LETTERS TO THE EDITOR

Subacute autonomic and sensory ganglionopathy: a postmortem case

Acute autonomic and sensory neuropathy (AASN) is characterised by severe autonomic dysfunction, sensory deficit, and relatively well or fully preserved motor nerve function.¹⁻⁴ The disease sometimes has a chronic course.^{2,4} Detailed information is limited because there have been so few reports of the postmortem examination of AASN.²⁻⁴ This case provides histopathological evidence for autonomic and sensory ganglionopathy in AASN.

A 30 year old Japanese man had abdominal pain and a rise in body temperature to 40°C on 1 January 1990. On 23 January, he felt prickling and paraesthesia in all his limbs. On 14 February he could no longer walk due to severe prickling of the entire body. On 2 March, he became bedridden because of orthostatic hypotension. He experienced mild weakness in the all limbs, dysarthria, and dysphagia. On 13 March, he was transferred to our hospital. Physical examination on admission showed anhidrosis, urinary retention, hyposalivation, and paralytic ileus. There was no history of intoxication by drugs or food preceding the illness. His blood pressure was 122/70 mm Hg when supine and 80/46 mm Hg when sitting with no increase in heart rate. His skin was dry. Neurologically, the right pupil was round and 5.5 mm in diameter, whereas the left was oval shaped and 6.0 mm in diameter. The light reflex was sluggish, and the convergence reflex absent bilaterally. Muscle power was mildly weak in his limbs, and there was moderate limb ataxia. Deep tendon reflexes were decreased. Sensation was lost to all modalities over his entire body, including the face. Complete blood cell and serum biochemistry findings were normal. Epstein-Barr virus antibody titres were not raised in the serum. His CSF was normal. Motor conduction velocities (MCVs) and compound motor action potentials were normal in the right median nerve and the right tibial nerve. No sensory nerve action potentials (SNAPs) were evoked in the bilateral sural nerves. The coefficient of variation of the R-R interval on his ECG was reduced (1.9%). In October, dysarthria, dysphagia, and muscle weakness gradually lessened. Despite the improvement in muscle power, severe sensory impairment and paraesthesia of the entire body, as well as

orthostatic hypotension persisted. His response to plasmapheresis and high dose corticosteroids was very poor. Two years later, at the age of 33, he died of heart failure.

No tumour was found on general pathological postmortem examination. The dorsal fasciculus at all levels of the spinal cord showed an almost complete loss of myelinated fibres, and the number of dorsal horn cells were decreased. Both the gracilis and cuneatus neurons of the medulla oblongata were slightly decreased. The dorsal roots were atrophic. No detectable changes could be seen in the lateral and ventral fasciculus; nor any clear reduction in the number of neurons in the ventral or lateral horn at Th4 levels. In the cervical (figure A), thoracic, and lumbar dorsal root ganglia, only a few neurons could be seen under low power, with Nageotte nodule formation. In the cervical (figure B) and lumbar sympathetic ganglia, the number of neurons were severely reduced without lymphocyte infiltration. Examination of the dorsal root showed severe loss of myelinated fibres, whereas the ventral root of L3 appeared normal.

This case seemed to be compatible with AASN. Parasympathetic failure was reflected in the loss of salivation, decreased intestinal peristalsis, and bladder atony. Absence of sweating, orthostatic hypotension, and slowness of pupillary dilatation indicated sympathetic failure. Sensory neuropathy was confirmed by an electrophysiological study. The absence of SNAPs in the normal MCVs is best explained by selective involvement of the neurons in lumbar dorsal root ganglia. Neuropathologically, there were no changes in the lumbar ventral roots, but there was severe loss of myelinated fibre in the dorsal roots. Severe degeneration was found in the lumbar dorsal root ganglia neurons at all levels. The slight decrease in the gracilis and cuneatus neurons in the medulla oblongata is thought to be due to anterograde trans-synaptic degeneration, as is the slight decrease in the number of dorsal horn cells. As judged by the pathological findings, the site of the sensory nervous system lesion in this case was the lumbar dorsal root ganglia. Similar severe degeneration was found in the sympathetic ganglion neurons, but neurons in the lateral horn remained intact. The site of the autonomic nervous system lesion in our case, therefore, is considered in the sympathetic ganglion. Our case showed the same degree of neuropathologically severe autonomic and sensory ganglionopathy. There have been a few postmortem records of AASN.²⁻⁴ Fagius *et al*² showed that the main lesions were in the dorsal root ganglia, dorsal roots, and posterior columns, but they did not examine the autonomic neurons. They speculated that the main lesion responsible for autonomic symptoms was in peripheral

nerves. Tohgi *et al*⁴ reported severe pathological changes in preganglionic and postganglionic neurons of the autonomic nervous system, posterior columns, and the peripheral nerves, but there they did not describe any pathological findings for the lumbar dorsal root ganglia. Thus they suggested that the main lesion of sensory symptoms was in the peripheral nerves judging from sural nerve biopsy. One report showing both autonomic and sensory ganglion involvement was by Stoll *et al*,³ who described a 68 year old man with AASN. He died of sudden cardiac arrest four months after onset. In contrast with our case, their patient showed rapid onset (two days) and a very good response to corticosteroids. A postmortem examination detected numerous lymphocytic infiltrates and degeneration in the autonomic and sensory ganglia and, to a lesser extent, in the dorsal roots, dorsal columns, and brainstem. Thus their case is similar to ours in neuropathological lesions. Despite the differences in response to therapy, inflammatory change, and disease course between their patient and ours the pathological findings indicate that the disease, selectively involving both autonomic and sensory systems, is ganglionopathy, not neuropathy.

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(A) Section from the lumbar dorsal root ganglia: There are only a few normal lumbar dorsal root ganglia neurons. (B) Section from the sympathetic ganglion: normal nerve cell bodies have disappeared and been replaced by clusters of cells ("nodules of Nageotte" (arrows)). Originally $\times 100$.

Intracranial calcification with IgG λ M-proteinemia: a case report

Recently Kosaka reviewed 16 cases of slowly progressive presenile cortical dementia thought to be a clinicopathological entity with pathological features characterised by circumscribed lobar atrophy, diffuse neurofibrillary tangles, and calcification of the Fahr type and named diffuse neurofibrillary tangles with

calcification.¹ However, the pathogenesis and biochemical findings of this new entity are not known in detail. Herein, we report on a patient with presenile dementia, intracranial calcification, and M-proteinemia, which may play some part in the development of intracranial calcification with dementia.

A 66 year old man was admitted with dementia, which had been apparent since about 60 years of age. At the age of 62 he started to lose spontaneity and at the age of 66 gait disturbance occurred. In addition he showed slurred dysarthria, mild muscle rigidity, bilateral pyramidal signs, and mild truncal ataxia. Dementia slowly progressed and his dementia scales were as follows. Hasegawa's dementia rating scale revised was 16/30 points, mini mental state examination was 20/30 points, the Japanese Wechsler adult intelligence scale revised showed verbal IQ 83, performance IQ 67, and total IQ 74. His routine laboratory investigations were normal. In particular, serum calcium and phosphorus were within the normal range. Twenty four hour urinary calcium and phosphorus were also within the normal range. Serum pyruvate, lactate, vitamins, including 1.25-(OH)₂-vitamin D, and analysis of amino acids were within normal limits. Wasserman's test, rheumatoid arthritis test, antinuclear antibodies, and DNA antibodies were all non-reactive. Endocrinological tests showed a slightly low concentration of parathyroid hormone (173 pg/ml; normal range 180–560 pg/ml), other tests,

including the Ellsworth Howard test and thyroid function, gave normal results. Immunoelectrophoresis showed the presence of IgG λ M-protein in serum. Bence-Jones protein was not detected in urine. Routine CSF tests were normal for cell counts and protein concentrations. The concentrations of amyloid β (A β) 1–40 and A β 1–42 in CSF measured by enzyme linked immunosorbent assay (ELISA)² were 1659 fmol/ml and 179.1 fmol/ml respectively, which were within the normal ranges. The concentration of tau protein in CSF measured by a sandwich ELISA (Innogenetics, Belgium) was raised at 457 pg/ml. Bone marrow was normal. Chest radiography and CT showed calcification of the aorta, pleura, pericardium, and diaphragm. Brain CT and MRI (figure) disclosed calcification in the basal ganglia, the floor of the cortices, subcortical white matter, and cerebellum. Magnetic resonance angiography showed no evidence of arteriosclerosis. The cerebral blood flow measured by ¹²³I-IMP SPECT showed hypoperfusion in the frontotemporal lobes (figure). Neurophysiological tests including auditory brainstem responses, sensory evoked potentials, and peripheral nerve conduction velocities were normal.

Diffuse neurofibrillary tangles with calcification is a presenile dementia as proposed by Kosaka¹ and its clinical characteristics are (a) presenile onset, (b) slowly progressive cortical dementia, (c) more common temporofrontal focal signs rather than parietooccipital signs,

(d) atrophy of the frontotemporal lobes on CT or MRI, (e) calcification of the bilateral globus pallidus and dentate nucleus, (f) hypoperfusion in the frontotemporal lobes on SPECT or PET, (g) normal serum calcium and phosphorus concentrations.

Our present case showed presenile slowly progressive cortical dementia and loss of spontaneity. Brain CT and MRI disclosed symmetric non-arteriosclerotic, intracranial severe calcification. Although parathyroid hormone was slightly low, other hormones measured and serum calcium and phosphorus were within normal limits, suggesting that intracranial calcification was idiopathic. The CSF study of A β and tau protein is considered a biological diagnostic marker for Alzheimer's disease.^{3–5} Decreased A β 1–42 and increased tau protein are specific for diagnosis of Alzheimer's disease. The CSF concentration of A β 1–42 was within the normal range and the CSF concentration of tau protein was high which may indicate the absence of deficits in A β metabolism but the presence of neurofibrillary tangles. Besides, our patient had IgG λ M-proteinemia without Bence-Jones protein. The study of bone marrow indicated no malignancy. The gammopathy was considered to be monoclonal gammopathy with undetermined significance. Previously Nishiyama *et al*⁶ reported a 41 year old woman with idiopathic intracranial calcification associated with M-proteinemia, followed by multiple myeloma. Her symptoms were dystonia, gait and speech disturbance, and dementia. This case suggested an association between M proteinemia and dementia with intracranial calcification. Tentolouris *et al*⁷ reported three cases of familial calcification of the aorta and calcific aortic valve disease associated with a monoclonal λ -chain gammopathy. They indicated that immunological abnormalities were associated with calcifications, but they did not assess the CNS.

Without the pathological evidence, clinically this case appeared to be consistent with the criteria for diffuse neurofibrillary tangles with calcification and CSF studies may indicated the presence of neurofibrillary tangles. At present, little is known about the biological and pathogenetic findings in diffuse neurofibrillary tangles with calcification. The present case suggests that M-proteinemia may play a part in the development of dementia with intracranial calcification such as diffuse neurofibrillary tangles with calcification. Further biochemical studies are necessary in patients with dementia and intracranial calcifications.

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Plain brain CT and ¹²³I-IMP SPECT. Brain CT showed severe calcification in the basal ganglia, floor of cerebral cortices, subcortical white matter, and cerebellum. ¹²³I-IMP SPECT showed hypoperfusion in the frontotemporal lobes.

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Subacute combined degeneration of the spinal cord after nitrous oxide anaesthesia: role of magnetic resonance imaging

Among all the possible causes of myelopathy, subacute combined degeneration of the spinal cord, neurological complication of vitamin B12 (cobalamin) deficiency, is one of the less often seen.

We report a case of subacute combined degeneration of the spinal cord occurring postoperatively after nitrous oxide anaesthesia in a patient previously undiagnosed to be vitamin B12 deficient.

A 73 year old woman underwent surgery for knee prosthesis; forty days later she suffered a femoral fracture due to an accidental fall. Two weeks after surgical stabilisation performed under general anaesthesia with nitrous oxide, the patient complained of gradual onset of loss of gait and weakness of the upper limbs associated with hypoaesthesia of her hands and feet. Neurological deficits progressively worsened so that the patient was admitted to the hospital with severe tetraparesis with bowel and bladder dysfunction. Neurological examination disclosed paraplegia with pronounced loss of strength of the arms, generalised hyporeflexia, and loss of vibration sense; cranial nerves were normal, mental signs were not evident. Magnetic resonance imaging (1.0 T) of the cervicothoracic spine disclosed considerable cord swelling; no abnormalities of signal intensity in T1 weighted sagittal images were evident, whereas abnormally increased signal intensity lesions were detected in T2 weighted images in the posterior cord (figure, A) involving, to a lesser degree, also the lateral columns (figure, C). Brain MRI was unremarkable. Laboratory studies showed macrocytic (mean corpuscular volume 110 fl, normal 82 to 96 fl; packed cell volume 38%) anaemia (12 g/dl), low concentrations of iron (16 μ g/dl, normal 37–145 μ g/dl), and vitamin B12 (53 pg/ml, normal >200 pg/ml); folate was within normal values.

Gastric endoscopy disclosed the presence of chronic atrophic gastritis. Iliac crest biopsy showed a hypercellular bone marrow with an appreciable number of megaloblastic forms.

Diagnosis of subacute combined degeneration of the spinal cord was established. Treat-

ment with cobalamin was immediately started (1 mg intramuscularly daily for seven days and thereafter once monthly), with continuous and progressive improvement; vitamin B12 values became normal in two weeks and remained stable. At eight month follow up the patient was able to stand up and walk unassisted; strength was normal in the upper limbs whereas hypoaesthesia with impairment of vibratory sense, even if improved, persisted altered in four limbs. Magnetic resonance imaging showed considerable improvement of previous abnormalities, only faint hyperintensities in the posterior columns of the cervical spinal cord persisting; cord swelling was no longer detected (figure, B, D).

Pernicious anaemia is the most common cause of vitamin B12 deficiency. The spinal cord is usually affected first by vitamin B12 deficiency and often exclusively.

Neurological dysfunctions are due to progressive demyelination, sometimes followed by axonal loss, which starts in the posterior columns and spreads anteriorly involving the lateral and anterior columns; the process begins in the lower cervical and upper thoracic cord, spreading up and down the cord as well. The same neuropathological pattern can be found also in peripheral and optic nerves and, more rarely, in the white matter of the brain.^{1,2}

The progression of pathological changes in the spinal cord is reflected in the course of the disease; this results in a clinical picture consisting of the association of myelopathy and polyneuropathy.

Mental signs are frequent, ranging from irritability, apathy, somnolence, suspiciousness, and emotional instability to a pronounced confusional or depressive psychosis with intellectual deterioration. Replacement therapy with cobalamin is usually followed by almost complete resolution of symptoms.

Demyelination is disclosed at MRI as high signal intensity lesions on T2 weighted images, explained by increased water content.² A slight degree of expansion was seldom noted.³ Pronounced, multifocal contrast enhancement of the cervical and thoracic sections of the spinal cord after administration of gadolinium DTPA, indicating blood-CNS barrier disruption, was recently reported.³ Even if involvement of posterior columns is the origin of a characteristic MRI pattern, it is important to notice that similar findings can be found also in cases of purely spinal forms of multiple sclerosis, combined system disease of non-pernicious anaemia type, peripheral neuropathy (as in POEMS syndrome), and other rare pathological conditions.

Our patient, not known as vitamin B12 deficient, developed subacute combined

GE T2 weighted images of the cervical spine in the midsagittal (380/18/18:TR/TE/FA) and axial (510/15/15:TR/TE/FA) planes at the level of C2 at admission (A, C) and 8 months later after replacement therapy with cobalamin (B, D). At admission cord swelling is evident; high intensity lesions involve the posterior (C, arrows), and to a lesser degree, also the lateral (C, arrowheads) columns of the entire cervical spinal cord. Control examination shows the persistence of only faint hyperintensities in the posterior columns (D, arrow); the volume of the spinal cord is normal.