar puncture yielded faintly opalescent CSF under pressure of 210 mm of water, protein 144 mg%, glucose 34 mg% (blood glucose 108 mg%), and 486 white blood cells per cu mm of which 81% were lymphocytes. The CSF smear, India ink preparation, bacterial culture, and acid-fast culture were all negative. Two blood cultures were negative. Urine cultures revealed E. coli and Ps. aeruginosa. X-rays of the skull and brain scan were negative.

Antibiotic therapy was begun on the first day, consisting of penicillin, chloramphenicol, and streptomycin. On the fifth day, a right-sided seizure occurred, which began in the face and progressed to a generalized convolution. The patient became more deeply comatose, and repeated lumbar punctures showed elevated CSF pressure and protein levels, pleocytosis, and negative bacterial cultures. Carotid arteriogram showed upward bowing and increased sweep of the anterior cerebral arteries without lateral displacement; this was attributed to enlargement of the lateral
ventricles (Fig. 3 left), but an intracranial mass was not demonstrated.

Operation. A right occipital burr hole revealed a creamy meningeal exudate. A pneumoencephalogram was attempted but was terminated when the patient exhibited decerebrate posturing. A ventriculogram was performed which revealed marked dilatation of the entire ventricular system, indicating a communicating hydrocephalus (Fig. 3 right). The patient became more responsive over the succeeding several days following a period of continuous ventricular drainage. Lumbar punctures revealed CSF pressures ranging between 120–170 mm of water, diminishing protein levels to 158 mg%, repeatedly negative cultures, and a drop in cell count to 57 white blood cells per cu mm with 94% lymphocytes by October 7, 1965.

However, the patient became somnolent once again and fever of 102°–103°F returned. Antibiotic therapy was broadened to include colymycin and tetracycline. An EEG was diffusely abnormal, showing symmetrical slow-wave activity of 4–7/second, predominantly in the frontal regions. His condition deteriorated further to the point of dementia with incontinence of feces. A pneumoencephalogram on November 4 demonstrated a diffusely dilated ventricular system and little air within the subarachnoid space over the convexity of the brain and basilar cisternae.

Second operation. A right lateral ventriculoatrial shunt (Holter valve) was performed. Thereafter, he became afebrile and, over the subsequent 2 months, he improved mentally to a remarkable degree. Serial EEG's through December 27 continued to show bilateral frontal and right temporal slow-wave activity, but an EEG recorded on January 10, 1966, had a normal pattern. When discharged from the hospital on February 23, the patient was ambulatory and exhibited no evidence of any mental deficit. He has remained slightly unsteady in gait, but has otherwise manifested no abnormal neurological signs or significant intellectual impairment.

Discussion

Limitations in our concepts of the pathogenesis of bacterial meningitis have been critically underscored by Harter and Petersdorf.14 Broad gaps in knowledge still exist with respect to such factors as portals of entry, host resistance, and virulence of invading organisms, and biochemical and other tissue responses of the body. Many questions remain to be answered by appropriately direct experimental methods as well as from carefully drawn clinicopathological correlation.

Neuropathological Aspects. The principal neuropathological features of Cases 1 and 2 were the purulent leptomeningitis, most pronounced over the basilar aspects of the brain, a diffuse ependymitis, an arteritis and a phlebitis, most conspicuous in the leptomeninges and subependymal tissue, and multiple foci of ischemic necrosis and abscess formation. The vascular lesions were characterized microscopically by acute fibrinoid necrosis of the walls of small arteries and infiltration of the walls of both arteries and veins with poly-
mphonuclear leucocytes, monocytes, and lymphocytes. Similar vascular lesions have been described in meningitis due to *E. coli* in infants, as well as in *H. influenzae* and pneumococcal meningitis. In addition, arterial thrombi were noted in Case 2, some related to foci of ischemic necrosis in the adjacent cerebral cortex and white matter. While acute arteritis is a recognized feature of *H. influenzae* meningitis, arterial thromboses occur rarely. Smith and Landing have postulated that phlebitis, rather than arteritis, is the mechanism responsible for brain damage in *H. influenzae* meningitis and that it does so by interfering with venous drainage. Cairns and Russell found that arteritis and phlebitis, with thrombosis of the meningeal and perforating blood vessels, were present in association with necrosis of the adjacent brain tissue in the early stages of pneumococcal meningitis in 14 of 28 cases not receiving chemotherapy. Fibrinoid necrosis of small subependymal arterioles was present in some of these patients and was accompanied by a necrotizing encephalitis.

The leptomeningeal exudate does not differ from that seen with purulent meningitis of other bacterial origin.

**Clinical Considerations.** Management of the meningitis is fundamentally a medical problem. The diverse manner of its clinical presentation, however, may simulate or, in fact, reflect increased intracranial pressure due to subdural hematoma (Case 1), brain abscess (Case 2), or postmeningitic hydrocephalus (Case 3).

Cairns, et al., from their experience in World War II before the era of effective antibiotic therapy emphasized the gravity of *E. coli* meningitis as a complication of open head injuries. Johnson encountered extremely virulent strains of *E. coli* which produced suppurrative meningitis and ventriculitis in patients with head wounds during the Burma campaign of 1944–45. A common clinical and pathological feature of these patients was the hemorrhagic component of the *E. coli* ventriculitis which was related to damage of blood vessel walls. The sudden appearance of bloody spinal fluid during the course of successive daily lumbar punctures was a common finding in these patients and was considered to reflect a grave prognosis. But analysis by Appelbaum in 1960 of a civilian series of 91 cases of meningitis following trauma to the head and face, revealed the pneumococcus to be the most frequent agent, whereas no instances of *E. coli* infection were recorded.

Meningitis may appear during the course of observation of an individual with a closed head injury (Case 1); the portal of entry may be through some superficial laceration of the skin or even remain unestablished. Clinical features of the meningitic infection with *E. coli* are apt to be bizarre and the disease may not be suspected (Case 2). The diffuse distribution of the vascular lesions may give rise to bleeding which may simulate subarachnoid hemorrhage from some other cause, such as from ruptured cerebral aneurysm, subdural hematoma, or intracerebral hemorrhage. Further, the characteristic encephalitic component of the infection may be responsible for neurological signs that simulate metabolic encephalopathies of varied causes.

Meningitis due to gram-negative bacilli has occurred with underlying diseases such as brain tumor, hydrocephalus, and congenital defects, and has insidiously developed in patients under observation or treatment for head injury, the underlying disease at times obscuring the clinical manifestations of meningitis.

Disclosure of *E. coli* meningitis in the adult should raise the question of an underlying chronic brain abscess that may have ruptured. Whereas a significantly decreased mortality from *E. coli* meningitis is to be expected with currently available antibiotic therapy, recovery may be complicated by delayed sequelae such as chronic abscess or hydrocephalus (Case 3) for which appropriately directed neurosurgical intervention may be required. Infection with unusual pathogens such as *E. coli*, should be suspected when the findings include meningitis in the presence of cellulitis, diabetes mellitus, urinary tract infection, or endocarditis. The importance of lumbar puncture in the confused debilitated febrile patient accordingly cannot be overemphasized.

**Summary**

The clinical manifestations of *E. coli* meningitis as seen in adults have been presented and discussed in terms of our experience with three patients, including postmortem observations on two of them. Cerebral arteritis,
phlebitis, and thrombosis were noted in the small vessels of the meninges and of the subependymal regions, and probably caused the bloody spinal fluid which has been a common clinical finding. The occurrence of brain abscess and hydrocephalus, added to the various manifestations of subarachnoid and intraventricular bleeding, emphasizes the neurological implications of this disease, particularly among adults with debilitating disease in whom E. coli infection is relatively common.

References