Br J Vener Dis 1983;59:225-7

Treatment of neurosyphilis with chloramphenicol

A case report

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SUMMARY Although penicillin is the drug of choice in syphilis, treatment failures with benzathine and procaine penicillin have occurred in neurosyphilis. Patients allergic to penicillin have traditionally been treated with tetracycline but, since this drug diffuses poorly into the cerebrospinal fluid, its use in neurosyphilis is uncertain. In the case reported here, a penicillin allergic patient with general paresis of the insane was successfully treated with chloramphenicol. This drug has been used in the treatment of syphilis and achieves high concentrations in the cerebrospinal fluid. Thus chloramphenicol may be a more appropriate agent than tetracycline in treating patients with neurosyphilis who are allergic to penicillin.

Introduction

Penicillin has been the accepted treatment for syphilis since the early 1940s. The drug is efficacious, safe, and easy to administer. The dosage and route of administration in early syphilis are now well standardised and agreed on but this is not the case in neurosyphilis. Treatment failures have occurred after treatment of neurosyphilis with procaine and benzathine penicillin.[1-6] The problem becomes much more complex in the patient who is allergic to penicillin. Tetracycline or erythromycin are the drugs recommended as alternatives to penicillin but, since neither drug passes the blood brain barrier well their effectiveness in neurosyphilis is uncertain.[7]

Chloramphenicol achieves adequate concentrations in the cerebrospinal fluid (CSF) and has been used successfully in the treatment of syphilis, although recently it has fallen into disrepute.[8-12]

We report a case of general paresis of the insane which was successfully treated with chloramphenicol.

Case report

A 49 year old married heterosexual white man was admitted to hospital in June 1981 with a two month history of dizziness, loss of balance, and pain in his right knee. He also felt anxious and nervous. He had not recently taken any medication and he did not abuse alcohol or drugs. He had not had any extramarital sexual contact in the previous 10 years and gave no past history of genital ulceration or syphilis. Serological test results had been negative in 1955. His past medical history was unremarkable except for a penicillin allergy. In 1968 he had been prescribed a course of penicillin for an upper respiratory tract infection and developed urticaria, fever, and rigors several hours after administration. There was no family history of psychiatric illness or syphilis. The patient's wife could not contribute any additional history.

On physical examination he was afebrile. He appeared nervous, defensive, and suspicious and had tremulous speech. He denied many of his symptoms and refused psychiatric assessment. There was no clinical evidence of memory impairment. His pupils were equal and accommodated to light. There was no neck rigidity. Examination of the cranial nerves, cerebellar function, and sensation showed no abnormality. Tendon reflexes, including plantar responses, were symmetrically present and normal. The palmomental reflexes were bilaterally positive and there was a fine tremor of the outstretched hands. There was no lymphadenopathy, rash, cardiac murmur, or evidence of a recent genital lesion.

Laboratory investigations showed a normal blood count and no impairment of renal or hepatic function. Blood glucose, serum vitamin B_{12}, and serum folate concentrations were within normal limits but the erythrocyte sedimentation rate was increased to 44 mm/first hour. Syphilis serology

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Accepted for publication 29 January 1983

showed a rapid plasma reagin (RPR) reactive to a dilution of 1/1024 and a reactive (4+) result to the microhaemagglutination test for *Treponema pallidum* (MHA-TP) and to the fluorescent treponemal antibody-absorbed (FTA-ABS) test. Lumbar puncture showed clear, colourless CSF under normal pressure but with a lymphocytic pleocytosis and increased protein and normal glucose concentrations. CSF syphilis serology showed a reactive result to both the Venereal Disease Research Laboratory (VDRL) (1/16) and RPR (1/8) tests as well as to the FTA-ABS test (4+) (table). CSF gammaglobulins were increased to 24% (normal <12%). Bacterial and viral cultures of the CSF showed negative results. At the time of the patient's illness, serum from his wife gave negative RPR, MHA-TP, and FTA-ABS test results.

Radiological examination of the knees and chest was normal but computed tomography (CT) of the brain showed a small area of decreased density in the posterior aspect of the left basal ganglia.

Because of the patient's penicillin allergy we decided to treat him with chloramphenicol rather than to attempt desensitisation. He received chloramphenicol 1 g intravenously every six hours for 14 days. After the end of treatment his clinical condition and his CSF abnormalities improved (table); he was then discharged home.

He was readmitted three months later for reassessment complaining of weakness in his legs and an inability to cope with daily life. On examination he showed impairment of judgment and recent memory, irregular tremor of the hands, loss of facial expression, hypokinesia, and slight rigidity of all four limbs. A repeat CT scan was normal. An electroencephalogram was mildly dysrhythmic. Results of both blood and CSF serology are shown in the table. The patient was discharged without any further antimicrobial treatment. Twelve months after treatment his mental and physical conditions were stable but he was unable to return to work. Syphilis serology showed a decrease in the RPR titre to 32. Repeated attempts to admit the patient to hospital for more extensive investigations were unsuccessful.

Discussion

Since the introduction of antibiotics the incidence of neurosyphilis has fallen dramatically, and unusual forms presenting with dementia and personality changes are seen more commonly than the classical tabes dorsalis or general paresis of the insane.[13] A precise diagnosis of neurosyphilis may be difficult to establish but examination of the CSF cell count showing pleocytosis, raised protein concentration, and a reactive VDRL test result have been taken as indicators of active disease.[14] The CSF FTA-ABS test is very sensitive but used alone is not a reliable indicator of active disease, since reactivity may be caused by transudation of immunoglobulins from the serum into the CSF.

Successful treatment of neurosyphilis is most easily assessed by a rapid fall in the CSF cell count followed by a decrease in the protein concentration. The presence of antibodies in the CSF or in the blood after treatment does not indicate continuing activity of the disease provided that the VDRL and RPR titres have decreased.

Our patient clearly had symptoms and signs of general paresis of the insane with impairment of intellectual function and memory, moodiness, and lack of insight. His abnormal physical findings of tremor and tremulous speech further supported the diagnosis, which was confirmed by examination of the CSF. After treatment the quantitative dilutions in the RPR test rapidly decreased fivefold, together with a dramatic improvement of his CSF abnormalities. Failure of neurological symptoms and signs to improve does not indicate failure of treatment.[8] His past history of a penicillin allergy is unlikely to

TABLE *Results of laboratory investigations*

	Blood			*Cerebrospinal fluid*					
	RPR test titre	*MHA-TP test*	*FTA-ABS test*	*Leucocytes (×10⁶/l)*	*Glucose (mmol/l)*	*Protein (g/l)*	*VDRL test titre*	*RPR test titre*	*FTA-ABS test*
Initial admission (June 1981)									
Before treatment	1/1024	R(4+)	R(4+)	49 (80% lymphocytes)	3·55	1·05	1/16	1/8	R(4+)
After treatment	1/256	R(4+)	R(4+)	22 (predominantly lymphocytes)	3·66	0·76	1/8	1/8	R(3+)
Second admission (September 1981)	1/128	R(4+)	R(4+)	6	3·55	0·7	1/4	1/4	ND
May 1982	1/32	R(4+)							

ND = not done; R = reactive; RPR = rapid plasma reagin (test); MHA-TP = microhaemagglutination *T pallidum* (test); FTA-ABS = fluorescent treponemal antibody-absorbed (test); VDRL = Venereal Disease Research Laboratory (test).

represent a Jarisch-Herxheimer reaction, as urticaria is not a component of this reaction.[8]

To be spirocheticidal recommended treatment regimens in syphilis should maintain a serum penicillin concentration of not less than 0·031 μg/ml.[15] This concentration should also be maintained in the CSF in cases of neurosyphilis. The use of 2·4 million units benzathine penicillin does not produce adequate CSF concentrations, and treatment failures have occurred when this preparation has been used in the treatment of neurosyphilis.[15-17] This has led to the recommendation that neurosyphilis should be treated with intravenous penicillin in high doses that will achieve adequate spirocheticidal concentrations in the CSF.[15-17]

The penetration of drugs into the CSF depends on their small molecular size, little or loose binding by plasma proteins, their lipid solubility, the presence and strength of ionic charge, the concentration of the agent in the blood, and the presence of inflammation.

Tetracycline does not pass the blood brain barrier well, achievable concentrations being only 10% of those in the serum.[18] Chloramphenicol is unique in its ability to penetrate into the CSF, where the concentration in healthy subjects is 33-50% of that in the blood.[19] Chloramphenicol is lipid soluble and has low protein binding and a small molecular size. Because of the association of aplastic anaemia with chloramphenicol its use has been restricted, but this complication is rare and occurs in only about 1 in 25 000 people exposed.[19]

Although the follow up of this case was not ideal, we consider that the treatment was successful and suggest that intravenous chloramphenicol may be a more appropriate agent than tetracycline in penicillin allergic patients with neurosyphilis and should be further evaluated.

We thank Mrs A Kujda for help in the preparation of the manuscript.

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Br J Vener Dis 1983 59: 225-227
doi: 10.1136/sti.59.4.225