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REVIEW

# Tuberculous encephalopathy: a reappraisal

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**Abstract** Forty years ago Dastur and Udani described a form of diffuse cerebral damage in tuberculosis, which they called tuberculous encephalopathy. Their pathological and clinical observations led them to propose an immune pathogenesis. Although there have been no convincing independently reported series, the entity is now established in the tuberculosis literature. We review the literature on tuberculous encephalopathy, and suggest alternative aetiopathogenetic explanations for the appearances of the brain in these cases. We propose that tuberculosis is one of many infections which may be associated with a range of immune, drug-related, hypoxic–ischaemic and toxic diffuse brain pathologies.

**Keywords** Tuberculosis · Encephalopathy · Cerebral oedema

## Introduction

In 1966, Dastur and Udani [12] described the pathological features of diffuse cerebral damage in tuberculosis, speculated on its pathogenesis, and coined for it the term "tuberculous encephalopathy" (TBE). They subsequently reviewed and expanded upon their initial observations [11, 58]. Despite having been reported only rarely since, the entity appears to have been widely accepted and features in most reviews and textbooks on CNS tuberculosis [25, 33]. However, in our experience of treating over 300 cases of CNS tuberculosis in Southern Africa over the past 25 years, we have not seen a single convincing clinical, radiological or pathological example. It is conceivable that antigenic differences between tubercle bacilli in India and elsewhere [39] may explain this striking discrepancy, but the possibility must also be considered that TBE is not in fact a single clinicopathological entity but rather a heterogeneous group of conditions, immune and non-immune. We therefore review the relevant literature to reassess the significance of TBE.

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## Tuberculous encephalopathy

### Original descriptions

Dastur and Udani [12] originally described the clinical and pathological features of 20 cases of diffuse brain damage in patients with tuberculosis. All were children (18 less than 10 years old and 15 less than 5 years), with an equal sex incidence. The rate of onset and subsequent course of the illness were variable, ranging from fulminating or acute, rapidly fatal cases ($n = 7$) to subacute ($n = 7$), chronic ($n = 5$) or "residual" cases lasting several years ($n = 1$). Clinical features said to be typical of tuberculous meningitis (TBM) were recorded in 15 of the 20 patients. Four major clinical syndromes were

proposed: (a) TBM with encephalopathy, (b) serous meningitis with encephalopathy, (c) tuberculous encephalopathy without meningitis and (d) acute haemorrhagic encephalopathy. Clinical features common to most cases included signs of raised intracranial pressure, papilloedema or optic atrophy, coma or semicoma, seizures, involuntary movements, paralysis, pyramidal, extrapyramidal and cerebellar signs, decerebrate spasms and rigidity. All patients received streptomycin, isoniazid and prednisolone as soon as tuberculosis was suspected clinically. Twelve patients died, and of the 8 survivors 4 had serious neurological deficits.

The autopsy or biopsy neuropathology findings were also heterogeneous. The most striking naked eye brain abnormality in the ten autopsied cases was "oedema", predominantly of white matter. Meningitis was variably defined, but histologic evidence of meningitis was documented in 17 cases, 7 of which had the fibrinous exudate, granulomatous inflammation and vasculitis typical of TBM. The most consistent histologic abnormality was diffuse and/or patchy white matter oedema, with myelin loss and variable, but usually minor, astrogliosis. Axonal loss was described as "almost commensurate" with myelin loss. Most cases showed at least some perivascular astrocytes or inflammatory cells, but in only four cases was there a marked cellular reaction. White matter inflammatory nodules were noted in four cases. Grey matter changes were also emphasised, including "chromatolytic degeneration of neurones", pericellular space enlargement and shrunken, dark neurones in both cortex and deep grey nuclei.

Enlarged perivascular spaces or perivascular "demyelination" were a feature in 13 cases. A total of three cases showed vessel wall necroses and minor petechial haemorrhages. One 17 year old girl, with previously untreated miliary TB, developed a fulminant, rapidly fatal monophasic haemorrhagic leucoencephalopathy the day after streptomycin and isoniazid therapy was instituted, with multiple white matter "ring" and "ball" haemorrhages, vascular necrosis and micro-infarction.

In summary, the authors considered that four main pathological processes were operative:

1. oedematous, predominantly white matter, encephalopathy ($n = 13$);
2. post-infectious encephalitis ($n = 4$);
3. purpuric or necrotising haemorrhagic leucoencephalopathy ($n = 2$);
4. post-meningoencephalitic residual cerebral damage ($n = 1$).

It was suggested that these cases represented para- or post-infectious allergic encephalitides. Toxic, inflammatory and vascular mechanisms were considered less likely. The florid haemorrhagic case was regarded as a form of acute haemorrhagic leucoencephalopathy (AHL or Weston Hurst disease). Some cases showed similar but less dramatic petechial bleeds, consistent with the idea that postinfectious encephalomyelitis and AHL are part of a spectrum of immune brain disorders [18, 23, 24, 55].

The same authors subsequently reviewed these and other cases of TBE, 30 in all, emphasising the high mortality (17 of 30 cases) and the high incidence of neurological deficits (5 mild and 4 severe) in survivors [58].

Finally, 20 years after the original publication, Dastur [11] again reviewed the entity, based on studies of about 30 brains and 25 spinal cords. He added examples of focal demyelinating lesions in nerve roots in some cases of spinal TB, regarding them as a manifestation of immune myelitis, and as further evidence in support of a cell-mediated immune pathogenesis.

## Subsequent reports

In the 40 years following the original description of TBE, there has been a dearth of further reported cases, despite claims that the pathology has subsequently been described by "many workers" [38].

Estanol et al. [17] described diffuse white matter oedema in association with what are likely to have been multiple tuberculomas in a 24-year-old woman with miliary TB. Dastur's [11] definition of TBE specifically excluded cases with large tuberculomas, since perilesional oedema is a common radiologic finding in such cases. Other authors have misused the term TBE to describe either TBM [20] or multiple cerebral tuberculomas [51].

To our knowledge, there have been only two subsequent case reports of possible TBE. Char and Morgan [7] described a 16-year-old girl with cavitating pulmonary TB who developed limb weakness 4 days after starting triple anti-TB chemotherapy. CT scan showed multiple irregular bilateral ring enhancing white matter lesions. Subsequent autopsy showed white matter softening with oedema, demyelination with relative axonal sparing and macrophage infiltration, but without evidence of tuberculous brain infection. Whilst this may represent immune demyelinating pathology, it is difficult to be certain when the brain appears recently to have been involved by multiple tuberculomas. Furthermore, the illustrated lesions appear to lie in arterial borderzone territories and may have been at least partly ischaemic in nature. More convincingly perhaps, Chetty et al. [8] described the case of a 45-year-old

man with AIDS and miliary TB who, in the course of treatment, developed a rapidly fatal haemorrhagic white matter disease, which autopsy confirmed as consistent with AHL. They argued that treatment-related mycobacterial lysis might have triggered an acute cerebral hypersensitivity reaction. This is a plausible explanation, although immune reactions to HIV itself or to another pathogen, or to antituberculous drugs, are also possible.

## Aetiopathogenesis

### The original proposal: an immune/hypersensitivity reaction?

Dastur and Udani's proposal that TBE represents a spectrum of immune-mediated white matter damage derives mainly from a postulated pathologic similarity to acute disseminated encephalomyelitis (ADEM), and to experimental allergic encephalomyelitis (EAE). Wisniewski and Bloom's [62] experiments in tuberculin-sensitized guinea pigs suggested that cell mediated immunity to tubercular proteins may indeed manifest as brain, cord or nerve root demyelination, and they noted a pathologic similarity to human neurotuberculosis.

ADEM (also known as postinfectious, perivenous or postvaccinial encephalomyelitis) is an acute, classically monophasic, demyelinating disease of children or adults that may follow a variety of viral illnesses or vaccinations [2, 15, 24, 31, 50, 57]. Recovery is often rapid, but about 20–30% of cases prove fatal, usually within 11–22 days of onset. The classical pathology is of multiple perivenous hemispheric white matter foci of demyelination with relative axonal sparing, lipid-laden macrophages and microglia, a lymphocytic infiltrate around vessels and in the leptomeninges and mild astrocytosis. There may be subpial demyelination in the spinal cord and brain stem, rare involvement of spinal and cranial nerve roots or an uncommon necrotizing myelopathy. The brain pathology in the majority of Dastur and Udani's cases of TBE differs significantly, in that there was no relative axonal preservation in areas of myelin loss, and the inflammatory infiltrate was in most cases not prominent. However, some authors have emphasised the pathologic heterogeneity of ADEM. Thus, DeVries [15] described an "encephalopathic" variant, particularly in young children, showing diffuse oedema, no demyelination, mild inflammation and petechial haemorrhages, and others have emphasised a spectrum of changes in ADEM [24] and EAE [18]. If one accepts a broader neuropathologic definition, potentially more of Dastur and Udani's cases are therefore compatible with an ADEM-like disease. However, whilst Hart and Earle accepted a pathologic similarity of their cases to EAE, they conceded the possibility of toxic and hypoxic mechanisms. Further, in four of their 30 cases there were glial nodules which they considered suggestive of direct viral brain infection. Similar nodules were described in 4 of the original 20 cases of TBE, raising the possibility that at least some cases may have been a response to a superimposed viral brain infection.

The brain in cases of long surviving ADEM may be normal, or may show variable perivascular or diffuse myelin pallor and gliosis [35]. Such changes are, however, non-specific, and Dastur and Udani's single case of "post-meningoencephalitic residual cerebral damage" is difficult to accept as necessarily the legacy of an immune-mediated ADEM-like disease.

Thus, many cases of TBE differ significantly enough from classical descriptions of immune encephalomyelitis to warrant consideration of other possible causes. However, Dastur [11] does describe a single case, not typical of the group, with multiple foci of white matter perivascular myelin pallor containing large and small mononuclear cells, which is more consistent with the typical pathology of ADEM. It is possible that this type of brain damage may on rare occasion occur as an immunologic complication of tuberculosis.

The similarity of rapidly fatal TB-associated haemorrhagic leukoencephalopathy [12, 58] to classical descriptions of AHL [18, 23, 24, 53] is more compelling. Their occurrence in relation to recently instituted anti-tuberculous chemotherapy may suggest an immune response to treatment-related release of tuberculous lipoproteins. Furthermore, the demonstration of cases of TBE with minor degrees of petechial haemorrhage is also perhaps consistent with the notion that AHL represents the hyperacute end of a spectrum of immune-mediated brain damage. However, before a diagnosis of AHL can be made, other causes of "brain purpura" must be excluded, perhaps in particular disseminated intravascular coagulopathy (DIC). The possibility also exists that these cases represent hypersensitivity reactions to drugs rather than to bacteria or bacterial products, for drug reactions may on occasion be neuropathologically indistinguishable from AHL [2, 23]. Even if one does accept these cases as immune, it is surely more appropriate to classify them as AHL, adding *Mycobacterium tuberculosis* to the list of potential pathogens which may trigger this disease.

## Diffuse encephalopathies in tuberculosis: alternative explanations

### Multiple sclerosis

An epidemiologic, and perhaps therefore aetiopathogenetic, relationship between multiple sclerosis (MS) and tuberculosis has been proposed, based on geographic co-localisation [43, 61], and on associations between the two diseases in population cohort studies [32]. In particular, a causal immune-mediated association between pulmonary tuberculosis and Devic's neuromyelitis optica [5, 27, 41, 44, 54] and acute necrotic myelopathy [27] has been suggested. Although these demyelinating syndromes are considered by many to be distinct from classical MS, some cases of TB-associated diffuse white matter disease may represent diffuse or acute variants of MS.

Acute (Marburg) and diffuse (Schilder) types of MS do show clinical and pathological similarities with TBE [46, 47, 50]. CSF lymphocyte counts and protein levels in acute and diffuse MS are normal or mildly elevated, as they usually are in TBE, and there are common clinical features. Although meningeal signs and fever are typically absent in these MS variants and were present in most cases of TBE, in the latter, fever was usually related to tuberculous disease in general, and meningeal signs to TBM in particular, rather than to TBE itself [58].

Pathologically, there is overlap between these conditions. Marburg MS is *usually* characterised by multiple plaques in brain, cord and optic nerve, with a predilection for periventricular regions—an appearance which immediately suggests the diagnosis of MS. However, cases with a more restricted distribution are described, limited to the centrum ovale. Optic nerve [12] and periventricular [11] lesions are both described or illustrated in some cases of TBE. The brain in Marburg MS may therefore appear very similar to that described in TBE.

Schilder's MS variant is characterised by the acute development of large single or multiple inflammatory demyelinating lesions in one or both cerebral hemispheres. Whilst some "transitional" cases also have typical MS plaques, "pure" cases, particularly in children, with large diffuse bilateral hemispheric lesions appear similar to TBE. Whilst classic MS plaques show myelin loss with relative axonal preservation, Schilder's lesions, like TBE, may have marked axonal loss [55], even with areas of cavitation or multiple cystic changes. Prominent oedema [4, 36, 47, 55] and a relatively minor lymphocytic brain infiltrate [4] are also common to acute or diffuse MS and TBE. At least some of the original TBE cases appear to fulfill Poser's criteria for Schilder's disease, namely signs, symptoms and CSF findings atypical for MS and large bilateral areas of demyelination of cerebral white matter [48]. It is therefore of interest that a possible relationship between Schilder's disease and primary TB has been postulated in South African children [49](Fig. 1).

### Hypoxia–ischaemia

Dastur and Udani [12] claimed that "cases with strong clinical evidence of vascular occlusion or infarction

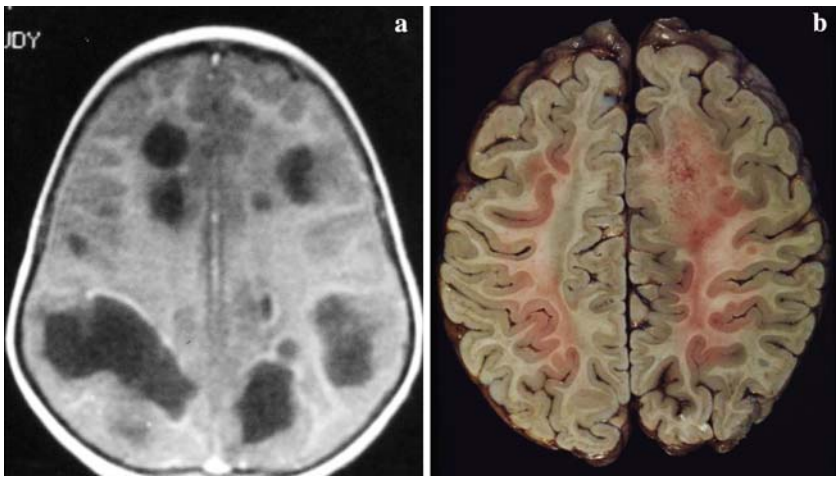


**Fig. 1** Schilder type demyelinating disease in young South African children. **a** Axial T1-weighted gadolinium enhanced MRI scan from a 6-year-old girl with a positive history of tuberculosis contact and a strongly positive Mantoux skin test (reference 49, case 2, with permission). Bilateral, symmetric hypointense lesions of white matter with incomplete ring enhancement. **b** Autopsy brain of a 2-year-old Angolan boy with sudden onset of weakness and blindness, and a positive Mantoux. On admission he was stupurous, with bilateral optic atrophy and dilated, non-reacting pupils. He deteriorated and died on the fifth day in the hospital. At autopsy the brain showed large demyelinating plaques affecting hemispheric white matter bilaterally and brainstem

were excluded" from their original TBE series. However, 6 of the 20 cases had macroscopic "compression of basal arteries", of which 4 had subintimal fibrosis of the internal carotid and middle cerebral arteries [12]. Infarction was considered not to have occurred in these cases on the basis that "total occlusion was not present". It is, however, clear from the study of basal artery atherosclerosis that perforating artery infarcts are often mediated by non-occlusive parent artery disease [19]. Furthermore, histological evidence of TBM was present in the majority of the index cases, seven with tuberculous fibrinous exudates, granulomatous reaction and vasculitis. "Many of the autopsied cases" showed evidence of "small or large foci of perivascular inflammation and vasculitis" [12]. Therefore, a significant vascular contribution is likely, particularly in the TBM-with-encephalopathy cases (15 of 30) [58]. For example, Case KDM No 18 NP-C-507 was described as showing TBM with vasculitis and internal carotid artery stenosis, associated with white matter oedema and multifocal vascular necrosis. A significant hypoxic–ischaemic component cannot be said to have been excluded in such a case. Similarly, the examples of "chronic tuberculous encephalopathy following meningitis" [58], which showed cortical degeneration and patchy white matter pallor, could clearly have been, at least in part, ischaemic.

The histological hallmarks of TBE (white matter oedema, myelin loss with commensurate axonal loss and focal necroses) are all potentially ischaemic in nature (Fig. 2), and some illustrated lesions appeared to be centred on small cerebral vessels. The predilection for white matter damage does not exclude an ischaemic pathogenesis, as other types of CNS vasculitis may present with predominant or exclusive white matter disease [26]. The TBE case showing laminar cortical degeneration [12] is highly suggestive of ischaemic damage, whilst other brains with loss of neurones in selectively vulnerable basal ganglia, Purkinje cells and dentate nuclei, could also represent damage of this sort. Finally, it should be remembered that ischaemia need not produce pan-cellular necrosis of brain tissue—ischaemia of lesser duration or severity may result in so-called "incomplete infarction" with preservation of structural brain integrity [21, 30]. Hypoxia–ischaemia does not appear to have been satisfactorily excluded as a significant contributory factor in all cases of TBE.

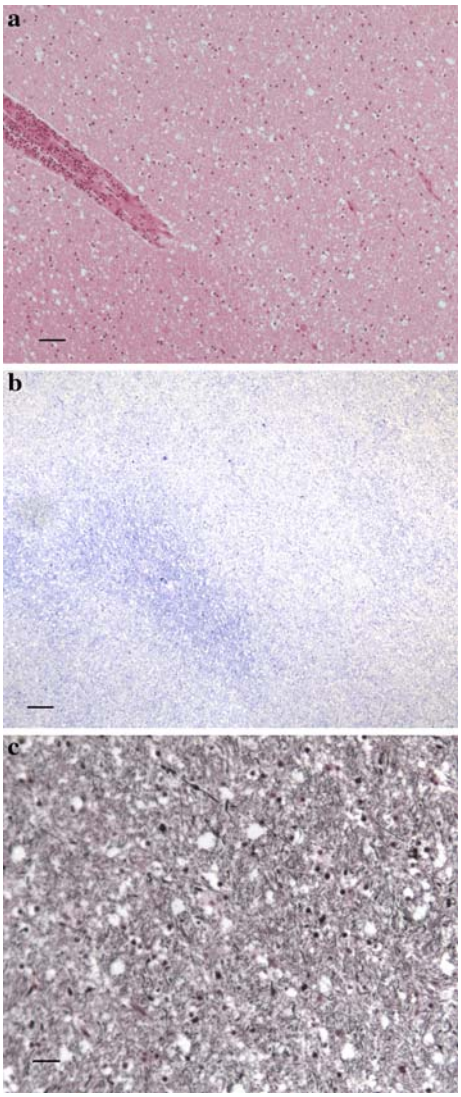


**Fig. 2** Hypoxic–ischaemic white matter damage in a two-and-half year old girl with miliary TB and TB meningitis. **a** White matter pallor and vacuolation (oedema), with a perivascular lymphocytic infiltrate (haemotoxylin and eosin. Bar = 100 μm). **b** Diffuse myelin pallor, with some perivascular sparing (*luxol fast blue/cresyl viol*et. Bar = 200μm). **c** Axonal loss commensurate with myelin loss (Bielschowsky's silver stain. Bar = 50 μm)

## Drug reactions

Dastur and Udani [12] did consider a possible role for anti-TB chemotherapeutic agents in the pathogenesis of their cases of TBE, but favoured an immune response to tuberculous infection. However, rapidly fatal brain purpura has been documented following administration of a number of antibiotics, resulting in numerous petechial haemorrhages, plasma exudation and oedema, with occasional foci of oedema, fibrin exudation and neutrophils [2, 23]. AHL-like variants of TBE may therefore represent fulminant drug hypersensitivity reactions.

Direct toxic encephalopathies complicating both streptomycin and isoniazid therapy are also reported [29]. Meyer et al. [37] drew attention to immediate profound clinical deterioration in a number of patients

with TBM, following introduction of treatment with isoniazid or, in particular, a combination of isoniazid and streptomycin. No brain pathology was available, and they suggested this might be a manifestation of a Herxheimer-like reaction, although isoniazid neurotoxicity cannot be excluded. CNS side-effects of isoniazid in humans, particularly in slow acetylators, are rare but do include confusion, seizures and coma [9, 13]. Neuropathologic correlates in humans are not, however, documented. The same drug may also cause a pellagra encephalopathy, particularly in malnourished patients, and often without the typical dermatitis [28]. Autopsy in these cases reveals characteristic widespread central chromatolysis of neurones, an appearance emphasised in the original neuropathology descriptions of some cases of TBE. In experimental animals, isoniazid may cause white matter vacuolation and oedema [6]. There are, therefore, brain changes described in TBE which may reflect drug toxicity rather than, or as well as, immune-mediated damage. The onset of neurological symptoms shortly after the introduction of anti-TB drugs was a striking feature in some cases of TBE.

Toxic/metabolic

The pathological appearances of the brain in TBE, according to Dastur and Udani [12] "seem to constitute more than a toxic or anoxic encephalopathy such as that described by Lyon et al.". Lyon et al. [34] had reviewed the confusing literature on acute childhood encephalopathies characterised clinically by reduced conscious level and seizures, accompanied by fever, often previously referred to as acute toxic encephalopathy. They described 16 new cases, 14 with autopsy, in 11 of which the brain was swollen. They could find no specific microscopic brain abnormality, although secondary hypoxic–ischaemic damage was common. They considered bacterial infection or bacterial toxins, together with fever, to be likely causal factors, with electrolyte imbalances and hypoxia secondary contributing factors. Their detailed clinical and pathological descriptions are similar to many of those of TBE, and it is therefore unclear how a similar "toxic" or "septic" encephalopathy can be so confidently excluded as a possible pathogenetic factor in Dastur and Udani's cases. Current understanding of so-called septic encephalopathy is incomplete, but the pathogenesis is likely to be multifactorial, with microemboli, metabolic derangement, damage from bacteria or bacterial breakdown products, hypoxia, poor cerebral perfusion and toxic drug effects likely to be causal factors. Contrary to Dastur and Udani's [12] claim that toxins comparable to those of other bacteria play no role in tuberculous lesions, septic shock due to tuberculosis, usually pulmonary, *may* occur [3, 22, 42, 63], perhaps mediated by tumour necrosis factor (TNF-α)[45]. TNF-α has been associated with disease progression in neurotuberculosis [56] and, amongst other effects, may "open" the blood–brain barrier [16]. Some cases of TBE may therefore represent a non-immune septic encephalopathy analagous to that caused by a variety of other bacterial infections.

There are other causes of oedematous encephalopathy reported in CNS and non-CNS TB, including hyponatraemia/water intoxication [40, 59, 60], and renal or renovascular hypertension [10, 14, 52], as well as encephalopathies with less well characterised neuropathologic correlates such as hypercalcaemic encephalopathy [1]. It is assumed that such causes would have been excluded by routine clinical and biochemical investigations in Dastur and Udani's series of TBE patients.

## Summary

Dastur and Udani described diffuse, predominantly white matter, encephalopathies associated with childhood tuberculosis. The neuropathologic features and purported lack of direct tuberculous CNS involvement led them to propose an immune pathogenesis comparable to ADEM or EAE. The cases were, however, clinically and pathologically heterogeneous, and at least some may have been drug-related, hypoxic–ischaemic or toxic complications of infection. TB may be added to the list of infections causing such reactions in the brain. It is perhaps more useful therefore to suggest that TB may be an uncommon cause of, or link with, such disorders as ADEM, AHL, Schilder-type MS or septic encephalopathy, rather than lumping these potentially distinct clinicopathologic entities under the umbrella term "TBE". Careful study and published description of future cases will shed further light on their pathogenesis and appropriate classification.

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