

Atypical serology in neurosyphilis

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In a previous paper, Dewhurst (in press) surveyed the incidence, course, and natural history of the neurosyphilitic psychoses by analysing the clinical histories of 91 patients whose illnesses necessitated their admission to mental hospitals between 1950 and 1965. Selection bias was avoided as only patients requiring treatment in *mental* hospitals were included. In spite of the advanced stage of the disease, and the concomitant psychosis, nearly half (44 or 48%) of them were eventually discharged from hospital. Twenty-seven (30%) have become chronic mental hospital inmates, 18 died (20%) and two were treated in other mental hospitals.

In this paper, conflicting serological reactions in blood and cerebrospinal fluid are related to clinical data and, in particular, to the effect on treatment and prognosis.

RESULTS

Full serological investigations on sera and cerebrospinal fluid were carried out on 86 patients. Ten (12%) had a positive serum Wassermann (WR), Kahn, or other test for syphilis, whereas similar examinations on cerebrospinal fluid were negative. Conversely, there were three patients (3%) whose blood serology was negative for syphilis, although their spinal fluids were positive. Both blood and cerebrospinal fluid serology gave positive reaction for syphilis in the remaining 73 patients.

(A) POSITIVE SERUM AND NEGATIVE CEREBROSPINAL FLUID In general, these patients had been treated previously, although therapy had been started too late to influence the course of the psychosis. They were admitted on account of the following psychiatric syndromes: confusional state and dementia (3), depression (2), depression with paranoid delusions and fits (4), and hypomania (1). There was a history of previous treatment in five patients. In eight patients the disease had been arrested, but two patients showed continued deterioration in spite of a normal cerebrospinal fluid.

CASE REPORTS

CASE 1 A farm labourer, aged 52, was admitted to Littlemore Hospital on the 19 May 1951 after assaulting

a boy. He was demented; his speech was slurred, and he had Argyll-Robertson pupils. There was some slight left-sided facial weakness. Reflexes were brisk in the upper limbs. The right knee jerk was absent; both ankle jerks were absent, with a left-sided plantar extensor response. He had received no previous treatment for syphilis.

On 20 May 1951 the results of WR and Kahn blood tests were positive.

On 21 May cerebrospinal fluid showed cells 1 lymphocyte/cm; globulin was positive; protein 25 mg/100 ml.; WR and Kahn negative; Lange negative.

He was diagnosed as suffering from tabo-paresis and given a total of 20 Mu soluble penicillin. Deterioration continued and he was given a further 15 Mu soluble penicillin. During the next 18 months he gradually deteriorated further. He became confused and unable to give an account of himself. On 8 August 1953 both knee and ankle jerks were absent. He was given a third course of penicillin totalling 20 Mu. He began to get gastric crises. On 30 August 1953 he had retention with overflow that was thought to be due to a neuro-pathic bladder. He was catheterized and 60 fl. oz. were removed.

On 27 August 1952 WR and Kahn blood tests were positive. Cerebrospinal fluid showed: cells 4 lymphocytes; protein 30 mg/100 ml.; Lange negative.

Gastric crises with vomiting continued. He became restless, confused, unco-operative, and refused food. Large bedsores developed on his buttocks. He died on 4 November 1953. No necropsy was carried out.

CASE 2 A woman, aged 60, was admitted on 30 May 1963 to Knowle Hospital, Fareham, having become increasingly withdrawn and depressed since she fractured her hip two years previously. She was apathetic, depressed, and occasionally expressed paranoid delusions. She was disorientated in time and place, and had several aggressive outbursts. Absent ankle jerks and sluggish knee jerks were the only abnormalities in the central nervous system. There was no previous history of anti-syphilitic treatment.

On 26 June 1963 blood tests showed WR, Kahn, and Reiter to be positive. Cerebrospinal fluid showed: cells 1 lymphocyte/cm; protein 40 mg/100 ml.; Lange negative. WR negative.

On 11 July 1963 she completed a total course of 14 Mu penicillin, but remained depressed and disorientated. Two months later she developed epileptiform seizures which became more frequent in spite of another course of penicillin. She died of bronchopneumonia on 24 February 1964. There was no necropsy.

(B) NEGATIVE BLOOD AND POSITIVE CEREBROSPINAL FLUID Of three patients with this potentially more serious serological combination two died, and one remains permanently in a mental hospital.

CASE REPORTS

CASE 1 A male journalist, aged 31, was admitted to St. Crispin's Hospital, Northampton, on 27 May 1960 with a diagnosis of schizophrenia. Six weeks previously he had been involved in a car crash, and subsequently became slow and forgetful. He was worried about his job, displayed marked lassitude, and stayed away from work. His personality changed: he began to boast and exaggerate, whereas previously he had been quiet and reserved. His behaviour became erratic, and, on one occasion, he returned home very late with his young child. The patient's father said that he discussed the possibility of having a garden on the roof of his home. There was some emotional flattening. No physical abnormalities were present.

His personal history disclosed normal schooling. He spent two years in the army. He was married with two children aged 6½ years, and 20 months. His wife was pregnant and gave birth to a third child while the patient was in hospital. There was no past history or family history of mental illness.

Investigations showed a negative Kahn.

He was treated with 10 ECT's (electric convulsion therapy) and Largactil 100 mg t.d.s. There was some improvement when he was discharged on 20 July 1960, although he remained somewhat retarded and apathetic.

On 7 April 1961 he was admitted to Northampton General Hospital after taking an overdose of Largactil in an attempted suicide pact with his wife. After emergency treatment, he was transferred to St. Crispin's Hospital, where he was found to be apathetic, lacking in insight, confused and disinterested, with marked flattening of affect. Apart from the rather flaccid muscular tone and sluggish reflexes, there were no other physical abnormalities.

He was given 10 ECT'S, and Largactil 75 mg/t.d.s., but became more confused, disorientated, withdrawn, and often incontinent. In spite of a negative serum Kahn test, the course of the patient's illness suggested an organic lesion and on 9 May 1961 a lumbar puncture was performed.

Cerebrospinal fluid showed globulin positive; protein 70 mg/100 ml.; WR positive; Lange 144 432 1000-0. He was given a total of 12 Mu soluble penicillin. On 16 May 1961 another cerebrospinal fluid specimen showed protein 80 mg/100 ml. globulin positive; chlorides 760 mg/100 ml.; Lange 555 554 3100-0. An electroencephalogram carried out on 26 June showed an abnormal record with excess beta activity consistent with general paralysis of the insane. In spite of penicillin therapy, he rapidly deteriorated and developed extensive pressure sores and moist sounds in the chest. On 21 June he began a course of erythromycin 1 g daily. Six days later he was started on achromycin 500 mg stat. and 250 mg q.d.s. Rapid deterioration indicated an extension of cerebral syphilis. On 1 July he was started

on chloromycetin 250 mg q.i.d., but died on 4 July 1961.

The cause of death was bronchopneumonia and GPI. No necropsy was performed.

CASE 2 A woman, aged 56, was admitted to St. John's Hospital, Stone, on 20 May 1957, with a diagnosis of depression. She had been apathetic, tearful, lacking in energy, and interests for the past six weeks. She woke early in the mornings and showed a moderate degree of psychomotor retardation. Admitted to suicidal urges. She had no physical abnormalities, and there was no past history or family history of mental illness.

Investigations carried out on 11 February 1958 gave negative results for WR and Kahn blood tests.

The diagnosis was depression in a woman of low intelligence.

She was given a course of seven ECTs, and was still slightly depressed and hypochondriacal when discharged on 3 July 1957. On 18 February 1958, she was readmitted to St. John's Hospital from Amersham General Hospital with a left hemiplegia. Cerebrospinal fluid showed WR and Kahn positive with Luetic Lange curve. Globulin was positive. She had been given a total of 10 Mu soluble penicillin before transfer. She was correctly orientated but had patchy memory defects, and her conversation was disjointed and rambling, stereotyped and repetitive. She complained of her husband having put her in hospital 'as a mental case', and said that he frequently beat her. Occasionally her mood became euphoric.

Investigations carried out on 4 March 1958 showed cerebrospinal fluid WR positive; cells 148 RBC/cm; protein 46 mg/100 ml.; sugar 44 mg/100 ml.; chlorides 780 mg/100 ml.; Lange 012 332 1000-0. She was discharged on 6 August 1958.

On 15 March 1959 she was readmitted to St. John's Hospital, Stone, in a state of severe depression with suicidal tendencies. She was very talkative, but was unable to give an account of her recent movements, and was childish and lacking in judgement. She remained hypochondriacal, but was able to do a simple job in the Industrial Unit. In October 1960 she had her first grand mal seizure. Her condition deteriorated and in September 1964 she was quite incapable of doing even simple jobs. She remains in hospital as a chronic patient.

CASE 3 A road worker, aged 50, was seen at the psychiatric out-patients of Northampton General Hospital on 3 February 1953. He had been well until June 1952, when he scalded his left wrist with hot tar while road repairing. Since then he had slowed down both mentally and physically. His speech was slurred, and he was apathetic and disinterested. He had been off work for two weeks, and spent his time staring into the fire. He was easily upset and worried. The provisional diagnosis was arteriosclerotic encephalopathy, in view of a history of hypertension. As his mental and physical condition deteriorated, he was admitted to St. Crispin's Hospital, Northampton, on 12 May 1953.

He was confused, disorientated, and moderately demented. On physical examination there was poor coordination and slight deafness. Deep reflexes were

diminished. The pupils were unequal—the right being larger than the left—and the reaction to light was sluggish. Blood pressure was 128/90 mm Hg. On 16 May Kahn blood test was negative.

On 18 May an unsuccessful lumbar puncture was attempted. On 1 June he had two grand mal seizures. In view of the early memory loss and the negative Kahn the diagnosis was revised to presenile dementia.

On 4 June 1957, the cerebrospinal fluid showed: cells 20/cm (lymphocytes) and 100 RBC's/cm; sugar 74 mg/100 ml.; chlorides 740 mg/100 ml.; Lange 555 544 331-00. Next day the patient appeared to have a stroke. Head and eyes were turned to the right. He was stuporous and could be aroused only by painful stimuli. Temperature was 102°. There were moist sounds in the chest. There was a moderate degree of neck stiffness. The left pupil was larger than the right and irregular in outline. Both pupils were unreactive to light, but reacted to accommodation. There was a left conjunctival haemorrhage. The fundi were normal. In the upper limbs the biceps and triceps reflexes were more brisk on the left than on the right. The supinator jerk was absent on the right, and knee and ankle jerks were absent on both sides. The plantar reflexes were flexor.

This combination of sudden pyrexia, neck stiffness, and fits suggested either subarachnoid haemorrhage or meningitis. Another lumbar puncture was performed on 6 June 1953. The cerebrospinal fluid showed cells 70/cm (lymphocytes); proteins 220 mg/100 ml.; Nonne Apelt, strong positive. Lange, 555 421 0000-0; chlorides 760 mg/100 ml.; blood sugar 87 mg/100 ml.; Kahn positive. On 10 June ESR was 15 mm in the first hour (Westergren); blood urea was 31 mg/100 ml.; Hb = 94% WBC 9,450/ml. On 9 June a chest radiograph showed an old fracture of the ribs, with an increased transverse diameter of the heart and aortic prominent knuckle. No lung lesions were seen.

On 5 June 1953 the patient was started on penicillin $\frac{1}{2}$ Mu q.d.s. He improved at first, but later developed moist sounds in the right lung. On 10 June his general condition deteriorated in spite of penicillin, and he ran a hectic temperature. He died on 12 June 1953. There was no necropsy.

DISCUSSION

The treatment and prognosis of neurosyphilis has been greatly influenced by the writings of Dattner and his associates. Dattner and Thomas (1944) regard a normal cerebrospinal fluid cell count as a sign of inactivity of the disease and an indication that the patient has been adequately treated *irrespective of the clinical picture*. These views were later reiterated by Dattner, Thomas, and de Mello (1951) and have subsequently received widespread support, including that of Martin (1956) in Britain. There is no doubt that a normal cerebrospinal fluid cell count is one of the most important prognostic signs in most cases of neurosyphilis, but,

when the Dattner-Thomas formula is too slavishly followed in all cases of neurosyphilis and clinical data are ignored, there is a tendency to treat the cerebrospinal fluid rather than the patient. Those with normal cerebrospinal fluid may continue to deteriorate clinically, as illustrated by the first two cases in this series. This may occur, for example, in patients whose cerebrospinal fluid has returned to normal after treatment and who subsequently develop epileptic seizures. Kofman (1956) also found that some patients with neurosyphilis continued to deteriorate clinically despite having an inactive cerebrospinal fluid and a normal cell count.

Deterioration in chronic neurosyphilis has been investigated by Kral and Dörken (1953), using serological and psychological tests on 52 institutionalized patients. They found that patients with seronegative spinal fluids had a more pronounced deficit of intelligence and of personality than those in the active phase of the disease. Clinically, serologically negative patients can be further subdivided into a large group in whom there is no further progression of the disease, and a minority in whom, despite a permanently negative spinal fluid, there is a slow but definite clinical deterioration. They postulate two pathogenic factors causing deterioration in dementia paralytica. One, an inflammatory process responsible for cerebrospinal fluid abnormalities and influenced by antibiotics; the other, a longer acting factor uninfluenced by therapy and responsible for the progressive deterioration in patients with normal spinal fluid. Merritt, Putnam, and Campbell (1937) suggested that the longer acting factor causing deterioration is of a vascular nature. And Heyck (1962), who investigated blood flow in 28 cases of cerebral syphilis, found a diminished oxygen and glucose uptake in all of them.

Short, Knox, and Glicksman (1966) treated 26 patients with active neurosyphilis with the rather low total dosage of 4.8 M μ benzathine penicillin G. Cerebrospinal fluid was examined at intervals of six, 12, 18, and 24 months after treatment. They found that 10% failed to respond, although their condition was not as severe as that of patients in this series who were all psychotic. In his follow-up of 200 tabetic patients in Budapest, Orban (1957) came to the conclusion that the recommendations of Dattner and Thomas are reliable only in patients with asymptomatic neurosyphilis. In the treatment of tabes dorsalis he regards clinical factors, rather than the cerebrospinal fluid serology, as being of paramount importance.

It would seem, therefore, that a small number of patients with neurosyphilis continue to deteriorate in spite of an inactive cerebrospinal fluid picture

and a normal cell count. Rather than adopt the therapeutic nihilism of Dattner and Thomas, it is suggested that combined fever and penicillin therapy may be beneficial in these cases. Dewhurst and Todd (1965) have shown that fever significantly increases the penetration of penicillin across the blood cerebrospinal fluid barrier. The effectiveness of penicillin in the treatment of neurosyphilis depends partly upon its concentration in the spinal fluid. Any safe method of increasing the concentration of penicillin in the cerebrospinal fluid, including direct intrathecal injections or a combination of antibiotics in high doses together with cerebral vasodilators, should be tried in order to arrest deterioration.

The more potentially serious combination of negative blood serology and a positive spinal fluid has been described by Wilson (1954) as 'not very rare'. Eskuchen (1925) observed such atypical serological combinations in 33 out of 346 (9.5%) cases of neurosyphilis. More recently, Spangler, Jackson, Fiumara, and Warthin (1964) found 24 patients in whom syphilis had not been diagnosed initially because of negative blood tests. Taggart, Russell, and Price (1956) followed up 27,786 syphilitic patients, veterans of the second world war. They found that 18.8% had a positive serum, and 4.2% were doubtful. In 4.2% of patients the cerebrospinal fluid was positive or doubtful. Those with a positive serum at the time of the spinal fluid examination showed a higher percentage of abnormal spinal fluids. In doubtful cases of neurosyphilis, Lopez Ibor and Olivares (1953) suggested reactivating the spinal fluid by intrathecal injection of 5,000-30,000 u. penicillin. They obtained a positive cerebrospinal fluid by this method in two doubtful cases of tabes and one of dementia paralytica. After reporting three cases of neurosyphilis with negative treponema immobilization tests, Fluker (1965) stressed the importance of taking into consideration the clinical data and the social histories in all doubtful cases, instead of relying entirely on the serological findings. The last three cases in the present series illustrate the importance of keeping the patient's history and clinical findings in mind rather than relying entirely on laboratory reports. If the clinical picture suggests the possibility of neurosyphilis then the spinal fluid should be examined, even though blood tests for syphilis are negative.

Many reports indicate that Reiter's protein complement fixation test is one of the most sensitive tests for syphilis and should be used in all doubtful cases. Sequeira (1959) showed that Reiter's test is more specific than the treponema WR reaction. This was confirmed by Wilkinson and Johnston

(1959) who compared the sera of 1,046 syphilitics. They found Reiter's test was more sensitive than either the treponema WR, the standard WR, or the treponema immobilization test. Spangler *et al.* (1964) also recommend Reiter's test and the treponema immobilization test in all doubtful cases.

The possibility of conflicting serology in neurosyphilis should be considered. In doubtful cases an early examination of the cerebrospinal fluid or the use of more sensitive tests, such as Reiter's, may confirm the diagnosis and allow treatment to begin before the disease progresses to an irreversible state.

SUMMARY

An analysis of the serological investigations on 86 patients has shown that 10 patients (11.6%) had a positive serum Kahn or WR and a negative cerebrospinal fluid test. Conversely, there were three patients (3.3%) whose blood tests were negative, whereas their spinal fluids showed strongly positive WR and Kahn tests.

The case histories of patients with conflicting serological reactions are presented.

It is suggested that Reiter's *protein* complement fixation test should be used in doubtful cases of neurosyphilis as it is more sensitive than either the standard Kahn or Wassermann. Lumbar punctures should be done early, in spite of negative findings in the serum, in any doubtful cases.

A small number of patients with neurosyphilis deteriorate clinically in spite of a normal cell count in the spinal fluid. It is suggested that such patients be treated more vigorously, either with combined fever and penicillin or intrathecal penicillin.

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