Neurocysticercosis — a comprehensive approach to medical treatment

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Summary
The incidence of cysticercosis in South Africa may well be alarming. Cysticercosis of the central nervous system (CNS) is almost exclusively confined to the parenchyma of the brain. Before the introduction of computed tomography (CT), invasion of the CNS by the parasite could only be suspected on the basis of evidence of previous infestation. The use of praziquantel in the treatment of cysticercosis is a major step towards eradicating the disease, but to be effective treatment must take cognizance of re-infection, the allergic reaction caused by the dying parasites, and the possible need for repeated courses of treatment. The therapeutic regimen is outlined and the efficacy of the treatment as monitored by CT evaluated.

Cysticercosis is the most common parasitic disease affecting the central nervous system in man.1 It is endemic in Africa, South America, India, Pakistan, Honduras, Mexico and eastern Europe.2 For example, the parasite was detected in 3.6% of general autopsies in Mexico.3 Recognition of the disease has trebled since the advent of computed tomography (CT).4 This is borne out by comparing the number of patients with cerebral cysticercosis detected at two large Los Angeles hospitals in the pre-CT era5 and since CT came into general use.6

In recent years there has been an upsurge of interest in cerebral cysticercosis. There have been two major reasons for this — firstly, the increased diagnostic expertise brought about by CT,7 and secondly, the discovery in 1978 that porcine cysticercosis could be treated successfully by pyrazinoquinoline, now generally known as praziquantel.1 This was followed in 1980 by the report by Robles and Chavarria8 of a patient with neurocysticercosis treated successfully with praziquantel. Treatment had previously been essentially symptomatic, but the advent of praziquantel has resulted in cure of cerebral cysticercosis.1

At Ga-Rankuwa Hospital, cerebral cysticercosis is frequently diagnosed and treated with a standard regimen incorporating praziquantel as the main anthelmintic drug.

The life cycle of the tapeworm
Cysticercus cellulosae was first identified in 1855 when Kuchenmeister and Leukart (cited by Carbajal et al.9) described the life cycle. It is the larval form of Taenia solium, the pork tapeworm. Penetration of the intestinal wall by the ciliated larva takes place and haematogenous dissemination occurs. Sites of predilection for the cystercer to develop are the central nervous system (CNS), skeletal muscle, heart muscle, and the eye.4 Cysticercosis of the CNS results in its most pernicious manifestations.10 Cerebral cysticercosis may take the following forms: (i) parenchymal; (ii) meningeval; (iii) ventricular; (iv) mixed; and (v) asymptomatic.11

The most common form is parenchymal cysticercosis occurring as scattered calcified lesions mainly in the white matter of the brain. Calcified lesions are usually asymptomatic but can act as epileptogenic foci. The active, parenchymatous form, however, is of interest in that praziquantel offers a cure for this form of the disease that is generally not amenable to surgery or other forms of medical treatment, and CT of the brain offers an objective measurement of treatment efficacy.1

Diagnosis of cerebral cysticercosis
The diagnosis of parenchymal cerebral cysticercosis rests on the following:
1. Serological tests, e.g. the indirect haemagglutination (IHA) test and the complement fixation test. These have false-negative rates ranging from 10% to 40%.12,13 A new radioimmunoassay is being developed.14
2. CSF analysis, which may show a predominantly lymphocytic pleocytosis, eosinophilia and elevated protein levels, especially of IgG.15,16 The IHA test may also be performed on CSF,11 but the changes are not specific for cerebral cysticercosis.
3. Soft-tissue calcification may occur.10,12,17
4. Plain radiographs of the skull show calcifications of various sizes in 10 - 13.6% of cases.5,9
5. CT may show a variety of lesions ranging from completely calcified to cystic and homogeneously enhancing.5 A combination of the above lesions may be seen in a single patient, which is presumptive evidence of auto-infection.3
6. The larvae may be surgically removed from subcutaneous tissue or the brain.

Treatment
Treatment of cysticercosis may be surgical, symptomatic or medical.10,14,18 Symptomatic treatment has been aimed mainly at control, by routine anti-convulsants, of the most common symptom, epilepsy, which occurs in 92% of cases.10 Control of seizures may be total within a few years.18 Corticosteroid therapy has been used to reduce cerebral oedema,14 raised intracranial pressure and meningismus.20 Improvement occurs after steroid therapy, whether given as interrupted short courses for acute exacerbations of symptoms or long term.14 In one study,17 however, in spite of clinical improvement, 5 patients treated with steroids alone showed no evidence of improvement on follow-up CT scanning.
radiological improvement. De Ghetaldi et al. treated their patient for 2 months with dexamethasone alone and found resolution of cerebral oedema on CT, but no changes in either cyst size or number. We have recently found the same results on re-scanning a patient after 2 weeks of steroid therapy alone (unpublished data).

As recently as 1984 the opinion was expressed that as soon as the parasites have invaded the brain and meninges, medical therapy can offer very little. In spite of this, reports concerning the efficacy of praziquantel have been encouraging. Praziquantel is an acylated isoquinoline-pyrazine derivative identified in 1972 and found to have a wide spectrum of anthelmintic activity. It is an effective antischistosomal agent, active against all Schistosoma species infecting humans. It is also effective against cestodal infections, including the Taenia species Hymenolepis nana and Diphyllobothrium latum. Praziquantel is active against the adult worm T. solium and is also effective against cysticercosis. The drug is rapidly absorbed after oral administration and the metabolites are excreted primarily in the urine. Peak serum levels of 1 μg/l are reached 1 - 2 hours after an oral dose of 50 mg/kg body weight in the healthy adult. CSF concentration is about 14 - 20% of the total amount of free plus protein-bound praziquantel in the plasma. Praziquantel is apparently not metabolized by cestodes but exerts its action by increasing the permeability of the plasma membrane of the worms to calcium ions, resulting in the loss of intracellular calcium.

Praziquantel is well tolerated by man and no reports of long-term toxicity have been received to date. Studies have not shown toxicity at doses of 50 mg/kg body weight, and even doses of 75 mg/kg body weight in healthy volunteers were well tolerated. Sotoelo et al. reported treating 26 patients suffering from parenchymal cerebral cysticercosis with praziquantel. CT showed improvement in 25, with total cyst remission in 9 patients.

Three patients treated with praziquantel, steroids and mebendazole at the Ga-Rankuwa Hospital have been selected for discussion; 1 patient treated with praziquantel as sole agent is cited in contrast.

Case reports

Case 1

A 55-year-old black man was admitted to hospital because of focal fits involving the left side of his face, his left arm and leg. These had been present almost continuously for some days. There was no previous history of epilepsy.

Examination revealed multiple subcutaneous nodules (Fig. 1). Skull and soft-tissue radiographs revealed no calcification. Excision of a nodule and histological examination confirmed the presence of cysticercus. A lumbar puncture specimen of CSF was normal. CT demonstrated scattered well-circumscribed low-density areas, most of which contained a hyperdense nodule. Contrast agent administration showed no enhancement. Seven macroscopic cysts were counted.

The patient was treated with intravenous diazepam and phenytoin which controlled the seizures. Afterwards he was given mebendazole 100 mg twice daily on 3 consecutive days, followed by prednisone 5 mg 3 times daily. On the 3rd day of steroid treatment, praziquantel therapy was begun at 50 mg/kg body weight in 3 divided doses for a period of 15 days. Steroid treatment was continued throughout this period and for 2 days after the course of praziquantel was completed. Oral phenytoin therapy was continued throughout. The patient experienced no untoward effects during therapy.

Two weeks later repeat CT demonstrated complete resolution of the cystic lesions seen in the previous scan. The subcutaneous nodules had also disappeared. The patient was discharged on maintenance phenytoin therapy, and remained well 6 months after discharge.

Case 2

A 40-year-old black man was referred from a peripheral hospital after a generalized seizure. He had no previous history of epilepsy but had had an almost constant headache for about a year, and admitted to passing tapeworms in his stool. Neurological examination was unremarkable, but general examination revealed multiple subcutaneous nodules, which biopsy specimens showed to be cysticerci. Skull radiographs showed numerous small calcifications scattered diffusely throughout the area, and radiographs of the thighs and shoulders revealed multiple elongated 'rice-grain' calcifications suggestive of cysticercosis. CT of the brain demonstrated multiple small low-density areas scattered throughout both hemispheres and cerebellum, frequently containing a small hyperdense nodule. A count of macroscopic cysts numbered 152. There were also areas of punctate calcification in these cystic regions. CSF was normal.

The patient passed an adult T. solium after a course of mebendazole. He was put on a course of praziquantel, steroids and mebendazole similar to that described in case 1, with no untoward reactions during treatment.

After 1 month, CT of the brain revealed a marked decrease in the number of cysts. A course of steroids and praziquantel was repeated and CT 1 month later showed complete clearance of the cystic lesions (Fig. 3), although the punctate calcification was unaffected. The patient experienced no ill-effects during treatment, and renal and liver functions were normal at the end of the two courses of praziquantel. The patient was discharged on maintenance anti-epileptic treatment, which had been instituted on admission.

Fig. 1. Subcutaneous nodules in case 1.
Fig. 2. Two separate CT scans in case 2 showing viable cysticerci before treatment.

The patient was well during treatment and biochemical tests of renal and hepatic function remained normal throughout.

Case 4
A 36-year-old white woman was seen by C.M.L. complaining of constant severe headache and visual disturbances of about 3 months' duration. On examination, the only positive finding was bilateral papilloedema. CT revealed multiple cystic areas in both hemispheres compatible with cysticercosis. A macroscopic count of the cysts numbered 32. She was treated with a course of praziquantel and steroids (dexamethasone 4 mg 6-hourly), improved considerably, and was discharged from hospital. Four months later she was readmitted with a recurrence of symptoms and a depressed level of consciousness. CT revealed that the number of cysts had increased to 50, and a positive history of the passage of tapeworm segments was obtained; highly suggestive of re-infection. The patient became comatose and died. Permission for autopsy was refused.

Discussion
The major criterion for selection of patients was the appearance on CT of multiple cysts consistent with the radiological diagnosis of cysticercosis. Histological confirmation was obtained by removal of subcutaneous cysticerci in cases 1 and 2, and of a cerebral cysticercus at craniotomy in case 3. In case 4, the CT appearance was highly suggestive of cysticercosis.

All 4 patients came from the Transvaal, which is not an endemic area for hydatid disease, and the CT appearances were unlike those of *Echinococcus* cysts. Serological testing for cysticercosis was not carried out; however, others, have shown that the tests available add little to the diagnosis because of low positive and high false-negative rates.

Clinical evaluation of the efficacy of praziquantel is not reliable because of the well-recognized fluctuating course of the disease. CT provides a means for objective evaluation of drug effectiveness as regards cyst number and size. Our cases highlight certain aspects of the treatment of parenchymal neurocysticercosis.

Repeated courses of praziquantel, if steroid cover is given, are not accompanied by serious side-effects. In the study of Sotelo et al., beneficial effect apparently continued in some cases 6 months after treatment; in others, there was no remarkable improvement on CT done at 3 months after the post-treatment scan. In our study, the neurocysticercosis cleared completely in the first 2 patients after only 1 and 2 courses of praziquantel respectively. Case 3 required 4 courses of treatment, but this patient's cysts were considerably larger than in case 1 and 2. Smaller cysts seem therefore to be more easily eradicable. However, even large cysts respond to repeated courses of praziquantel by diminishing in size and finally disappearing completely. Whether courses of praziquantel

<table>
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<th>Patient</th>
<th>Pretreatment scan No. of cysts</th>
<th>No. of courses required</th>
<th>Last scan — No. of cysts</th>
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<tr>
<td>1</td>
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<td>1</td>
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<tr>
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The subdural haematoma was drained and at operation a superficial cysticercus (confirmed histologically) was removed. One week postoperatively the patient was placed on anticonvulsant medication, steroids and praziquantel, as in case 2. He was also given a course of mebendazole.

CT 1 month later showed some improvement and the course of medication was repeated. One month later, CT showed reduction in the total number of cysts, and 50% reduction in size of some cysts near the anterior horns of the lateral ventricles. A 3rd course of treatment was given and follow-up CT showed improvement. After a 4th course of praziquantel, CT showed only 3 small residual cysts.

TABLE I. SUMMARY OF RESULTS OF TREATMENT

Case 3
A 37-year-old black man was seen because of a severe headache of about 1 week's duration. He had a history of excessive alcohol intake and for the past year had also had convulsions about once a month.

Neurological examination was normal except for mild weakness of the left arm. CT revealed a fresh right-sided subdural haematoma (the patient later admitted to a head injury the previous week) and multiple cystic lesions of various sizes, some with an exentric hyperdense nodule. A macroscopic count of the cysts numbered 27. There was no surrounding oedema and the lesions were not enhanced by contrast agent. There were also scattered areas of calcification in both hemispheres. Skull radiographs showed calcifications but there were none in the soft tissue.

The subdural haematoma was drained and at operation a superficial cysticercus (confirmed histologically) was removed. One week postoperatively the patient was placed on anticonvulsant medication, steroids and praziquantel, as in case 2. He was also given a course of mebendazole.

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should be repeated (it is relatively non-toxic), and if so, at what intervals, is uncertain! at this stage and deserves further study. Sotoel et al. were not sure about continuing improvement with subsequent courses, but our data suggest benefit from repeated courses of praziquantel.

Administration of praziquantel may be accompanied by an exacerbation of neurological symptoms (92% in the series of Sotoel et al. — severe headache, vomiting and fever. De Ghetaldi et al. regard this as a possible response to degenerating larvae and similar to the Jarisch-Herxheimer reaction. In Sotoel et al. series steroid cover was purposely not given. These unpleasant reactions were noticeably absent in our patients, who were treated simultaneously with steroids, and for this reason we feel that steroid cover, while not curative, has a role in the treatment of cysticercosis with praziquantel by damping down the allergic reaction.

Praziquantel is active against the adult worm, but in case 4, where mebendazole was not given, there was a temporary clinical remission and then a dramatic increase in cyst number, leading to the patient’s death.

In one series 26% of patients with cysticercosis had a tapeworm at the time. It is well recognized that reverse peristalsis may deposit proglottides in the stomach, leading to auto-infection. It is conceivable that praziquantel is not as effective on the adult worm as on the larvae and, in case 4, intraretinal re-infection took place in spite of effective larvicidal action by praziquantel in the brain. Simultaneous use of an intraluminal vermicide to eradicate the intestinal worm is therefore recommended.

Conclusions

We recommend that the treatment of active parenchymal neurocysticercosis should consist of the simultaneous administration of praziquantel as the major anthelmintic drug, steroid cover to dampen the allergic reaction to dying larvae, mebendazole to eradicate the intestinal adult worm to prevent auto-infection and, where convulsions have been a feature, anticonvulsant therapy. There may also be a place for repetition of treatment by praziquantel in the brain. Simultaneous use of an intraluminal vermicide to eradicate the intestinal worm is therefore recommended.

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