SPINAL CORD LEVEL SYNDROME FOLLOWING INTRATHECAL AMMONIUM SULFATE AND PROCAINE HYDROCHLORIDE. A CASE REPORT WITH AUTOPSY FINDINGS * †

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THE administration of intrathecal ammonium sulfate for the treatment of certain types of pain received its impetus from the original work of Judovich (1) on the pitcher plant, Sarracenia purpurea. In recent papers by Bates (2) and Bates and Judovich (3) the rationale and method of administration are discussed. Bates and Judovich (3), who were familiar with 50 cases, mentioned that "temporary motor effects were observed in several cases. Two cases had a temporary urinary incontinence lasting twenty-four to forty-eight hours, respectively. One patient had a temporary bowel and bladder effect." However they apparently never encountered a case of permanent flaccid paraparesis. Bishop (4) has encountered a case with a spinal cord level syndrome, which persisted for months following the intrathecal administration of ammonium sulfate and procaine hydrochloride. Bates and Judovich (3) cautioned that "free dilution and repeated barbotage are essential" in order to prevent "loss of skin sensation, and sphincter and motor paralysis."

The following case report, with the findings at necropsy is, to our knowledge, the first recorded instance of irreparable spinal cord injury associated with the use of intrathecal ammonium sulfate and procaine hydrochloride.

CASE REPORT

A 64-year-old shop keeper was admitted to the East Service of Doctor Irving Pardee on July 21, 1943. At that time the patient, a diabetic, complained of pain in the lower extremities associated with marked weakness and an inability to void. About four months before admission the patient first experienced severe pain along the distribution of the sciatic nerve in the left lower limb and he remained in bed for about one month. On May 6, 1943, the patient entered another hospital and at that time a weakness of the left quadriceps with hypotonia of both lower extremities was noted. The upper extremities were unimpaired. The knee jerks could not be elicited. Hyperalgesia was present in both lower extremities and the saddle area was unimpaired. The remainder of

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the neurologic examination was within normal limits. There was no history of any disturbance of the sphincters. The diabetes mellitus was readily controlled by diet and 10 units of zinc protamine insulin each day. However, the pain persisted and he was treated for diabetic neuropathy. Several lumbar punctures were performed and there was never any evidence of a block in the subarachnoid space. The spinal fluid proteins ranged about 45 mg. per cent and there were no cells. Roentgenograms of the lumbar spine gave essentially negative results. The patient's pain did not abate and he was given intrathecal ammonium sulfate.

On July 14 a lumbar puncture was performed by a neurologist who had previous experience with this form of therapy. The needle was introduced between the first and second lumbar vertebrae without any difficulty while the patient

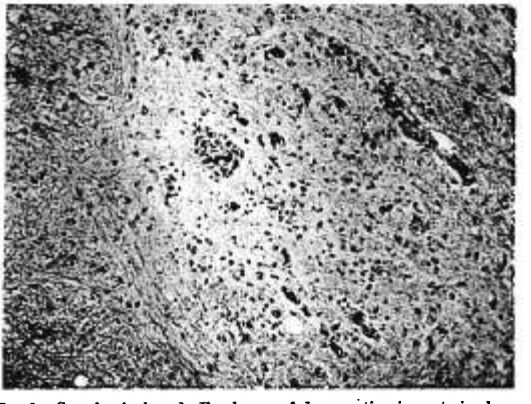

FIG. 1. Sacral spinal cord: Focal area of degeneration in posterior horn. Hematoxylin-eosin stain. × 110.

remained in the lateral recumbent position, and 10–12 cc. of spinal fluid was removed with ease. Four hundred milligrams of ammonium sulfate (supplied by Dr. B. D. Judovich, Philadelphia) and 25 mg. of procaine were dissolved in 5 cc. of sterile distilled water and injected into the subarachnoid space in about one minute. In so far as we are aware, barbotage was not performed. The patient was then placed in the supine position. It was reported that within several hours following this treatment, the patient experienced an accentuation of his pain with an almost complete loss of motor power in the lower extremities and retention of urine which necessitated the introduction of an indwelling catheter.

At the time of admission to the Neurological Institute, one week after the administration of the ammonium sulfate and procaine, the patient was afebrile and his blood pressure was 120 mm. systolic and 75 mm. diastolic. He appeared to be chronically ill and complained of sharp shooting pains in the lower limbs. The significant findings consisted of a flaccid paraparesis. The right lower limb could be flexed and extended in a feeble fashion and only incomplete dorsiflexion

of the foot could be performed on the left. The upper abdominal reflexes were unimpaired while the lower ones were markedly diminished. Cremasteric responses were absent. No deep tendon reflexes could be elicited in the lower extremities. Plantar response was deficient on the right and weak on the left. There was a band of hyperpathia to all superficial modalities from the eighth to the twelfth thoracic bilaterally, but this was more marked on the left. Below the first lumbar dermatome there was hypesthesia, hypalgesia and hyperthermesthesia. There was perianal anesthesia and analgesia. Muscle-tendon and vibration sensibilities were also markedly impaired in the lower extremities. Rectal sphincter tone was poor, and the prostate was not enlarged.

The laboratory studies revealed a hemoglobin of 82 per cent (11.9 Gm.); erythrocytes numbered 4,400,000, leukocytes 7,000, with 78 per cent polymorpho-

FIG. 2. Upper lumbar spinal cord: Focal area of degeneration in posterior horn showing loss of myelin sheaths. Mahon stain. × 110.

nuclear leukocytes, 20 per cent lymphocytes and 2 per cent monocytes. Repeated nonprotein nitrogen studies were within the limits of normal and the blood Kline test gave negative results. Erythrocyte sedimentation rate was 43 mm/1 hr. The diabetes mellitus was well controlled by diet and insulin. The patient had a persistent bacilluria, Streptococcus hemolyticus. Lumbar puncture was performed with ease on three occasions. The initial pressure was always too low to read, i.e. below 35 mm. of water. The manometric studies never revealed any block of the subarachnoid space. At first the spinal fluid was distinctly xanthochromic and contained brownish-black particles, about 0.5 mm. in size. The spinal fluid protein ranged between 100–125 mg. per cent and the cell count was repeatedly normal. The spinal fluid Wassermann and colloidal gold curve tests gave negative results. Stained smears of the brownish-black particles showed many white cells but no neural elements. Chronaxia studies showed evidence of neuromuscular degeneration in the muscles supplied by the left sciatic nerve. The medial part of the left quadriceps was wasted and could

not be stimulated; its lateral portion was normal. On the right side there was a slight increase of the chronaxia of the muscles supplied by the sciatic nerve, without actual evidence of degeneration. The right quadriceps had a diminution in the amplitude of its contraction. These findings suggested that we were dealing with a diffuse lesion of the spinal cord rather than a transverse myelopathy. The degeneration in the left leg was more marked in the extensors and peronei muscles than in the tibialis anticus. This latter finding was thought to be suggestive of a so-called neuritis. The chronaxia studies, therefore, indicated a diffuse myelopathy associated with a so-called neuritis. Unfortunately cystometric studies were not obtained.

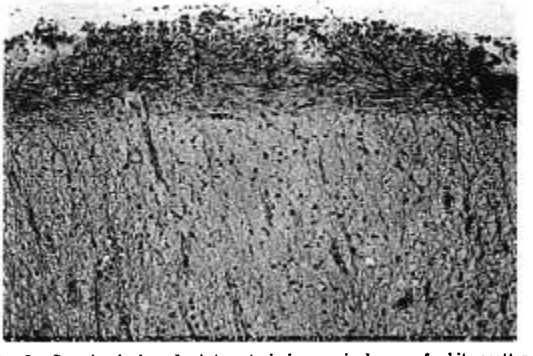

FIG. 3. Sacral spinal cord: Astrocytosis in marginal zone of white matter. Phosphotungstic-acid hematoxylin stain. × 110.

The patient's course in the hospital was stationary. Tidal drainage was necessary and the paraparesis remained unchanged. The patient had asthma for ten years prior to admission and on the thirteenth hospital day he went into status asthmaticus and died. Epinephrine was administered only several hours before death.

AUTOPSY FINDINGS

A complete necropsy was performed but only the findings in the spinal cord and the cauda equina are pertinent for this report.

GROSS ANATOMY

The spinal dura was smooth and glistening. The spinal cord was normal in contour, color and consistency. No gross abnormalities of the cauda equina were observed. The leptomeninges were slightly congested but were thin and translucent. Section of the spinal cord at a number of levels revealed no gross abnormal changes.

HISTOLOGIC EXAMINATION

Sciatic Nerves.—The left sciatic nerve showed moderate loss of myelin sheaths and small loss of axones with an increase in Schwann nuclei. Occasional small clusters of lymphocytes were noted about some of the blood vessels in the endoneurium. Identical but less marked changes were found in sections of the right sciatic nerve.

Roots.—One of the nerve roots going into a lumbar spinal ganglion, at its point of exit from the dorsal ganglion, showed a decrease of axones and myelin sheaths in the affected portion and a considerable increase in Schwann and endoneurial nuclei. Several other nerve roots

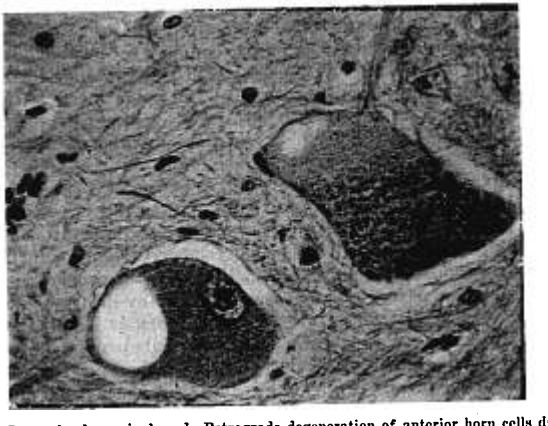

FIG. 4. Lower lumbar spinal cord: Retrograde degeneration of anterior horn cells due to nerve root degeneration. Hematoxylin-eosin stain. × 460.

from sacral, lumbar, thoracic and cervical levels were studied and proved to be unchanged.

Leptomeninges.—The leptomeninges were within the limits of normal except for one region in the sacral cord. There was an area over the posterolateral aspect of the spinal cord which revealed a small number of lymphocytes.

Gray Matter.—In the sacral cord the anterior horn cells showed varying stages of central chromatolysis, and in some areas the cells had completely disappeared. There were circumscribed foci of degeneration and disappearance of neural elements in the posterior horns. This degeneration of nerve cells, axones, and myelin sheaths, which was associated with a moderate number of lipoid-laden phagocytes and hypertrophied fibrillary astrocytes was most marked in the lower lumbar

cord. The focal lesions were less prominent in the upper lumbar cord. Some of the anterior horn cells in the thoracic cord exhibited central chromatolysis.

White Matter.—There was a slight diffuse loss of axones and myelin sheaths in the column of Goll and to a less extent in each lateral column. The external glial membrane was markedly thickened in the lumbar and sacral region of the spinal cord and was associated with a microcystic appearance of the marginal portion of the white columns.

COMMENT

The degenerative lesions noted in the peripheral nerves were evidently a neuropathy associated with the diabetes mellitus. Following the injection of ammonium sulfate and procaine into the spinal subarachnoid space for the relief of pain, a spinal cord level syndrome developed. The degenerative lesions discovered at autopsy in the lower thoracic, lumbar and sacral segments of the spinal cord were so distributed as to make it likely that the injurious agent penetrated from the subarachnoid space to the periphery of the spinal cord, injuring it directly. The lesions were distributed about the margin of the involved segments and consisted essentially of a necrosis of local neural and neuroglial elements. An interesting feature of the process was the occurrence of focal lesions at the tips of the anterior and posterior horns. These were sharply outlined, somewhat removed from the surface, and suggested a vascular mechanism for their origin. However, none of the leptomeningeal or parenchymal vessels showed any injury or disease of their walls. One may conjecture that the injurious agent, the ammonium sulfate and/or the procaine, had penetrated along perivascular spaces to reach a segment of the deeper tissue or had produced a temporary effect on the blood vessel walls resulting in vasospasm and injury to the area of supply to the given vessel. There was no direct evidence, however, to support either of these views. Ammonium sulfate has been used in similar fashion for the alleviation of pain apparently without the production of lesions such as those present in this case. Procaine is widely used intrathecally, although occasional untoward incidents have been reported. There have been several reports of the production of spinal cord lesions following the subarachnoid injection of procaine and related spinal anesthetics (Brock, Bell and Davison (5), Brain (6) and Russell (7). The essential feature of these lesions was their peripheral, as well as focal, distribution in the spinal cord. In general, they resemble those reported in this instance. Intrathecal administration of magnesium sulfate without any of the cocaine derivatives has produced a similar clinical and pathologic picture (Guttman and Wolf (8)).

SUMMARY

The case report described a spinal cord level syndrome which followed the intrathecal administration of 400 mg. of ammonium sulfate

and 25 mg. of procaine hydrochloride. A flaccid paraparesis, with loss of sphincter control, persisted until the time of death, twenty days after the injection of these agents.

Anatomical studies provided conclusive evidence that the ammonium sulfate-procaine hydrochloride solution was not injected into the parenchyma. The lesions were distributed about the margin of the involved segments (lower thoracic, lumbar and sacral) and consisted essentially of a necrosis of local neural and neuroglial elements. There were also focal lesions at the tips of the anterior and posterior horns. Examination of the remainder of the spinal cord and brain failed to reveal any abnormalities.

Two possible mechanisms for the production of these lesions have been suggested but neither of them can be proved. However, we can only conclude that this method of therapy has certain dangers and is sufficiently hazardous to warrant extreme caution in clinical application.

Doctor Abner Wolf performed the anatomical studies and was most helpful in the preparation of this report.

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