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Tuberculosis in children in India-II

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CHEMOTHERAPY FOR TUBERCULOSIS

Tubercle bacilli readily become resistant to the common drugs, and resistant bacilli are more likely to proliferate if they are present in the patient at the start of treatment. So always use more than one drug. The only possible exception is prophylaxis for an asymptomatic case with a normal X-ray.

CAUTION! (1) Never give intermittent (twice or thrice weekly) treatment unless every dose can be supervised by a health worker. Daily treatment is usually mandatory. (2) When you give more than one drug, give them both at the same time, so that high blood levels coincide; do not give one drug daily and the other drug less often.

THE DOSES of the commonly used drugs for daily and intermittent treatment in children and adults are:

Isoniazid (H) 5 mg/kg/24 hours if he is moderately ill and 10 mg/kg/24 hours if he is severely ill. The dose for a twice weekly course is 15 mg/kg.

CAUTION! Opinions on the dose of isoniazid vary. Some consider 10 mg/kg/24 hours too much for an Indian child and always give 5 mg.

Rifampicin (R) 10 mg/kg/24 hours, or 10 mg/kg twice weekly.

Pyrazinamide (Z) 35 mg/kg/24 hours, 75 mg/kg twice weekly or 50 mg/kg thrice weekly, is an important drug for short course treatment, so try to include it whenever it is mentioned in the regimes below.

Streptomycin (S) 10-20 mg/kg/24 hours, or 40 mg/kg twice weekly, to a total of not more than 0.75 g. Streptomycin is painful, so avoid it if you can. If you give it, inject in different places each day, because repeated injections into the same site are painful.

Ethambutol (E) 25 mg/kg/24 hours for 2 months, then 15 mg/kg/24 hours. Avoid ethambutol in younger children (under 12); they are unable to complain of the early symptoms of retrobulbar neuritis (blindness).

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Thiacetazone (T) 4 mg/kg/24 hours to a maximum Of 150 mg; unsuitable for intermittent treatment.

REGIMES for adults and children are complex, so select a suitable one and standardize your treatment. Use daily regimes if a child is severely ill, particuiarly with tuberculous meningitis, miliary tuberculosis or a tuberculous spine, and twice weekly ones if he is not so ill, as with glandular tuberculosis or the primary complex.

A daily regime if he is less severely ill: rifampicin and isoniazid for 6 to 9 months, preferably with pyrazinamide in the first month.

An intermittent treatment if he is less severely ill: twice weekly streptomycin, isoniazid, rifampicin and pyrazinamide for 2 months, followed by twice weekly streptomycin and isoniazid, or rifampicin and isoniazid, for 4 months. Alternatively, for less severly ill children, use isoniazid and rifampicin daily for a month followed by twice weekly isoniazid (15 mg/kg) with twice weekly rifampicin for 8 months.

For the more severely ill, child, especially with meningitis: daily rifampicin and isoniazid, with or without streptomycin or ethambutol for 2 months, followed by twice weekly rifampicin and isoniazid for 4 to 7 months. Give him 10 mg/kg isoniazid (see above) and also pyridoxine 5 mg/24 hours to prevent neurological toxicity. Continue for 9 months. Short course (6-month) chemotherapy is effective in tuberculous meningitis.

CAUTION! (1) lsoniazid and only one other drug such as intramuscular streptomycin are not enough if he has tuberculous meningitis. (2) If necessary give the drugs parenterally or by stomach tube. (3) When you have established his drug schedule satisfactorily, do not change it, except for weight gain (give more), or toxicity. Do not reduce it if he loses weight. If he is over 14 years old give him the adult dose. (4) Intrathecal streptomycin is now outmoded, particularly under less than ideal circumstances.

The use of steroids is controversial and they have never been properly evaluated. Some paediatricians give these if he has a high cerebrospinal fluid (CSF) pressure, severe focal signs suggesting vasculitis, or a spinal block, or if he is very ill. If you decide to use steroids, give him prednisolone 2 mg/kg/24 hours orally for 6 weeks and then gradually lower the dose.

TOXIC EFFECTS are jaundice from isoniazid, pyrazinamide and rifampicin (5% of cases in doses exceeding 12 mgkg, less common with smaller doses), which is reversible if this is stopped, and a rash from thiacetazone. If necessary, you may start the same drugs again as jaundice subsides, but be cautious about doing this with pyrazinamide.

FOLLOW UP. If he has completed an effective course of treatment the relapse rate should be low. Ask his mother to bring him back immediately if she is worried.

DIFFICULTIES WITH TUBERCULOSIS IN CHILDREN

If a mother is PREGNANT, she and her baby will be unaffected by isoniazid, rifampicin, ethambutol or pyrazinamide.

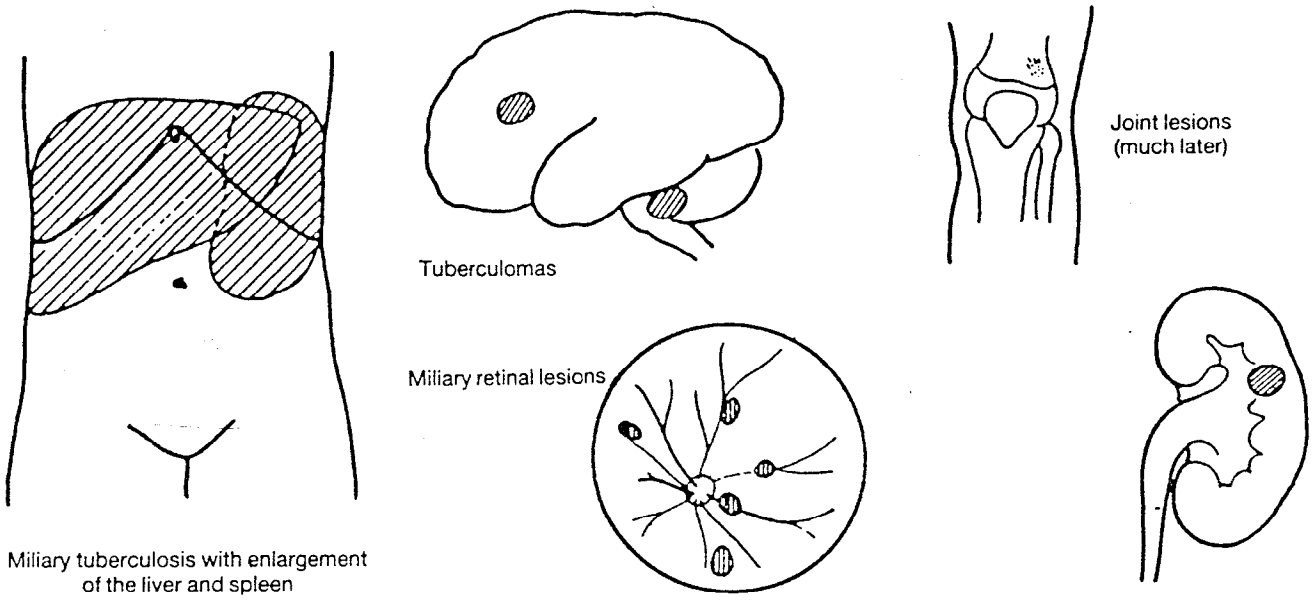

FIG. 1 Haematogenous spread

Give her short course chemotherapy, including initially pyrazinamide but avoiding streptomycin if possible. She should be sputum negative by the time the baby is born.

If he is a neonate and she is SPUTUM POSITIVE, give him isoniazid alone 5 mg/kg/24 hours for 3 months, or until she is sputum negative, followed by BCG immunization. If the active case is his mother, do not separate them, and do not interrupt breast feeding. If possible, give isoniazid resistant BCG at birth.

If he has CONGENITAL or NATAL TUBERCULOSIS (rare), it may be: (1) Pulmonary and present as an acute pneumonia; gastric aspiration will yield many bacilli. (2) Hepatic, and present as jaundice. Both require chemotherapy.

If you suspect MILIARY TUBERCULOSIS, base your diagnosis on the other features of tuberculosis combined with some or all of the following: a miliary appearance on his X-ray, a large liver and spleen, and choroidal tubercles. Give him chemotherapy and manage him as any other child with tuberculosis, if possible at home, after a few days admission if necessary for initial treatment and perhaps tube feeding.

If his LYMPH NODES ENLARGE, tuberculous lymphadenitis is one of the differential diagnoses. Search his skin in the drainage area of the node for an ulcer that might be a tuberculous skin lesion (uncommon). If necessary, and you have a good pathology service, consider a node biopsy to confirm the diagnosis. Send half the specimen for histology and half without preservative for culture. Give him chemotherapy. Do not excise enlarged nodes merely because they are large. Do not worry if his nodes enlarge temporarily during or rarely after, chemotherapy, or if they discharge. The sinuses will heal leaving a scar.

If his PHALANGES OR METATARSALS ARE THICKENED, his fingers indurated and red with limited movement, occasionally symmetrically in both his hands and feet, he may have tuberculous dactylitis (not uncommon). Take an X-ray to exclude syphilis and haemolytic anaemia; test for syphilis.

If he has DYSPNOEA (respiratory distress), suspect: (1) Progressive primary disease. (2) Pleural effusion; this is less common than in adults; his breathing is embarrassed, tap it. (3) Massively enlarged mediastinal nodes with pulmonary collapse; these should respond to chemotherapy (watch him carefully because bronchiectasis may follow). (4) Advanced miliary tuberculosis. (5) Pneumothorax.

If he has ASCITES, A PAINLESS ABDOMINAL MASS which does not respond to antihelminthics, or CHRONIC DIARRHOEA with large mucoid stools and does not respond to antihelminthics or metronidazole, suspect abdominal tuberculosis, tap and culture the fluid, and if possible, do a peritoneal biopsy.

If he has any CHRONIC OR UNUSUAL SKIN LESION that does not respond to other drugs, consider the possibility of primary tuberculosis of his skin, or one of the other forms of skin tuberculosis.

If tuberculosis is common and he has signs of a SPACE OCCUPYING LESION OF HIS BRAIN (headache and vomiting), there is about a 50% chance that he has a tuberculoma.

If a JOINT BECOMES PROGRESSIVELY PAINFUL and stiff with muscle wasting, suspect tuberculous arthritis and look for the characteristic X-ray lesions.

If he has a CHRONICALLY DISCHARGING EAR which fails to respond to antibiotics, it may rarely be tuberculous.

BE EVER WATCHFUL.
DO NOT BE AFRAID TO START TREATMENT ON REASONABLE SUSPICION.
WHEN YOU DO START TREATMENT, FINISH IT COMPLETELY.

TUBERCULOUS MENINGITIS

Tuberculous meningitis is the most dangerous form of the disease. If you diagnose a child early, his prognosis is good, if

you diagnose him late, he will die, or be left with serious complications. So watch for it constantly, and make sure your staff do so too.

Tuberculous meningitis is comparatively common. Treatment takes a long time and is expensive in staff effort; a child needs several drugs, repeated lumbar puncture, and prolonged hospital care and follow up. It is also difficult to diagnose; you will often find that you have several children in the ward who *might* have tuberculous meningitis, but you cannot be sure. If you admit an unconscious child he will probably die, and even if he is still conscious, he only has a 50% chance of surviving-in a good unit. Even if he lives, he has a 20% chance of being intellectually impaired (common), or of having crania1 nerve lesions (blindness. deafness and squint), or residual hemiplegia or paraplegia, or fits.

A child with tuberculous meningitis can present in several ways, of which the following are the most important.

Insidiously

Suspect tuberculous meningitis in any child who is 'off colour' for more than a week. Although the diagnosis is usually one of exclusion, a history of vomiting once or twice (because of his. raised intracranial pressure) should make you suspicious. If he is less than three or four years old, he will not complain of headache, and even if he is older he will not do so early enough. Fever, a stiff neck and a positive Kernig's sign are comparatively late signs.

Typically, a mother says that her child has 'lost interest', 'he is not himself' and is not playing normally. Usually, there is some obvious cause for this, such as malnutrition (which affects his energy and interest early), or some infection that is readily excluded by the screening tests described below. If these tests are negative, and he is not malnourished, tuberculosis meningitis is the most likely diagnosis. *The earliest signs of neck stiffness are:* (1) that he winces when you flex his neck fully, and (2) that he is reluctant to put his forehead on his knees ('knee kissing'). These are such useful tests that you must make sure that your staff do them. An infant with early meningitis may be unable to sleep, or to rest his head on his mother's shoulder, because his neck is stiff. Often, he has focal or generalized fits.

Later, he has more advanced signs that include drowsiness, coma and focal neurological signs due to tuberculomas, or to tuberculous inflammation around his blood vessels, or his cranial nerves (see below).

As a complication of malnutrition

If he has kwashiorkor, this will make him profoundly miserable. But after 4 to 5 days of intensive feeding as an inpatient, he should become more alert, and he should start to smile again within 10 days. If he does not do this, do a lumbar puncture.

Tuberculous meningitis can also present as a complication of already diagnosed tuberculosis. In a young child it can also present as an acute encephalopathy (headache, vomiting, neck stiffness and fits) suggesting acute bacterial meningitis or a subarachnoid haemorrhage.

What should you do in a district hospital if your resources are already stretched to the limit? We suggest that you: (1) Try to diagnose tuberculous meningitis early, in Stage One, *before* a child's neck is stiff; this is difficult. (2) Assess his prognosis carefully, according to the criteria we give and, if his chances are reasonable, do all you can for him.

The only certain way to diagnose meningitis early is to do a lumbar puncture on any child who might have it. Readiness to do this is thus one of the great attributes of a good paediatrician. The equipment can easily be boiled in a saucepan, or better, heated in a pressure cooker. Lumbar puncture can be done as an outpatient or by a genera! practitioner; it should be readily possible and done often in every health centre. Pandy's test (see below) will tell you if his CSF is abnormal.

Early diagnosis is *critical,* so is sustained chemotherapy with four drugs. Start treatment on the suspicion that he might have tuberculous meningitis, and do not wait for bacteriological confirmation, if indeed this is possible.

'KNEE KISSING' IS THE EARLIEST TEST FOR MENINGITIS

The child is usually young (3 months to 3 years).

SCREENING TESTS FOR OTHER INFECTIONS. If he is unwell, examine his skin, his eyes (particularly for anaemia), his ears, his throat, and his chest, and feel his abdomen. Quickly squeeze his bones in the most likely sites for osteomyelitis. Examine his urine and look at a blood film for malaria. A high white count suggests a pyogenic infection.

When these tests are negative, think next of early tuberculous meningitis. The first sign of neck stiffness is his reluctance to put his head between his knees (see above). Later, he will have obvious neck stiffness, positive Kemig's sign, a bulging fontanelle, papilloedema and cranial nerve palsies (see below).

DIAGNOSIS AND STAGING Typically, he progresses through three stages, although these are not clear cut. He may present in any of them.

Stage One before the development of a stiff neck lasts 2 to 8 weeks and is the insidious onset described above. He has a varied combination of malaise, vomiting (an important early sign), irritability, behavioural change and developmental regression, insomnia, lethargy, anorexia, headache and abdominal pain. He has a low (or occasionally high) fever, and often (50%) some signs of tuberculosis elsewhere, especially loss of weight; look for them.

Stage Two begins when he develops a stiff neck and a positive Kernig's sign. Headache and vomiting are more marked. This is the stage at which focal neurological signs are usually seen, although you may see them earlier when they greatly assist in the diagnosis. If you find any of them when you are investigating a child for vague symptoms; suspect tuberculous meningitis. These are general or focal fits, papilloedema, hemianopia, hemiplegia, hemiparesis, paraplegia, aphasia, and especially cranial nerve lesions: II (blindness), Ill (ptosis and a dilated pupil), IV and VI (squint), VII (facial palsy), VIII (deafness), IX (palatal palsy) and XII (tongue deviation). You may occasionally find choroidal tubercles.

Stage Three. He is unconscious or delirious, commonly with quadriplegia, decerebrate rigidity and severe opisthotonos.

HIS CHEST X-RAY may be normal. If you are uncertain whether to do a lumbar puncture, seeing a primary focus on his X-ray should persuade you. Look for miliary shadows.

CHOROIDAL TUBERCLES are very useful diagnostically, but are difficult to find if he is restless. Dilate his pupils and if necessary give him 2 brief anaesthetic to complete the examination.

TUBERCULIN TEST. A negative result does not exclude tuberculous meningitis.

LUMBAR PUNCTURE is essential, even if you only suspect tuberculous meningitis. The only exception is the presence of papilloedema, when lumbar puncture may occasionally result in fatal 'coning' ofthe medulla (it is even more likely if he has pyogenic meningitis). Early, his CSF opening pressure is high (a serious sign) and Queckenstedt's test is negative. Later, his CSF opening pressure may be low and Queckenstedt's test positive.

Queckenstedt's test will tell you if he has a spinal block due to adhesions obstructing the free flow of his CSF. It is not so easy or so useful in a child, because it needs his cooperation. With the spinal needle in place connected to a CSF manometer (an intravenous giving set with Luer fitting cut off 30 cm from the Luer end), compress both his jugular veins by squeezing his neck. If the pressure in the manometer rises, the test is negative and he is normal in this respect. If it does not rise, the test is positive, and he has a spinal block.

His CSF is usually slightly, cloudy; in later stages it may set as a yellow jelly. A spider web clot may form if you leave it to stand. Measure the protein. Count the cells; for this you will need a counting chamber and a microscope. If possible, measure his CSF sugar.

Pandy's test is old fashioned but useful. Take a screw capped bottle of about 100 ml. Fill it a quarter full with phenol (crystals in cold weather, liquid when hot). Fill it nearly full with water and shake. Leave it overnight; there will be an oily lower layer of phenol and an upper layer of water saturated with phenol. Pour (or, better, pipette) a few ml of the upper layer into a small tube. Add a few drops of CSF. Examine this against light. Normal CSF causes no cloudiness. If there is cloudiness, its protein is increased and it is abnormal.

Test his CSF with 'Albustix' for protein and 'Dextrostix' for sugar. If he has more than 30 mg/dl of protein with the 'Albustix', his CSF is abnormal. If his CSF sugar is less than 4.5 mg/dl with the 'Dextrostix', immediately measure his blood sugar with it. If his CSF sugar is less than two-thirds of his blood sugar, this is abnormally low. These two tests will help you to diagnose tuberculous meningitis immediately after a lumbar puncture; his CSF will have a high protein and low sugar.

If your laboratory facilities are minimal, put a single drop of CSF from the lumbar puncture needle onto a clean slide, cover it with a coverslip, and preferably let a drop of methylene flow under it from one edge. Pure lymphocytes suggest viral meningitis. Polymorphs suggest pyogenic meningitis, especially if they are in clumps. In tuberculous meningitis there are often some polymorphs, but lymphocytes predominate.

THE MAIN DIFFERENTIAL DIAGNOSES are pyogenic and viral meningitis (Table I). All three cause an increase in the white cells and protein content of his CSF.

In bacterial and tuberculous meningitis the CSF is usually cloudy. In viral meningitis it is usually clear. In pyogenic meningitis the cells are mostly polymorphs. In the others they are mostly lymphocytes. The protein is high in all three. The sugar is low in pyogenic and tuberculous meningitis (<40 mg/dl) and normal in viral meningitis (>40 mg/dl), so you cannot distinguish tuberculous from pyogenic meningitis by means of the protein or the sugar. A Gram-stained film usually shows bacteria in pyogenic meningitis.

TABLE I. The differential diagnosis of the three common types of meningitis

CSF	Tuberculous	Pyogenic	Viral
Colour	Usually cloudy	Usually cloudy	Usually clear
Cells	Mostly lymphocytes	Mostly polymorphs	Mostly lymphocytes
Protein	High	High	High
Sugar	Low	Low	Low
Gram's stain	Negative	Bacteria	Negative

Look for mycobacteria in this manner: centrifuge as much CSF (10-20 ml) as long and as hard as possible in a conical tube; carefully remove the supernatant with a very fine pipette to leave only a tiny button of cells. Transfer this to a small area of slide, let it dry as a thick film and stain it for mycobacteria. Search it a// systematically for at least half an hour. The equipment is simple, but it needs skill and patience. If possible, culture his CSF.

If your laboratory facilities are poor, and he has a cloudy CSF with more than 50% lymphocytes, treat him for tuberculous meningitis.

If he has already been given antibiotics, his CSF may be abnormal, but you may find no bacteria. You may never know whether he had tuberculous or pyogenic meningitis, so treat him for both.

If you are not sure if he has tuberculous or viral meningitis (the differential diagnosis may be difficult before the sugar falls, or if you cannot measure it), start him on chemotherapy for tuberculosis. Viral meningitis has no treatment and is usually self limiting. In most viral infections the CSF returns to normal in 3 to 4 weeks, but in tuberculosis it is seldom normal in under 4 months.

If you are not sure if he has tuberculous meningitis; bacterial meninigitis, or malaria, treat him for bacterial meningitis and malaria only, and watch him for 3 days. If he has either of these, he should improve in a few hours or within 3 days, so you can stop treatment. If he is still ill, he is more likely to have tuberculous meningitis, so start treating this.

CAUTION! (1) Occasionally, the CSF in pyogenic meningitis has many bacteria and few cells. (2) There are other rare causes of meningitis, such as cryptococci (which can easily be seen by staining with India ink).

CHEMOTHERAPY. Give him the treatment for 'more severely ill children' (see above) for at least 9 months. Intrathecal streptomycin is now outmoded, especially under difficult circumstances.

MANAGEMENT. Do a lumbar puncture on him daily for the first few days, letting the fluid escape slowly to avoid coning. Then reduce the frequency of lumbar puncture as he improves. As soon as he is improving satisfactorily, stop doing lumbar punctures. His CSF takes a long time to return

to normal, it is unpleasant and may induce infection. His clinical condition should improve and the frequency of his fits lessen. Medication should mostly prevent them, but his underlying tendency to have them persists.

CAUTION! (1) Do not do repeated lumbar punctures if he has a spinal block. (2) Increase the dose of isoniazid as he gains weight.

HIS PROGNOSIS. If he is admitted unconscious (Stage Three) he is almost sure to die. If he is conscious he has about a 50% chance of survival in good hands. His prognosis then depends on: (1) The stage at which the diagnosis is made—the earlier the better. (2) His age; it is worse in younger children. (3) His nutrition. (4) His family circumstances–will they be able to bring him for the outpatient care he will need later, and pay for the treatment he needs? If they cannot, palliation may be all you can do.

SYMPTOMATIC TREATMENT. Prevent his fits with phenobarbitone, phenytoin or carbamazepine. If they occur, treat them with intravenous or rectal diazepam.

DIFFICULTIES WITH TUBERCULOUS MENINGITIS

If his consciousness is impaired, with severe headache, ocular palsy, pyramidal signs in his lower limbs, incontinence of urine and persistently raised CSF pressure, suspect that hydrocephalus is developing. If his head starts to enlarge, this confirms it. if possible, refer him for surgical relief, whatever the duration of his chemotherapy.

If he has a high and rising CSF protein, and a low CSF pressure, he has a CSF block. Unfortunately, there is nothing you can do except give him steroids.