SOME NEUROLOGICAL COMPLICATIONS OF SERUM THERAPY

BY

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Involvement of the nervous system as a factor complicating serum therapy is not at all common; it seems to have been first noted by Thaon (1910) in describing a case of peripheral neuritis following the prophylactic injection of tetanus antitoxin. Subsequently Dyke (1918) reported a similar case in this country, while the subject has attracted much attention in France, notably by Lhermitte (1919, 1938), and, latterly, in America and elsewhere (Kraus and Chaney, 1937). Allen (1931) reviewed forty-two reported examples then extant in the literature, and he described the second case (which followed scarlatina antitoxin administration) to appear in this country. Out of 120 authentic cases that we have been able to discover on record more than half have followed the prophylactic injection of tetanus antitoxin in young adults, usually males, although every type of serum commonly employed has been incriminated. Recently Smith (1939) has reported a case in which deltoid paralysis developed after the transfusion of human blood on two separate occasions.

The characteristic lesions have been carefully discussed and classified by Bineau (1938), and appear to be localized either in the central or, more commonly, in the peripheral nervous system. In particular the fifth, sixth, and seventh cervical nerve roots are affected, and occasionally the lumbar plexus. The onset is usually coincident with the signs and symptoms of serum disease, beginning about eight to fifteen days after serum administration with intense pain in the neck and shoulders which is probably radicular in origin and is accompanied by little or no objective sensory loss. This is followed by paralysis and by rapid and intense wasting of the muscles supplied by the nerves affected which reaches its maximum in from one to four days. The resulting syndrome is comparable to the Duchenne-Erb type of palsy. Tendon reflexes are diminished and changes occur in the electrical reactions, or, alternatively, a typical peripheral neuritis may occur. Involvement of the central nervous system is ushered in by a general serum reaction followed by collapse, vomiting, and, rarely, coma, and may be succeeded by hemiplegia, hemi-anaesthesia, or other protean signs suggesting widespread lesions. Optic neuritis and certain cranial nerve palsies—in particular, involvement of the third, seventh, eighth, and tenth nerves—have all been noted on occasion. The cerebrospinal fluid usually shows an increase of cells up to about thirty, mainly lymphocytes, the albumin being, as a rule, within normal limits. The pleocytosis is sometimes preceded by a slight rise in the sugar content. Finally, confusional states may occur, always, however, of a very temporary nature.

Considering their widespread employment, symptoms referred to the nervous system following the injection of anti-streptococcal and anti-scarlatinal sera appear to be very uncommon; we have been able to discover only ten cases in the literature. The following two cases therefore appear to be worthy of record.

Case I

A youth aged 17, an office clerk of normal physique, was admitted to the South-Eastern Hospital on February 2, 1939, with a moderate attack of scarlet fever of one day's duration. There was nothing relevant in the past history. He received 40 c.cm. of anti-scarlatinal serum intramuscularly into the right thigh. On the tenth day following he complained of pain in the right shoulder, but no serum rash or albuminuria developed. He was treated symptomatically for serum arthritis, and he improved slightly, though pain persisted. On March 4, twenty-four days after serum administration, a general reaction occurred; the temperature was 101°, pulse 120, and respirations 26, and he complained of inability to raise his right arm at the shoulder and of continuation of the pain in the shoulder and neck. By March 7 paralysis of the right deltoid was almost complete, with much wasting, and there was slight weakness of the right biceps. There was no objective sensory disturbance, and radiography and examination of the rest of the nervous system showed nothing abnormal. Unfortunately, owing to lack of facilities, the electrical reactions of the muscles could not be tested at this stage. By March 10 the pain was much less, though present on deep palpation, and the temperature was normal, but the deltoid paresis was unchanged, except for slight return of power in the anterior fibres. The right triceps jerk was diminished, but no other nervous lesion was detected; the optic fundi appeared normal. Subsequently the pain gradually decreased and the paralysis improved slightly. On March 24 he was sent home with instructions to attend as an out-patient at a general hospital for physiotherapy, where, on examination, the muscles were found still to respond to faradism. When seen again on May 4 he had some weakness and wasting, but muscular power was returning and the electrical reactions were normal.

Case II

A plumber aged 56 was admitted to the Grove Hospital on May 5, 1938, with a well-marked attack of scarlet fever. Previously he had always been healthy and there was no history of allergic manifestations. He was given 20 c.cm. of scarlatinal antitoxin intramuscularly, and he made excellent progress for six days, after which he collapsed and vomited with the onset of a serum rash. He recovered, and the following day there was glycosuria. On the eighth day after serum administration severe generalized urticaria was present, and the same afternoon he complained of occipital headache and appeared drowsy and mildly confused. On examination there was strabismus due to paralysis of the right external rectus muscle, nystagmus, and some weakness of the right side of the face; but the pupils reacted normally and the ocular fields were full, though the edges of the optic disks appeared blurred. Voluntary power, tendon reflexes, and plantar responses showed no abnormality. The abdominal reflexes were absent, there were no cerebellar signs or spasticity, but doubtful right ankle-clonus was noted. The patient did, in addition, exhibit a definite right hemi-hyperaesthesia affecting the arm, leg, and trunk, but there was no astereognosis, aphasia, or other objective sensory change. Lumbar puncture yielded 20 c.cm. of blood-stained cerebrospinal fluid under pressure, analysis of which showed protein 200 mg. per 100 c.cm. with increased globulin, chlorides 789 mg. per 100 c.cm., sugar 60 mg. per 100 c.cm., and cells 180 per c.cm., of which 95 per cent. were neutrophil leucocytes and 5 per cent. lymphocytes, with numerous red blood cells. After injection of adrenaline and coramine he recovered rapidly, the headache disappearing with subsidence of the serum rash. The following day there was still slight squint, doubtful right ankle-clonus, and right hemi-hyperaesthesia, which was confirmed by the visiting neurologist. Twenty-four hours later the serum rash and all neurological signs had disappeared, and the patient, apart from some drowsiness and exhaustion, seemed completely recovered. He was allowed up on May 23, and was discharged home quite well on June 10.

Discussion

The first case conforms in the main to the usual peripheral type of nervous lesion. It has, however, a feature of special interest—namely, the pain on the eighth day occurring in place of and not along with the serum rash, and preceding by a long interval the onset of paralysis accompanied by general reaction. The absence of urticaria may cast doubt upon the diagnosis, but the time of onset of the pain and the lack of any further cause appear to be conclusive, a point which has been noted in other reported cases.

With regard to the second case, the age of the patient and the changes in the cerebrospinal fluid suggested at the time an alternative diagnosis of cerebral thrombosis or some other acute meningo-vascular disturbance. The sudden onset of neurological signs, coincident with the onset of serum disease, and the rapid recovery with disappearance of the serum rash, are characteristic of such rare cases, however, and were considered to be sufficiently conclusive.

Although the pathogenesis of serum neuritis and other nervous complications of serum therapy has given rise to much conjecture its exact aetiology remains obscure. Among various theories of origin, the one now generally favoured supposes that a perineural oedema, comparable to the oedema of serum disease, causes a compression or ischaemic paralysis of nerve trunks. Other theories have suggested direct toxin action on the nervous system, affecting nerves of low chronaxie, as in lead poisoning, or a perivascular infiltration with widespread capillary haemorrhages in brain and spinal cord, such as has been found experimentally in acute anaphylaxis.

A high percentage of the recorded cases have followed the injection of tetanus antitoxin, but this may be accounted for by its frequent use as a prophylactic agent. Certain other factors—such as the age of the serum, degree of refinement (we have not been able to trace any reference to nervous complications after the use of crude horse serum), and sensitization of the patient by a previous administration of serum—may be of aetiological importance.

Though recovery may take several months the ultimate prognosis in the majority of cases appears to be good. According to Bennett (1939), however, about 20 per cent. of cases are left with a varying degree of disability. Nevertheless, in view of the great rarity of such manifestations the consensus of opinion is that the remote possibility of this occurrence should not affect the employment of one of our most valuable therapeutic measures.

Summary

Involvement of the nervous system as a complication of serum therapy is discussed.

Two cases showing symptoms referred to the nervous system following the injection of anti-scarlatinal serum are recorded.

Theories of the origin of the nervous complications are reviewed.

The prognosis in the majority of cases appears to be good.

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LOCAL TREATMENT WITH PRONTOSIL SOLUBLE

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The value of local treatment with chemotherapeutic drugs is still unsettled, but if the method proves satisfactory it will have the obvious advantages of economy and atoxicity. The result of using prontosil soluble locally in one case was so striking that the procedure was tried in a variety of conditions. Five of these cases are reported below.

Case Reports

Case 1.—A young woman who was admitted to hospital with lobar pneumonia developed a pneumococcal empyema which drained for over four months, about 60 oz. of thick greenish pus being discharged in the twenty-four hours. Her general condition was poor, and nursing was rendered difficult because of marked oedema extending from the lower costal margin to the feet. As the condition did not respond to the usual method of treatment 5 c.cm. of 5 per cent. prontosil soluble was injected into the pleural cavity; the next day the discharge was very much thinner and contained only flakes of pus. Twenty-four hours after the second injection, given on the third day of treatment, the drainage was much less, there was no frank pus, and the fluid was sterile on culture. A third injection was given on the fifth day; the discharge from the pleural cavity rapidly diminished and the oedema began to recede. A fortnight after starting treatment the tube was removed. The patient rapidly regained her health, and four weeks later she was discharged from hospital fully recovered.

Case 2.—A middle-aged female melancholic in poor physical condition developed an abscess in the gluteal region to the left of the sacrum. Following treatment with fomentations a cavity large enough to hold a tennis ball was discovered. This appeared to be walled off by gangrenous muscle, while the discharge consisted of foul-smelling greenish-black pus containing strips of necrotic tissue. Treatment with eusol packings over a period of a week produced no improvement. The cavity was then packed with gauze soaked in prontosil soluble. Within twenty-four hours the foul odour had practically disappeared and the wound was remarkably clean. The cavity now rapidly filled with healthy granulation tissue, and epithelium started growing at the edge. Three weeks after the first treatment with prontosil soluble the wound was completely healed and was covered with healthy skin.

Case 3.—This patient, a female, suffered from a varicose ulcer four inches in diameter on the outer aspect of the right leg; it had resisted all attempts at treatment. The discharge was copious, and each dressing was filthy when removed. An ointment containing 5 c.cm. of prontosil soluble to the ounce of lanolin was prepared, and was applied to the ulcer once daily. The odour disappeared in twenty-four hours; healthy epithelium began to invade the raw surface, and in four weeks the ulcer had healed completely and was covered with healthy skin.

Case 4.—A female mental defective, this patient complained of pain in the anal region, and on examination a perineal ulcer about the size of a five-shilling piece was discovered.