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Tuberculosis of the spine in the new millennium

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Abstract Tuberculosis of the spine is probably one of the earliest diseases to have affected the human race. Over the past few decades, the epidemiology, pathology, natural history and diagnostic methodology have been well studied. The multinational prospective study on the efficacy of conservative chemotherapy and surgical treatment coordinated by the Medical Research Council has just completed a final 15-year follow-up report. Although it appears from this study that conservative treatment is as effective as surgical intervention for earlier and milder

diseases, there are still reservations on the effect of such treatment at much longer follow-ups and for more severe diseases. Further developments in diagnosis using molecular genetic techniques, more effective antibiotics and more aggressive surgical protocols in the next millennium may help in solving the problems of late severe deformity and paraplegia in the debilitated immunocompromised patients.

Key words Spinal tuberculosis · Paraplegia · Deformity · Chemotherapy · Surgery

History of tuberculosis

The bacteria *Mycobacterium tuberculosis* has probably been in existence for as long as, if not longer than, the history of mankind and tuberculosis is probably one of the oldest diseases that affect the human race [7, 27, 33]. The lung is the most commonly affected organ because of the affinity of the bacteria for oxygen and the ease of airborne transmission. Before the advent of chemotherapy, pulmonary tuberculosis was the top killer, and unfortunately in this modern era this is still true in many underdeveloped countries. Tuberculosis of the spine was first described as a distinct clinical entity by Percival Pott in 1779 [30]. It is known to produce severe deformities of the spine and also different degrees of paraparesis and paraplegia from spinal cord compression. Over the past few decades, a lot of progress has been made in the management of the disease, but today at the turn of the millennium, it is time to review our achievements, or failures, and formulate the strategy for the future.

What have we achieved so far?

Epidemiology

The epidemiology of the disease is now quite well understood. Like all other infections, the prevalence is a result of the race between the virulence of the organism and the resistance of the host. It is directly related to the socioeconomic and general hygiene levels and the standard of health of the society concerned. Over the years, the virulence of the organism might not have changed, but the liberal use of antibiotics has produced more resistant strains. While the living condition of the third world is improving in general, various acquired immunodeficiency diseases resulting from steroid treatment, sexually transmitted viral infections and immunosuppressive agents are responsible for the reappearance of the disease in first world countries. The mismatch between the rising incidence and the availability of medical personnel experienced in the disease entity in these countries can be a problem. There is no

consensus on the value of BCG vaccination in changing the prevalence of the disease. It is thought that the improvement in living conditions in countries where the vaccination has been used probably has played a bigger role.

Pathology and clinical presentation

The two common sites of primary infection by tuberculosis are the respiratory and the genito-urinary systems. The spine is usually affected through lymphatic spreading of the organism when the primary site might have turned quiescent. Typically the vertebral bodies are affected with bony destruction and caseous necrosis with abscess formation. As the abscess elevates the anterior longitudinal ligament and periosteum, the disease is spread to the adjacent segments resulting in further avascular necrosis of the vertebrae and collapse. Unlike pyogenic infections, which destroy tissues by proteolytic enzymes, tuberculous infections cause destruction through a delayed hypersensitivity reaction of the body with the formation of granuloma and the typical Langerhans giant cells. The vertebral bony and intervertebral disc debris together with the abscess find their way either posteriorly into the spinal canal, causing spinal cord compression, or anteriorly, penetrating into adjacent viscera or paraspinal muscles (Fig. 1). The abscess may also discharge externally through sinus tracts and the spinal focus may then become secondarily infected by pyogenic organisms.

The clinical presentation and natural history of tuberculosis of the spine is well-described in the literature [1]. Depending on the location of the disease, the age of the patient and the number of vertebrae affected, the patient

may present with symptoms ranging from simple systemic upsets or back pain to severe spinal deformity and neurologic deficits. Less commonly, the neural tissue may become directly affected, causing pachymeningitis and meningomyelitis.

Pott's paraplegia is the most dreaded complication of spinal tuberculosis, which occurs in about 10% of patients [6, 8, 12]. It can be early in onset when the spinal cord is being compressed by debris and pus from the active disease or there is direct neural tissue involvement with meningomyelitis. Paraplegia of late disease can occur years after the acute infection, where the spinal cord may be compressed by healed bony bars, calcified caseous material, fibrosis, increasing deformity at the internal kyphus or, not uncommonly, reactivation of the disease.

Diagnosis

In experienced hands and in places where the disease is prevalent, the diagnosis is usually made on clinical grounds. Plain radiograph is still the most economical investigation. The disease typically affects the vertebral bodies with early narrowing of the disc spaces (Fig. 2). Caseous supuration elevates the anterior longitudinal ligament and spreads the disease to the adjacent vertebral bodies. In children, the anterior wall of the vertebrae may be scalloped resembling that due to an aneurysmal compression (Fig. 3). Collection of a cold abscess in the thoracic spine when viewed against a dark background of air in the lung fields produces the typical fusiform swelling on plain radiographs,

Fig. 1 Coronal magnetic resonance (MR) image of a patient with tuberculosis of the spine showing the infection, which started from the vertebral body, has ruptured into the psoas muscles bilaterally

Fig. 2 Lateral radiograph (*left*) in a case of early infection showing narrowing of the disc space with erosion and rarefaction of the adjacent vertebral endplates. The anteroposterior radiograph (*right*) shows typical fusiform paravertebral abscess

Fig.3 Lateral radiograph of the thoracolumbar spine in a child infected by tuberculosis showing anterior vertebral body scalloping resembling aneurysmal syndrome

while in the lumbar spine the abscess will produce a swelling of the psoas shadow. Multiple vertebral body involvement with collapse and preservation of the posterior elements results in an acute kyphosis. With appropriate treatment the disease may become quiescent. The kyphosis may continue to progress until bony fusion occurs, especially after secondary superimposed pyogenic infection sets in. Despite all these typical radiological findings [11], one must remember that tuberculosis is an excellent mimic and there is no single diagnostic pathognomonic sign that distinguishes it from other pathologies [2].

The tine skin test has lost its specificity in diagnosing tuberculous infection, especially in endemic areas where BCG vaccination is routine or subclinical exposure to tuberculosis is common. The identification of the *mycobacterium* bacilli with Ziehl-Neelsen staining in biopsy specimens gives the definitive diagnosis. Biopsies can now be obtained more readily through minimally invasive endoscopic techniques or under image guidance. Unfortunately, because of the typically low bacterial loads in tuberculosis of the spine, the bacteria are only identifiable in less than 50% of the cases. The polymerase chain reaction (PCR), which amplifies the *mycobacterium* DNA, is considered as a major breakthrough in the diagnosis of pulmonary tuberculosis. However, there are still limitations of this technique in extrapulmonary diseases [3, 29, 31].

Fig.4 Sagittal T2-weighted MR image (*left*) showing the infected vertebra and a sequestrum in the postero-superior corner, compressing the dura. After administration of intravenous gadolinium (*right*), the abscess is greatly enhanced, with the sequestrum signal remaining low

In the past two decades, the less invasive computerized tomography (CT) and magnetic resonance imaging (MRI) have largely replaced myelography in the assessment of spinal cord compression [13]. CT scan permits visualization of the bony configuration much better than conventional radiographs and tomograms in complex deformities. The typical rim enhancement seen on gadolinium-enhanced MR images are diagnostic of an infective lesion, and early marrow involvement of the adjacent vertebrae is also readily seen before plain radiological changes appear (Fig.4).

Treatment

The most important achievement in the treatment of tuberculosis is the introduction of combination chemotherapy, initially for pulmonary tuberculosis, consisting of streptomycin, isoniazid and rifampicin. Because of the bacteriostatic nature of these antibiotics, the treatment regime has to be continued for an extended period of time, up to 9–12 months. This has led to a high non-compliance rate amongst patients which also explains the emergence of resistant strains and late reactivation of the disease in apparently treated patients. Second-line drugs, including ethambutol and pyrazinamide, are necessary for patients with poor immuno-hematologic response or demonstrated drug-resistant bacilli strains.

In a prospective study conducted by the Medical Research Council (MRC) in Korea, it was found that isoniazid plus rifampicin for 6 or 9 months was as effective and successful as 18 months of isoniazid plus para-aminosalicylic acid or ethambutol [25]. At present, most centers

Fig.5 Lateral radiograph of the thoracolumbar junction demonstrating the anterior strut grafting with multiple ribs after a radical debridement and fusion

treating tuberculosis are adopting these shorter regimes and the results appear to be satisfactory.

The other significant contribution to the treatment of tuberculosis of the spine is the development of the anterior surgical approach to the spine first described by Ito et al. in 1934 [15] and subsequently popularized by Hodgson and Stock in 1956 [10]. The development of this surgical technique in Hong Kong was made out of necessity, because Hodgson noticed continued bony destruction despite appropriate drug treatment, and attempted posterior spinal fusion had met with many failures. Direct access to the anterior disease focus permitted complete clearance of the abscess, tissue biopsy for diagnosis and, more importantly, insertion of strut grafts under compression at the kyphus [9] (Fig. 5).

To inform the debate over the relative merits of the conservative and surgical approach to the treatment of TB spine, the Medical Research Council of the United Kingdom initiated and coordinated probably one of the most important clinical trials of the century. A series of studies was carried out from 1965 in multiple centers in the world where the disease was prevalent. The patients were carefully selected, documented and followed up for as long as 15 years prospectively. The results of these works have been published in a series of reports that every spine surgeon must read [22–24, 26]. First of all, the efficacy of in-patient complete bed rest treatment was compared with that of ambulatory out-patient treatment using conservative combination chemotherapy in Korea [17, 18, 20, 21,

Table 1 Outcome of patients treated with in-patient bed rest and out-patient ambulatory programs in Korea^a

Status at 10 years	In-patient 6 months bed rest		Out-patient ambulatory	
	No. of patients	%	No. of patients	%
Unfavorable	6	7	10	13
Favorable	73	92	70	88
Total	79		80	

^a Modified from the 9th report of the Medical Research Council Working Party on Tuberculosis of the Spine [24]

24]. This study was important in the era when the disease was so prevalent that the hospitals simply could not afford to admit all patients to the wards. The results showed that ambulatory treatment was in general as effective as in-patient bed confinement treatment, provided drug compliance was ensured (Table 1). This finding has enabled underdeveloped countries to handle the vast number of patients with their limited medical resources.

At the same time, the efficacy of surgical treatment was compared with that of conservative drug treatment. In Rhodesia, Korea and Hong Kong, patients were randomly allocated to either the drug treatment group, debridement group or radical debridement plus anterior spinal fusion group [19]. The inclusion criterion was clinical or radiological evidence of tuberculosis of any level except the cervical spine. However, patients with significant neurological deficit and who ‘cannot walk across the room’, those who had been given antituberculous drugs for more than 1 year, those who had significant extraspinal disease and, for the fusion group, those who had more than three levels of vertebral destruction were excluded from the study. All patients were given 18 months of two or three drug combination chemotherapy. In the debridement group, the abscess, the sequestrum and the loose disc fragments were removed to achieve spinal cord decompression and no fusion was performed. In Hong Kong, the radical surgery group received a radical debridement of the necrotic tissue until healthy bleeding bone was reached. This was then followed by an anterior strut graft fusion using autogenous rib, iliac or fibula grafts. The results reported at the 5-, 10- and 15-year reports indicated that all three groups achieved the same 87% favorable outcome (Table 2). For a favorable outcome, the patient should have no evidence of central nervous system involvement, no sinus or clinically evident abscess, no radiological evidence of disease activity and no restriction of normal physical activity. However, when these data are analyzed in greater detail, it was evident that the radical surgery group treated in Hong Kong did have a distinct advantage over the other two groups. There was much quicker relief of pain, earlier resolution of the sinus tracts and abscesses, and there was no neurologic involvement during treatment in this group.

Table 2 Results at 15 years treated in Korea and Hong Kong^a

	Total no. of patients	Favorable		Doubtful		Unfavorable	
		No. of patients	%	No. of patients	%	No. of patients	%
Korea							
All series	271	236	87	1	< 1	34	13
Hong Kong							
Debridement alone	54	47	87	0	0	7	13
Debridement + fusion	52	45	87	0	0	7	13

^a Modified from the 13th report of the Medical Research Council Working Party on Tuberculosis of the Spine [26]

Table 3 Bony fusion rate (%) at 18 months and 5, 10 and 13–15 years^a

	0–18 months	0–5 years	0–10 years	13–15 years
Korea				
Chemotherapy alone	15	46	73	72
Hong Kong				
Debridement alone	52	84	90	94
Debridement + fusion	85	92	97	94

^a Modified from the 13th report of the Medical Research Council Working Party on Tuberculosis of the Spine [26]

There was a much higher rate of bony fusion of 85% at 5 years, which rose to 94% at 15 years. This compared with 46% at 5 years and 72% at 15 years for the group treated conservatively in Korea (Table 3). The progression of the deformity was also different between the three groups. In the conservatively treated group, there was an increase of 21° at 5 years, which further increased to 25° at 15 years. The corresponding figures for the debridement group were 8° and 11° respectively. In contrast, the radical surgery group showed an improvement of 3° at 5 years, and this was maintained at the final 15-years follow-up assessment. It is also worth noting that in 5% of the conservative group, there was an alarming increase of kyphosis from 51° to 70°.

Based on the results of this series of studies, the Medical Research Council concluded in its 13th report [26] that:

1. Chemotherapy on an out-patient basis produces results that are not improved by supplementary interventions.
2. Conservative drug treatment, debridement alone and radical debridement and fusion all achieved similar favorable outcome in the majority of patients.
3. The excellent results at 10 years are sustained at 15 years with no late relapse or late-onset paraplegia.
4. The only advantage of radical operation is less late deformity compared with debridement.

When one re-examines the patient inclusion criterion of the MRC trial, it is obvious that only those with relatively mild diseases were recruited. For patients who have significant neurologic deficit and severe spinal deformity

from multilevel involvement, the treatment protocols may not be applicable and may not be effective. With the improvement of anesthetic techniques and the availability of surgical expertise, radical surgery together with chemotherapy has become the standard treatment except for the very mild and early cases. Posterior surgery has largely been abandoned. Early decompression provides a better chance of neurological recovery, especially for paraplegia of early onset. Solid anterior fusion avoids not only progression of deformity but also paraplegia of late disease [9].

The overall prognosis for paraplegia of late or healed disease is poor. Excision of the stony hard internal kyphosis is difficult and risky. There is a definite risk of neurologic deterioration, and the recovery time even after adequate decompression can be prolonged [14]. The experience of Hsu et al. also indicated that if the late paraplegia is due to soft compression from reactivation of disease, the prognosis would be much better.

Deformity correction

In early active disease, the deformity is usually flexible and can be quite readily corrected by anterior strut grafting. However, in late cases the kyphoses are usually severe and rigid, with compensatory hyperlordosis in the spinal segments proximally and distally [16]. In addition to the cosmetic deformity, the severe kyphosis may compromise cardiopulmonary or even abdominal visceral functions. Symptoms resulting from impingement of the rib cage on the iliac crest is sometimes an indication for correction of the deformity. The associated neurologic deficits in these patients further increase the risk of surgical correction. In Hong Kong, the halo-pelvic distraction apparatus was developed in the early 1970s, which enabled a gradual correction of the deformity while the neurologic status was being closely monitored [28, 32]. The whole process involves multiple staged surgical procedures carried out over an extended period of time. Avascular necrosis of the odontoid process, accelerated disc degeneration and spontaneous fusion are known complications at the cervical spine as a result of the prolonged distraction [4, 5]. The author recommends that these kind of surgeries should only be car-

Fig. 6A–C Serial photographs of a patient with severe kyphotic deformity of the thoracolumbar spine. **A** Preoperative, **B** during halopelvic distraction and **C** after completing correction of the deformity and circumferential fusion

ried out in specialized centers with the necessary expertise, and not by the occasional spine surgeon (Fig. 6).

What are the unsolved problems?

The timely publication of the final report by the MRC just before the end of this millennium helped summarize the achievements we have made so far in the management of tuberculosis of the spine, and marks the end of a very successful clinical trial. However, as we march into the next millennium, we know that the disease is still around and we are still faced with patients who are beyond what our present knowledge and technology can handle.

Despite the finding from the MRC trial that conservative drug treatment is as effective as surgical treatment, a constant stream of patients who were conservatively treated over 30 years ago are now presenting themselves to our hospitals with paraplegia of late disease. In an unpublished series reviewed in Hong Kong of 60 patients who had previously been treated conservatively, 25 of them developed late onset paraplegia. Over 65% of them presented with

Fig. 7 Lateral radiograph of the thoracolumbar spine of a patient who presented with paraplegia of late disease 28 years after having undergone conservative treatment for the disease. Note the severe kyphosis, the lack of solid anterior fusion and the multiple levels of vertebral body destruction

neurologic deficit more than 15 years after the onset of the initial disease. These middle-aged patients have severe kyphotic deformities and markedly compromised pulmonary function, which make them high-risk surgical candidates. Most of the kyphoses are not solidly fused, with or without disease reactivation, and the amount of bony destruction had been severe (Fig. 7). The most common presenting symptoms include a slowly progressive weakness or numbness of the lower limbs, occasional loss of urinary control or an unsteady spastic gait. If left untreated, the neurologic deficit will inevitably run a slow downhill course. The author strongly believes that the 15 years' follow-up in the MRC study is not long enough. Disease that is apparently under control by chemotherapy can still recur many years later. Myelomalacia as a result of the slow progressive compression leaves the spinal cord with very little reserve in the way of vascular supply and potential for neural recovery. By the time clinical signs of neurologic dysfunction appear, the balance is already tipped. Even if adequate decompression of the cord and rigid stabilization can be achieved, the chances of significant recovery would be low and the results are not guaranteed (Fig. 8). However, it is difficult to justify a very risky surgical procedure before the patient develops any signifi-

Fig. 8 Transverse image computed tomographic myelogram of a patient who underwent a successful anterior decompression of the internal kyphus through a costotransversectomy approach. Note the very atrophic spinal cord outlined by the contrast inside the dural sac

cant symptoms. Furthermore, there is no good way of assessing the vascular status or the degree of intrinsic damage of the very atrophic spinal cord so that treatment can be started before irreversible changes occur. Angiographic studies are technically impossible. The electroconductive property of these spinal cords are usually so poor that so-

matosensory or motor-evoked potentials are not recordable. Functional MRI mapping for the brain are not applicable for a ribbon-thin spinal cord. Further research in this area will help in deciding when is the best time to intervene. But until then, in order to avoid getting into this unresolvable situation, one should be more aggressive in the treatment of even the milder early diseases. One should aim at decompression and early stabilization of the infected focus by fusion of the anterior column. Deformities should be prevented and if necessary be corrected early before secondary degenerative changes occur.

Emergence of drug resistant strains of *Mycobacterium tuberculosis* is another major problem. This is further complicated if these strains infect patients immunocompromised by chronic diseases or HIV infection. It is uncertain how much longer the second-line antibiotics that we are using today will remain effective in controlling these strains.

Conclusion

Although the result of conservative drug treatment appears to be satisfactory in the first 15 years, it is obviously not maintained at the much longer follow-up. Radical surgery should be the treatment of choice, with the aim of preventing late deformity and paraplegia which can be unresolvable. Hopefully, with further development of newer vaccinations, more sensitive diagnostic methods and more potent antibiotics in the next millennium, tuberculosis can be prevented or even eradicated.

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