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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.

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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.

transfusion at the age of 32. Sclerosing treatment had been performed twice for oesophageal varices. She had had no episodes suggestive of cerebral haemorrhage or hepatic encephalopathy.

Neurological examination was normal. She had no mental impairment or extrapyramidal signs. T1 weighted MRI of the brain showed symmetric high signal intensity in the globus pallidus, subthalamus, cerebral peduncle, substantia nigra, and the periaqueductal region of the mesencephalic and upper pontine tegmentum (figure). T2 weighted MRI and brain CT were normal. Abnormal data in routine laboratory tests included erythrocyte sedimentation rate 44 mm/hour, red blood cell count 3240 000/mm³, white blood cell count 2200/mm³, and platelets 64 000/mm³, packed cell volume 27%, haemoglobin 8.8 g/dl, total bilirubin 1.7 mg/dl, and raised values in other liver function tests. A test for antihepatitis C virus antibody was positive. Metals in serum were (normal range in parenthesis) iron 45 (56–117) µg/dl, unsaturated iron binding capacity 416 (150–336) µg/dl, copper 148 (103–159) µg/dl, zinc 48 (61–121) µg/dl, and manganese 0.55 (0.1–0.27) µg/dl. Whole blood contained 8.33 (0.4–2.0) µg manganese/dl. The patient's orbital pain disappeared spontaneously. She was given ferrous sulphate (320 mg per day), and was recommended to avoid manganese rich foods.

Hyperintensity in T1 weighted MRI in the basal ganglia and in the midbrain tegmentum was the characteristic MRI finding in our patient. An increased lipid, melanin, and methaemoglobin concentration, or calcified tissues, and ectopic Schwann cells in neurofibromatosis may cause similar

MRI changes.^{4,5} In our patient, the possibilities of raised methaemoglobin, calcified lesions, or ectopic Schwann cells were ruled out by normal CTs, no stigmata of neurofibromatosis, and no history of stroke. Symmetric hyperintensity of basal ganglia in T1 weighted MRI has been reported in patients with chronic liver diseases and possible manganese intoxication.^{2,3,6,7} Pujol *et al*² reported that on T1 weighted MRI, 33 of 45 patients with advanced liver dysfunction had symmetric high signal intensity in the globus pallidus. In seven of 11 patients who had liver transplants, MRI abnormalities decreased, and disappeared in four patients, suggesting a direct linkage between MRI findings and liver dysfunction. Manganese shortens spin lattice relaxation times via its paramagnetism and increases signal intensity on T1 weighted MRI.³ The high manganese concentration in whole blood in our patient suggested that the changes on MRI may reflect manganese accumulation, as postulated in chronic hepatopathy.⁷ T1 hyperintense lesions in the basal ganglia have not been reported in patients with Hallervorden-Spatz or Wilson's diseases, which result in iron or copper deposition in the brain, especially in the basal ganglia.^{8–10} Therefore, we postulate that the hyperintensity in T1 weighted images may represent an alteration resulting from an accumulation of paramagnetic substances such as manganese, but not such non-specific changes as cell loss, necrosis, or glial proliferation. In iron deficiency anaemia the enteric absorption of iron and manganese is increased.¹¹ Thus in our patient iron deficiency may have enhanced manganese absorption, whereas liver dysfunction may have resulted in the reduction of manganese excretion.

Several experimental and clinicopathological studies on manganese intoxication emphasised vulnerability of the basal ganglia, especially the globus pallidus.^{3,11} The present patient showed T1 high signal intensity in the tegmentum of the upper brain stem as well as changes in the basal ganglia. The pattern of distribution was almost identical to that seen in our previous patient with manganese intoxication during total parenteral nutrition.⁶ These two findings suggest that the basal ganglia and the periaqueductal structures in the tegmentum of the upper brainstem may have common metabolic characteristics with respect to certain trace metals.

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Transient amnestic syndrome after spontaneous haemorrhage into a hypothalamic pilocytic astrocytoma

The aetiology of the syndrome of transient global amnesia is unknown.^{1,2} A relation with migraine has been proposed and in a case-controlled series, no association was found with cerebrovascular disease, but 7% of patients developed epilepsy within one year of their first attack.¹ Controversy exists as to the relation between tumours or structural brain lesions and transient global amnesia, and in the reported cases the

Axial and coronal T1 weighted MRI (TR 500 ms, TE 15 ms) showing high signal intensity in the basal ganglia and periaqueductal region of the upper brain stem (arrow).