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Seronegative dementia paralytica: report of a case[1]

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SUMMARY Dementia paralytica may present diagnostic difficulties when routine serological test using a non-treponemal antigen is non-reactive. We present an illustrative demented patient who initially had negative VDRL test both in his serum and cerebrospinal fluid. However, the brain biopsy specimen showed active meningoencephalitis. By special staining technique, a spiral organism was found in the brain exhibiting morphology perfectly compatible with treponema pallidum. Later in the course, the VDRL became reactive in the blood but remained non-reactive in the cerebrospinal fluid. On the basis of the experience of other workers in the field and ours with this patient, we advise the use of FTA-ABS test as a screening procedure in patients with neurological problems of possible syphilitic origin. We urge further research in this field.

Dementia paralytica may present diagnostic difficulties, which increase when a routine serological test for syphilis using a nontreponemal antigen yields a negative result in a patient with disease of the central nervous system. Specific treponemal tests yield more sensitive results in late syphilis; these, however, are usually done only when the initial reagin test is positive or equivocal, unless the history, clinical signs, or other evidence arouses the clinician's suspicion. Because of the negative reagin test in the patient here reported, diagnosis was delayed.

Still another problem confronts the clinician: should one take great pains to obtain a definitive diagnosis in a grossly demented patient whose disease appears irreversible? In our patient, diagnosis rested on a brain biopsy since the family demanded a tissue diagnosis to exclude the presence of familial neuropsychiatric disease.

CASE REPORT

On 13 November 1968 we first saw this 38-year-old Caucasian man who was referred to our hospital because of persistent intermittent frontal headaches for six months and a psychiatric disorder of at least 15 years' duration. From the family history, we learned that the patient's father died of complications of what was diagnosed as amyotrophic lateral sclerosis.

The patient's psychiatric problems started in the early 1950s while he was in the Army. Here he was charged for not returning a borrowed car. Later, he began to live beyond his means, exhibited grandiose behaviour, and on at least one occasion tried to commit suicide. In 1959 he disappeared from home. When he returned 10 months later he was quiet and seclusive; however he was still able to manage the farm and help his mother without great difficulty. In May 1968, the patient began to lose weight. He developed right-sided headaches which sometimes were severe and throbbing. He manifested gradual mental deterioration, and was unable to recognize his brother in August 1968. He became suspicious and claimed that his neighbour put poison in his drinking water. Subsequently he was admitted to his local hospital where he complained of a frontal, throbbing headache, which was not aggravated by coughing, sneezing, straining, or change of head position. He denied venereal disease, but readily admitted that he had had urethral stricture. At that time nothing of significance was found on physical examination nor on the neurological examination save for disturbances of cortical function. In addition his blood count, urinalysis, blood urea nitrogen, and blood sugar were normal; radiographs of the chest and skull were negative; and his electroencephalogram was slightly abnormal. A lumbar puncture was performed on 8 September 1968 and the results are listed in Table 1.

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TABLE 1

SPINAL FLUID EXAMINATION[1]

Date	*Pressure (mm CSF)*	*Cell count (/c.mm)*	*Protein (mg/100 ml.)*	*Sugar (mg/100 ml.)*	*Chloride (mg/100 ml.)*	*Colloidal gold*
1968						
8 Sept.[2]	320/280	3 polys.	62		123	0011111000
21 Nov.	70/65	15 polys. 13 lymphs.	76	62	122	
16 Dec.		0	70	55	120	0111000000
1969						
20 Feb.		0	62·5	53		1223210000
9 Apr.		0	66			1233321000

[1]Fluid was grossly clear on each occasion and dark field examinations were negative for spirochaetes. Several cultures and examinations for fungi and tubercle bacilli were also negative.
[2]Lumbar puncture was performed at the local hospital.

PHYSICAL EXAMINATION On admission to our hospital he was disorientated, his attention span was short, and his judgement and recent memory inpaired. Intellect appeared to be poor. He mumbled and frequently talked to himself. Otherwise, the physical and neurological examinations remained negative.

LABORATORY FINDINGS The haematocrit was 37% and the white cell count 13,800 per c.mm with 80% neutrophils, 13% lymphocytes, 6% monocytes, and 1% basophils. The erythrocyte sedimentation rate, fasting blood sugar, urea nitrogen, serum electrolytes, creatinine, uric acid, calcium and phosphorus levels, alkaline and acid phosphatase, protein-bound iodine, and liver function profile were all within normal limits. A routine urinalysis was negative. The urine was also negative for porphobilinogen and metachromatic granules. The urine lead excretion was 0·2 mg/l. per 24 hours and arsenic compound was not found in the hair and nails. Serial determinations of the serological reactions to syphilis were performed and the findings listed in Table 2. Several spinal punctures were done during his hospitalization and the results were as shown in Table 1. Routine radiographs of chest, skull, and upper cervical spine were unremarkable. On 19 November 1968 a lumbar pneumoencephalogram showed slight dilatation of the ventricular system and slight widening of the subarachnoid sulci indicative of mild cerebral atrophy. The electroencephalogram was normal on 15 November 1968. Normal cerebrospinal fluid dynamics were demonstrated by intrathecal radioiodinated serum albumin (RISA) and serial brain scan. An oral cholecystogram was normal. Sensory and motor nerve conduction were within normal limits.

TABLE 2

SUMMARY OF SEROLOGICAL REACTIONS

Date	*Blood*			*CSF*
	VDRL	*RPCF*	*FTA-ABS*	*VDRL*
1968				
4 Sept.	NR			
18 Nov.				NR
1969				
28 Jan.			Brain biopsy	
31 Jan.	NR			
1 Feb.	R	R		
14 Feb.			R	
19 Feb.	Started on proc. penicillin 1·2 M I.M. b.i.d.			10 days
20 Feb.				NR
24 Feb.	R	R		
7 Mar.			R	
2 Apr.	R	R		
9 Apr.				NR
23 Apr.	R (4 dils)			

R = Reactive. NR = Non-reactive

BRAIN BIOPSY On 28 January 1969 a biopsy of the right frontal lobe of the brain was performed by Dr. Robert L. White who found the arachnoidal membrane to be thickened and firm and the area of the brain visible appeared atrophic and gliotic.

Sections (two) of the brain biopsy showed meninges, cortex, and underlying white matter. The thickened meninges showed a diffuse infiltration by lymphocytes and plasma cells along with occasional macrophages containing haemosiderin (Figs. 1 and 2). Some of the blood vessels in the meninges as well as in the underlying cortex and white matter showed similar infiltration of their walls as well as a striking perivascular cuffing (Figs. 1, 3, 4). In addition, there was a marked neuronal degeneration and an increase in astrocytes and microglial cells in the cortex (Figs. 4 and 5).

A portion of the brain biopsy specimen was frozen for immunofluorescence studies. Cryostat sections were stained for treponema pallidum using an absorbed indirect fluorescent antibody technique. A spiral organism, which stained brightly, was found exhibiting perfect morphology compatible with treponema pallidum.

HOSPITAL COURSE During the entire hospital course the patient manifested severely disturbed cortical function, otherwise the examination was completely negative. Two days after the brain biopsy, the patient developed a focal seizure which was subsequently controlled by phenobarbitone. On 19 February 1969, in view of the positive serological test and the brain biopsy findings, a 10 day course of penicillin, totalling 24 million units, was given. The patient's condition remained unchanged and he was later transferred back to his local hospital.

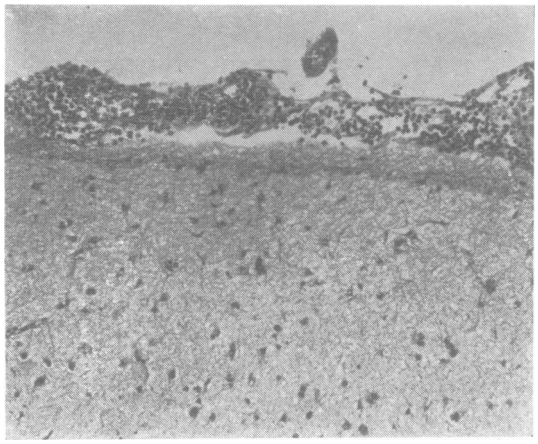

FIG. 1. *Meningeal thickening and inflammatory infiltrate. H and E, × 62.*

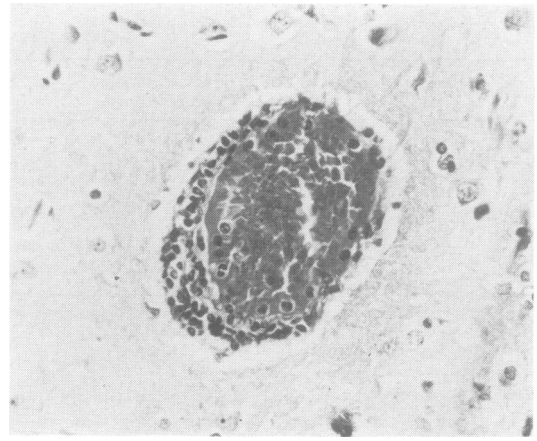

FIG. 3. *Perivascular inflammatory infiltrate in cortex. H and E, × 160.*

DISCUSSION

In the past few years there has been renewed interest in syphilis, chiefly because of the increased incidence of the disease despite the availability of modern treatment and preventive measures. It is alarming that nearly half of the recent cases occurred in teenagers and young adults, and reported cases of infectious syphilis among teenagers have increased as estimated in 1966 by more than 213% since 1956 (Olansky and Norins, 1966). We can expect to encounter more and more cases of syphilis involving the central nervous system including dementia paralytica in the younger age group.

The history of the demented patient is often unreliable or unobtainable and the cerebrospinal fluid findings often vary (Table 1). As a result, the specific clinical diagnosis of the disease has to depend heavily on the serological findings.

The different types of serological tests used as aids in the diagnosis of syphilis may be classified as non-treponemal and treponemal tests. Among the non-treponemal tests, the VDRL is one of the most commonly used tests for the detection of reagin in human serum by using non-specific

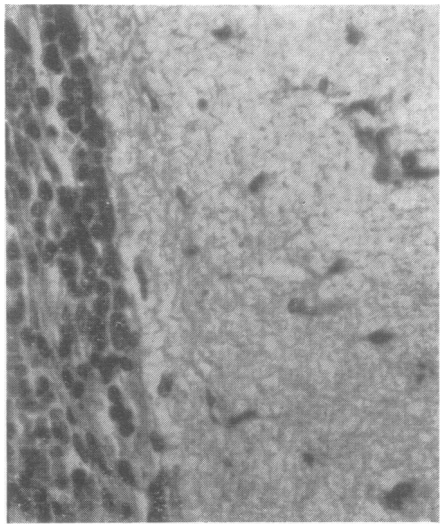

FIG. 2. *Meninges: perivascular and vascular infiltration by lymphocytes and plasma cells. H and E, × 240.*

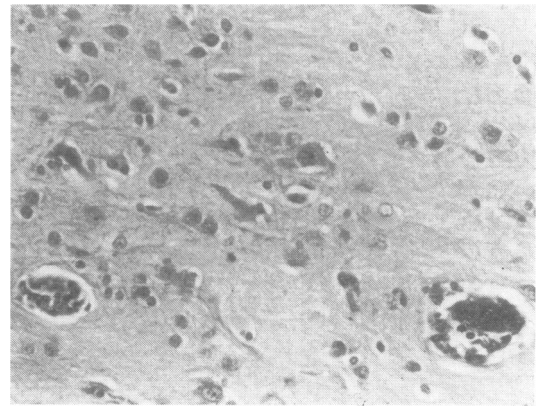

FIG. 4. *Increase in astrocytes and microglia with perivascular infiltrate. H and E, × 80.*

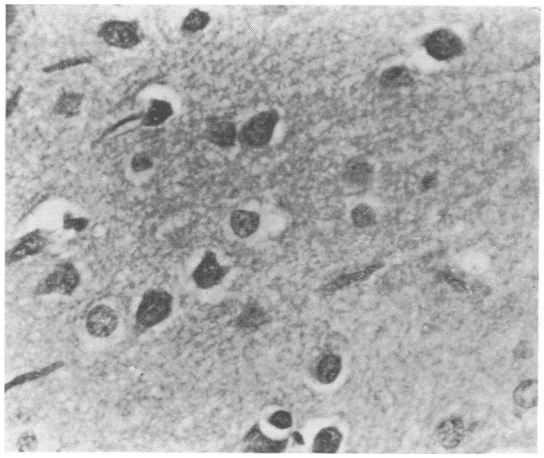

FIG. 5. *'Rod cells' and astrocytes in cortex. H and E, × 250.*

lipid antigens. In the early phases of latent syphilis (one to two years after infection) reagin titres may remain high, whereas several years later the titres are usually low. The sera of a considerable number of patients with late syphilis may be non-reactive to the non-treponemal tests (Olansky and Norins, 1966). Despite this, the test is still widely used as a screening device in many institutions including mental hospitals (Banks, 1968). For more specific purposes one must rely on tests utilizing a treponemal antigen. Treponemal tests, including TPI and FTA-ABS, are not designed for routine use. They are ordinarily reserved for diagnostic problems when requested by the clinician (Wallace, 1965). They cost more and are harder to do. However, the value of treponemal tests has been demonstrated by the remarkably uniform experience of different authors.

On evaluating the various tests for late syphilis, Huriez, Martin, and Baelden (1961) found only 77% of the TPI reactive patients had reactive VDRL tests and the findings of Wilkinson and Rayner (1966) were essentially the same—namely, only 78% of the patients with reactive TPI had detectable reagins. Harner, Smith, and Israel (1968) demonstrated that, among patients with late syphilis identified by the FTA-ABS test, only 61% were VDRL reactive. Smith and Taylor (1965) found seven patients with late syphilis whose sera were non-reactive to the VDRL and TPI tests; all seven had a reactive FTA-ABS. Tinkler (1968) reported an interesting case of a mother who had latent syphilis of long standing in whom the standard serum test for syphilis was negative. However, she gave birth to a congenital syphilitic baby. The serum FTA-ABS test, although by far the most reliable serological test for syphilis now available, is not infallible (Schroer and Civin, 1968). In fact, active neurosyphilis cannot be excluded from the differential diagnosis even if all the available serological tests are negative.

Earlier reports cast some doubts on the belief that spirochaetes may survive after penicillin therapy (Yobs, Rockwell, and Clark, Jr., 1964; Yobs, Olansky, Rockwell, and Clark, Jr., 1965). From more recent studies, it is apparent that spirochaetes can stay alive (Yobs, Clark, Jr., Mothershed, Bullard, and Artley, 1968) and late syphilis involving the central nervous system can develop in a person with initial subclinical infection or in a person whose treatment was considered adequate (Banks, 1968). Smith and Israel (1968) were able to demonstrate motile treponemes in the aqueous humor and treponemes by fluorescent-antibody staining of a liver biopsy specimen from a patient with treated tabes on whose serum the FTA-ABS, TPI, and VDRL tests were all negative. It has been estimated that as many as 10 to 33% of patients with late active syphilis may have negative cardiolipin tests, and a significant number of patients may react negatively to both treponemal and non-treponemal tests. Therefore, there is ample reason to believe that many patients with dementia paralytica have escaped detection.

In a group of penicillin-treated general paretics, an unexpected high rate of central nervous system complications with new gross neurological abnormalities was found to develop long after the initial therapy (Wilner and Brody, 1968). The effectiveness of the penicillin therapy, in this patient, is uncertain without long-term follow-up.

CONCLUSION

From the case of seronegative active meningoencephalitis reported in this communication and the experiences of other authors, we believe a non-reactive non-treponemal test result is insufficient to exclude active late syphilis. When the FTA-ABS test becomes more widely available, we advise its use as a routine screening test in addition to the reagin test in all patients with neurological problems of possibly syphilitic origin. Further research in this field is, of course, urgently needed.

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