Review Articles

Leprosy and the anesthesiologist

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Purpose: To discuss particular aspects of leprosy (complications treatment, special population) that have implications for anesthetic management in leprous patients scheduled for surgery.

Source: MEDLINE and manual searches of relevant literature. Multiple MEDLINE searches (from 1966 onwards) were done, using LEPROSY as a common Medical Subject Heading (MeSH). Other headings used were: anesthesia, surgery, cardiovascular system, respiratory system, eye, skin, nervous system, genitalia, pathology, psychology and pregnancy. A large number of references were retrieved, but only 18 of them were relevant to our topic. Others were obtained by manual search and cross referencing.

Principal findings: Leprosy, especially lepromatous leprosy, is a systemic disease, affecting many organs and systems of the body, e.g., cardiovascular (cardiac dysautonomia), respiratory (impaired cough response, nasal obstruction), hepatobiliary (hepatitis), renal (nephritis), ocular (anesthesia), hematological (reduced red, white and platelet count) and osseous systems (bone resorption).

Conclusion: Investigation of the systems likely to be affected by leprosy (e.g., complete hemogram, liver, lung and kidney function tests, Valsalva response, assessment of ocular anesthesia) should form part of a preanesthetic check up in patients with leprosy.

Objectif : Discuter des aspects particuliers de la lèpre (traitement des complications, population spéciale) ayant des implications anesthésiques chez les patients atteints de cette maladie qui doivent subir une intervention chirurgicale.

Source : MEDLINE et des recherches manuelles dans la documentation appropriée. Des recherches multiples ont été faites dans MEDLINE (à partir de 1966) en utilisant le terme LÈPRE comme principal sujet médical commun. Les autres ont été : anesthésie, chirurgie, système cardiovasculaire, système respiratoire, yeux, peau, système nerveux, organes génitaux, pathologie, psychologie et grossesse. Du grand nombre d'articles retenus, seulement 18 d'entre eux concernaient notre recherche. On a obtenu d'autres articles par recherche manuelle et références croisées.

Constatations principales : La lèpre, en particulier la lèpre lépromateuse, est une maladie généralisée qui affecte de nombreux organes et systèmes de l'organisme, comme les systèmes cardiovasculaire (dysautonomie cardiaque), respiratoire (altération du réflexe de toux, obstruction nasale), hépato-biliaire (hépatite), rénal (néphrite), oculaire (anesthésie), hématologique (numération érythrocytaire, leucocytaire et plaquettaire réduite) et osseux (résorption osseuse).

Conclusion : Une exploration des systèmes pouvant être affectés par la lèpre (hémogramme complet, tests des fonctions hépatique, pulmonaire et rénale, épreuve de Valsalva, évaluation de l'anesthésie oculaire) devrait faire partie de l'examen préanesthésique chez les patients atteints.

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LEPROSY is a chronic granulomatous infection caused by *Mycobacterium leprae*[1] and is first of the three leading causes of severe neuropathy in developing countries.[2] Lepromatous leprosy, a disease primarily of the skin and peripheral nerves, commonly involves the superficial tissues such as skin, mucosa of the upper respiratory tract, subcutaneous portions of the nerves and the anterior chamber of the eye.[2] Nerve affliction in leprosy results in motor paralysis and sensory loss and is attributable to the affinity of the M. leprae for Schwann cells.[3] It also affects the autonomic nervous system,[4] bones, liver, kidney and endocrine glands.[5–9]

However, anesthetic implications in patients with leprosy have not been well explored. Search of the medical literature over the past 20 yr revealed only two references on the anesthetic aspects of leprosy,[10,11] whereas a large number of such patients are being operated upon for corrective and rehabilitative procedures under different kinds of anesthesia.[12,13] This paucity of the anesthesia literature on leprosy is surprising, given that leprosy is now understood as a systemic disease affecting many organs and systems that may have direct or indirect bearing for an anesthesiologist dealing with such cases. It is difficult to determine whether this is a reflection of western literature bias or the clinical impact of leprosy to the anesthesiologist is less than anticipated from theoretical concerns. This review aims at discussing the possible complications associated in patients with leprosy and their implications in the field of anesthesia.

Method

MEDLINE and manual searches of relevant literature were done. Multiple MEDLINE searches (from 1966 onwards) were done, using LEPROSY as a common Medical Subject Heading (MeSH), other MeSHs included: anesthesia, surgery, cardiovascular system, respiratory system, eye, skin, nervous system, genitalia, pathology, psychology, and pregnancy. A large number of references were retrieved but only 18 were directly relevant to our topic. Other references were obtained by manual search and cross-referencing.

TABLE I Clinical features of leprosy and factors influencing pathogenesis

1. Leprosy is characterized by one or more of the following cardinal features.
   a) Hypopigmented patches.
   b) Partial or total loss of cutaneous sensation in the affected areas (earliest sensation affected being light touch).
   c) Presence of thickened nerves.
   d) Presence of acid fast bacilli in the skin or nasal smears.
   The clinical diagnosis is not made unless at least one of the cardinal signs is present.

2. Factors influencing pathogenesis.
   a) The degree to which cell mediated immunity is expressed.
   b) The extent of bacillary spread and multiplication.
   c) The appearance of immunological reaction: lepra reaction, type I and type II.
   d) The development of nerve damage and its complications.

Epidemiology and clinical features

Leprosy is named after the Greek word 'Leper', which means 'scaly'. Modern day leprosy dates from 1873 when Hansen of Norway discovered *M.leprae*. During the middle ages, leprosy was widespread in almost all parts of the world. Thereafter, it declined slowly in European countries. For many years there was no effective remedy for leprosy. The introduction of sulphone drugs in the treatment of leprosy in 1943 marked the beginning of a new era in the field of leprosy.

The disease has a world-wide distribution but there is no uniformity in distribution of its various clinical forms. The bulk of cases occur in South East Asia, Africa and the Western Pacific.[1] In northern Europe, Hawaii, Japan, the continent of America and Venezuela, there has been a progressive "natural decline" in the incidence of indigenous leprosy.[1]

Leprosy has a global prevalence of 5.7 per 10,000 population. In India, the prevalence rate of leprosy is 2.4 per 1,000 population. India accounts for about one third of the leprosy cases in the world and has by far the greatest number of cases among individual countries.[1]

Table I shows the clinical features and the various factors influencing the pathogenesis of leprosy. We will review the various systemic involvements in leprosy along with their potential implications in the anesthetic management of patients with leprosy.

Cardiovascular system

Leprosy is a systemic disease affecting multiple organs during the bacillemic phase which occurs at one stage of the disease. Involvement of the cardiovascular system in leprosy has been reported by several authors.[14–24] Mathur *et al.* reported cases of congestive cardiac failure in leprosy patients.[16] The electrocardiographic changes in patients with lepra reaction showed ST and T wave changes in 16.66%, bundle branch block in 0.7%, extrasystoles in 3.7% and increased Q-Tc intervals in 44%.[15,17,18] The last feature suggests an increase in the rate of diastolic depolarisation.

Autonomic function is affected to varying degrees and the important manifestations of such dysfunction include orthostatic hypotension, baroreflex dysfunc-

tion and postprandial hypotension.[2,19–24] Involvement of the sympathetic nerves is manifested earlier than that of the parasympathetic nerves.[20] The cause for this has been attributed to infiltration of dorsal root ganglia and sympathetic chain by the acid fast bacilli.[3] Lepromatous and borderline patients also have considerably higher prevalence of tachycardia and arrhythmias due to cardiac dysautonomia.[20]

Patients with lepromatous leprosy have elevated high density lipoprotein cholesterol which acts as a protective factor against ischemic heart disease, but recent studies show that there are changes in the small blood vessels feeding the peripheral nerves distributed around the arteries in the epicardial adipose tissues resulting in paralytic arterial changes promoting ischemic cardiac disease.[22]

Studies in patients with lepromatous leprosy show impairment of responses to the Valsalva maneuvre, heart rate and blood pressure response to standing. These patients have hyporeactive blood pressure and heart rate response to standing[23] and Valsalva maneuvre.[3] Jain *et al.* reported abnormal Valsalva response in 8% of leprosy patients.[19] The sympathetic function of the heart is also affected, as evidenced by absence of blood pressure response of standing, sustained hand grip, and heart rate response to single large dose of intravenous atropine. Impairment of vagal function is evidenced by absence of reflex bradycardia after Valsalva maneuvre and loss of heart rate variability to deep breathing. All these are more pronounced in patients with longer duration of disease.[3,24]

Respiratory system

The respiratory system in leprosy patients is affected. Anatomical involvement of the respiratory tract includes areas frequently dealt with by anesthesiologists, i.e. nose, larynx and pharynx. The nose is a major site of lepromatous infiltration and the largest source of output of leprosy bacilli. Involvement of the pharynx in lepromatous leprosy develops later than in the nose, and is thought to originate not from direct extension from the nose but by hematogenous or lymphatic spread.[25] The most affected part tends to be the uvula. In the larynx, the site of predilection is the free margin of the epiglottis, which is the first part to be affected. Involvement of the vocal cords is a late but possible development.

Leprous patients have impaired respiratory function tests, breath holding time and response to cough.[4] These have been postulated to be the result to compromised pulmonary chemosensitive function due to blockade of vagus and sympathetic plexus.[26,27] Respiratory dysautonomia was observed in 48%[27] of the cases and patients failed to increase Peak Expiratory Flow Rate (PEFR) following adrenaline injection, presumably due to hyporeactivity of pulmonary beta-2 receptors in leprosy.

Hepatobiliary system

The liver is frequently involved in advanced lepromatous leprosy as a result of bacteremia. Bungeler,[28] in the presulphone era found hepatic changes in 251 out of 285 lepromatous patients. Hepatic involvement is much less common in tuberculoid type though small granulomata have been described.[29] The basis of the lesion described is multiple small lepromata in the periportal connective tissue. The lepra reactions might he associated with hepatitis along with Kupffer cell hyperplasia.

Nigam *et al.*[30] studied 50 cases of leprosy for clinico-biochemical and histological features pertaining to hepatobiliary system involvement. The specific granulomatous lesions suggestive of leprous hepatitis were mainly seen in lepromatous leprosy (40%), whereas, granulomata in liver were seen in all types of leprosy (70%). Some of the hepatic lesions progressed to stellate fibrosis and early cirrhotic changes (40%). Most importantly, however, functional derangement was the main feature in lepromatous cases irrespective of the extent and duration of the disease. The uniform elevation of total serum proteins was mainly due to increase in serum globulin with reversed albumin-globulin (A/G) ratio, indicating deranged hepatocyte function and hyperplasia of reticuloendothelial cells. The findings of deranged A/G ratio were confirmed in patients with lepromatous leprosy and those with lepra reaction subsequently.[31] Hyperbilirubinemia was chiefly seen in lepromatous leprosy.

Renal involvement

Renal involvement in leprosy is frequent and glomerulonephritis of all types, interstitial nephritis and arnyloidosis have all been reported mainly in lepromatous leprosy.[32–35] Grover *et al.*[36] performed kidney biopsy in 54 cases of leprosy, of which 45 were of lepromatous, four of tuberculoid arid five of borderline types. A wide range of renal pathology was found. Membranous glomerulonephritis (31.5%) was the commonest type of glomerular lesion, followed by interstitial nephritis and diffuse proliferative glomerulonephritis (22.2% each). Renal lesions were seen ire nonlepromatous types of leprosy as well. Clinically, of the 54 cases, four developed nephrotic syndrome, two presented as acute renal failure, 11 cases had microscopic hematuria and others had asymptomatic proteinuria. Blood urea was raised in nine cases (all the cases with amyloidosis, interstitial nephritis and rapidly progressive glomerulonephritis).

Rapidly progressive glomerulonephritis, presenting as acute renal failure, has been reported in lepromatous leprosy previously.[37]

Involvement of other organs and systems

EYES: The primary ocular lesions of leprosy (those directly due to the bacillus) affect all parts of the anterior chamber of the eye and, in advanced lepromatous disease, almost all patients are affected. Secondary complications follow damage to the fifth and seventh cranial nerves, causing anesthesia and ulceration, lagophthalmos, exposure keratitis and, finally, blindness. They may be seen in any form of leprosy.[38] A recent study of newly diagnosed leprosy patients in Nepal found 37% prevalence of eye lesions; 4.6% had sight-threatening lesions such as lagophthalmos, iris involvement and corneal anesthesia.[39] Blindness is usually a sequel to corneal lesions (following corneal anesthesia and lagophthalmos) and complicated cataract.[40]

BONES: Chronic osteomyelitis is a feature of the late stage of lepromatous leprosy. It is due to invasion and destruction of the bony trabeculae by lepromatous granulation tissue which is subsequently followed by fibrosis.[41,42] There is also osteoporosis and resorption of digits, a process that is exacerbated by chronic vasculitis. Infiltration of lepromatous granulation tissue also causes destruction of nasal cartilage and bone. In advanced tuberculoid leprosy, chronic nonspecific osteitis may necessitate amputation.

SKELETAL MUSCLE: Skeletal myositis may be encountered in lepromatous leprosy. This is an interstitial myositis which may produce painful nodules during leprae reactions. Superficial muscles of the limbs are commonly involved.[43] Simple neuropathic disuse atrophy of muscles is frequently seen.

ENDOCRINE GLANDS: Patients with leprosy may present with orchitis and gynecomastia. These patients have decreased plasma concentration of testosterone and raised levels of gonadotrophin.[9] Orchitis is a common complication of lepromatous infection.

OTHERS (AMYLOID): Secondary arnyloidosis is a recognized complication of lepromatous leprosy. It commonly affects the kidneys resulting in the mortality of 50% patients within one year. In non-lepromatous patients amyloidosis may occur as a complication of severe ulceration.[44]

Treatment-related aspects

Dapsone (diphenyl sulphone), a folate antagonist, has been used to control leprosy for more than 30 yr.[45] Its important adverse effects include hemolytic anemia, methemoglobinemia, agranulocytosis, hepatitis, peripheral neuropathy, psychosis and lepra-reaction. Other drugs currently used for multi-drug therapy for leprosy are rifampicin and clofazimine. Rifampicin, other than abnormal liver enzymes levels, may produce some intermittent toxic syndromes, e.g. flu syndrome, shock syndrome, and rarely thrombocytopenic purpura.[46]

Pregnancy-related aspects

Pregnancy has long been associated with the first presentation of clinical leprosy or aggravation of the existing disease. Pregnancy is also known to be a precipitating factor for both Type I and Type II reaction states of leprosy (these are acute inflammatory episodes of allergic nature: Type I is due to delayed hypersensitivity and is the main cause of nerve damage in leprosy, whereas Type II refers to erythema nodosum leprosum). Sometimes, emergency Cesarean section has to be performed due to card iotocographic pathology[47] or due to other complications such as erythema nodosum leprosum (ENL) or leprous neuropathy.[48] Hempenstall and Holland,[10] in the only published case report of anesthesia for emergency Cesarean section in a lepromatous leprosy patient, described many such problems encountered in such cases. During pregnancy, since clofazimine and rifampicin are contraindicated, their patient was put only on dapsone to which she developed a reaction with fever, hemolytic anemia and neurotropenia, leading to withdrawal of dapsone. Later, she developed pulmonary edema and still later, sudden fetal distress necessitating emergency section under regional anesthesia with combined spinal-extradural block. Their patient also had a low platelet count and a raised activated partial thromboplastin time though other tests of coagulation profile were normal.

Implications for Anesthesia

The above review shows how leprosy affects many systems of the body which are of potential relevance to the anesthesiologist (Table II). Given this background, it is surprising to find the lack of relevant literature (e.g. difficult intubation or perioperative anesthetic problem in leprous patients). In fact, only two recent publications have dealt with this issue directly.[10,11] The reasons for this lack are unclear. In any case, the basic clinicopathological findings as reported in the literature reviewed above should not be ignored.

Although most of the pronounced systemic changes are seen best in lepromatous leprosy (and hence this type of leprosy deserves the greatest concern for anesthesiologists), it must be emphasized that no particular subtype of leprosy is immune to these changes. Some of these (e.g. cardiovascular) have been associated with a longer duration of disease, but some may be seen in even new-onset leprosy (e.g. ocular changes). Drug

TABLE II Systemic changes in leprosy: implications for anesthesia and a proposed checklist of investigations

System	*Changes*	*Implications*	*Proposed investigations*
Cardiovascular	Impaired autonomic nervous function (cardiac dysautonomia); impaired myocardial contractility; cardiac ischemia	• Cardiorespiratory arrest; sudden death may occur due to failure of the heart to compensate for expected changes due to intubation and extubation and various drugs. • Hyporeactive heart rate and blood pressure response • Dysrhythmias	Cardiovascular assessment, focusing especially on cardiovascular autonomic function, e.g. Valsalva response, ECG changes to Respiration and blood pressure changes to posture and hyperventilation.
Respiratory	• Decreased cough response; respiratory dysautonomia • Nasal obstruction; vocal cord involvement	• Delayed postoperative recovery • Risk of infection • Risk of aspiration • Difficult intubation • Airway assessment	• Pulmonary function tests • Indirect laryngoscopy • Respiratory arrhythmia during sleep • Prophylaxis for aspiration
Hepatobiliary	Hepatitis (leprous or drug-induced); reversed A/G ratio	• Impaired metabolism of drugs during anesthesia	Liver function tests including A/G ratio.
Renal	Various types of glomerulo-nephritis; interstitial nephritis; renal amyloidosis	• Decreased renal clearance of drugs during anesthesia	Renal function profile
Ocular	Anesthesia and analgesia	Trauma and infection during anesthesia and surgery	Ophthalmologic examination
Hematological	Anemia; methemoglobinemia; agranulocytosis; thrombocytopenia	• Decreased oxygen carrying capacity; • impaired clotting; • postoperative infection.	Complete hemogram and coagulogram
Bones	• Osteomyelitis • Bone resorption	• Pathological fracture during positioning • Difficult nasal intubation	• History and relevant radiological investigation • Nasal patency
Neurological	Nerve damage and sexual impotence	Neurological deficit following nerve blocks, regional anesthesia.	• Neurological assessment • Electromyography

treatment in leprosy is an important consideration, especially for hematological side-effects, and a detailed drug history must always be obtained while contemplating anesthesia in these patients. Documentation of nerve damage and sexual impotence should be made prior to regional anesthesia. Spinal and epidural blockage should be used cautiously in patients with long standing disease as autonomic nervous system involvement may cause profound hypotension and problematic urinary retention.

Leprosy is a highly infectious disease of low pathogenicity.[4 9] The nasal mucosa of lepromatous cases harbour millions of M.leprae which are discharged during sneezing. The bacilli can also exit through ulcerated or broken skin of infected patients. These facts may leave implications for the anesthesiologists when such patients come for surgery or for treatment in intensive care units. Fortunately, it has been found that local application of rifampicin drops or spray destroys most of the bacilli within a short period.[50,51] This may be relevant before taking up such patients for surgery and anesthesia.

A proposed checklist (Table II) of investigations in patients with leprosy, especially of the lepromatous type, is suggested before planning surgical procedures in such patients. While not exhaustive, these should serve as guidelines to make the anesthesiologist aware of the potential challenges to be faced while dealing with the patient during and after surgery. However, it must be noted that these recommendations are based on review of the literature and not on controlled studies. Thus, the level of certainty regarding the validation status of these recommendations is low, and these may currently be accepted as Level 5 evidence (i.e. opinion of reviewer is sufficient).

Conclusion

Leprosy is a common disease in India and some other parts of the world (e.g. Africa, some Asian countries). It is likely that these patients may require anesthesia ser-

vices for various reasons, including surgical interventions. With increased immigration and global travel, leprosy is a disease more likely than before to be encountered in parts of the world where it is uncommon today. The suggested guidelines may help in the safe conduct of anesthesia in these cases. However, empirical testing of these needs to be done in future studies.

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