The Neurological Complications of Brucellosis

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SUMMARY: *Neurological complications of brucellosis have seldom been reported. Typical cases of meningoencephalitis, myelitis, and peripheral nerve involvement due to brucellosis, which have been collected over the past ten years, are described. Only four cases of extradural brucellar abcesses have been published previously. We now add four new observations. A CSF electrophoresis was done in the cases of meningoencephalitis and meningomyelitis and showed a marked increased of gamma globulin. This has never been reported previously.*

RÉSUMÉ: *Les complications neurologiques de la brucellose ont rarement été rapportées ces dernières années. Des cas typiques de méningoencéphalites, myélites et de neuropathies périphériques dues à la brucellose et étudiées au cours des dix dernières années sont présentés. A date, seulement 4 cas d'abcès extraduraux secondaires à la brucellose ont été décrits dans toute la littérature; à ceux-ci, nous ajoutons maintenant 4 nouvelles observations. Une électrophorèse du liquide céphalo-rachidien fut faite dans les cas de méningoencéphalites et méningomyélites, montrant une forte augmentation de la gamma globuline; ceci n'avait jamais été rapporté jusqu'à maintenant.*

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INTRODUCTION

Neurological manifestations of brucellosis were extensively studied in earlier years, especially in centers located in endemic areas of the disease. The French schools at Montpellier and Marseilles (Roger and Poursines, 1938; Rimbaud and Janbon, 1933) and the Spanish school at Barcelona (Pedro-Pons and Ferreras-Valenti, 1944) have issued numerous publications on the subject. Fewer but well documented cases were also reported in the earlier English literature (De Jong, 1936; Nelson-Jones, 1951; Nichols, 1951; McCullough, 1958; Spink, 1956; Thomason and Poston, 1936). However, in more recent years there have been few papers on the subject, due to more rigid observance of sanitary regulations (Boughton, 1966; Debono, 1964, Finchman et al, 1963; Sahadevan et al, 1968). In this respect, it is interesting to note that a large survey of brucellosis among abattoir personnel, involving 160 cases collected in the United States between 1960 and 1972, failed to mention a single well documented neurological complication of the disease (Buchanan et al, 1974).

Another factor which could explain the paucity of reported cases is the difficulty in establishing a precise diagnosis. In most cases, the neurological complications occur many months or years after the acute systemic involvement. Seldom in such a chronic condition can the organism be recovered from body fluids. In absence of this specific requirement, Spink (1951) has enumerated three other criteria for a proper diagnosis: 1) history of exposure to the disease; 2) objective as well as subjective evidence of illness; 3) the presence of brucella agglutinins, especially in a titer of one to 100 and above. In all our cases, these criteria have been fulfilled. Further, we may add an extra criteria for the proper diagnosis: the unequivocal and rapid improvement in both the clinical condition and the brucella agglutinins titer following specific therapy.

Over the past ten years, we have been able to collect 11 cases of brucellar involvement of the nervous system. All come from Navarre, a mainly rural province of Northern Spain where brucellosis is endemic.

This report reemphasizes the wide variety of CNS manifestations produced by brucellosis. The original contribution consists in the findings of the CSF electrophoresis which showed, as in many other chronic inflammatory processes, a constant elevation of gamma globulin.

CASE REPORTS

A) Meningoencephalitis and Meningomyelitis

Case 1. This 52 years old farmer's wife was admitted for the first time in April, 1968. For the past year, she had complained of intense headaches, maximal in the nuchal region, often accompanied by nausea and vomiting. She also noted some loss of hearing and, from time to time, brief attacks of vertigo. In addition, there was evidence of asthenia, poor appetite and a weight loss of 14 kilos. It was apparent to her relatives that, in addition to a marked apathy, there was a progressive intellectual deterioration.

Since the start of her headaches, she had experienced 10 episodes of sudden onset of dysesthesia starting in the fingers of the right hand and ascending rapidly to the arm, shoulder, and right half of the face; these were associated with some speech difficulty. There was no motor involvement and no alteration of consciousness. These attacks lasted for about 2-5 minutes.

Four months prior to admission, the headaches became more frequent and intense and there was a sudden deterioration in her hearing. Two years prior to admission, she had a bout of systemic

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brucellosis: blood agglutinin titer for brucellosis done in the provincial central laboratory was 1: 2560. The dosage and duration of antibiotic therapy were unknown.

General physical examination failed to disclose any abnormal findings. Temperature and vital signs were normal. Neurological examination showed a well oriented, dull looking, and apathetic woman. There were no signs of meningeal irritation. Eye grounds were normal as were the visual fields. External ocular movement were full. No nystagmus was present. There was a moderate sensorineural hearing loss on both sides. While walking, the legs were slightly separated and there was a discrete dysmetria as well as postural deviation toward the left side. Muscle tone and power were normal as well as deep tendon reflexes. All modalities of sensation were normal.

Laboratory findings revealed a normal hemogram and a sed. rate of 8 mm. within the first hour. Blood agglutinin titer for brucellosis was 1:640. Serum protein electrophoresis and immuno electrophoresis were normal. CSF showed a WBC count of 85 (all monocytes), a glucose level at 33 mg%, and a protein level at 183 mg%. CSF agglutinin titer for brucellosis was 1:320. The CSF electrophoresis showed a marked increase in gamma globulin (see Table 1). Blood and CSF cultures were negative. Electroencephalogram (EEG) showed 3-4 c/sec polymorphous slow wave activity, registered intermittently over the left temporo-parietal region; the background activity was normal. A pneumoencephalogram was considered to be within normal limits. A left carotid angiogram disclosed diffuse spasm of all vessels; during this procedure the patient complained of a transcient episode of dysesthesia similar to the ones she experienced before. This was accompanied by some dysphasia which cleared completely within 24 hours.

She received a one month course of tetracycline 500 mg every 6 hours orally and streptomycin 1 gm B.I.D. intramuscularly for 15 days and 1 gm daily for the next 15 days. She was relieved of her headaches in a short period and there was a marked improvement in her intellectual function. At a follow-up examination 3 months later, she was free of headaches and there had been no further right-sided episodes. Her psychological status was judged to be satisfactory by her relatives. There was no improvement in her hearing, but the vertiginous attacks had stopped. However, shortly thereafter she noted some weakness in her legs. The neurological examination at that time exhibited paraparesis of a marked degree; knee and ankle strech reflexes were hyperactive, there was bilateral ankle clonus and a positive Babinski sign on both sides. At the follow-up examination 6 months later, the weakness in both lower extremities was worse and, in addition, she had difficulty with micturition and marked constipation. Repeated lumbar puncture in the recumbent position gave an opening pressure of 175 mm H_2O; the myelogram was considered to be normal. CSF contained 15 monocytes, the glucose level was 55 mg%, the protein level 122 mg%. CSF electrophoresis again revealed an increased level of gamma globulin (see Table 1). CSF agglutination titer for brucellosis was 1:40. The patient then received another course of tetracycline and streptomycin. When last seen in December 1970 (20 months later), there was no change in her spastic paraparesis. Otherwise, except for the hearing loss, there was no other evidence of CNS involvement. CSF at that time showed no cells, the glucose level was 66 mg% and the protein level was 76.5 mg%. CSF electrophoresis showed a decrease in the gamma globulin (see Table 1). Agglutinin titer for brucellosis was negative in blood and CSF.

Case 2. This 46 years old housewife was seen in October, 1968 with a 6 month history of intense progressive headaches. Recently they had been accompanied by nausea and vomiting. At the end of August, rather suddenly, she presented a state of intense agitation, incoherent language, and bouts of shouting; she also complained of excruciating diffuse headaches accompanied by frequent vomiting. She was then seen by a psychiatrist and admitted to a mental institution. She was given heavy doses of sedatives and her condition improved. She was discharged without a specific diagnosis. By the end of September, she complained of intense headaches and on the day of admission to this Center, October 9, her relatives noted a delirious state with extreme agitation and improper language. This was followed by loss of consciousness and 2 brief generalized motor seizures. Her temperature had been 39° C accompanied by chills and profuse sweating for the past two days.

Upon discovery of her high blood titer for brucellosis, the information was provided by relatives that in the previous year there were two sows which had aborted their litters. During the same period, the patient had experienced marked fatigue, arthralgia, and bouts of high fever, chills and profuse sweating for about 2 or 3 weeks at a time.

On admission temperature was 38.8° C. The patient was slightly confused and uncooperative. There was no neck stiffness. Examination of the fundi revealed bilateral papilledema. The rest of the neurological and general physical examination was normal. Skull X-rays were normal. The EEG gave a background activity at 8c/sec intermingled with 2-

TABLE 1

CSF Protein Cellulose Acetate Electrophoresis

	CASE 1			CASE 2		CASE 3	
	April 68	July 68	Dec. 70	Oct. 68	Jan. 69	June 73	July 73
Pre-albumin (%)	2.0	3.0	3.6	3.0	3.0	4.1	2.4
Albumin (%)	41.0	45.0	48.6	42.0	58.0	36.4	48.3
Alpha—1 (%)	5.5	3.0	4.6	5.0	3.0	3.4	4.7
Alpha—2 (%)	9.5	7.5	8.1	12.0	6.0	4.7	8.7
Beta—1 (%)	12.0	11.5	13.8	9.0	12.0	7.6	11.2
Beta—2 (%)	9.0	10.0	11.2	4.0	8.0	9.6	9.2
Gamma (%)	21.0	20.0	10.1	25.0	10.0	34.2	15.5
Total protein (mg/100 cc)	183.0	122.0	76.5	80.0	58.5	202.5	145.0

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3c/sec delta waves which were projected bilaterally throughout the tracing. A lumbar puncture revealed an opening pressure of 400 mm. H_2O. CSF contained 145 RBC and 170 WBC (all monocytes). The glucose level was at 38 mg% and the protein level was at 80 mg%. CSF agglutinin titer for brucellosis was 1:320. CSF protein electrophoresis demonstrated high levels of gamma globulin (see Table 1). Blood and CSF cultures were negative. The WBC count was 7,900 per cubic mm. Sed. rate was 13 mm. within 1 hr. Serum protein electrophoresis and immuno electrophoresis were normal. Blood titer for brucellosis was 1:1280. The patient was then given the usual course of tetracycline and streptomycin. Corticosteroids were added for the cerebral edema. After a week of this therapy, some improvement was noted; her behavior was normal and her headaches had decreased in intensity. No seizures were observed while she was in hospital. A CSF obtained after 2 weeks showed 84 cells (85% lymphocytes), a protein level of 74 mg%, and a glucose level of 35 mg%, brucella CSF titer was now 1:160. She had bouts of pyrexia up to 39° C until her 16th day in hospital. A pneumoencephalogram was performed on the 3rd week in hospital. It showed a great amount of air trapped in the subarachnoid space and a slight increase in the size of the ventricles, suggestive of some brain atrophy. The patient was discharged after one month in hospital, symptom free. In January, 1969, 2 months after discharge, CSF showed absence of cells, a sugar value of 58 mg%, and a protein level at 58.5 mg%. CSF electrophoresis demonstrated a decrease in the gamma globulin (see Table 1). No agglutinin for brucellosis could be detected in CSF. Three months later, there were no cells in the CSF and the values for protein and glucose were normal.

Case 3. This 47 year old farmer was admitted in June, 1973 for investigation of a progressive paraparesis. Four years previously he had been treated in another hospital for a systemic episode of brucellosis, diagnosed on the basis of a high blood agglutination titer (1:2,560). About 2 years after discharge he noted a progressive loss of strength in both legs. He also complained of difficulty with micturition and a marked degree of constipation. The paraparesis had progressed slowly but unremittingly and at the time of admission he had great difficulty in walking and was unable to climb stairs. Micturition was greatly impaired and often he had incontinence of urine.

Neurological examination showed diminished muscle strength in both legs, more so distally, with slight diffuse atrophy. Knee and ankle jerks were hyperactive and clonus could be elicited on both sides. There was a bilateral Babinski sign. All modalities of sensation were found to be normal. The white cells count was 8,800 with a normal differential; sed. rate (Westergren) was 11 mm per hour. The brucella · blood titer was 1:40. Protein electrophoresis and immuno electrophoresis were normal. EEG and radiographs of skull were normal. A myelogram was done and reported as normal. CSF contained 18 white blood cells (all lymphocytes) and had a glucose level of 50 mg% and a protein level of 202.5 mg%. CSF protein electrophoresis had a greatly increased amount of gamma globulin (see Fig. 1 and Table 1). A CSF titer of 1:16 for brucellosis was found. Blood and CSF cultures were negative for brucellosis.

The patient was treated with the usual dose of tetracycline and streptomycin for 3 weeks, corticosteroids were also added to the regimen. In the first 2 weeks, streptomycin had been given intrathecally.

On follow-up examination a month after discharge from hospital, the patient felt improved but no change in the neurological signs was noticed. CSF examination revealed a decreased amount of total protein and a negative titer for brucellosis. CSF protein electrophoresis (see Table 1) showed a decrease of gamma globulin. An additional lumbar puncture was planned but the patient was lost to follow-up.

COMMENTS

Case 1 and 2 are typical of brucellar meningoencephalitis. In both, the symptomatology started with severe protracted headaches associated with frequent nausea and vomiting; this was indicative of CNS hypertension as evidenced by the papilledema and increased pressure on manometric recording. Personality and mental changes were also prominent. In both cases, evidence of systemic infection with brucellosis was present, the longest interval between the systemic illness and the start of the neurological complaints being approximately 2 years. In most cases of neurobrucellosis, an interval of less than 1 year has been found (Nichols, 1951). Focal symptomatology in the form of a motor or sensory deficit, speech disorder, or visual field defects are common (Roger and Poursines, 1938). Various types of seizures have been described. The short paroxysmal episode, in the form of a sensory seizure as experienced by our first patient, is typical of this condition. Roger and Poursines (1938) have postulated that those attacks may be secondary to cerebral vasospasm. While we were performing a carotid angiogram the first patient experienced one of her typical focal sensory seizures; the angiogram taken at that time disclosed evidence of a diffuse vasospasm in the territory of the middle cerebral artery.

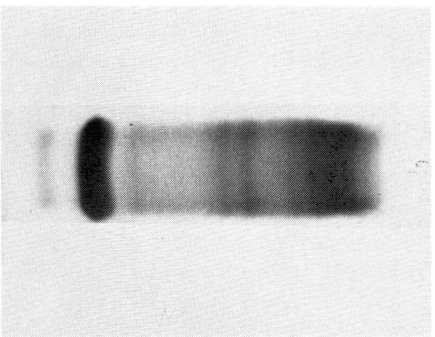

Figure 1 — Cellulose acetate electrophoresis of CSF protein showing a marked increase of the Gamma Globulin fraction. (Case 3).

Involvement of cranial nerves is frequent (Roger and Poursines, 1938; Rimbaud and Janbon, 1933; Pedro-Pons and Ferreras-Valenti, 1944; Nichols, 1951). The most commonly affected are the second, third, sixth, seventh and eighth nerves. The acoustic nerve has been described by the majority of authors as the most frequently involved, with both cochlear and vestibular functions being affected.

CSF usually shows a mild lymphocytic pleocytosis with a slight decrease of glucose, and with proteinorachia of variable degree. An increase in the agglutinins titer for brucellosis confirms the diagnosis. Cultures are rarely positive. These abnormal findings reverse to normal after appropriate therapy. A significant increase in the CSF gamma globulin was found. Neurobrucellosis should be added to the enlarging list of neurological conditions which modify the CSF immunoglobulins (Lowenthal, 1964).

Meningomyelitis, either in the course of encephalitic involvement by brucellosis as in our first case, or

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isolated as in the third case, has been reported by various authors (Roger and Poursines, 1938; Rimbaud and Janbon, 1933; De Jong, 1936; Nelson-Jones, 1951; Nichols, 1951). In a few cases the CSF has been normal. In general, the specific symptomatology appears gradually. The clinical picture is one of a spastic paraplegia with little sensory or sphincter involvement. If treated early, slow gradual improvement is the rule and there are usually few residual signs. The most likely explanation for spinal cord involvement is segmental arachnoiditis. In some cases, a limited medullary infarct secondary to a vascular lesion has been suggested (Pedro-Pons et al, 1972). Thus far, none of these hypotheses have been substantiated by pathological studies. A compressive lesion secondary to spondylitis or extradural abscess should be excluded.

B) Extradural Brucellar Granuloma

A review of the literature revealed four other cases of extradural abscess due to brucellosis (Pedro-Pons et al, 1972; Sumner, 1950; Ganado and Craig, 1958; Aguilar and Elvidge, 1961). We had the opportunity of observing four more cases; the detailed course of one of these will be given, and summaries of the others are to be found in Table 2. All these patients presented a similar clinical picture; they all recovered completely after surgical intervention and specific antibiotherapy, except for one who remained with a residual peroneal paresis.

Case 4. This 60 year old shepherd was seen for the first time in April, 1969. In August, 1967, he started complaining of lower back pain, which progressively became more intense and was aggravated by walking, sitting, or standing. There was no radiation of the pain and it was not alleviated by analgesics. Two months later, the patient had a bout of systemic brucellosis, which was substantiated by a blood agglutination titer of 1:1280. Along with the systemic manifestations of recurrent fever, malaise, etc., he also developed a left orchitis. The treatment led to some improvement of his back pain. In January, 1968, he noted a slowly progressive decrease of muscle strength in both legs and a month later started complaining of intense bilateral sciatica.

Physical examination showed a marked difficulty in walking due to excruciating sciatic pain. There was absence of the left ankle jerk and a weak right one. Hypoalgesia over the left S1 dermatome and left gluteal muscle weakness were also noted. Lasègue sign was positive on both sides. There was marked tenderness over the lumbosacral region and limited mobility of the spine.

The hemogram was normal; sed. rate was at 30 mm per hour; blood titer for brucellosis was 1:160. X-rays of the spine showed some narrowing and anterior destructive lesion at the L5-S1 junction and also some osteophytic bridging at the L3-L4 and L4-L5 levels. Radiological changes, typical of sacroiliac arthritis, were found on the right side. Frontal view of a myelogram showed a bilateral anterior extradural filling defect from L5 level downwards. The CSF contained 15 lymphocytes, with a protein level of 68 mg% and glucose level of 40 mg%. The agglutination titer for brucellosis in CSF was 1:40.

An L5-S1 laminectomy was carried out. In the left anterolateral aspect of the canal, above the S1 nerve root, a shiny yellow mass resembling a protuded disc was visualized. This was incised and a few drops of a yellowish liquid were collected; subsequent culture of this fluid was negative. On evacuation of this abscess, a hard reddish-grey granulated epidural mass was noted at the level of the left S1 nerve root. This abnormal tissue extended in the anterior extradural space, invading both L5-L1 roots. The whole mass, which contained many microabscesses, was totally resected. The L5 disc space contained similar granulation tissue, which was also extirpated. Histological examination revealed typical brucellar granuloma, characterized by a great number of macrophages with abundant eosinophilic cytoplasm and vesicular nuclei and by a few epitheloid cells surrounding necrotic tissue; the inflammatory reaction, composed mainly of lymphocytes, plasma cells and eosinophilic granulocytes, was intense. After an uneventful post-operative course, the patient went back to work, free of all symptoms.

COMMENTS

The occurrence of an extradural brucellar granuloma is rare. The question arises as to how the extradural space is invaded by the brucellar organism. In as much as we observed granulation tissue destroying the disc and occupying the intervertebral space in all four of our cases, a direct extension from a primarily infected disc is probably the best explanation. This seems more likely since there was no convincing evidence of a spondylitic infection in our cases. As previously demonstrated by Aguilar and Elvidge (1961), it seems that the brucellar organism, which has a special predilection for growth in embryonic tissue, would selectively affect the intervertebral disc in the course of a systemic infection, since this tissue is considered to be embryonic in its derivation from the notochord. This leads to the formation of a granuloma which spreads to the antero-lateral part of the dural sac, as was seen in our cases.

Other authors have suggested that the disc might be secondarily infected in continuity with a primarily involved spine. Brucellar spondylitis has been recognized frequently (Ganado and Craig, 1958; Mantle, 1955). Clinically, it is similar to tuberculous spondylitis. Cases have been described of severe compressive myelopathy secondary to destructive changes in the spine (Ganado and Craig, 1958).

C) Neuritis

Single nerve involvement due to brucellosis is more frequent and experience of such manifestations has been quite uniform. All four cases presented here consulted because of a history of sciatica. As all the cases showed clear X-ray evidence of sacroiliac arthritis, impairment of the sciatic nerves was most likely due to its continuity with the inflammatory process.

The first case is presented in some detail; the other cases are summarized in Table 3.

Case 8. This 31 year old farmer was first seen in November, 1972. He had been complaining of back pain since he fell from his tractor 3 months previously. He was then seen by a general practitionner who put him in a thoracic cast for a month. During that period, although he was relieved of the pain, he felt tired, had recurrent bouts of fever and chills, and lost about 5 kilos. A few days after the cast was taken off and the patient was allowed to resume his work, he started compalining of a typical sciatic pain in his right leg. The pain became more intense and incapaci-

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TABLE 2

Cases of Extra Dural Granuloma

Case	Sex/Age, Year	Interval After Onset of Infection	Presenting Complaints	Physical Signs	Laboratory Findings and X-rays	Findings at Surgery
5	M/29	8 months	4 month history of lower backpain radiating to R pelvic and gluteal region, severe in intensity and aggravated by standing or walking.	Acute lumbosacral pain, with antalgic position. Loss of normal lordosis and R scoliotic deviation. Positive passive straight leg raising on R side. Normal deep tendon. reflexes.	Sed. rate: 12mm per hour; CSF: no cells; glucose level: 45mg%; protein level: 66 mg%; brucellar agglutinins: 1:20; blood agglutination for brucellosis: 1:320; myelogram: large lateral filling defect behind the L5-S1 intervertebral space on the L-side.	L5-S1 laminectomy: epidural space invaded by granulation tissue containing microabscesses, filled with yellow pus, which displaced medially the L S1 root and extended itself to the anterior aspect of the dural sac. The L5-S1 disk space is also invaded by this abnormal tissue. Subsequent culture of this purulent material was negative.
6	M/39	11 months	6 month history of backpain radiating to hips and anterior aspect of both thighs.	Tenderness over lumbo sacral region and spasm of lumbar muscles. Absent L ankle jerk. Hypoesthesia over L L5 dermatome. Paresis of L peroneal muscle. Bilateral positive Lasègue signs.	Sed. rate: 54mm per hour; CSF: 18 lymphocytes; glucose level: 53mg%; protein level: 95mg%; brucellar agglutinins: 1:40; blood agglutination for brucellosis: 1:640; myelogram: complete anterior block at the level of the L4 vertebral body except for a filiform flow of pantopaque through the posteromedial aspect of the dural sac. (See Fig. 2A & B).	L4-L5 laminectomy: bilateral involvement of the L4-L5-S1 nerve roots by a hard greyish-red mass located in the anterior aspect of the dural sac. This epidural tissue contained a few microabscesses and occupied the L4-L5 intervertebral space.
7	M/29	6 months	2 month history of lower backpain radiating to left S1 matome, which became very intense for the past month and was accompanied by a temperature of 40°(C).	Severe L costovertebral angle tenderness with marked paraspinal muscle spasm. Absence of L ankle jerk. Positive Lasègue sign on L side. Hypoesthesia over L S1 dermatome.	Sed. rate: 25mm per hour; CSF: 8 lymphocytes; glucose level: 50mg%; protein level: 72mg%; brucellar agglutinins: 1:160; blood agglutination for brucellosis: 1:1,280; myelogram: L5-S1 filling defect.	L5-S1 laminectomy: S1 nerve root compressed by an epidural granulation tissue which extended itself to the anterior aspect of the dural sac bilaterally from L4 to S1 and involved the L5-S1 roots on both sides, the L S1 root being more markedly implicated. This granulation tissue contained several microabscesses and communicated with the L5-S1 intervertebral disc which was partially destroyed. Culture of the pus obtained from this tissue was negative.

tating and was clearly aggravated by physical activity. He had no further episodes of fever.

General physical examination was normal except for a slight splenomegaly. Tenderness was noted on palpation of the spinous process at the T7 level and the right sacroiliac joint. Straight leg raising was positive at 60° on the right side. The

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TABLE 3

Cases of Peripheral Neuritis

Case	Sex/Age, Year	Interval After Onset of Infection	Presenting Complaints	Physical Signs	Laboratory Findings and X-rays before Treatment	Laboratory Findings After Treatment and Follow-up
9	M/27	4 months	3 week history of L sacral pain and sciatica.	Positive Lasègue sign at 45° on L and 60° on R. Pain with pressure over L sacroiliac joint. No loss of DTR.	Sed rate: 24mm/hour; WBC: 9,300; blood agglutination for brucellosis: 1:640; normal CSF; X-rays of pelvis: signs of sacroiliac arthritis.	Sed. rate: 6mm/hour; blood agglutination: 1:60; asymptomatic.
10	M/18	6 months	1 week history of lumbar and sacroiliac pain. Bilateral sciatica. Intermittent fever.	Bilateral positive Lasègue sign. Antalgic attitude on lateral decubitus. Severe pain with pressure over both sacroiliac joints. No loss DTR.	Sed. rate: 32mm/hour; blood agglutination: 1:1280; normal CSF; X-rays of pelvis: signs of bilateral sacroiliac arthritis.	Blood agglutination: 1:160; asymptomatic.
11	M/49	3 months	3 month history of low backpain and L sciatica.	Amyotrophy and slight decrease of strength of L quadriceps. Diminished L knee jerk and both ankle jerks. Spasm of L paraspinal muscle. No Lasègue sign.	Sed. rate: 12mm/hour; WBC: 7,000; blood agglutination: 1:640; Normal CSF; X-rays of pelvis: signs of bilateral sacroiliac arthritis. X-rays of spine: normal.	Blood agglutination: 1:40; asymptomatic.

right ankle jerk was abolished and the left one diminished. There was no motor or sensory deficit. Walking provoked a limp or the right leg.

The hemogram was normal and sed. rate was at 26mm. per hour. Brucella blood titer was 1:640. A lumbar puncture revealed an opening pressure of 130mm. of CSF, which contained 1 cell and had a glucose level of 47mg% and a protein level of 28mg%. No agglutination for brucellosis was present in the CSF and the protein electrophoresis was normal. Blood and CSF cultures were negative. X-ray of the spine was normal; X-ray of pelvis showed loss of osseous contours on both sides, with widening of the sacroiliac articulations; those signs were suggestive of sacroiliac arthritis.

The patient was treated with the conventional therapy for three weeks. All the symptoms disappeared and follow-up neurological examination was entirely normal. Control sed. rate was at 4mm. per hour and brucella blood agglutination titer had dropped to 1:80.

COMMENTS

Peripheral nerve involvement is a common manifestation of neurobrucellosis (Roger and Poursines, 1938; Pedro-Pons and Ferreras-Valenti, 1944; Nelson-Jones, 1951). In general, radicular involvement is secondary to arachnoiditis. Cases of brucellar polyradiculoneuropathy with a clinical course similar to the Guillain-Barré syndrome and showing a similar albuminocytologic dissociation have been described (Roger and Poursines, 1938).

Involvement of a single nerve, without a radicular component, is a rare occurrence. Amongst these mononeuritic conditions, lesions affecting the radial or circumflex nerve have been described (Nelson-Jones, 1951; Pedro-Pons et al, 1972). However, sciatica is an exception to this observation since it has been described in most large series of neurobrucellosis. Pedro-Pons et al (1972) give four possible explanations for its development: it could be secondary to spondylitis and this may be substantiated by appropriate X-ray studies; the roots could be trapped by a hypertrophic pachymeningitis as a consequence of adhesive arachnoiditis; the sciatic nerve could also be involved in a toxic infectious process similar to an allergic neuritis; finally, as in our cases, the involvement could be due to continuity of the sciatic nerve with the inflammatory process involving the sacroiliac joints.

DISCUSSION

For many years, it has been recognized that the brucellar organism has a special neurotropic affinity. Neurological complications of brucellosis may simulate a wide spectrum of clinical conditions. The most characteristic CNS involvement of brucellosis is meningoencephalitis. In this instance CSF usually shows a moderate pleocytosis (predominantly mononuclear cells) and an increased amount of total proteins. As a rule, a positive titer for brucellosis is found in the CSF. However, cases have been described where it was low, and the diagnosis was then confirmed by a positive CSF culture (Fincham et al, 1963). In this variety of neurobrucellosis the mode of presentation of the disease may be quite variable: signs of acute intracranial hypertension, with or without meningeal irritation; an acute psychiatric condition mimicking some form of psychosis, with none or minimal positive neurological findings. Riser et al (1961) have described a large number of patients whose

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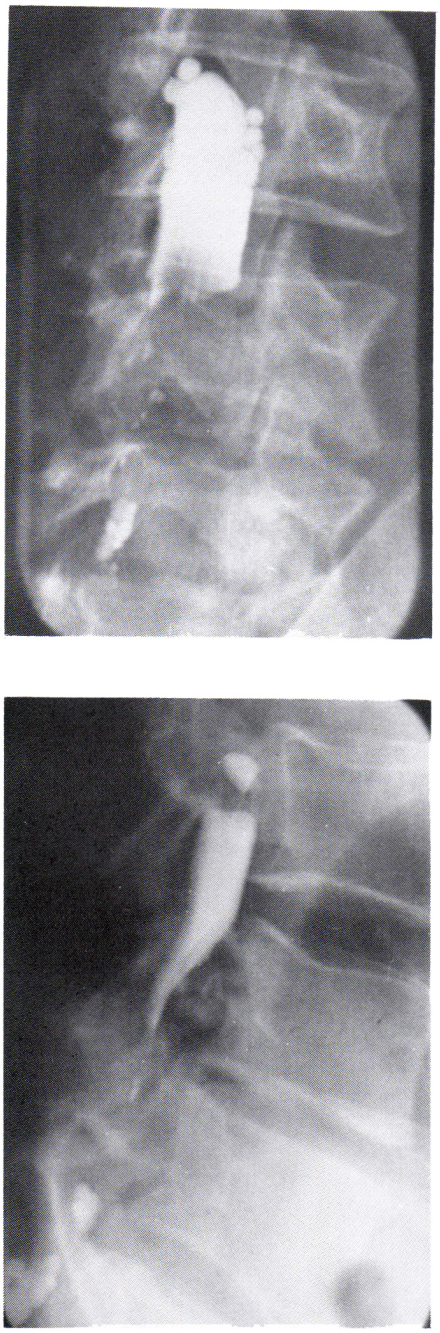

Figure 2A & B—Myelogram in a case of extradural brucellar granuloma (Case 6). Anterior and lateral views show a nearly complete extradural block at the level of the fourth lumbar vertebral body.

brucellar CNS involvement manifested itself by transitory paroxysmal episodes with Jacksonian motor or sensory seizures. They suggested these attacks were probably produced by cerebral angiospasm. Our first case favors such a pathophysiology. Other cases have been described as presenting with typical migraine attacks, some of them accompanied by visual impairment or a transitory motor or sensitive deficit.

In some large series (Roger and Poursines, 1938; Pedro-Pons and Ferreras-Valenti, 1944) cases have been observed in which permanent focal cerebral lesions were noted. These are rare complications; the nature of such lesions, although not confirmed by autopsy, was attributed to a cerebrovascular accident, or to a direct inflammatory process deep in the cerebral parenchyma, or in the superficial cortex by contiguity with the meningeal inflammation.

Impairment of a single cranial nerve, most often transient, has also been described in the course of a brucellar meningoencephalitis (Roger and Porsines, 1938). The 8th nerve seems to be the one more frequently affected. One of our cases showed such involvement. The recovery of function usually is parallel to the favorable outcome of the diffuse brain process. Rare cases of extrinsic and intrinsic ophthalmoplegia and of optic neuritis have been described (Pedro-Pons and Ferreras-Valenti, 1944).

Direct involvement of the spinal cord constitutes an infrequent complication of brucellosis (Roger, 1954) and usually occurs as a consequence of arachnoiditis. In most cases, the motor deficit appears gradually over a period of years and often after the acute CNS brucellar episode. Nevertheless, in a few cases signs of meningomyelitis, often of a fulminating nature, are present in the acute stage of the disease. The most typical picture is that of a spastic paraparesis with little sensory involvement and discrete sphincter problems.

Finally, neurobrucellosis may manifest itself with only peripheral involvement of either single or multiple roots and nerves. In a brucellar polyradiculoneuritis when the CSF shows a cyto-albuminic dissociation, the condition is indistinguishable from the Guillain-Barré syndrome (Roger and Poursines, 1938). This is, however, an exceptional presentation and a proper investigation will give the clue to the correct etiology. Contrary to this extremely rare occurrence in which the spinal roots are trapped in the greatly inflammed meninges, a root or single nerve could be involved by direct compression, either by an intervertebral disc infected with the brucellar organism (Aguilar and Elvidge, 1961), by a spondylitis (Ganado and Craig, 1958; Mantle, 1955), or as in our cases and the four other ones reported in the literature (Pedro-Pons et al, 1972; Sumner, 1950; Ganado and Craig, 1958; Aguilar and Elvidge, 1961) by an epidural granuloma. A purely neuritic involvement, without compression, is clearly illustrated by our four cases in which the sacroiliac arthritis was most likely responsible for the sciatic nerve impairment.

In as much as the clinical presentation may vary, great stress has to be put on laboratory findings in order to confirm the diagnosis. Since the direct culture of the organism is seldom realized, a correct diagnosis can be made only with a positive agglutination test. Spink (1956) considered a serum titer of 1:160 to 1:320 as being necessary for a definite diagnosis; hovever, a rising titer when the original ones are low is also significant. On the other hand, some cases, although rare, have been found with negative titers and the diagnosis was made by a positive culture (Fincham et al, 1963). In the CSF, even a low titer should always be considered suspicious.

Thus far, no cases have been published where a CSF electrophoresis was reported. We have been fortunate to discover in three of our patients with meningoencephalitis a marked elevation of gammaglobulins in the CSF. It seems, as in many other neurological conditions, that the chronic brucellar antigenic aggression provokes a peculiar CNS immunological response. Such a CSF hypergammaglobulinemia is usually seen in chronic inflammatory processes of the CNS (Lowenthal, 1964). As Cutler et al (1970) have shown, it seems most probable (and it has been clearly demonstrated in some of these clincial entities) that this increased

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production of gammaglobulin originates intrathecally. The amount of the protein is in proportion to the antigen's capacity to provoke an immunological response and to the duration of the process.

For a long time brucellosis has been diagnosed by determination of specific agglutinins in the serum, a fact which demonstrates its great capacity, similar to syphilis and to some viral processes, to induce the formation of antibodies. Thus, the CSF agglutinins encountered in the course of CNS involvement and the increase of gammaglobulin probably reflect a specific immunological mechanism of the CNS.

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