A 35 year old man, with no medical history and no alcohol, tobacco, or drug misuse, presented in December 1992 because of weakness and tingling in both legs, fatigue, and recent diplopia. The symptoms began in June 1992, two weeks after a third injection of plasma derived hepatitis B vaccine (Hevac B, Pasteur), and gradually worsened. The patient reported the same symptoms, that lasted a week, after a second injection in May 1992, and he had experienced nausea and unsteadiness of 10 days duration, three weeks after the first injection of a recombinant hepatitis B vaccine (GenHevac B, Pasteur) in March 1992. These symptoms were at that time misinterpreted as digestive by the general physician and no reliable information on the neurological examination could be obtained.

Examination showed a Romberg positive sign, spastic paraplegia, right sided hyperreflexia, and Babinski's sign, without any evidence of impaired sensation.

Hepatitis B serology was positive for anti-HbS antibodies (34 UI). Cerebrospinal fluid showed a raised total protein (82 mg/100 ml), with 9 blood cells/mm³ (90% lymphocytes), and no evidence of intrathecal immunoglobulin synthesis or oligoclonal bands. Blood cultures and tests for syphilis, Lyme disease, toxoplasmosis, and HIV were all negative. Electroencephalography was normal. Nerve conduction studies showed a diffuse sensory neuropathy of both arms and legs. Visual evoked potentials showed a bilateral delay; somatosensory potentials of the tibial nerve and auditory potentials were abnormal. T2 weighted MRI showed multiple high signals in the brain white matter. Blood HLA typing showed the B7, DR2 haplotype.

The patient was treated with adrenocorticotrophin for one month with a good clinical response, and there was no relapse during a two year follow up. In September 1994, the patient returned to a full time job. Physical examination showed no more gait disturbance, but a right sided pyramidal syndrome was still present. Repeat MRI showed unchanged multiple signals in the white matter.

Vaccination against B hepatitis is usually safe and efficient.² In 1991, however, Herroelen *et al* described two patients who developed demyelination in the CNS after recombinant B hepatitis vaccination.³ Both patients had the B7, DR2 HLA haplotype, which is associated with multiple sclerosis, and indeed one patient had a history of multiple sclerosis. Despite this HLA haplotype, in our patient the absence of a medical history, of intrathecal immunoglobulin synthesis, the presence of a diffuse sensory neuropathy, and the temporal association with vaccination argue against the diagnosis of multiple sclerosis. Nevertheless, it is difficult to establish whether neurological symptoms are directly and only due to vaccination, or if the vaccine simply triggers the onset or the relapse of an underlying multiple sclerosis. The findings of the B7, DR2 haplotype in these three cases of severe CNS demyelination might be trivial, indicating underlying multiple sclerosis, but might also suggest a pivotal role of this haplotype, possibly through special antigen presentation. The immune response might then induce non-specific lesions of CNS demyelination, with clinical and radiological expression similar to those in multiple sclerosis.

This finding, in addition to previous reports, suggests that vaccination against hepatitis B could potentially induce CNS complications in patients with the HLA B7, DR2 haplotype, with or without a history of multiple sclerosis.

G KAPLANSKI
F RETORNAZ
J M DURAND
J SOUBEYRAND
Service de Médecine Interne,
Hôpital Sainte-Marguerite,
270, Boulevard Sainte-Marguerite,
13009 Marseille, France

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A case of progressive subcortical gliosis associated with deposition of abnormal prion protein (PrP)

In 1967 Neumann and Cohn used the term of progressive subcortical gliosis to describe four patients presenting with a dementing neurological illness.¹ The principal histological finding in all four cases was pronounced gliosis of the white matter, basal ganglia, thalamus, brain stem, and ventral horns of the spinal cord, in the absence of diagnostic hallmarks of either Alzheimer's disease or Pick's disease. Although up to now only a small number of cases have been described, progressive subcortical gliosis, synonymous with Pick's disease type II, has been accepted by some of the standard neuropathological textbooks.²

In this *Journal* a case of progressive subcortical gliosis was reported from our institution in 1989.³ In summary, a 58 year old woman experienced difficulty in focusing and reading for three years before presenting with a general deterioration in intellectual function, including a deficit of short term memory. She was also found to have an akinetic rigid extrapyramidal syndrome and oculomotor signs usually associated

with the Steele-Richardson-Olszewski syndrome. Neuropathological examination of the brain showed "atypical features", which included pronounced astrogliosis in some cerebral cortical areas and subcortical structures such as white matter, caudate, putamen, and globus pallidus as well as Ammon's horn. Several brain stem structures and the cerebellum were similarly affected. There was a complete absence of cortical or subcortical neurofibrillary tangles and Pick bodies.

Recently, positive immunochemical findings suggestive of prion disease were detected in cases of the familial form of progressive subcortical gliosis.⁴ This gave us the impetus to review our case and apply the 1A8 anti-PrP antiserum (courtesy of Dr C F Farquar) with formic acid pretreatment, which showed a striking positive reaction in the neuropil of the granular cell layer of the cerebellum. The PrP positive deposits were either rather diffuse or small, compact, and plaque like (figure). Immunocytochemistry with an anti-β/A4 antibody (Dako Ltd) was also carried out, but no immunoreactivity was detected. Appropriate negative controls were used by omitting the primary antibody, and these showed no staining. In association with immunostains for PrP adjacent sections stained with Congo red and thioflavin T for amyloid were also studied, but no birefringent or fluorescent structures, suggestive of amyloid, were seen.

The immunocytochemical findings in this case have important implications for the classification of progressive subcortical gliosis and suggest that at least some forms of the condition are part of the range of human prion disorders rather than a subtype of Pick's disease in which pathological PrP does not occur.⁵ These results also emphasise the value of applying modern immunocytochemical and molecular biological techniques to cases with a presenile dementing illness, in which specific histological markers of known neurodegenerative diseases are absent.

T REVESZ
S E DANIEL
A J LEES
R G WILL
Department of Neuropathology,
Institute of Neurology,
Queen Square,
London WC1N 3BG, UK

Small PrP positive, plaque like deposit in cerebellar cortex (arrow); PrP immunostain $\times 400$.

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Low lumbar CSF concentrations of homovanillic acid in the autosomal dominant ataxias

The autosomal dominant ataxias (ADA) are a genetically heterogeneous group of disorders with similar phenotypes. There are few studies describing monoamine metabolites in CSF in patients with ADA. Low concentrations of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) and the dopamine metabolite homovanillic acid (HVA) in CSF are found in patients with cerebellar cortical atrophy and Friedreich's ataxia.¹ The low CSF concentrations of 5-HIAA may reflect a diminished contribution from the spinal cord and the cerebellar serotonergic pathways, whereas the low concentrations of HVA indicate involvement of the basal ganglia and other neural structures adjacent to the lateral ventricles. By contrast with other forms of ataxia, cerebellar signs did not improve in patients with ADA during trials evaluating the therapeutic efficacy of the serotonin precursor 5-hydroxytryptophan.¹ To determine the basis for this unresponsiveness, we measured CSF monoamine metabolites in patients with ADA with at least two different genotypes.

The Institutional Review Board of the National Institute of Neurological Disorders and Stroke approved this research project to study families with more than three consecutive generations of ataxia. After five days on a standard low monoamine diet and after eight hours of bed rest, a lumbar puncture was performed with the patient in the lateral decubitus position. Routine CSF studies were carried out on the initial 4 ml of CSF; for assay of HVA and 5-HIAA an additional 10 ml was collected in four 2.5 ml aliquots. All aliquots of CSF were frozen immediately on

dry ice and stored at -70°C. To minimise the effects of CSF monoamine concentration gradients, the tube containing the fourth aliquot of CSF was used for analysis. Extraction, derivatisation, and measurement of HVA and 5-HIAA were performed as previously described² on a Hewlett Packard MSD 5970 mass spectrometer-gas chromatograph 5890 with preserved acid extracts of CSF supernatant. For genetic characterisation, the polymerase chain reaction was performed with oligonucleotides flanking the CAG triplet repeat region on chromosome 6p and chromosome 14q as previously described.^{3,4} Magnetic resonance imaging was performed on a 0.5 Tesla unit scanner (Picker International Inc, model HPQ). Three 5.0 mm mediosagittal images were obtained parallel to the longitudinal fissure. The pontine (an elliptical pontine area bounded by the anterior surface of the pons, the interpeduncular fossa, and the putative medial lemniscus) and the cerebellar areas in the mediosagittal plane were quantified with ANALYZE version 6.2 software (Biomedical Imaging Resources, Mayo Foundation) on a DIGITAL DEC station 5000/125. Triplicate samples were measured to compute the mean area in mm² and the SD. Identical areas from 10 normal volunteers were used for comparisons.

Mean concentrations of HVA and 5-HIAA in CSF were calculated and statistical differences were determined by paired two tailed *t* test. The relation between the monoamine metabolites and cerebellar and pontine areas was examined by linear regression.

All 20 patients (12 male, eight female) had variable degrees of cerebellar ataxia without parkinsonian signs. Five study participants from two families showed a repeat expansion on chromosome 6p (spinocerebellar atrophy type 1; SCA1), nine patients from three families showed a repeat expansion on chromosome 14q (SCA3) and six patients from three families had neither genotype. In the entire group of patients with ADA, the mean (SD) pontine (315.9 (82.1)) and cerebellar (731.3 (178.6)) areas were significantly (*P* < 0.01) smaller than normal (pons 393.5 (44.7); cerebellum 1120.0 (133.4)). The pontine area was linearly related to the decreasing concentrations of HVA in CSF (*P* = 0.05, *r* = 0.50, *y* = -2.3 + 0.09) but the cerebellar area was not related to the concentrations of HVA or 5-HIAA in CSF. The HVA concentrations in CSF and the ratio of CSF HVA/5-HIAA were significantly lower in the entire group of patients with ADA than in normal controls (table). Although the cerebellar size was smaller (*P* = 0.01) in patients with SCA1 (607.5 (112.6)) than in patients with SCA3 (858.3 (126.0)), no dif-

ferences in the concentrations of monoamine metabolites were found between these genotypes.

The cerebellum receives serotonergic innervation from the raphe nuclei but there is no appreciable dopaminergic innervation. In a large Cuban pedigree with ADA linked to chromosome 12q (SCA2),⁵ decreased concentrations of HVA in CSF were attributed to the neuronal depletion found in the substantia nigra at necropsy. We report here decreased concentrations of HVA in CSF, with normal concentrations of CSF 5-HIAA in patients with SCA1 and SCA3. Therefore, we suggest that at least three of the five known ADA genotypes have low concentrations of CSF HVA with normal concentrations of CSF 5-HIAA. These findings may explain the lack of a therapeutic response to pharmacological agents that alter serotonin metabolism in patients with ADA. The lack of parkinsonian signs in our patients with SCA1 and SCA3 implies that striatal dopamine deficiency is not pronounced early in the course of ataxia but the direct relation between CSF HVA concentrations and the midsagittal pontine area on MRI indicates that depletion of dopaminergic neurons does play a part in the pathogenesis of these genetic disorders.

JOSEPH J HIGGINS
Clinical Neurogenetics Unit
JUDITH D HARVEY-WHITE
IRWIN J KOPIN
Aminergic Mechanisms Section,
Clinical Neurosciences Branch,
National Institute of Neurological Disorders
and Stroke, National Institutes of Health,
Bethesda, Maryland, USA

Correspondence to: Dr Joseph J Higgins, Clinical Neurogenetics Unit, National Institute of Neurological Disorders and Stroke, Room 5N234, Bethesda, Maryland 20892-1430, USA.

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Liver dysfunction and probable manganese accumulation in the brainstem and basal ganglia

Because absorption and excretion of manganese is regulated by the hepatointestinal circuit,¹ advanced liver dysfunction may result in a reduction of manganese excretion and its accumulation in various organs including the brain.²

A 58 year old housewife was referred to us because of left orbital pain but normal ophthalmological examination. She had liver cirrhosis due to hepatitis C virus infection, which had developed after a blood

CSF monoamine metabolites in patients with autosomal dominant ataxia

	HVA (ng/ml)	5-HIAA (ng/ml)	Ratio HVA/5-HIAA
SCA1 (n = 5)	20.66 (3.05)**	12.89 (2.53)	1.67 (0.14)
SCA3 (n = 9)	20.23 (3.55)**	15.03 (1.28)	1.38 (0.21)**
Not SCA1 or 3 (n = 6)	36.81 (9.53)	16.78 (4.00)	2.10 (0.28)
Total SCA (n = 20)	25.31 (3.61)**	15.02 (1.42)	1.67 (0.14)**
Controls (n = 20)	39.08 (3.02)	17.26 (1.26)	2.30 (0.12)

Results are means (SEM).

**p < 0.01, paired two tailed *t* test.