MOTOR NEUROPATHY APPEARING DURING THE COURSE OF TREATED TUBERCULOUS MENINGITIS

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Isonicotinic acid hydrazide has now been in use for over 5 years in the treatment of tuberculosis in its various forms. Many toxic effects of the drug have been reported, including a number of cases of peripheral neuritis. This paper deals with a patient suffering from tuberculous meningitis who developed a lower-motor-neurone lesion during the course of treatment. The problems to decide were, firstly, whether the neuropathy was part of the disease or was due to one of the antituberculous drugs; secondly, whether or not to continue with the antituberculous therapy.

CASE REPORT

L.T., a 40-year-old Bantu male was admitted to Baragwanath Hospital on 10 December 1954, complaining of headache and cough for the previous week. On examination he looked ill and drowsy. He was afebrile and the rest of the physical examination was negative. Two days later his headache grew worse, his temperature rose to 103°F and he developed neck rigidity. Lumbar puncture revealed slightly turbid cerebrospinal fluid; the pressure was normal and there was no intrathecal block. Chemical and microscopic examination of the fluid showed 90 polymorphonuclears and 160 lymphocytes per c.mm., protein 13 mg. %, sugar 38 mg. %, chlorides 645 mg. %. He was regarded as a case of tuberculous meningitis and treated with 1 g. of streptomycin daily by intramuscular injection, and 150 mg. of Rimifon *tds* and 3 g. of para-aminosalicylic acid 4 hourly by the mouth. On 17 December tubercle bacilli were found in the cerebrospinal fluid on direct microscopic examination.

Over the next 4 weeks the patient gradually improved and his temperature settled. His cerebrospinal fluid still showed moderate pleocytosis, but as his general condition was good he was allowed out of bed.

About a month later, i.e. 2 months after admission and while still on therapy, he complained of low back pain and weakness in the legs. On examination he showed weakness of the flexors, extensors, abductors and adductors of the thighs, and the flexors and extensors of the knees and foot. Within 10 days wasting appeared and was marked below the knees. The knee and ankle jerks disappeared and he developed bilateral foot-drop. There was no sensory loss to light touch, pinprick or temperature; vibration and position sense were intact. Electrical stimulation of the nerves gave a reaction of degeneration. The cerebrospinal-fluid findings were 4 polymorphonuclears and 50 lymphocytes

per c.mm., protein 138 mg. %, sugar 48 mg. %, chlorides 705 mg. %.

The development of neuropathy in a patient who appeared so well clinically led to a suspicion that one of the drugs might be responsible for both the neurological signs and the persistent cerebrospinal-fluid pleocytosis. Accordingly all therapy was stopped for a week. Then all 3 drugs were administered in turn for 5 days. The cerebrospinal-fluid findings were unchanged after each trial period.

It was therefore concluded that there was no sensitivity to the drugs and that the pleocytosis indicated tuberculous activity. It seemed more likely that the neuropathy was a toxic effect of a drug than an expression of tuberculosis. Nevertheless it seemed to us more important to avoid recrudescence of the meningitis even if continued drug-therapy meant disabling the patient. We decided to give streptomycin and Rimifon with large doses of pyridoxine (150 mg. *tds*) and nicotinamide (100 mg. *tds*) as suggested by McConnel and Cheetham[1] and Biehl and Vilter.[2] On this regime, combined with physiotherapy, there was a gradual improvement in the patient's condition. At the end of 6 months he had little residual weakness, but his tendon jerks were still absent. The cerebrospinal-fluid findings at this time were 12 lymphocytes per c.mm., no polymorphonuclears, protein 86 mg. %, sugar 58 mg. %, chlorides 745 mg. %.

DISCUSSION

This patient while receiving 3 drugs developed a motor neuropathy and the question arose whether a drug was responsible. Except for one case of acquired hypersensitivity to PAS, streptomycin and penicillin, in which there were some sensory changes associated with pyrexia and skin rashes, the reported toxic effects of PAS do not include peripheral neuritis.

Although the neurotoxic effects of streptomycin are usually confined to the 8th cranial nerve, motor effects such as external ophthalmoplegia[3,4] and hemiplegia[5] have been reported following parenteral and/or intrathecal administration. Winters[5] considers that streptomycin causes organization of the subarachnoid exudate, dissolution of fibrin, and its replacement by actively proliferating fibroblasts and chronic inflammatory cells; tuberculous arteritis is transformed into a proliferative endarterial reaction causing severe stenosis and occlusion of vessels such as the spinal arteries, or those of the basal ganglia.

The toxic effects of INH are numerous, and the neurological reactions include psychosis, convulsions, euphoria, hyperreflexia, insomnia, disturbed vision, drowsiness and peripheral neuritis.[7,8,9,10]

The peripheral neuritis due to INH seems to follow a characteristic pattern.[8] Initially there is tingling of the fingers, followed by stiffness of joints; later the calves become tender, there is severe burning pain, and finally increasing weakness of the limbs. The reflexes are exaggerated at first and later disappear. Some authors[2,7,8] consider that the patient is more likely to develop neuritis if he has previously had INH and so is 'conditioned' to the drug. The onset of neuritis is variable and may take from 1 to 17 weeks[2,7,10].

Could the polyneuritis in this case have been due to thrombosis of the anterior spinal artery, arachnoiditis or pachymeningitis caused by the tuberculous meningitis? The first seems unlikely since it is usually associated with sensory loss and the signs of an upper-motor-neurone lesion. Arachnoiditis may cause multiple adhesions in the spinal canal which prevent free movement with respiration and thus interfere with the blood supply by pulling on vessels. Sometimes the arachnoid adhesions may enclose an encysted collection of cerebrospinal fluid which presents as a tumour. In either case there is usually some degree of blockage to the flow of cerebrospinal fluid, a situation which was not encountered in this case.

Tuberculous pachymeningitis only occurs as a result of extensive infection from tuberculous osteitis, which was not present in this case.

Treatment. The important practical problem in our case was whether to continue with antituberculous drugs or not. On the one hand the patient showed evidence of an active lesion, namely a cerebrospinal-fluid pleocytosis, which could not be left untreated. On the other hand he had developed a severe disability which, for all we knew, would not improve unless INH was withdrawn. We decided to persevere with INH, but added massive doses of nicotinic acid and pyridoxine, which are alleged to minimize the toxicity on nervous tissue.[1,2]

SUMMARY

A patient suffering from tuberculous meningitis, who was treated with INH, streptomycin and PAS, developed motor polyneuritis. Although it seems possible that INH was responsible for this lesion, the drug was not withdrawn and the patient made an excellent recovery.

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