1 Neumann MA, Cohn R. Progressive subcortical gliosis, a rare form of presenile dementia. *Brain* 1967;**90**:405–18.
2 Tomlinson BE. Ageing and the dementias. In: Adams JH, Duchen LW, eds. *Greenfield's neuropathology,* 5th ed, London: Edward Arnold, 1992:1284–410.
3 Will RG, Lees AJ, Gibb W, Barnard RO. A case of progressive subcortical gliosis presenting clinically as Steele-Richardson-Olszewski syndrome. *J Neurol Neurosurg Psychiatry* 1988;**51**:1224–7.
4 Tabaton M, Petersen R, Monari L, *et al.* Progressive subcortical gliosis: a new prion protein disease. *Society for Neuroscience Abstracts* 1993:**19**;842.
5 Jendroska K, Hoffmann O, Schelosky L, *et al.* Absence of disease related prion protein in neurodegenerative disorders presenting with Parkinson's syndrome. *J Neurol Neurosurg Psychiatry* 1994;**57**:1249–51.

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

The autosomal dominant ataxias (ADA) are a genetically heterogenous 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-hydroxytrytophan.[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 described[2] 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 mm^2 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 differences 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.

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.

1 Trouillas P, Renaud CB, Eynard N, Adeleine P. Serotonergic CSF abnormalities in human acquired and genetic ataxias. In: Trouillas P, Fuxe K, eds. *Serotonin, the cerebellum, and ataxia.* New York: Raven Press Ltd, 1993:311–22.
2 Polinsky RJ, Brown RT, Burns RS, Harvey-White J, Kopin IJ. Low lumbar CSF levels of homovanillic acid and 5-hydroxyindolacetic acid in multiple system atrophy with autonomic failure. *J Neurol Neurosurg Psychiatry* 1988;**51**:914–9.
3 Orr HT, Chung M, Banfi S, *et al.* Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nature Genetics* 1993;**4**:221–6.
4 Kawaguchi Y, Okamoto T, Taniwaki M, *et al.* CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32·1. *Nature Genetics* 1994;**8**:221–8.
5 Orozco G, Estrada R, Perry TL, *et al.* Dominantly inherited olivopontocerebellar atrophy from eastern Cuba. Clinical, neuropathological and biochemical findings. *J Neurol Sci* 1989;**93**:37–50.

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