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# Rapidly progressive dementia and ataxia in an elderly man

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## CASE PRESENTATION (DR RM AHMED)

### History

A 76-year-old man, a university educated retired engineer, was referred with a 2-month history of deteriorating balance and memory. He took metformin for type 2 diabetes mellitus. He attended with his wife within 2 days of the referral and brought his recent MRI scans of the brain and abdomen. He was not concerned by any memory problems (his wife certainly was), but felt off-balance when walking. It became apparent that he had actually been losing balance and memory for about 12 months, but this had progressed more rapidly in the last 2 months. He had no headaches, sensory or urinary symptoms. He was sleeping and eating well and had not lost weight. He was an accomplished pianist and his musical abilities had not deteriorated. He had never smoked and drank little alcohol.

### Examination

His wife said that he was his usual jocular self—possibly even fatuous. General examination, including heart, chest and abdomen, was normal. There was no cranial nerve abnormality, no papilloedema, no muscle wasting, normal muscle tone and strength throughout; reflexes were normal in the upper limbs, but knee jerks and ankle jerks were absent. His right plantar was extensor. Sensation was intact to pinprick; there was slight impairment of vibration and position sense at the toes. He walked with a wide-based unsteady gait and could not tandem walk; Romberg's test was positive. He scored 22/30 on the Mini-Mental State Examination, losing points for orientation, memory (recall) and repetition. On the Addenbrooke's Cognitive Examination he scored 62/100, losing points on memory (recall, anterograde and retrograde). Verbal fluency was

decreased. Language, naming and comprehension were intact. His scores were: attention and orientation 14/18, memory 10/26, fluency 0/14, language 24/26, visuospatial 14/16.

The MRI scan of brain (figure 1) he brought with him had been reported as follows: 'There is moderate cerebral atrophy with prominence of the cortical sulci and of the ventricular system with dilatation of the bodies and temporal horns of the lateral ventricles and of the third ventricle. The fourth ventricle is prominent. There is increased signal intensity in the peri-ventricular white matter suggesting periventricular cerebrospinal fluid (CSF) resorption. There is a CSF collection in the cisterna magna deforming the inferior aspects of the cerebellar hemispheres, suggesting an arachnoid cyst. The images show no small vessel ischaemia. The distal left vertebral artery is occluded. Comment: despite the cerebral atrophy, the appearances suggest normal pressure hydrocephalus.'

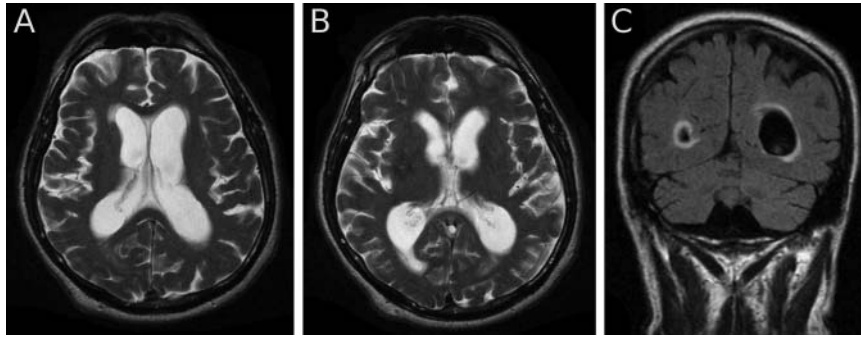
The abdominal MRI report described 'four cysts in the pancreas, without enhancement, mass effect, surrounding infiltration or duct dilatation'.

## DISCUSSION PART A (DR GM HALMAGYI)

This patient has three distinct clinical syndromes: dementia (impaired memory and fluency), ataxia (wide-based gait and positive Romberg's test) and sensory neuropathy (absent knee and ankle reflexes with distal sensory impairment). The ataxia might be from sensory impairment, cortical impairment or an unrelated cause such as cerebellar or vestibular impairment. The tempo of the dementia and of the ataxia is subacute; the tempo of the neuropathy is unknown. Box 1 details the possible diagnosis to consider. What single disease could cause all three of these syndromes? Possible conditions include vitamin B1



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**Figure 1** MRI scan of brain at presentation. Axial T2 (A, B) and coronal fluid attenuated inversion recovery sequences show cortical atrophy and ventricular enlargement with possible periventricular cerebrospinal fluid exudation.

deficiency (Wernicke–Korsakoff), vitamin B12 deficiency (subacute combined degeneration of the cord) and paraneoplastic disease.

1. *Vitamin B12 deficiency* would explain all the neurological problems<sup>1 2</sup> and a low serum B12 would clinch the diagnosis, even without haematologic changes. Neurological B12 deficiency can occur even with normal serum B12 levels,<sup>3</sup> particularly in patients exposed to metformin<sup>4</sup> or nitrous oxide (medical or recreational).<sup>5</sup> In such cases, high serum levels of homocysteine or methylmalonic acid—B12 intermediary metabolites—indicate functional B12 deficiency.<sup>6</sup> Brain MRI changes can occur in B12 deficiency<sup>3</sup> although spinal MRI changes are more usual.
2. *Wernicke–Korsakoff syndrome*, in the context of chronic alcohol abuse (to explain the peripheral neuropathy),<sup>7</sup> would also explain all the neurological abnormalities, even without ophthalmoplegia. However, the patient was well nourished and drank little alcohol, making this diagnosis unlikely. Wernicke’s encephalopathy has characteristic MRI abnormalities in the brainstem and the

basal ganglia, including T2 hyperintensity around the third ventricle, in the dorsomedial regions of the thalami, the periaqueductal areas of the midbrain, and the mamillary bodies.<sup>8</sup>

3. *Paraneoplastic disorders*. Paraneoplastic limbic encephalitis typically presents with cognitive changes, including short-term memory impairment, seizures, behavioural and personality changes;<sup>9</sup> there may be antibodies to Hu, CV2, Ma2 or voltage-gated potassium channels (VGKC).<sup>9</sup> Anti-Hu is also associated with paraneoplastic cerebellar degeneration and a sensory neuropathy,<sup>10</sup> which could explain this patient’s gait disturbance. On MRI, the mesial temporal structures may be swollen and hyperintense on T2-weighted sequences.<sup>11</sup> This patient had no behavioural and personality changes, psychiatric symptoms or seizures, and the lack of typical MRI abnormalities makes limbic encephalitis less likely.<sup>12</sup>

To investigate the possibility of limbic encephalitis further, we would need CSF, looking for mild leukocytosis and elevated protein.<sup>9</sup> EEG could show focal or generalised slowing or even epileptiform activity maximal in the temporal regions.<sup>12</sup> We also need to test for antineuronal antibodies and VGKC antibodies. He then needs imaging looking for an underlying tumour including a chest x-ray, whole body CT/positron emission tomography (PET) scan and also serum tumour markers (carcinoembryonic antigen (CEA), Ca19.9,  $\alpha$ -fetoprotein).

Among paraneoplastic causes, we should consider anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. This characteristic syndrome develops in three stages. The first features a prodromal illness of fever, headache, nausea, gastrointestinal or respiratory symptoms. This is followed by psychiatric symptoms, short-term memory and speech problems. In the third phase, patients develop decreased responsiveness, abnormal movements (typically orolingual facial dyskinesias) and autonomic symptoms. MRI is abnormal in half of all cases, with T2 or FLAIR signal hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem and rarely spinal cord. The CSF is abnormal in

### Box 1 The differential diagnosis for this patient includes

- *Hydrocephalus*: communicating (including normal pressure hydrocephalus, or as a result of infection, infiltration of meninges), non-communicating.
- *Neoplastic condition*: intraparenchymal and/or meningitic.
- *Paraneoplastic condition*: for instance, anti-Hu antibody-producing neoplasm causing cognitive deficit and ataxia, or voltage-gated potassium channels and anti-NMDA receptor encephalitis.
- *Infective encephalitis*: for instance, viral encephalitis, infective meningitis (TB, cryptococcal), HIV encephalitis, Whipple’s, syphilis.
- *Autoimmune*: for instance, sarcoidosis.
- *Sporadic Creutzfeldt–Jakob disease*
- *Toxic metabolic*: for instance, Hashimoto’s encephalitis, vitamin B1 deficiency, vitamin B12 deficiency, hyponatraemia and syndrome of inappropriate anti-diuretic hormone secretion.
- *Vascular causes*: cerebral vasculitis, cerebral venous thrombosis, small-vessel ischaemia
- *Late-onset white matter diseases*: for instance, hereditary diffuse leukoencephalopathy with neuroaxonal spheroids.
- *Drugs*: neuroleptic agents, benzodiazepines, recreational drugs.
- *Rapid progression of a chronic neurodegenerative disorder*: Alzheimer’s disease, frontotemporal dementia.

80%; including a lymphocytic pleocytosis, and normal or with mildly increased protein. There are CSF-specific oligoclonal bands in 60%.<sup>13</sup> This patient's age is against anti-NMDAR encephalitis, having a mean age of onset of 19 years. However, some cases are aged >70 years.<sup>13</sup> Testing for NMDA (N-methyl-D-aspartate) receptor antibodies would help to exclude this diagnosis.

In the setting of a possible paraneoplastic disorder, one should consider other possible causes of confusion, such as hyponatraemia (from the syndrome of inappropriate antidiuretic hormone secretion) and hypercalcaemia. Hence, we would need to see his serum electrolytes, osmolality and serum calcium, corrected for serum albumin levels.

If we assume that the peripheral neuropathy is chronic and diabetic and unrelated to his presentation, what then could cause just the subacute dementia and ataxia? The differential diagnosis becomes much broader. However, we should first consider the possibility that the dementia and ataxia are, in fact, due to the hydrocephalus, as suggested on MRI.

### Hydrocephalus

Ventricular enlargement follows from either a problem with CSF absorption (hydrocephalus) or from shrinkage of the brain tissue (cerebral atrophy) with neurodegenerative diseases and normal ageing. In practice, it is sometimes difficult to distinguish the reason for ventricular enlargement. Hydrocephalus is either communicating or non-communicating (ie, obstructive).

- *Obstructive hydrocephalus* implies a blockage to CSF flow within the ventricular system. Without an obstructing mass, it is often caused by stenosis of the aqueduct linking the 3rd and 4th ventricles: hence, the 4th ventricle is not enlarged.
- *Communicating hydrocephalus* implies that there is free passage of CSF through the ventricular system and out of the fourth ventricle, through the foramina of Luschka and Magendie. The problem is usually failure of CSF circulation or absorption in the subarachnoid space. In communicating hydrocephalus, the entire ventricular system, including the 4th ventricle is enlarged. Communicating hydrocephalus can occur acutely or chronically in patients who have, or have had, meningitis or subarachnoid haemorrhage.

A particular variety of chronic communicating hydrocephalus in the elderly has been called 'normal pressure', because the CSF pressure at a random single lumbar puncture is normal. It causes major diagnostic difficulties in elderly demented patients who are also off-balance and incontinent, as this particular triad of neurological problems, together with an enlarged ventricular system can be due to a neurodegenerative disease with cerebral atrophy, rather than to normal pressure hydrocephalus (NPH).<sup>14</sup>

Could this patient's problems be due to (communicating) hydrocephalus, as suggested by the brain MRI report, and could it be of the normal pressure variety? While his clinical syndrome (dementia+ataxia) is consistent with NPH, most patients with dementia and ataxia do not have NPH, even if they have the third component of the NPH triad (incontinence).<sup>14</sup> Studies that simply document gait disturbance, dementia, incontinence and ventriculomegaly probably overestimate the prevalence of NPH, which is probably equal to that of progressive supranuclear palsy.<sup>14</sup> Typically, NPH patients have subcortical/frontal cognitive dysfunction, most affected being memory, executive function, attention and psychomotor speed.<sup>15</sup> The neuropsychological profile can improve after shunt insertion.<sup>16</sup> However, other studies have found that while gait might improve initially, incontinence and cognitive features do not improve following shunt insertion, suggesting a high degree of overdiagnosis.<sup>14</sup> There is no definitive test for NPH. There are several supplemental tests to assist diagnosis, including the 'CSF tap test' (large-volume lumbar puncture), external CSF drainage by spinal drainage and CSF outflow determination with CSF infusion compliance studies.<sup>17</sup> However, these tests have variable sensitivities and specificities. The CSF tap test has a low sensitivity 26–61%. Clinical response to CSF removal by spinal catheter has a higher sensitivity 50–100%, specificity 60–100% and positive predictive value 80–100%.<sup>18</sup> However, it is an invasive procedure, requires expert management, and has a high complication rate.<sup>17</sup>

The rate of progression in this patient, over weeks, seems too rapid for NPH, which usually evolves over months to years. So if there really is communicating hydrocephalus, but is not of the normal pressure variety, what else could be causing it? One would have to think of infective or neoplastic causes.

### Infective and neoplastic causes

Many CNS infections can cause cognitive decline. CSF results help to differentiate these, including CSF protein and white cell count and viral PCR (herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and enterovirus). Against this in our patient, however, is the relatively subacute onset and lack of systemic features including fever. However, neurotropic viruses, such as enterovirus 71, can present with a subacute cognitive decline, which can be fatal.<sup>19</sup> Also, measles can cause cognitive decline in elderly patients<sup>20</sup> and mycoplasma can cause encephalitis.<sup>21</sup> In immunocompromised patients, CMV and EBV infections can cause encephalitis<sup>22</sup> and it would be important to know the patient's HIV status. There can also be a dementia-like presentation in Lyme disease.<sup>23</sup>

Chronic meningitis due to cryptococcal or tuberculous infection or leptomeningeal metastases may present with

dementia and ataxia and can cause intracranial hypertension, either with (ie, hydrocephalus)<sup>24 25</sup> or without ventricular enlargement (pseudotumour cerebri).<sup>26</sup>

Malignant meningitis presents with headache, dementia and ataxia in about half the cases.<sup>27</sup> Meningeal lymphoma can cause raised intracranial pressure with papilloedema and/or hydrocephalus.<sup>28</sup> Breast cancer (3%), small-cell lung cancer (6%), non-small-cell lung cancer (1%), gastrointestinal tumours (0.015–0.25%), carcinoma of unknown primary (3%) and melanoma (1.5%) can all produce neoplastic meningitis,<sup>27</sup> and could cause raised intracranial pressure and hydrocephalus through decreased CSF absorption by the arachnoid villi. In this patient, the ‘pancreatic cysts’ identified on MRI could represent a possible neoplastic lesion. The rapid clinical decline is also consistent with this diagnosis.

On MRI, one would look for leptomeningeal enhancement. It would be important to know the lumbar CSF pressure, protein, glucose and differential white cell count, as well as cytology and flow cytometry to detect any malignant cells. CSF protein and white cell count may be the most useful tests in differentiating between viral, bacterial and cryptococcal meningitis, while CSF glucose concentration is less useful.<sup>29</sup> A low glucose indicates a metabolically active process, but glucose can be low in both infective and neoplastic meningitis. It would also be important to know the results of cryptococcal antigen and tuberculosis (TB) PCR on CSF and cryptococcal serology on blood. The diagnosis of malignant meningitis might require several CSF examinations.

Could this be neurosyphilis, in one of its protean forms? The diagnosis depends on the results of serologic tests in blood and CSF; the interpretation of these results is often difficult—a positive result might not mean that syphilis is the cause. In the first instance, the blood syphilis serology should be checked and, if positive, the CSF examined. The diagnosis should be considered if the treponemal test is positive on CSF, there is an increased number of mononuclear cells, or if there is a positive venereal disease reference laboratory/rapid plasma reagin (VDRL/RPR) on the CSF. While a positive treponemal test on CSF does not confirm active neurosyphilis, a negative test excludes it.<sup>30</sup>

Neurological Whipple’s disease is also possible. Patients present with cognitive decline, psychiatric symptoms, seizures and oculopalatal myoclonus. MRI should show one or more multinodular enhancing lesions. The CSF serology for *Tropheryma whipplei* is not always positive, and brain biopsy might be needed for diagnosis.<sup>31</sup>

One should also consider progressive multifocal leukoencephalopathy. Typically, patients present with weakness, sensory change, hemianopia, cognitive decline and imbalance and gait difficulties. MRI is critical to the diagnosis, usually showing areas of hyperintensity on T2

and FLAIR imaging and hypointensity on T1. Typically, the subcortical white matter, cerebellar peduncles, basal ganglia and thalamus are involved.<sup>32</sup> The CSF should be checked for JC virus DNA.

#### Creutzfeldt-Jakob disease

Given the rapidity of the decline and cognitive and gait disturbance, it is important to consider sporadic Creutzfeldt–Jakob disease (sCJD). This can result in cognitive (39%), cerebellar (29%), behavioural (20%), constitutional (20%), sensory (11%), motor (9%) and visual (7%) symptoms.<sup>33 34</sup> To fulfil WHO diagnostic criteria for CJD, patients require two of the following: myoclonus, pyramidal/extrapyramidal findings, visual or cerebellar deficits, and akinetic mutism. This patient had an extensor plantar on the right, fulfilling the pyramidal finding, and the gait problem could represent a cerebellar deficit. The EEG result would be important, specifically looking for periodic epileptiform discharges. Also the CSF looking for 14-3-3 protein and neurone-specific enolase. On CSF, one would also expect a mildly elevated protein, normal glucose and no leukocytosis.<sup>35</sup> In sCJD, diffusion weighted (DWI) hyperintensities within the cortical and subcortical grey matter are highly sensitive and specific, and superior to either EEG, CSF neurone-specific enolase or 14-3-3 protein.<sup>36</sup>

#### Toxic/metabolic causes

We should also consider a toxic/metabolic cause. Hashimoto’s encephalopathy can present with cognitive decline and ataxia, though more typically with a relapsing-remitting course and stroke-like episodes or with seizures.<sup>37</sup> It would be important to know the thyroid function results and thyroid antibody results. Cognitive decline from intermittent exposure to carbon monoxide<sup>38</sup> can present with slowing and memory decline, along with gait abnormalities<sup>39</sup> and (unlike here) with globus pallidus abnormalities on MRI.<sup>40</sup>

#### Cerebral vasculitis

Isolated cerebral vasculitis can present with a subacute cognitive decline and non-specific symptoms. The diagnosis is difficult to make and relies on CSF examination, MRI/magnetic resonance angiography imaging and digital subtraction angiography. Both MRI and angiography can appear normal and have low diagnostic specificity. Brain biopsy is often required to help make the diagnosis.<sup>41</sup>

#### Cerebral venous thrombosis

Cerebral venous thrombosis of both the deep and superficial sinuses can present subacutely with non-specific signs and altered mentation and cognition. Cognitive decline can result from both white matter changes and venous hypertension, resulting in raised intracranial pressure.<sup>42</sup> It would be important to review the patient’s MRI and an MR venogram

looking for thrombus, and to measure the CSF opening pressure.

#### Late-onset white matter diseases

Adult-onset leukodystrophies can present with subacute cognitive decline, gait problems and ataxia. In particular, metachromatic leukodystrophy, adrenoleukodystrophy, vanishing white matter disease and hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) often present with mental deterioration and cognitive changes.<sup>43 44</sup> However, the lack of white matter changes on MRI, spasticity or other neurological findings make leukodystrophy unlikely, although cognitive decline may precede the MRI changes in HDLS.<sup>44</sup>

#### Autoimmune disease

We should consider autoimmune causes, such as sarcoidosis or Sjögren's syndrome. Blood tests including an autoimmune and vasculitic screen and a chest x-ray for hilar lymphadenopathy would help. MRI can show white matter changes and meningeal involvement.

#### Drugs

Drugs can show, cause cognitive decline. In particular, neuroleptic agents can cause rapid cognitive decline in patients with dementia with Lewy bodies. However, this patient had no hallucinations, REM sleep behaviour disorder or extrapyramidal features. Despite this, it would be important to double check the drug history to ensure he received no neuroleptic agents.

#### Chronic neurodegenerative diseases

Chronic neurodegenerative diseases can present subacutely and be mistaken for a rapidly progressive dementia. In a retrospective study, 23% of patients diagnosed as rapidly progressive dementia had frontotemporal dementia—motor neurone disease, and 9% had Alzheimer's disease.<sup>45</sup> In this patient, there was a 12-month history of decline, followed by 2 months of more rapid deterioration; it is possible that he had early Alzheimer's disease. In this situation, it would be important to perform a full septic screen (blood, chest x-ray and urine) to ensure one was not missing an infection that was worsening a chronic disorder. Careful examination of the MRI and volumetric MRI may be helpful in looking for focal atrophy that may point towards Alzheimer's disease or frontotemporal dementia.

#### TESTS TO BE REQUESTED

To investigate this patient, based on the list of differential diagnoses, I would want the results of the following tests.

Blood: full blood count, electrolytes, liver function tests, thyroid function tests, thyroid antibodies, autoimmune and vasculitic screen, vitamin B12 and folate, homocysteine, methylmalonic acid, antineuronal

antibodies, VGKC antibodies, NMDA receptor antibodies, syphilis serology and tumour markers (CEA,  $\alpha$  fetoprotein, Ca19.9)

Imaging: repeat MRI brain with contrast, chest x-ray, whole body PET/CT scan.

CSF: pressure, white cell count, microscopy protein, glucose, oligoclonal bands, TB, Whipple's, HSV, CMV, EBV and enterovirus PCR, cryptococcal antigen, cytology, flow cytometry and VDRL.

EEG.

#### RESULTS OF TESTS

##### Blood

- Electrolytes (sodium 136 mmol/l, potassium 4.5 mmol/l, chloride 98 mmol/l urea 7.6 mmol/l, creatinine 86  $\mu$ mol/l), full blood count and liver function tests: normal.
- Autoimmune and vasculitic screen (including ANA, ENA, double-stranded DNA, ANCA, rheumatoid factor, immunoglobulins, immune electrophoresis and cryoglobulins): negative.
- Vitamin B12 (285 pmol/l), serum folate (20.2 nmol/l), thyroid function (TSH 3.520 mIU/l, FT4 14.4 pmol/l): normal; thyroid antibodies negative.
- Homocysteine, methylmalonic acid: not done.
- Hepatitis B, C and HIV serology: negative.
- Syphilis antibodies EIA screen: non-reactive.
- Tumour markers CEA: 9.5  $\mu$ g/l, Ca19.9: 85 Ku/l, Ca15.3: 17 Ku/l,  $\alpha$ -fetoprotein: 1.3 IU/ml): all negative.
- Antineuronal antibodies to Yo, Hu and Ri: negative. VGKC and NMDA receptor antibodies were not done.

##### CSF

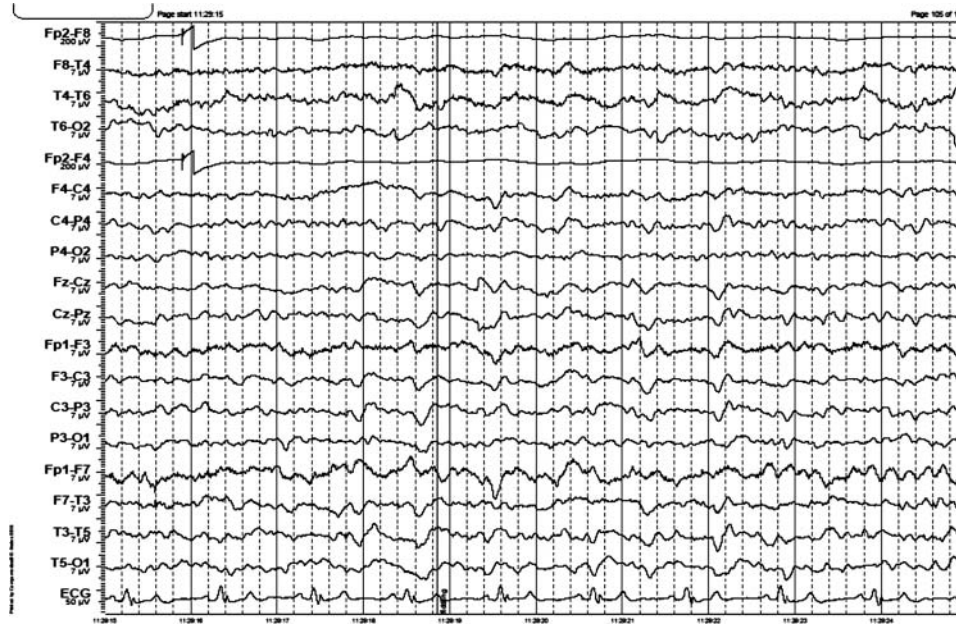
- Pressure 170 mm H<sub>2</sub>O, protein 1.31 g/l (n= <0.40), glucose 2.0 mmol/l (serum glucose 7 mmol/l), four white cells, 11 red cells.
- Oligoclonal bands: negative in both CSF and serum.
- CSF cytology: mild increase in mixed inflammatory cells.
- Flow cytometry: very few viable CD45+ cells, remaining cells are predominantly CD3+CD4+.
- CSF 14-3-3 protein: atypical positive result, but not typical for sCJD, given raised CSF protein (>1.0 g/l).
- Neurone-specific enolase positive.
- TB, HSV, EBV, enterovirus PCR negative.
- Cryptococcal antigen negative.

EEG: see figure 2.

Chest x-ray showed a suspicious lesion at the right lung base. Brain MRI was not repeated.

#### DISCUSSION PART B (DR GM HALMAGYI)

While the EEG and the CSF 14-3-3 protein result give soft support for a diagnosis of CJD, the high CSF protein and the low glucose<sup>46</sup> are against the diagnosis and also against the diagnosis of paraneoplastic limbic encephalitis: they more support a meningitic process—even with a normal white cell count. The negative CSF TB-PCR and cryptococcal antigen make



**Figure 2** EEG shows intermittent generalised 3–4 Hz activity lasting 1 s and continuous generalised 5 Hz activity. The EEG was reactive to eye opening. There are left hemisphere quasiperiodic triphasic waves.

it unlikely that the ‘suspicious’ lung lesion is causing tuberculous or cryptococcal meningitis, and I suspect a primary or secondary cancer. I would want a whole body PET/CT and then a biopsy of the lung lesion.

#### Progress

CT chest, abdomen and pelvis showed an infiltrating lesion at the right lung base, suggesting a cancer. There were masses in both adrenal glands suggesting metastases. PET scan was not done.

The patient continued to decline over the next 2 weeks, with decreased conscious level and was unable to walk. He was admitted to hospital and underwent bronchoscopy which showed extrinsic narrowing of the bronchus intermedius, the right middle lobe bronchus and the superior segmental bronchus of the lower lobe. Bronchial brushings showed malignant cells consistent with large-cell carcinoma of the lung. The patient and his family declined further treatment.

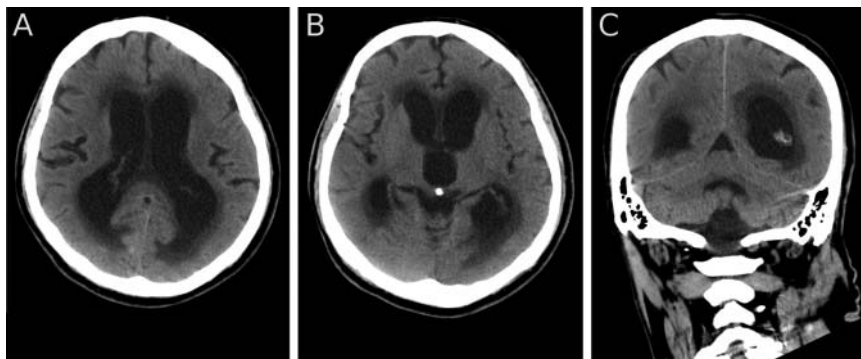
Over the following weeks he became less responsive, the ventricles continued to enlarge and periventricular CSF transudation increased (figure 3). He died 3 weeks following his initial presentation to the neurologist.

*Dr Halmagyi’s diagnosis: malignant meningitis.*

#### PATHOLOGY (DR M RODRIGUEZ)

A full autopsy was performed. There was a 4 cm diameter moderately well-differentiated adenocarcinoma in the apex of the lower lobe of the right lung. The right hilar lymph nodes were enlarged, matted together and contained metastatic carcinoma. There were no adrenal masses.

The brain weighed 1190 g. There was >90% stenosis of the distal vertebral artery by atheroma and a retrocerebellar arachnoid cyst. The foramina of Magendie and Luschka were patent. There was thickening and yellow/orange discolouration of the basal



**Figure 3** Axial (A, B) and coronal (C) CT 2 weeks after the MRI (figure 1) and 1 week before death showing an increase in the size of the ventricles and in CSF exudation.



**Figure 4** Coronal section of cerebrum at the level of the lateral geniculate nuclei showing marked symmetric enlargement of the lateral and third ventricles. The white matter pallor adjacent to the ventricles is due to periventricular oedema secondary to transependymal spread of cerebrospinal fluid.

leptomeninges. There was hydrocephalus with symmetric dilatation of the lateral and third ventricles (figure 4) as well as enlargement of the aqueduct and fourth ventricle. The septum pellucidum was neither fenestrated nor thinned. The periventricular white matter was pale and soft.

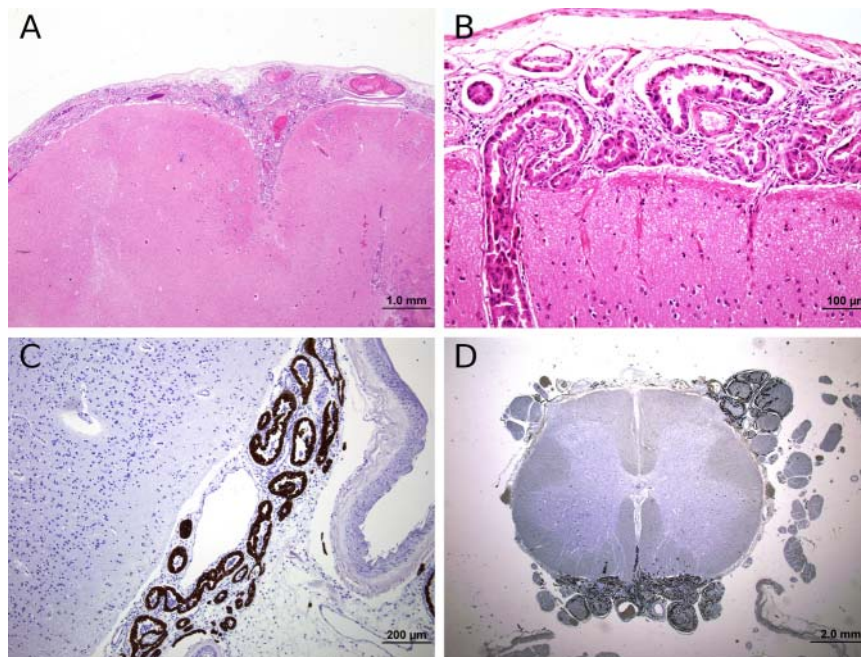
Microscopically, there was widespread leptomeningeal carcinomatosis in almost every section examined, with extension into the Virchow–Robin spaces, and there were several microscopic foci of superficial

parenchymal invasion. The tumour resembled the pulmonary adenocarcinoma (figure 5A,B). Tumour also infiltrated the extra-axial segments of several cranial nerves and the dorsal and ventral roots in the spinal cord (figure 5C,D), most marked in the lumbar region where several neurones in the ventral horns show central chromatolysis. There were also multiple areas of recent infarction, predominantly in the cerebral cortex, often associated with tumour infiltration into the Virchow–Robin spaces.

The mild small-vessel disease in the cerebral white matter was not severe enough to explain either the MRI or the clinical features. There was widespread microglial activation, but no inflammation to support a diagnosis of vasculitis or a paraneoplastic or autoimmune encephalitis. There were also no features of infection, prion disease, acute or chronic Wernicke's encephalopathy, subacute combined degeneration or chronic neurodegenerative disease including fronto-temporal lobar degeneration, Alzheimer's disease or dementia with Lewy body disease. The hydrocephalus was most likely due to obstruction of CSF flow in the subarachnoid space secondary to leptomeningeal carcinomatosis from the right lung adenocarcinoma.

#### CONCLUDING REMARKS

This patient presented with dementia, ataxia and communicating hydrocephalus due to malignant meningitis from a primary lung adenocarcinoma. Neoplastic meningitis only rarely results from a non-small-cell



**Figure 5** (A) Moderately well differentiated adenocarcinoma in subarachnoid space (H&E). Original magnification  $\times 100$  (B) Adenocarcinoma in subarachnoid space extending into Virchow- Robins space (H&E). Original magnification  $\times 400$  (C) Lumbar spinal cord with leptomeningeal carcinomatosis with dorsal and ventral root infiltration.  $\times 12.5$  (cytokeratin 8 immunoperoxidase). Original magnification  $\times 12.5$ . (D) Lumbar ventral roots showing tumour infiltration (cytokeratin 8 immunoperoxidase). Original magnification  $\times 400$ .

lung cancer, and occurs in only 1% of patients.<sup>27</sup> In a series of 640 patients with malignant meningitis, only 37 had hydrocephalus.<sup>47</sup>

The key to the diagnosis of neoplastic meningitis is contrast-enhanced MRI of both brain and spine, and CSF cytology. In a study of 137 patients with clinical symptoms of neoplastic meningitis, imaging was abnormal in 55%, including leptomeningeal, subependymal, dural or cranial nerve enhancement; superficial cerebral lesions or communicating hydrocephalus.<sup>48</sup> However, contrast-enhanced brain MRI might not be positive. A recent study of 44 patients with neoplastic meningitis found a sensitivity of 45% for detecting meningeal involvement: the sensitivity was higher for solid tumours (84.6%) and lower for leukaemia (20%) and lymphoma (37.5%).<sup>49</sup> In this case, neither MRI spine or contrast-enhanced brain MRI were performed, but the fact that the brain and spine were macroscopically normal at autopsy suggests there would not have been unequivocal contrast enhancement. It is possible that the patient did develop focal signs suggesting spinal involvement towards the end of his illness, but by then he was too obtunded to examine clinically. However, there are case reports of malignancy, particularly lymphoma, with leptomeningeal involvement of spinal nerve roots that have no localising signs,<sup>28</sup> and in some cases normal spinal imaging.<sup>50</sup>

The sensitivity of CSF cytology in malignant meningitis is influenced by sample volume and time to fixation.<sup>46</sup> In this patient, the clues to a meningeal process were a high protein and low glucose, but the cytology showed no malignant cells. The optimum CSF cytology sampling technique is to take at least 10 ml of CSF and to collect the sample into a tube with formalin fixative before sending it to the laboratory.<sup>51</sup> Cytology has a sensitivity of 93% for detecting neoplastic meningitis.<sup>49</sup> In this patient, the diagnosis would have been made sooner had a chest x-ray been requested at his initial presentation.

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**Contributors** RMA: case presentation and manuscript preparation. Takes overall responsibility for content of manuscript. GMH: discussant of manuscript, manuscript preparation. MLR: pathology presentation.

**Competing interests** None.

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## REFERENCES

1 Healton EB, Savage DG, Brust JCM, *et al.* Neurologic aspects of cobalamin deficiency. *Medicine* 1991;70:229–45.

- 2 Larner AJ, Janssen JC, Cipolotti L, *et al.* Cognitive profile in dementia associated with vitamin B12 deficiency due to pernicious anaemia. *J Neurol* 1990;246:317–19.
- 3 Sharrief AZ, Raffel J, Zee DS. Vitamin B12 deficiency with bilateral globus pallidus abnormalities. *Arch Neurol* 2012;69:769–72.
- 4 De Jager J, Kooy A, Leher P, *et al.* Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B12 deficiency: randomized placebo controlled trial. *BMJ* 2010;340:c2181.
- 5 Lin RJ, Chen HF, Chang YC, *et al.* Subacute combined degeneration caused by nitrous oxide intoxication: case reports. *Acta Neurol Taiwan* 2011;20:129–37.
- 6 Hermann W, Obeid R. Cobalamin deficiency. *Subcell Biochem* 2012;56:301–22.
- 7 Mellion M, Gilchrist JM, dela monte S. Alcohol related peripheral neuropathy: nutritional, toxic, or both? *Muscle Nerve* 2011;43:309–16.
- 8 Santos AC, Tavares LL, da Graça , *et al.* Non-alcoholic Wernicke's encephalopathy: broadening the clinico-radiological spectrum. *Br J Radiol* 2010;83:437–46.
- 9 Rosenbloom MH, Atri A. The evaluation of rapidly progressive dementia. *Neurologist* 2011;17:67–74.
- 10 Graus F, Dalmau J. Paraneoplastic neurological syndromes: diagnosis and treatment. *Curr Opin Neurol* 2007;20:732–7.
- 11 Urbach H, Soeder BM, Jeub M, *et al.* Serial MRI of limbic encephalitis. *Neuroradiology* 2006;48:380–6.
- 12 Lawn MD, Westmoreland BF, Kiely MJ, *et al.* Clinical, magnetic resonance imaging and electroencephalographic findings in paraneoplastic limbic encephalitis. *Mayo Clin Proc* 2003;78:1363–8.
- 13 Dalmau J, Lancaster E, Martinez-Hernandez E, *et al.* Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74.
- 14 Klassen BT, Ahlskog JE. Normal pressure hydrocephalus. How often does the diagnosis hold water. *Neurology* 2011;77:1119–25.
- 15 Solana E, Sahuguillo J, Jungue C, *et al.* Cognitive disturbances and neuropsychological changes after surgical treatment in a cohort of 185 patients with idiopathic normal pressure hydrocephalus. *Arch Clin. Neuropsychol* 2012;27:304–17.
- 16 Hellström P, Edsbacke M, Blomsterwall E, *et al.* Neuropsychological effects of shunt treatment in idiopathic normal pressure hydrocephalus. *Neurosurgery* 2008;63:527–35.
- 17 Gallia GL, Rigamnti D, Williams MA. The diagnosis and treatment of idiopathic normal pressure hydrocephalus. *Nat Clin Pract Neurol* 2006;2:375–81.
- 18 Marmarou A, Bergsneider M, Kilinge P, *et al.* The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal pressure hydrocephalus. *Neurosurgery* 2005;57:S17–28.
- 19 Ahmed R, Buckland M, Davies L, *et al.* Enterovirus 71 meningoencephalitis complicating rituximab therapy. *J Neurol Sci* 2011;305:149–51.
- 20 Nishiwaki T, Sawa N, Kikui S. Suspected measles encephalitis caused by modified measles that was difficult to diagnose: a case report. *Brain Nerve* 2011;63:75–8.
- 21 Tsiodras S, Kelesidis I, Kelesidis T, *et al.* Central nervous system manifestations of Mycoplasma pneumoniae infections. *J Infect* 2005;51:343–54.
- 22 Silva CA, Oliveira AC, Vilas-Boas L, *et al.* Neurologic cytomegalovirus complications in patients with AIDS:



- retrospective review of 13 cases and review of the literature. *Rev Inst Med Trop Sao Paulo* 2010;52:305–10.
- 23 Almeida OP, Lautenschlager NT. Dementia associated with infectious diseases. *Int Psychogeriatr* 2005;17(Suppl 1):S65–77.
  - 24 Liliang PC, Liang CL, Chang WN, *et al.* Shunt surgery for hydrocephalus complicating cryptococcal meningitis in human immunodeficiency virus-negative patients. *Clin Infect Dis* 2003;37:673–8.
  - 25 Rajshekhar V. Management of hydrocephalus in patients with tuberculous meningitis. *Neurol India* 2009;57:368–74.
  - 26 Cremer PD, Johnston IH, Halmagyi GM. Pseudotumour cerebri syndrome due to cryptococcal meningitis. *JNNP* 1997;62:96–8.
  - 27 Gleissner B, Chamberlain MC. Neoplastic meningitis. *Lancet Neurol* 2006;5:443–57.
  - 28 Ahmed RM, King J, Gibson J, *et al.* Spinal leptomeningeal lymphoma presenting as pseudotumor syndrome. *J Neuroophthalmol* 2012 (Epub ahead of print, 19 Jan)
  - 29 White K, Ostrowski K, Maloney S, *et al.* The utility of cerebrospinal fluid parameters in the early microbiological assessment of meningitis. *Diagn Microbiol Infect Dis* 2012;73:27–30.
  - 30 Jantzen SU, Ferrea S, Langebner T, *et al.* Late-stage neurosyphilis presenting with severe neuropsychiatric deficits: diagnosis, therapy, and course of three patients. *J Neurol* 2012;259:720–8.
  - 31 Mohamed W, Neil E, Kupsky WJ, *et al.* Isolated intracranial Whipple's disease—report of a rare case and review of the literature. *J Neurol Sci* 2011;308:1–8.
  - 32 Tan CS, Koralnik IJ. Beyond progressive multifocal leukoencephalopathy: expanded pathogenesis of JC virus infection in the central nervous system. *Lancet Neurol* 2010;9:425–37.
  - 33 Slee M, Pretorius P, Ansoorge O, *et al.* Parkinsonism and dementia due to gliomatosis cerebri mimicking sporadic Creutzfeldt Jakob disease (CJD). *J Neurol Neurosurg Psychiatry* 2006;77:283–4.
  - 34 Rabinovici GD, Wang PN, Levin J, *et al.* First symptom in sporadic Creutzfeldt Jakob disease. *Neurology* 2006;66:286–7.
  - 35 Geschwind MD, Shu H, Haman A, *et al.* Rapidly progressive dementia. *Ann Neurol* 2008;64:97–108.
  - 36 Shiga Y, Miyazawa K, Sato S, *et al.* Diffusion weighted MRI abnormalities as an early diagnostic marker in Creutzfeldt Jakob disease. *Neurology* 2004;163:443–9.
  - 37 Chong JY, Rowland LP, Utiger RD. Hashimoto's encephalopathy: syndrome or myth? *Arch Neurol* 2003;60:164–71.
  - 38 Amitai Y, Ziotogorski Z, Golan-Katzav V, *et al.* Neuropsychological impairment from acute low-level exposure to carbon monoxide. *Arch Neurol* 1998;55:845–8.
  - 39 Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. *Arch Neurol* 1983;18:127–34.
  - 40 Derry C, Allen C, Grant R, *et al.* Encephalopathy in a 45 year old woman: presented at the advanced clinical neurology course, Edinburgh 2010. *Pract Neurol* 2012;12:116–25.
  - 41 Amara AW, Bashir K, Palmer CA, *et al.* Challenges in diagnosis of isolated central nervous system vasculitis. *Brain Behav* 2011;1:57–61.
  - 42 Geraldes R, Albuquerque L, Ferro JM, *et al.* Rapidly progressive cognitive impairment, ataxia, and myoclonus: an unusual presentation of a dural arteriovenous fistula. *J Stroke Cerebrovasc Dis* 2012;21:619e3–619e5.
  - 43 Baumann N, Turpin JC. Adult onset Leukodystrophies. *J Neurol* 2000;247:751–9.
  - 44 Kohler W. Leukodystrophies with late disease onset: an update. *Curr Opin Neurol* 2010;23:234–41.
  - 45 Josephs KA, Ashkog JE, Parisi JE, *et al.* Rapidly progressive neurodegenerative dementias. *Arch Neurol* 2009;66:201–7.
  - 46 Green A, Sanchez-Juan P, Ladogana A, *et al.* CSF analysis in patients with sporadic CJD and other transmissible spongiform encephalopathies. *Eur J Neurol* 2007;14:121–4.
  - 47 Omuro AMP, Lallana EC, Bilsky MH, *et al.* Ventriculoperitoneal shunt in patients with leptomeningeal metastasis. *Neurology* 2005;64:1625–7.
  - 48 Freilich RJ, Krol G, De Angelis LM. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. *Ann Neurol* 1995;38:51–7.
  - 49 Pauls S, Fischer AC, Brambo HJ, *et al.* Use of magnetic resonance imaging to detect neoplastic meningitis: limited use in leukemia and lymphoma, but convincing results in solid tumors. *Eur J Radiol* 2012;81:974–8.
  - 50 Ohno T, Sakamoto T, Mizumoto C, *et al.* Leukemic and meningeal relapse of CD5(+) intravascular large B cell lymphoma with down modulation of CD20 after rituximab therapy. *Int J Hematol* 2006;84:74–8.
  - 51 Burn-McNulty P, Benedict M, Moxham N, *et al.* How to do it: How to get the most out of cerebrospinal fluid cytology. *Pract Neurol* 2012;12:241–3.