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Clinical Diagnoses of Neurocysticercosis

Arturo Carpio

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http://dx.doi.org/10.5772/52388

1. Introduction

Neurocysticercosis (NCC), the most common parasitic brain disease worldwide, is endemic in countries with poor sanitation, and is increasingly being reported in developed countries due to globalization and immigration. As of many decades ago innumerable papers have been published regarding the clinical diagnosis of NC. It has been typical to affirm that clinical manifestations are extremely heterogeneous because they depend on the number, location, size, viability, or evolutionary phase of the parasite, as well as on the immunological response of the patient [1,2]. One of the most intriguing aspects of NCC is that presumably a high percentage of the individuals harboring NCC remain asymptomatic [3]; however, among the symptomatic group, the only clinical manifestation in most patients with parenchymal NCC is seizures, and their neurological status is usually normal [2]. In some patients NCC develops clinical manifestations many years after the parasite lodges in the central nervous system [4], as either brain inflammation around the parasite or mass effect. It has also been stated that almost any neurological symptomatology may be found, ranging from mild headache or treatable acute seizures to very severe neurological manifestations, such as intracranial hypertension (ICH), dementia, or even death [5-8]. These assumptions are probably true, since empirical observation has shown that many of these factors are related to a specific clinical manifestation; however, to date there is no definitive study, using appropriate methodology, designed to address the precise role of each of these factors, or the interaction among them, on the development of symptoms or signs due to NC. This is why the clinical spectrum of symptomatic NCC is currently poorly understood [9].

2. Clinical manifestations of neurocysticercosis

A myriad of papers have reported a wide range of diverse symptoms and signs related to NC, such as manifestations of brainstem dysfunction, cerebellar ataxia, sensory deficits,
involuntary movements, stroke-like symptoms, extrapyramidal signs, dementia, Bruns syndrome, Kluver-Bucy syndrome, cortical blindness, etc [2,10]; however, in some cases it is not possible to establish a clear cause-effect relationship between these pathologies and NC, and a fortuitous relationship among them may occur. Most of this information comes from retrospective data based on uncontrolled studies, historical case series, and anecdotal reports collected mainly from hospital neurological settings. A systematic review was conducted to estimate the clinical manifestation frequencies of symptomatic NCC [9]. The authors reviewed 1569 papers and only 21, based on minimal quality standards, were included in the final analysis. Most of the studies report clinical manifestations of NCC based on hospital medical charts, which don’t present reliable information; the majority of them do not provided definitions of manifestations and, if they do, they vary from study to study. Among NCC patients seen in neurology clinics, about 79% had seizures/epilepsy, 38% severe headaches, 16% focal deficits, and 12% signs of increased intracranial pressure. Several other symptoms were also reported in less than 10% of the patients. The authors concluded that these estimates are only applicable to patients who are assisted in neurology clinics and likely over estimate the frequency of manifestations among all NCC cases [9]. Table 1 shows some representative studies which confirm the above mentioned clinical manifestations.

Clinical manifestations of NCC are determined mainly by the location of the parasite within the CNS, the evolutive phase of the parasite, and the immunological response of the patient, expressed as severity of disease activity. The clinical manifestations of parenchymal NCC are quite different from those of extraparenchymal NCC [11,12]. When the parasites are localized in the parenchyma, the main clinical manifestations are epileptic seizures or focal neurological deficits; if the parasites are localized inside the ventricles or the subarachnoid location there are signs and symptoms of cranial hypertension syndrome, cranial nerves abnormalities and hydrocephalus [12]. Regarding the parasite evolutive phase, the transitional or degenerative phase develops clinical manifestations due to the inflammatory reaction of the brain [13]. NCC predominantly affects adults in their third and fourth decade of life, and is relatively uncommon in children and the elderly [1,2] Reports of NCC are very rarely in children younger than 2 years of age because of the prolonged incubation period of T solium. Most often, the disease is recognized in children older than 7, due to this incubation period.

There is also clinical heterogeneity across geographical areas; most cases from the Indian subcontinent present single degenerative lesions, whereas those from Latin America present few viable cysts [14]. These differences are probably due to complex interactions between the host, parasite, and environmental factors [3]. Genetic differences in T. solium cysticerci have been reported from different countries [15,16] and may contribute towards the clinical variations among countries. A genetic susceptibility to NCC has been suggested by a reported positive association of HLA-DRBII 13 with single, contrast enhancing CT lesions [17]. However, familial aggregation of seizures in first degree relatives of NCC patients with seizures was not found [18].
<table>
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<th>Country (reference)</th>
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<th>Age</th>
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<th>design</th>
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</thead>
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<td>Brazil, (Forlenza OV, 1997)</td>
<td>Seizures 60%, depression 52%, intracranial hypertension 15%</td>
<td>38</td>
<td>18 to 59 years old</td>
<td>CT scans: small, multiple, calcifications or cystic, contrast enhanced or not, lesions within the parenchyma</td>
<td>historical cases from hospital records</td>
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<td>Brazil (Loureiro MG et al, 1997)</td>
<td>Seizures 91%, headache 23%, motor deficit 7%</td>
<td>44</td>
<td>All ages</td>
<td>Del Brutto et al diagnostic criteria *</td>
<td>historical cases from hospital records</td>
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<td>Mexico (Ruiz M et al, 1997)</td>
<td>Seizures, intracranial hypertension and learning disabilities</td>
<td>122</td>
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<td>CT scan (details not provided)</td>
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<td>Mexico (Saenz B, et al, 2006)</td>
<td>Seizures 80% adults, 56% children, headache 35% adults, 21% children</td>
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<td>CT scan or MRI (details not provided)</td>
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<td>USA (Rosenfeld EA et al, 1996)</td>
<td>Seizures 87%, headaches 32%, altered mental status 13%</td>
<td>47</td>
<td>1 to 15 years old</td>
<td>CT scan or MRI: single or multiple parenchymal, intraventricular, spinal, or subarachnoid lesions that were contrast-enhancing, cystic, or calcified</td>
<td>historical cases from hospital records</td>
</tr>
<tr>
<td>Ecuador (Carpio A, et al. 2008)</td>
<td>Seizures 62%, headaches 70%, depression 17%</td>
<td>178</td>
<td>All ages</td>
<td>CT scan or MRI: One or more active or degenerative parenchymal cysts associated or not with an extraparenchymal location</td>
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* Reference 31

Table 1. Clinical manifestations of neurocysticercosis
3. Parenchymal neurocysticercosis

As previously stated, the most common clinical manifestation of parenchymal NCC is epileptic seizure, which occurs in 60-90% of cases. A clinical study including 336 patients [12], reported that seizures were the most common manifestation in the parenchymal location (88%), in comparison with the extraparenchymal location (20%); similarly, focal deficits or motor abnormalities were commonest in the parenchymal location (24% vs. 14%). Focal neurological deficits, when present, are usually transient, over a period of a few days, weeks, or months, with periods of remission and relapse, most likely due to different evolutionary stages of the parasite.

Clinical manifestations are clearly different when comparing by age [19]. Most cases of childhood NCC present mild to moderate symptomatology and single lesions [20-22]. A study [23] specifically carried out to compare the clinical manifestations between pediatric and adult NCC patients reported that seizures were more frequent in children (80.4% versus 56.1%), intracranial hypertension and headaches were more frequent in adults (27.2% versus 15.2% and 35.1% versus 21.7%, respectively), and focal deficits were 17% in adults and 12% in children. Although these age-related differences seem clear, a single effect of age is difficult to demonstrate, since various confounding factors are probably involved [19].

Most paediatric cases show a single transitional cyst, also named solitary cysticercus granuloma [2,24]. The single transitional cyst or single enhancing lesion on CT (SECTL) or hyperintense lesion on magnetic resonance imaging (MRI), is a common finding in patients with newly identified seizures in developing countries. These patients, mainly children and young adults, have some benign and transitory clinical manifestations, predominantly partial or partial secondary generalized seizures, and occasionally Todd’s paresis or focal neurological deficits. SECTL tend to resolve spontaneously, without anticysticercal drugs or surgery, since the parasite is already in the degenerative phase and will eventually disappear or become calcified.

Symptomatology of altered mental state and psychiatric manifestations remains poorly described in the literature [9]. In two studies [25,26] which provided definitions of clinical manifestations, depression was reported about 53% and 15%, respectively. Differences on gender have also been identified. Inflammation surrounding parenchymal cysticerci is more intense in women [19]; and multiple degenerating parasites localized in the parenchyma are more frequently reported in young women. Regardless of the localization of the parasite, the inflammatory response, as expressed by cerebrospinal fluid (CSF) cellularity is also more intense in women [3]. A recent prospective study [19] confirms that there are significant gender and age differences in the local immune response, even after adjusting for differences in healthcare access.

4. Extraparenchymal neurocysticercosis

The extraparenchymal location (around 15–30% of cases) develops different clinical manifestations. Headache and signs of intracranial pressure are more frequent in the
extraparenchymal location [88%], in comparison with the parenchymal location (10%). [12] When cysticerci are located inside the ventricular system, life-threatening acute intracranial hypertension as a result of hydrocephalus may occur; as a consequence, severe headache, dizziness and consciousness alteration are the predominant clinical manifestations [5,27].

Cysts in the subarachnoid space may lodge in the Sylvian fissure or basal cisterns and grow to a big size (racemose form), causing intracranial hypertension. This is associated with an intense inflammatory reaction, and fibrosis and progressive thickening of the leptomeninges at the base of the brain [13]. There is an obstruction of the CSF circulation, resulting in hydrocephalus and progressive intracranial hypertension. Inflammation of meninges, cranial nerve involvement, chiasmatatic syndrome, and cerebral infarcts secondary to vasculitis may develop [5,6]. When hydrocephalus due to cysticercotic meningitis is present, the mortality rate is high (50%), and most patients die within 2 years after CSF shunting [6,8]. This is why ventricular and basal cisternal locations are considered to be malignant forms of NCC [28]. In cases with NCC meningitis, cerebrospinal fluid (CSF) may show mild elevation of protein, hypoglycorrhachia and lymphocytic pleocytosis, which is similar to other chronic basal meningitis, such as tuberculosis and mycosis.[2]

Spinal cord cysticercosis is rare. Patients experience nonspecific clinical manifestations, such as nerve root pain or spinal cord compression syndromes, according to the level of the lesion [29]. Severe forms of NCC may exceptionally occur, including cysticercotic encephalitis, which result in permanent neurologic sequel, such as amaurosis. Hydrocephalus and intraventricular NCC is extremely rare in children [23,30]

5. Immunological and imaging diagnosis

Two main techniques, the Enzyme-linked Immunosorbent Assay (Ab-ELISA) and Enzyme-Linked Immunoelctrotransfer Blot (EITB) Assay, are used for immunological diagnosis of NCC. ELISA test for antibodies or antigen detection have showed higher sensitivities and specificities in CSF than in sera [31]. EITB sensibility seems to be not significantly different in sera and CSF while specificity is higher in CSF [32]. Sensibility of either tests falls in cases of single cysts in parenchyma or when they are calcified [33]. In patients with reliable diagnosis of NCC by imaging studies, immunological test is not required, since a negative test will not discard a NCC. When imaging of extraparenchymal cysts is doubtful, determination of antigens by ELISA in CSF may be helpful [31].

Computed tomography and magnetic resonance imaging have been useful in the study of the parasite evolution within the brain parenchyma [2]. Once the oncosphere has passed into the parenchyma, it grows and evolves through vesicular, colloidal, granular-nodular, and calcified phases [13]. In the vesicular phase the larva lives inside a translucent liquid-filled cystic structure surrounded by a thin membrane. The CT scan depicts circumscribed, rounded, hypodense areas, varying in size and number, without enhancement by contrast media [34]. With the MRI, the vesicular larva appears with a CSF-like intensity signal on all sequences. Both MRI and CT may show a high intensity, 2-3 mm. mural nodule, depicting the scolex, in the interior of some vesicular cysts (Figure 1). It is better seen on fluid attenuated inversion recovery (FLAIR) sequence [35].
A: vesicular cysts  B: colloidal cysts  C: nodular cysts  D: calcified cysts

Figure 1. Imaging of parenchymal neurocysticercosis

As the cyst degenerates, the CT scan shows an annular or nodular enhancement surrounded by perilesional edema. In this stage, the fluid content gives slightly higher signal than CSF and is sometimes isodense with the parenchyma on MRI-T1 and/or proton density-weighted, and high signal on T2 images. The capsule shows higher signal than the adjacent brain with thick ring enhancement on T1 images, while on T2 images there is a low ring signal surrounded by high signal lesion, due mostly to edema. Finally, when the cyst dies it may disappear or become an inactive calcified nodule of homogenous high density on CT, or low intensity on proton-weighted MRI [2] (Figure 1).
Extraparenchymal NCC is more difficult to detect by imaging because the attenuation and signal intensity of the cyst’s content is similar to that of CSF, the cystic wall is usually very thin and the cysts lack frequently of a scolex and generally not enhanced after contrast administration. In these cases, new MRI techniques such as fluid attenuated inversion recovery (FLAIR) and fast imaging employing steady-state acquisition (FIESTA) sequences, that seems to permit a better diagnosis (34-36) (Figure 2). A common neuroimaging finding is hydrocephalus related to inflammatory occlusion of Luschka and Magendie foramina and
basal fibrous arachnoiditis [36]. Cysts located within CSF cisterns usually have a multilobulated appearance (racemose form), displacing neighboring structures as a mass occupying lesion (Figure 2).

6. Difficulties with clinical diagnosis of neurocysticercosis

Del Brutto et al. proposed a diagnostic criterion for NCC in 2001 [37]. In spite of the fact that this proposal has not been validated so far, it has been an important contribution to current NCC knowledge. This proposal includes four categories of criteria—absolute, major, minor, and epidemiologic. A combination of these criteria results in degrees of diagnostic certainty: definitive and probable. Diagnosis of definitive NCC is made by the presence of one absolute criterion or of two major plus one minor or one epidemiologic criterion [37].

These diagnostic criteria may be useful to identify patients with mainly parenchymal forms of NC, but it is not for patients with extraparenchymal forms of NCC [31]. Among minor criteria are considered “manifestations suggestive of neurocysticercosis” which include seizures, focal neurologic deficits, increased intracranial pressure, and intellectual deterioration, which are predominantly related to parenchymal location of lesions, but not necessarily to extraparenchymal clinical manifestations such as those associated with intraventricular cysts or NCC meningeal inflammation. Among absolute criteria are considered “Cystic lesions showing the scolex on CT or MRI” or “spontaneous resolution of small single enhancing lesions” It is extremely rare to see scolex on CT or MRI inside the ventricles or the subarachnoid location, and it is also very difficult to demonstrate spontaneous resolution of small single enhancing lesions in the extraparenchymal location.

This diagnostic criteria proposal may be a source of bias even in the event of diagnosing parenchymal NC. For example, a patient who lives in any country where cysticercosis is endemic (epidemiologic criterion), with seizure or headache (1 minor criterion), a CT showing a calcification (one major criterion), and a positive serum enzyme-linked immunoelectrotransfer blot assay –EITB– (one major criterion), according to this proposal, should be categorized as “definitive NC”. However, it could be erroneous to diagnose this patient as having NC, since headache is extremely unspecific, a positive EITB means just exposure to the parasite, and a calcification could correspond to many other pathologies, but not necessarily NC. The selection of these patients in some reports, especially those community-based, is probably over-diagnosing NC.

There are additional problems related to this proposal that could lead to a misleading diagnosis. According to these diagnosis criteria, two major criteria fulfill a definite NCC diagnosis criterion. In this context, a patient with a positive immunologic test for the detection of anticysticercal antibodies (major criterion) plus a plain X-ray films showing “cigarshaped” calcifications in thigh and calf muscles (major criterion) could be diagnosed as NC. It is very hard to accept that such a patient may unquestionably have cysticerci in the brain. Some authors have claimed that the generalized use of Del Brutto et al [38] criteria have created some distortion in the present perception of NCC [31] A broad consensus now
exists that these criteria should be revised to incorporate current scientific knowledge, in order to achieve a new consensus on the diagnosis of NCC.

7. Conclusion

So far, diagnosis of NCC is mainly done by neuroimaging. New imaging techniques have improved detection of the scolex inside the cysts, which can be considered pathognomonic of neurocysticercosis. There is no a typical clinical manifestation of NCC. Prospective cohort studies addressed to analyzing NCC clinical manifestations, including definitions and appropriate methodology, which make them comparable, are extremely scarce in the medical literature. Location of the parasite in the CNS, age, sex, and immunological response of the patient, all seem to play an important role in occurrence of symptoms and signs; however, the relative contribution of these factors, alone or in combination, is still unknown.

In the parenchymal location, seizures are the most frequent clinical manifestation, followed by headache, motor focal deficits, and psychiatric and cognitive symptomatology. These clinical manifestations may have periods of remission and exacerbation, according to the evolutionary phase of the parasite inside the parenchyma. Diagnosis of extraparenchymal NCC is even more difficult, considering that unspecific symptoms and signs of intracranial hypertension and meningitis may occur, with or without signs of CSF inflammation. The clinical manifestations due to parenchymal location are usually benign and are sometimes transitory in time; on the contrary, clinical presentation of the extraparenchymal location is life-threatening and may develop permanent sequelae.

Properly-designed studies with similar methodology are needed to learn more about the natural history of the disease and the true distribution of clinical manifestations. There is also an urgent need to develop new consensus diagnosis criteria for NC.

Author details

Arturo Carpio
School of Medicine, University of Cuenca, Ecuador
G.H. Sergievsky Center, Columbia University, New York, USA

8. References


