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### Assessment of Specificity of a Recombinant 10-kDa Protein Antigen in Differential Diagnosis of Neurocysticercosis

**To the Editor**—In their recent article, Chung et al. [1] evaluated the recombinant 10-kDa protein antigen of *Cysticercus cellulosae* in diagnosis of human neurocysticercosis (NCC), particularly its potential for differentiating active NCC from chronic NCC. The authors concluded that the mortality, chronic morbidity, and economic loss could be avoided by the control and prevention of human NCC, which can be achieved by serological screening of pigs infested with *C. cellulosae*, from which the authors have already obtained encouraging results.

Researchers often have difficulty in differential diagnosis of chronic meningitis in determining whether it is tuberculous meningitis (TBM), cryptococcal meningitis, or NCC, because these infections are highly endemic in many underdeveloped and developing countries, and various clinical manifestations of NCC overlap those of other diseases of the central nervous system (CNS) [2]. Therefore, it would have been ideal if the specificity of recombinant 10-kDa protein antigen had been tested in cerebrospinal fluid (CSF) from patients with proven TBM, cryptococcal meningitis, and carcinomatous meningitis. For immune diagnosis of NCC, it would be appropriate to detect antibody/antigen in CSF or CSF/serum and not in serum alone, as de novo synthesis of anticysticercal antibodies in the

CNS compartment has been shown in cases of NCC [3]. The authors claim that recombinant 10-kDa protein antigen was exclusive to meningitis vesicular cyst fluid (CF). The antigenic relationship between the 10-kDa antigen protein of CF and those of 2 other 10-kDa antigens of *C. cellulosae* with different epitopes (10a and 10b), purified from scolex proteins by monoclonal antibody–ligand immunochromatography, has not been studied, because 10a and 10b also had been found to be highly specific [4]. My colleagues and I recently observed a true immune response to the 10-kDa antigen of sonicate-extract whole *C. cellulosae* in CSF samples from 10 patients with chronic meningitis, 3 of whom proved to have TBM (data not shown). This suggests that the 10-kDa antigen could be a stress or heat shock protein (HSP) that is highly conserved across many genera [5]. This hsp10 is abundantly expressed in *Mycobacterium tuberculosis* [6]. Comparing the sequence homology of the recombinant 10-kDa protein of CF with those of the 10a and 10b of scolex proteins and hsp10 would clarify whether the 10-kDa protein of CF is unique to *C. cellulosae*.

I agree with the authors' findings that it would be difficult to distinguish active NCC from chronic NCC when computed tomography/magnetic resonance imaging scans reveal that a patient has both multiple low-density regions and calcified cysts. It possibly could be achieved by detecting excretory/secretory (E/S) products of *C. cellulosae* or cysticercal antigens released into CSF as a consequence of an immune reaction. Detection of E/S products or components of *C. cellulosae* (antigens) per se would be more advantageous than antibody detection in differential diagnosis of NCC, because live cysticerci only elaborate E/S products, thus indicating the active state of the disease. Detection and quantitation of cysticercal antigens would help in prognosis of the disease. The relative merits of antigen detection versus antibody analysis have been reviewed elsewhere [7]. My colleagues and I selectively demonstrated 2 cysticercal antigens in human CSF from patients with proven NCC, with molecular masses of 24–28 and 64–68 kDa, of which the 24–28 kDa antigen was found to be highly specific [8].

Because the immune response to various cysticercal antigens (CF, scolex, membrane, antigen B, immunoaffinity-purified parasite antigens, and nonruptured whole *C. cellulosae* from human and porcine sources) has been found to be heterogeneous, and certain immunodiagnostic parasitic antigens are exclusive to CF, scolex, and membrane [9, 10], use of the 10-kDa antigen alone in immunodiagnosis of NCC could possibly yield a false-negative result. Therefore, ideally a homogenate of nonruptured whole metacestodes of *Taenia solium* should be used for further purification of parasitic antigens, as it contains all the components of different anatomical parts of the cyst [9]. Earlier, antigenic differences between *C. cellulosae* of porcine and human sources and antigenic variations in *C. cellulosae* obtained from infested pigs from different regions of the Indian subcontinent were observed [11, 12]. Hence, (1) antigenic variations in *C. cellulosae*, (2) use of different antigenic prepara-

tions, and (3) hosts' heterogeneous immune responses would all explain possible reasons for inconsistency in the sensitivity and specificity of the many immunoassays described for diagnosis of NCC [9, 11].

For control of NCC, it is necessary to accurately diagnose the disease, which could be achieved by use of purified "parasitic" antigens prepared from a pool of cysts derived from infested pork obtained from different regions of the world, as parasites are known to exhibit antigenic drift [11, 12]. For prevention, it is essential to breach the life cycle of *T. solium*, which could be achieved by (1) educating vulnerable populations, (2) their adopting strict hygienic practices in their lifestyles, (3) nongrazing of pigs in open defecated areas, and, finally, (4) cessation of pork consumption. Pig rearing is a viable economic proposition for many people in underdeveloped and developing countries, because almost no financial expenditure is required. NCC will continue to exist as long as pigs are allowed to graze in open defecated areas and as long as the life cycle of *T. solium* is not breached.

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#### Reply

**To the Editor**—We appreciate the comments and suggestions given by Dr. Katti [1] on our recent publication [2]. We agree that the diagnostic value of our recombinant 10-kDa protein of *Taenia solium* metacestodes (TsMs) should be evaluated further with cerebrospinal fluid (CSF) samples from patients with meningitides and vascular or tumor lesions, because neurocysticercosis (NCC) showed highly protean clinical and imaging manifestations. As Dr. Katti pointed out, differentiation of NCC from other brain diseases is very important for the appropriate treatment of the patients. The immunoglobulin levels in CSF samples from patients with these diseases may be increased by different mechanisms. In NCC, specific antibodies in CSF are considered to be the products of intracranial synthesis rather than a consequence of exudation or transudation from patients' blood [3], and this is a possible explanation for the fact that the levels of certain antibodies persist longer in CSF than they do in serum. In tuberculous meningitis, IgG levels in CSF could rise due to exudation and intracranial synthesis [3]. On the other hand, in the cases of intracranial hemorrhage, elevation of IgG levels is likely to be associated with transudation through damaged blood-brain barriers. The increase of immunoglobulin levels in CSF is supposed to give rise to nonspecific antibody reaction in immunological assays, especially those involving the use of crude antigens. However, applying a simultaneous multiantigen system can identify this nonspecific cross-reaction. In addition, such nonspecificity can be ruled out if a single, specific diagnostic antigen is used.

We have examined the antibody responses against the recombinant 10-kDa protein by performing immunoblot assays on CSF samples from 15 patients with NCC and from 5 patients with other brain diseases (4 with tuberculous and 1 with cancerous meningitis). While all NCC patients had antibodies that recognized the 10-kDa protein, no cross-reactions were observed in patients with other diseases (data not shown). These results are consistent with those obtained from serum samples. Significantly, 1 CSF sample (>100 mg/dL protein) from a patient with tuberculous meningitis showed cross-reactions to crude antigens of TsMs, *Paragonimus westermani*, and *Spirometra mansoni* plerocercoid but did not react with the recombinant 10-kDa antigen (data not shown). These collective data indicate that the TsM 10-kDa antigen is also highly specific to CSF samples. However, because the CSF samples are not readily available, we suggest that the assay using serum samples will be more practical in terms of application. While it is necessary to conduct further studies using large numbers of CSF