PostScript

CORRESPONDENCE

Benefit of folic acid supplementation in parkinsonian patients treated with levodopa

We read with interest the recent excellent review by Reynolds on the role of folic acid and the risks and benefits of its supplementation in the nervous system.[1] It emphasises the beneficial importance of folate on the numerous methylation processes in combination with S-adenosylmethionine (SAM), which donates its methyl group to prevent hyperhomocysteinaemia.[1] However SAM deficiency, which is associated with, for example, cognitive decline and/or mood disturbances, and increased total homocysteine levels, which support onset of vascular disease, may also caused by drugs, for example, levodopa.[2 3] Levodopa is administered with dopa decarboxylase inhibitors (DDI) to prevent its peripheral degradation. This increases conversion of levodopa to 3-O-methyldopa (3-OMD) by the ubiquitious enzyme catechol-O-methyltransferase (COMT) in blood, peripheral tissues and in nigrostriatal neurons.[2 3] COMT requires Mg^{2+} as cofactor and SAM as methyl donor. Thus O-methylation of levodopa to 3-OMD is associated with conversion of SAM to S-adenosylhomocysteine and subsequently homocysteine.[2 3] We already demonstrated this association between homocysteine, SAM and 3-OMD in treated Parkinson's disease (PD) patients,[2 3] who often suffer from depression and bradyphrenia in the course of the disease and show an increased mortality risk of vascular disease.[4] The objective of our follow up study[2 3] was to determine total plasma homocysteine in 212 levodopa treated and 29 previously untreated PD patients and 110 controls. Standardised measurement of total homocysteine plasma concentrations with high performance liquid chromatography was only performed in subjects with no metabolic disturbances, like diabetes mellitus, hypertension, reduced levels of vitamin B6, cobalamine and/or folic acid or neurological diseases other than PD. Each PD patient fasted and was withdrawn from drug treatment for at least 12 hours before taking of blood samples in the morning. All participants gave informed consent, the local ethical committee approved this study. Homocysteine levels were significantly (analysis of covariance $F_{(dF\ 2,\ dF\ 346)} = 17.5$, p=5.9E-08; post hoc analysis (Tukey's HSD test): levodopa treated PD patients compared with controls: p=2.2E-05, previously untreated compared with levodopa treated PD patients: p=0.005; previously untreated PD patients compared with controls: p=0.92) increased in levodopa/DDI treated PD patients (17.3 (8.2) µmol/l (mean (SD)) compared with previously untreated PD patients (11.4 (5.8) µmol/l) and controls (12.2 (5.5) µmol/l). There was no significant impact of covariates age, sex, daily levodopa dose, and Hoehn and Yahr Stage (data not shown). An effective therapeutic approach for reduction of homocysteine levels is additional folic acid supplementation, as folic acid and cobalamine catalyse and increase metabolism of homocysteine to methionine,[2 3] or, hypothetically, application of peripherally acting COMT inhibitors as adjunct to levodopa/DDI treatment.[3] Methionine acts in combination with pyridoxalphosphate or S-methyl-α-keto-butyric acid as a strong scavenger of strong oxidants, which in turn induce endothelial dysfunction.[5] Homocysteine induced endothelial dysfunction may further promote atherosclerotic disease in striatal cerebral vessels with subsequent onset of differential susceptibility to impaired energy metabolism, oxidative stress, and basal ganglia dysfunction.[5] Endothelial response to homocysteine depends on the synthesis of nitric oxide.[5] Exposure of the endothelium to homocysteine induces release of nitric oxide, a further excitotoxic compound under suspicion for the contribution of the ensuing neuronal degeneration in PD.[2 3 5] Nitric oxide and reduced methionine levels support increased appearance of free radicals, in particular superoxide. Superoxide and nitric oxid generate peroxynitrite.[2 3 5] Peroxynitrite mediates tyrosine nitration, which further impairs activity of a variety of enzymes and inactivates tyrosine kinases.[2 3 5] These kinases are used by a variety of neuroprotective and neurorestorative growth factors, for instance glial cell line derived neurotrophic factor.[2 3] Accordingly in vitro trials showed neurotoxic effects of homocysteine and its oxidation product homocysteic acid on various types of cultured human neuronal cell lines and their excitotoxic activity partially via N-methyl-D-aspartate agonistic and mimicking properties.[5] In conclusion, additional folic acid supplementation with concomitant lowering of total homocysteine levels in levodopa/DDI treated PD patients will hypothetically reduce progress of PD and increased hazard ratios for both ischaemic heart—and cerebrovascular disease in treated PD patients.[4]

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Dysphagia due to Chiari I malformation mimicking ALS

We read with interest the article by Paulig and Prosiegel[1] concerning a patient initially diagnosed with amyotrophic lateral sclerosis (ALS), who had suffered from progressive swallowing difficulties, fibrillations, and tongue atrophy for a year, in the context of a flaccid bulbar palsy. Brain and spinal MRI showed a Chiari I malformation with descent of the cerebellar tonsils. The authors accompany their article with an illustration of the patient, showing extensive bilateral paresis and atrophy of the tongue. The article notes the importance of carrying out an MRI examination on those patients who show bulbar palsy mimicking bulbar onset type ALS in order to rule out Chiari I malformation.

Chiari I malformation has also recently been reported as being associated with bulbar onset ALS.[2] Nevertheless, the marked improvement in the dysphagia after neurosurgery suggests that Chiari I was the cause of the patient's bulbar palsy.

Dysphagia with predominant signs of lower motor neurone disease as the sole manifestation of adult Chiari I malformation is unusual.[3] Pressure exerted by the cerebellar tonsils on the hypoglossal nuclei and other swallowing centres located in the medulla is hypothesised by the authors to be a main cause of the dysphagia.

The importance of the reported case was the appearance of tongue atrophy over a relatively short period of time. In the three patients with dysphagia as the sole manifestation of Chiari I reported to date, the complaint had been present for at least three and a half years and none of the patients had tongue atrophy.[4–6]

We would like to comment on the importance of asymmetry of the face and mouth. A detailed examination of the picture[1] shows deviation of the mandible to the right, suggesting that there was at least trigeminal nerve motor involvement. Another important clinical detail that was not mentioned is whether the patient had speech abnormalities. The muscles used in speech are basically the same as those used in swallowing (innervated by the hypoglossal, vagal, glossopharyngeal, facial, and trigeminal motor cranial nerves).[7]

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