syndrome (n=3), atypical Miller Fisher syndrome (n=3), and acute cerebellar ataxia (n=1). Araki *et al.*³ however, reported on a patient with Guillain-Barré syndrome who had prominent cerebellar signs. That patient had high monospecific anti-GD1b IgG antibody titre in the acute phase of the illness, but did not have anti-GQ1b IgG. These findings led us to examine whether some patients in whom acute cerebellar ataxia has been diagnosed have anti-GD1b IgG antibodies.

Serum samples were obtained from 39 patients for whom acute cerebellar ataxia or acute cerebellitis had tentatively been diagnosed. One patient who had associated anti-GQ1b IgG was excluded because the tentative diagnosis was acute cerebellar ataxia and the final one ataxic Guillain-Barré syndrome. Serum IgM or IgG antibodies to GM1, GM2, GD1a, GD1b, GT1b, GQ1b, or GQ1ba were measured by an enzyme linked immunosorbent assay as described elsewhere.⁴ GQ1ba is a possible target molecule for serum antibodies from patients with sensory ataxic neuropathy.¹ Serum was considered positive when the antibody titre was 500 or more. One of the 39 patients had a high anti-GD1b IgG titre of 16 000 but carried no antibodies to the other six gangliosides. His clinical presentation is that described later. The other 38 patients had no antibodies to those gangliosides. Further study showed that serum from the patient who had anti-GD1b IgG did not react with asialo-GM1, fucosyl-GM1, GM1b, GalNAc-GM1b, GalNAc-GD1a, GD3, GT1a, GT1aa, or sulfated glucuronyl paragloboside.

A 55 year old man had a cough and nasal discharge that disappeared after a few days. After resolution of this illness, he noted paraesthesias in his fingers and toes (day 1) which worsened, and he developed an unsteady gait on day 3. He was apyrexial and fully conscious. Blepharoptosis was absent. Ocular movement was not limited, but smooth pursuit was saccadic. His pupils were normal, and light reflexes prompt. Neither facial nor oropharyngeal palsy was present. Limb weakness was insignificant. Deep tendon reflexes were absent. Babinski's sign was negative. Finger to nose and heel to knee tests were dysmetric and uncoordinated. Romberg's sign was negative, but standing in a tandem position was unsteady. Tandem gait was impossible, and assistance was needed to walk. Paraesthesias of the glove and stocking type were present. There was no impairment of pinprick, touch, position sense, or vibratory sensation. Autonomic nervous function was normal except for hyperhidrosis in the palmar and plantar surfaces. On days 3, 4, 6, 8, and 10, he underwent immunoadsorption treatment. The neurological signs rapidly disappeared. Motor and sensory nerve conduction values were normal on days 7 and 21. Protein in CSF was 32 mg/dl on day 3, and 60 mg/dl on day 10 with normal cellularity. On day 24 he was discharged without clinical signs, but still with mild paraesthesias in the right fingers. No external ophthalmoplegia was found during the course of the illness.

Acute cerebellar ataxia had been tentatively considered, but the ataxic form of Guillain-Barré syndrome, as proposed by Richter,¹ could be diagnosed. This is important because some patients in whom acute cerebellar ataxia has been diagnosed may have ataxic Guillain-Barré syndrome, and they could benefit from undergoing established treatment for the syndrome—namely, plasmapheresis or intravenous administration of

immunoglobulins. Serum samples from patients for whom acute cerebellar ataxia or acute cerebellitis is diagnosed should be tested for anti-GD1b and anti-GQ1b IgG antibodies in order not to overlook cases of ataxic Guillain-Barré syndrome.

Monospecific anti-GD1b IgG antibodies have been detected in a patient with Guillain-Barré syndrome who had prominent sensory ataxia and in a patient who had acute distal paraesthesias and areflexia after upper respiratory tract infection.^{5,6} Whether the presence of monospecific anti-GD1b IgG is correlated with a particular clinical condition, therefore, is uncertain. By contrast, a patient with cerebellar ataxia and chronic polyneuropathy has been reported to have IgM M-protein to GD1b, GM1, and asialo-GM1.⁷ Both the monoclonal IgM with anti-GD1b activity and murine monospecific anti-GD1b monoclonal antibody bind to the human cerebellar granular layer. The binding of anti-GD1b IgG to the cerebellar granular layer or spinocerebellar 1a fibres in the peripheral nerves may have produced the patient with cerebellar ataxia reported by Araki *et al.*³ and our present patient.

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Analysis of adenosine deaminase isoenzyme-2 (ADA₂) in cerebrospinal fluid in the diagnosis of tuberculous meningitis

The outcome of tuberculous meningitis is influenced by the stage of disease at the start of treatment. Initiation of antituberculous therapy is often delayed because of the inadequacy of presently available laboratory tests. Management of patients with possible tuberculous meningitis would thus be advanced by the development of an accurate, reliable, and rapid diagnostic test, particularly if it could be applied in settings with poor resources.

Adenosine deaminase (ADA), an enzyme involved in purine catabolism, exists in at least three forms. ADA₁ is a monomeric protein with a molecular mass of approximately 35 kDa and two ADA₁ molecules joined via a connecting protein form the dimeric

ADA₁₊₂. The third isoenzyme ADA₂ seems to be produced only by monocytes.¹ Total CSF ADA has been suggested as a marker for tuberculous meningitis^{2,3}; however, considerable variability and overlap, particularly with acute bacterial meningitis, has led some authors to question its clinical usefulness.⁴

An increased proportion of ADA₂ has been suggested to be a more specific means of diagnosing tuberculous effusions.² However, the use of CSF ADA₂ in the diagnosis of tuberculous meningitis has not been described.

Study subjects (all adults) were from a prospective cohort of patients undergoing a diagnostic lumbar puncture for suspected meningitis. Patient characteristics and investigations have previously been described in detail.⁵ In addition, CSF specimens from 10 patients at the Johannesburg Hospital were included (four tuberculous meningitis, four cryptococcal meningitis, two acute bacterial meningitis). Serum and CSF ADA analysis was performed on 11 specimens from patients with tuberculous meningitis (nine established by culture, two probable), nine with cryptococcal meningitis, 13 with acute bacterial meningitis (nine *Neisseria meningitidis*; two *Streptococcus pneumoniae*), nine with aseptic meningitis, and 19 with a normal lumbar puncture. All patients with tuberculous meningitis, cryptococcal meningitis, or aseptic meningitis, six of 13 with acute bacterial meningitis, and 10 of 19 of the normal lumbar puncture groups were HIV positive. Ethical approval was obtained from the committee for research on human subjects of the University of the Witwatersrand.

Tuberculous meningitis was confirmed if the CSF culture yielded *M tuberculosis*. Probable disease was diagnosed in the presence of a lymphocytic pleocytosis (>20 cells/mm³), high CSF protein (>0.8 g/l), low CSF glucose (<60% of matched plasma glucose), and evidence of pulmonary tuberculosis. Cryptococcal meningitis was diagnosed if either the indian ink stain, CSF fungal culture, or CSF cryptococcal antigen were positive. Acute bacterial meningitis was diagnosed in patients with acute onset of symptoms, pyrexia, a CSF neutrophilia with high protein, and low CSF glucose. Aseptic meningitis was diagnosed if there was a predominantly lymphocytic pleocytosis, a normal or moderately raised CSF protein (>0.7 g/l), and negative serology and bacterial, fungal, and mycobacterial culture.

Analysis of CSF was considered normal when there were < 5 leucocytes/mm³, protein <0.45 g/l, and negative culture and serology.

Matched CSF and serum samples were frozen within 6 hours of collection, stored at -20°C (the enzymes are stable for at least 4 weeks) and analysed within 1 week of collection. Tests were performed with laboratory staff unaware of the diagnosis. Total ADA activity was measured by an enzymatic spectrophotometric method on a Cobas Mira autoanalyser (Roche Diagnostics, Switzerland). Erythro-9-(2-hydroxy-3-nonyl)-adenine, a selective ADA₁ and ADA₁₊₂ inhibitor, was added to the reaction mixture at a concentration of 200 µM, allowing for the measurement of ADA₂ activity (in the same enzymatic system). The between batch coefficient of variation of the test at a dilution of 6 U/l was 8%. The proportion of total ADA which comprised ADA₂ could only be reliably estimated when total ADA was >2 U/l. ADA₂ isoenzyme analysis is therefore only reported in the groups with a median total CSF ADA of >2 U/l.

Total CSF and serum ADA and CSF ADA₂ in patients with meningitis or a normal lumbar puncture (LP)

Diagnosis	Total ADA	CSF ADA ₂	% ADA ₂	Serum Total ADA
TBM (n=11)	6.9 (4.2-69)	7.0 (3.5-57)	88.1 (80.5-100)	47.8 (43.5-85.1)
CM (n=9)	4.4 (2.5-10.9)	3.9 (1.2-6.1)	68.2* (43.6-93.2)	45.9 (26.6-48.7)
ABM (n=13)	3.6 (1.1-11.4)	1.7 (0.1-5.4)	37.9 (5.6-56.7)	15.7 (7.0-34.4)
Aseptic (n=9)	0.3 (0-2.7)	—	—	25.7 (10.3-42.4)
Normal LP (n=19)	0 (0-3.7)	—	—	37.3 (10.7-97.8)
p Value (ANOVA)	0.005	0.027	<0.0001	<0.0001

All results are median and range, except for %ADA₂ (mean and range). TBM=tuberculous meningitis; CM=cryptococcal meningitis; ABM= acute bacterial meningitis.

*Three subjects with CM had %ADA₂ >80%.

Data were analysed using EpiInfo 6.04 (CDC, Atlanta) and PRISM 2.01 (GraphPad Software, USA). Continuous variables were compared using analysis of variance (ANOVA) and a 5% level of significance was used.

Comparison of total CSF and serum ADA and CSF ADA₂ in the diagnostic categories is shown in the table. Total CSF ADA was highest in patients with tuberculous meningitis. Using a cut off of ≥ 6 U/l, the test was 90.9% sensitive in detecting tuberculous meningitis (10 of 11). The specificity was 94% (47 of 50) in all patients and 77.3% (17 of 22) compared with those with cryptococcal meningitis or acute bacterial meningitis. There were no significant differences between those with tuberculous meningitis established by culture and probable disease. Similarly, there were no significant differences in the CSF ADA concentrations in HIV positive and negative patients in the acute bacterial meningitis (mean 4.88 U/l vs 3.71 U/l; $p=0.49$) and normal lumbar puncture groups (mean 0.74 U/l v 0.12 U/l; $p=0.14$). Serum ADA concentrations were highest in patients with tuberculous meningitis or cryptococcal meningitis and significantly lower in those with acute bacterial meningitis.

There were significant differences in the mean proportion of total ADA that comprised ADA₂ in patients with tuberculous meningitis, cryptococcal meningitis, or acute bacterial meningitis ($p<0.001$). Using a cut off of 80% for the proportion of CSF ADA₂, the test was 100% sensitive and 86.4% specific in detecting tuberculous meningitis (positive predictive value 78.6%, negative predictive value 100%). An ADA₂ of >80% was found in three of nine of those with cryptococcal meningitis and none with acute bacterial meningitis. A cut off of 90% changed the sensitivity and specificity to 36.4% (four of 11) and 95.5% (21 of 22) respectively.

The diagnosis of tuberculous meningitis remains a challenge. Acid fast bacilli are typically identified by microscopy in less than a quarter of patients and mycobacterial culture, the present "gold standard" for diagnosis is positive in 45%–90% of cases and may take up to 8 weeks to yield results. Recent advances in rapid automated liquid culture may reduce culture times. The use of the polymerase chain reaction (PCR) to detect *Mycobacterium tuberculosis* specific DNA may be of potential value; however, problems with its specificity have been encountered.

Sensitivities of 100% and specificities of 99%³ have been described for total CSF ADA. However, others have reported lower sensitivities and specificities and have suggested that CSF ADA measurement has "no advantages over conventional diagnostic criteria".⁴ Possible reasons for the varying usefulness in different studies include different disease profiles, times to presentation, and ages, as children with tuberculous meningitis have lower ADA values.⁴

We were able to differentiate patients with tuberculous meningitis from those with aseptic meningitis or a normal lumbar puncture on the basis of the total CSF ADA. However, there was overlap between patients with tuberculous meningitis and those with cryptococcal meningitis or acute bacterial meningitis. A proportion of ADA₂ isoenzyme of >80% seems to be a reliable marker of tuberculous meningitis, yielding a sensitivity of 100% and specificity of 86.4%. The only other diagnostic category with patients who had >80% ADA₂ was cryptococcal meningitis, which is easily diagnosed on indian ink staining and serology. Serum ADA concentrations were not useful in differentiating the cause of meningitis.

The laboratory technique for measuring ADA₂ is inexpensive (about £1 per test), relatively simple to perform, and can be adapted to an autoanalyser. It may thus be used in laboratories with limited resources. Measurement of ADA₂ produces results rapidly, thus potentially decreasing delays before therapy for tuberculous meningitis is initiated. These results seem promising and may make a valuable contribution to the early and accurate diagnosis of tuberculous meningitis. The use of CSF ADA₂ in the diagnosis of tuberculous meningitis should be further evaluated in larger series, including patients with other lymphocytic meningitides and different settings.

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CORRESPONDENCE

Unilateral focal lesions in the rostralateral medulla influence chemosensitivity and breathing measured during wakefulness, sleep, and exercise

We have read with interest the article entitled *Unilateral focal lesions in the rostralateral medulla influence chemosensitivity and breathing measured during wakefulness, sleep, and exercise* by Morrell *et al*,¹ which shows that unilateral ischaemic lesions of the rostralateral medulla may lead to an abnormal ventilatory CO₂ response and sleep apnoea. We have recently conducted a similar study on five patients with syringobulbia. Syringobulbia has a predilection for autonomic nuclei of the cardiorespiratory network localised in the caudal medulla and this may cause severe respiratory and cardiovascular abnormalities.² On occasion, a syrinx may extend to the rostral and ventral medulla.³

Out of five patients with syringobulbia studied with MRI, ventilatory CO₂ response and polysomnography, one showed bilateral syringomyelic cavities in the caudal dorsal medulla with unilateral extension to the rostralateral medulla (figure). This 40 year old patient showed the following respiratory abnormalities: end tidal CO₂, 47.3 mm Hg; p 0.1, 0.21; ventilatory CO₂ response, 1.78 l/mm Hg; apnoea index, 52 events/hour of sleep, with a total number of 212 obstructive sleep apnoeas, four central apnoeas, and 39 hypopnoeas. Maximal duration of obstructive sleep apnoeas was 125 seconds and oxygen saturation values during apnoeic episodes lower than 50%. There was also evidence of severe autonomic dysfunction with orthostatic hypotension, arterial hypotension at rest, and complete loss of sinus arrhythmia. Despite the severity of the respiratory abnormalities recorded, the patient refused to receive any respiratory support, and to date has not developed any cardiorespiratory complication during a follow up of 9 years.

It seems that extension of the syrinx to ventral and rostral medullary areas may lead to more severe respiratory and cardiovascular abnormalities. Three stages in the progression of syringobulbia may be described in involvement of autonomic and respiratory structures: (1) initial involvement of the