

Case study

Spinal neurobrucellosis is an unusual cause of nontraumatic paraplegia in Zaria, Northern Nigeria: A report of 3 cases and review of current literature.

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Running title: report of spinal neurobrucellosis as an unusual cause of nontraumatic paraplegia

25 SUMMARY

26 **Background and Objective:** Brucellosis is a zoonotic febrile infection common among farmers
 27 or herdsmen who come into contact with animals or animal products. Neurological
 28 complications are uncommon, but when they occur can be confused with other neurological
 29 diseases, particularly those due to tuberculosis. This report is intended to remind health workers
 30 and people living in Brucella endemic communities that spinal neurobrucellosis can mimic Potts'
 31 disease as the cause of nontraumatic paraparesis or paraplegia.

32 **Patients and materials:** We report the cases of three patients who presented with paraplegia
 33 following months of constitutional symptoms of fever, headache, malaise and weight loss. All
 34 were exposed to cows and goats and sheep. One patient had received antituberculous therapy for
 35 18 months with minimal recovery. Serology and neuroimaging were used to confirm the
 36 diagnosis.

37 **Result:** All the patients recovered within 6 to 12 weeks of rifampicin, doxycycline,
 38 trimethoprim-sulfamethoxazole or streptomycin, but with residual paraparesis.

39 **Conclusion:** spinal neurobrucellosis can be confused with Pott's disease with consequent poor
 40 treatment outcome.

41 **Keywords:** spinal neurobrucellosis, zoonosis, paraplegia, serology, neuroimaging

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48 **Introduction**

49 Brucellosis, also called Malta fever or Mediterranean fever (it was first described in Malta in the
 50 Mediterranean region) is caused by intracellular gram-negative bacteria of the genus *Brucella*. It
 51 is the most common zoonosis in the world, accounting for the annual occurrence of more than
 52 500,000 cases¹. All *Brucella* infections are caused by direct or indirect exposure to animals or
 53 animal products (e.g., milk, milk products and raw meat), although possibility of aerosolized
 54 person to person transmission exist. Human disease is caused by any four species: *Brucella*
 55 *melitensis* (affecting goats, sheep, camel); *Brucella abortus* (cattle); *Brucella suis* (pigs, hogs)
 56 and *Brucella canis* (dog). Symptoms are variable and non specific because any organ or system
 57 in the human body can be affected, but the main features are remittent fever which can be
 58 intermittent, relapsing and undulant in nature. Others are somatic symptoms of headache, body
 59 pains, night sweats, anorexia, fatigue, malaise, weight loss, and depression. The infection affects
 60 the reticuloendothelial system primarily, and the most common site is the osteoarticular sites².
 61 In endemic areas, isolation of bacteria from serum or cerebrospinal fluid (CSF) is the gold
 62 standard but appropriate serological tests such as IgG agglutination titers of >1:160 in CSF or
 63 >1:320 in serum can be diagnostic, particularly if there are rising titers in serial testing³.
 64 Treatment of neurobrucellosis entails use of triple drugs selected from rifampicin, doxycycline,
 65 gentamicin, streptomycin, trimethoprim-sulfamethoxazole and ciprofloxacin, usually for periods
 66 of 6 weeks (streptomycin) and 3 months (for others). Recovery of patients with acute
 67 neurobrucellosis is typically excellent, but prognosis of chronic neurobrucellosis is variable.
 68 Clinical improvement as well as improvement in CSF pleocytosis and fall in CSF and
 69 blood *Brucella* titers should occur after appropriate treatment. Poor outcomes are associated with
 70 complications such as raised intracranial pressure, stroke, endocarditis, intracranial mycotic

aneurysm and haemorrhage; and osteospondylitis with compressive myelopathy or radiculopathy⁴. Because acute symptoms are similar to many tropical fevers, the infection may be misdiagnosed with dire consequences. Therefore, this report is to remind physicians that neurobrucellosis is a differential diagnosis of non-traumatic paraplegia, particularly in endemic areas.

Case Reports

1. A.R, a 15 year old Fulani milkmaid, who also ingested unpasteurized milk regularly, developed intermittent fever of 5-7days intervals, profuse night sweats, anorexia, fatigue, malaise and hearing loss for 8 weeks. At the 7th week she developed insidious non- radiating band-like, low back pain, and progressive lower limb weakness culminating in paraplegia and double incontinence at the 8th week. She therefore became bedbound leading to development of multiple gluteal sores and anterior right thigh abscess. At 10th week, she presented to our centre when she developed severe tetanus of one day duration.

On examination, she was chronically ill-looking, asthenic, conscious, but febrile (temperature 38.7 °C), diaphoretic and pale. She had multiple gluteal and trochanteric ulcers discharging cheesy/putrid materials; and episodic titanic spasms with locked-jaw, trismus, opisthotonus and rigidity. She also had spastic paraplegia, bilateral extensor plantar reflexes, scoliosis, and sensory level at T12, but no obvious vertebral deformity or gibbus. She was incontinent of both faeces and urine, and had a diaper on.

She was treated with intravenous human tetanus immunoglobulins 10,000 international units (I.U) stat after a test dose, metronidazole infusions 500 mg 8 hourly, and intermittent diazepam 20-40 mg in 5% dextrose saline 8-12 hours until spasm free. She received 3 pints of packed cells

94 blood transfusion, and recovered from tetanus within 2 weeks of admission. She was also
 95 investigated for brucellosis, found positive and was treated with antibiotics. She recovered and
 96 was discharged home with residual paraparesis at 12th week of admission. The results of
 97 laboratory investigations, drug regimen and outcome of treatment are summarized in table 1.

98 2. J.N, a 13 year old student developed intermittent fever of 5-7 days intervals, headache, neck
 99 pain and loss of consciousness for 2 weeks. He was treated for (? Pyogenic) meningitis with
 100 parenteral ceftriaxole at a private hospital where he first presented; and regained consciousness
 101 after 10 days. However, the fever continued and he developed paraplegia, urinary retention and
 102 incontinence within 4 weeks of illness. There was no history of antecedent diarrhea, upper
 103 respiratory tract infection, or recent vaccination. Eight weeks later, he developed a sinus above
 104 the gluteal cleft which discharged a cheesy material. He worked in his father's animal farm
 105 which consisted of pigs, goats and sheep, but did not ingest unpasteurized milk.

106 On examination, he was fully conscious, febrile (temperature 37.6⁰ C), pale and dehydrated. He
 107 also had nuchal rigidity with positive Brudzinski and Kernig's signs, flaccid paraplegia, and loss
 108 of sensation below the knee joints (L 4 and below). There was a sinus which was discharging
 109 cheesy material from a slit-like opening above the gluteal cleft on the midline. He was
 110 incontinent of urine, but not of faeces, and there was no obvious vertebral deformity or no
 111 gibbus.

112 He was investigated for brucellosis, found positive and treated with antibiotics. Constitutional
 113 symptoms of brucellosis resolved within 2 weeks of treatment as shown by the pattern of fever at
 114 presentation and 15 days after (in figures I and II respectively), but his neurologic deficit
 115 persisted. He was instructed to continue his drug regimen for 16- 24 weeks but was discharged

on request with residual paraparesis at 12th week of therapy. He was lost to follow-up. The results of his laboratory tests, drug regimen and outcome of treatment are summarized in table 1.

3. M.D, a 56 year old man who worked as a veterinary health extension worker in Kaduna State Ministry of Agriculture and Animal resources presented with 2 years history of headache, anorexia, weight loss, fatigue and progressive lower limb weakness resulting in paraplegia and urinary incontinence. He had completed 18 months course of antituberculous therapy for suspected Pott's disease with minimal improvement. His daily routine of more than two decades was vaccination of herds of cows, sheep, goats and pigs. He never ingested unpasteurized milk. On examination, he was fully conscious, pale, afebrile and mildly wasted. He had spastic paraplegia, bilateral extensor plantar reflexes, sensory level at T10, and urinary incontinence. There were multiple vertebral deformities and gibbus.

He was put on anti-brucella therapy after investigations, and within 12 weeks muscle power in his lower limbs improved from 0/5 to 3/5. He was instructed to continue his drug regimen for 16-24 weeks, but was also lost to follow-up. The details of his laboratory results, drug regimen and outcome of treatment are summarized in table 1.

Discussion

Northern Nigeria is indigenous to herdsmen and cultures engaged in animal husbandry; and since the risk of brucellosis is proportional to the degree of contact with Brucella-infected animals, their excreta, or their edible byproducts; the disease is expected to be endemic in our environment⁵. Yet, cases of acute uncomplicated brucellosis are not commonly reported in our hospitals. Underreporting may be either because health workers are unfamiliar with the infection, or the similarities of its acute constitutional symptoms are confused with those of other tropical infectious diseases particularly malaria fever, typhoid fever and tuberculosis⁶. This may explain

139 why all 3 patients were misdiagnosed at the peripheral hospitals where they first presented before
 140 they were referred to us because of the complications they developed. Prolonged contact with
 141 animals and their edible byproducts were main risk factors for the disease in all the patients.
 142 Neurobrucellosis affecting the central (CNS) or peripheral nervous system (PNS) has been
 143 described in 3–5% of patients, with a variety of clinical manifestations and imaging
 144 abnormalities that mimic other neurologic diseases⁴. Although our patients had similar
 145 constitutional symptoms and neurological signs, the patterns and extent of spinal cord damage
 146 were different. In the first and second patients (case 1 and 2), paraplegia was due to
 147 inflammatory changes in the spinal cord (myelitis & demyelination of white matter), and spinal
 148 cord and nerve roots (myelitis, demyelination of white matter & polyradiculitis) respectively; in
 149 the third patient (case 3), osteospondylitic extraaxial compression of the spinal cord (by
 150 granuloma formation) was responsible. These lesions are said to result from direct or indirect
 151 immunological processes involving cytotoxic T lymphocytes, microglia and humoral immune
 152 activation leading. Therefore spinal neuroimaging may be show normal architecture (if lesion is
 153 early and mild), or abnormal enhancement (for inflammatory changes and demyelinating
 154 lesions)⁷.
 155 An understanding of the behavior of the humoral immune system is important in the diagnosis of
 156 brucellosis. The level of immunoglobulin M (IgM) antibodies begins to rise at the end of the first
 157 week of infection, peaks at about one month, and will remain elevated for years; even in the
 158 absence of active infection. IgA antibodies are elaborated late but may also persist for years. On
 159 the other hand, IgG antibodies begin to appear at approximately one month of infection, and
 160 begin to disappear thereafter. Therefore, persistent elevation of IgG antibodies is an indication of
 161 chronic active infection, or a relapse of the illness⁸. In our centre, we use the sera of our patients

162 against the IgG antibodies of *B melitensis* because this organism is the most common cause of
 163 human brucellosis globally.

164 Recovery of *Brucella* organisms from cultures of CSF or blood is usually very low in
 165 neurobrucellosis because the organisms are chiefly intracellular in locations, although the CSF
 166 may exhibit pleocytosis, hypoglycorrhachia, and elevation of protein concentration. The CSF
 167 findings of this disease can thus mimic those of other intracellular organisms such as
 168 mycobacteria, fungi and toxoplasma⁹.

169 Rapid diagnosis and treatment often leads to prompt and complete recovery in acute infection,
 170 but response to appropriate antibiotic is variable in chronic brucellosis. Standard treatment for
 171 adults with acute spinal brucellosis comprises capsule doxycycline 100 mg BD and tablets
 172 trimethoprim-sulphamethaxole 960 mg BD, or capsule rifampicin 600 mg for at least 12 weeks,
 173 combined during the first 3-4 weeks with IM streptomycin. Treatment is prolonged for 18-24
 174 weeks in chronic neurobrucellosis¹⁰.

175 In conclusion, neurobrucellosis is a treatable disease with a favorable outcome but the presence
 176 of complications like meningoencephalitis and myelopathy worsens the prognosis. The disease
 177 will continue to be an important health problem in developing countries except certain steps are
 178 taken to reduce its incidence. The steps must include avoidance of unpasteurized dairy products,
 179 animal contact or improperly cooked meat; regulation of abattoirs; surveillance, culling and
 180 vaccination of herds of sheep, goats, cows and pigs.

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203 Table i. Summary of Laboratory test results, drug regimen, duration of therapy and outcome.

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Investigations	Case 1	Case 2	Case 3
HIV I & II	Negative	Negative	Negative

Mantoux skin reaction	< 5 mm (negative)	< 5 mm (negative)	< 5 mm (negative)
Chest X ray	Normal	Normal	Normal
Leucocytes (normal 2-11x10 ⁹ /L)	Lymphocytic pleocytosis	Lymphocytic pleocytosis	Normal
Hemoglobin (normal 11- 16 g/dl)	6.9 (severe anemia)	10.2 (mild anemia)	14.0 (normal)
Initial Brucella abortus IgG serology	1/320	1/320	1/320
Brucella abortus IgG serology 4 weeks & 12 weeks respectively	1/16, <1/16	1/16, < 1/16	1/64, 1/16
CSF analysis *Relative to random blood sugar	Pleocytosis, markedly elevated protein, lymphocytosis, *hypoglycorrhachia		Lumbar puncture was constrained by vertebral spine deformities
CSF culture	Negative	Negative	Not done
Histopathology of cheesy material	Non caseating granuloma	Non caseating granuloma	Not applicable
Spinal MRI	Figure III(area of hyper-intensity on a segment of spinal cord)	Figure IV(areas of hyper-intensities on many segments of spinal cord & spinal nerve roots)	Not done

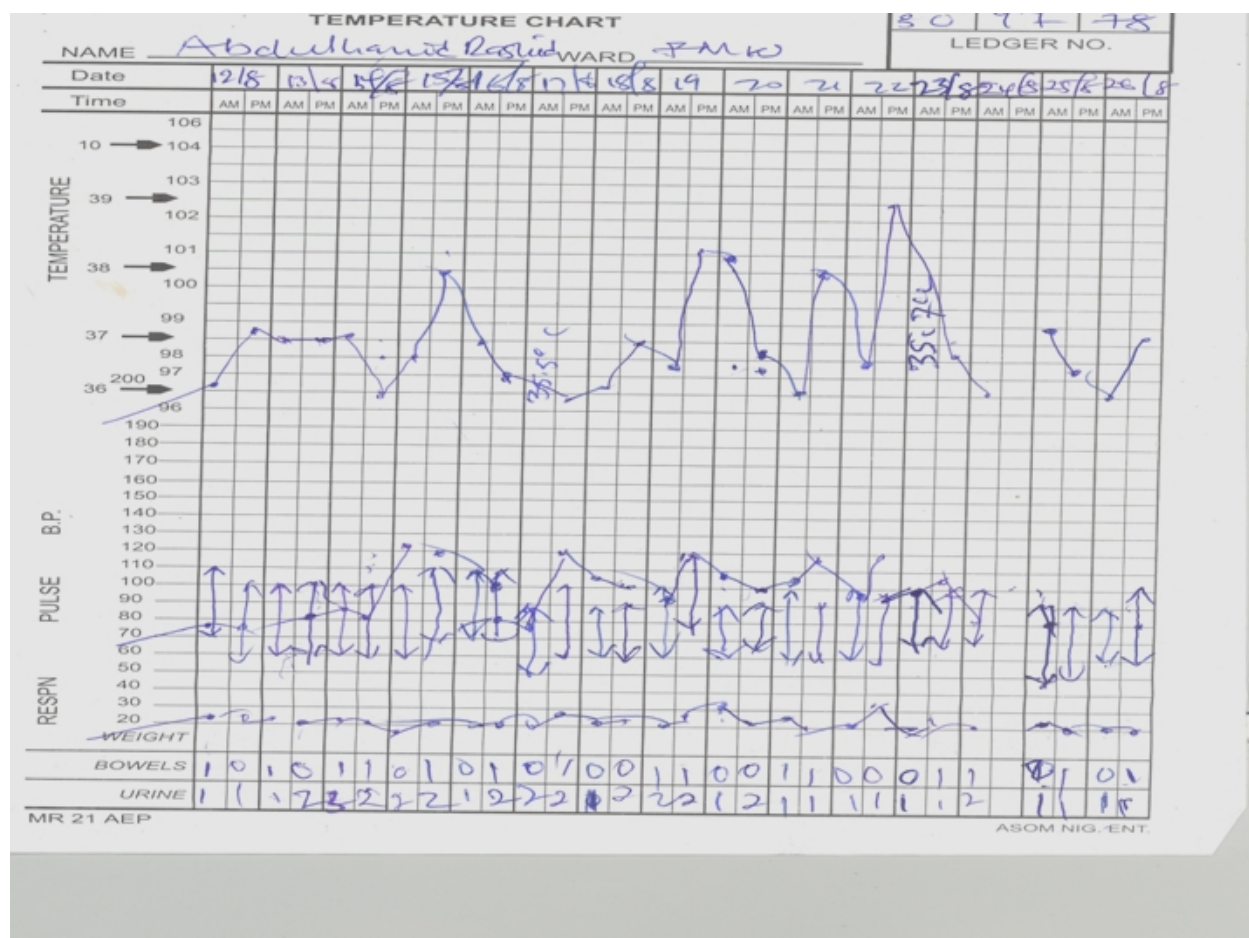
Spine vertebral X ray	Normal	Normal	Destruction of intervertebral discs and vertebral bones T12, L1, L2
Diagnosis	Transverse myelitis	Transverse myelitis and polyradiculitis	Osteospondylitic extraaxial compressive myelopathy
Drugs and duration of therapy	12 weeks of caps rifampicin 450 mg daily, doxycycline 100mg BD and tabs trimethoprim- sulphamethaxole 960 mg BD. To continue regimen for 16 weeks	Intramuscular streptomycin 750 mg daily for 4 weeks, caps rifampicin 450 mg daily for 12 weeks, and caps doxycycline 100 mg BD for 12 weeks. To continue regimen for 16-24 weeks	Intramuscular streptomycin 1 gram daily for 12 weeks, caps rifampicin 600 mg daily for 24 weeks, and caps doxycycline 100 mg BD for 24 weeks.

Outcome	Discharged home	Discharged home	Discharged home on
	on walking frame	on wheelchair	wheelchair (lower
	(lower limbs	(lower limbs	limbs muscle power
	muscle power 4/5)	muscle power 3/5)	3/5) at 12 weeks
	at 12 weeks	at 12 weeks	

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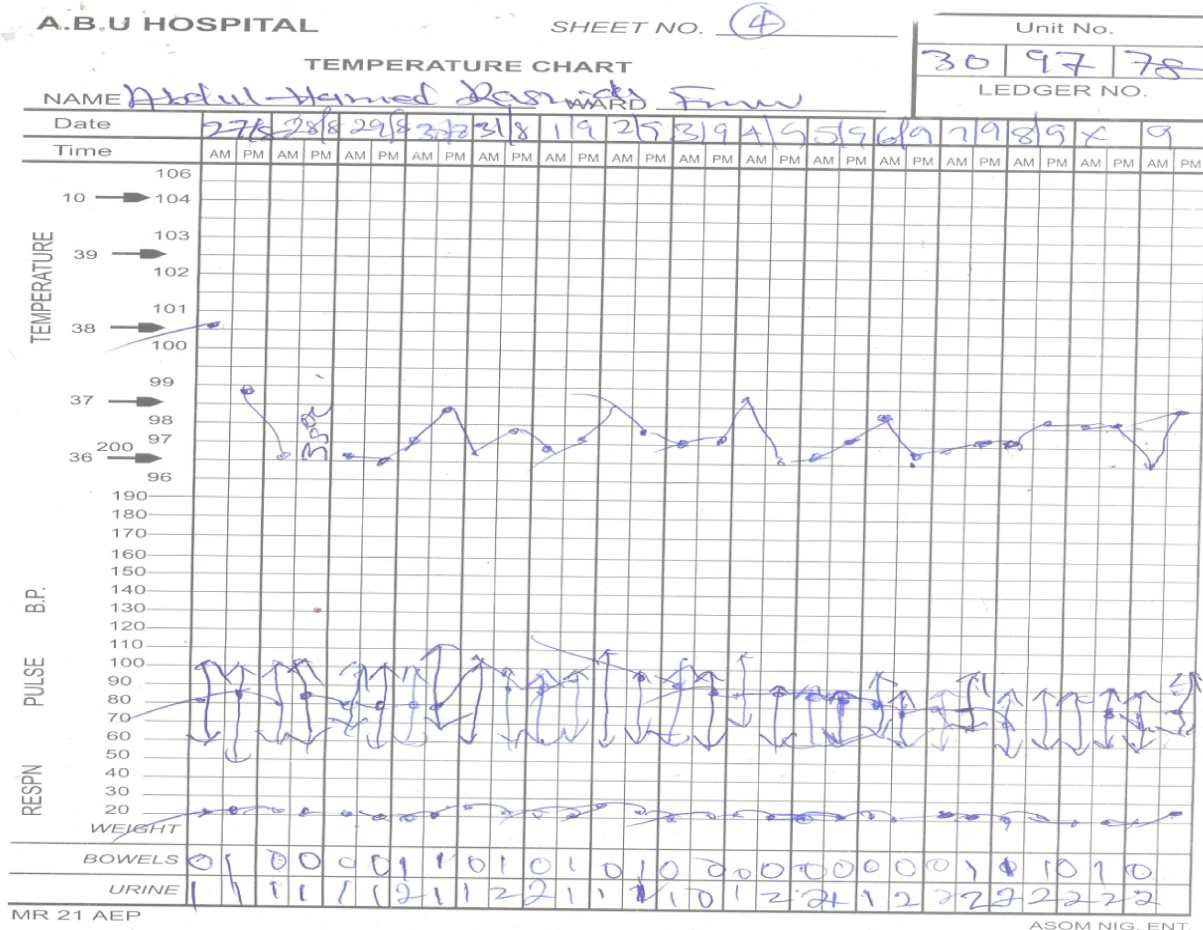
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209 Figure 1. Undulant and intermittent temperature pattern before treatment (case 2)

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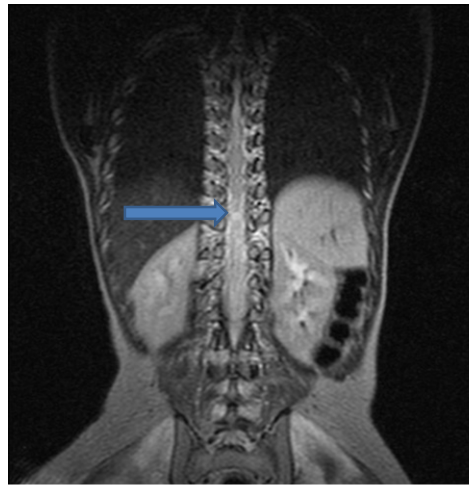


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214 Figure 2. Normal temperature pattern after 15 days of treatment (case 2)

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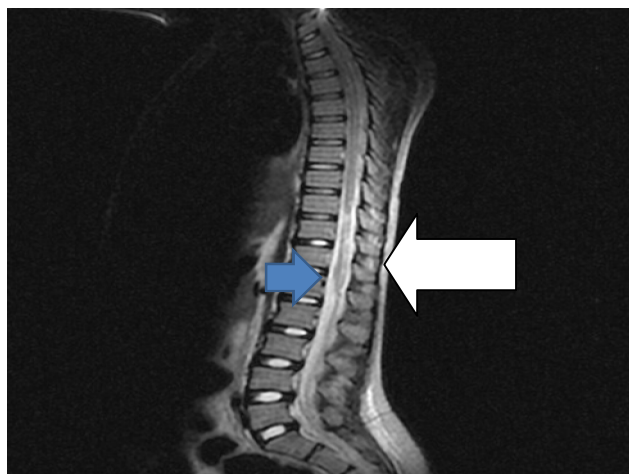
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Figure 3. Coronal view of T2 weighted spinal MRI showing area of hyperintensity on a segment of the cord.



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222 Figure 4. Sagittal view of T2 weighted spinal MRI showing areas of hyper
223 intensities on many segments of the spinal cord and spinal nerve roots
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