

The young age of the patient, appearance of his symptoms after a stroke, spontaneous improvement unrelated to treatment, lucencies seen on CT within the basal ganglia, and a relatively high level of HVA in cerebrospinal fluid, higher than usually seen in idiopathic Parkinson's disease,⁹ are in favour of this diagnosis. Other causes of Parkinsonism, such as normal pressure hydrocephalus or neuroleptic treatment were excluded.

While earlier reported cases of vascular Parkinsonism represent additional probable examples of this condition, they are open to question in a number of respects. Hughes and others described a 39-year-old hypertensive man who developed a Parkinsonian mask following a stroke, and who had bilateral caudate infarcts revealed at necropsy.¹⁰ It is not clear from the report if the patient had Parkinsonian features beyond facial masking. Tolosa and Santamaria reported three elderly men, two of whom were hypertensive, who had the insidious onset of Parkinsonism and who had infarcts of the basal ganglia revealed by CT scan.¹¹ Although these cases are likely to be valid examples of vascular Parkinsonism, the insidious onset at a late age makes it difficult to definitely exclude the coincidental occurrence of idiopathic Parkinson's disease with what could have been silent basal ganglia infarctions. The concept of vascular Parkinsonism is supported by the study of Parkes *et al* who noted higher CSF HVA levels in patients with vascular Parkinsonism, diagnosed by clinical criteria, as compared with patients with idiopathic Parkinson's disease.¹²

Our patient, and those cited above, represent probable examples of lacunar cerebrovascular disease, and there was associated hypertension in most cases. It is this type of cerebrovascular disease, rather than large vessel atherosclerotic disease, which has been associated with vascular Parkinsonism.^{7,8} Although Critchley titled his paper "Arteriosclerotic Parkinsonism" he emphasised the presence of lacunes on pathological examination. There is no evidence that multiple cerebral infarcts on the basis of diffuse atherosclerotic disease cause Parkinsonism, and it is this unsubstantiated relationship which has been the subject of many rebuttals of the concept of vascular Parkinsonism.^{3,4}

Although we presume our patient represents an example of vascular Parkinsonism, which is distinguished from idiopathic Parkinson's disease, we suspect that Parkinsonism is rarely vascular in aetiology. The rarity of this condition is indicated by the paucity of well-documented examples of it

in the literature, and by its infrequency in a large series of Parkinsonian patients.¹³

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ANDRZEJ FRIEDMAN
UN JUNG KANG
THOMAS K TATEMACHI
ROBERT E BURKE
*Department of Neurology,
College of Physicians and Surgeons,
Columbia University and
The Neurological Institute of
New York, Columbia-Presbyterian
Medical Center*

*Address for correspondence: 710 W 168th St, New York, New York 10032, USA.

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Beneficial effect of physostigmine on clinical amnesic behaviour and neuropsychological test results in a patient with a post-encephalitic amnesic syndrome

Sir: A beneficial effect of physostigmine medication on memory function as measured by neuropsychological tests has been described in patients with an amnesic syndrome due to Alzheimer's disease,¹⁻⁵ trauma^{6,7} and herpes encephalitis.⁸ We report a patient with an amnesic syndrome due to herpes simplex encephalitis who showed a marked improvement of both neuropsychological test results and amnesic behaviour after medication with physostigmine in combination with lecithin.

A 20-year-old female had acute encephalitis caused by herpes simplex virus type I as confirmed by a significant rise of HSV type I antibody titres in CSF in comparison with blood. A CT scan on admission was normal, but after three days vague hypodense areas could be delineated in the right temporal lobe and the left Sylvian fissure. She recovered without focal neurological deficits; however, behavioural abnormalities and a severe amnesic syndrome persisted. The first neuropsychological investigation five weeks after onset of her illness showed a cooperative woman with a retrograde amnesia up to one year prior to the illness. Her intelligence was above average,⁹ and there were no abnormalities of speech or writing. Digit span was five digits forward and four backward. On a serial verbal learning test with fifteen items the score remained within the first decile with no recognition on delayed recall. On the recurring figure test¹⁰ she obtained a minimal score. She was apathic but periods of uninhibited behaviour occurred. She was not able to learn faces or names of medical personnel and she lost her way on the ward. After discharge she needed constant supervision by relatives. The amnesic and behavioural abnormalities remained unaltered up to five months after the onset. She was then re-admitted and was given five daily doses of oral physostigmine titrated to an optimal subtoxic dose of 2.5 mg. A daily dose of 10 mg lecithin (30% phosphatidylcholine) was added. Memory function was monitored by the Selective Reminding Test,¹¹ that is before titration and during the titration period after the second, third and fourth daily dosages of physostigmine. Parallel Dutch versions were used to minimise learning effects. Each version consisted of ten items with a maximum of 15 trials. In the following period of 75 weeks, she was tested at irregular intervals in the outpatient clinic (weeks 4, 10, 13, 15, 26,

31, 39, 41, 46, 52 and 75 (fig)). In order to assess the continued efficacy of the drug, placebo or lecithin was given during weeks 4, 11–15 and 32–39. In week 52, that is 17 months after onset, the medication was discontinued. Final neuropsychological examination was carried out in week 75. At home the medication regimen was supervised by her mother, who also informed us of her daily performances. During the medication periods no side effects were observed.

Baseline tests (weeks 0 and 2) resulted in a mean score on the Selective Reminding Test of 79 (range 77–80). In the titration period the scores increased with the doses of physostigmine and were optimal at a dose of 2.5 mg (mean total score 98, range 97–122). In the outpatient follow-up period the mean total score was 107 (range 93–145) after physostigmine/lecithin medication and 84 (range 80–87) after placebo/lecithin medication. With physostigmine/lecithin both mean long-term retrieval (LTR) and mean long-term storage (LTS) were significantly improved as compared with mean LTR and mean LTS in baseline tests and after placebo/lecithin in weeks 4 and 11–15 ($p < 0.05$, Mann Whitney U test).

However, after week 32 a gradual improvement of LTR and LTS was measured after placebo/lecithin medication. With respect to the amnesic and behavioural disturbances a remarkable improvement was observed as soon as physostigmine/lecithin medication was started in the titration period. She became oriented in time and place and with an increasing dosage she started to remember faces and names of medical personnel. She remembered time and purpose of daily tests and was finally able to find her way around the ward without getting lost. In addition, she became more active and socially adjusted and the periods of uninhibited behaviour no longer occurred. Initially, during placebo/lecithin medication periods the disturbed behaviour

recurred, but after week 32 this difference between physostigmine and placebo medication periods diminished. Although amnesic and behavioural disturbances were diminished, 75 weeks after starting the medication periods, memory function was still impaired to such an extent that she depended on the relatively sheltered surroundings of her family.

The severe neuropsychological sequelae in survivors of herpes simplex encephalitis have been well described.^{12–14} Partial or complete recovery of amnesic and behavioural abnormalities tend to occur especially in the first six months after onset.^{12–14} Little is known about recovery after a longer follow-up period.^{13–14} In our patient an amelioration of amnesic and behavioural disturbances were observed between 5 and 17 months after onset. However, after physostigmine/lecithin medication a similar improvement of both amnesic and behavioural abnormalities could be observed much earlier, in the fifth month after onset. In the light of the cholinergic theory this observation may suggest that cholinergic neurons which survived the brain insult of encephalitis were brought to a functional level by the cholinesterase inhibiting capacity of physostigmine. This would imply that in survivors of herpes encephalitis with a residual population of cholinergic neurons a clinically important improvement of amnesic and behavioural disturbances may be derived with physostigmine medication, which may be of prognostic significance for the final future functioning of the patient. In addition, this may be helpful in shortening the length of institutional care and alleviate the burden of this dramatic illness for relatives. This is illustrated by the observation in a second patient with a postencephalitic amnesic syndrome, who on CT scan, however, showed large hypodense areas in the right orbitofrontal region and both temporal regions. Ten months after onset she

received physostigmine/lecithin medication for one month, but neither clinically nor on test results did she show any improvement of the amnesic syndrome. Also in the subsequent follow-up period of one year no further changes were observed.

Therefore, in our opinion, it is worthwhile to administer physostigmine to all patients with a postencephalitic amnesic syndrome, and if there is a positive reaction to continue this drug until no further spontaneous recovery of memory function occurs. The question arises if even earlier administration of physostigmine/lecithin immediately after the acute illness when amnesic and behavioural disturbances are not yet stabilised will also be of prognostic significance for the future final functioning of these patients.

CE CATSMAN-BERREVOETS

F VAN HARKAMP

A APPELHOF

Academic Hospital Rotterdam-Dijkzigt,
Department of Neurology,
dr. Molewaterplein 40,
3015 GD Rotterdam,
The Netherlands

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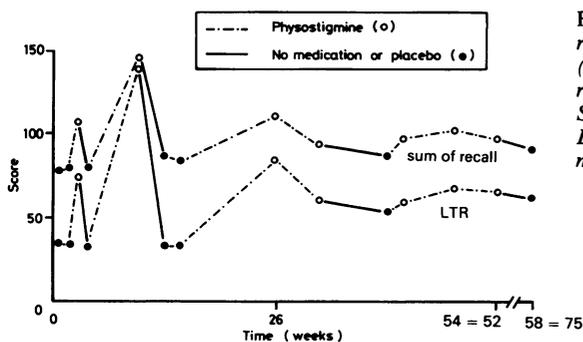


Fig Diagrammatic representation of the scores (sum of recall and long-term recall, LTR) on the Selective Reminding Test of Buschke during the medication periods.

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Matters arising

Arginase deficiency and phenylketonuria

Hyland *et al*¹ report clinical similarities between arginase deficiency and phenylalanine hydroxylase deficiency, two inborn errors causing progressive neurological damage. The similarity in the changes of homovanillic acid (HVA) and 5-hydroxy-indoleacetic acid (5HIAA) levels in cerebrospinal fluid and plasma of the deficient patient reported was striking.

We have measured the dihydropteridine reductase (DHPR) activity in rats loaded with phenylalanine and rats loaded with arginine. Inborn DHPR deficiency is responsible for the "atypical" phenylketonuria (PKU) which unlike its classical variant is not controllable by strict dietary regimes.² The effect on the brain and blood DHPR activity of loading phenylalanine or arginine was in both cases a similar dramatic reduction.

Brain tyrosine can be synthesised from phenylalanine by tyrosine hydroxylase.³ Lowered brain tyrosine of untreated PKU is

therefore not explicable by amino acid competition for brain entry. We suggest that the action of hyperargininaemia and hyperphenylalaninaemia on catecholamine and serotonin metabolism may be indirectly due to a reduction in DHPR activity.

PAUL CUTLER

Department of Molecular Sciences,
University of Aston
Birmingham B4 7ET, UK

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CSF and plasma levels of pro-opiomelanocortin-related peptides

Sir: Of great interest was the report by Nappi *et al*¹ demonstrating increases in CSF beta-endorphins of patients with ischaemic attacks and strokes. The authors suggested that the increase of beta-endorphins was possibly related to augmentation of 5-HT release or to the unknown phenomenology of diaschisis or in some more direct way to hypoxia, acidosis or hypercapnia. We believe that whatever the mechanism of beta-endorphin release, their actions in this setting serve primarily the protection of neurons at risk from hypoxic or ischaemic demise. Although it has been suggested,² that administration of naloxone may be beneficial in improving stroke outcome, this may as we have recently proposed,³ actually be detrimental to survival of neurons at risk due to metabolic stressors. Indeed, Claperon *et al*⁴ have shown an apparent deleterious effect of naloxone on rat brain hypoxic insults, and Cutler *et al*⁵ have reported worsening of neurological deficits following administration of naloxone in humans with stroke.

The effects of opioids on neuronal function include reduction in voltage-dependent calcium transport, increase potassium conductance and presynaptic inhibition of neurotransmitter release.⁶ Thus they diminish electrophysiologic (neuronal⁷ and synaptic⁸) activity and also may depress neuronal metabolism by inhibiting cyclic-

AMP directly, and indirectly through inhibition of noradrenergic locus coeruleus mechanisms.⁹ Thus the net result of opioid action would be expected to reduce neuronal metabolic demand. Indeed, opiates are known to reduce CMRO₂ by 85% with a lesser reduction of CBF.¹⁰ In addition, areas rich in opioid receptors have been shown to have their oxygen consumption specifically decreased by low-dose morphine.¹¹ Thus it is quite conceivable that the dramatic increases in the release of beta-endorphins during ischaemic act teleologically to decrease neuronal activity and oxygen consumption. This may possibly represent an extension of a physiological modulatory role of the intrinsic opioids during periods of metabolic stress.

ROBERT P IACONA*

REUVEN SANDYK†

Department of Surgery (Neurosurgery)*
and Neurology,† The University of
Arizona Health Sciences Center,
Tucson AZ 85724, USA

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C E Catsman-Berrevoets, F Van Harskamp and A Appelhof

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