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A CASE OF PODOPHYLLUM POISONING WITH INVOLVEMENT OF THE NERVOUS SYSTEM

BY

A. N. G. CLARK, M.D.
Lately Registrar

AND

MAURICE J. PARSONAGE, M.B., B.Sc.
M.R.C.P., D.C.H.
Assistant Physician

Neurological Department, the General Infirmary at Leeds

There are a number of toxic substances which, after absorption via one route or another, may lead to the development of a disturbance of function in the nervous system with or without ensuing structural damage. Quite often the peripheral nerves appear to be principally involved, this resulting in the production of a more or less symmetrical type of peripheral neuropathy; moreover, in such cases there may be severe structural changes, with the result that recovery of function, although tending ultimately to be complete, may be long-delayed. There may also be involvement of the central nervous system by the toxic action of the ingested substance, and, although the exact *modus operandi* may not be known, it seems likely that in many such cases the upset of function in the nervous system may well be the result of interference with various enzyme systems.

The following case report is of a patient who developed a fairly severe disturbance of central and peripheral nervous function after taking an overdose of a podophyllum extract by mouth. We have not been able to find a similar case in the literature. For this reason, and also because the effects of this substance upon living tissue have recently been the subject of investigation, we felt that the case should be placed on record.

Case History

A married woman aged 25, believing herself to be pregnant, drank 1 fl. oz. (28.4 ml.) of a proprietary concentrated alcoholic extract of American podophyllum root (*P. peltatum*) one evening on the advice of a friend. There were apparently no immediate ill effects, but the next day she began to vomit repeatedly, becoming confused and finally comatose within 24 hours. The same evening vaginal haemorrhage also supervened and she was transferred to hospital as a gynaecological emergency. On admission she was found to be confused, noisy, and restless, hiccuping, yawning, and retching in turn. A bruise was present over the right eye, but her colour was good and her tongue moist and clean. The ocular fundi and pupils were normal, the knee-jerks were present and equal, but the abdominal reflexes were absent and the plantar responses extensor. The pulse rate was 60 a minute, the temperature 97.8° F. (36.6° C.), and the blood pressure 120/80 mm. Hg. On clinical examination no abnormalities could be detected in the cardiovascular, respiratory, or gastro-intestinal systems, and, although a gynaecological examination revealed the presence of a blood-stained watery discharge from the vagina, the cervix and vagina itself were normal in appearance, there being no evidence of enlargement or abnormality of the uterus.

A provisional diagnosis of poisoning was made in view of the clinical history, and gastric lavage was performed shortly afterwards. From the time of admission the patient was able to take fluids by mouth, and a marked lessening in the severity of her confusional state had occurred two days after admission. It was recorded at this stage that the tendon reflexes had become sluggish, while a lumbar puncture revealed a clear cerebrospinal fluid at a pressure of 210 mm. of water; it contained: protein, 45 mg. per 100 ml.; chlorides, 680 mg. per 100 ml.; sugar normal in amount; and about 3,000 red blood cells per c.mm.; the latter was probably the result of accidental contamination.

The patient was first seen by one of us (M. J. P.) eight days after her admission to hospital. She was then mildly confused and somewhat restless, and uninhibited in her behaviour. Neurological examination revealed no abnormalities of the cranial nerves apart from a sluggish reaction of the pupils to light and an inconstant horizontal nystagmus on conjugate lateral deviation of the eyes. There was, however, a fairly severe degree of general weakness of the limbs, which were hypotonic and exhibited gross incoordination with associated pseudo-athetotic movements of the outstretched hands and fingers. The plantar responses were flexor in type, but the tendon-jerks were either extremely sluggish or absent, and there was impairment distally in the limbs of all modalities of sensation, postural sense being lost in the digits. A further lumbar puncture next day showed a spinal fluid pressure of 105 mm. of water; the fluid contained: protein, 200 mg. per 100 ml.; chlorides, 620 mg. per 100 ml.; sugar within normal limits; cells, nil. At this stage the blood pyruvate level was 0.85 mg. per 100 ml., the serum alkaline phosphatase level 11 units (King–Armstrong), the serum bilirubin 0.4 mg. per 100 ml., and thymol turbidity 0.9 unit, the thymol flocculation test being negative.

On the eleventh day of her illness the patient was transferred to a neurological unit for rehabilitative treatment. By this time her mental state had become almost normal. Examination of the cranial nerves disclosed that there was still an inconstant horizontal nystagmus on conjugate lateral deviation of the eyes to the right, together with sluggish responses of the pupils to light. The weakness, hypotonia, and incoordination of the limbs were unchanged. The tendon reflexes had remained virtually absent and the previously observed sensory changes were still demonstrable.

Progressive improvement in the symptoms and signs ensued during the course of the next three weeks, at the end of which a further lumbar puncture was performed. The fluid was under a resting pressure of 35 mm. of water, and the Queckenstedt test was negative; it contained two cells per c.mm. (one polymorphonuclear leucocyte and one lymphocyte) and had a protein content of 60 mg. per 100 ml.; the Pandy test for globulin was weakly positive, but the sugar content was within normal limits (47 mg. per 100 ml). Both the Lange gold curve and W.R. were negative. No abnormalities were found in the urine, spectroscopic examination

and the Waldenström test being negative; a heavy growth of coliform organisms was, however, obtained on culture. The latter finding may well have accounted for the moderately raised E.S.R. (34 mm. in the first hour) which was observed at this time. The results of a full blood count were essentially normal. An E.E.G. examination carried out a month after admission showed normal cortical electrical activity.

At the end of a month of rehabilitative treatment the patient was able to stand without support, but her balance was impaired and she could not walk unaided. After a further two months she was able to walk without help, although her gait remained ataxic and widespread weakness of the limb musculature was still present. There was pronounced tenderness of the calf muscles. The tendon reflexes had not returned and there was still some impairment of all sensory modalities in the limbs, postural sense remaining considerably impaired in the digits. The patient was, nevertheless, considered fit enough to be allowed to return home at this stage.

When examined as an out-patient seven months after the onset of illness her condition had improved considerably; motor functions and the tendon reflexes were then found to be normal in the arms. There was still, however, some weakness of dorsiflexion of the feet and of the great toes, and the knee- and ankle-jerks remained absent. Vibration and postural sense were virtually normal in the arms but were still slightly impaired in the toes.

A final examination was made 16 months after the commencement of the illness. At this time the patient was walking normally and complained only of slight tenderness and occasional cramps in the calves. Her mental functions appeared to be quite normal, and full neurological examination revealed only sluggishness of the knee-jerks, absence of the ankle-jerks, some impairment of vibration sense in the legs, and minimal impairment of postural sense in the left hallux.

Discussion

Subsequent analysis of a sample of the podophyllum extract ingested by this patient revealed that it had been prepared from American podophyllum root (*P. peltatum*) and that it contained 9.96% of podophyllin resin in 75% alcohol. It is estimated that she must have taken 2.8 g. of the resin by mouth, this amount being approximately 44 times the maximum stated *B.P.* dose of the resin. Furthermore, the fatal dose of the resin is stated to range from 0.3 to 0.6 g. (Gonzales *et al.*, 1954), and the patient had in fact ingested more than four times this amount. However, a probable important mitigating factor arises from the fact that the resin has the physical property of becoming precipitated from strong alcoholic solution into dense curds in water and in acid fluids such as stomach contents; vomiting therefore might possibly have resulted in the removal of some of the resin.

Podophyllin is a resin mixture obtained from the dried rhizome and roots of *P. peltatum* (May apple). Its purgative action was accidentally discovered 120 years ago (Zakon, 1952), and it has long been a popular lay remedy for constipation and the "sluggish liver." Its principal use in recent years has been in the treatment of genital warts, as it possesses the power of arresting epidermal mitoses (Sullivan, 1949). On account of its anticarcinogenetic properties its possible toxicological effects have been carefully studied recently. Experimental overdosage with this substance in rats has been found to result in the development of abnormalities of gait, muscular flaccidity, and coma (Sullivan *et al.*, 1951); furthermore, in the cat, weakness and incoordination of the posterior extremities have been found to occur (Ormsbee *et al.*, 1947). In addition, Miller *et al.* (1949) have shown experimentally that podophyllotoxin, one of the constituents of the resin, inhibits respiration *in vitro* in various cellular organs, including the brain.

The occurrence of fatal systemic poisoning following podophyllin treatment of a large condyloma acuminatum of the vulva in a negro girl of 18 was reported by Ward *et al.* (1954). The local lesion had been cleansed with an antiseptic soap, after which multiple biopsy specimens were taken. Within 24 hours of the local application of a 25% podophyllin ointment the patient lapsed into a state of deepening coma with associated nitrogen retention, and died at the end of a week. At necropsy congestion of all the organs was found; in addition, the brain exhibited rarefaction of the cortex, fragmentation and swelling of the white matter, which contained many capillaries with wide perivascular spaces, and increase of the glial elements. These authors concluded that failure to remove the podophyllin ointment was probably the principal reason for the poisoning; they also thought that its application to the site from which multiple biopsy specimens had been taken may have resulted in more rapid absorption than would have occurred from an intact surface. They were unable to find any record in the literature of a similar type of occurrence, but drew attention to a fatal case quoted by Peterson *et al.* (1923) in which the podophyllin had been taken orally. This concerned a woman who became comatose and died just over 30 hours after taking by mouth 5 gr. (0.35 g.) of the resinoid podophyllin.

The only really comparable example of poisoning of a human subject that we have been able to discover in the literature concerns a case of colocynth poisoning recorded by Kroll (1938). This author recorded the clinical findings in a female patient who developed a flaccid paralysis of the legs with muscular atrophy and a reaction of degeneration, with considerable improvement after two months and complete recovery at the end of four months. The cause of this syndrome was ascribed to the effects of a laxative which the patient had been taking for over a year and which on analysis was found to be an essence of colocynth with an alcohol content of 35 vol.%. Other possible causes of the condition—infection, organic poisons, etc.—were regarded as excluded, and the author points out that it has been shown experimentally that the administration of colocynth to dogs, cats, and rabbits can produce a fatal polyneuritis. Although podophyllin and colocynth are unrelated chemically, they are both powerful intestinal cathartics, and it would appear, therefore, that the administration of alcoholic extracts in the cases described by Kroll and ourselves produced similar sequelae.

In our patient the ingestion of the podophyllum extract resulted in a severe disturbance of nervous function, although the effects were not observed until the following day. There then ensued a state of mental confusion leading to coma within the next 24 hours. The patient did not, however, remain long in a comatose state, and at a later stage a detailed neurological examination revealed that she had developed a severe peripheral type of neuropathy, the spinal fluid protein content having by this time risen to 200 mg. per 100 ml. A variable nystagmus had also been observed, and by the eleventh day the patient's mental state had still not returned to normal. Recovery proved to be a slow process and was still incomplete at the end of six months. We consider, therefore, that there must have been a disturbance of both central and peripheral nervous function, and in the light of the experimental evidence it seems to us likely that this occurred as a result of interference by the podophyllin with the metabolism of the nervous system. The disturbance of brain function which occurred was of far shorter duration than that which developed in the peripheral nerves, and the slow recovery indicates that in the case of the latter comparatively severe degenerative changes must have taken place.

It could also be argued that the alcohol content (75%) might have played some part in the production of the syndrome, since it was the only other constituent of the extract that might conceivably have been important as an aetiological agent. The amount of alcohol present was the equivalent of 21 ml. of absolute alcohol (¾ oz.), and it seems unlikely that so small an amount could itself have been of any consequence. Whether the podophyllin or colocynth in combination with alcohol is apt to be more toxic than either of these agents alone is perhaps rather less certain.

Summary

A case of poisoning as a result of the ingestion of an alcoholic podophyllum extract is described.

The resulting toxic effects comprised an initial severe disturbance of consciousness followed by a state of confusion, and a fairly severe type of peripheral neuropathy.

A substantial amount of recovery of function had occurred at the end of six months after ingestion of the podophyllin, but a residual neurological deficit was still evident at the end of 16 months.

The mode of action and probable effects of the podophyllum extract are discussed briefly.

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ANKYLOSING SPONDYLITIS AND CHRONIC INFLAMMATORY LESIONS OF THE INTESTINES

BY

V. L. STEINBERG, M.B., M.R.C.P.Ed.

Senior Registrar, Department of Physical Medicine, London Hospital

AND

GEOFFREY STOREY, M.D., M.R.C.P. D.Phys.Med.

Consultant in Physical Medicine, Hackney and Central Group

This paper describes six cases in which ankylosing spondylitis was associated with chronic non-specific inflammatory lesions of the intestines. Four of these cases had chronic ulcerative colitis, one had Crohn's disease, and one had ulcerative colitis and Crohn's disease. The aetiology of ulcerative colitis and Crohn's disease is uncertain. Although it seems unlikely that they represent different manifestations of the same diseases, nevertheless there appears to be enough similarity between them to make differentiation difficult at times (Butler, 1953 ; Crohn, Garlock, and Yarnis, 1947), and we may be justified in considering them together. The diagnosis of Crohn's disease was made at operation in both our cases, while radiology with a barium-filled colon was relied on for the diagnosis of ulcerative colitis.

The English literature has few references to the association of ankylosing spondylitis and ulcerative colitis. West (1949) makes no mention of the two conditions in his discussions of the aetiology of ankylosing spondylitis, and Hart (1955), reviewing 184 cases of ankylosing spondylitis, does not mention ulcerative colitis or Crohn's disease (although he refers to other diseases of the intestines). However, Romanus (1953) describes three cases of ulcerative colitis associated with ankylosing spondylitis, and, indeed, French authors have always believed that ankylosing spondylitis might be related to disorders of the intestines. Forestier (1939) stated that the primary focus in ankylosing spondylitis lay in the genito-urinary system or in the lower bowel. Further, dysentery and post-dysentery syndromes have always, since Reiter's (1916) original description, been recognized as aetiological factors in Reiter's syndrome, and it is recognized that involvement of the sacro-iliac joints may be a part of this syndrome (Marche, 1950 ; Ford, 1953). We have been unable to find any reference to the association of ankylosing spondylitis and Crohn's disease.

Case Reports

Case 1.—A man aged 42 was first admitted to the London Hospital in 1938 with an acute attack of diarrhoea and blood in his stools. Sigmoidoscopy revealed changes typical of ulcerative colitis. Following treatment he was much improved. Since that time he has been readmitted five times for recurrences of ulcerative colitis, and on the last occasion a barium enema showed changes of advanced ulcerative colitis throughout the whole of the large intestine, and possibly some involvement of the small gut. Three years after the diagnosis of ulcerative colitis was made he complained of pain in the lumbar region lasting for three months. In 1945 he had a recurrence of low back pain, associated with aching pain and stiffness in his neck. At that time he began to develop a stoop. The ulcerative colitis was still active. Examination showed an upper dorsal kyphosis and rigidity throughout the spine. Chest expansion was limited to ½ in. (1.3 cm.). The right temporo-mandibular joint was also affected. *X*-ray examination showed obliteration of the sacro-iliac joints and calcification of the anterior longitudinal ligaments. These changes were regarded as typical of ankylosing spondylitis. Radiotherapy was given, but had to be discontinued as severe diarrhoea developed after a few treatments. In 1949 the symptoms of ankylosing spondylitis became more severe, and he was given a course of radiotherapy, with marked relief.

Case 2.—A man aged 50 began in 1949 to have diarrhoea with blood in his stools. This improved with treatment, and for several years he had little trouble. In 1954 he complained of pain in the right knee, followed by pain in the back. Examination showed rigidity of the thoracic and lumbar spines, and limitation of movement of the cervical spine. There was an effusion in the right knee. *X*-ray examination showed typical changes of ankylosing spondylitis, with obliteration of the sacro-iliac joints and calcification of the spinal ligaments. Erythrocyte sedimentation rate was 20 mm. in one hour. He was treated by physical methods, with improvement. One month before this was written he had a further relapse of diarrhoea, with blood, and a barium enema showed a loss of haustration involving the descending and pelvic colon. For some years this man had had diffuse psoriasis.

Case 3.—A man aged 48 complained in 1937 of diarrhoea and bloody stools. He was admitted to hospital, and ulcerative colitis was diagnosed. In 1942, while in hospital with a further attack, he first noted stiffness of his spine. Since then he has had intermittent attacks of ulcerative colitis. He also found that his neck was bending forward, and that he was unable to look up. In 1949 a diagnosis of ankylosing spondylitis was made. He was treated with deep *x*-ray therapy. Following this he developed his first attack of iridocyclitis, affecting the left eye. In 1950 he experienced a severe attack, affecting the right eye. *X*-ray examination revealed obliteration of both sacro-iliac joints, typical of ankylosing spondylitis.

Case 4.—A married woman aged 49 developed umbilical pain and vomiting eight years ago. She attended the London Hospital for investigation. A barium-meal examination revealed a filling defect in the colon. Laparotomy was performed, and a right hemicolectomy, with removal of 3 ft.