Pediatr Radiol (2008) 38:1306–1313
DOI 10.1007/s00247-008-1028-1

ORIGINAL ARTICLE

Magnetic resonance imaging of miliary tuberculosis of the central nervous system in children with tuberculous meningitis

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Received: 4 July 2008 / Revised: 19 August 2008 / Accepted: 2 September 2008 / Published online: 18 October 2008

Abstract
Background Tuberculous meningitis (TBM) is closely associated with miliary tuberculosis and a pathogenetic relationship is suspected, although it has been proposed that the two processes are unrelated.
Objective To describe miliary tuberculosis of the central nervous system (CNS) on MRI in children with TBM.
Materials and methods A retrospective descriptive study of 32 paediatric TBM patients referred for MRI. The presence of miliary nodules in the CNS was recorded. Lesions were categorized according to their distribution, enhancement pattern, size and signal characteristics.
Results A miliary distribution of nodules was present in 88% of patients. All patients with a miliary distribution had leptomeningeal nodules and 18% of these patients had deep parenchymal nodules in addition. At least one tuberculoma with central T2 hypointensity was identified in 39% of patients.
Conclusion The high prevalence of miliary leptomeningeal nodules in the CNS of children with TBM is significant because it points to a pathogenetic relationship that has long been suspected on epidemiological grounds. Our findings challenge the concept that miliary tuberculosis is only an incidental finding in TBM patients and suggest that it plays an integral part in the pathogenesis.

Keywords Tuberculosis · Meningitis · Granuloma · MRI · Children

This work was presented in part at the 45th Annual Meeting of the European Society of Paediatric Radiology, 4 June 2008, Edinburgh, UK.

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Introduction

Mycobacterium tuberculosis infection (tuberculosis, TB) continues to be of major international concern. Commonly considered a disease of developing nations, the burden of disease in developed nations is increasing [1]. Young children, in particular, are the most susceptible to tuberculous meningitis (TBM) [2].

TBM is much more closely associated with miliary TB than other varieties of disseminated TB and a pathogenetic relationship has long been suspected. Rich and McCordock [3] emphasized the presence of a pre-existing caseous lesion in the cortex or meninges older than any concurrent miliary TB. They dissociated miliary TB from a role in the pathogenesis of TBM [3]. This remains a common hypothesis in the literature although it is controversial. The role that miliary TB plays in the development of TBM is still uncertain.

The aim of this study was to describe the prevalence, appearance and distribution of miliary TB of the central nervous system (CNS) on MRI in children with TBM. The role that direct haematogenous spread to the meninges may play in the pathogenesis of TBM is discussed.

Materials and methods

The study was retrospective descriptive and was reviewed and ethically approved by the committee for human research at our institution. Children 13 years of age and under who were referred for MRI scan between August 2006 and April 2008 were considered for inclusion in the study. From this pool, patients diagnosed by a paediatric neurologist as having TBM on clinical grounds were selected for the study if they fulfilled the following criteria:

A. Positive cerebrospinal fluid (CSF) culture of *M. tuberculosis*, or
B. Radiological diagnosis of TBM (basal leptomeningeal enhancement on T1-weighted (T1-W) gadolinium-enhanced MRI according to objective criteria) [4]. In addition these patients had to fulfil at least one of the following criteria:
    a. CSF chemistry supportive of TBM.
    b. Positive *M. tuberculosis* cultures/microscopy from a site other than the CSF (i.e. gastric aspirate, bronchoalveolar lavage fluid or bone marrow aspirate).

The clinical diagnosis was made by a paediatric neurologist if two or more of the following criteria were present in the presence of the characteristic history and CSF changes associated with TBM: a positive history of contact with an adult with TB, a positive tuberculin skin test (Mantoux), a chest radiograph suggestive of pulmonary TB, poor weight gain or weight crossing the centiles documented on the patient's growth chart, positive identification of acid-fast bacilli from gastric washings (microscopy or culture) and a cranial CT scan demonstrating the characteristic features of TBM.

Children with an equivocal diagnosis of TBM or with an MRI scan without a T1-W gadolinium-enhanced sequence were excluded from the study.

The stage of the disease at presentation was recorded according to the Medical Research Council guidelines [5].

Imaging at 1.5 T was performed using a standardized protocol on a Magnetom Symphony scanner (Siemens, Erlangen, Germany). A T2-W turbo spin-echo sequence (TR/TE 4,000/104 ms) was used in the axial and sagittal planes. A FLAIR sequence (TR/TE 8,000/109 ms) and T1 turbo spin-echo sequences (TR/TE 531/14 ms) before and after intravenous contrast medium administration (0.1 mmol/kg, Magnevist; Bayer Schering, Leverkusen, Germany) were used in the axial plane.

The MRI scans were reviewed retrospectively by two radiologists (one consultant paediatric radiologist with extensive TBM imaging experience, one second-year radiology resident) from a radiology department in an endemic TB area. Final arbitration resided with the senior reader. The presence of miliary nodules in the CNS on gadolinium-enhanced T1-W images was recorded. The spinal cord was not evaluated.

Lesions were considered *miliary* when multiple small lesions (1–10 mm) were present. They were considered to be *leptomeningeal* when they were in the leptomeninges, cortical ribbon or on the surface of the brainstem. Lesions were categorized according to their distribution, enhancement pattern (ring or nodular), size of the largest lesion, and signal characteristics on T2-W images. T2 hypointensity in at least one lesion was considered to be indicative of the characteristic gummatous necrosis pattern [6]. In addition, lesions were categorized as being *deep parenchymal* when they were in the white matter, deep grey matter or in the brainstem away from the surface. Whether these lesions had surrounding oedema was also recorded. Follow-up imaging was only done when clinically indicated due to resource constraints, and was not reviewed as part of this study.

Results

Included in the study were 32 patients (15 male, 17 female; average age 4.6 years, median 2.7 years, range 0.3–13.2 years). Seven patients (22%) satisfied criterion A (proven TBM) and 25 patients (78%) criterion B (probable TBM). One patient (3%) had stage I, 14 patients (44%) stage II, and 17 patients (53%) stage III TBM at presentation.

A miliary distribution of nodules was present in 28 patients (88%). All patients (100%, 28) with a miliary distribution had leptomeningeal nodules and five (18%) of these patients had deep parenchymal nodules in addition. The four remaining patients (12%) did not have any nodular enhancing lesions (Table 1).

The leptomeningeal nodules were most prevalent between the cerebellar folia (24 patients, 86%) and in the region of the vermis and quadrigeminal cistern (24 patients, 86%). Leptomeningeal nodules near the prepontine, cerebellopontine and medullary cisterns (14 patients, 50%) as well as over the cerebral convexities (11 patients, 39%) were less prevalent. Leptomeningeal nodules in the sylvian cisterns (7 patients, 25%), middle cerebral artery cisterns (2 patients, 7%) and on the cranial nerves (1 patient, 3.6%) were also present occasionally. No nodules were present in the suprasellar cistern (Figs. 1, 2, and 3).

Of the patients with leptomeningeal nodules, 15 (54%) had lesions that were only nodular enhancing and 13 (46%) had mixed nodular and ring-enhancing lesions. The largest lesion was measured in each patient where leptomeningeal nodules were present. The maximum size of the largest leptomeningeal lesion in these patients ranged from 1 mm

Table 1 Characteristics of 32 patients with tuberculous meningitis and their MRI findings.

Patient	Age (years)	Gender	Criterion	Stage	Nodules present	Miliary distribution	Leptomeningeal location	Largest leptomeningeal lesion (mm)	Deep parenchymal location	Vasogenic oedema	T2-W hypointense lesion
1	9.2	F	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern	3	Hemispheric parenchyma, cerebellar vermis	No	–
2	4.3	F	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, sylvian cistern, convexities	4.5	–	n/a	Sylvian cistern
3	7.9	M	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern	3.6	Hemispheric parenchyma	Yes	Vermis/ quadrigeminal cistern
4	1.7	M	B	III	+	+	Cerebellar folia, brainstem/pontine cistern	2	–	n/a	–
5	2.0	F	B	III	+	+	Cerebellar folia, convexities	5	–	n/a	Cerebellar folia
6	2.0	M	B	II	+	+	Sylvian cistern, convexities	4	–	n/a	–
7	6.8	F	B	III	−	−	n/a	n/a	–	n/a	–
8	3.5	M	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern	2	–	n/a	–
9	2.3	F	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern	4	–	n/a	–
10	0.9	M	A	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, sylvian cistern, convexities	5	–	n/a	Vermis/ quadrigeminal cistern
11	10.8	F	A	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, middle cerebral artery cistern, convexities	5	–	n/a	Brainstem/ pontine cistern
12	0.8	M	B	II	+	+	Cerebellar folia	7	–	n/a	Cerebellar folia
13	13.0	M	A	II	+	+	Vermis/quadrigeminal cistern, brainstem/ pontine cistern, cranial nerves	3	–	n/a	–
14	0.3	F	A	II	+	+	Vermis/quadrigeminal cistern, brainstem/ pontine cistern	3	–	n/a	–
15	9.0	F	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, convexities	5	–	n/a	Convexities
16	3.1	M	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern	1	–	n/a	–
17	4.2	F	A	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern	1	–	n/a	–
18	8.3	F	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, sylvian cistern	4	–	n/a	Cerebellar folia
19	0.8	F	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern	1	–	n/a	–
20	1.1	F	A	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, sylvian cistern	11	–	n/a	Brainstem/ pontine cistern
21	1.0	M	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern	1	–	n/a	–
22	3.4	F	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern, convexities	5	–	n/a	Middle cerebral artery cistern

Table 1 (continued).

Patient	Age (years)	Gender	Criterion	Stage	Nodules present	Miliary distribution	Leptomeningeal location	Largest leptomeningeal lesion (mm)	Deep parenchymal location	Vasogenic oedema	T2-W hypointense lesion
23	1.0	M	B	III	−	−	n/a	n/a	–	n/a	–
24	0.5	F	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern	7	Hemispheric parenchyma	Yes	Cerebellar folia
25	12.8	F	B	II	+	+	vermis/quadrigeminal cistern, convexities	2	Brainstem parenchyma	No	–
26	4.3	M	B	III	−	−	n/a	n/a	–	n/a	–
27	12.4	F	A	I	−	−	n/a	n/a	–	n/a	–
28	13.2	M	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, sylvian cistern, convexities	4	–	n/a	–
29	1.8	F	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern	2	–	n/a	–
30	1.9	M	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, middle cerebral artery cistern	4	–	n/a	–
31	1.5	M	B	III	+	+	Cerebellar folia, vermis/quadrigeminal cistern	3	–	n/a	–
32	1.5	M	B	II	+	+	Cerebellar folia, vermis/quadrigeminal cistern, brainstem/pontine cistern, sylvian cistern	3	Brainstem parenchyma	No	–

n/a unavailable or not applicable.

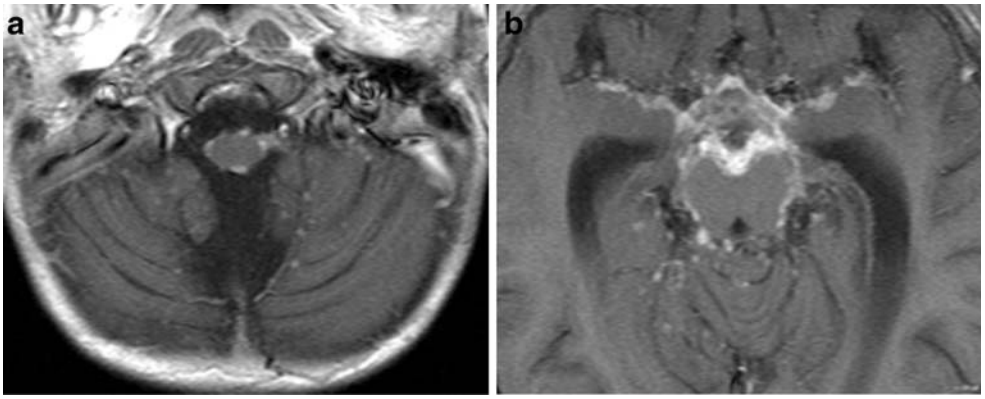

Fig. 1 Axial gadolinium-enhanced T1-W MR images demonstrate miliary leptomeningeal nodules in the cerebellar folia (**a**) and quadrigeminal cistern (**b**). There was also nodular enhancement of the leptomeninges in the middle cerebral artery cistern in this patient

to 11 mm with the average size of the largest lesion being 4 mm (median size 3.6 mm).

At least one leptomeningeal nodular lesion with central T2 hypointensity was identified in 11 patients (39%) (Fig. 4). The maximum size of these lesions varied between 4 mm and 11 mm with an average size of 5.6 mm (median size 5.0 mm). Six of these lesions were ring enhancing, three were nodular enhancing and two had mixed nodular and ring enhancement on the comparative gadolinium-enhanced T1-W images.

Of the five patients who also had deep parenchymal nodules, only two (40%) had lesions with surrounding parenchymal oedema on T2-W imaging.

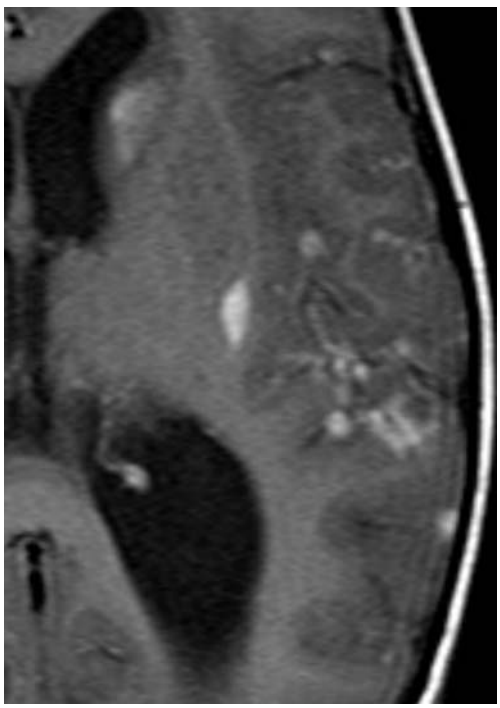

Fig. 2 Axial gadolinium-enhanced T1-W MR image demonstrates enhancing leptomeningeal nodules in the sylvian cistern

Discussion

TBM in children remains important because it is a very common, life threatening and severely debilitating disease. In the event of delayed diagnosis, particularly in young children, a dire outcome is to be expected [7, 8]. In certain communities in the catchment area of our hospital, the incidence of TB in children exceeds 1,000/100,000 population and TBM is now the commonest identifiable form of bacterial meningitis at our institution [2, 9]. Due to the insidious onset of nonspecific symptoms, the early diagnosis of TBM remains challenging and is of the utmost importance in achieving optimal patient outcome. Although effective therapies for TB have been known for decades, the continual emergence of multidrug-resistant (MDR) and more recently, extremely drug-resistant (XDR) strains is a source of great concern [10]. An improved understanding of the pathogenesis of TBM can hopefully lead to earlier diagnosis, which translates directly into better patient outcomes.

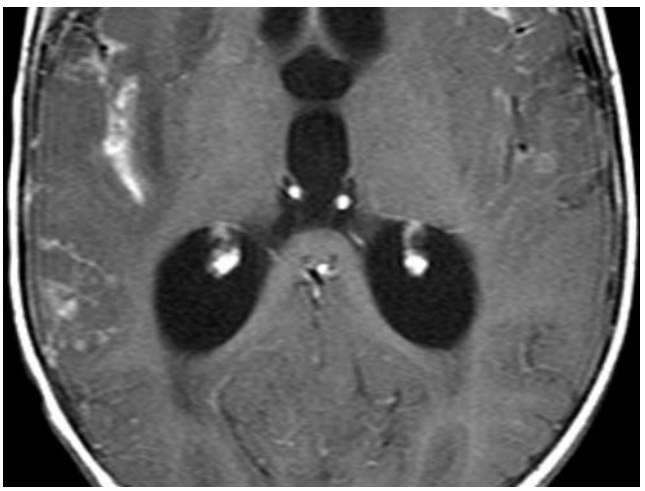

Fig. 3 Axial gadolinium-enhanced T1-W MR image shows miliary leptomeningeal nodules over the right temporoparietal convexity

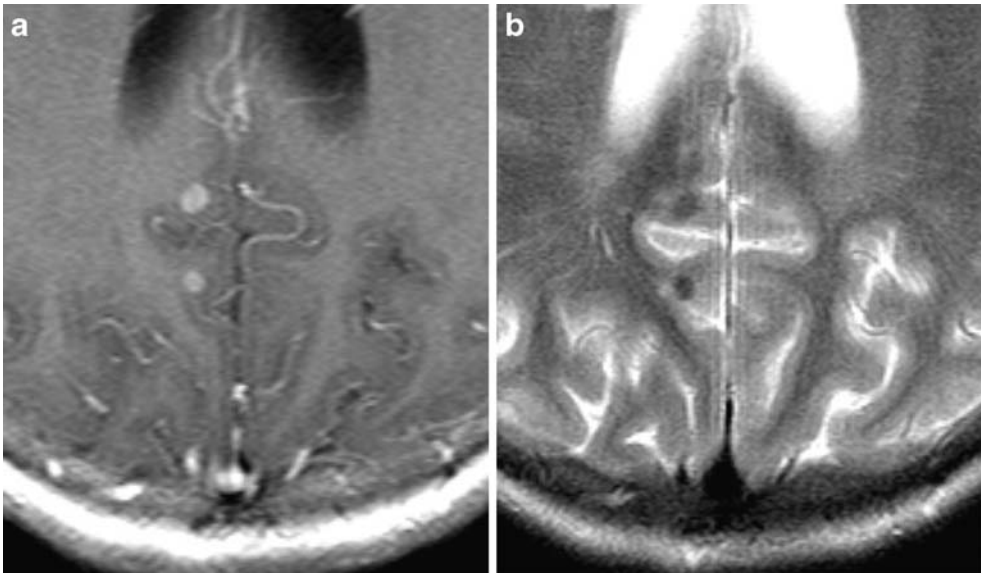

Fig. 4 Tuberculomas. **a** Axial gadolinium-enhanced T1-W image shows small ring-enhancing leptomeningeal nodules. **b** Axial T2-W image demonstrates corresponding hypointensity confirming that they are tuberculomas. This patient also had miliary nodules in other locations

The traditional mainstay of the diagnosis of TBM is the combination of CSF chemistry, microscopy and *M. tuberculosis* culture. However, numerous drawbacks including false-negatives and time delay hamper these methods [11, 12]. MRI is increasingly being used to evaluate patients with suspected TBM, not only for complications, but also primarily for rapid early diagnosis. MRI in these patients allows the opportunity to improve our understanding of the clinical and diagnostic features of the disease.

TBM is caused by a granulomatous hypersensitivity response to the presence of TB bacilli. This leads to a gelatinous exudate, which forms and accumulates with a predilection for the interpeduncular and suprasellar cisterns, covering arteries and cranial nerves. The sequelae are due to obliterative endarteritis with resultant infarctions, direct damage by the exudates to the parenchyma (border zone encephalitis) and impairment of CSF flow dynamics with resultant hydrocephalus [13]. The well-known MRI features of TBM (including basal leptomeningeal enhancement) are representative of these pathological processes. Two possible mechanisms that have been proposed for the pathogenesis of TBM are direct meningeal seeding during tuberculous bacillaemia or the concept of a subpial/subependymal granuloma (the Rich focus) that ruptures into the subarachnoid space [14, 15].

Pathologically the leptomeninges are known to be affected by multiple granulomas [3, 16]. The nodular form of leptomeningeal enhancement in cases of TBM is due to pial tuberculomas [4, 8, 17]. There are variable granulomatous reactions to TB that give rise to difficulty in classification. Some authors classify them as noncaseating granuloma (T1 hypointense, T2 hyperintense, homogeneous gadolinium enhancement), caseating granuloma with a solid centre (T1 iso-/hypointense, T2 iso-/hypointense, rim enhancement), or caseating granuloma with a liquid centre (T1 hypointense, T2 hyperintense, rim enhancement) [8]. Other authors describe the commonest type of necrosis in the CNS as gummatous and not caseous. These two processes are indistinguishable macro- and microscopically using standard methods, but can be reliably differentiated using the reticulin stain. More importantly, they can also be distinguished radiologically. A gummatous granuloma is T1 isointense and T2 hypointense whilst a caseous granuloma is T1 iso-/hypointense and T2 hyperintense. Gummatous granulomas are presumed to be tuberculous in the CNS, especially in South Africa, since neurosyphilitic gummas are very rare nowadays [6]. It is apparent that the signal intensities of caseating granuloma with a solid centre and the gummatous granuloma are the same. This also applies to the terms ‘caseating granuloma with a solid centre’ and ‘caseating granuloma’. For the sake of simplicity we refer to lesions that enhance on T1-W imaging with hypointensity on T2-W imaging as tuberculoma and regard the MRI characteristics as sufficient.

A close relationship between specifically miliary TB and TBM has been well described and a pathogenetic relationship has been suggested and was taught during the 19th and early 20th centuries. Clinical epidemiological data show that in children TBM develops most often within 3 months of primary infection, as does miliary TB [18, 19]. Thus there is a temporal correlation between the two conditions that suggests that they are pathogenetically related. Rich and McCordock performed post-mortem studies on TBM patients and found a caseous focus in either the brain cortex or the meninges in 36 out of 40 patients (90%) [20]. Their opinion was that this focus was usually older than the lesions of any simultaneously occurring miliary TB. This led them to conclude “the development of meningitis … is

a fortuitous event, depending not upon the existence of miliary tuberculosis but upon the chance extension of infection from an established caseous focus which happened to develop adjacent to the meninges or ventricles" [3]. However, this theory has been contested and remains controversial. Rich and McCordock noted that in some cases of miliary TB, TBM did not develop, although a number of small meningeal tubercles could be found in such cases and *M. tuberculosis* could be cultured from the CSF in some of these patients who did not have TBM. Also, the argument that the meningitis could not have developed at the same time as the other visceral tubercles in patients with miliary TB because the "age and character" of the granuloma did not correspond with that of the meningitis is in contrast to earlier work by the same investigators in 1929. They showed in animal studies that injecting a single bolus of bacilli resulted in organs later being affected by granulomas of different ages and sizes [3].

Children with miliary TB and TBM are also significantly younger than those with TBM only [2]. Haematogenous dissemination of bacilli may commence soon after the primary focus is established. This is especially true in very young children and immunocompromised patients, and the direct haematogenous route may be a more common mechanism in such patients [21]. The young median age of 2.7 years in our study population confirms this vulnerability to TBM.

The outstanding and significant finding in our study is that in a high proportion (88%) of children with TBM there is evidence of miliary leptomeningeal nodules on MRI. In 39% of these patients there was at least one lesion that was a confirmed tuberculoma according to MRI signal characteristics (Fig. 4). Concomitant deep parenchymal nodules were present in the minority of patients (18%). This finding concurs with that of neuropathologists who found that "examination of granulomas of different aetiologies in fixed brain specimens leaves us in no doubt that, contrary to imaging opinion, the majority are meningeal or cerebromeningeal in location. Properly intraparenchymal lesions, by comparison are rare" [6]. In our experience the tuberculomas are easily overlooked on T2-W images when viewing them in isolation and much easier to detect when the gadolinium-enhanced T1-W images are displayed side by side, since they lack vasogenic oedema.

The distribution of the miliary leptomeningeal nodules in our study showed a predilection for the posterior fossa and basal subarachnoid cisterns (Fig. 1). The lesions in these areas were also the most conspicuous. We cannot explain this predilection for the infratentorial compartment. It may be that observer sensitivity is greater in these areas because the anatomical configuration of the leptomeninges between the cerebellar folia and around the basal cisterns makes these lesions easier to detect. Alternatively, the posterior circulation and its characteristics may have a role to play. Gravity leading to pooling of slow-flowing venous blood that may increase the chance of infection in an area is another option that may be considered. It is stated in the literature that diseases that show disseminated haematogenous spread all share the common feature of the foci often being at the grey/white matter interface, because of narrowing of the arterioles [22]. While this is true of certain haematogenously spread diseases, such as metastases and neurocysticercosis, it may be erroneous in the context of TB. The diameter of red blood cells ranges from 6 to 8 μm, while the TB bacillus measures 2–4 μm in length and 0.2–0.5 μm in width.

The pathogenesis of TBM is thus still not completely understood. The well-documented findings of pathologists need to be reconciled with the equally well-established epidemiological facts. We are optimistic that neuroradiology can unearth this 'missing link'. With the exception of direct spread from adjacent structures (such as the temporal bone), tuberculous bacilli must reach the meninges by haematogenous spread to cause these pial tuberculomas. Thus, miliary TB must be associated with bacillaemia. We suggest that the exudates in TBM may be the result of miliary colonization of the leptomeninges and the subsequent development of widespread (probably more than MRI can detect) tuberculomas eliciting an inflammatory response in the leptomeninges. The complications of TBM are a result of the exudates that predominate in some of these areas and lead to infarctions and hydrocephalus. Some authors have proposed that it is likely that miliary TB increases the probability that a cortical or meningeal focus will be established that can lead to TBM. The same authors have also concluded "a sympathetic re-reading of the work of Rich and McCordock makes it apparent that their own semantics clouded their interpretation of the role of miliary tuberculosis in the pathogenesis of TBM" [3].

The imaging differential diagnoses for nodular leptomeningeal enhancement in children include fungal meningitis (i.e. *Cryptococcus neoformans*), metastatic spread into the subarachnoid space by either primary CNS neoplasms (i.e. medulloblastoma, ependymoma, glioblastoma) or extraneurological malignancies (i.e. lymphoma, neuroblastoma, leukaemia) and neurosarcoidosis [23, 24]. In our experience, such cases are extremely rare. The presence of a characteristic T2 hypointense leptomeningeal granuloma should alert the radiologist to the diagnosis of TB. Taking into consideration the clinical presentation and biochemical parameters of the patients in our study, the differential diagnosis was limited.

This study was limited by being retrospective and having no anatomical-pathological correlation available. Such correlation is increasingly difficult to obtain since the

diagnosis is often known, and in children parents are resistant to consenting to post-mortem examination.

Conclusion

The true pathogenesis of TBM is still not proven. The high prevalence of miliary nodules with a predominantly leptomeningeal distribution in the CNS of children with TBM is significant, because it points to a pathogenetic relationship that has long been suspected on epidemiological grounds. Whether it is due to an increased likelihood of a tuberculoma 'rupturing' into the subarachnoid space, or whether the bacilli have a direct effect on the leptomeninges is open to debate and further research. Our findings challenge the concept that miliary TB of the CNS is only an incidental finding in patients with TBM and suggest that it plays an integral part in the pathogenesis.

Acknowledgements We would like to thank Professors R.H. Hewlett and P.R. Donald for their comments.

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