Unusual Presentations of Neurocysticercosis

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Abstract: Neurocysticercosis is an endemic disease in India. It is the most common helminthic infection of the CNS and the most common cause of adult onset seizures worldwide. Rightly designated among the ‘neglected infections of poverty’ by the CDC, this devastating disease has few case-control studies for management, less practical diagnostic criteria and lesser clear treatment guidelines. In this article we present two unusual cases of neurocysticercosis. The first is a case of parenchymal neurocysticercosis with all stages simultaneously found in a single patient. The second is the rare variety of subarachnoid racemose neurocysticercosis with a fatal outcome. We also review the pathogenesis, types and stages with radio-pathologic correlation, dilemmas in diagnosis and treatment and the current trends in management of neurocysticercosis.

Key words: Racemose · Parenchymal · Stages · Types · Diagnostic Criteria

INTRODUCTION

Neurocysticercosis (NCC) was first described by Rumler in 1558 when he found liquid filled vesicles adhering to the dura during the autopsy of a patient who died of seizures. In India it was first found by Armstrong in 1888 in a coolie who died of seizures. NCC is caused by the larva of Taenia solium (pork tapeworm). It is prevalent in unsanitary environment where there is contamination of food with human faeces. It is common in vegetarians also which is against the misconception that cysticercosis occurs only in pork consumers. Cysticercosis is a “biological marker of social and economic development” of a community [1]. 26.3% to 56.8% of adult onset seizures in developing countries is attributed to NCC [2]. Rajaseker et al. has reported a seizure prevalence of 3.83 per 1000 in a population based door-to-door community survey of 50,617 people from Vellore district in Tamilnadu [3]. NCC was found in 28.4% of them by CT scan. Hence the disease burden of NCC in India surpasses many other developing countries [4].

CASE 1: A 42 years Indian female from a poor socio-economic background from Arakkonam in Tamil Nadu was referred for new on set recurrent seizures(6 episodes) for 12 hours. She did not regain consciousness after the 3rd episode. Her daughter gave a history of holocranial dull aching headache in the patient for 2 months with occasional vomiting but without vertigo or tinnitus or blurring of vision. No weakness of limbs or sensory disturbances were reported. She had no significant past history and consumed mixed diet. Family history was significant in that her mother had recurrent seizures since 40 years of age for several years for which she had not taken treatment and had died during a seizures episode 4 years ago. A detailed environmental and diet history revealed pig rearing in home for sacrificial slaughter and pork consumption during festivals.

On examination the patient was drowsy and disoriented with GCS of 11/15 and stable vitals. She had hypotonia of all 4 limbs with depressed deep tendon reflexes and bilateral extensor plantar. Pupils were normal in size and reaction and fundus showed mild blurring of disc margins bilaterally. The patient was immediately treated as per status epilepticus protocol.

A CT scan revealed multiple cysticerci in various stages throughout the brain (Fig.1,2,3). X-ray of the chest showed a calcified lesion in left lung above aortic knuckle (Fig. 4). X-rays of the deltoid and thigh muscles revealed multiple rice grain calcifications (Fig. 5). An ocular examination did not reveal any ocular cysticercus. Stool exam was negative for ova and parasites and occult blood.

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A diagnosis of disseminated cysticercosis was made and patient was started on dexamethasone 8mg iv b.i.d., albendazole 400mg PO b.i.d., phenytoin 100mg iv t.i.d., pantoprazole 40mg iv b.i.d. The patient improved rapidly with steroids and regained full function in 24 hours.

**Interesting Aspects of this Case:**

- All stages of parenchymal NCC found in her brain
- Calcified cysticerci in muscles and lung
- Probable familial clustering from history of seizures in mother
- Clear history of adult onset seizures presenting as status epilepticus.
- Environmental factor of pig rearing

**Case 2:** A 38 years old male was diagnosed to have subarachnoid NCC at our centre after his first episode of seizure 6 years ago. MRI showed racemose NCC with cluster of grapes appearance. HIV serology was negative. He was treated with 8 prolonged courses of albendazole over 6 years. He was on follow up in epilepsy clinic for recurrent seizures and was treated with continuous antiepileptic and steroid therapy. But the patient discontinued medications. After 3 weeks he developed headache with altered sensorium for which he was treated at a different
centre. He also developed paucity of movements in his left upper and lower limbs which progressed to complete paralysis after 3 days and he gradually lapsed into a coma. He was again referred to our centre after he developed status epilepticus while in a comatose state.

On examination he was unconscious and hypotensive with GCS 5/15, absent movements on his left side, bilateral papilledema and sluggish pupillary response and prominent neck stiffness. A CT was done which revealed persistent racemose subarachnoid NCC and a right MCA territory infarct in the corona radiata.

A diagnosis of subarachnoid meningoencephalitic NCC with vasculitic infarct was made and the patient was treated with dexamethasone 10mg iv and mannitol 1g/kg iv infusion. A ventriculo-peritoneal shunt was also planned. But we lost the patient before the procedure when he developed refractory seizures.

Interesting aspects of this case:

- Rare variety of racemose NCC
- Recurring lesions refractory to medical therapy
- Meningoencephalitic presentation
- Rare complication of vasculitic infarct
- Fatal nature of the disease

RESULTS AND DISCUSSION

The Parasite: Taenia solium is an intestinal cestode with complex life cycle with 2 hosts. Pigs are intermediate hosts. Porcine cysticercosis is endemic in areas where human faeces are accessible to pigs. Humans are the only definitive hosts and can develop two forms of disease – taeniasis and cysticercosis.

Taeniasis-Humans acquire infection by eating undercooked pork infested with cysticerci and develop taeniasis. Humans harbour adult worms in the gut and release proglottids containing fertilised ova in faeces.

Cysticercosis-Human cysticercosis occurs from ingestion of ova from food contaminated with faeces or from auto-inoculation. The former is important in India as sewage irrigation is common in our country. Following consumption, the oncospheres penetrate the mucosa and the larvae disseminate in the body and form cysticerci.

In humans, cysticerci have been identified in the skeletal muscle, brain, eye, subcutaneous tissue and even lungs. In most locations cysticerci spontaneously degenerate. The minority that invade the CNS develop into NCC. Incidental calcified granulomas are found in 10-20% of population. Hence, symptomatic NCC patients represent only the tip of the iceberg of the disease burden in our population.

Types of NCC:

- Parenchymal
- Extra-parenchymal
- Sub-arachnoid
- Ventricular
- Spinal
- Ocular
- Mixed

Parenchymal NCC: These are usually small, 1-2 cm lesions found in the cerebral cortex or cortex-subcortex junction areas. Some argue that “parenchymal” location of NCC is the cross-sectional view of subarachnoid NCC located deep in sulci or perforating branches in perivascular spaces [5]. Active parenchymal NCC is the most common form of NCC in symptomatic patients. They may have radiologic evidence of parasite degeneration and inflammation. It has 5 patho-radiologic stages [6] which are not found in subarachnoid and ventricular forms of the disease.

- Non-cystic stage– The larva has not yet developed into a cyst. It is asymptomatic with no radiologic findings.
- Vesicular stage– The stage of viable larval cyst without host response. They appear on CT as non-enhancing, small, round, well demarcated, low density areas without peri-lesional edema. They have the pathognomonic ‘hole-with-dot’ or ‘pea-in-pod’ appearance. When found extensively, the brain can have a ‘swiss cheese’ pattern. The scolex may appear as a small 2-3mm isoattenuating structure inside the lesion. In this stage patients are asymptomatic. Fig.1 shows a cysticercus in vesicular stage in the left occipital lobe.
- Colloid stage– It is the first stage of involution where the transparent fluid is replaced by a viscous colloid. It represents the ‘acute encephalitic phase’ of NCC. CT shows ill-defined, contrast enhancing, hypo or isodense lesion with perilesional edema. Symptoms start developing in this stage. Fig.2 shows a colloid stage cysticercus in the left frontal lobe.
- Granular stage– The scolex is no longer viable. The cyst wall thickens and becomes fibrotic and collapses. The lesion becomes more edematous and has greater contrast enhancement. Also some specks of calcification appear. Fig.3 shows an agranular stagecysticercus with calcified scolex and spotty calcifications in cyst wall with perilesional edema in the right frontal lobe.
Subarachnoid NCC: In this devastating variety, NCC are found in the fissures and basal cisterns. Cysts can enlarge to several centimetres forming giant cysticerci which can have mass effect. Multiple grape-like clustered non-viable unencapsulated bladders which lack scolecis form the racemose NCC. Hydrocephalus is the most common CT finding in this form. Ischemic cerebrovascular complications can occur. In a study of 28 patients with subarachnoid form of NCC 53% had angiographic evidence of middle or posterior cerebral artery occlusion [7]. Figs 6, 7 and 8 show racemose NCC. Fig. 8 also shows a right corona radiata infarct occurring as a complication.

Ventricular NCC: They appear as lesions causing distortion of ventricular cavity which are isodense to CSF. They are easier to identify in an MRI. Intermittent or persistent hydrocephalus features predominate. The cysts move with changes in patient’s head position (ventricular migration sign in MRI).

Range of Clinical Presentations in NCC: Factors influencing the presentation in NCC:

- Number of lesions
- Location of lesions
- Stage of development or involution
- Intensity of host inflammatory response
- Recently host genetic factors have been found to play a role. Polymorphisms in Toll like receptors (TLR-4) were found to have influence over host inflammatory response [8].

The clinical presentation ranges from asymptomatic to life threatening. Seizures are the most common presentation in parenchymal form. They are usually generalised tonic-clonic or simple partial seizures. Focal neurologic deficits can also occur. In children and young women acute inflammatory response to massive cysticercal infection can cause acute diffuse cerebral edema presenting as a syndrome of confusion, clouding of consciousness, headache, vomiting and papilledema which is termed cysticercotic encephalitis. Psychiatric manifestations like depression and psychosis have been described in parenchymal form.

Subarachnoid form can present with mass effect, or produce basal arachnoiditis resulting in multiple cranial nerve entrapment or hydrocephalus. Lacunar infarcts in posterior limb of internal capsule and corona radiata are

- Inactive or calcified stage– Hyperattenuating calcified nodules without peri-lesional edema represent burnt out end stage lesions. Figs 2 and 3 show multiple calcified cysticerci scattered throughout the brain giving a starry sky pattern.
common due to occlusion of the lenticulostriate branches from intense inflammatory response. Large cerebral infarctions secondary to occlusion of internal carotid, anterior or middle cerebral vessels can also occur.

Ventricular NCC can present with acute hydrocephalus and sudden death due to occlusion of third or fourth ventricle. Brunn’s syndrome is constellation of episodic headache, papilledema, neck stiffness, vertigo induced by rotatory movements of head, nausea, vomiting, drop attacks, loss of consciousness with rapid recovery and long asymptomatic periods. It is caused by NCC in the fourth ventricle.

Calcified stage of NCC has been presumed to be inert. But recent findings have proved that recurrent transient perilesional edema can occur around calcified NCC and cause refractory seizures [9], MRI shows evidence of perilesional edema in calcified lesions in 50% of patients with recurrent seizures [10]. Histopathologically, calcified lesions are surrounded by marked astrocytosis, microgliosis and inflammatory infiltrates [11]. Both single and multiple small punctuate cerebral calcifications are common in NCC in endemic areas and this pattern is uncommon in other infectious diseases. There are 3 evidences to suggest calcified NCC lesions provoke seizures. 1) High prevalence of calcifications in patients with seizures of undetermined etiology. 2) High prevalence of seizures in people with brain calcifications in endemic areas. 3) Increased risk of continued seizures in NCC granulomas that calcify [12].

Ocular NCC can present as scotomas, iridocyclitis, panophthalmitis or insidious progressive loss of vision.

**Diagnostic Criteria:** The diagnostic criteria which was proposed for NCC in 1996 has been revised and Del Brutto et al. have proposed a more accurate and stringent modified criteria devoted exclusively for diagnosis of human cysticercosis in 2001.

**Absolute Criteria:**
- Histological demonstration of parasite
- CT or MRI showing cystic lesion with scolex
- Visualisation of parasite by fundoscopy

**Major Criteria:**
- CT or MRI showing lesions suggestive of NCC
- Positive electro-immuno transfer blot assay (EITB)
- Resolution of cystic lesion spontaneously or with therapy.

**Minor Criteria:**
- Lesions compatible with NCC in CT or MRI
- Clinical manifestations suggestive of NCC
- Positive CSF ELISA
- Cysticercosis outside the CNS

**Epidemiologic Criteria:**
- Residence in endemic area
- Travel to an endemic area
- Household contact with an individual infected with T. solium

**Drawbacks in Current Diagnostic Criteria:** Unfortunately, most of our patients do not meet the diagnostic criteria. Visualisation of the parasite by fundoscopy and the scolex by imaging and identification of extra-neuronal cysticercosis is rare in our population. Histological demonstration of parasite in NCC is usually not done. Epidemiologic criteria is of no use as ours is an endemic nation. EITB and CSF ELISA for NCC are not widely available in India. Majority of our patients present with a single enhancing lesion in which EITB assay is often falsely negative. EITB has a specificity approaching 100% and sensitivity from 94-98% only in patients with two or more lesions. EITB is also falsely negative in patients with calcified lesions.

Rajashekar and Chandy proposed the following diagnostic criteria to identify NCC easily in India based on their studies and clinical experience [13].

**Clinical Criteria:**
- Partial or generalised seizures as the initial symptom
- Absence of persistent raised intra-cranial pressure
- Absence of progressive neurological deficit
- No other active systemic disease

**CT Criteria:**
- Solitary contrast enhancing lesion
- Lesion less than 20mm in diameter
- Absence of midline shift or severe cerebral edema

The validity and accuracy of the above criteria has not been widely evaluated. Further studies are required to arrive at a reliable and feasible diagnostic criterion in endemic developing nations.
Treatment of NCC

General Concepts of Treatment:

- Treatment should be based on the viability, number of lesions and location.
- A growing cysticercus should always be treated with anti-parasitic drugs.
- In patients with NCC and increased intracranial tension, the intracranial hypertension should be treated first. Anti-parasitic therapy is never the priority in this setting.
- Anti-epileptics are the primary therapy for seizure control in NCC. Anti-parasitic drugs do not substitute for anti-epileptics [14].

Medical therapy for NCC: For viable and degenerating cysts, albendazole 15mg/kg PO up to a maximum of 800mg in 2 divided doses was recommended for 1 month. The duration of treatment has been reduced to 15 days and lately to 1 week after subsequent studies. To prevent exacerbation of symptoms which occur between second to fifth day of therapy albendazole is always given along with high dose glucocorticoids (dexamethasone 4.5-12mg/day) and anti-seizure medications. Mannitol at doses of 2g/kg/day can be used for acute reduction of intracranial tension. For calcified cysts no cysticidal therapy is indicated. Albendazole is preferred over praziquantel as it has better CSF penetration, does not interact with steroids and is also cheaper.

For subarachnoid NCC, trials have shown that prolonged intensive medical treatment can be very effective even with giant cysts and neurosurgery is required only when there is imminent risk of death [15].

There have been arguments whether anti-parasitic therapy is really necessary in NCC as the cysts follow a benign course, degenerate and heal with natural evolution. Also, acute brain inflammation with anti-parasitic therapy will exacerbate symptoms transiently. But recent studies have shown a benefit with anti-parasitic therapy with reduction in number of active cysts and better seizure control. There is also complete resolution of lesions with therapy and less frequent residual calcifications [16]. Patients with multiple lesions benefit more from anti-parasitic therapy than patients with solitary lesions. But these reports need confirmation.

Duration of anti-epileptic therapy is also not clear. In a study from Chandigarh, short duration anti-epileptic therapy for 6 months has been found to be adequate in patients with complete resolution of lesions. In patients with residual calcifications longer duration (up to 2 years) of anti-epileptic therapy may be necessary but it does not alter the chances for seizure recurrence [17].

Surgical Therapy for NCC: Before anti-parasitic drugs were available surgery was the primary therapy for large parenchymal cysts and intra-ventricular cysts. Now the role of surgery is limited to placing ventriculo-peritoneal shunts for emergency management of hydrocephalus. The main problem is frequent shunt blockage in these patients. Prolonged steroid therapy is advocated for avoiding shunt block. Neuroendoscopic resection can be done for intra-ventricular cysts with obstructive hydrocephalus.

Community Treatment and Prevention: Clean hygienic practices will go a long way in prevention and control of NCC. Sewage irrigation should be stopped and all fresh vegetables and fruits should be peeled and cleaned before consumption. Regular inspection of slaughter houses for infected pork and chemotherapy for pigs will prevent transmission of taeniosis to humans. Mass chemotherapy in humans is not advocated because taenoidal eradication may produce adverse effects in people with occult NCC.

CONCLUSION

Neurocysticercosis is an underestimated menace to our society as there is poor epidemiologic data for the estimation of its potential threat. Better guidelines, suitable for our country, need to be developed for its identification and management. Probably, the best treatment is to assess each case of NCC individually for its management. Community prevention and eradication depends on the development of better hygiene, waste disposal practices and improvement in the infrastructure of the society.

REFERENCES