NEUROPATHOLOGICAL CONFERENCE

Editor: David A. Ramsay

A 58-year-old woman with progressive vertigo, deafness and weakness

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PATIENT DESCRIPTION

Clinical presentation

The patient was a 58-year-old, retired teacher, previously in good health. In October she developed flu-like symptoms and a sore throat that was treated with penicillin. She developed persistent vertigo and vomiting and became aware of a rapidly progressive hearing loss. She presented to her family doctor in mid-November with severe hearing loss and incapacitating vertigo. She collapsed in the waiting room and was sent to the local emergency department.

She was noted on admission to have a right ptosis, generalized weakness and dehydration. A provisional diagnosis of viral labyrinthitis and possible cochleitis was made and she was started on prednisone. Three weeks had passed with no improvement when she was referred to a neurologist because of progressive proximal weakness. She was awake, alert and co-operative. Right ptosis, bifacial weakness, nasal phonation, dysarthria, and bilateral deafness were noted. Upper limb weakness was graded 1/5 proximally and 2 to 3+ distally. In the lower limbs strength was graded 4/5 except for hip flexion which was graded 2/5. Deep tendon reflexes were graded 2- in the upper limbs and were absent in the lower limbs. Plantar reflexes were flexor. The sensory exam was normal. The diagnosis of Guillain-Barre syndrome was entertained.

Over the following four days she was noted to be intermittently confused and her ventilatory status deteriorated, requiring intubation and ventilation. Her prednisone was discontinued and IVIg was started. Screening bloodwork and urinalysis were normal. Her ESR was 9. Head CT with and without contrast was reported as normal. Her CSF contained 3 $x10^6$ RBC, $4x10^6$ nucleated cells/L, a glucose of 5.6 mmol/Land elevated protein at 1222 mg/L. The following day her blood pressure became labile (ranging from 60/40 to 155/77 mmHg) and she developed rapid, unstable and refractory atrial fibrillation. She was started on amiodarone and sedated for transfer to London Health Sciences Centre (LHSC).

On arrival at LHSC, her cardiac status had stabilized. She could open her eyes only momentarily, and followed commands poorly. Her pupils were slow but reactive and measured 4 mm on the right and 3 mm on the left. Right sided ptosis remained. Maximal power was graded 3 in all limbs with weak withdrawal to nailbed pressure. Reflexes were graded 1-2 with absent right biceps and triceps reflexes. Plantar reflexes were flexor. General physical examination was unremarkable aside from moderate vitiligo.

Her past medical history included osteoporosis, treated with Fosamax 10 mg od. A breast nodule was negative for malignancy. She was an ex-smoker.

Differential Diagnosis

Dr. Strong: This 58-year-old woman's history can be summarized as a subacute, progressive disorder of approximately seven to eight weeks duration. She begins with a flu-like illness for which she receives penicillin. Four to six weeks into the course of her illness, during which it is not clear if she has a full recovery, she develops bilateral sensorineural hearing loss, vertigo and a right ptosis suggesting bilateral 8th nerve dysfunction, and a potential Horner's syndrome. We do not know the extent to which she had miosis or conjunctival injection. She is diagnosed as having a viral labyrinthitis, but clearly this cannot be the case in that the involvement of ptosis suggests a process which is intra-axial in nature, either involving sympathetic fibers giving rise to a Horner's syndrome or very early manifestation of a third nerve palsy. Therefore, the diagnosis of vestibular neuronitis would be untenable at this point and indeed points toward a rhombencephalitic process. She was treated with prednisone and within three weeks developed progressive, severe proximal weakness, bifacial weakness, dysarthria, nasal phonation (all of which suggests that she has bulbar dysfunction) and is found to be areflexic in her lower limbs with down-going toes. The time course of prednisone therapy is insufficient to have accounted for this severe

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weakness. This suggests that her disease is more disseminated, that it clearly involves the brain stem and, at least for the lumbosacral region, has a polyradicular component. The profound degree of weakness suggests a superimposed myopathy. Within three days of this, she develops severe respiratory compromise to the extent that she required intubation. One would not have predicted such a difficulty based on her neurological examination, raising the possibility of parenchymal pulmonary disease.

Interestingly, she then receives a course of IVIg on the premise that this is an acute demyelinating process. While this cannot be substantiated in retrospect based on her clinical examination, it does provide some evidence of an immune based disorder in that her subsequent neurological examination shows a return of reflexes in the lower limbs with a patchy loss in the right upper limb. At this point, however, she is now markedly confused, indicating an encephalopathic component.

There is no documentation of sensory dysfunction or of cerebellar dysfunction to the limits that it can be examined. Specifically, she shows no evidence of primary position nystagmus, ocular bobbing or dysconjugate gaze. She has no abnormalities on her physical examination with the sole exception of vitiligo. If this is of recent onset, it would be supportive of an underlying autoimmune disorder, although if it is chronic, it is of less assistance to us in our differential diagnosis. It would appear that her bowel and bladder function is similarly spared. She has no evidence of hepatosplenomegaly, nor of lymphadenopathy.

In summary, the clinical features suggest a subacute, progressive, multisystems dysfunction with multiple cranial neuropathies, a possible polyradiculopathy, late onset encephalopathy and potentially myopathy. At this point, it is prudent to know if there is an antecedent history of autoimmune diseases. Specifically, has there been a history to suggest lupus, arthritis, Behcet's, pulmonary or nasal involvement (for instance hemoptysis, oral crusting of blood, nasal erosions) or a history of diabetes or thyroid dysfunction?

Dr. Chong: The history is negative for all of these. Her vitiligo appeared several years prior to presentation.

Dr. Strong: At the time of her admission was there evidence of muscle atrophy, fasciculations, or other features which might be consistent with a chronic lower motor neuron disease?

Dr. Chong: There were no features of lower motor neuron disease aside from the nonspecific hyporeflexia.

Dr. Strong: The differential diagnosis at this time can then be broken into several categories. Clearly, this is unlikely to be a metabolic or mitochondrial disorder and given her age and the rapid progression, the possibility of an inflammatory or malignant process needs to be a primary consideration. Amongst the inflammatory processes, this can be divided into infectious and noninfectious diseases. Amongst the infectious diseases, given the initial onset with hearing loss and parenchymal brain stem involvement (suspecting that this was indeed a Horner's at presentation), Listeria, Whipple's, Lyme disease or HIV all need to be considered. Listeria can certainly present as a primary brain stem involvement, but almost always has cerebellar or cerebellar outflow involvement as well. Whipple's disease, while generally systemic with secondary CNS involvement, can have central nervous system involvement initially. However, dementia is the most common presenting manifestation, followed by visual impairment, papilloedema, seizures, ataxia or myoclonus. Patients often have a malabsorption syndrome a nondeforming

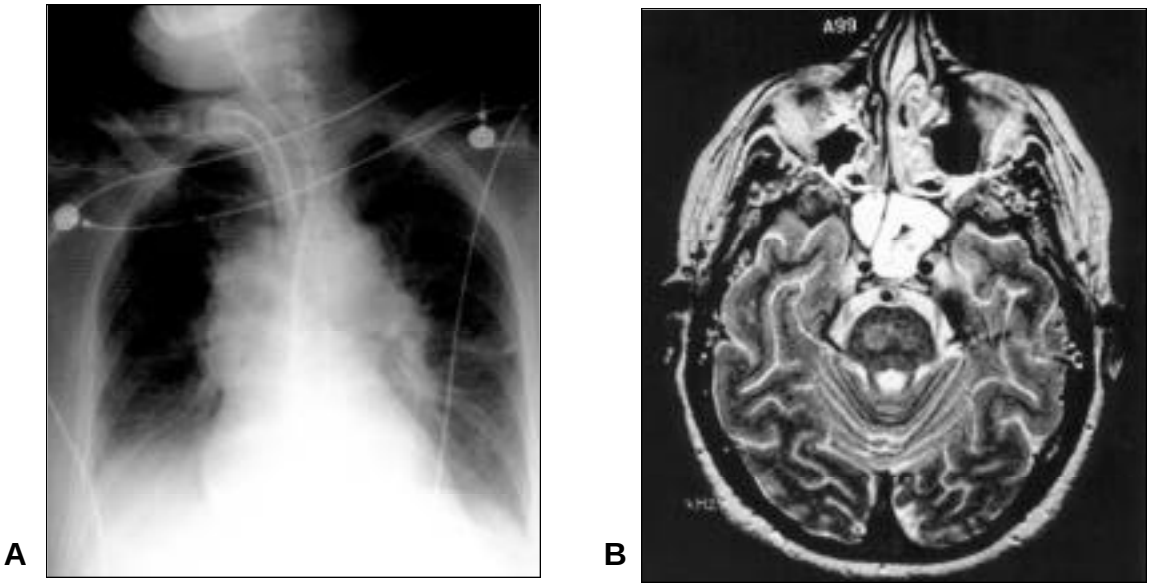

Figure 1: A) *Chest X-ray January 15/02: Prominent right hillum. Suggestive of hillar lymphadenopathy.* ***B)*** *Repeat MRI head and cervical spine January 15/02: T2-Weighted; ill-defined hyperintensity in the centre of the pons, without enhancement on T1-weighted image (not shown). Differential diagnosis includes small vessel ischemic changes, demyelination, low-grade inflammation, but is unlikely to be neoplasm.*

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arthritis, or lymphadenopathy – none of which are evident here. There are no obvious risk factors from the history to suggest Lyme disease and in the absence of either an arthropathy or cardiac involvement (until late in the disease) this would be unusual. We have nothing to suggest that she is immunocompromised on the basis of HIV infection.

This leads one to consider the noninfectious etiologies of an inflammatory process. Sarcoid should be a primary consideration here, given the presentation with multiple cranial neuropathies. Thirty percent of patients will also have optic changes, including iritis, papilloedema or visual field defects. Dysphagia or bulbar dysfunction is quite common. Bilateral 8th nerve involvement is the second most common neurological presentation following bilateral 7th nerve involvement. Cerebral sarcoidosis could also produce the confusional state and spinal leptomeningeal sarcoid could give rise to the polyradiculopathy which would appear to have been evident in the lower limbs. The response to IVIg may be indirect support of evidence of such. Finally, a proximal myopathy would be consistent with such a diagnosis. While one generally expects to see a mild pleocytosis on the cerebrospinal fluid analysis, this is not always the case and elevation in protein alone may be your only marker. Finally, one would also need to consider the rapid pulmonary deterioration and indeed primary pulmonary sarcoid with CNS involvement would be an adequate consideration.

Having raised the possibility of sarcoid, both tuberculosis and histoplasmosis should be considered and indeed an adequate chest x-ray would be important. However, neither would produce such severe degrees of proximal muscle weakness.

Within the noninfectious inflammatory etiologies, either isolated CNS vasculitis or CNS vasculitis as a consequence of a systemic vasculitic process needs to be considered. Both Wegener's and polyarteritis nodosa would be considerations here, particularly given the pulmonary involvement. Cryoglobulinemia and Churg-Strauss syndrome similarly should be considered. Each can present with bilateral sensorineural hearing loss as the primary manifestation in a painless fashion with progression to multisystems involvement. Hence a full collagen vascular screen will be important.

In the second broad category are malignant syndromes. Both lymphoma (Hodgkin's) and paraneoplastic syndromes related to small cell carcinoma of the lung need to be considered. The latter is an attractive differential, particularly given the prominent history of smoking, the marked deterioration in her pulmonary function, the initial presentation with cranial neuropathies and the subsequent progression to what may well be a paraneoplastic limbic encephalitis. Again, adequate radiological imaging of the chest will be critical.

For completeness one would need to consider an acute disseminated encephalomyelitis. However, the relatively slow progression of symptoms and the lack of cerebellar findings in what would otherwise be a brain stem process is indeed quite unusual as is the difficulty with the proximal weakness. Because of this I would dismiss ADEM or any other variant of multiple sclerosis.

We have yet to address the cardiac dysfunction. I tend to think this is a secondary event in the course of her illness, rather than a primary cardiac disease. Atrial myxoma or a myocarditis should be considered amongst this category of illness, but again, the rather diffuse nature of her neurological difficulties would mitigate against this.

Investigations

Electromyography (EMG) and nerve conduction studies (NCS) were consistent with a sensory and motor axonal polyneuropathy. No abnormal decrement was seen with 3 and 20 Hz repetitive stimulation. A tensilon test was negative. An MRI/MRA examination of the head and spine was reportedly unremarkable. Chest X-rays showed no significant abnormalities within the ICU context.

Other investigations included repeated lumbar punctures, each with negative cytology, slightly increasing pleocytosis (21 x 10^6 nucleated cells/L) and a consistently elevated protein. Oligoclonal IgG banding was present. Her ESR was persistently over 100. Her CH50 was 132 (normal 30-100 units), and C4 was low at 0.11 (0.16-0.45 g/L). The remainder of the collagen vascular screen was negative.

Dr. Chong: How does this information affect your differential diagnosis, Dr. Strong?

Dr. Strong: Based on this information, I would realign my differential diagnosis and place as my primary diagnosis a malignancy of the lung, with consideration to small cell CA firstly and then lymphoma secondly. I think a CT of the chest is warranted.

Dr. Chong: A number of other investigations were done, including ultrasound of the abdomen and CT of the chest, abdomen and pelvis.

Dr. Kalapos: The IV contrast injection for the CT scan went interstitial, so subtle abnormalities may not have been easily seen. The CT chest reported a few mildly prominent precarinal and paratracheal lymph nodes (1.5cm) and a small pleural effusion but was otherwise normal. The other exams were essentially unremarkable. Repeat MRI examination was performed one month later, on January 15, 2002, and it now revealed T2-weighted and diffusion-weighted imaging hyperintensity in the pons that was, in retrospect, faintly visible on the prior examination. There was no contrast enhancement on either exam. A gallium scan was unremarkable.

Dr. Chong: Cytology of the pleural effusion was negative. Serum angiotensin converting enzyme level was normal. Repeat EMG/NCS demonstrated a motor, greater than sensory, non-length dependent axonal polyneuropathy. There was no response to phrenic nerve stimulation, with EMG recruiting few diaphragmatic motor units. A sural nerve biopsy identified only axonal degeneration. One episode of prolonged left gaze preference with clockwise rotatory nystagmus prompted an EEG examination which demonstrated sporadic bisynchronous epileptiform spike discharges.

The patient continued to require full ventilatory support. Occasional respiratory and urinary tract infections arose and were treated, but she continued to spike fevers with no obvious infectious source. Her neurological status continued to deteriorate. Within weeks, she had progressed to having only a flicker of external rotation of the left leg and weak movements of the hands. She remained deaf, with auditory brainstem evoked responses abnormally delayed. Her ability to communicate fluctuated. She seemed unable to read, and this was felt to be due

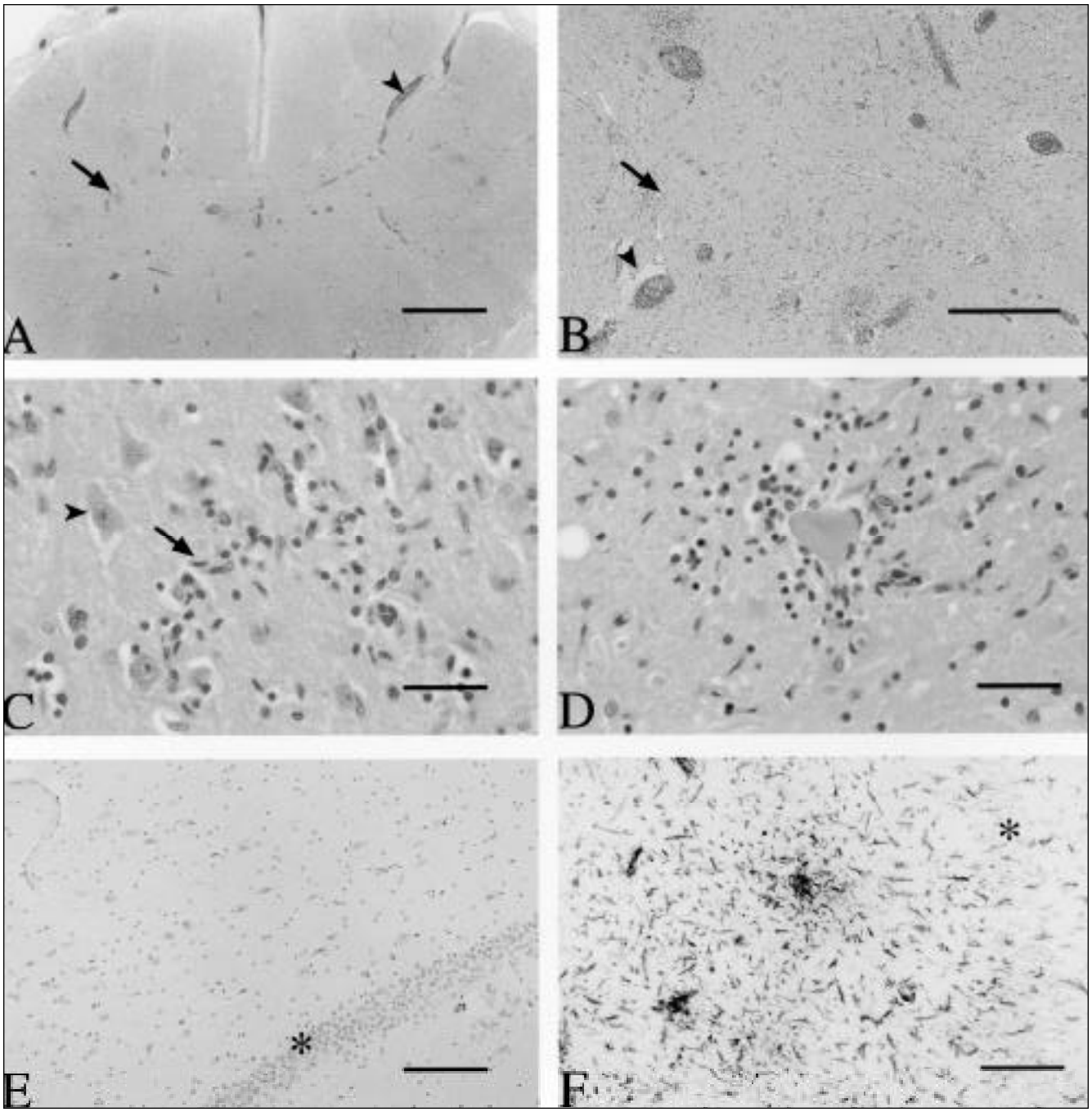

Figure 2: *A) Cross section of spinal cord showing abundant perivascular inflammation (arrowhead) and prominent microglial nests (arrow), H&E, bar = 1mm. B) Spinal cord anterior horn showing perivascular lymphocytic infiltrates (arrowhead) and microglial nests (arrow), H&E, bar = 0.5 mm. C) Right cingulate cortex with microglial activation and nest formation (arrow = microglial cell, arrowhead = neuron), H&E, bar = 50 μm. D) Neuronophagia of lumbar spinal cord anterior horn motor neuron, H&E, bar = 50 μm. E) Age matched control right hippocampus Sommer's sector and adjacent dentate fascia (asterisk) with no appreciable reactive microglia, anti-HLA-DR (clone CR3/43, DAKO, Mississauga, ON), bar = 200 μm. F) Present case, analagous field to E) from right hippocampus showing marked microglial activation, proliferation and nest formation (dentate fascia marked by asterisk), anti-HLA-DR (clone CR3/43, DAKO, Mississauga, ON), bar = 200 μm.*

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Table: The severity of inflammation within each region was scored by four independent assessors. The average of their scores is shown

Region	Left	Right	Region	Score
Frontal cortex	+++	+	Optic chiasm	++
Claustrum	0	++	Hypothalamus	+
Cingulate gyrus	+	+	Ventral anterior thalamus	++
Hippocampus	++	+++	Midbrain	+
Entorhinal cortex	+	++	Pons	++
Insula	+	+	Medulla	++
Temporal neocortex	0	+	Cervical cord	+++
Lateral geniculate	++	+++	Thoracic cord	+++
Calcarine	0	0	Lumbar cord	++
Caudate nucleus	++	++	Cauda equina	+
Dentate/cerebellar white	-	++		

(+++) Severe (++) Moderate (+) Mild (O) None (-) not assessed.

to a loss of extraocular muscle control, reduced visual acuity and intermittent confusion.

The mediastinal lymphadenopathy seen on CT examination was initially ascribed to her recent pneumonia. It was only on a dedicated re-review of her entire file that her first and most recent chest X-rays were compared, revealing a subtle, progressive fullness in the superior mediastinum. A trans-bronchial mediastinal biopsy was performed which led to the diagnosis of an anaplastic, poorly differentiated small-cell carcinoma. She was felt to be a poor candidate for chemotherapy and palliative care was instituted. Cerebrospinal fluid (CSF) studies for paraneoplastic antibodies returned anti-Hu positive.

Clinical Diagnosis:

Paraneoplastic encephalopathy, cranial neuritis and poly-radiculoneuropathy.

Dr. Strong's diagnosis: Paraneoplastic encephalopathy with polyradiculopathy secondary to small cell CA of lung.

Pathology:

Dr. Hammond: On general autopsy, a 4 x 3 x 3.5 cm pretracheal white and black mass and a 1 cm metastatic pleural focus were discovered. It was found to be an undifferentiated small cell carcinoma with extensive necrosis on microscopic examination. The tumour cells expressed sparse chromogranin, moderate synaptophysin and cytokeratin and abundant neuron specific enolase. Gross inspection of the brain, brainstem, cerebellum and spinal cord was unremarkable.

Histological sections from all regions of the CNS were remarkable for a widely disseminated inflammatory pathology affecting neocortex (including cingulum and insula), hippocampus, cerebral white matter, caudate and lentiform nuclei, thalamic and hypothalamic nuclei, brainstem, cerebellum, spinal cord as well as cranial and spinal nerve roots. The leptomeninges contained scant chronic inflammatory cells. Parenchymal changes of note included extensive microglial activation, perivascular lymphocytic infiltrates and neuronophagia. In response to the inflammatory insults, the surrounding tissue showed capillary proliferation, endothelial cell hypertrophy, gliosis and focal areas of tissue vacuolation and pallor. Some levels of spinal cord, especially lumbar segments, were devastated by the inflammatory and associated changes.

Neuropathological Diagnosis:

Paraneoplastic encephalomyeloneuritis.

Discussion

The clinical and pathological features of this case are particularly severe, but are in keeping with current literature of the anti-Hu paraneoplastic syndrome.[1] This patient suffered a rapid decline in motor and sensory function until she was essentially locked-in. In addition to the sensorimotor neuronopathy, encephalitis became more clinically evident and the neuropathology examination concurred, in addition to identifying involvement of the optic chiasm and spinal roots. Anti-Hu antibodies were identified in the CSF.

Paraneoplastic disorders are becoming well-recognized neurologic syndromes. It has been postulated that the host immune response against tumour antigens becomes directed against the host through molecular mimicry.[2] Many antibodies have been identified, with features such as clinical syndrome, primary tumour association, auto-antigen and outcome becoming increasingly well-defined.[2,3]

Unlike auto-antibodies against ion channels, such as seen in Lambert-Eaton myesthenic syndrome (voltage gated Ca channel), myesthenia gravis (acetylcholine receptor) and neuromyotonia (voltage-gated K channel),[4] the relationship between the anti-neuronal paraneoplastic antibody and the pathophysiology of the related syndromes is unclear.[5] The neuronal antigens are typically intranuclear or intracytoplasmic which raises the question of antibody accessing antigen within an intact neuron. Although anti-ds-DNA antibodies in rheumatological disease have been shown to react directly with the nucleus, it is not thought to be a major mechanism of cell death.[6] Even so, animal evidence supporting direct injury from anti-neuronal antibodies is scarce. Human anti-neuronal antibodies bind to *in vitro* mouse neuronal tissue, but do not bind

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after an *in vivo* intravascular injection.[7] The antibodies do not seem to have clinical or pathological effects either, when introduced into live animals passively or actively.[8]

Although the primary mechanism of paraneoplastic neuronal death is still controversial,[9] evidence is pointing to involvement of cytotoxic T-cells.[3,5,10] Although most healthy neurons do not express the major histocompatability complexes (MHC-I and II) required for T-cell recognition and activation, expression is seen after exposure to inflammatory mediators such as interferon-gamma.[10,11] Alternatively, because MHC-I has now been found naturally expressed in select neuronal populations, it is postulated that this results in select vulnerability following blood-brain barrier breakdown.[12]

Elucidating the pathogenesis of anti-neuronal paraneoplastic disorders is not solely academic. The treatment of paraneoplastic disorders involving anti-ion channel receptor antibodies, such as myesthenia and Lambert-Eaton myesthenic syndrome, have been found to be responsive to plasmapheresis and immunomodulation, in stark contrast to the very poor results in the anti-neuronal syndrome.[13,14] These latter syndromes have shown inconsistent responses to treatment of the primary tumour.[15,16] Uncovering the pathophysiology may pave the way for developing new treatment strategies for these and other neuroimmunological disorders.

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